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Carcinogenic Properties of Ionizing and Nonionizing Radiation

Volume III - Ionizing Radiation

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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A CURRENT LITERATURE REPORT ON THE CARCINOGENIC PROPERTIES OF IONIZING AND NONIONIZING RADIATION

III. Ionizing Radiation

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. To provide relevant data from which valid criteria and effective standards can be deduced, the Division of Biomedical and Behavioral Science of the National Institute for Occupational Safety and Health conducts a formal program of research and information dissemination. The users of this information include basic and clinical researchers, legislators, research and biohazards administrators, occupational safety and health professionals, teachers, and students.

In keeping with its mandate, the Division of Biomedical and Behavioral Science requested The Franklin Institute Research Laboratories' Science Information Services to review the world's biomedical literature and to prepare a general reference document on the known or potential carcinogenic hazards of occupational exposure to ionizing and non-ionizing radiation. The purpose of the study was 4-fold:

1. to identify and document radiation types which have been shown to be actual or potential carcinogens;
2. to review recent findings regarding (a) current substantive issues and (b) impressions of distinguished investigators regarding the types of cancer induced by radiation, carcinogenic dose-response relationships, radiocarcinogenic mechanisms, and synergistic (co-carcinogenic) effects;
3. to predict the expected excess of cancers (or, for potentially carcinogenic types of radiation, the potential risk of cancer) either under commonly encountered conditions of occupational exposure or at the currently accepted maximum permissible dose limits; and
4. to identify specific gaps in the present knowledge of radiation carcinogenesis, and to recommend specific areas in need of further investigation.

In the course of the Franklin Institute study, five types of radiation were examined: ionizing, ultraviolet, visible, infrared, and microwave/radio-frequency radiation. The range of energies, frequencies, and wavelengths for each of these is as follows:

Type of Radiation	Energy Range	Frequency Range	Wavelength Range
Ionizing	above 12.4 eV	above 3,000 THz	below 100 nm

Type of Radiation	Energy Range	Frequency Range	Wavelength Range
Ultraviolet	6.20-3.10 eV	1,500-750 THz	200-400 nm
Visible	3.10-1.77 eV	750-429 THz	400-700 nm
Infrared	1.77 eV-1.24 meV	429 THz-300 GHz	700 nm-1 mm
Microwave	1.24 meV-1.24 μeV	300 GHz-300 MHz	1 mm - 1 m
Radiofrequency	1.24 μeV-1.24 neV	300 MHz-300 kHz	1 m - 1 km

Due to the volume of material, the study was limited to literature published since 1970, with only brief supplemental use of older materials when needed. The study is being published in three volumes:

I --- Optical Radiation (Ultraviolet, Visible, and Infrared).

II -- Microwave and Radiofrequency Radiation.

III - Ionizing Radiation.

The present volume documents the current status of knowledge regarding the carcinogenic hazards of occupational exposure to ionizing radiation. In general, the term "ionizing radiation" refers to a variety of particulate and electromagnetic radiations, each with sufficient energy (>10-12 eV) to ionize molecules. Alpha- and beta-particles, and cosmic rays consist of highly energetic charged particles capable of directly ionizing biological materials. Gamma rays and X-rays are short wavelength electromagnetic radiation which indirectly ionize biomolecules by liberating secondary particles which, themselves, are directly ionizing. Since the literature dealing with the different types of ionizing radiation is voluminous, much of the information reported has been gathered from reviews by distinguished investigators in the field. The information presented has been spot-checked against the original papers for accuracy, and supplemental information has been taken from the original literature when needed. The authors' intent is to present a general non-technical overview with selective follow-ups.

Standardized units of measurement are used throughout the present volume. The unit of measure for the absorbed dose (D) of ionizing radiation is the rad (1 rad = 100 ergs absorbed per gram of irradiated matter = 10^{-2} J/kg). The linear energy transfer (LET) of ionizing radiation measures the rate of energy loss of charged particles as they traverse through biological materials (usually in keV/μm of water in tissue), and the quality factor measures the ability of a given type of radiation to penetrate matter. The kinetic energy of secondary particles released per unit mass of tissue by ionizing radiation is called the kerma (usually given in rads). When the kerma and absorbed dose have nearly the same value, a state of radiation equilibrium is said to exist.

Types of Ionizing Radiation Commonly Encountered
in Occupational Settings

Type	Comments
α -particles	Charged helium nuclei. Poor penetration but dense ionization due to high linear energy transfer (LET). Directly ionizing.
β -particles	Electrons and positrons. Moderately penetrating. Directly ionizing.
Cosmic Rays	Mixture of highly accelerated atomic nuclei. Different energies, highly penetrating and of galactic or solar origin. Most are excluded from the Earth by the Van Allen layers. Directly ionizing.
γ -rays	Short wavelength electromagnetic radiation. Highly penetrating. Indirectly ionizing.
X-rays	Short wavelength electromagnetic radiation. Highly penetrating. Indirectly ionizing.
Neutrons	Electrically neutral particles. Highly penetrating. Indirectly ionizing.

The unit of exposure to X- and γ-radiation, the Roentgen (R), is based on the ability of these indirectly ionizing radiations to ionize air. In most cases, exposure to 1 R results in an absorbed dose of 1 ± 0.1 rad. The biological effectiveness of a given type of ionizing radiation is the absorbed dose of that radiation needed to produce a specific reproducible effect. The relative biological effectiveness (RBE) of two types of radiation is the ratio of absorbed doses needed for an equal effect. Thus, the RBE of radiation B relative to radiation A equals D_A/D_B. The quantity of absorbed ionizing radiation required to produce the same effects in man as 1 rad of X-rays is called the rem (Roentgen-equivalent-man).

ABSTRACT

This report presents a general overview of the known and potential carcinogenic hazards of occupational exposure to ionizing radiation based on a review of the literature published since 1970. Recent findings are reported, and current substantive issues and the impressions of investigators regarding the evidence for ionizing radiocarcinogenesis, dose-response relationships, synergistic (cocarcinogenic) effects, and proposed radiocarcinogenic mechanisms are identified. The risk of excess radiation-induced cancer under commonly encountered conditions of occupational exposure is estimated, and specific gaps in the present knowledge of radiation carcinogenesis are identified. Specific areas in need of further investigation are recommended.

This report is part of a larger survey of the carcinogenic properties of ionizing and non-ionizing radiation. It was submitted in partial fulfillment of Contract No. 210-76-0145 by The Franklin Institute Research Laboratories under the sponsorship of the National Institute for Occupational Safety and Health.

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EVIDENCE FOR IONIZING RADIOCARCINOGENESIS

The first link between cancer and occupational exposure to ionizing radiation came in 1911 when Frieben reported a case of epidermoid carcinoma on the right hand of a radiologist. Dozens of similar cases were reported in the ensuing decades. Within 15 years of Roentgen's discovery of X-rays, Hesse reported at least 94 cases of skin cancer among physicians, X-ray technicians and radium handlers. Multiple squamous cell and basal cell carcinomas of the hand were the most common, though fibrosarcomas were also prevalent (Upton, 1975). Cronkite et al. (1960) have reported over 200 cases of radiation-induced leukemia between the years 1911-1959.

The main sources of data regarding human exposure to ionizing radiation are listed in Table 1. These sources of data are epidemiologic in nature, and few are considered suitable for establishing quantitative dose-response relationships (Watson, 1975). The most reliable data comes from studies of the survivors at Hiroshima and Nagasaki and of patients treated with X-rays. The other exposure groups are either too small for statistical analysis or the actual doses received are undetermined. Table 2 lists the sites of involvement which have been linked to exposure to ionizing radiation. The most common neoplasm is leukemia, followed by cancer of the thyroid, lung, and bone. Ideally, positive confirmation of radiation carcinogenesis consists of discernable dose-response patterns in the epidemiologic data plus corroboration in the laboratory from animal experiments. In practice, however, the lack of quantitative data and the relative susceptibilities of different species often limit researchers to analyses of the number of excess lesions in populations with given histories of exposure.

One of the strongest supports for the link between ionizing radiation and carcinogenesis comes from the Japanese atom bomb survivors. These data have been recently updated by Ishimaru et al. (1971) on the basis of improved total-dose estimates of the neutron and gamma exposures in the two cities. As noted by Kellerer & Rossi (1975) and others, the leukemia data from Hiroshima and Nagasaki differ both in the observed dose-response curves (Figure 1) and in the dominant type of leukemia. The population in and around Hiroshima was exposed both to neutron and to gamma radiation. The biological effects appear to have been dominated by neutron exposure, and the incidence of excess leukemia was roughly proportional to the estimated dose. The ratio of acute lymphocytic to chronic granulocytic leukemia was approximately 1. In Nagasaki, the population was exposed primarily to gamma radiation. Here, the incidence increased with the square of the dose, and the ratio of acute to chronic leukemia was 4:1. In general, there appears to have been a 5-year latency period prior to the onset of excess leukemia in these two cities. The incidence of tumor appearance peaked in 1951 (6 years after exposure), and 25 years later, excess leukemia was still apparent (Figure 2). The tumor sites and number of deaths from other forms of cancer in atom bomb survivors between 1950 and 1970 are shown in Tables 3-4.

Table 1

Main Sources of Human Data on Radiation Carcinogenesis*

Use	Type of Exposure
Military	Survivors of Hiroshima and Nagasaki
	Fallout exposure from H-bomb test at Bikini
Occupational	Radiologists
	Luminous dial painters (radium)
	Uranium miners
Medical	Radium injections and patent medicine nostrums
	Thorium-X treatment for spinal tuberculosis and ankylosing spondylitis
	Thorium use as an X-ray contrast material
	Phosphorus-32 treatment of polycythemia
	X-ray treatment for ankylosing spondylitis
	X-ray treatment for enlarged thymus glands, ring worm, inflammation of the breast and some gynecological disorders
	X-ray fluoroscopy for pulmonary tuberculosis
	X-ray diagnostic procedures in pregnant women

* After Watson (1975), Upton (1975) and NAS-NRC (1972).

Table 2

Sites of Radiation-Induced Cancer in Man*

Type of Exposure	leukemia	thyroid	breast	lung	stomach	GI organs	skin	bone	head & neck	pancreas	liver	other childhood cancers
Atomic bomb survivors	X	X	X	X	X	X						
Atomic fallout in S. Pacific		X										
Radiologists/dentists	X						X					
Luminous dial painters								X				
Uranium miners & millers				X								
Radium injections & medicines								X	X			
Thorium treatment for spinal tuberculosis								X				
Thorium dioxide (Thorotrast)	X			X					X		X	
^{32}P-treatment: polycythaemia	X											
X-ray treatment: ankylosing spondylitis	X			X	X	X	X	X		X		
X-ray treatment: enlarged thymus, ring worm, breast, gynecologic disorders, etc.	X	X	X			X	X		X			
X-ray fluoroscopy for tuberculosis			X									
X-ray diagnosis in pregnant women	X											X

* Watson (1975) and from data in Ishimaru et al. (1971), NAS-NRC (1972), Rossi & Kellerer (1974), Upton (1975), Barnett (1976).

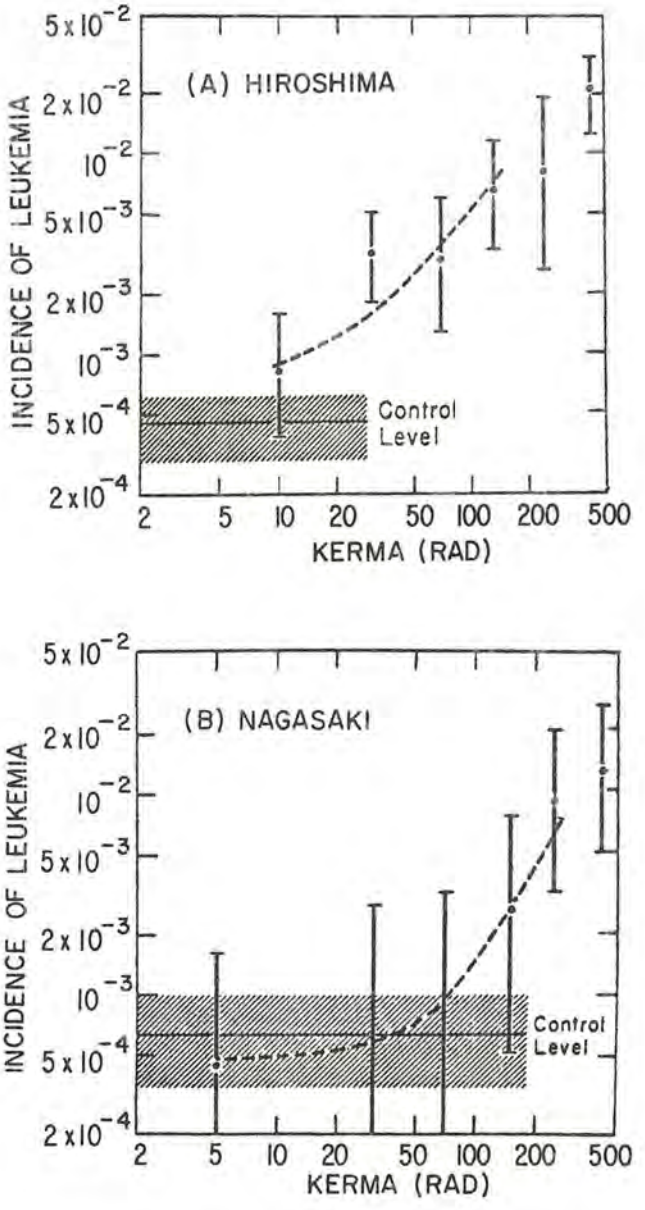

Figure 1. Incidence of leukemia for the period October 1950 to September 1966 vs. kerma at A) Hiroshima; and B) Nagasaki. The bars represent 95% confidence limits; the shaded area is the 95% confidence region for the unirradiated population of the city. The broken curve is the result of a least-squares fit. (From Rossi & Kellerer, 1974.)

