The Carcinogenic Hazards
of Ionizing Radiation
in Diagnostic
and Therapeutic Radiology

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Because of the remarkable advances being made in medicine, both in diagnosis and therapy, the enactment of medicare and cancer, heart and stroke legislation plus the continuing education of both the lay public and the medical profession, it can be readily predicted that the use of radiological procedures will increase both in quantity and quality. It can be anticipated that more than half of the U.S. population will be exposed to ionizing radiation either through the use of X rays or from the administration of radioactive material during the diagnosis and treatment of disease.

In a remarkably short period of time since the discovery of X rays (1895), of radioactivity (1896), and of radium (1898), the entire field of the radiological sciences has progressed with lightning rapidity. What has been accomplished represents only the beginning of greater things to come. The specialty of radiology has only been in existence 72 years.

During recent years the demand for diagnostic X ray examination has increased at an annual compounded rate in excess of 7%, and nuclear medicine services at 15%. The necessity for radiation therapy will continue to increase because of the growth of the population, the advances in medicine, and the increasing length of the life span.

As a result of studies which suggest a correlation between ionizing radiation and the later development of thyroid cancer and of leukemia, a more cautious attitude has developed, especially toward exposure of infants and children to ionizing radiation.

Sources of Radiation Exposure
to the Population

Before any attempt is made to discuss the carcinogenic potentialities of ionizing radiation, it is necessary to know just how much radiation is usually received by the population.

From birth until death we are constantly being exposed to ionizing radiation from outer space, the earth's crust, building materials, the disintegration products of radon in the air and emanations from potassium, radium, radon, and carbon existing within the body and, since 1945, from the fallout from atomic radiation. (Table 1.)

It has been estimated that 120 milli-rads is the average annual gonadal dose which results from the radioactivity in the soil, food and body materials, and from building materials. The amount of natural radiation will vary depending upon such factors as geographic location and the type of building materials used. The naturally occurring radiation accounts for approxi-
Radiation

Radiation effects

The effects of radiation can be divided into acute or chronic. It is necessary to know whether the total body was irradiated or only a limited area, whether the radiation was used as an aid in diagnosis or for therapy, and whether a single dose or repeated doses were given, the type of equipment, filtration, and collimation used, the amount of radiation delivered, and over what period of time.

The mechanism of the transfer of energy from radiation to cellular material is called ionization and it takes place in a fraction of a second. The atom is ionized when an orbital electron is removed from the atom. When an electron is displaced to a different energy level within an atom, this is called excitation. As a result of either ionization or excitation of the atoms, a series of physical and chemical phenomena occur which eventually may lead to detectable biological changes.

There is great variation in individual response to ionizing radiation. Even when death is caused by an overwhelming dose of ionizing radiation, only one out of each 100-million cells in the body has been ionized or has absorbed the penetrating energy.

The changes produced may be somatic, that is, occurring during the lifetime of the individual who received the radiation, or they may be of genetic significance and be transmitted to future generations.

The principal potential harmful effects of exposure to total body radiation may be the production of cataracts, anemias, shortening of life, skin and kidney injury, and the development of malignant tumors including leukemia. (Table 2.)

It is not known what the threshold dose is for the development of somatic injury, that is, the amount of radiation to which an individual or part of an in-
### Table 2

| SOME POTENTIAL HARMFUL EFFECTS OF EXPOSURE TO TOTAL BODY RADIATION |
|---------------------------------------------------------------------|
| 1. Cataracts                                                        |
| 2. Anemias                                                          |
| 3. Life shortening                                                  |
| 4. Internal organs and skin damage                                  |
| 5. Development of cancer including leukemia                         |

Individual may be exposed before permanent injury occurs.

There may be no threshold dose for the causation of genetic effects. The effect on the population is through the hereditary pool by an increase in the number of radiation-induced mutations. A basic characteristic of genes is stability. A change in a gene which may be inheritable is known as a mutation. Ionizing radiation and chemicals are mutagenic agents. It is not possible to tell the difference between mutations which occur spontaneously and those caused by radiation.

