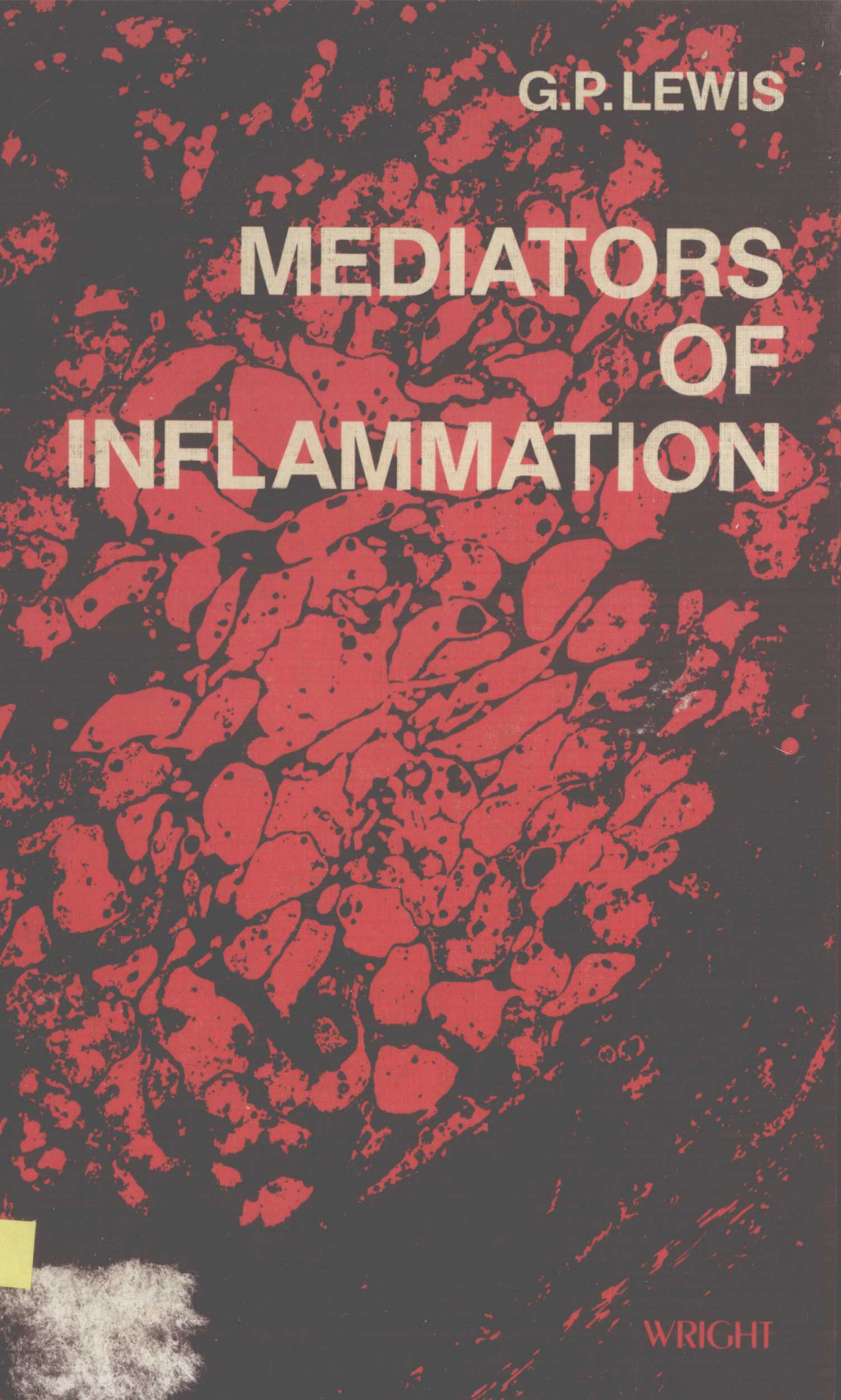
G.P. LEWIS
MEDIATORS OF INFLAMMATION
WRIGHT

Mediators of Inflammation

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with a Foreword by Professor Gerald Weissmann

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MEDIATORS OF INFLAMMATION

Preface

The purpose of this book is to present an introduction to students and to research workers who need to know something about the ever-expanding field of inflammation. I hope it will also be useful to doctors who wish to revise their knowledge of the mechanisms involved in this most fundamental pathological process.

