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THE RADIOSENSITIVENESS OF CELLS AND TISSUES AND SOME MEDICAL IMPLICATIONS[1]

By Dr. ARTHUR U. DESJARDINS

SECTION ON THERAPEUTIC RADIOLOGY, MAYO CLINIC, ROCHESTER, MINNESOTA

CASUAL reading of contemporary medical records bearing on the action of roentgen rays and radium often gives the impression that little of such action is known, in spite of the fact that substantial or conclusive experimental data are available to indicate or to clearly establish the nature of such action. In some cases indeed the experimental indications are absolute. In other cases the experimental evidence may be inadequate, but the clinical data may be sufficient to suggest the probable effect of irradiation. It is true that many problems relating to radiotherapy are still the subject of controversy and that the large number of experiments which have been made has yielded only partial answers to many questions. Nevertheless, the facts already brought to light are sufficiently numerous to provide an imposing, although admittedly incomplete, scientific background. Unfortunately, the evidence furnished by experiments on animals and clinical observation has never been analyzed and correlated, and much of it has been lying on library shelves, buried in medical or other journals which are seldom read. Even among medical radiologists knowledge of the experimental background is not widely diffused.

The law based on the extensive investigations of Bergonié and Tribondeau (1904–1907), according to which young or immature cells are more radiosensitive than old or adult cells, has been generally recognized and has long been regarded as the essential foundation of radiotherapy. Numerous experiments have shown that direct irradiation of the pregnant uterus or of the young soon after birth causes retardation of growth of the skeleton and of various organs, including the brain. The degree of such effect varies with

[1] Abridged form, as read before the summer meeting of the American Association for the Advancement of Science, Pasadena, California, June 15 to 20, 1931.

the dose, the age of the animal and the natural life cycle of the species. The cells and tissues of a given species rapidly become less sensitive as the animal emerges from the early phase of its existence, during which growth is a prominent feature. Indubitable as is the relation of the age of cells to radiosensitiveness, analysis of the experiments made to test the susceptibility of different organs and tissues brings out the even more important fact that each variety of cell in the body has a specific sensitiveness, or rather a specific range of sensitiveness, to radiation. This is not intended to imply that all cells of one kind, such as lymphocytes or squamous epithelial cells, react in precisely the same way to a given dose of rays. A certain measure of variation in reaction must necessarily occur, because different cells of the same kind are struck by the rays while in different stages of metabolism. Other still unknown factors also may play a part. However, if allowance be made for such variation, and if reaction time be taken as a criterion, the specific sensitiveness of each kind of cell looms up as the dominant single fact of radiology and deserves to be recognized as a law. And yet, if we may judge by present-day writings, the existence of such a law and of its medical and biological implications is not at all realized. For years much has been made of the dogma that pathologic cells are more radiosensitive than normal cells of the same kind, but, as Lazarus-Barlow and others have shown, the foundation on which this dogma rests is tenuous and insecure. The physiologic condition of cells undoubtedly has some influence on their sensitiveness, but, as I shall bring out presently, such influence is small as compared with the specific natural susceptibility of each variety of cell. Although the factors responsible for such specificity have not yet been determined, the sensitiveness peculiar to each kind of cell appears to be related chiefly to the natural life cycle. Thus the lymphocytes, whose metabolic cycle among human cells is the shortest, are also the most radiosensitive, and the nerve cells, whose life cycle is the longest, are also the most resistant to irradiation. But to this question as to many others the final answer has not been given.

When a living tissue or organ is exposed to roentgen rays or radium, a more or less important proportion of cells may subsequently exhibit temporary inhibition of metabolic activity or complete and permanent disintegration, or may not show any deleterious effect. Moreover, if the time intervening between irradiation and perceptible reaction is taken as a criterion, it will be found that certain species of cells react more rapidly than others to a given dose, or the degree of reaction to the same dose is greater for some kinds of cells than for others. According to our present knowledge cells may be classified, according to their radiosensitiveness, in the following order:

Lymphoid cells (lymphocytes).
Polymorphonuclear and eosinophile leukocytes.
Epithelial cells:
(1) basal epithelium of certain secretory glands, especially the salivary glands;
(2) basal epithelium (spermatogonial cells) of the testis and follicular epithelium of the ovary;
(3) basal epithelium of the skin, mucous membranes, and of certain organs, such as the stomach and small intestine;
(4) alveolar epithelium of the lungs and epithelium of the bile ducts (liver), and
(5) epithelium of tubules of the kidneys.
Endothelial cells of blood vessels, pleura and peritoneum.
Connective tissue cells.
Muscle cells.
Bone cells.
Nerve cells.