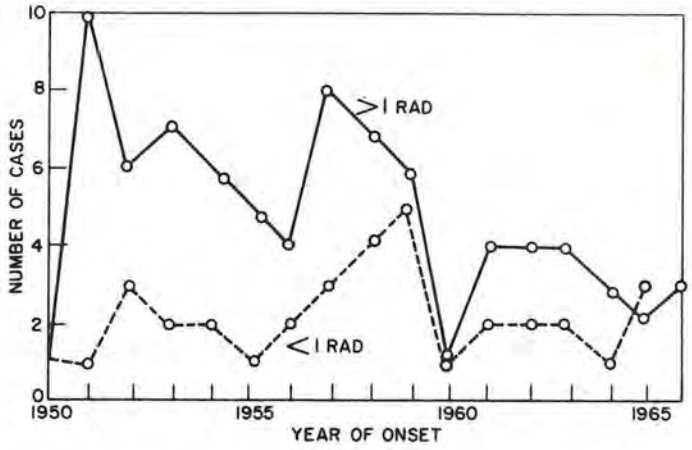

Figure 2. Distribution of incidence of definite and probable leukemia (all forms) among A-bomb survivors in the master sample (Hiroshima & Nagasaki combined) by year of onset and T65 total dose. —— Indicates survivors exposed to >1 rad; --- indicates those exposed to <1 rad. (After Ishimaru et al., 1969.)

Table 3

Deaths from Cancer of the Digestive Organs and Peritoneum 1950-1970*

Malignant Neoplasm of:	Number of deaths	Percentage
Esophagus	134	5.2
Stomach	1600	61.7
Small intestine, duodenum	9	0.3
Large intestine (excluding the rectum)	109	4.2
Rectum & rectosigmoid junction	133	5.1
Liver & primary intrahepatic bile ducts	6	0.2
Gallbladder & bile ducts	77	3.0
Pancreas	109	4.2
Peritoneum & retroperitoneal tissue	44	1.7
Unspecified digestive organs	28	1.1
Respiratory & digestive systems (secondary)	344	13.3
	2,593	

* Atomic bomb survivors data from Jablon & Kato (1972).

Table 4

Deaths from Other Non-Leukemic Malignancies 1950-1970*

Malignant Neoplasm of:	Number of deaths	Percentage
Tongue	22	4.6
Salivary gland	5	1.0
Lip, gum & mouth	6	1.3
Pharynx	11	2.3
Bone	23	4.8
Connective & other soft tissue	8	1.7
Skin	21	4.4
Ovary, fallopian tube & other female genital organs	51	10.7
Prostate	26	5.5
Testis and other male genital organs	4	0.8
Bladder & other urinary organs	88	18.4
Brain	2	0.4
Thyroid	14	2.9
Other endocrine glands	2	0.4
Ill-defined, secondary & site unspecified	120	25.2
Lymphosarcoma, reticulum cell sarcoma	34	7.1
Hodgkin's disease	21	4.4
Other lymphoid	8	1.7
Multiple myeloma	11	2.3
	477	

*Atomic bomb survivors data from Jablon & Kato (1972).

Excess leukemia has also been seen among radiologists. This is especially true among the early users of X-rays, who were largely unaware of the hazards of ionizing radiation and often accumulated large doses. Braestrup (reported in NAS-NRC, 1972) has estimated that between 1933 and 1937, radiologists may have received 100 Roentgen/yr (R/yr), versus 1 R/yr in 1957. This implies possible life-time occupational exposures of 2,000 R or greater for radiologists dying during the period 1930-1954. Seltser & Sartwell (1965) have reported a higher incidence of leukemia among physicians and dentists who use X-rays than among those who do not. More significantly, the higher incidence of leukemia was confined largely to older radiologists, who presumably received much of their exposure in the 1930-1950's when protective measures were not as widely employed as they are now. Kitabake et al. (1973) discuss the most recent findings for Japanese X-ray workers, which include 28 deaths from leukemia (average latency period, 17.7 years) and 30 deaths from skin cancer (22.2 years average latency), but they do not report the expected background incidence. The estimated radiation dose received by these workers is given in Table 5.

Leukemia and other forms of cancer have also been seen in patients with a history of X-ray therapy. In the past, infants and children with respiratory distress were often diagnosed as having enlarged thymus glands and were treated with therapeutic doses of X-rays. X-ray therapy was given for many other problems, including enlarged tonsils, adenoids, and acne. This practice has led to 19 cases of thyroid cancer in 2,878 patients followed up by Miller (1975) [expected rate was 0.1/2,878] and 50 cases of malignant papillary or

Table 5

Estimated Radiation Dose Received by X-Ray Workers in Japan*

Calendar Year	Estimated Dose (R/yr)
1921	900
1922-1926	680
1927-1930	520
1931-1935	350
1936-1940	240
1941-1945	90
1946-1953	9.3
1954-1957	1.55
1958-	0.31

* From Kitabake et al. (1973).

follicular adenocarcinoma in 1,032 patients reported on by Colman et al. (1975). Colman et al. (1975) report a 19 to 35 year latency period for X-ray induced cancer, and McConahey & Hayles (1976) note a tumor-induction period of 5-30 years.

Similar findings have been obtained from children receiving X-ray epilation for tinea capitis (ringworm of the scalp) and from women receiving repeated X-ray fluoroscopies while undergoing artificial pneumothorax therapy for tuberculosis. Modan et al. (1974) report a significant increase in the number of benign and malignant neoplasms in 10,902 Israeli children receiving 75-100-kV X-rays between 1949 and 1960. The estimated doses received in conventional tinea capitis treatment are shown in Table 6, and the principal types of cancer reported by Modan et al. include cancer of the thyroid, cancer of the brain, lymphoma, and leukemia. In the case of multiple X-ray fluoroscopy, Barnett (1976) reports a 4- to 8-fold increase in the incidence of breast cancer, with a strong correlation between the affected breast and the side of the chest positioned closest to the X-ray source. MacKenzie (see NAS-NRC, 1972) reports a breast cancer incidence rate of 13/271 for one Nova Scotia sanatorium (versus 1/570 without fluoroscopy), and Myrden & Hiltz (NAS-NRC, 1972) report an incidence of 22/300 cases (versus 4/483 without fluoroscopy).

Obstetric radiography may also be linked to carcinogenesis. Many authors (Watson, 1975; NAS-NRC, 1972, etc.) report that diagnostic prenatal X-irradiation increases the risk of leukemia, neuroblastoma, cerebral tumors, Wilms' tumor, and other forms of childhood cancer. Mole (1974) has found that in England, the relative risk of leukemia in singletons exposed prenatally to

Table 6

Estimated Doses Received by Children During Conventional X-ray Treatment of Tinea Capitis *

Region	Dose (rads)
Scalp	500-800
Brain	140
Thyroid	6 ± 2
Pituitary	49 ± 6
Parotid gland	39
Skin (face & neck)	20-40

* After data in Harley et al. (1976).

one or more diagnostic X-rays is 1.5 times that of unirradiated controls, while the corresponding risk for twins is 2.2. The correlation between clinical risk and the antenatal radiography rate in England (10% for singletons, 55% for twins) suggests a causal relation. Diamond et al. (1973) have reported similar data for 20,000 *in utero* irradiations between 1947 and 1959. A 3-fold increase in the incidence of leukemia in white children was found but there was no significant increase in the incidence level among blacks. The possibility of differential sensitivity to prenatal irradiation offers a potential explanation for the notable absence of prenatal carcinogenicity among the survivors at Hiroshima and Nagasaki. Another explanation for the absence of prenatal carcinogenicity among the Japanese is that fetal cells, which are known to be more radio-sensitive, are killed rather than merely transformed at the higher doses to which the Japanese were exposed (Munoz, 1967). In general, the number of cells killed by ionizing radiation increases exponentially with dose (Watson, 1975 and Brent, 1977). If the induction of cancer in susceptible cells is proportional to dose, the observed incidence will be less than expected as the dose increases, and may eventually decrease with increasing dose. Evidence supporting this suggestion has been reported by many authors (see Kellerer & Rossi, 1975 and the references therein).

Pioneering studies by Martland and others (Upton, 1975) have also linked carcinogenesis to occupational and medical exposure to radionuclides. The basis for the present ongoing study of internal contamination with radioactive materials was laid by Evans (1966) and has since been extended to a number of different situations. A follow-up study of 770 luminous dial painters who ingested varying amounts of radium (see NAS-NRC, 1972) revealed 51 bone sarcomas and 21 carcinomas of the head and paranasal sinuses. No sarcomas were noted below an accumulated mean bone dose of 900 rads, but the incidence of cancer rose sharply above this value. Clinical and autopsy findings from 42 New Jersey dial painters who survived their initial industrial exposure to ^{226}Ra and ^{228}Ra in the 1910's and 1920's revealed 24 persons with malignancies or blood dyscrasias (Sharpe, 1974).

One hundred and fifty cases of lung cancer among uranium miners who were exposed to cigarette smoke, diesel fumes, and other potential carcinogens have also been reported (Saccomanno et al., 1971). Small cell and undifferentiated cell carcinomas occurred in 75% of these cases. Archer et al. (1973) report excess cancers in all groups of uranium miners who exceeded 120 working level month's exposure (WLM) to radionuclides*, and Archer et al. (1974) report the occurrence of epidermoid, small cell undifferentiated, and adenomatous bronchogenic carcinomas. In the latter study, small cell undifferentiated carcinoma was the predominant cell type. Though all three cell types are also elevated among cigarette smokers, they were found in different relative proportions in cigarette-smoking uranium miners.

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* 1 WLM = 170 hr exposure to 1.3×10^5 MeV of α-particles per liter of air inhaled

Still further data regarding the carcinogenic properties of ingested or inhaled radioisotopes comes from studies of the Marshall Islanders. The incidence of thyroid nodules among these people was found to increase from 0 to >80% in Marshallese children who were less than 10 years of age when accidentally exposed to fission radioisotopes from an American nuclear test (latent period = 8-16 yr). Upton (1975) estimates that these children received an exposure of 700-1,400 rads from internally deposited ^{131}I and 175 rads from external gamma radiation. Conrad (1974) reports a ^{131}I exposure of only 130-335 rads in Marshallese adults, due to the larger volume of their thyroid glands.

Carcinogenesis has also been noted in patients given thorium dioxide (Thorotrast), a naturally occurring radioactive material, for diagnostic purposes (NAS-NRC, 1972). Da Silva Horta et al. (1972) report a large excess both of hemangioendotheliomas (16/988) and local lesions at the sites of injection and retention in Portugese patients given Thorotrast between 1930 and 1955. A further epidemiological and follow-up study of 1,230 of the 2,432 Portugese given Thorotrast during this period revealed 23 fatal dyscrasias (including 12 acute leukemias), 13 cervical granulomas, 23 hepatic cirrhoses, and 104 malignant tumors. Sixty-four of these tumors were hepatic, of which 14 were hemangioendotheliomas. Cholangiocarcinomas were also observed (Da Silva Horta et al., 1974).

Laboratory animal experiments provide yet another line of evidence for ionizing radiocarcinogenesis. Some of the early experiments are outlined in Table 7 and some of the observed effects of radionuclides in experimental animals are shown in Tables 8-9. In general, most animals are like man in that they are susceptible to radiation-induced leukemia (Storer, 1975). Unlike man, animals exhibit a greater range of tissue sensitivities, even between different strains of the same species. Sprague-Dawley rats, for instance, are extremely prone to radiation-induced mammary tumors (Shellabarger et al., 1969), while burros are resistant to any type of tumor (Brown et al., 1965). Experiments begun by Upton et al. and recently completed by Storer et al. at Oak Ridge further illustrate the relative tissue sensitivity between different species. In these experiments (Storer, 1975), a total of 12,000 10-week-old female RFM/Un mice were irradiated with gamma-rays (10-400 rads, whole body), and an additional 4,000 mice were kept as controls. The preliminary results are shown in Table 10. Tissues listed as highly sensitive were those showing significant tumorigenesis at 25 rads. "Moderate" and "low" sensitivities correspond to threshold doses of 50-150 rads and >150 rads, respectively. The relative sensitivity of human tissues, as derived from the Japanese data, is given in Table 11 for comparison.

The evidence for ionizing radiocarcinogenesis is overwhelming. In many instances, however, the types of tumors induced are not distinct from spontaneous tumors of the same site (Warren, 1974). Given this fact and the often poorly defined dose-response relationships in human radiocarcinogenesis, direct causality can often be inferred only from known past histories or by epidemiological techniques.

Table 7

Early Experiments on Radiation Carcinogenesis *

Author	Date	Radiation or isotope	Species	Type of tumor
Marie et al.	1910	X-ray	Rat	Sarcoma, spindle-celled
Marie et al.	1912	X-ray	Rat	Sarcoma, spindle-celled
Lazarus-Barlow	1918	Ra	Mouse, rat	Carcinoma of skin
Bloch	1923	X-ray	Rabbit	Carcinoma
Bloch	1924	X-ray	Rabbit	Carcinoma
Goebel and Gerard	1925	X-ray	Guinea pig	Sarcoma, polymorphous
Daels	1925	Ra	Mouse, rat	Sarcoma, spindle-celled
Jonkhoff	1927	X-ray	Mouse	Carcinoma - sarcoma
Lacassagne and Vinzent	1929	X-ray	Rabbit	Fibrosarcoma, osteosarcoma, rhabdomyosarcoma
Schûrch	1930	X-ray	Rabbit	Carcinoma
Daels and Biltris	1931	Ra	Rat	Sarcoma of cranium, kidney, spleen
Daels and Biltris	1931	Ra	Guinea pig	Sarcoma of cranium, kidney, spleen
Schûrch and Uehlinger	1931	Ra	Rabbit	Sarcoma of bone, liver, spleen
Uehlinger and Schûrch	1935-1947	Ra, Ms-Th	Rabbit	Sarcoma of bone, liver, spleen
Sabin et al.	1932	Ra, Ms-Th	Rabbit	Osteosarcoma
Lacassagne	1933	X-ray	Rabbit	Sarcoma, spindle-celled myxosarcoma
Petrov and Krotkina	1933	Ra	Guinea pig	Carcinoma of biliary tract
Sedginidse	1933	X-ray	Mouse	Carcinoma, spindle-celled
Ludin	1934	X-ray	Rabbit	Chondrosarcoma
Daels and Biltris	1937	Ra	Chicken	Carcinoma of biliary tract, osteosarcoma

* From Lacassagne (1954 a, b,), Furth and Lorenz (1954), and Upton (1968).

