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RADIATION HISTOPATHOLOGY

Volume II

George W. Casarett

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Radiation Histopathology

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PREFACE

Radiation histopathology may be defined here broadly as that branch of radiation biology which is concerned with the microscopic study of organized tissue and organ changes caused in vivo by radiation directly and/or indirectly. This book is concerned only with the effects of ionizing radiations on normal tissues and organs as observed by means of light microscopy.

Radiohistopathologic effects represent the consequences of cellular radiobiologic effects and constitute the bridge between cellular radiobiologic effects and gross pathologic and clinicopathologic consequences in the sequences of pathogenetic mechanisms of these gross effects and consequences. Although some biophysical and cellular radiobiologic background is provided, this is neither a cellular radiobiologic nor a clinical radiation pathology book, and is not intended to be a comprehensive treatise of the many and complex interdisciplinary facets of either of these fields. Nor is this book intended to be either an atlas, manual, or comprehensive reference source for radiation histopathology, but rather a treatment of this subject in pathogenetic terms with illustration of the principal features.

This book describes and illustrates the histopathology of ionizing radiations and discusses the pathogeneses of the major somatic degenerative, nontumorous, nonteratogenic effects of ionizing radiations. From the practical point of view, the principal thrust of the book is directed at those changes capable of developing into functional and/or structural impairments or lesions that may cause significant detriment in body systems and adversely affect health. The main focus of the book is the attempt to express radiohistopathologic observations in terms of the cellular dynamics of tissues and organs and to consider radiation histopathology in the general context of tissue response to injury rather than merely the special result of a specific type of injury or agent. As such, the treatment of the subject in this book is primarily concerned with general sequences, pathogeneses, and mechanisms, rather than with great detail and anecdotal material.

By means of reasonably broad classifications and generalizations, this book represents and consistently applies interpretations, theories, concepts, and schemes of relative radiosensitivity and of direct and indirect mechanisms of radiation damage of cells, tissues, organs, and systems in vivo which appear to be highly compatible with the experimental and clinical evidence and which permit reasonable prediction of radiopathologic damage. Permanent, progressive, and delayed radiation effects are considered as well as acute effects. The additivity of these radiation effects with other changes occurring with time or increasing age and the influence of this additivity on the time of appearance and degree of pathologic expression of the radiation injury are also stressed.

Most of the information on which these concepts and interpretations of pathogenetic sequences and mechanisms are based has come from extensive experimentation, with a lesser amount from occasional well-designed extensive studies of human organs and consideration of the aggregate of great numbers of more anecdotal human case reports. Disagreement with some of the author's interpretations, concepts, or criteria is expected in such an interdisciplinary, multilevel field of investigation as that of radiobiology in which there are still so many large gaps in knowledge. The gap between basic cellular radiobiology and clinical radiopathology is still very large. For purposes of study of pathogenetic sequences and mechanisms, there is more valuable radiohistopathologic information, and illustration, for some organs, which have been studied intensively for this purpose, than for other organs. For this reason, certain organs and tissues have been given more or less consideration and illustration in this book.

The illustrative materials used in this book are largely those developed from the research of, and for graduate teaching by, the author in the field of radiation histopathology over the past thirty years. The literature listed as being cited specifically and/or as other sources omits of necessity many of the vast numbers of publications which have more or less bearing on the subject. The references and other sources include those articles and books used in the review of specific subject matter. It is from this diversity of selected background information that the text of this book has been derived.

The author hopes that this book will help the reader, whether a researcher or clinician, to understand better the translation of cellular effects of ionizing radiation into subsequent detriment in the body.

George W. Casarett, Ph.D.

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The author wishes to express his gratitude to all of those people who have contributed to the experience on which this book is based: to research scientists in this field, past and present; to his collaborators in research over the past three decades; to the many graduate students, who have contributed much of the information used in the book; and to his technical associates who have contributed vitally to his research.

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George W. Casarett

THE AUTHOR

George W. Casarett, PH.D. is Professor of Radiation Biology and Biophysics, and of Radiology at the University of Rochester School of Medicine and Dentistry, Rochester, New York.

