BIOCHEMICAL MECHANISMS IN INFLAMMATION

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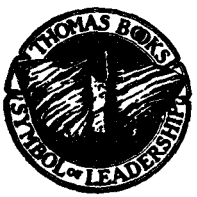

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To

S. in affection
and to
my Children
Lucy, Gabriel, Valy, Jr.
and Paul

Preface to the Second Edition

THE very extensive growth of the field of inflammation in the last few years has necessitated a revision of the present monograph. Instead of the original five chapters the monograph now consists of ten chapters. Additional observations by many investigators as well as those of the writer have been incorporated in the text. Various problems, such as the present status of leukotaxine, have been critically surveyed. The views of other workers have been described as accurately as possible; but in several cases the inferences and conclusions drawn by them have been evaluated on the basis of the factual information supplied.

New data, accumulated many years ago in the Harvard Laboratories, on the level of some inorganic elements in exudative material have now been published for the first time in the present monograph (Chapter 2). The possible significance of this information is pointed out. The problem of repair is now treated in a separate chapter. The importance of this process, the possible mechanism involved, and the relation of this phenomenon to cellular injury and precancerous lesions are discussed at some length (Chapter 8). An attempt is made at integrating the local inflammatory reaction in conjunction with hormonal influences and nervous regulatory processes. The problem of enhanced diabetes with inflammation is critically surveyed; and the possible relation of this significant problem to current trends in carbohydrate and endocrine metabolism is pointed out.

New experimental observations are listed concerning the relationship of pyrexin, the pyrogenic factor of particularly

acid inflammatory exudates, to bacterial pyrogens. Finally, a separate chapter deals with the all important modern field of anti-inflammatory corticoids and ACTH. From the original observations made by the author in 1940 and 1942, reinforced by the brilliant observations of the Mayo Clinic workers on arthritis in 1949, there now has developed one of the most active fields in experimental and clinical medicine. Recent observations on the mechanism involved are discussed. The monograph ends with suggestions as to future possibilities in attacking various still unsolved problems, such as the relation of injury to neoplastic formation, the elucidation of the precursors of the chemical factors liberated in inflammatory exudates, and the further chemical purification and more exact identification of these factors. There are, of course, many other problems that deserve exploration. It is hoped that the reader will find some interest in probing further into the biochemical mechanisms of the injured cell, as manifested by inflammation.

With all due humility, the author has attempted in this second edition of *Newer Concepts of Inflammation* under the title *Biochemical Mechanisms in Inflammation*, to link the various trends of this all important and fundamental problem in pathology, so that a local inflammation may be regarded as a unit having repercussions on the organism as a whole. The various factors liberated by injured cells are specific and reasonably explain many of the biologic manifestations of inflammation; but as the writer carefully points out a large amount of work is still ahead in our endeavor to bring these specific factors to the state of absolute chemical purity. This fact, it is hoped, will interest properly equipped chemists to attack these substances which now stand out as defined specific biologic units.

The writer acknowledges that some contributions have been omitted. A real effort has been made to be certain to in-

corporate in the text the references that aid in the further understanding of the thesis presented in this monograph. Other studies, which no doubt are very valuable contributions, had to be omitted here owing to limit on space or to their irrelevant relation to the central theme.

My thanks are due to all my past and present assistants and associates who so conscientiously helped me in the accumulation of our experimental data. This has led to the reasonable formulation of a biochemical theory of inflammation. I wish to express particularly my appreciation to my present assistants, Dr. W. Kalnins, Miss Irene Goldman, and Mrs. Alma Kunkulis. I am especially appreciative to my secretary and assistant, Miss Irene Goldman, for her extensive aid in the laborious secretarial work involved in the preparation of the present monograph. I am indeed indebted to Dr. Augustin R. Peale of the Department of Pathology of the Temple University School of Medicine for carefully going over many of the microscopic sections pertaining to the repair and precancerous studies described in Chapter 8. I also wish to thank Dr. Edwin S. Gault of the same Department for taking some of the photomicrographs utilized in this edition. My appreciation is extended to my son and assistant, Gabriel Menkin, for aid in the proof reading of parts of the manuscript. Finally, the reader should be cognizant of the fact that in a recent Spanish translation of the first edition of the present monograph (*Nuevos Conceptos sobre Inflamación*), kindly undertaken by Dr. Carlos Tanturi of Buenos Aires (1955), an additional chapter has been added in which many of the new observations since 1950 have been incorporated. I am also appreciative to the John Simon Guggenheim Research Foundation for the tenure of a Fellowship in 1951; to the Marine Biological Laboratory, Woods Hole, Massachusetts for laboratory facilities to carry observations on sea urchin ova (chapter 9); to the United State Public Health Service;

and to the Dr. A. Wander, S.A., Berne, Switzerland for financial aid in carrying out many of the studies of the last few years since the publication of the first edition. Finally, I wish to express my thanks to the *British Journal of Experimental Pathology*, the *International Archives of Pharmakodynamie et Thérapie*, the *International Archives of Allergy and Applied Immunology*, the *American Journal of Physiology*, *Science*, the *New York Academy of Sciences*, the *Revue Canadienne de Biologie*, the *Proceedings of the Society for Experimental Biology and Medicine*, and the *Archiv Experimental und Pharmakologie* for permission to reproduce many of the illustrations from some of the writer's scientific papers.

The materials from the First Edition of this study were originally presented before the Midwest Seminar of Dental medicine at Maxwellton Braes, Bailey's Harbor, Wisconsin, September 19-23, 1948.