Table 8

Effect of Multiple Injections or Ingestion of ^{89}Sr or ^{90}Sr by Experimental Animals*

Animal	Route of Administration	Total Dose (μCi/kg)	Myeloid Leukemia	Myeloid Hypoplasia	Osteosarcoma	Fibrosarcoma	Chondrosarcoma	Angiosarcoma	Reticulum Cell Tumor	Giant Cell Tumor	Lymphoid Leukemia	Reference
Monkey	po	500-1,000	+		+		+					Casarett et al. (1962)
Dog	po	150			+	+	+	+				Pool et al. (1972)
	inj	150	+		+	+		+				Dungworth et al. (1969)
	inj	15	+		+	+	+	+			+	Finkel et al. (1972)
Swine	po	—	+	+	+					+	+	Finkel et al. (1972)
Rats	po	330-790	+		+			+	+		+	Casarett et al. (1962)
	inj	0.1-3.5			+	+		+	+			Kuma and Zander (1957)
	inj	4.4			+	+	+	+		+		Skoryna and Kahn (1959) Skoryna et al. (1958)

*For references, see Vaughan (1973). inj = injections; po = ingestion

Table 9

Effects of Single Injection of ^{89}Sr or ^{90}Sr on Experimental Animals *

Animal	Route of Administration	Total Dose (μCi/kg)	Myeloid Leukemia	Myeloid Hypoplasia	Osteosarcoma	Fibrosarcoma	Chondrosarcoma	Angiosarcoma	Reticulum Cell Tumor	Giant Cell Tumor	Lymphoid Leukemia	Reference
Dog	iv	63.6-97.9			+			+				Dougherty and Mays (1969)
	iv	10-500			+	+		+			+	Finkel et al. (1972)
Swine	iv	1,869-6,160			+					+		Howard et al. (1969)
Rabbits	iv	50-1,000			+							Vaughan and Williamson (1969)
Rats	ip	5-500	+		+							Moskalev et al. (1969)
Mice: CBA	iv	20			+			+				Barnes et al. (1970)
CBA	-	200-1,600	+		+	+	+	+				Nilsson (1970)
CF1	iv	41-2,200	+		+	+	+	+				Finkel et al. (1959)

* For references, see Vaughan (1973). iv = intravenous; ip = intraperitoneal

Table 10

Relative Tissue Sensitivities in RFM Female Mice to the Induction of Radiogenic Cancer *

High sensitivity (<25 rads)	Moderate sensitivity (25-150 rads)	Low sensitivity (>150 rads)
Thymus	Pituitary	Bone
Ovary	Uterus	Skin
	Breast	Stomach
	Myelopoietic tissue (myeloid leukemia)	Liver
	Lung	Gastrointestinal tract
	Harderian gland	Other tissues

* From Storer (1975).

Table 11

Relative Sensitivity of Various Human Tissue to the Induction of Radiogenic Cancer*

High Sensitivity	Moderate Sensitivity	Low Sensitivity
Myelopoietic tissue (Acute leukemia and myeloid leukemia)		Skin
	Lung	Bone
Thyroid	Salivary gland	Stomach
Breast		Other tissues (including other lymphomas)

* From Storer (1975) and Upton (private communication).

DOSE-RESPONSE RELATIONSHIPS

Dose-response relationships are important for establishing a causal link between ionizing radiation and carcinogenesis and for further clarifying the mechanisms of radiation carcinogenesis. When known, they also play the major role in determining adequate safety measures. It is important, then, to know whether radiocarcinogenesis exhibits threshold phenomena. It is equally important to know what physical and host factors are important for each species, tissue, and type of tumor.

Traditionally, there have been two approaches to the question of dose-response relationships. What Storer (1975) calls the administrative approach was introduced in 1956 by the International Commission on Radiological Protection (ICRP) [Watson, 1975]. Those who adhere to this "linear-no threshold" hypothesis consider any dose of ionizing radiation, no matter how small, to be deleterious. The risk of cancer is considered to be directly proportional to the dose and to be independent of the dose rate and the quality of radiation. The "scientific" approach, in turn, seeks to uncover the functional form of the dose-response relationship. This approach seeks to discover the nature and mechanisms of carcinogenesis and the factors involved in the expression of neoplasms. Of the two approaches, the linear-no threshold hypothesis has the virtues of simplicity and conservatism. At the same time, the linear hypothesis tends to depart from the data, especially at low and high doses. The known dose-response data for lung cancer in American uranium miners is shown in Figure 3. Similar data for breast cancer in patients receiving diagnostic fluoroscopies are given in Figure 4. In these two instances, the data are adequately described by the linear hypothesis. The data for thyroid nodules resulting from X-ray therapy to the upper chest of infants and children also appear to be linear (Key, 1976). This is not the case, however, for bone cancer in luminous dial painters (Figure 5) or for lung cancer in Newfoundland fluorospar miners and in the Japanese survivors (Figures 6-7). In these instances, the data are only poorly approximated by the linear hypothesis. However, the uncertainties are such that the linear hypothesis cannot be definitively ruled out.

As opposed to the human data, animal data are more clearly nonlinear. In general, few experimental dose-response curves have been linear, except over a restricted dose range. At low-dose levels, the initiating effects of irradiation dominate and are, to some extent, reversible (Upton, 1975). At intermediate levels, the initiating effects can be further amplified by other enhancing and promoting effects (see below). At higher levels, both initiating and promoting effects fail to be fully expressed, due to side effects and excess injury (Walburg, 1974; NCRP, 1976; and Sacher, 1976). As a result, the dose-response curve is often sigmoidal, sometimes exhibiting a threshold and usually dependent on many variables, including the rate and geometry of absorption; the relative biological efficiency (RBE) of the radiation; variations in species, tissue, and cell sensitivity; and differential sensitivity among individuals of the same species (see Walburg, 1974; Storer, 1975; NCRP, 1976; and Figures 8-9).

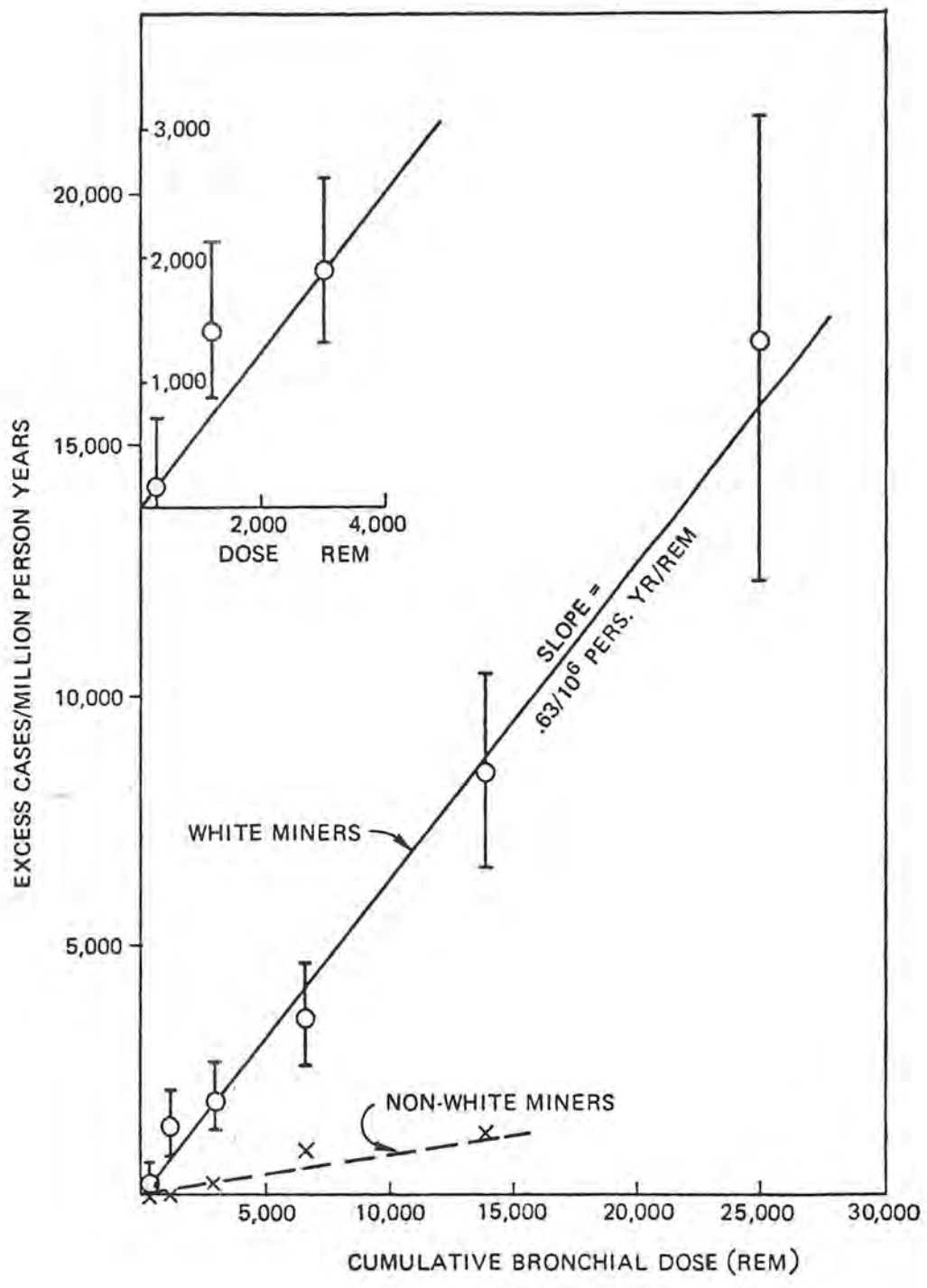

Figure 3. Dose-response data for lung cancer in U.S. uranium miners expressed as excess cases per million person years. The assumption is made that 1 working level month equals 5 rem. Error bars for white miners include the 90% range for Poisson statistics. (From data reported reported in NAS-NRC, 1972.)

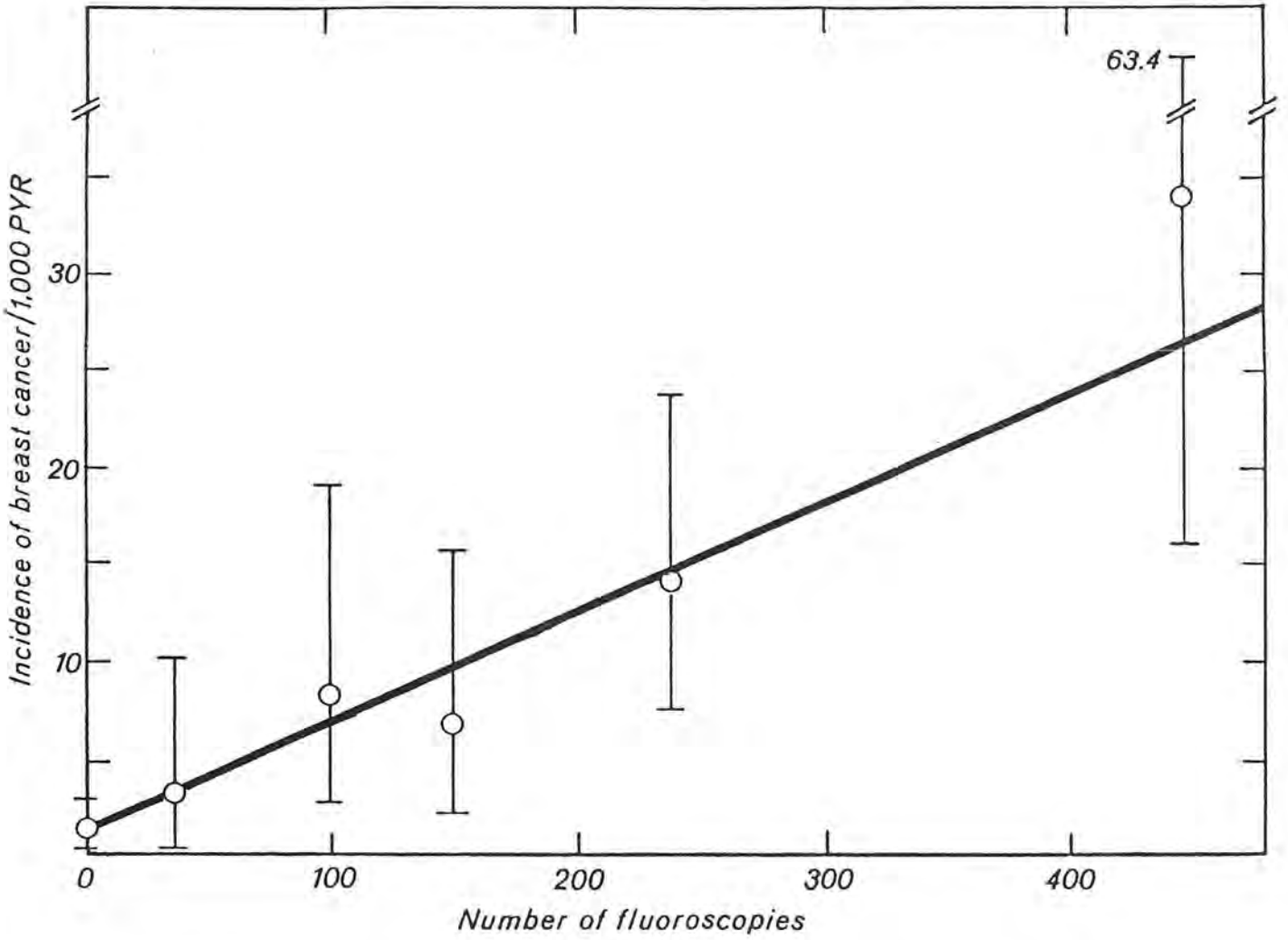

Figure 4. Dose-response data for breast cancer among patients receiving diagnostic fluoroscopies expressed as cases per thousand person years. The error bars represent 90% confidence intervals and the solid line is the best fitting weighted least squares regression line. (From NAS-NRC, 1972.)