Dr. Casarett obtained his premedical education at the University of Toronto (1938-1941) and the University of Rochester (1943-1945). He undertook his Graduate studies at the University of Rochester where he earned his Ph.D. in Anatomy (Pathology) in 1952. Since 1943, Dr. Casarett has held numerous Research and Academic positions at the University of Rochester School of Medicine.

Dr. Casarett is currently Chairman of Scientific Committees #1 and #14 of the National Council on Radiation Protection and Measurements, of which he has been a Director. He is a recent past Chairman of the National Academy of Sciences Advisory Committee on Biological Effects of Ionizing Radiation.

Among his numerous past activities in national and international organizations, Dr. Casarett has been a member of the National Academy of Sciences Advisory Committees to the Federal Radiation Council and to the Atomic Bomb Casualty Commission, the National Cancer Institute Research Training Committee, and Committee #1 of the International Commission on Radiological Protection, and a consultant to the United Nations Scientific Committee on Effects of Atomic Radiation and the Nuclear Regulatory Commission. His membership and Fellowship in numerous scientific societies include memberships in the American Association of Pathologists, Radiation Research Society (former councillor and associate editor of journal), American Association of Anatomists, and Society for Experimental Biology and Medicine.

Dr. Casarett has authored over 200 papers on various aspects of radiation research. His major fields of research are in Radiation Pathology, Radiation Biology, Carcinogenesis, Gerontology, and Cancer Biology.

DEDICATION

For Marion

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Chapter 1

RESPIRATORY TRACT

I. HISTOLOGY

The nasal passage (excepting the continuation of the skin in the vestibule), the larynx, the trachea, and the bronchi and their branches are lined by pseudostratified, ciliated, columnar epithelium containing numerous goblet cells and resting on a basement membrane which is located between the epithelium and the underlying layer of connective tissue with its mixed mucous glands. The nasopharynx is lined by ciliated columnar epithelium. These epithelia are composed of reverting postmitotic cells which are relatively radioresistant.

The primary bronchi branch into secondary bronchi, and these into bronchioles, then terminal bronchioles, respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (Figure 1A). The mucous membrane of the bronchi is continuous with that of the trachea and is of the same type (Figure 1B). The pseudostratified ciliated columnar epithelium rests on a basement membrane separating it from the lamina propria. Small cuboidal cells are found on the basement membrane in the epithelium of the trachea, bronchi, and their branches, and are usually the cells which divide when required to replace the more specialized cells which are lost. The turnover time of bronchial epithelium is relatively long.

The functional unit of the lung consists of a respiratory bronchiole and the structures extending from it, the alveolar ducts, alveolar sacs, and alveoli. The ciliated columnar epithelium of the bronchial tree changes to low cuboidal epithelium in the respiratory bronchioles. The short respiratory bronchioles branch into variable numbers of alveolar ducts of varying length, which are long, tortuous, thin-walled, branching tubes which give rise to thin-walled alveolar sacs (outpouchings containing more than one alveolus) or alveoli (Figure 1A). The alveolar duct wall between the openings of the alveolar sacs contains collagenous and elastic fibers and smooth muscle cells. The alveolar walls contain close, highly anastomosing networks of capillaries, supported by a fine network of reticular fibers, and a small number of elastic fibers. The alveoli are lined by a thin, simple, low epithelium separated from the capillary endothelium by a thin basement membrane (Figure 1C). The free macrophages that are sometimes found in alveoli (alveolar phagocytes) are like macrophages found elsewhere in the body. They are derived mainly from hematogenous lymphocytes and monocytes; the name septal phagocytes has been given to cells in the septa that have been observed to assume the appearance and function of macrophages.

Normally, the blood capillary networks in the alveolar walls are separated from the air only by a thin membrane through which oxygen and carbon dioxide easily diffuse. The reserve functional capacity of the normal lung is large, so that at rest the human body requires the use of only a small fraction (about 1/20th) of the aerating surface. The epithelial lining of the respiratory structures of the lungs consists of reverting postmitotic cells, which are relatively resistant to the direct destructive actions of radiation.

