Action of Radiation on Tissues

An Introduction to Radiotherapy

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Preface to the Second Edition

THE SUB TITLE, "INTRODUCTION TO RADIOTHERAPY," of the volume written in 1939 and published originally in 1941, indicated the purpose of the authors' evaluation of the accumulated data concerning "The Action of Radiations on Tissues." This book was addressed to young physicians preparing for the practice of a specialty demanding radiobiologic knowledge which they had not been able to obtain in the course of their general medical studies. Clearly, this little book seems to have met a need, for copies of this edition have long been exhausted.

Before a second edition could be published, however, the text had to be revised extensively because of the important changes which have occurred in the field of radiobiology during the last 15 years.

The extensive development of the use of artificial radioisotopes in hospitals, laboratories and industry, the creation of powerful atomic centers, and the increased possibility of dangerous exposure to radiation by external or internal routes require more people than ever before to understand the essential facts of radiobiology.

The authors have revised the book in this light, correcting the previous text extensively and extending each chapter to include the recent advances in radiobiology, mentioning preferentially recent publications with extensive bibliographies. The important chapter on total body irradiation has been deservedly expanded to a greater extent than the rest. The increased breadth and detail of the resulting volume seemed to require changing the title to "The Action of Ionizing Radiations on the Body."

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Translators' Note

THIS TRANSLATION* WAS MADE BECAUSE AMERICAN radiopathology suffers from an obscurity of its sources, resulting, for the most part, from a scarcity in English of adequate analytic condensations of the early fundamental investigations carried on in Europe. Few living Americans are still broad enough in their radiopathologic interests and have enough historic insight, as well as the time, to synthesize a critical review of the research in radiobiology carried on from 1892 to 1942. Moreover, few modern American students and investigators are fluent enough in foreign languages to obtain more than the bare meaning from a foreign article. As a result, the usual "review of the literature" reads like a condensation of Nuclear Science Abstracts. The review of Lacassagne and Gricouroff translated here is not only very comprehensive, but is colored throughout by analytic comments stemming from their years of extensive investigation and clinical practice. The first edition was, unfortunately, lost to us through World War II and, since then, through the scarcity of copies of the book. Recently the authors extended the coverage of the book by bringing the references as up-to-date as possible in a new edition, thereby relating the pre-atomic bomb research reviewed in the first edition with the enormous amount of radiobiologic research now going on in America. Although they do not pretend that the new edition is a complete review of the most recent literature, we have included as a Translators' note at the end of each chapter a few additional references, mostly American, which in our opinion extend the usefulness of this work as an up-to-date reference-text of previous radiopathologic accomplishments.

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Foreword

KNOWLEDGE OF RADIOBIOLOGY IS INDISPENSABLE TO the understanding and to the safe practice of radiotherapy. The student entering the field of therapeutic radiology who seeks some basic information on radiobiology is often discouraged by abundant, apparently irrelevant literature; he finds mountains of works on total body irradiation of lower animals, speculative theories on the biochemical effects at the level of the cell, and numerous other efforts in basic radiobiology. Let us acknowledge that progress in radiotherapy depends in great part on the penetration of some of these cellular secrets, but the physician-student is more prepared to understand the knowledge of *radiophysiology* of tissues which forms most of this book. As he assimilates information on historadiophysiology he becomes more capable of dealing with the more intricate details of cellular radiobiology.

The development of atomic research, the use of atomic power for war, the tests of atomic weapons and their consequent radioactive fall-out, the vast potential uses of atomic power in industry, in addition to the wider use of radioactive isotopes in medicine and research, have resulted in a staggering demand for information in respect to radiation effects and radiation injury. No longer is this information sought by radiotherapists only; a large number of other investigators and professionals, as well as responsible executives and administrators, have often wished for a summary presentation of the facts of observation and experiment that is achieved in this book. A basic bibliography will lead them, when desired, to the *original* sources.