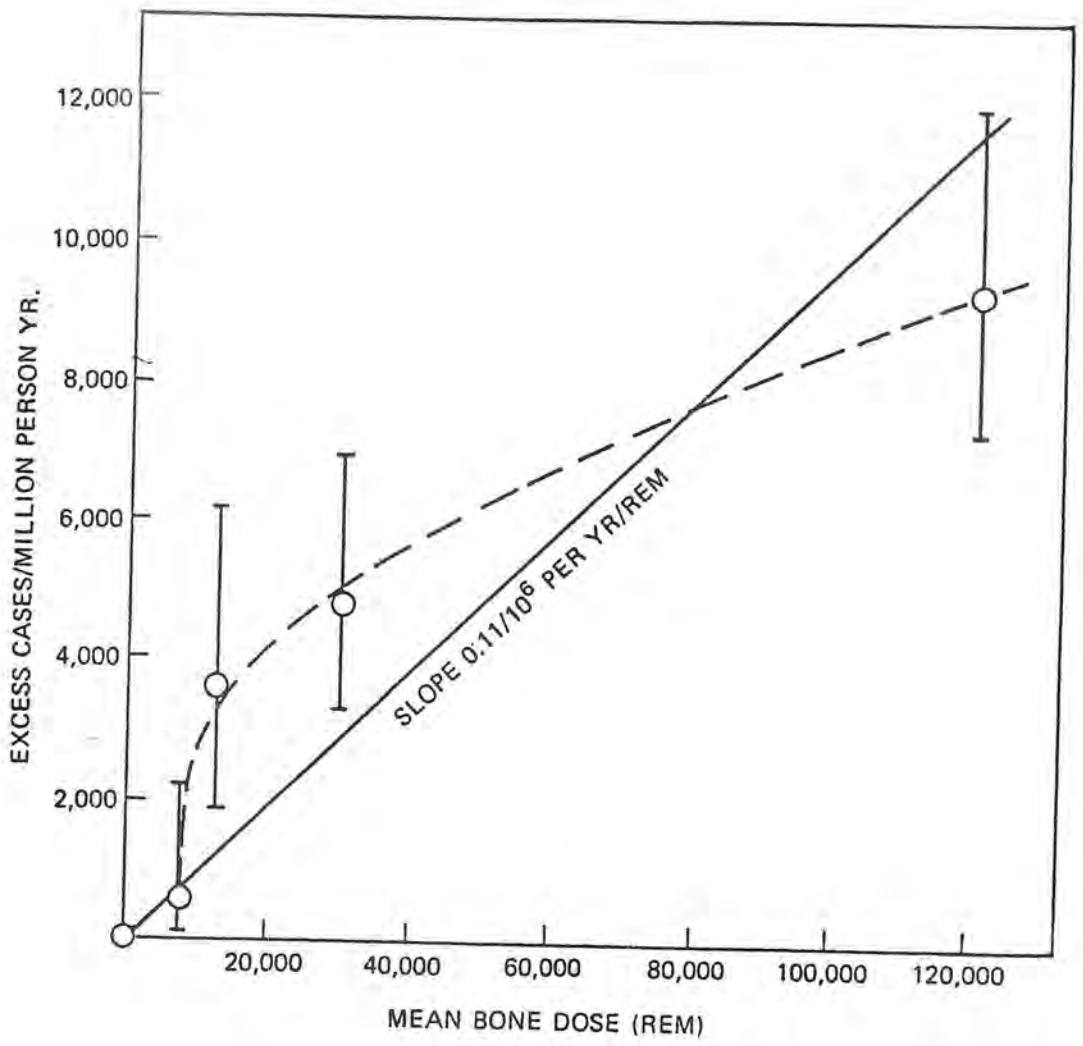

Figure 5. Dose-response data for bone cancer in an Argonne National Laboratory series of subjects exposed to radium-226, including both luminous dial painters and some patients given radium therapeutically. Error bars represent the 90% confidence interval using Poisson statistics and the solid line represents the weighted mean slope calculated via the administrative assumptions of strict linearity and no threshold affects. (After NAS-NRC, 1972).

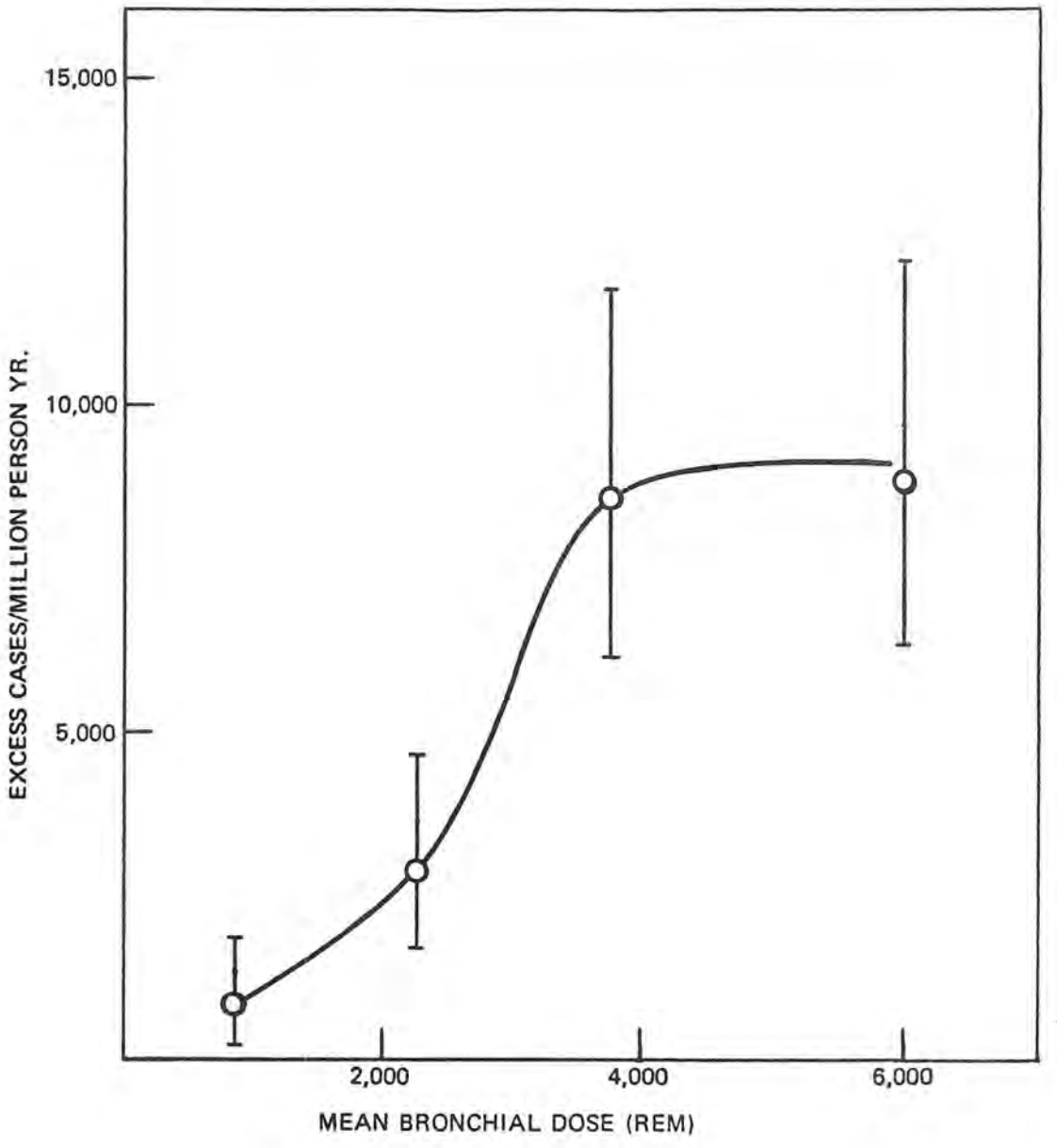

Figure 6. Dose-response data for lung cancer in Newfoundland fluorospar miners expressed as excess cases per million person years. The mean bronchial dose is calculated on the basis that miners were exposed at 5 WL and that 1 WLM = 5 rem. Error bars include the 90% range based on Poisson statistics. (From data by de Villiers et al., 1969.)

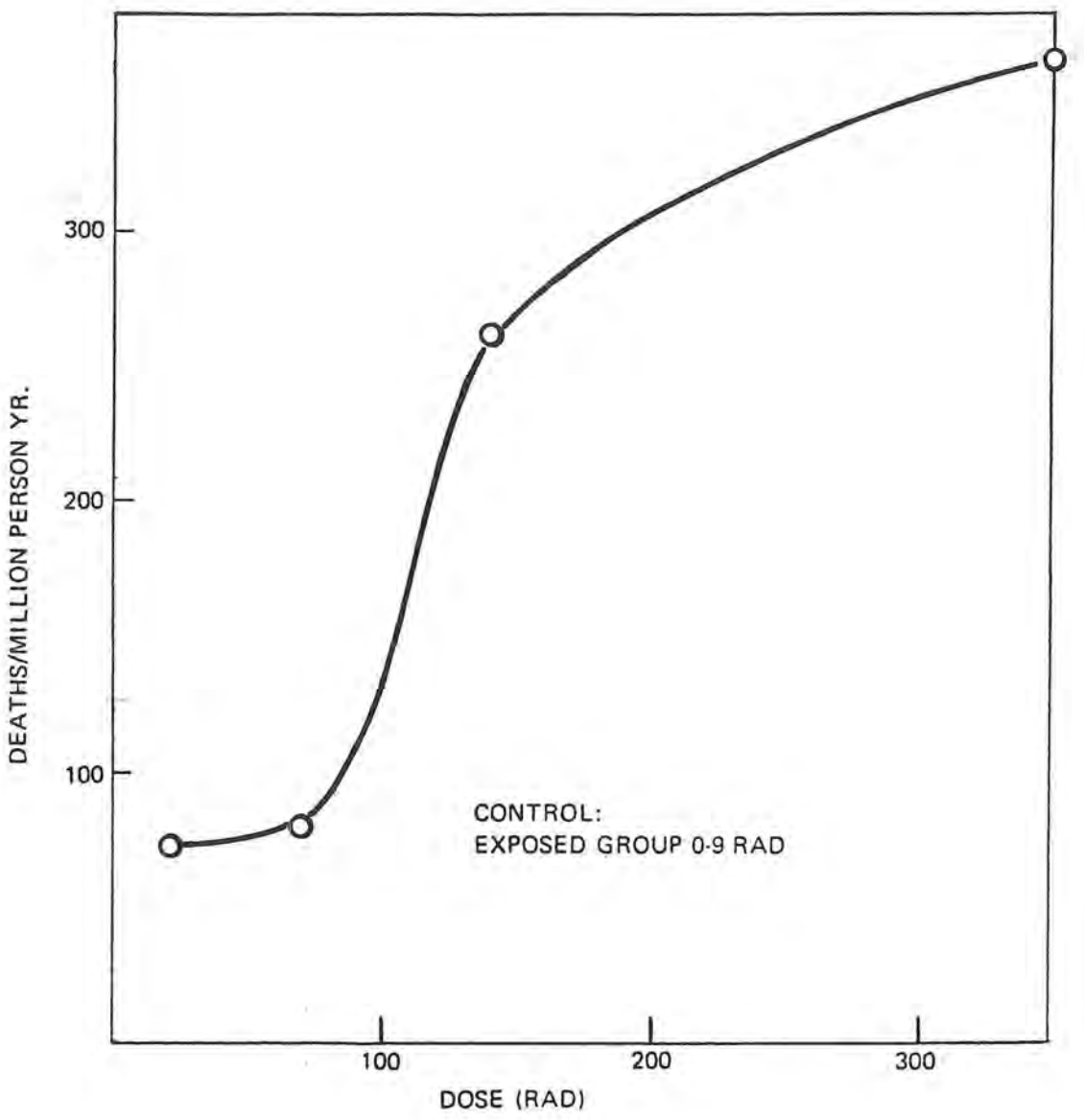

Figure 7. Dose-response data for lung cancer in Hiroshima and Nagasaki survivors expressed as excess deaths per million person years. The data are corrected for dose attenuation and a neutron RBE of 5. (From data by Jablon & Kato, 1972.)