II. RADIATION HISTOPATHOLOGY

So-called radiation pneumonitis may be regarded as an inflammatory reaction in which there is first a phase that is predominantly exudative. This reaction may either

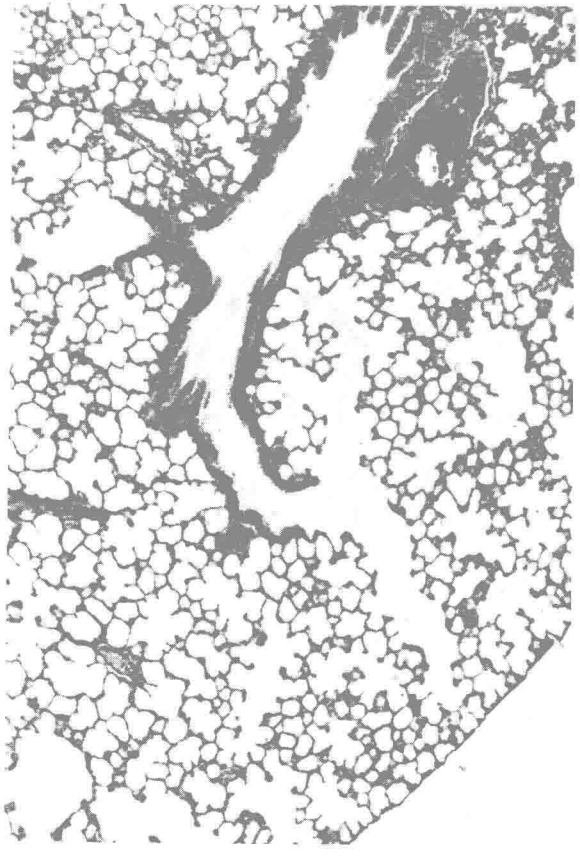

FIGURE 1. Sections of normal rat lung. A. Section (approximately 100×) showing bronchial branch, terminal bronchiole, alveolar duct, alveolar sacs, and alveoli.

FIGURE 1B. Section (approximately 800×) showing branch of bronchus.

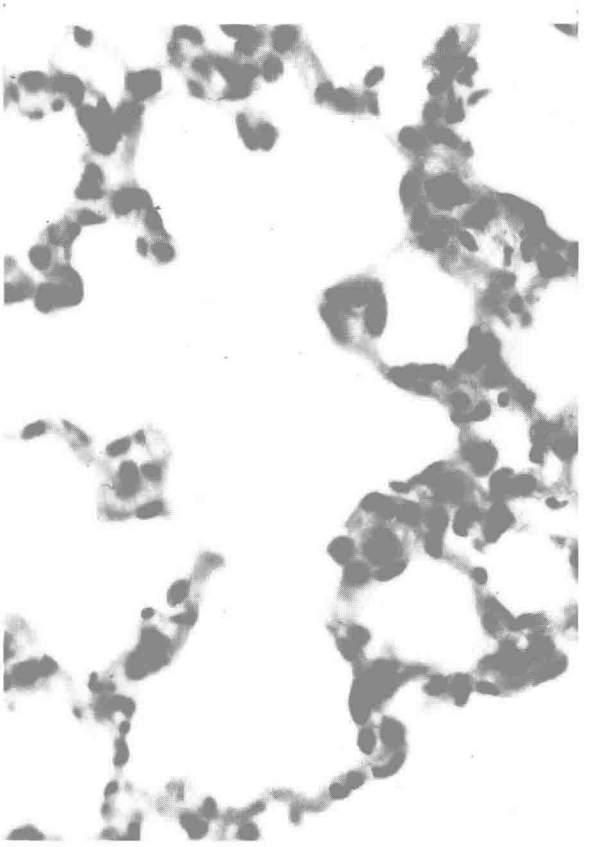

FIGURE 1C. Section (approximately 800 ×) showing alveolar sac and alveoli. (H. and E. stains.)

resolve and leave little or no histopathologically detectable change, except perhaps for subtle vascular changes, or it may progress to a chronic or delayed late phase with chronic inflammation and fibrosis as the prominent features. On a clinicopathologic basis, radiation pneumonitis cannot easily and at all times be sharply divided into acute or exudative and chronic or fibrotic periods, since the earlier phase may merge subtly or mix with the other, and complete or partial resolution may occur either early or late in the overall process.