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Preface To The First Edition

THIS monograph essentially represents supplementary data to an earlier publication entitled *Dynamics of Inflammation.**

In this earlier study an analysis of the mechanisms of infectious processes was attempted. Relatively brief space was devoted to the isolation of various biochemical factors from inflammatory exudates. This, to a large measure, was due to the fact that these factors had not as yet been identified in exudative material. For the past ten years or so, studies have been largely focused in an attempt to understand the basic mechanisms involved in the development of this elementary immunological response in vertebrates. It has been found that many of the biological attributes of an acute inflammation are referable to the liberation by injured cells of biochemical units, in turn liberated by the injured cell. It has become, therefore, of the utmost importance to focus one's attention on the biochemistry of injured cells. If this little book can in any way stimulate the interest of the reader in this direction, then its mission will have been in large part accomplished. To provide an integral view of the whole problem, it has been found indispensable to have some degree of overlapping with some of the material already described in *Dynamics of Inflammation.*

It is true that some contributions have been omitted from this monograph. This is partly due to the limitation of space, and also, in part, to an unwillingness to clutter the thesis of the writer with material which, although important, is not exactly relevant to the topics discussed. The pertinent literature, how-

* Macmillan Co., New York, 1940.

ever, has been reviewed as adequately as possible in additional footnotes.

The few chapters in this book represent essentially four lectures delivered before the Annual Midwest Seminar of Dental Medicine at Maxwellton Braes, Bailey's Harbor, Wisconsin, from September 19 to September 23, 1948. These lectures were also given to the medical students in pathology, at the Temple University School of Medicine, during the years 1947 to 1949.

Before closing these few introductory remarks, I should like to express my appreciation to my past and present assistants for the faithful technical aid rendered in reaching the present conclusions; particularly, in this regard, to my present assistants, Miss Louise Pirovane, Miss Margaret Jaep, and Mr. Carl Friedhofer. My thanks are due to Mrs. Lois Todd for her unfailing secretarial help in the preparation of this monograph. My thanks are also due to the Agnes Barr Chase Foundation for Cancer Research of Temple University School of Medicine and to the National Advisory Cancer Council for their financial aid in the recording of some of the observations reported in this book. I am also obliged to various Journals for permitting me to reproduce many of the present illustrations and material used in the text. These include the *Archives of Pathology*, the *American Journal of Physiology*, *Cancer Research*, *Lancet*, *Science*, the *American Journal of Pathology*, the *Proceedings of the Society for Experimental Biology and Medicine*, the *Annals of the New York Academy of Sciences*, the *Journal of Experimental Medicine*, and the *American Journal of the Medical Sciences*.

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Contents

BIOCHEMICAL MECHANISMS IN INFLAMMATION

— 1 —

The Problem of the Initial Increased Capillary Permeability and the Migration of Leukocytes in Inflammation (Leukotaxine)

INFLAMMATION can properly be regarded as a sort of defense reaction on the part of higher animals to the presence of any injurious stimuli, or rather what is often termed an irritant. An irritant is any foreign agent which interrupts the normal metabolic processes in the cell organization. An irritant can be physical in nature, such as sunlight; it may be chemical in nature, such as bile or various toxins liberated by pathogenic microorganisms. The irritant may be bacterial or protozoan in origin. Thus, there are two kinds of irritants, namely, viable and non-viable. All these irritants induce what is loosely termed an "inflammatory reaction," when introduced into the tissues of a vertebrate host. Pathologists have often in the past interpreted inflammation as caused solely by bacterial irritants. This is not strictly correct. However, when one is dealing with bacterial infections, inflammation may truly be regarded as the physical basis of infectious disease.

An irritant may induce in tissues a barely perceptible reaction or a hyperemia, up to the production of an abundance of pus or what is termed a suppurative process. The reaction of inflammation tends to be stereotyped. It proceeds by the interdependence of various sequences. In our analysis of the phenomenon of inflammation, we shall attempt to trace the various mechanisms concerned in the development of these sequences. I shall point out experimental evidences which demonstrate the mechanisms involved. If you have a clear

idea of this fundamental phenomenon, you will find it rather simple to understand the concrete examples as illustrated in specific diseases, for inflammation follows a definite pattern which is only modified in individual cases by the anatomical location of the disease process and also by the chemistry of the irritant involved.

Inflammation is a manifestation of severe cellular injury in vertebrate animals. There are many different definitions given to inflammation. To me it is the complex vascular, lymphatic, and local tissue reaction elicited in higher animals by the presence of micro-organisms or of non-viable irritants.[1] It represents a basic or elementary reaction to injury whereby the deleterious agent tends to be localized and ultimately destroyed. The various complex sequences frequently go under the one name of "inflammatory reaction." One can regard this reaction as an immunological mechanism of definite significance in bodily economy.

Inflammation is initiated by a disturbance in fluid exchange. The normal filtration equilibrium through the capillaries is altered, as pointed out in the last century by Cohnheim.[2] The cellular wall of the affected or injured cells also becomes more permeable, so that fluid from the cells pours out in the extracapillary spaces. These areas become filled with fluid from vascular channels as well as from the injured cells. This fluid, consisting of plasma and products of cellular injury, is known as the *exudate*. As you are aware, if the exudate is largely made up of plasma and the products of injured cells, it forms what is known as a *serous exudate*. If it contains considerable number of red cells, we have what is known as a *hemorrhagic exudate*. If the consistency is thicker due to the presence of a large number of dead or injured white cells, one is dealing with a *purulent exudate*. If there is much fibrin present and dead cells, the exudate is often referred to as a *fibrinopurulent exudate*.