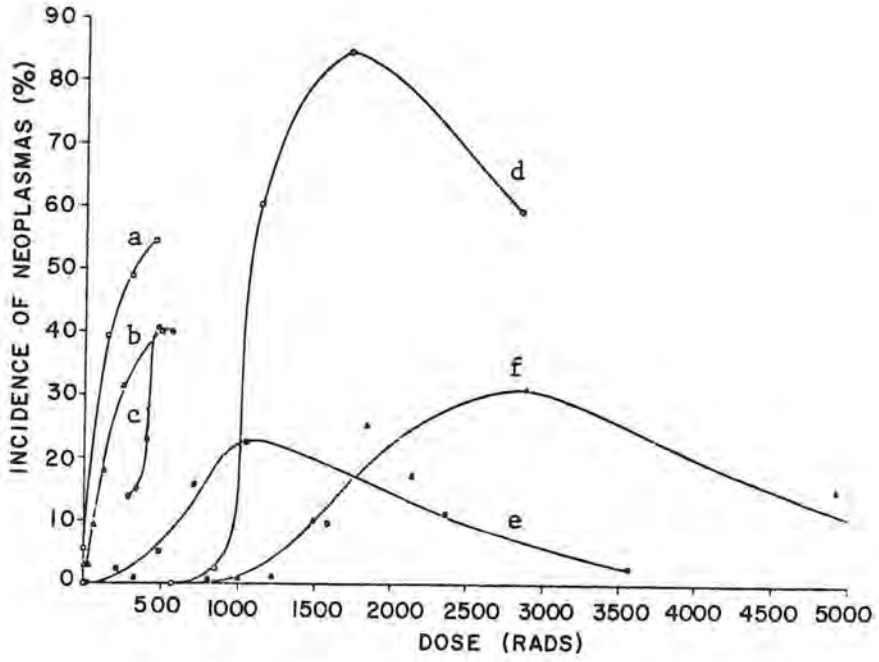

Figure 8. Dose-response curves for different types of tumors following exposure to external radiation: (a) myeloid leukemia in mice by X-rays (Upton et al., 1958); (b) mammary tumors in 12 mo old rats by γ-rays (Shellabarger et al., 1969); (c) thymic lymphoma in mice by X-rays (Kaplan & Brown, 1952); (d) kidney tumors in rats by X-rays (Maldague, 1969); (e) skin tumors in rats by alpha particles (percent incidence X 10, Burns et al., (1968); (f) skin tumors in rats by electrons (percent incidence X 10, Burns et al., 1968). (From Walburg, 1974.)

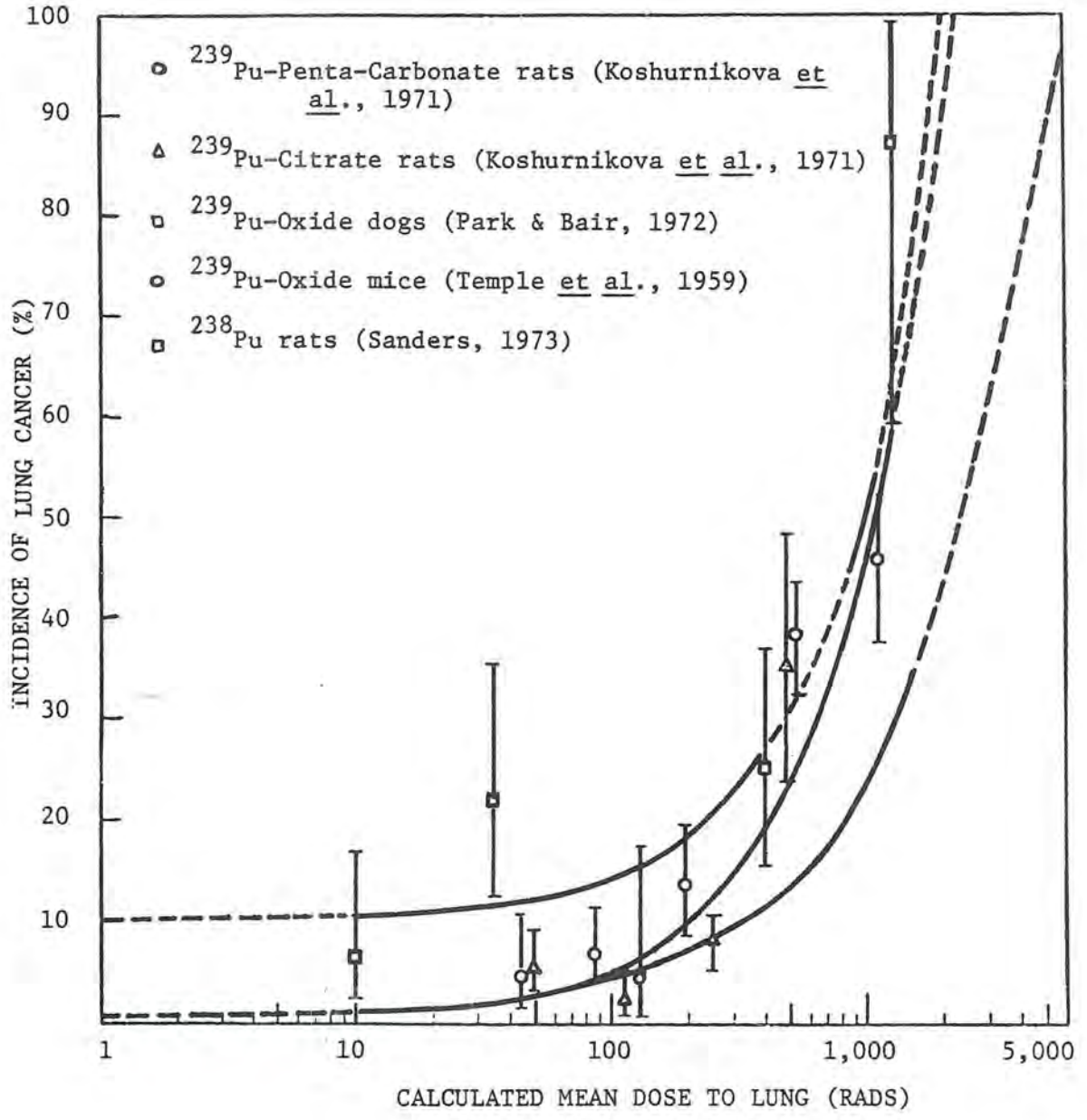

Figure 9. Incidence of pulmonary tumors in several species of experimental animals vs. the mean dose to the lung from inhaled alpha-emitters. (From Thomas & Blair, 1974 as reported in NCRP, 1976.)

Several factors affecting dose-response relationships have previously been discussed. Sprague-Dawley rats are extremely prone to radiation-induced mammary tumors (Shellabarger et al., 1969), while burros are resistant to any type of tumor (Brown et al., 1965). Even within a single species, different tissues and cell lines are more highly susceptible to tumor induction than others. The relative tissue sensitivities in RFM female mice are shown in Table 10, and the corresponding sensitivities of human tissues, as derived from the Japanese data, are given in Table 11 for comparison. Variability in radiocarcinogenicity also occurs among individuals of the same species or strain (Upton, 1975). Since carcinogenesis seems to involve a number of alterations, many of which can conceivably be caused by irradiation, the dose required for tumor induction in a particular tissue may depend on the extent to which mechanisms other than irradiation contribute. This, in turn, depends on the age, biological status, and medical history of the individual being irradiated. Not all the Japanese survivors, for instance, were equally susceptible to leukemogenesis (Figure 10).

Additional stochasticity is introduced by the nature of the mechanisms for depositing energy by ionizing radiation within neighboring and even within individual cells. The induction of mammary neoplasms in Sprague-Dawley rats and other radiobiological phenomena appear to result

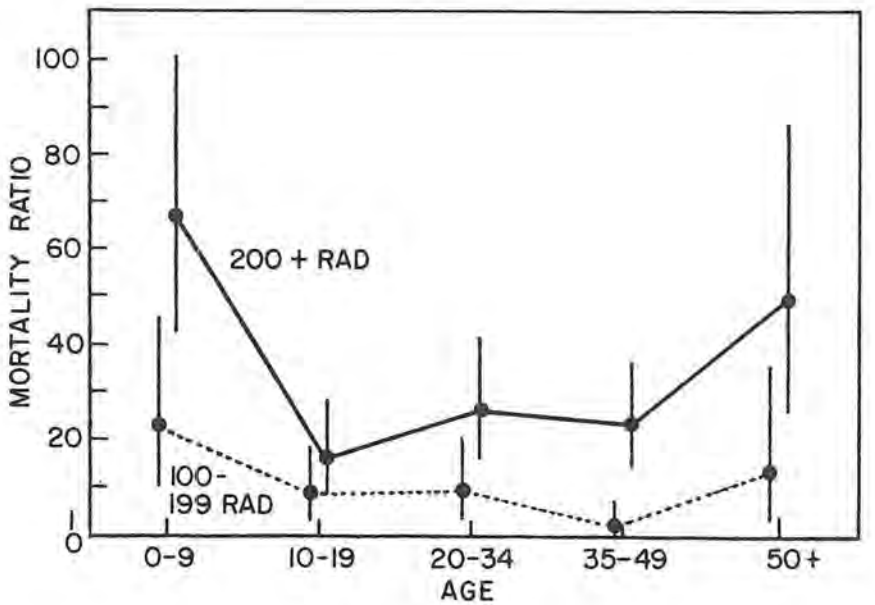

Figure 10. Mortality ratios (deaths from leukemia) and 80% confidence limits for 200+ rads and 100-199 rads groups of Japanese survivors. Ages are at time of exposure. (From Jablon & Kato, 1972.)

from multicellular responses to radiation injury (Kellerer & Rossi, 1975). The energetics of other effects seem to require multiple hits at or near a single site (Walburg, 1974). In each case, fluctuations in energy deposition can be appreciable, especially at low-dose levels. They depend, in part, on the volume in which the energy is to be concentrated, the absorbed dose per hit, and the Linear energy transfer (LET) of particles traversing through the given volume (Kellerer & Rossi, 1975). At high doses, the number of particles traversing a given volume is large. Statistical fluctuations are relatively small, and the actual energy deposited in a region of given mass (the specific energy) is not likely to differ greatly from the average absorbed dose (Kellerer & Rossi, 1975). At lower doses, fluctuations become more important, since the number of traversals is lessened. When the average number of traversals per unit volume is less than one, the shape of the observed distribution of energy deposition becomes independent of the dose. A further reduction of dose merely results in a decrease in the amplitude of the spectrum, with the remainder of the distribution appearing at the origin. The mean values of the specific energies produced by different types of ionizing radiation in such single events are shown in Figure 11.

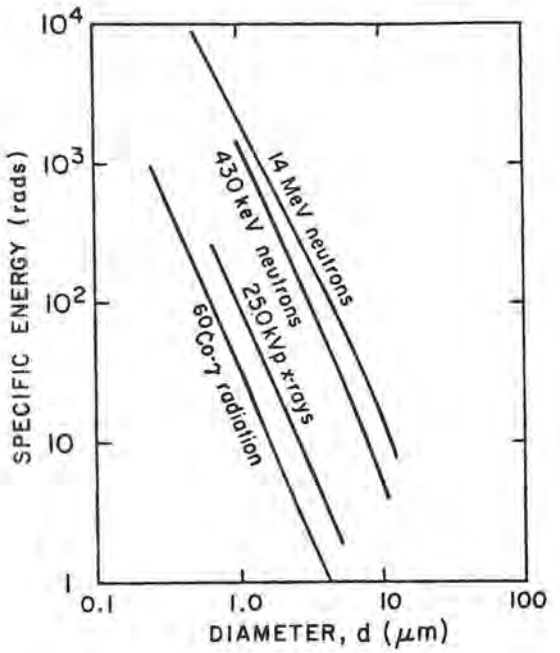

Figure 11. Mean value of the specific energy produced by different types of ionizing radiation in single events in spherical tissue regions of diameter d. (From Kellerer & Rossi, 1975.)

Experimentally, below the dose (~750 rads) at which the average number of events per cell is less than one, the incidence of cancer in mice exposed to localized thoracic X-rays is proportional to the dose and independent of the rate of irradiation (Yuhas, 1976), in keeping with microdosimetric considerations. When the critical dose of 750 rads is exceeded, the dose-response curve exhibits a log-log slope >>1, indicating the presence of a cooperative effect between multiple hits. It is at this point that the incidence of cancer also becomes sensitive to the rate of administration, due to competition between progressing radiation damage and intrinsic repair processes. This is especially true of low LET radiation, which at low dose rates is only 1/5 to 1/10 as effective as the same total dose given at higher rates (Storer, 1975). The carcinogenic properties of high LET radiations, such as alpha particles and neutrons, are relatively independent of the dose rate, due to their greater effective rate of energy deposition. The precise relative biological effectiveness (RBE) of different radiations appears to vary with the total dose and dose rate needed for a particular biological effect.

Though there are relatively few instances in which the mutual influence of the total dose, dose rate, and energy accumulation has been systematically analyzed, some generalizations have already been reached (NCRP, 1976). The efficiency of high LET radiation per unit dose is greater than that of low LET radiation and is relatively constant over a wide range of doses and dose rates. The efficiency low LET radiation decreases with the dose and rate of administration. The RBE of high LET radiation tends to increase with decreasing dose and dose rate (Figures 12-13). However, since the total dose, dose rate, and LET may have different effects at the cellular, tissue, organ, and systemic levels, their exact interrelationship may vary with the type of neoplasm, the dose and combination of cells and tissues being irradiated, and the relative susceptibility of individuals in the population at risk (NCRP, 1976).

Animal data <u>strongly</u> suggest that the form of most oncogenic dose-response curves is sigmoidal. However, for readily induced tumors where host factors are minor (see Storer, 1975), it is difficult to distinguish between linearity and a rapidly rising sigmoidal curve with a very short tail at the low-dose end. The available human data support similar inferences (NCRP, 1976), although this data is incomplete, especially at the low-dose end where deviations from linearity are expected. Consequently, linear relationships cannot be positively ruled out. But if the bulk of the experimental data can also be viewed as providing a valid conceptual framework for interpreting the human data, the dose-response curve for human populations may be assumed to include a polynomial function comprising a linear-dose term plus one or more power-dose terms. When cell killing and other high-dose effects are considered, the general form of this curve would be:

$$Y = (C + aD + bD^2)\ (e^{-\alpha D} + \beta D^2\ \ldots.) \qquad (1.)$$

where Y is the expected incidence of cancer, C is the control frequency, D is the absorbed dose, and a, b, α, and β are defined by the system under study (NCRP, 1976).