The "doubling dose" or the amount of radiation which will double the natural mutation rate has been stated to be within the range of 30 to 80 roentgens. The production of mutations by radiation of the Drosophila fruit fly was first described by Muller in 1927. Neel, in 1955, made the following comment with regard to the attempted extrapolation of experimental data to man: "Many of the conclusions derived from experiments with Drosophila and mice, such as the role of natural selection, cannot be interpolated because man is neither an overgrown fruit fly nor an oversized mouse."

Stone has recommended that every precaution be taken to protect the patient from any unnecessary radiation; however, he also commented that "A method of comparing the genetic danger to our human race from allowing the mentally deficient to reproduce with the genetic danger of using roentgen rays in medicine has not been developed. If geneticists would produce as much education material on the dangers of propagating known mental defects as they are producing on the dangers of roentgen rays they might even accomplish even more for posterity than they are now."

Crow has stated that most mutations are manifested "simply as an increase in the type of abnormality, disease and death that are already occurring." Four to five percent of all live births in the United States represent defects such as epilepsy, mental defects, congenital malformations, hematological and endocrine defects, neuromuscular, visual and other defects.

In the United States the average amount of permissible radiation to the gonads for the general population is 5 rem during the 30-year reproductive period. Different dose rates are listed for radiation workers. It must be emphasized that there is no level of radiation exposure below which there can be absolute certainty that harmful effects will not occur to at least a few individuals when sufficiently large numbers of the population are exposed.

Physicians, and particularly radiologists, began to take steps to deal with the hazards of ionizing radiation and in 1920 the American Roentgen Ray Society formed a committee to study means of providing protection against stray radiation. Since that time, committees both national and international have been constantly studying the problem and making recommendations.

The tolerance dose of radiation was listed as 0.2 r per day in 1931; 0.1 r per day (measured in air) in 1936; in 1948, the National Committee on Radiation Protection gave the maximum permissible dose as 0.3 r per week. Film methods for measuring exposure were available at that time.

In 1957, Braestrup reported the results of his study on past and present...
radiation exposure to radiologists from the point of view of life expectancy.\textsuperscript{10} He found that the average accumulated exposure dose received by radiologists using nonprotected equipment was of the order of 100 r per annum. With standards of protection available in 1957, the yearly dose to radiologists was reduced to about 1 r per year.

**Leukemia in Radiologists**

Studies on the effects of radiation on the life span of radiologists, and also regarding leukemia, were based upon a time before the improvements in technique, equipment, and increased knowledge of radiobiology. Warren's earlier studies indicated that radiologists have a reduced life span as compared with physicians not using radiation in their practice.\textsuperscript{11}

March, in 1944, noted a significantly higher incidence of leukemia among radiologists as compared with other physicians.\textsuperscript{12} During a 15-year period, the incidence of leukemia was over 10 times as great as the incidence in non-radiological physicians. In 1950, March noted a decrease in the excessive incidence of leukemia in radiologists in more recent years.\textsuperscript{13}

Court Brown and Doll found no life shortening and no excess of leukemia in radiologists in the United Kingdom who have entered practice since 1921.\textsuperscript{14}

Warren and Lombard have noted a decrease in the incidence of leukemia in recent years and they have also stated that "since 1935, this evidence of life shortening has lessened, more strikingly, since 1945, and disappeared by 1960."\textsuperscript{15} They believe that current occupational maximal permissible dose levels provide adequate protection. The present international standard of lifetime dose for occupational exposures is calculated according to the following formula: $5(N-18)$ roentgen equivalents man (rem). This is approximately 250 rems total per lifetime. The accumulated maximum permissible dose equals $5(N-18)$ where $N$ is the age and is greater than 18. This applies to all critical organs except the skin, for which the value is double.