Although the difference in susceptibility between the most sensitive and the least sensitive varieties of cells is considerable, none of the cells is wholly invulnerable to radiation; all cells, whatever their variety, may be destroyed or injured if exposed to a sufficiently large dose of rays, especially if doses within the therapeutic range are disregarded.

RADIOSENSITIVENESS OF DIFFERENT SPECIES OF CELLS

Lymphoid cells: Of the different kinds of cells which make up the tissues and organs of the body, the most susceptible by far are the lymphocytes. This important fact was brought to light by the early and extensive experiments of Heineke (1903, 1904, 1905) and has since been fully confirmed by the subsequent investigations of Warthin (1906), Krause and Ziegler (1906–1907), and Fromme (1917), Hartmann (1920), Jolly (1924), Tsuzuki (1926), Piepenborn (1929) and others. When the entire body of different species of animals was exposed to roentgen rays, Heineke found that most of the tissues and organs remained unaffected, but that the spleen, lymph nodes, intestinal lymph follicles, circulating blood, bone-marrow and all agglomerations of lymphoid cells showed a more or less pronounced destruction of lymphocytes. The degree of such destruction was proportional to the dose of rays and varied with the interval between irradiation and death. In the spleen, lymph nodes and other lymphoid structures the destruction of lymphocytes started around the germinal center and gradually extended toward the periphery of the follicles. As the number of intact lymphocytes diminished the stroma became prominent, and often this feature was so pronounced that the follicles could be recognized only by the blood vessels and the concentric arrangement of the stroma. Heineke observed such destruction of lymphocytes as early as two hours after irradiation. The extent and duration of this destructive phase depended on the intensity of irradiation, continued for several days, and was accompanied by a progressive reduction in volume or atrophy of the affected structures.

As described by Heineke, such destruction is characterized by disorganization and fragmentation of the nuclear chromatin, scattering of the fragments of chromatin between the remaining intact cells and in the reticular spaces, where the fragments gather into clumps or balls. Then the clumps or balls of degenerate chromatin are gradually taken up by some of the reticular cells which assume a phagocytic property and swell as the amount of ingested chromatin débris increases. The disposal of chromatin material from the destroyed cells continues until all such material has undergone phagocytosis. The nuclear débris ingested by the phagocytes apparently undergoes intracellular digestion, because the number and size of the ingested fragments diminish steadily. Some hours later, the phagocytic reticular cells themselves begin to disappear. After a single massive irradiation or repeated moderate doses, all the lymphocytes may be destroyed, but after a single small or moderate dose, a certain proportion of the cells appear to resist the action of the rays. From one to three weeks after exposure, if the irradiation has not been sufficiently intense to destroy all the lymphocytes, more or less regeneration of the lymphoid tissue may be observed and complete cellular restoration may occur. Two or three days after exposure to roentgen rays, degenerative alteration of other cells, notably the polymorphonuclear leukocytes and eosinophiles, also becomes perceptible, and many of these cells disappear from the splenic pulp and bone marrow.