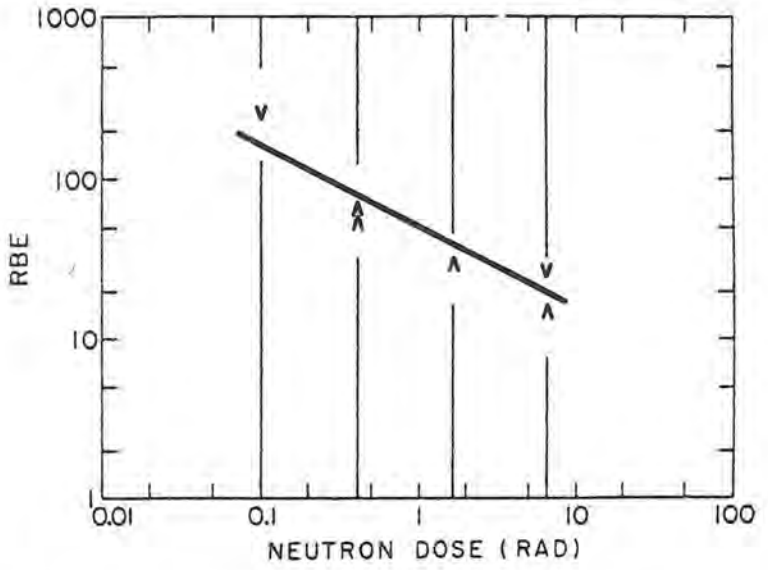

Figure 12. RBE of 430 KeV neutrons relative to sparsely ionizing radiation for the induction of mammary tumors in Sprague-Dawley rats. The vertical bars indicate the ranges of RBE values which are excluded with a statistical significance of 95%. (From data by Shellabarger et al., 1974 as analyzed by Kellerer & Rossi, 1975.)

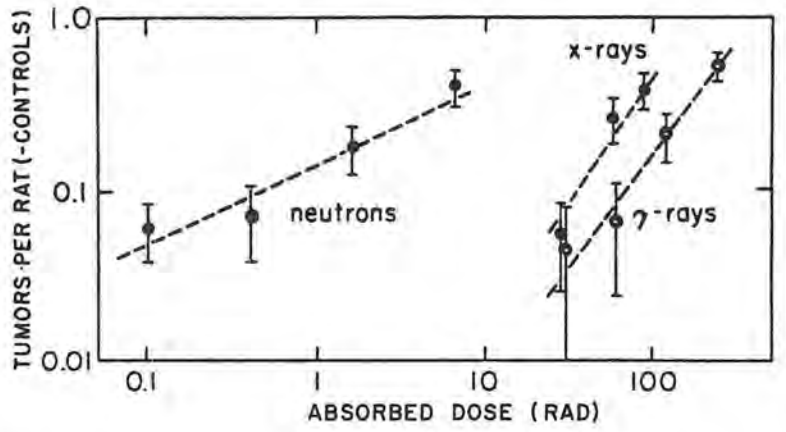

Figure 13. Mean number of tumors per rat minus the spontaneous incidence 400 days after exposure to neutrons, X-rays and gamma-rays. The broken lines have no mathematical significance and are merely inserted to indicate the trend of the data. The vertical bars represent the standard deviations. (From data by Shellabarger et al., 1973, 1974 and Bond et al., 1960 as presented by Kellerer & Rossi, 1975.)

Due to the complexity of radiocarcinogenesis (see below), even equation 1 may represent a gross oversimplification. Although it may have some validity for assessing the overall incidence of radiation-induced cancer, it cannot be expected to apply equally in every instance. Furthermore, since longer periods are required to accumulate a given dose at low-dose rates, less time remains during the normal life expectancy in which carcinogenic effects may be expressed (Albert & Altschuler, 1973). Data by Upton (1961), Evans (1974), and Jones et al. (1975) also suggest an increased latency period with a decreasing dose rate, and a similar effect has been seen in animal experiments (Figures 14-15). Even apart from the usual age-dependent variability in sensitivity, there is reason to expect a reduction in observed carcinogenicity when exposure is protracted beyond certain limits. In short, there may be no single linear term that is strictly invariant over an individual's entire life span, especially at the low-dose rates of interest (NCRP, 1976).

The possibility of protracted exposure at low-dose rates also leads to what Storer (1975) terms "practical" thresholds. Such thresholds have been seen

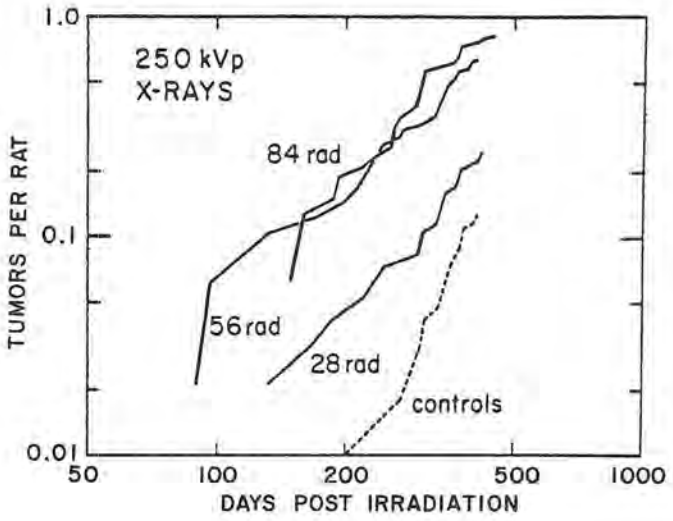

Figure 14. Mean number of mammary tumors in Sprague-Dawley rats as a function of time after exposure to different doses of 250 kVp X-rays. (From data by Shellabarger et al., 1974 as presented by Kellerer & Rossi, 1975.)

both in animal studies and in the human data. The data regarding bone tumors in luminous dial painters (Evans et al., 1969, 1972, and Figure 5), for instance, reveal two distinct dose regions. At doses <900 rads, no bone tumors have been seen; above 1,000-1,200 rads, there is a high incidence of tumors (roughly 30%). These results have been interpreted as implying a latency period exceeding the remaining average life-expectancy of the affected workers. The current state of knowledge is such that, due to the extreme difficulty of proving negative results, few would be willing to state that there is some dose below which there is absolutely no increased probability of developing cancer. As one might expect, there appear to be no unique radiation-induced cancers. What is usually observed is an increased cancer incidence seen against a variable "noise level" of spontaneous, but otherwise identical tumors. This variability reduces the statistical certainty with which the natural cancer rate can be utilized as a basis of comparison (Storer, 1975).

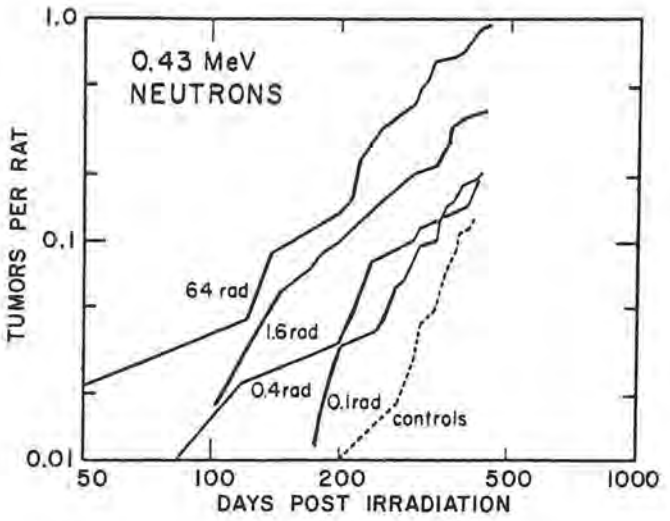

Figure 15: Mean number of mammary tumors in Sprague-Dawley rats as a function of time after exposure to different doses of 0.43 MeV neutrons. (From data by Shellabarger et al., 1974 as presented by Kellerer & Rossi, 1975.)

SYNERGISTIC EFFECTS OF EXPOSURE TO OTHER AGENTS

To predict the incidence of cancer in a given situation, factors other than radiation exposure alone must be considered. Carcinogenesis appears to involve a complex of alterations, many of which can conceivably be caused by ionizing radiation. Thus, the dose required for tumor induction may depend on the extent to which mechanisms other than irradiation contribute. Such mechanisms may, in part, reflect the effects of other physical agents, chemical carcinogens, and, at least in certain animal systems, oncogenic viruses. Unfortunately, these mechanisms are poorly understood.

Perhaps the best known example of synergistic effect between exposure to ionizing radiation and other carcinogens in the human data comes from studies of lung cancer in uranium miners. Saccomanno et al. (1971) report 150 cases of lung cancer among miners who were also exposed to cigarette smoke, diesel fumes, and other potential carcinogens; the incidence of cancer among non-smoking miners was lower. Archer et al. (1973) report excess cancers in miners exceeding 120 WLM exposure, and Archer et al. (1974) report the occurrence of epidermoid, small cell undifferentiated and adenomatous bronchogenic carcinoma. Though all three cell types are also elevated among cigarette smokers, they were found in different relative proportions in cigarette-smoking uranium miners.

Synergistic effects have also been seen in combined therapy with chemotherapeutic agents and therapeutic doses of ionizing radiation. Canellos et al. (1974) report data for 438 patients with Hodgkin's disease. Patients receiving intensive cyclic chemotherapy (MOPP) plus >3,500 R total nodal irradiation had a 10.4% incidence of secondary cancer. The incidence of secondary neoplasms in patients receiving either modality alone was only 2.3% ($p<0.05$). The types of secondary cancers observed in the combined-therapy group included squamous cell carcinoma of the skin, undifferentiated mucin-secreting carcinoma of the lung, fibrosarcoma of the chest wall, and acute myelomonocytic and acute myeloblastic leukemia.

Of the three carcinogenic agents most widely studied for synergism (radiation, chemical carcinogens, and viri), the animal studies have focused largely on the chemical carcinogens. Particular emphasis has been placed on their effect on irradiated skin, liver, and bronchial tissues; some of the early studies are summarized in Tables 12-15. At first glance, many of the results of these studies appear to be contradictory, due to wide methodological variations, many of which are not yet comparable. Despite the paucity of systematic studies, these data do suggest several qualitative generalizations. Most early experimenters concluded that for some sites, such as the lung, ionizing radiation actually suppressed the development of chemically-induced cancer. Studies such as those by Heston et al. and Duplan (see Table 14 for details) have served to strengthen this view, and additional support

Table 12

Combined Action of Ionizing Radiation and Chemical Carcinogens on the Skin

Type of Radiation	Chemical Agent	Results	Reference(s)*
X-rays (400 rads)	methylcholanthrene (MC) [repeated post-irradiation sc applications]	high rate of benign fibromas, fibrosarcomas & polymorphocelluar sarcomas in normally resistant guinea pigs. Optimum interval between the two treatments is 2-8 days. No effect seen with either agent alone.	Mendeleeff (1950, 1951)
alpha particles (radium)	"	spindel-cell sarcoma, reticulosarcoma in guinea pigs. No effect with either agent alone.	"
^{32}P or ^{91}Y	topical MC subcutaneous MC	enhanced rate of skin tumors carcinogenic effects of MC inhibited.	Cloudman et al. (1955)
X-rays (300 rads whole-body or partial to the caudal region)	o-tolidine (1.16 mg sc, 3 month after irradiation)	shortening of latent period, increased incidence and greater ease of dissemination of most skin tumor types in mice.	Gubareva & Pliss (1966)

*For complete bibliographic details, see Kondrateva (1969).

Table 13

Combined Action of Ionizing Radiation and Chemical Carcinogens on the Liver

Type of Radiation	Chemical Agent	Results	Reference(s)*
X-rays or intra-splenic injection of radiogold	m-dimethylaminoazobenzene [added to diet]	increased frequency of hepatic tumors in rats.	Williand et al. (1951)
X-rays (560-650 rads, whole-body)	p-dimethylaminoazobenzene [added to diet]	"	Horie Kenya (1964)
Fast neutrons (165-306 rads, whole-body) - or - X-rays (500 rads)	subsequent single injection of CCl_4 (0.15 ml 2, 12, 14, 15 or 18 mo post-irradiation)	3 times as many hepatomas in mice as seen with irradiation alone. No effect with CCl_4 alone.	Cole & Nowell (1964)
X-rays (500-3,000 rads)	p-dimethylaminoazobenzene [added to diet]	prior irradiation inhibits the carcinogenic effect of p-DAB in rats.	Lacassagne et al. (1959, 1960, 1961, 1962, 1964)
2 or 20 μCi β-emitters 2 μCi α-emitters	n-methylaminoazobenzene [0.06% added to diet]	reduced number of hepatic tumors in rats.	Dennis et al. (1965)

*For complete bibliographic details, see Kondrateva (1969).

Table 14

Combined Action of Ionizing Radiation and Chemical Carcinogens on the Lungs

Type of Radiation	Chemical Agent	Results	Reference(s)*
X-rays (1,200-2,400 rads)	urethan (dose N.R.)	carcinogenic effect of urethan suppressed in proportion to the extent of radiation damage to murine lung tissue.	Duplan (1962)
X-rays (900 rads whole-body)	embikhin (0.25 mg i.v. X 2 ten days post-irradiation)	only 38% of mice developed tumors vs. 93% with embikhin alone and 24% with X-rays.	Heston et al. (1953)
X-rays (300 rads whole-body)	urethan (1 mg/gm i.p.)	no significant lowering or enhancement of the carcinogenic effect in mice.	Chouroulinkov et al. (1965, 1966)
γ-rays from cobalt-60 (200 rads, whole-body)	urethan (50 mg i.p., 4-6 mo post-irradiation)	carcinogenic action of urethan in mice was significantly enhanced by irradiation at 200 R.	Kozlova (1961, 1963, 1965)

* For complete bibliographic details, see Kondrateva (1969).