**Life Shortening**

Failla has calculated the life shortening in man from exposure to radiation to be approximately one day for each roentgen of accumulated dose for chronic exposure at a dose rate in excess of 0.5 r per day.\textsuperscript{16} Jones believes that life shortening in man from exposure to radiation is 15 days per roentgen.\textsuperscript{17}

Curtis has found that even small doses of radiation will shorten the life span of mammals and that the chief features of the syndrome resemble the natural aging process very closely.\textsuperscript{18}

**The Delayed Effects of Radiation**

Within a short period of time after the discovery of X rays by Roentgen and of radium by the Curies, fluoroscopes were in use and many treatments were given for benign and malignant conditions. Soon, reports began to appear of severe skin reactions, or epilation, and later of radiation-induced cancers. There were no known safeguards nor guidelines from previous experience to go by. Fluoroscopes were used without any protection for the patient or the physician. Proper dosages for treatment using X rays or radium were not known. The biological and delayed changes which occurred were not anticipated. Many benign conditions were treated and most of them probably overtreated.

From a few years to 25 or more years after the radiation therapy which was given for acne, ringworm of the scalp, removal of excess hair, thyrotoxicosis, lupus, tuberculosis of the cervical lymph nodes, nevi, and other conditions, some carcinomas occurred in the treated areas. The changes which almost
invariably preceded the development of the carcinomas were intense skin reactions, later thinning and atrophy of the skin, subdermal fibrosis, telangiectasis, loss of hair, and in some instances, ulcerations.

Even today, patients who had treatments many years ago for the above named conditions still appear with severe radiation damage to the treated areas, and some also with carcinomas developing in the irradiated area. In heavily irradiated damaged tissue of this type the possibilities for the development of cancer are always present, also in skin which has been damaged by a burn from fire, gasoline, or a similar source.

Although the carcinogenic effects of ionizing radiation have been known for years, the mechanisms of the carcinogenic effects of radiation remain unknown. The carcinogenic action may be both a direct and indirect effect. Radiation doses which can produce a carcinogenic effect may be large or small. Radiation is one of the best mutagenic agents and this action may produce the malignant change by altering the hereditary material of the cell and rendering it free of the normal growth control.

The effect of irradiation on the germ plasm of the testicle or ovary is cumulative no matter from what source it comes—medical X-ray examination, fallout, or from the environment.

**Medical Data**

Considerable medical data has accumulated concerning: (1) the effects on the body following the therapeutic uses of external radiation from X rays, cobalt 60, radium, and from the use of radionuclides, such as radioactive $^{131}$iodine, $^{32}$phosphorus, $^{198}$gold, et cetera; (2) data from a study of the pioneers in radiology, cyclotron workers and from persons who have been involved in nuclear accidents and others; and (3) the survivors of Hiroshima, and Nagasaki, and persons irradiated in the fallout in the Marshall Islands.

Furth and Yokoro have concluded that a “survey of facts on radiation carcinogenesis points to a heterogeneity of events. Two types of factors are clearly recognized—one bringing about an apparently irreversible modification of the radiated cells; another, the promoting and restraining forces which alone are not primarily carcinogenic”. 

Furth is also of the opinion that the observations which have been made in man, mostly in the Japanese who were exposed to total body irradiation, raises doubts that radiation is as great a carcinogenic hazard in man as it is in the rodent. He comments that “the large number of events triggered by a single split second irradiation of a rodent and absence of such an effect in man, with the exception of leukemia, are amazing.”

A study of 644 women who had received roentgen therapy for a tissue dose of approximately 65 r to the ovaries and 90 r to the pituitary was made by Kaplan. There was a follow-up in over 50% of cases of from 5 to 35 years. He found no increase in genetic damage in 644 married women and the incidence of genetic damage to the children and grand children of the group was less than in the general population. I know of no radiologist using this method of radiation for treating infertility and sterility at the present time.