Warthin's description of the effect of roentgen rays on the lymphoid structures corroborates the observations of Heineke in every particular, except that, by examining the tissues soon after irradiation, Warthin found unmistakable evidence of the disintegration of lymphocytes within fifteen minutes after exposure of the animals to the rays, and the cellular degeneration continued for several days. Similar effects were obtained with radium by London (1903), Heineke (1904), London (1905), Thies (1905) and Lazarus-Barlow (1922). Rudberg (1907), Aubertin and Bordet (1909), Arella (1910), Regaud and Crémieu (1912) and others have likewise shown that roentgen rays and radium exert precisely the same influence on the small round cells of the thymus gland, and their work strongly supports Hammar's conclusion that the small cells of the thymus gland are indeed lymphocytes. Others, notably Senn (1903), Heineke (1903, 1905), Guilloz and Spillmann (1904), Aubertin and Beaujard (1904, 1905, 1908), Brown (1904), Bryant and Crane (1904), Capps and Smith (1904), Helber and Linser (1905), Benjamin, von Reuss, Sluka and Schwarz (1906), Aubertin and Delamarre (1908), Taylor, Witherbee and Murphy (1919), Russ (1919, 1921) and Leitch (1921), have proved conclusively that the lymphocytes in the circulating blood are equally sensitive to irradiation and also destroyed in large numbers by exposure to roentgen rays or radium.

Epithelium of the salivary glands: Next to the lymphocytes in point of radiosensitiveness are the basal epithelial cells of the salivary glands. Actually these cells are more sensitive to radiation than the polymorphonuclear and eosinophilic leukocytes. This is evidenced by the fact that, whereas microscopically perceptible changes in the two latter varieties of cells can seldom be found within the first six hours after exposure to the rays, clinical signs of salivary reaction can usually be observed in from three to six hours after irradiation. These signs consist in swelling, redness, and tenderness in the region of the irradiated glands and, when bilateral, may stimulate the salivary phase of mumps. If all the glands on both sides have been exposed to the rays, the foregoing clinical signs may be rapidly followed by decrease in salivary secretion, often leading to dryness of the mouth lasting from a few days to two or more weeks. Such reaction of the salivary glands is characterized by mucoid degeneration of the basal epithelium. The cells swell, the excretory ducts become occluded, and the secretion accumulates within the glands; hence swelling and tenderness of the glands, and dryness of the mouth. Following a single irradiation salivary reaction is always transient; after a time, usually from twenty-four to seventy-two hours, the acute phase of the reaction subsides and the clinical signs gradually abate. Following repeated irradiation, however, the secretory function of the glands may cease and dryness of the mouth may persist for a long time. Such effects occur only when the glands on both sides have been exposed to the direct action of the rays. Salivary reaction does not occur when other parts of the body are irradiated, and exposure of the glands on one side causes a reaction on that side only. When the reaction is unilateral, dryness of the mouth is seldom noticed, undoubtedly because the glands on the opposite side furnish a sufficient quantity of saliva to lubricate the oral mucosa. The experiments of Lazarus-Barlow (1922) and of Mottram (1923) indicate that epithelial cells which produce mucus are much more sensitive to irradiation than other epithelial cells. The first effect is mucoid degeneration with excessive and abnormal production of mucus, followed by arrest of mucus formation. This has been shown to occur in the intestine, and the behavior of the salivary glands under irradiation make it seem likely that the mucus-producing cells in the epithelial lining of these glands are similarly affected by the rays.

Epithelium of the testis and ovary: The testis is not so sensitive as some of the leukocytes or the salivary glands, but with the exception of these is the most sensitive structure in the body. The radiosensitiveness of the organ is due to susceptibility of the spermatogonial cells, which are affected deleteriously even by a moderate dose of roentgen rays. The cells of Sertoli are relatively resistant to irradiation, and this fact tends to support the view that they supply nourishment to the basal layer of seminal cells, the spermatogonia. The spermatocytes of the first and second order, as well as the spermatids and mature spermatozoa, are distinctly less sensitive than the spermatogonia and are affected only by larger doses. Even so, much of the cellular degeneration is probably secondary to the direct action of the rays on the basal cells. After a sufficiently large dose, degeneration of spermatogonia proceeds to complete disintegration. This is accompanied by failure of the cells to evolve into spermatocytes and mature spermatozoa, and the final result is permanent azoospermia. After a dose insufficient to cause permanent azoospermia, a certain proportion of the spermatogonia may be able to survive and serve as a nucleus for histologic regeneration and functional restoration. Large doses repeated at comparatively short intervals are almost certain to induce permanent castration. The interstitial tissue, on the other hand, is much more resistant and is not perceptibly influenced by ordinary therapeutic irradiation.