Table 15

Combined Action of Ionizing Radiation and Chemical Carcinogens -- Other Sites

Type of Radiation	Chemical Agent	Results	Reference(s)*
β-particles from iodine-131 (5, 30 or 32 μCi, i.p.)	methylthiouracil or 2-acetylaminofluorine	increased frequency & size of thyroid adenomas in rats.	Doniach (1950, 1953)
" (100 μCi, i.p.)	"	no synergistic effect.	"
X-rays (500, 600 & 1,000 rads to gastric region)	DMBA (0.3 mg thrice weekly for 10 wk after irradiation)	gastric papillomas, plano-cellular cancers & sarcomas plus lymphocytic leukemia and tumors of the lungs, ovaries & pancreas. Lower frequency in mice receiving DMBA alone.	Erkki & Saxen (1952)
X-rays (400 rads to ventral surface of caudal region)	3-methylcholanthrene (<2 mg)	induction period for mammary tumorigenesis shortened & incidence increased vs. rats receiving only 1 agent.	Skay et al. (1962)
"	3-methylcholanthrene (>2 mg)	inhibition of tumor development.	"
X-rays (250 rads, single whole-body)	DMBA (10 mg)	bone tumors in rabbits appear within 12-61 d vs. 3-10 mo in unirradiated controls.	Gal'perin (1966)

* For complete bibliographic details, see Kondrateva (1969).

has come from studies of hepatic carcinogenesis by Lacassagne et al. and Dennis et al. (Table 13). Other authors, however, have noted positive synergistic effects at lower doses, and Lindop & Rotblat (1966) have concluded that irradiation inhibits bronchial carcinogenesis in rats only when the dose exceeds a threshold of 300 R. Data by Chouroulinkov et al. and by Kozlova (Table 14) suggest a similar conclusion.

The concept of tissue-specific thresholds below which the oncogenic properties of ionizing radiation may be chemically enhanced is further supported by Doniach's early study of thyroid adenomas and by Skay et al.'s study of mammary tumorigenesis (Table 15). This concept makes good biological sense and, if correct, would go far in explaining the apparent contradictions in Tables 12-15. Implicit in such a concept is the view that chemical carcinogens promote not only the carcinogenic effects (see, for instance, Takeichi, 1975) but also the cell killing and other high-dose effects of ionizing radiation. When the combined effect of radiation and chemical toxicity exceeds a certain level, the cell killing effects will dominate; below this level, neoplastic transformations are more probable. At present, however, the existence of synergistic thresholds remains unproven, and as Kondrateva (1969) notes, the apparent inconsistencies in the data are also explicable in terms of the underlying methodological differences. More rigorous and systematic study is required to clarify the situation.

Additional study is also required to explore the possible synergistic effects both of physical agents and of oncogenic viri. Burns et al. (1976) have studied the interaction between ionizing radiation and ultraviolet radiation (UVR). They report no evidence of synergism in 28-day-old rats irradiated with 690, 1,380, 2,060, or 3,450 rads of electrons, followed by erythemal UVR (4.2×10^6 or 2.1×10^7 ergs/cm^2/week x 20). Except for a delay in electron-induced tumorigenesis during the 20 weeks of UVR exposure, the carcinogenic effects of these two agents appeared to be strictly additive and independent of either. Apart from this, there have been few studies of synergism between ionizing radiation and other physical carcinogens.

The literature dealing with the interaction of ionizing radiation and oncogenic viruses is also relatively sparse. Frazier (1975 reports the presence of reverse transcriptase, which is indicative of retravirus or oncornavirus infection, in radiation-induced canine osteosarcomas. Other authors (see Rubin & Bakemeier, 1974) have suggested that radiation-induced leukemia is mediated through the activation of latent RNA viri. Experiments with normally resistant X/Gf mice (Goldfeder, 1976) suggest that X-rays and other immunosuppressive agents activate endogenous viral genomes in target mammary gland cells. Finkel et al. (1976), on the other hand, suggest that ionizing radiation inactivates viral inhibitors, and Hirashima & Kumatori (1974) suggest that radiation serves to sensitize animal cells to oncogenic viral infection. Though a positive contributory role for radiation has yet to be established in human cancers, there is a growing body of indirect evidence to suggest the presence of oncogenic viruses. To date, however, there have been few systematic studies of these questions, and further quantitative exploration is required.

PROPOSED MECHANISMS FOR IONIZING RADIOCARCINOGENESIS

The mechanisms of ionizing radiocarcinogenesis require clarification. Despite impressive advances in our understanding of the neoplastic process, the general mechanisms by which cells lose proliferative control and acquire metastatic properties remain unknown. The detailed mechanisms by which ionizing radiation induces these disturbances and the reasons for the wide differences in susceptibility are also unknown.

At the macrodosimetric level, the most important physical quantity for studying mechanism of radiocarcinogenesis is the absorbed dose or the average energy deposited in a given tissue volume and mass. Microscopically, the important quantity for study is specific energy. At high doses, the number of particles traversing a given volume is large. Statistical fluctuations in the incident radiation are relatively small, and the specific energy is not likely to differ greatly from the absorbed dose (Kellerer & Rossi, 1975). As the number of traversals is lessened, fluctuations become more important, and the specific energies deposited by radiations of different qualities approach the limiting case (depicted in Figure 11).

For indirectly ionizing particles (photons, neutrons, etc.) the absorbed dose is measured in kerma and depends on the quantity of incident kinetic energy released, mainly through the production and subsequent absorption of secondary particles and fluorescent radiation (Kellerer & Rossi, 1975). This kerma reaches its maximum value at the depth corresponding to the mean free path of the secondary particles produced by indirectly ionizing radiation. The range and LET of electrons and protons, on the other hand, differ both from one another and from those of indirectly ionizing particles. The higher rate of energy transfer and shorter range of protons, reflect the fact that the interaction between directly ionizing particles and absorbing materials is proportional to the square of the particles' charge and inversely proportional to the square of their velocity (Kellerer & Rossi, 1975).

The ways in which interactions between ionizing radiation and absorbing materials relate to the general mechanisms of radiation carcinogenesis are not clear. The interactions lead ultimately to a variety of intracellular free radicals (Miller et al., 1976). These radicals are electrophilic in character and can be generated directly or indirectly by reactions between macromolecules and other radicals produced in the radiolysis of water. Molecular oxygen, which can assume a diradical character, is also capable of generating and reacting with radicals to form a variety of oxidation products.

At the level of DNA, ionizing radiation has been shown to induce a number of effects, including mutations, chromosomal anomalies, and misrepair (Warren, 1974 and Oleinick & Rustad, 1976). Many of the cellular effects

of ionizing radiation may also result from radiation-induced damage within the nucleus (Walburg, 1974). The detailed mechanisms of such damage are unknown, but the radiation effect on enzymes is thought to reside at the level of transcription, rather than in the direct inhibition of enzymatic activity *per se*. Walters & Enger (1976) suggest that the latter effect results from irreparable base alterations in nonredundant genes. Since pre-existing mammalian mRNA (half-life of 13-42 hr) is more stable than DNA, the effect would be expressed as a deficiency in metabolism only after a long period of latency. Elkind & Redpath (in press) relate such radiation-induced deficiencies to the misrepair of altered genes. Alternately, the observed latency of radiation-induced metabolic deficiencies may result from defective genetic expression, rather than genetic mutations in nonredundant genes. Klein (1976) notes that irradiated cells must undergo one or two divisions prior to the appearance of neoplastic transformations. The occurrence of such transformations is greatest in cells allowed to divide shortly after treatment, suggesting a trigger mechanism dependent upon competition between altered genetic expression and intrinsic repair mechanisms. Such competition, if real, would explain the greater sensitivity of rapidly growing tissue to neoplastic transformation. The role of altered genetic expression, rather than genetic mutations *per se*, would also explain the results of Mintz & Illmensee (1975) and Illmensee & Mintz (1976) in which subcutaneously transplanted fetal tissue gave rise to teratomatous growth in mice. Nuclei from the latter teratomas have directed normal fetal development when retransplanted into a uterine environment.

Another potential initiating mechanism for neoplastic transformations is the release or activation of latent oncogenic viri. Early work by Kaplan and by Upton has implicated viral mechanisms in the induction of murine leukemias by radiation, and Finkel & Biskis (1968) have isolated an infectious virus capable of inducing osteogenic sarcoma in mice (Walburg, 1974). Frazier (1975), in turn, reports the presence of reverse transcriptase, which is indicative of oncornavirus infection, in radiation-induced osteosarcomas in beagles. Similarly, Lieberman et al. (1976) note that radiation-induced lymphomas in C57BL/Ka mice differ from those induced by passaged viri in that viral antigens are not fully expressed in thymic lymphoma cells. They suggest that once endogenous viral genomes have been activated, only partial virus expression is required to initiate oncogenesis in susceptible cells. Tennant et al. (1976) find that products from cells possessing the FV-1 locus can transfer resistance to specific oncornaviri. They suggest that radiation-induced oncornavirus activation involves the deactivation of specific provirus repressors, possibly through a decreased affinity between these repressors and proviri. Finally, Levy et al. (1976) have related both the sensitivity of BALB/c mice to murine leukemia virus (MuLV) and the early expression of virion proteins to a radiation-induced increase in the frequency of cell division. Tennant et al. have also implicated cell division in the initiation of endogenous provirus transcription.

In addition to "initiating" mechanisms, several promoting mechanisms may be important in the overall radiocarcinogenic process. The two most extensively discussed mechanisms are alterations in the rate of cellular proliferation and in immunocompetence (Walburg, 1974). Changes in the rate of cellular proliferation are related both to the altered expression of gene-

tic information and to the initiation of provirus transcription. In general, treatments which induce cell proliferation often increase the incidence of neoplasia in irradiated tissue. The data for murine mammary gland neoplasms, bone tumors in the shaft of fractured long bones, ^{90}Sr-induced osteolytic tumors in mice following estrogen treatment, and thyroid tumors in rats following goiterogen treatment support this view (Walburg, 1974). Since many chemical carcinogens cause a reduction in DNA synthesis, followed by recovery and increased cell division, the promoting role of cellular proliferation may provide a partial explanation for their synergistic effects with ionizing radiation.

Alterations in immunocompetence are another extensively discussed promoting mechanism for radiocarcinogenesis. Exposure to ionizing radiation and other immunosuppressive agents results in a transient immunosuppression during what is thought to be a critical period in the development of neoplastic cells (Walburg, 1974). Ihle et al. (1976) have found that mice which are highly susceptible to radiation-induced lymphomas are only marginally immunologically responsive to MuLV. Mice which are highly resistant to radiation-induced leukemia have high titers of natural (gp71) antibody and a very low incidence of spontaneous leukemias. Van Bekkum (1974) notes that most radiation-induced tumors possess weaker neo-antigens than those observed in chemically induced tumors. Alexander (1968), Cole & Nowell (1970), Severi (1970), and others, in turn, have shown that radiation-induced immunosuppression permits a more rapid growth of neoplastic cells, results in more metastases, and permits tumor transplantation across weak histocompatibility barriers. When combined with the general evidence for an increased tumor incidence following immunosuppression and the increased ease of transplantation in immunosuppressed animals (Walburg, 1974), it is difficult to deny a place for immunosuppression in the overall mechanisms of radiocarcinogenesis. Depending on the antigenicity of the specific radiation-induced tumors, immunosuppression may be a major determinant of the rate of tumor growth, as well as the tumor latency, final incidence, and rate of metastases.

Ionizing radiocarcinogenesis appears to be a very complex and as yet only partly understood phenomenon. Both initiating and promoting mechanisms seem to be involved, and the relative contributions of each may vary from case to case. Further quantitative study is required before the effect of both mechanisms in determining the overall risk of occupational cancer can be ascertained.

PREDICTION OF EXCESS CANCERS IN OCCUPATIONAL SETTINGS

In the absence of adequate dose-response, synergistic, and mechanistic data, the prediction of excess cancers in occupational settings (i.e., at low dose levels and rates) is difficult. Such predictions are normally based on the dose-response curve for the specific effect(s) in question. When only fragmentary dose-response data is available, extrapolation to the low-dose range requires a theory regarding the underlying mechanisms, the dose rate, the statistical distribution of individual thresholds within the population at risk, and the appropriate latent period(s), as influenced by both the dose and the dose rate. In practice, however, knowledge of the exact interrelation of these latter factors for specific neoplasms, tissue types, populations, age distributions, and qualities of radiation cannot be had apart from the dose-response data. Many authors and regulative bodies, therefore, have adopted the conservative linear-no threshold hypothesis.

According to the conservative linear-no threshold hypothesis, any dose of ionizing radiation is considered deleterious, no matter how small it may be. The risk of cancer is considered to be directly proportional to the dose and to be independent of the dose rate and quality of radiation. Thus if, as NAS-NRC (1972) estimates, about 1% of the spontaneous cancers in the U.S., or 3,000-4,000 deaths per year, are caused by the average background radiation of 0.1 rem/year, the cancer incidence at higher levels of exposure is predicted to be a linear multiple of this rate. The question of radiation protection from this point of view becomes one of balancing risks against the benefits accrued. The advantage of this approach is that it allows the relation of incidence to a simple mean accumulated dose characterizing the exposure of different groups under nonuniform conditions (NAS-NRC, 1972) to be estimated.

Typical risk estimates based on the linear hypothesis are shown in Tables 16-24 (NAS-NRC, 1972). Table 16 summarizes the NAS-NRC estimated risk of leukemia based on data from the Japanese survivors and patients receiving therapeutic doses of X-rays.* In both groups, the risk of leukemogenesis appears to be greater for those under 10 years of age at time of irradiation. The absolute risk is estimated to be 1-3 excess cases per 10^6 persons per year per rem for adults and 1-8 cases for children. The corresponding percent increases in relative risk (incidence in the exposed group divided by incidence in unexposed persons) are 2-4 and 6-11 per rem in adults and children, respectively. The absolute risk of leukemia

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* Strictly speaking, the two groups of subjects listed in Table 25 are not comparable, since the Japanese survivors received whole-body irradiation and many of those receiving therapeutic doses of X-rays received only partial exposures.

