J Forensic Sci, Oct. 1974, Vol. 19, No. 4

Shields Warren,[1] *M.D.*

Pathologic Criteria of Radiation Injury

The many lesions associated with response to radiation are best considered on the base of dose, amount of body irradiated, duration of the radiation exposure, and time since exposure. Ionizing radiation of different types—X-ray, radium, neutrons—produces essentially similar effects, allowing for differences in dose and in linear energy transfer. The symptomatic reaction to overwhelming whole-body doses of radiation—thousands of rads—is almost immediate disorientation or coma with prompt death. There is no distinctive lesion present at death because of insufficient time for its development. In those few who survive some hours, generalized erythema appears. When tissues are examined histologically, there is little obvious change. Necrosis may be present in lymphoid tissues, as well as congestion and phagocytosis of lymphocytes and red blood cells by reticulum cells and macrophages. Mitosis is absent in tissues where normally active, such as germinal centers of lymphoid tissue, hematopoietic tissue in general, crypts of the intestinal glands, and testes.

With acute doses to the whole body between 400 and 1000 rads, nausea, diarrhea, weakness, and anorexia develop promptly and persist up to three to six months in those who survive [*1,2*]. (The 50 percent lethal dose at 30 days for a given population is about 400 to 450 rads.) The more heavily exposed persons show leukopenia and later loss of head and body hair. After about two weeks purpura appears. In a number of cases sore throat and ulceration of the tonsils may also develop as well as phagedenic ulcers of the skin [*3*]. In some cases the gastrointestinal symptoms predominate and death is due to infection, often by usually nonpathogenic organisms. In others, hematopoietic damage predominates as characterized by leukopenia, anemia, and purpuric complications. In those who survive, the symptoms tend to ameliorate within four to six weeks and generally disappear after four to six months. Between 100 and 400 rads the symptomatology is much the same, though milder, but may remit for a few days or appear only after a latent period of several days' duration. Survivors of whole-body radiation rarely show persistent late effects so far as cutaneous changes are concerned. Transient or partial epilation may occur. As a rough rule of thumb, permanent sterilization does not occur at a dose level that fails to produce permanent epilation. The most serious late complications are rare. Prominent among them are increased risk of leukemia and cancer, particularly of the thyroid and of the lymphoid system.

Below 100 rads there are usually no symptoms. Detectable gross or histologic changes are not induced, but chromosomal or genetic damage may occur [*4,5*].

With localized radiation, as in therapy, for example, there is little generalized

Presented at the 26th Annual Meeting of the American Academy of Forensic Sciences, Dallas, Texas, 14 Feb. 1974. Received for publication 25 Feb. 1974; accepted for publication 15 March 1974.

[1] Scientific Director, *Emeritus,* Cancer Research Institute, New England Deaconess Hospital, Boston, Mass.

sympotomatology unless the liver or intestines are in the field of treatment. Radiation therapy is usually administered in divided doses to permit the incidentally irradiated normal tissue to recover to a considerable degree and to obtain greater benefit from the differential effect on growth between normal tissue and neoplastic tissue. This permits recovery of much of the normal tissue in the field. However, epilation is a usual result, and erythema or even desquamation may occur. Months or years later degenerative skin changes appear, usually little more than loss of pigmentation and slight atrophy, but at times telangiectasis or even ulceration may appear. Scar tissue following radiation is more pliable, less redundant, and attended by less contraction than that from trauma or thermal burns. Sweating is usually diminished or absent in irradiated skin. As these cutaneous changes progress, cancer of the skin, usually of epidermoid type, may appear [*6*].

Doses of over 500 rads to the kidney may produce glomerular sclerosis [*7*]. With heavier doses interstitial fibrosis may occur.

If the eye has received over 1000 rads of X-radiation, or one tenth that dose of neutron radiation, the epithelium of the lens has been seriously damaged. Cataract will probably appear within months or years. This cataract characteristically develops in the lens posteriorly [*8*]. Atrophy of the retina is also a possibility [*9*].

Since vascular endothelium and indeed blood vessel walls as a whole are easily damaged by radiation, disturbance of the vascular bed is an almost consistent finding. It ranges from telangiectasis or occlusion of smaller vessels to extensive damage of the wall of larger vessels. This results in impaired circulation, often with partial atrophy of the affected part.