In 1948, routine diagnostic pelvimetry was done at the Chicago Lying-In Hospital at the first or second visit. Each fetus received between 1.5 and 3 rads. Half of the patients who received the exposure in utero also were exposed for five films on the first day of life to the entire body and head. The dose estimated to have been received by the infants was less than 500 millirads.

Routine pelvimetry was not done at that institution before or after 1948.
study of 1,008 infants exposed to radiation in 1948 and 1,008 born before and 1,008 born after 1948 was made. Fifteen years later, 2,774 children were actually contacted out of the 3,024 children studied. There was no significant increase in leukemia and no increase in the number of eye abnormalities. There was a significant increase in the number of hemangiomas.

Chadwick and Abrahams have summarized the epidemiological studies on cases of thyroid carcinoma in children and adults. There were 532 children with thyroid cancer; from 45 to 80% had a history of radiation in the dose range from 100 to 6000 r for benign diseases of the head, neck and chest; or no disease. The age range at the time of radiation varied from the newborn to 16 years. The possible latent period varied from 3 to 24 years. There were 23 adults with thyroid cancer with 70% having a history of previous radiation varying from 500 to 6000 r given between 18 and 63 years of age for thyrotoxicosis or tuberculosis adenitis, with a possible latent period of from 5 to 14 years.

Albright and Allday state that “as nearly as can be determined from the literature of those patients in whom thyroid carcinoma developed after irradiation in adolescence, over 80% had received only ‘incidental’ thyroid irradiation.” They reported five patients who were treated for acne during late adolescence with ionizing radiation and who later developed thyroid cancer.

Jelliffe and Jones reviewed the published information concerning thyroid carcinoma following irradiation in adult life. They concluded that “there is certainly no proof that previous irradiation in adults can cause thyroid cancer, but the possibility is a very real one.”

Simpson and Hempelman made a study of a group of 1,722 children who received radiation to the thymus gland during the preceding 27 years; 1,502 were traced. Also, information about 1,933 of their untreated siblings was obtained. Eighteen malignant tumors were reported in the treated group which was a significant number over the expected. The largest number of cases occurred in the thyroid. The incidence of leukemia was also increased.

They concluded “that further investigation should be made to determine whether these tumors are really the result of radiation.” These tumors apparently followed smaller amounts of radiation than previously considered carcinogenic. They suggested that children not be exposed to radiation without careful consideration.

A case of multicentric papillary carcinoma of the thyroid occurring 12 years after irradiation for medulloblastoma was reported by Andrews and Kerr. There is no other report in the British literature and only two similar cases in the American literature. The dose received in 29 days by the thyroid, at age 6 years, was 750-1150 r.

Duff suggests the restriction of the use of 131iodine, including tracer doses, in the young patient until the results of further studies of radiation carcinogenesis in the neonatal and childhood period are available. He believes that there is no evidence, clinical or experimental, that radiation can cause cancer in adult thyroid tissue.

Snegireff made a preliminary report of a study of 148 persons who received roentgen irradiation in childhood and infancy because of enlarged thymus gland, of a group of 23 untreated patients with thymic enlargement, and a comparison group of 162 patients without detectable thymic enlargement. Up to the date of the report, no evidence of malignant disease was found either in the treated or control group.

Cade has described three peaks of incidence of radiation-induced cancer in man as follows: the first peak occurred
immediately after the discovery of X rays and radium and the latent period was from 6 to 20 years and the radiation-induced cancers developed in locally irradiated tissues; and the second peak with a latent period of 10 to 50 years followed the radiation of patients with benign conditions and both carcinomas and sarcomas developed in some of these patients; the third peak will follow the use of diagnostic and therapeutic radiation by megavoltage equipment and from the use of isotopes. He did not predict what the latent period will be.

Cade reported a collected series of 34 patients with radiation-induced cancer. The majority of the patients had been treated with radiation for benign conditions, such as nevi, superfluous hair, tuberculous lymph nodes, goiter, scleroderma, actinomycosis, and syringomyelia. The latent period varied from 8 to 56 years and the cancer developed at the exact site of the tissue severely damaged by radiation.