Table 16

Summary of Risk Estimates for Leukemia*

Population	Irradiated as Adults (>10 yr)		Irradiated as Children (1-10 yr)	
	Absolute Risk (cases/10^6/yr/rem)	Relative Risk (% increase in rate ppm)	Absolute Risk (cases/10^6/yr/rem)	Relative Risk (% increase in rate/rem)
Atom bombs Survivors (1945)				
Hiroshima & Nagasaki	0.76-1.8	3.7	1.1-3.3	6.5
Hiroshima alone	0.86-2.6	4.3	-	-
Nagasaki alone	0.09-0.98	2.3	-	-
Spondylitics (1935-1954)	1.0-1.7	2.9	-	-
Menorrhagia Patients	0.5-2.4	2.7	-	-
Thymus Patients (1926-1957)	-	-	1.3-5.6	8.1
Tinea Capitis Patients (1940-1949)	-	-	0.9-7.7	11

*Summarized from data reviewed in NAS-NRC (1972).

during the first 10 years following diagnostic intrauterine exposure is estimated to be as high as 41 cases above the spontaneous incidence rate per 10^6 persons per year per rem (Table 17). There is, however, no evidence of leukemogenesis in Japanese survivors irradiated *in utero*. Linear risk estimates for all other forms of cancer among the Japanese survivors and spondylitis patients are presented in Table 18. Again, the relative risk is greatest for children under 10 years of age. Linear risk estimates for other forms of cancer are given in Tables 19-24. Table 19 summarizes the NAS-NRC risk estimates for bone cancer in persons treated with ^{226}Ra and ^{224}Ra and in the spondylitics. The relative risk of radiation-induced skin cancer, based on the linear hypothesis, is outlined in Table 20, and the NAS-NRC linear estimates for breast cancer are summarized in Table 21. Estimates for lung, stomach, and other forms of gastrointestinal cancer are given in Tables 22-24. In each table, doses are converted from rads to rem on the assumption that the RBE is 10 for α-particles, 5 for neutrons, and 1 for γ-rays.

In general, the linear approach to risk estimates is conservative and tends to overestimate the carcinogenic effects of both low and high doses of ionizing radiation. NAS-NRC (1972) reports no detectable excess of leukemia in populations exposed at dose rates comparable with present occupational exposure limits. UNSCEAR (1964) reports that the actual incidence of radiation-induced leukemia approximates that of all other radiation cancers, and ICRP (1965) estimates the incidence of other radiation-induced cancers to be 2-3 times the rate of leukemogenesis. Jacobi (1976) estimates a real mean cancer risk of not greater than 0.001%/rad at doses <50 rads, and

Table 17

Summary of Risk Estimates for Leukemia after Fetal Irradiation*

Population	Absolute Risk (cases/10^6/yr/rem)	Relative Risk (% increase in rate/rem)
England (1943-1965)	23-32	1.63
U.S. (1947-1954)	12-41	1.54
A-bomb survivors (Hiroshima and Nagasaki, 1945)	0-5.9	0.0

* Summarized from data reviewed in NAS-NRC (1972).

Table 18

Summary of Risk Estimates for all Cancer Except Leukemia*

Population	Absolute Risk (cases/10^6/yr/rem)	Relative Risk (% increase in rate/rem)
A-bomb survivors		
(children, 1-10 yr)	0.07-2.2	2.9
(>10 yr of age)	0.0-26.0	1.1
Spondylitics	2.6-9.4	2.2

* Summarized from data reviewed in NAS-NRC (1972).

Table 19

Summary of Risk Estimates for Bone Cancer*

Population	Absolute Risk (cases/10^6/yr/rem)	Relative Risk (% increase in rate/rem)
^{226}Ra patients		
(adults >20 yr)	0.11	0.71
^{224}Ra patients		
(adults >20 yr)	0.55	5.5
(children 1-20 yr)	0.96	9.6
Spondylitics		
(adults >20 yr)	0.10	1.4

* Summarized from data reviewed in NAS-NRC (1972).

Table 20

Relative Risks for Skin Cancer at Various Exposure Levels after Therapeutic Radiation*

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

* From NAS-NRC (1972).

Table 21

Summary of Risk Estimates for Breast Cancer*

Population	Absolute Risk (cases/10^6/yr/rem)	Relative Risk (% increase in rate/rem)
A-bomb survivors (Hiroshima and Nagasaki, 1945)	0.39-4.0	2.0-3.9
Fluoroscopy series (1940-1949)	8.4	10.5
Mastitis patients	2.5-11.0	2.6

* Summarized from data reviewed in NAS-NRC (1972).

Table 22

Summary of Risk Estimates for Bronchial Cancer
(Adults only, and with cigarette smoking assumed to be characteristic)*

Population	Absolute Risk (cases/10^6/yr/rem)	Relative Risk (% increase in rate/rem)
Uranium Miners (white only)	0.63	0.18
Fluorospar Miners	1.61	0.61
Spondylitics	1.2	0.19
A-bomb Survivors	0.60	0.19

* Summarized from data reviewed in NAS-NRC (1972).

Table 23

Summary of Risk Estimates for Stomach Cancer*

Population	Absolute Risk (cases/10^6/yr/rem)	Relative Risk (% increase in rate/rem)
A-bomb survivors (Hiroshima and Nagasaki, 1945)	0-1.4	1.00
Spondylitics (1935-1954)	0.3-1.1	1.61

* Summarized from data reviewed in NAS-NRC (1972).

Table 24

Summary of Risk Estimates for all G.I. Cancer Except Stomach*

Population	Absolute Risk (cases/10^6/yr/rem)	Relative Risk (% increase in rate/rem)
A-bomb survivors (Hiroshima and Nagasaki, 1945)	0-1.8	1.1
Spondylitics (1935-1954)	0.1-0.76	2.0

* Summarized from data reviewed in NAS-NRC (1972).

Frigerio et al. (1973) note that the number of deaths from cancer actually decreases with small increments in background radiation. Thus, the true risk of cancer from occupational exposure to ionizing radiation may not significantly exceed the spontaneous rate. If, on the other hand, one accepts the NAS-NRC (1972) estimate of 3,000-4,000 deaths per year due to background radiation (15-20 deaths per 10^6 persons per year), the linear hypothesis predicts a major increase in the absolute incidence of cancer due to occupational exposure.* According to this hypothesis, the risk for those receiving the maximum allowed cumulative whole-body dose (5 times the person's age beyond 18 years of age, an average of 5 rem/yr) would be 750-1,000 deaths per 10^6 persons per year of exposure above the spontaneous rate of 1,500-2,000 per 10^6 per year. The absolute risk of occupationally induced death from cancer prior to age 65 for radiation workers exposed to the maximum cumulative safety level since age 18 would be 35,000-47,000 per 10^6 persons or 3.5-4.7%. Allowing for a 10-year induction period, these figures, are reduced to 27,500-37,000 occupationally-related deaths from cancer per 10^6 workers so exposed. Although compatible with the uncertainties in the known data, these figures appear to be high and serve to emphasize the potential errors introduced by so simple a method of risk estimation.

Perhaps the most important task in radiation protection is the prediction of risks incurred at various levels of exposure. To date, however, there is no reliable means of doing this. Linear extrapolation is unreliable at low levels of exposure and ignores many of the factors which must be considered. The previously described polynomial model (equation 1) seems technically more correct, but the epidemiological data is inadequate for a proper numerical analysis. It is thus impossible to accurately estimate the margin of safety afforded by current practices. If our estimates are overly conservative, precious man-hours of work will be lost; on the other hand, the human implications of underestimating risk are severe.

On a strictly interim basis, an as yet unpublished report by the National Council on Radiation Protection and Measurement's Scientific Committee 40 (NCRP, 1976) recommends the incorporation of statistical "dose effectiveness factors" for low-level, low-LET radiation. As summarized in Table 25, there is much evidence suggesting that low LET radiation is less effective at low dose rates than at higher rates. If for the present, the more reliable high dose and high dose rate data are used as a basis for extrapolating to lower levels where the data is less certain, the NCRP Scientific Committee 40 recommends correction factors such as those listed in Table 26. These factors (which are still undergoing refinement and which have not yet been accepted as policy by the NCRP) range from a minimum ratio of 0.2 for all doses received at <1 mrad/min to 1.0 for annual doses >200 rads received at rates >1 mrad/min. Though differing in detail, these ratios are in general agreement with those proposed in the Rasmussen report (1975). However, the use of such factors is necessarily arbitrary, and further quantitative work is required before more reliable methods of risk estimation will be available.

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* It should be kept in mind that the NAS-NRC estimate of 3,000-4,000 deaths per year is itself based on the linear hypothesis.

Table 25

Effect-to-Dose Ratios for Low LET Radiation at Low as Opposed to High Dose Rates for Various Late Somatic Effects in Animal and Human Populations*

Data	Ratio of Effectiveness at Lower Dose-Rate to Effectiveness at Higher Rate
Life shortening in beagles (0.006-0.6 R/min vs. 8 R/min)	0.08
Life shortening in RF male mice (0.004-0.07 rad/min vs. 80)	0.07
Life shortening in RF female mice (0.004-0.07 rad/min vs. 7)	0.45
Leukemia in RF male mice (0.004-0.06 rad/min vs. 80)	0.14
Leukemia in RF female mice (0.004-0.07 rad/min vs. 7)	0.026
Leukemia in CBA and C57B1 mice (0.02 rad/min vs. 1.35)	0.15
Leukemia in LAF_1 female mice (0.01-0.05 R/min vs. 2-20)	0.2
Bone sarcomas in CF1 female mice (0.0001-0.01 rad/min vs. 0.02-0.09)	0.05
Mammary tumors in S.D. female rats (0.03 R/min vs. 10)	0.68
Thyroid tumors in Lister & Long-Evans rats (~1 rad/min vs. 150)	0.1
Leukemia: U.S. radiologists vs. spondylitics & A-bomb survivors	0.2-0.5
Overall cancer mortality: U.S. radiologists vs. spondylitics, etc.	0.2-1.0

* From NCRP (1976).

Table 26

Dose-Effectiveness Factors for Genetic and Late Somatic Effects of Low LET Radiation in Relation to Dose Rate and Dose Magnitude*

Yearly Dose (rad)	Effect-to-Dose Ratio at	
	<1 mrad/min (1 rad/d)	>1 mrad/min (1 rad/d)
0 - 5	0.2	0.2
5 - 50	0.2	0.3
50-100	0.2	0.5
100-200	0.2	0.7
200+	0.2	1.0

* From NCRP (1976).

GAPS IN KNOWLEDGE AND RECOMMENDATIONS FOR FURTHER STUDY

Both theoretical and experimental reviews of radiocarcinogenesis raise complex issues. In general, linear risk estimation has been repeatedly criticized (McLean, 1963; Evans et al., 1971; UNSCEAR, 1972), and much damaging evidence has been gathered (Rossi & Kellerer, 1974; Yuhas, 1974; NCRP, 1975, 1976). Data from animal studies often show a large decrease in the number of tumors induced by a given dose of low LET radiation when the dose is fractionated or delivered at low dose rates. This data provides the best experimental evidence that linear extrapolation from the human data might overestimate the effect at low doses and/or dose rates. On the other hand, the dose-response curves for two-hit chromosomal aberrations in mammalian cells (Kellerer & Rossi, 1975) suggest that there is a linear component which dominates the low LET response up to approximately 100 rads. Brown (1976) suggests that in some cases, linear extrapolation from high to low doses may actually underestimate the risk of low doses of high LET radiation. The question of linear extrapolation and the general applicability of animal data to the human situation deserve closer attention in the future.

Further investigation in the following specific areas is also recommended:

1. An examination of the known mechanisms of radiation carcinogenesis, together with their likely dose-response curves, indicates that no simple curve can apply in all cases. With proper adjustment of the parameters, however, a polynomial function, such as that in equation 1, can accommodate most of the possibilities. This is an area of fruitful future research.

2. In animal experiments, either fractionation of the dose or reduction of the dose rate generally, but not always, results in fewer malignancies per rad than does a single acute exposure. It is not clear, however, whether the mechanisms which apply to these animal models also apply, to a similar extent, to human radiocarcinogenesis. Further basic research and epidemiologic data are needed to clarify these points.

3. The relationship of radiocarcinogenesis to the RBE and dose rate does not appear to support both a linear dose-response curve for high LET radiation and a dose-squared relationship for low LET radiation in all cases. At least two important exceptions exist: acceleration of breast tumors in rats and the induction of some types of leukemia in humans. Such inconsistencies point to other potentially fruitful avenues of research.

4. Studies of X-ray-induced transformations in embryonic mammalian cells suggest a linear dose-response curve. These studies also

demonstrate a greater radiation sensitivity to cell killing on the part of transformed (or transformable) cells. Further study along these lines could yield significant mechanistic information.

5. Dose-effect studies at low doses and dose rates are needed to compare the effects of low LET and high LET radiation in animals and to provide more information about the mechanisms of radiation-induced carcinogenesis, even if this data may not be directly applicable to man.

6. Further studies of in vitro cellular transformations and other radiation effects are needed to differentiate between the initiator and promoter functions of ionizing radiation.

7. More data are needed on the synergism between ionizing radiation and other agents, such as viruses, chemical carcinogens, and other physical carcinogens.

8. Finally, research into the relationship between the latency of tumor induction and life span, both in small laboratory rodents, larger animals, and in man, may shed further light on the species-specific differences in radiation-induced tumorigenesis. A more detailed understanding of these differences might facilitate more accurate extrapolations from the animal data.

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