Whereas the clinical observation of the effects of radiations on human tissues was an early accidental consequence of the applications of radium and roentgen-rays in medicine, scientific experiments and histologic studies of the mechanism of action on the different tissues followed with surprising rapidity. Heineke's description of the effects of radiations on lymphoid tissue, in 1903, is remarkably complete.

Pusey's detailed description of the chronologic effects on human skin, published in 1904, contrasts with the lack of such understanding by many who practice radiotherapy today. Regaud's minute study of the effects on the seminal epithelium, reported in 1906, gave a basis for our understanding of the selective and latent character of the effects of irradiation. Lacassagne's thesis on the radiophysiology of the ovary, in 1913, remains an unexcelled classic.

Following the first World War, Regaud and Lacassagne undertook to review the already extensive world-wide contributions to the field of experimental radiophysiology, correlating them with clinical and histologic observations of the effects on man. Their series of articles, devoted to different organs or tissues and accompanied by extensive bibliography, appeared in the "Archives de L'Institut du Radium—Radiophysiologie et radiotherapie" published by the *Presses Universitaires de France:* this rare publication containing the original contributions of the workers of the *Fondation Curie* appeared irregularly in fascicles which were gathered in three volumes from 1928 to 1938. The quest, by many, for the valuable information gathered in these out-of-print encyclopedic archives, motivated Lacassagne and Gricouroff's effort to summarize some of the data therein contained in this book, first published in 1941 and now recently brought up to date by the authors.

Dr. Lushbaugh and Miss Riese have taken an unselfish step that will be of considerable help to residents in training in therapeutic radiology, for nowhere else is there such a comprehensive and succinct presentation of the effects of radiations and their English version has kept all of the clarity and forcefulness of the original. In the name of residents in training in radiology, and all those who have long waited for this useful book, I am pleased to congratulate and thank them for their achievement.

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Contents

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Ideas on the Biological Action of Radiations

RADIOBIOLOGY, IN THE STRICT SENSE OF THE WORD, encompasses a wide area of investigation. It consists of the study of the action of very dissimilar radiations on living organisms. These radiations include electromagnetic radiations of all wave lengths from cosmic rays to Hertzian rays and corpuscular radiations, such as alpha and beta particles, neutrons and mesons.

A division between the two main groups of radiations may be based on the fact that only one group possesses the ability to ionize the materials which absorb them. This difference, fundamental from the physical point of view, is equally fundamental from the biological point of view if it is conceded that ionizing radiations act on living organisms by means of the ions produced during their absorption.

Ionizing radiations include x-rays, gamma rays, electrons, protons, neutrons, alpha particles and mesons.* Of these radiations, the ones about which we know the most form part of the armamentarium of radiotherapy. The study of the biological action of radiations used by the radiotherapists is thus, in essence, the study of the action of ionizing radiations.

I. Action of Various Ionizing Radiations

1. The course of alpha and beta particles emitted by radioactive materials through living tissue is easily imagined. Numerous photographs of the trajectories of these particles in the supersaturated atmosphere of a Wilson cloud chamber have defined the character of this phenomenon. When an alpha particle or a proton traverses the supersaturated atmosphere of the chamber it forms a short line a frac-

*Ultraviolet rays are transitional between ionizing and non-ionizing radiations. These rays will not be discussed here, however.

tion of a millimeter in length. This line consists of dense clusters of ions. The path of a beta particle will usually be longer, more irregular and less dense since the ionizations are more dispersed.

2. The effect of electromagnetic radiations is exerted at the point of their absorption. In the case of x-rays and gamma rays, the energy of a quantum of incident radiation is sufficient to eject an electron from an atom of absorbing material. This secondary electron (beta ray) then pursues a variable course in the tissue depending on its initial energy, which in turn is proportional to the energy of the incident quantum. The ions formed along the path of the electron are responsible for the biological effect of electromagnetic radiations.

3. Finally, when neutrons are absorbed by the nuclei of light atoms, especially hydrogen in tissue, there is an emission of a proton (hydrogen nucleus) which has a mass one-fourth that of an alpha particle and a course about four times that of an alpha particle. Ions are then formed along the path of this proton.