The radiosensitiveness of the ovary is essentially the same as that of the testis, and the cells to which the specific susceptibility of the gland is due are the ova and the epithelium of the follicles. The sensitiveness of different follicles varies according to the stage of development. Depending on the dose of rays to which the ovary has been exposed or to the number of times a given dose has been repeated, the effect of irradiation may be disintegration and disappearance of a certain proportion of the follicles or complete and permanent destruction of every follicular structure. A certain proportion of the primordial follicles may escape if the dose has been small. Moreover, the steps in the reaction of the follicles are analogous to those of spontaneous physiologic atresia.

Epithelium of the skin, mucous membranes and gastro-intestinal tract: The skin can tolerate with impunity a considerable single dose of roentgen rays, but when the limit of tolerance is exceeded it may undergo a series of reactive changes. The first clinical manifestation of excessive irradiation is a readiness of the hair to fall out in the exposed territory. After a still larger dose, not only does epilation occur, but varying degrees of reactive inflammation of the skin may take place. Dermatitis may appear as a slight erythema lasting a few days and followed by pigmentation corresponding to the exposed area; as a more pronounced, bright red erythema with a sensation of heat, followed by the formation of vesicles and later by itching, exfoliation of the epidermis and deep pigmentation; or, in extreme cases, as an intense, painful erythema, with or without fever, and followed by more or less extensive ulceration of the entire thickness of the skin. Mild radiodermatitis may not leave any permanent marks beyond slight atrophy of the irradiated area of skin, provided the inflammatory reaction results from a single exposure. When such reaction appears after the same area of skin had been exposed several times, it is likely to be followed, from one to three years later, by telangiectasis. The sudoriferous and sebaceous glands of the irradiated skin also undergo degenerative changes. Radiodermatitis accompanied by the formation of vesicles is followed by more extensive desquamation or by the actual formation of small, rounded or large, irregular cutaneous scars. When severe radiodermatitis is followed by ulceration, the ulcers are slow to heal. This is due partly to the peculiar character of injury produced by irradiation and partly to secondary infection which so commonly complicates the ulceration.

The sensitiveness of the epithelium of mucous membranes is much the same as that of the skin. Excessive single irradiation causes first anesthesia, then dryness, redness from hyperemia and edema. Depending on the dose, these clinical manifestations may abate and disappear or may be followed by ulceration. The radiosensitiveness of specialized mucous membranes, such as the mucosa of the stomach and intestine varies with each structure. Irradiation of the stomach causes temporary reduction in the secretion of gastric juice, and this affects the production of hydrochloric acid and pepsin. If the stomach is exposed repeatedly at relatively short intervals, the gastric acidity and pepsin fall lower and lower, and this may continue for weeks or months. If the exposures were repeated indefinitely the secretory activity of the gastric mucosa might be completely and permanently arrested. The susceptibility of the intestine varies in its different parts. The mucosa of the colon is relatively insensitive to the action of the rays; at least, it is much less sensitive than that of the small intestine. The most sensitive portion of the mucosa of the digestive tract is that of the duodenum and jejunum, which may be irritated by doses insufficient to disturb the overlying skin. When the upper half of the abdomen is exposed to a therapeutic dose of roentgen rays, anorexia, nausea and vomiting often follow within a few hours, and diarrhea may appear several days later. Exposure to excessive doses, such as have been employed in many experiments on animals, causes mucoid degeneration of the intestinal epithelium, hyperemia, edema of the mucosa and submucosa, and such changes may be followed by desquamation of the epithelium. According to the severity of reaction, the epithelium may regenerate or the breach in the mucosa may be repaired by connective tissue.

Epithelium of the lungs, liver and kidneys: The lungs, liver and kidneys are only moderately sensitive to irradiation. Grossly excessive doses may cause cellular degeneration and reactive inflammation, and the injury may be repaired by connective tissue, which may lead to slight or pronounced impairment of function.