It is not a textbook, but more of a monograph in which I have included many of my own views and interpretations. Experts in the various areas that I have discussed might well disagree with some of my interpretations. However, to guard against presenting a totally erroneous view, I have consulted with many experts who have given their help most generously and who have been mentioned in my acknowledgements. I am most grateful to Gerald Weissmann, who is perhaps the greatest expert of all in the field of inflammation, for agreeing to have a final check in order to write the Foreword. I know that whatever criticisms he will have he will present with his usual understanding and generosity.

In order to deal with each aspect of mediators fully, it would have been necessary to prepare a large volume for each of the twelve chapter headings. Thus, having reduced each to no more than a precis, it was impossible to refer in detail to the many research papers on each subject. I must therefore apologise in advance to all those worthy scientists whose work I have not quoted.

I have tried to give an overview in which I hope it becomes clear that there are many amplifying, as well as inhibitory, systems which interact with one another and there is considerable overlapping and duplication of the final biological effect. It appears that nature provides several systems to produce similar effects to ensure that a minor fault does not lead to a complete breakdown.

I have made a point of illustrating topics wherever possible, sometimes even simple ones, because I feel that a pictorial presentation helps most people to gain an understanding and to remember it.

G.P.L.

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Chapter 1 — *Figs* 1–3 by permission of the President and the Council of the Royal College of Surgeons of England.

Chapter 2 — The thermographs in *Fig.* 5*a* and *b* were kindly supplied by Dr Graham Parr, Rheumatology Research Unit, Addenbrooke's Hospital, Cambridge.

Chapter 6 — I am grateful to Dr Gillian Bullock and Dr John Baker of Ciba-Geigy Laboratories, Horsham, for the electron micrographs shown in *Fig.* 1*a* and *b* and the scanning micrographs in *Fig.* 1*c* and *d*; and to Steve Gschmeissner, of the Royal College of Surgeons, for the scanning micrograph of *Fig.* 2. I am grateful to the Editor of *Prostaglandins* for permission to reprint *Fig.* 3*a* and *b*.

Chapter 8 — Professor Malcolm W. Greaves, of the Institute of Dermatology, generously supplied material for *Figs* 2, 5, 7 and 9 and *Fig.* 8 was kindly provided by Dr R. Barnetson.

Chapter 9 — I am grateful to Dr Gillian Bullock and Dr John Baker for the electron micrograph of *Fig.* 1 and to Steve Gschmeissner for *Fig.* 2. The PCA photograph in *Fig.* 3 was kindly supplied by Professor M. W. Greaves from data in Yamamoto, Francis and Greaves (1976) *Clin. Exp. Immunol.* **25,** 583. Professor Greaves also supplied the example of dermographism in *Fig.* 7.

Chapter 11 *Fig.* 8 was kindly supplied by Dr J. M. Blackwell, Dr M. B. Roberts and Dr J. Y. Channon.

Chapter 12 The micrographs of *Figs* 1 and 2 were kindly supplied by Dr Gillian Bullock and Dr John Baker, and that of *Fig.* 3 by Steve Gschmeissner.

Foreword

by Gerald Weissmann

Professor of Medicine
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In this post-literate decade we are presented with many treatises but few books, many facts but few thoughts, many images but few pictures. Professor Lewis here presents us with a thoughtful book in which he describes the picture of inflammation as we apprehend it today. As a general account for the curious biologist or clinician this volume displays the scholarship for which its author has been recognized around the world; as a readable volume in this jargon-ridden field it has no equal.

Inflammation was recognised by the ancients as the response of man and beast to cuts or climate. In the last century, when microbes were finally recognised as the major culprits of disease, inflammation was attributed to their mischief. Nowadays we have learned that our own cells and fluids collaborate with hostile invaders to provoke inflammation; sometimes these Quislings or Lavals turn on us in the absence of any enemy. This formulation reminds me that our generation tends to write the scenario of inflammation in terms appropriate to old war movies. Redness and swelling with heat and pain are not only the four cardinal signs of inflammation, but also the cardinal emotions of 'Casablanca'.