Therefore, whatever the kind of such radiation, the common property of ionization of the absorbing material is always found. This reason for the similarity of the biological action of ionizing radiations has been well established.

All living matter subjected to ionizing radiation undergoes progressive alterations which are increasingly extensive as the amount of energy absorbed increases. This is true, moreover, in all living things such as a totally irradiated animal, a microscopic organism, a seed, or a cell of any tissue. However, a characteristic biological phenomenon creates a difference between all these objects: the same pathologic changes which cause death are produced by doses of radiation which vary extremely, depending upon the kind of organism or the cellular species. This variable amount of absorbed energy necessary to cause similar radiolesions depends upon differences in the reactibility of irradiated living objects and constitutes the radiosensitivity peculiar to each of them.

II. Radiosensitivity

1. The concept of radiosensitivity was composed gradually by physicians and investigators, who after the discovery of x-rays by

Röntgen in 1895, tried this new agent on various living organisms. Since the apparatus in use then furnished radiations of poorly penetrating intensities, the lesions appearing in the most superficial organ, the skin, were the first to be studied and standardized. A selective action causing loss of hair without alteration of the epidermis was among the various modifications of skin which extend to massive necrosis, indicating that under certain technical conditions one could dissociate the unequal effects of irradiation on the various components of an organ.

On the other hand, biologists who tried these new rays on microorganisms like bacteria and protozoa found that prolonged irradiation produced the death of some without injury to others.

In small animals it was found possible to destroy especially sensitive cells in deep organs, such as lymphatic nodules, bone marrow, testes, and ovary, without producing severe injury of the skin across which the beam of radiation had passed to reach these organs.

Following all these studies, radiosensitivity appeared to be a manifestation of a primary cellular difference and one strove to find in the behavior of various living elements the causes for the inequality of their reaction to ionizing radiation. The conclusion of the early investigators was summarized in 1906 by Bergonié and Tribondeau, as three laws which stated that radiation acts more intensely on cells: (1) when the reproductive activity of the cells is greatest, (2) when the mitotic process is prolonged, and (3) when differentiation and functions are less definitely established or fixed.

2. The discovery of radium by the Curies in 1898 placed at the disposal of investigators a new means of administering ionizing radiant energy, through the direct introduction of radioactive substances into the interior of the body. The almost complete absorption of the enormous amount of energy released by such radiation permitted the use of minute amounts of such substances. The hope was raised in numerous studies that, by being able to shield organs selectively from such action, it would be possible to irradiate only certain diseased organs.

Consideration of chemical reactions without apparent cellular destruction, such as the decomposition of uric acid which occurred after irradiation, seemed to justify the use of such radioactive substances in diseases like gout. The toxicity, however, of these substances when introduced into the body even in very minute amounts prevented the development of this method of therapy.

3. The perfection of x-ray apparatus and the increase of the amount of useable radium permitted the exposure of deep organs to significant amounts of radiation and the irradiation of whole animals even of great size with relatively homogeneous dosages. Unexpected sensitiveness of particular organs and generalized important reactions caused by such techniques have caused the gradual revision of the old concepts of radiosensitivity. The discovery of artificial radioactivity by the Joliots in 1934 and the rapid development of methods of production of numerous radioisotopes led to new possibilities for radiotherapy: pure beta therapy by means of small amounts of radioelements like P^{32} or Sr^{90}, telegammotherapy at great intensity with Co^{60}, and internal curietherapy of more specific and less toxic nature than that which had been tried, without much success, with the natural radioelements previously introduced into the organism. Now a radioisotope could be chosen according to its metabolic properties, so that it could be localized in a particular organ or tissue where the physical action of its radiation would be exerted most efficiently for maximum therapeutic effect.

III. Modes of Action of Ionizing Radiations

The ability of radiation to form ions in living matter (Bordier, 1913) did not completely explain its mode of action. For a long time no definitive fact permitted ascribing the cause of destruction of molecular structures to either physical, physiochemical, or chemical action. Among the various chemical theories were those concerned with immediate coagulation of the protoplasm by heat at the site of absorption of radiation (Dessauer, 1924), consecutive floculation from modification of electrical charges, changes of permeability of cellular membranes, modifications of pH, change in the viscosity of the cytoplasm, denaturation or actual destruction of albumin molecules, destruction of lecithins, liberation of acetylcholine, change in potassium or calcium content, inactivation of enzymes, depolymerization of macromolecules, etc.