The inflammatory, degenerative, and fibrotic changes which radiation can cause in tissues of various kinds are of special significance when they occur in the lung where their presence interferes directly and early with vital and urgent functions. In the lungs, as compared with more compact organs (those tightly encapsulated and relatively inactive physically), hematogenous exudates more easily and rapidly enter critical functional space, the respiratory air space, in relatively large amounts, aided by the bellows-like action of the lung. Therefore, the exudative aspects of the early or late periods of radiation response easily and rapidly interfere with respiratory function by increasing the barrier to the diffusion of gases between capillaries and alveoli, as well as by reducing the available alveolar air space. Likewise, the dependence of the respiratory function of the lung on a thin alveolar membrane and ready diffusion of gases allows for rapid and easy interference with this function by a relatively small degree of increased cellularity or proliferative response as is involved in the inflammation and fibrosis of radiation pneumonitis.

Because of the relative radioresistance of epithelial tissues of the lungs, the early and late consequences of irradiation of the lungs are due largely to vascular and connective tissue effects. Transient acute responses may be caused in the fine vasculature and connective tissue by relatively small or moderate doses (e.g., a few hundred to 1200 rads), and such responses increase in degree and duration with larger doses. The chronic and delayed effects in the lung are caused primarily by progressive vasculoconnective tissue changes with secondary effects on parenchymal cells. The complication of pulmonary infection may also play an important role in the development and persistence of the process in some cases.

Early histopathologic changes in the lung after irradiation include hyperemia and vascular congestion, edema of alveolar walls, lymphangectasia, exudation of proteinacous fluid from the blood into the alveolar spaces, leakage of red cells and diapadesis of hematogenous polymorphonuclear leukocytes into alveolar spaces, increases in phagocytic cells, increased mucus secretion by the bronchial epithelium, and some degenerative changes in small numbers of alveolar and bronchial epithelial cells, followed by rapid recovery of the latter changes.

The sequence of early changes (within two months after thoracic irradiation) in rat lungs after various single localized doses of X-rays (600 to 3600 rad) is illustrated in the following figures. Pulmonary congestion and edema, slight at two days, becomes more marked within a week. There is edema of alveolar walls, alveolar spaces, bronchial walls, vessel walls, and into pleural space, where fibrinous pleuritic membranes are formed on the outer lung surface (Figure 2). By two weeks after irradiation there has been virtually complete resolution of the alveolar edema, but alveolar walls are thickened at the expense of alveolar lumens, perhaps a result of infiltration of mononuclear cells, there are numerous alveolar phagocytes in some regions, and small arteries show degenerative and obstructive changes as well as persistent edema (Figure 3). There is also evidence of hyperplasia, disorganization, and some degenerative change in epithelium of bronchi, associated with the beginning of fibrosis in their submucosal tissue (Figures 4A and 4B). By one month after irradiation, there are foci of emphysema and areas of marked increase in mononuclear inflammatory cell infiltration in alveolar septal walls, and to a lesser extent in alveolar spaces associated with relatively dense fibrinous deposits in alveolar spaces (Figure 4C). Occasional fibroblasts or transitional forms between mononuclear cells and fibroblasts are present in alveolar septa or spaces (Figure 4D). By the second month after irradiation, the process of chronic inflammation and fibrosis is more active and extensive, depending on dose, both in alveolar walls and spaces and in pleuritic membranes (Figure 5).

Jennings and Arden[148], in their studies on rats, found that there was little significant difference in the changes in lungs subjected to single or fractionated exposures. Septal thickening was of about the same degree in animals given 3000 rads of thoracic irradiation fractionated at 600 rad per week for five weeks and those given 1000 rads followed in 50 days by 2000 rads, as compared with a single dose of 3000 rads. They cited one possible differential effect of fractionation, a response of the pulmonary blood vessels. At 60 days after irradiation, those animals given the dose fractionated for five weeks at 600 rads per week showed a more marked thickening of blood vessels than was seen in the other groups. Many of the smaller blood vessels in the lungs showed prominent subintimal hyalinization. At times, later than two months after irradiation, the changes in the alveolar septa appeared to be slowly progressive. At the end of a year there was marked generalized fibrosis in alveolar septa throughout the lung, with the alveolar walls being three to six times as thick as normal. The thickening was due chiefly to proliferation of fibrillar tissue. Reticulum fibers proliferated and condensed. The fibrosis appeared to be the result of the organization of the persistent fibrin-rich edema fluid seen in the alveolar septa soon after irradiation.