Happily, Professor Lewis has done more than simply 'round up the usual suspects': complement, kinins, amines and prostaglandins. He has traced for us the politics of inflammation, the motivation, so to speak, with respect to ontogeny and phylogeny of cellular contributors to inflammation: neutrophils, platelets, macrophages and so on. In working out for their various roles and treasons, he has made it clear that nothing about these suspects is simple: alliances shift; affinities wane; wounds heal, but scars remain.

We learn along the way of this book why we become sick when the body is inflamed in part or in whole; for it has become clear that many of the subjective, psychological responses to injury or illness are mediated by defined reactants released into our bloodstream. These 'acute phase reactants' make us febrile, debilitated, sleepy and cross

even as they sound the alarms which rouse battalions of lymphocytes. Professor Lewis ably recounts how the messages of acute inflammation are received by cells which are linked in the network of immunity; the allies of cellular and humoral immunity are summoned to aid the heroes of local resistance. For Professor Lewis, as for many of us, the story of inflammation is the story of an armed encounter with the enemy in the course of which damage is done but resolution not invariably achieved.

You might have gathered the impression from the foregoing that this monograph is a scientific version of a cinematic romance. Nothing could be further from the truth. For it is filleds to the brim with clear argument supported by accurate information. But when the story of inflammation is laid out with the sort of verve and panache one finds here, we might be excused for confusing the narrative with one of the genres of pleasure. From reading his comparison of the creative with the inflammatory process, one gathers that Edmund Wilson would have liked this book: 'Reason and imagination, like leukocytes accumulating themselves at the place where the infection, in the physical system, has occurred, rush at once to the breach and, ingesting the alien elements, are discharged in the form of art . . . and the wound is presently healed.'

Contents

Chapter 1

Introduction

HISTORICAL DEVELOPMENT

When a tissue is damaged or injured, a local reaction takes place which is referred to as the inflammatory response. Man has been aware of inflammation since Egyptian times and possibly before and, as early as the time of Christ, Celsius enunciated the four cardinal signs of acute inflammation as redness, heat, swelling and pain.

John Hunter (*Fig.* 1.1) was one of the first investigators to make a scientific study of inflammation, reporting in very accurate detail his observations in man as well as his experimental results in animals. It is a tribute to his skill as a scientist that it is still possible to quote his observations reported in his book—*A Treatise on the Blood, Inflammation and Gun-shot Wounds*—which was published in 1794 (*Fig.* 1.2).

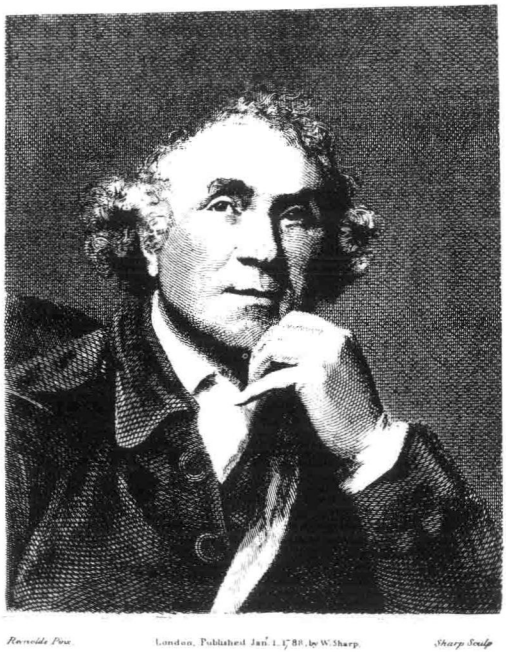
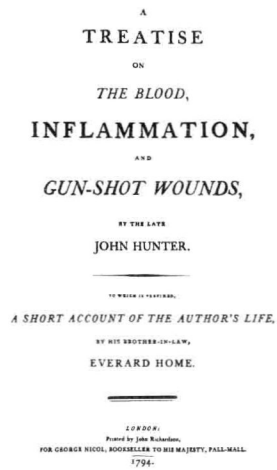


Fig. 1.1. John Hunter FRS (1728–1793). From the original by Sir Joshua Reynolds, Hunterian Museum, Royal College of Surgeons of England.