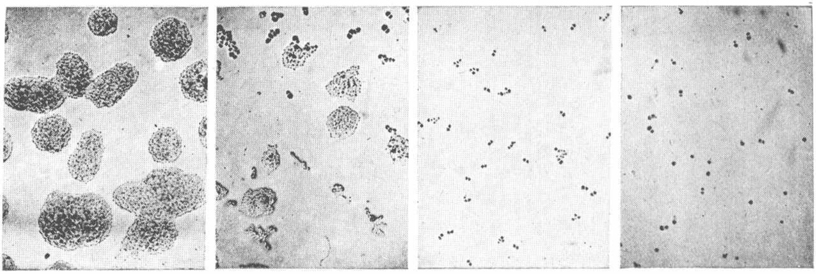
It is quite evident that irradiation of a part of the entire organism results in absorption of the ionizing radiation to a more or less marked degree in the cells, extracellular substances, and fluids. It would appear logical to consider that ionization, whatever the inner mechanism of its action, will have very different consequences depending on whether it happens on absorption in a cell, a fiber, or the plasma. Let us consider these three eventualities successively and try to distinguish the cytologic, exoplasmic, and humoral effects produced by radiation in a living organism.

1. Cytologic Effects

These effects are the best known because of the numerous unicellular organisms which are so favorable for study. Such studies allow the interpretation of the various cellular radiolesions on the basis of the quanta theory as it concerns the discontinuous absorption of radiation. This interpretation was envisaged by Crowther in 1924, and applied by Condon and Terrill in 1927, who explored the variably great radioresistance of drosophila eggs. It was developed further by Holweck and Lacassagne after 1928, who showed that, when using objects such as yeasts and certain protozoa where cytologic modifications produced by irradiation could be followed microscopically or even photographically, there was agreement between the amount of damage produced in the cells and that which the calculations predicted. It has been shown that cells as similar as possible, irradiated under identical technical conditions by means of monochromatic rays, develop lesions of every unequal seriousness. In the same field one can find dead individuals along-side others multiplying normally, while all the intermediate degrees of cellular injury are represented (fig. 1).

The principal stages of these changes due to cellular injury by radiation have been identified and found in all species studied. They are in order of decreasing seriousness: immediate death, suppresssion of motility, suppression of reproduction, abortive anomalies of cellular division, retardation of growth, and hereditary transmission of radiomutations. A possible explanation for these unequal injuries to neighboring and identically treated cells has been given by Bergonié and Tribondeau (1906).

Indeed, under strict experimental conditions it is possible to



A *B* *C* *D*

Fig. 1. Effects produced by an irradiation on yeast. *A*. Control yeast colonies 24 hours after seeding with isolated cells. *B*. Unequal growth 24 hours after a short exposure of similarly implanted cells to a homogeneous radiation. Along side of cells that died immediately are apparently normal colonies. Intermediate phases are present between these two extremes. *C*. A more prolonged irradiation under the same conditions resulted in a predominance of elements which underwent delayed death after one or two divisions. *D*. Very intense radiation caused a predominance of cells that died immediately.

calculate for a cellular species, whose morphologic characteristics such as the volume of motor centers, the centrosome, the nuclei, and the cytoplasm are known, the probable fraction of the photoelectrons of a given dose of radiation which should affect each of the various cellular organelles. Microscopic examination of a field of irradiated cells confirms these probability calculations. Each of the principal kinds of radiolesions is found in numbers proportional to the volume occupied by a special region in the cell. So, we have been led to conclude that: 1. The simultaneous absorption in a cell of a great number of ionizing particles which destroy several constituent regions causes immediate death. 2. The injury of motor centers (such as those at the base of the flagella of a flagellated protozoa) causes inhibition of movement. 3. The destruction of the centrosome results in the suppression of cellular division. 4. The destruction of variable quantities of nuclear chromatin impedes the normal completion of mitotic division. 5. The partial disintegration of cytoplasm results in retardation of growth. 6. The occurrence of very fine lesions at a particular point of the chromosomic material or gene causes mutations.