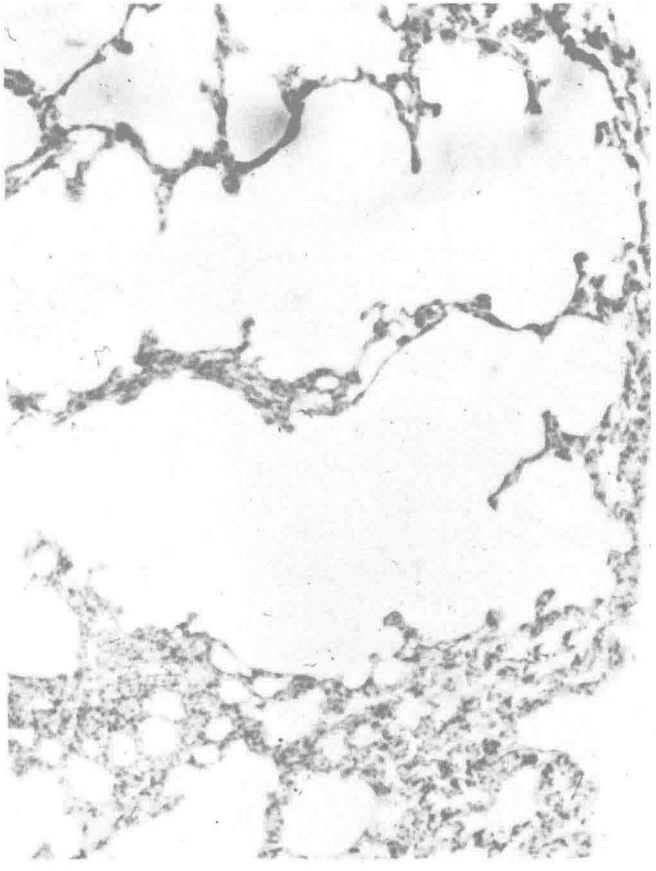

FIGURE 2. Sections of rat lungs 1 week after thoracic X-irradiation. A. Section (approximately 100×) after 600R, showing an area of edema and emphysema.

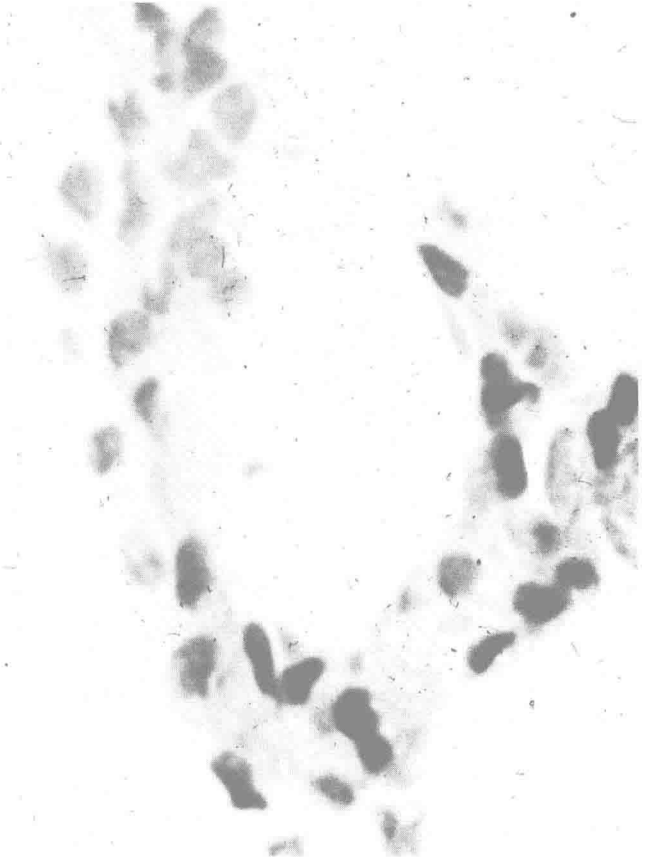

FIGURE 2B. Section (approximately 1,000×) after 1200R, showing edema of alveolar walls.

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