It is assumed that the developing fetus and infants are more susceptible to radiation injury than are adults, and the permissible dose levels of radiation exposure of general populations are set to reflect this [*4,10*]. The evidence is largely derived from experimental animals, although there is some equivocal evidence in man [*11*]. In the event that through accidental, occupational, or other exposure certain radioactive substances may have been deposited in the body, there are techniques available for their detection.

In the case of the longer lived internal emitters, such as ^{90}strontium, ^{137}cesium, radium, thorium, plutonium [*12*], and other transuranic elements, radioautography of bone obtained postmortem may give valuable information. Of the internal emitters, the alpha emitters are more apt to produce tumors of osteogenic tissue, while the beta emitters may also produce tumors of the bone marrow as well [*13,14*]. Radium and thorium give off gaseous emanations in the form of radon and thoron which continue to be formed in very slight amounts, even when deposited in the body. These emanations may be measured by appropriate means in the breath. In this way these internal emitters can be detected and the body burden approximated. For those radioactive elements that emit gamma rays, whole-body counters with gamma ray can determine quite precisely the element and quantity involved. If postmortem or surgical tissue is available, given a sufficient amount for gamma-ray spectrometry, a wide variety of radioactive elements can be identified. On the other hand, radiation from most man-made sources, such as X-ray apparatus and bevatrons, leaves no physical trace and hence cannot be detected by physical means once the exposure has ceased.

At the cellular level many functions are damaged, and these are evidenced by morphologic changes ranging from necrosis to transient vacuolization. Cells in mitosis are particularly sensitive to injury, and if germinal epithelium is injured genetic damage follows. However, our present concern is with somatic cells.

As a by-product of this disturbance of mitosis, giant cells, often with large and abnormally shaped nuclei, will appear. The giant nuclei appear to develop through

production of new DNA without cell division. When mitosis does occur, the chromosome numbers of many cells are seen to be aneuploid, often polyploid. Such cells can be well seen among fibrocytes of subcutaneous tissue that has been subjected to therapeutic radiation in the range of hundreds to thousands of rads given in divided doses. If such giant cells, similar to those seen in many tumors, are combined with hyalinization of collagen and thickening of blood vessel walls, the lesion is pathognomonic of radiation. These abnormal mitoses tend to be gradually eliminated from the body by death of the particular cell line involved, but may persist for months or even 30 or more years.

Chromosomal abnormalities following radiation may be detected by examining cells in mitosis as determined from tissue culture, from direct examination of biopsied bone marrow, or from cultures of circulating lymphocytes in the peripheral blood. This last is the most practical means of study for medicolegal purposes, as lymphocytes are easily damaged by radiation and are readily cultured. Study of the so-called karyogram provides a very delicate means of detection of injury by radiation or a radiomimetic agent [*15*]. Loss or fragmentation of chromosomes is common, resulting in reduction of the number of chromosomes from the normal 46. Not infrequently fragments of chromosomes will stick to other chromosomes or to themselves, resulting in translocations which may take bizarre forms. Dicentric or ring forms, together with polyploidy (where chromosomes have divided but the usual nuclear division has failed) are suggestive of injury due to radiation. Dicentrics are not, however, pathognomonic for radiation, although the presence of ring forms is, for all practical purposes. Chromosomal changes in general are not pathognomonic of radiation injury but may be produced by some toxic agents also, particularly the radiomimetic drugs such as nitrogen mustards [*15*]. However, there cannot have been an injurious amount of whole-body radiation and/or indeed significant radiation of even a modest fraction of hematopoietic tissue, without chromosomal abnormality in the lymphocytes cultured from peripheral blood.

There is a rough relationship between frequency of chromosomal abnormalities and dose of radiation [*16*]. As little as 22 rads of whole-body radiation has caused chromosomal abnormalities, but a study of atomic workers in England has suggested that at doses below 50 rads there will be less than four percent lymphocytes with dicentric chromosomes. These disappear exponentially, with a half-life of about three years. A man exposed to about 400 rads 20 years earlier showed only a few chromosomal deletions. Thus, with the passage of years the frequency of aberrations tends to decrease, but some persist for many years. For all practical purposes, one may say that significant tissue damage cannot be due to radiation if chromosomal abnormalities were not produced, provided, of course, some lymphoid or hematopoietic tissue had been irradiated. Conversely, a number of chromosomal abnormalities may be caused by a variety of agents, apparently including the effect of age itself, but if the abnormalities take the form of dicentric and particularly ring forms, radiation exposure has in all probability occurred.