Endothelium: The radiosensitiveness of the endothelium of blood vessels, pleura and peritoneum is approximately the same as that of the skin. The effect of excessive irradiation is swelling of the endothelial cells, which degenerate and desquamate into the lumen of the vessel. The media also may swell. As the acute reaction subsides the cellular injury may be repaired by hyperplasia of adjacent cells or the entire wall of the vessel may thicken, and the lumen may be narrowed or completely obliterated.

Connective tissue, muscle, bone and nerve tissue: The sensitiveness of these different tissues decreases in the order named. Bone and nerve cells are the most resistant of all cells, but it must not be inferred that they are wholly insensitive to irradiation. A sufficient dose of roentgen rays or radium can readily retard the development of bone in a young rapidly growing animal, and even the mature bones of adult animals may be devitalized. Nerve cells can tolerate comparatively large doses without giving perceptible evidence of direct injury. The cellular changes in nerve tissue observed after irradiation appear to be indirect and secondary to action of the rays on more sensitive elements, such as the endothelium of the blood vessels which supply the nerve tissue.

Stimulating effect of irradiation: For years the legend that roentgen rays or radium, under certain conditions of dosage, may increase the growth and metabolism of cells has gained wide circulation. This notion has arisen from the attempt to apply to these agents the so-called Arnt-Schulz law, according to which small doses stimulate and large doses depress cellular metabolism. Based on pharmacologic grounds, this doctrine has not been generally accepted, even by pharmacologists. The attempt to apply it to the action of roentgen rays is unwarranted, because the experimental evidence on which it is based is extremely meager and apparently invalid. That a measure of acceleration in cellular metabolism may occur under certain conditions has been shown repeatedly both in animals and plants, but such unusual acceleration is a transient phase of reaction and is invariably followed by more or less pronounced inhibition of function and cellular degeneration. Another factor in the propagation of this notion of a stimulating action of the rays has been the regression of pathologic lesions after exposure to small doses of roentgen rays. Such regression is best explained by the exceptional radiosensitiveness of certain varieties of cells. As the result of primary degeneration of certain cells a secondary and indirect stimulation may sometimes be observed. Such is the increase in connective tissue cells in certain tissues and organs after repeated irradiation; the connective tissue is laid down to replace other cells which the rays have caused to undergo degeneration. Any primary or direct acceleration of cellular metabolism must be regarded as an effort of the cell to counteract or compensate for the noxious influence of the rays; in other words, it is purely a defense reaction. Continued acceleration of metabolism can not be induced by roentgen rays or radium, which always cause degenerative changes or have no effect whatever. Irradiation of certain tissues, such as the skin, repeated over a long period of time may cause hyperplasia of the epithelium, and this in turn may lead to malignant transformation. This is not stimulation in the sense here employed, but the alteration of a normal to an aberrant function due to chronic irritation.

Comparative influence of rays of different wavelength: Roentgen rays and radium have the same general effect on living tissue. Such variations as may be observed can be accounted for by difference in the methods of irradiation with each agent. Unfiltered radium buried in the substance of a tissue produces an intense destruction of cells immediately adjacent to the radioactive unit. The degree and extent of destruction can be modified at will by filtration. The conditions under which roentgen rays are generated prevent anything but external irradiation. If the effect of external irradiation with radium is compared with that of similar irradiation with roentgen rays, any variation attributable to difference in wave-length will be small; the greater part of the difference must be charged to variation in the total quantitative dose of each kind of energy. Quality of radiation plays a definite part in the effect, but this part is much smaller than the part played by quantity of radiation. To illustrate this further, I need only draw your attention to the difference of action between unfiltered roentgen rays of relatively long wave-length and rays of short wave-length generated at voltages of 80 and 200 peak kilovolts, respectively. A dose of the former beyond the tolerance of the skin to an area more than one inch in diameter is likely to result in ulceration, whereas a corresponding dose of rays of short wave-length seldom causes ulceration, but usually induces a dense brawny induration of the skin and subcutaneous tissues and adhesion of the underlying muscles.