Pack and Davis stated that only 125 cases of occupational and 63 of therapeutic carcinoma resulting from radiation had been reported from all countries up to 1942. They reported a series of 59 cases of roentgen and radium carcinoma of the skin resulting from postirradiation dermatitis. The latent period averaged nine years in the therapeutic group and 14 years in the occupational group. In a review of 700 cases of radiodermatitis collected from the literature they found the overall incidence of cancer was 24%.

Petersen, in 1953, reported 21 cases of radiation-induced cancer of the skin. Radiation was given initially for such benign lesions as angioma (4), tuberculous cervical adenitis (2), tuberculous arthritis (1), Graves' disease (3), eczema (2), and acne (2). The latent period varied from 4 to 41 years. He found that the literature contained only about 200 cases of radiation-induced cancer. He believed that all such cases had not been published and particularly those affecting physicians but that this type of lesion will constantly decrease in frequency as the technique and the methods of protection are improved.

Stout believes that malignant fibrosarcomas may develop in tissues damaged by irradiation but that the incidence is very low. He reported only four such cases which followed treatment for benign lesions.

Cahan et al., in 1948, reported 11 patients in whom osteogenic sarcoma developed in irradiated bones 6 to 22 years after roentgen or gamma-ray therapy. They believed that a tissue dose of 3000 r was required, but that the tumors could occur following lower dosages. They could give no satisfactory explanation why so few bone sarcomas develop in the thoracic bones following irradiation for breast cancer or in the pelvic bones after irradiation for uterine cancer.

Martland reported 10 cases of osteogenic sarcoma which occurred in radiuim dial workers from 7 to 12 years after exposure. Sabanas et al. reviewed the literature up to 1955 and found only 53 examples of postradiation sarcoma of bone.

Sabanas et al. also reported 17 additional cases. The diagnoses of the primary bone lesion for which the initial radiation was given were as follows: (1) healthy bone in the radiation field, three cases; (2) aneurysmal bone cyst, one case; (3) giant cell reparative granuloma, one case; (4) fibrous dysplasia, one case; (5) giant cell tumor, (possible aneurysmal bone cyst), two cases; (6) giant cell tumor, nine cases.

In 1965, Steiner reported 12 cases of postradiation sarcoma of bone. Five of the 12 cases were radiated for the treatment of benign giant cell tumors. In most of the cases the histologic pattern of the postradiation tumor was
that of a fibrosarcoma. The latent period varied from 4 to 30 years with an average of thirteen and one-half years.

A latent interval of from 4 to 24 years between the completion of roentgen-ray therapy and establishment of the diagnosis of osteogenic sarcoma was found by Cruz et al.\textsuperscript{26} Sarcoma arose in previously normal bone in six cases and in preexisting bone lesions in five. Those arising in normal bone occurred in patients who were irradiated for lymphangioma (1), cancer of the breast (1), epidermoid cancer of buccal mucosa (1), cellulitis of nail bed and hyperkeratosis (1), Hodgkin’s disease (1), and prophylactic treatment for seminoma of the testis (1). In two patients with giant cell tumor the tumor doses ranged from 1000 r to 5389 r delivered over a period of from one month to nine years.

Boyer and Navin found only two cases in the literature of an extraskeletal sarcoma originating in an irradiated field.\textsuperscript{30} They reported a case of a 29-year-old naval officer who was operated on for seminoma of the testicle and who received postoperative radiation therapy. He later developed a perforated peptic ulcer which was treated surgically. A second operation was required because of obstruction. The pathological report of the ulcer revealed radiation changes. Four years later, he developed an osteosarcoma of the soft tissue of the back.

Soloway reported 22 cases of radiation-induced neoplasm following curative therapy for retinoblastoma and reported three new cases.\textsuperscript{40} Twenty-four of the 25 growths were malignant, and the majority were of the osteogenic type and its variants. Eighty-six percent of the tumors appeared before the 15th year postirradiation.