Among the cells most susceptible to chromosomal damage are lymphocytes. Chromosomal abnormalities of these can be readily demonstrated in cytologic smear preparations by appropriately treated cultures made from the peripheral blood. Chromosomes may not only be fragmented by radiation but may be rendered abnormally sticky so that transposition, as well as loss of fragments, may occur. In one case from our laboratory, abnormal chromosomes suggesting radiation injury were found in lymphocytes cultured from the peripheral blood of a patient who could remember no exposure to radiation. Careful review of her hospital records indicated that some 20 years before, Thorotrast® had been administered, the injection having been made to determine the existence of a cerebral aneurysm.

Chronic radiation exposure may have occurred without the subject being aware of it, as in the case of industrial internal radiation poisoning with internal emitters or the repeated small exposures experienced by the pioneer radiologists before adequate protection standards were established.

One of the most striking aspects of injury from either chronic radiation or the late effects of acute radiation is the long latent period. Thus, the average period of exposure for miners in the radon-rich mines of Joachimsthal was 17 years before lung cancer appeared; that for the peak development of leukemia among the Hiroshima-Nagasaki survivors was 10 years.

It will be of particular interest to members of the American Academy of Forensic Sciences that the first evidence of chronic radium poisoning was reported by a forensic pathologist, Harrison Martland, who called attention to the problems of the radium watch-dial painters. These took two general forms: bone marrow damage resulting in leukopenia or anemia from heavier doses, or radiation osteitis, sometimes followed later by osteogenic sarcoma or rarely by cancer of the cranial sinuses.

Osteogenic sarcomas have arisen after skeletal doses ranging from 3000 rads to over 15,000 rads, with an average latent period of about nine years [*17*].

Although it is estimated for the sake of radiation protection that even small doses of radiation may be harmful, it is assumed that the relative risk of the mean dose to bone will be increased over that of an unirradiated patient from a fraction of one to ten percent per year per rem. This is estimated only by extrapolation from much larger doses. Evans et al [*18*] have shown that among the hundreds of cases carrying body burdens of radium there is apparently a practical threshold, in that as yet no case has developed sarcoma with a dose under 1000 rads.

In chronic radiation exposure these is little histologic evidence of acute injury, but sometimes small foci of necrosis and traces of fibrin may be found where a few cells have died from loss of blood supply, infection in poorly vascularized tissue, or direct injury.

In contrast with the response of normal tissues to radiation which in the aggregate is quite characteristic, there is no way of identifying any cancer as definitely radiation induced. A cancer so caused, whether leukemia or of fixed-tissue type, looks exactly like the spontaneous form of the disease. Only by history, statistical prevalence, or association with other destructive lesions characteristic of radiation injury can causation by radiation be determined. Hence, the determination of cause must largely rest on the basis of probability. If, for example, the incidence rate of leukemia is 5/100,000 in the general population and the rate is 50/100,000 among radiologists who were practicing in the 1930s, many of whom had received on the average many times the permissible dose levels of radiation, it would be a fair assumption that the increased incidence was due to the radiation that they had received [*19*].

If a person has a history of whole-body exposure to 100 rads or over and develops leukemia or cancer three years or more following that exposure, the probability is strong that the disease was radiation induced. If a person has a history of localized radiation of 1000 rads or over and any tumor develops in the region subsequently, the probability is strong that the tumor was induced by the radiation.

The forensic pathologist should suspect injury due to radiation, recent or past, on the basis of history or one of the following gross findings:

(1) chronic obstructive ulcers of the gastrointestinal tract,
(2) radiation changes or chronic ulcers of the skin,
(3) epilation,
(4) unexplained bone or cartilage necrosis, or
(5) unexplained anemia, leukopenia, or marrow atrophy.

The best histologic criteria for recognition of radiation injury are:

(1) vascular damage ranging from telangiectatic to occlusive,

(2) hyalinization of collagen and increase in intercellular substance including elastica,
(3) partial atrophy or disappearance of some cells with fibrosis,
(4) presence of giant cells with large nuclei, and
(5) presence of chromosomal aberrations, particularly dicentric and ring forms, in smears of cultured lymphocytes from the peripheral blood.

Acknowledgment

This investigation was supported by U.S. Atomic Energy Commission Contract AT(11-1)-3017 with the New England Deaconess Hospital.