OUTSTANDING MEDICAL IMPLICATIONS

To attempt to deal adequately with this phase of my subject would be to risk overtaxing your patience. I shall confine myself, therefore, to a brief outline of the more important medical relationships.

Radiotherapy for inflammatory conditions: Knowledge of the specific sensitiveness of different species of cells to roentgen rays or radium is of fundamental importance in the treatment of inflammatory lesions as well as in the diagnosis and treatment of certain neoplastic processes. It has long been known that many acute or chronic, suppurative or non-suppurative, inflammations are favorably influenced by roentgen rays or radium. In some of these conditions indeed irradiation has been found to be the therapeutic method of choice. Among the acute inflammations amenable to such treatment may be mentioned furuncle, carbuncle, lymphadenitis, pneumonia in certain stages, parotitis and erysipelas. The more acute the process the more quickly it responds to irradiation and the smaller the dose required. Exposure of such lesions at an early stage (phase of leukocytic infiltration) usually causes them to undergo rapid resolution. Irradiation at a slightly later stage (phase of beginning suppuration) hastens the suppurative process. In both cases, but especially in the former, the course of the inflammation is shortened and pain is quickly allayed. Usually, a single exposure to the rays is sufficient. Tuberculous lymphadenitis, tuberculosis of the cornea and iris, trachoma, actinomycosis, and many diseases of the skin may be cited as examples of chronic inflammation amenable to radiotherapy. In such conditions, however, treatment must be repeated at intervals for some time. The rate and mode of reaction of inflammatory lesions indicate that the rays act chiefly by destroying the infiltrating lymphocytes, the exceptional sensitiveness of which has already been pointed out. The rate of reaction of acute inflammations corresponds so closely to the rate at which normal lymphocytes are known to be destroyed by the rays that, even in the absence of other evidence, the analogy can not be regarded as a coincidence. Moreover, confirmatory evidence has been provided by frequent microscopic observation, in irradiated lesions of this kind, of lymphocytic destruction in every respect similar to that which was first observed and described by Heineke.

Leukocytic, and especially lymphocytic, infiltration is an early and prominent feature of most inflammatory conditions. Especially is this true in inflammations caused by bacterial infection. If it can be assumed that the leukocytes, which the organism mobilizes around the site of infection, represent an effort to localize the infection and get rid of the infectious material by phagocytosis or otherwise, it must be inferred that the infiltrating cells contain or elaborate within themselves the protective substances which enable them to neutralize the bacterial or other toxic products which give rise to the defensive inflammation. If these assumptions are well founded, it seems not unreasonable to deduce that irradiation, by destroying the infiltrating lymphocytes, causes the protective substances contained by such cells to be liberated and thus be made even more readily available for defensive purposes than they were in the intact cells. All the circumstances surrounding the behavior of inflammatory lesions after irradiation are in harmony with this view. The same process also undoubtedly plays an important part in the reaction of chronic inflammatory lesions, but in such cases the reaction is modified according to the degree of leukocytic infiltration on the one hand and to the amount of connective tissue on the other. This probably explains why the resolution and cure of chronic inflammations, such as those mentioned, require that irradiation be repeated at intervals for some time.

Radiotherapy and the genital glands: The radiosensitiveness of the genital glands is important from more than one point of view. The relative ease with which testicular or ovarian function can be abolished by irradiation furnishes a simple method of accomplishing this result whenever functional arrest is necessary or desirable. The method has seldom been applied to the male, but it is commonly employed in the female as an increasingly valuable method of treating hemorrhagic disturbances and fibromyoma of the uterus. Functional arrest of the ovaries indirectly causes atrophy of the uterus and of the fibroid tumors. Both in the male and female, roentgen rays or radium might well be utilized to castrate the feeble-minded, a method which would remove the objection to surgical operation. The danger of sterilization to professional radiologists and non-professional technical assistants has long been realized. Fortunately, modern methods of protection, if applied, remove all danger from such employment.