Discussion

Many of the conditions for which radiation therapy was given in the past are infrequently or seldom irradiated at the present time. Infants with enlarged thymus glands were treated frequently with radiation therapy after this method of therapy was described by Friedlander in 1907.\textsuperscript{41} The treatment for enlarged thymuses received its greatest popularity in the 1930’s after which this method of therapy began to decline.

The incidence of leukemia in patients with ankylosing spondylitis treated by radiation therapy has been reported as approximately 10 times that of the general population. Howard reported the risk of leukemia as 1 in 2,225 patients in his series. He also suggested the possibility that the increased incidence may be inherent in patients suffering from ankylosing spondylitis.\textsuperscript{42} In 400 cases of ankylosing spondylitis which were not treated by radiation, Brown and Doll found no patients with leukemia.\textsuperscript{43} The radiation doses which have been given by British radiologists have been high. Few radiologists in this country treat many cases of ankylosing spondylitis with radiation. No increased incidence of leukemia has been reported in patients whose vertebrae have received substantial doses of radiation therapy during the treatment of malignant lymphomas or other malignant tumors.

There has been considerable reduction in the use of pelvimetry in pregnant women, in the use of unnecessary diagnostic X-ray and fluoroscopic examinations in infants and children, and in the treatment of benign conditions in general, and especially in the head and neck region. Patients with acute toxic goiter are no longer treated by radiation.

Brown has pointed out that approximately 38% of the X-ray examinations which are made each year in the United States are performed or supervised by nonradiologist physicians who own and operate or supervise the operation
4. Sciences—National February College Illinois, 2.

There is no question but that ionizing radiation can be carcinogenic in action. However, in only a tremendously small percentage of cases is this true. Many thousands of patients with skin cancer have been successfully treated using radiation therapy without any appreciable deleterious effect when proper techniques are used. A great many women have been cured of cervical cancer and I am not aware of any published data to indicate that, in spite of relatively high dosage, there is a greater incidence of leukemia, bladder, bowel, ovarian or bone cancer in these patients. Also, many patients with testicular cancer have been successfully treated by radiation therapy. These patients are usually in the younger age groups and have received relatively high doses of radiation to the thoracic and lumbar vertebrae with no reported increase in the incidence of bone sarcoma or of leukemia. Thousands of patients with breast cancer have been irradiated and it is exceedingly rare to find case reports of either skin, soft tissue, or bone cancers alleged to have been caused by radiation in this area.

Takahashi et al. are of the opinion that "the late effects of irradiation, especially carcinogenesis have been proved to occur by experiment in animals, but in humans, although there have been numerous case reports of similar occurrence, the actual relationship between radiation and carcinogenesis and evaluation of the risks involved remain to be clarified." Kitabatake and Okajima found that between 1926 and 1935, radiation therapy was widely used in Japan for the treatment of inflammatory or tuberculosis disease. The total skin dose was considered to vary from 1150 to 3900 r for cervical lymphadenitis. After 1946, there was a gradual decrease in the use of radiation for benign diseases.

Conclusions

Patients accept risks who undergo surgical operations and in taking drugs of various types. There should be no hesitancy of anyone having diagnostic X-ray examinations or of accepting radiation therapy when indicated and properly administered.

Every possible effort is being made to improve radiation equipment, techniques, and the education of physicians and technicians using such equipment to further reduce the amount of radiation exposure to the population.

Although there are carcinogenic hazards which may result from the use of ionizing radiation in diagnostic and therapeutic radiology, when the radiation is used under proper conditions the potential hazards are exceedingly minimal.

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Science and technology were once the conduits of our civilization. More recently they have been regarded as vitamins, tiny quantities of which could prevent stunted growth and enable us to absorb our industrial nourishment. Now they must be reckoned as the very meat and potatoes of our economy."

—Professor Derek J. de Solla Price, "The Scientific Foundations of Science Policy." Nature 206: 233-238, 1965; page 237.