References

[1] Warren, S. and Bowers, J. Z., "The Acute Radiation Syndrome in Man," *Annals of Internal Medicine,* Vol. 32, 1950, pp. 207-216.
[2] Oughterson, A. W. and Warren, S., *Medical Effects of the Atomic Bomb in Japan,* Division VIII—Vol. 8, *National Nuclear Energy Series,* Manhattan Project Technical Section, McGraw-Hill, New York, 1956.
[3] Liebow, A. A., Warren, S., and DeCoursey, E., "Pathology of Atomic Bomb Casualties," *American Journal of Pathology,* Vol. 25, 1949, pp. 853-1027.
[4] "Report of the United Nations Scientific Committee on the Effects of Atomic Radiation," General Assembly Official Records: Thirteenth Session, Supplement No. 17 (A/3838), United Nations, New York, 1958.
[5] Advisory Committee on the Biological Effects of Ionizing Radiations, "The Effects on Populations of Exposure to Low Levels of Ionizing Radiation," Division of Medical Sciences, National Academy of Sciences-National Research Council, Washington, D.C., 1972.
[6] Wolbach, S. B., "The Pathological Histology of Chronic Dermatitis and Early X-Ray Carcinoma," *Journal of Medical Research,* Vol. 21, 1909, pp. 415-449.
[7] Luxton, R. W. and Kunkler, P. B., "Radiation Nephritis," *Acta Radiologica,* Vol. 2, 1964, pp. 169-174.
[8] Lerman, S., "Radiation Cataractogenesis," *New York State Journal of Medicine,* Vol. 62, 1962, pp. 3075-3085.
[9] Benedict, W. H., Christenberry, K. W., and Upton, A. C., "Spontaneous and Radiation-Induced Iris Atropy in Mice," *American Journal of Ophthalmology,* Vol. 40, 1955, pp. 163-168.
[10] Warren, S. and Gates, O., "Effects of Continuous Irradiation of Mice from Conception to Weaning" in *Radiation Biology of the Fetal and Juvenile Mammal,* M. R. Sikov and D. D. Mahlum, Eds., *Proceedings,* Ninth Annual Hanford Biology Symposium at Richland, Wash., 5-8 May 1969, U.S. Atomic Energy Commission, Division of Technical Information, Oak Ridge, Tenn., 1969, pp. 419-437.
[11] Stewart, A. and Kneale, G. W., "Radiation Dose Effects in Relation to Obstetric X-Ray and Childhood Cancers," *Lancet,* Vol. i, 1970, pp. 1185-1188.
[12] Vaughan, J., Bleaney, B., and Taylor, D. M., "Distribution, Excretion, and Effects of Plutonium as a Bone-Seeker" in *Handbook of Experimental Pharmacology, New Series,* O. Eichler, A. Farah, H. Herken, and A. D. Welch, Eds., Vol. XXXVI, H. C. Hodge, J. N. Stannard, and J. B. Hursh, Eds., Springer-Verlag, Berlin, 1973, Chapter 10, pp. 349-502.
[13] Vaughan, J. M., *The Effects of Irradiation on the Skeleton,* Clarendon Press, Oxford, 1973, p. 249.
[14] Finkel, M. P. and Biskis, B. O., "Osteosarcomas Induced in Mice by FBJ Virus and Strontium-90" in *Delayed Effects of Bone-Seeking Radionuclides,* C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, Eds., University of Utah Press, Salt Lake City, 1969, pp. 417-435.
[15] Warren, S. and Meisner, L., "Chromosomal Changes in Leukocytes of Patients Receiving Irradiation Therapy," *Journal of the American Medical Association,* Vol. 193, 1965, pp. 351-358.
[16] Dolphin, G. W., Lloyd, D. C., and Purrott, R. J., "Chromosomal Aberration Analysis as a Dosimetric Technique in Radiological Protection," *Health Physics,* Vol. 25, 1973, pp. 7-15.
[17] Bloch, C., "Postradiation Osteogenic Sarcoma. Report of a Case and Review of Literature," *American Journal of Roentgenology,* Vol. 87, 1962, pp. 1157-1162.

[*18*] Evans, R. D., Keane, A. T., Kolenkow, R. J., Neal, W. R., and Shanahan, M. M., "Radiogenic Tumors in the Radium and Mesothorium Cases Studied at M.I.T." in *Delayed Effects of Bone-Seeking Radionuclides*, C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, Eds., University of Utah Press, Salt Lake City, 1969, pp. 157-194.

[*19*] Warren, S., "Longevity and Causes of Death from Irradiation in Physicians," *Journal of the American Medical Association*, Vol. 162, 1956, pp. 464-468.

Cancer Research Institute
New England Deaconess Hospital
194 Pilgrim Rd.
Boston, Mass. 02215