Radiotherapy for benign and malignant tumors: The specific sensitiveness of different kinds of cells constitutes the most important single factor in the treatment of neoplasms. The value of roentgen rays or radium in different varieties of tumor depends mainly on this feature. The susceptibility of tumors to irradiation agrees closely with the radiosensitiveness of normal cells of the same kind as those from which the tumors are derived and of which they are largely composed. Thus, the inordinate hyperplasia of lymphoid structures which characterizes Hodgkin's disease, lymphosarcoma, and lymphatic leukemia retrogresses under irradiation at the same rate as normal lymphocytes are known to be destroyed by similar exposure. In fact, so striking is the parallel that irradiation is now being used daily as a means of distinguishing such conditions when their clinical features do not permit absolute identification. In some cases, indeed, the radiotherapeutic method of diagnosis is more accurate and dependable than microscopic examination.

The only tumor which approaches lymphoblastoma in susceptibility to irradiation is the embryonal carcinoma, or seminoma, of the testis, the radiosensitiveness of which corresponds to that of normal spermatogonial cells. This is the most common neoplasm affecting the organ and heretofore has often been mistakenly regarded as a variety of sarcoma. Primary and secondary growths of this kind retrogress rapidly and some disappear completely after irradiation. The reaction of mixed, or teratoid, tumors of the testis is less rapid and seems to vary with the proportion of spermatogonial epithelium entering into their structure.

Knowledge of the relative radiosensitiveness of different cells has enabled Ewing and others to distinguish a group of bone tumors from other neoplasms which affect the skeleton. Ewing has designated this tumor as endothelial myeloma, because endothelial cells are a prominent feature. Among the malignant tumors of bone they are the most sensitive to irradiation. In fact, the other malignant growths which attack bone can hardly be said to have any sensitiveness; rather they are noteworthy for their resistance. Endothelial myeloma, on the contrary, is distinctly sensitive, and large tumors of this kind melt away with astonishing rapidity. The only other bone tumor which is radiosensitive is the usually benign giant-cell tumor, but its reaction to irradiation is unlike that of any malignant neoplasm. Instead of being followed by rapid or slow, but steady regression, irradiation of such growths causes them to swell and become tender. The patient and the uninitiated physician may naturally conclude that exposure to the rays has stimulated the tumor to increased growth, and the limb may be unnecessarily sacrificed. Such inflammatory reaction is a transient phase which lasts two or three weeks and is followed by slow regression and repair of the tumor by deposition of new bone. This characteristic reaction of giant-cell tumor constitutes at once a valuable means of identification and treatment and furnishes additional evidence that tumors of this kind, at least at the outset, are not true neoplasms but chronic inflammatory lesions.

Many other examples might be mentioned, but the foregoing are sufficient to illustrate the important bearing on medical diagnosis and treatment of the radiosensitiveness of cells and tissues. Heretofore, for some reason, biologists have seldom made use of radiation for experimental purposes. As soon as they begin to realize its possibilities, they will find in the method a means of acquiring much valuable information, and such increase in knowledge will help to extend the diagnostic and therapeutic applications.

OBITUARY

JAMES WILLIAM TOUMEY

JAMES WILLIAM TOUMEY, D.SC., D.FOR., professor of silviculture at the Yale School of Forestry, died at his home in New Haven on May 6, 1932. He was one of the pioneers and founders of American forestry. He was a great teacher and educator, a scientist of distinction, an author, and an influential leader in advancing the movement of forestry. He had been associated with the Yale School of Forestry from the time of its establishment in 1900. His part in building the school, in setting and maintaining high educational standards, and making the institution a force in the development of forestry in the nation can not be measured.

Trained as a botanist, he brought his extensive knowledge of plant science to bear on the problems of forestry. By his own study and experience he mastered the technical aspects of forestry and made a large contribution to the application of forestry principles to American conditions. His power as a teacher lay in his unflagging enthusiasm, in his personal interest in students and sympathetic understanding of their needs, and in his ability to stimulate individual effort on their part. He possessed high qualities as a scientific investigator, keen perception, unusual sense of values, originality and ingenuity in research, and persistence in carrying his studies to a conclusion. He had unfaltering faith in the work he