Considered from this aspect, radiosensitivity in each cellular species seems to be the product of two principal factors: the histologic make-up which determines the respective volume of sensitive zones whose injury by ionizing particles defines the lesion and its importance, and the physiochemical composition which determines the number of particles necessary for the destruction of the constituent molecules of these organelles.

With this concept the expression of "lethal dose" has no precise significance in radiobiology. The cells of even a like species, irradiated at the same time under the same conditions, die after having received extremely varied doses. On the other hand, it can be determined with very great accuracy for each dose the percentage of damaged, wounded, or killed cells. At the same time the laws of Bergonié and Tribondeau no longer apply precisely and have often been found in error. These laws are based simply on a frequent coincidence of a large relative volume of certain sensitive zones (centrosome, nuclei) and the reproductive activity of the cellular species. Also certain lesions, in particular of chromatin, are morphologically apparent only at the time of the cell division. The cells of a stable organ which normally divide only at very long intervals can be considered as much more radioresistant than the cells of an organ with a rapid cellular turnover. Even though such cells may have been subjected to as serious damage, the cytologic lesions are kept at the inapparent stage during a prolonged latent period.

The quanta theory of cellular radiosensitivity explains why, when a complex organ or one of its parts has been irradiated, it is not possible to obtain a universal selective effect on a single cellular species however radiosensitive it may be. Irradiation, also, is inevitably accompanied by lesions and destruction of a certain number of cells of other irradiated organs or tissues, even though they may be much more radioresistant. Consequently, the total and permanent sterilization of an organ of apparently great radiosensitivity is always difficult; it demands a quantity of radiation which greatly exceeds that which is necessary to cause the death of the greatest number of constituent elements of the organ; it is not possible to obtain it without producing more or less marked cellular destruction in neighboring organs.

Finally, the general or local irradiation of a complex organism always entails the immediate or deferred death of a more or less great number of cells. These cells disintegrate, liberating products of decomposition which can partially be eliminated to the exterior in case of an ulceration, but which most often are reabsorbed into the interior where they temporarily modify its composition and produce secondary effects.

The mechanism which has just been outlined corresponds to what is now called the *direct action of ionizing radiation.* Ions produced at the locus of absorption of radiant energy are considered the cause of molecular changes where intracellular alterations result and become manifest as various types of typical radiolesions.

However, from the beginning of radiobiological research, another interpretation was considered, even before the concept of discontinuance in the absorption of ionizing radiation was suspected. It was felt that radiation could act by freeing toxic chemical products in the region. Cellular lesions were thus due to an indirect action; a chemical process interposed between the primary physical process and the final biological one. At first no experimental confirmation was found to support this theory and it was soon abandoned.

It was taken up again after 1923 when Petry reported an increased radiosensitivity of seeds and rootlets in the presence of an oxidizing agent such as hydrogen peroxide, and a radioresistance in the case of oxygen deficiency. In 1939 Piffault showed that paramecia put into water that had been very strongly irradiated with x-rays died in less than an hour, showing that the radiation had altered the oxygenated water sufficiently to kill the protozoa without they themselves being irradiated. A similar experiment carried out with virus vaccine by Bonet-Maury (1941) led to the same result. Loiseleur (1942) tried to explain the mechanism of action by means of an in vitro experiment in which organic molecules were irradiated in solution and concluded that x-rays act by altering the molecular oxygen present in the dissolved state in the irradiated medium so that all radiation carried out in the presence of oxygen appears like a radio-oxidation. Lacassagne (1942) demonstrated this phenomenon in vivo by showing that newborn mice irradiated in an atmosphere deprived of oxygen resist a lethal dose. In 1944 Weiss attributed this *indirect action of*