A

TREATISE

ON

THE BLOOD,

INFLAMMATION,

AND

GUN-SHOT WOUNDS,

BY THE LATE

JOHN HUNTER.

TO WHICH IS PREFIXED,

A SHORT ACCOUNT OF THE AUTHOR'S LIFE,

BY HIS BROTHER-IN-LAW,

EVERARD HOME.

LONDON:

Printed by John Richardson,

FOR GEORGE NICOL, BOOKSELLER TO HIS MAJESTY, PALL-MALL.

1794.

Fig. 1.2. Title page of *A Treatise on the Blood, Inflammation and Gun-shot Wounds* by John Hunter, published in 1794.

Even nearly 200 years ago he realised the importance of the subject: 'This operation of the body termed inflammation requires our greatest attention, for it is one of the most common and most extensive in its effect of any in the animal body'.

During his experimental work, Hunter showed that the local heat as well as the redness produced during inflammation was probably due to the vasodilatation of the local blood vessels and that the blood was the source of heat. He went on to observe: 'The parts inflamed . . . become to appearance more vascular than when in the natural state . . . both from new vessels being set up in the inflamed part . . . beside the vessels of the parts are enlarged'.

He pointed out a simple fact about the redness which is not always appreciated even today in definitions of inflammation. The blush is only 'the first act of inflammation . . .' and not inflammation itself: '. . . inflammation sets out from this point'.

On the third cardinal sign, swelling, Hunter writes: '. . . and afterwards a new action begins which is probably first a separation of coagulating lymph (plasma) and the throwing it out of the vessels'. 'The increase in volume is owing to the extravasation of the coagulating lymph and serum in proportion to the inflammation . . .'. Hunter not only appreciated the two earliest signs of inflammation, vasodilatation and plasma exudation, and managed to observe and describe them separately, but also reported '. . . both the colour and swelling correspond very much, since they both depend on the same principle . . .'.

This interesting point of the relationship between blood flow and oedema formation will be discussed at some length in Chapter 7 in connection with a mechanism which involves the collaborative actions of two types of chemical mediator.

Concerning the fourth cardinal sign, pain, Hunter reports in his book (*see Fig.* 1.3).

> The quantity of natural sensibility is, I believe, proportioned to the quantity of nerves, under any given circumstance; but I apprehend, the diseased sensibility does not take place at all in this proportion, but in proportion to the diseased action of the materia vitæ. Thus a tendon has very little sensation when injured in a natural state; but let that tendon become inflamed, or otherwise diseased, and the sensation shall be very acute.

Fig. 1.3. Quotation from *A Treatise on Blood, Inflammation and Gun-shot Wounds.*

Thus he formulated a simple view of hyperalgesia which, although straight-forward to us now, was relatively novel 200 years ago. Again, we can now offer some explanation of hyperalgesia in terms of the modulating effect of certain chemical mediators on nerve endings (*see* Chapter 5).

Hunter was therefore able to conclude: 'I shall call by the name of inflammation, whatever produces the following local effects, *vis.* pain, swelling, redness'. At that time, research was directed mainly to description and attempts to interpret the meaning of inflammation in terms of the body as a whole.

Much of the more recent research on inflammation has been devoted to trying to find the chemical mediators which are responsible for causing the cardinal signs and the mechanisms by which they are produced and released. Although this task is by no means completed, it has become clear that there are many factors involved and almost all of them in some way alter the activities of the others. This interrelationship varies from a many-fold amplification to suppression of one system by another.

EARLY MICROSCOPIC STUDIES

Another aspect of inflammation was opened up by the use of the microscope, with the studies of Cohnheim on the migration of white corpuscles from the blood vessels into the tissues and Metchnikoff, who advanced the theory that phagocytosis was the central phenomenon. Cohnheim, in the second half of the 19th century,

described the pathophysiology of inflammation based on his experiments on the frog's eye. After touching it with a stick of caustic, he found the edge of the necrotic area had become infiltrated with white blood cells. Cohnheim's research focused attention on the vascular changes in inflammation and their consequences—the exudation of fluids and migration of white blood cells into inflammatory sites.

Metchnikoff developed his primary interest, around the end of the same century, in the cellular basis of inflammation. He argued that the only way an organism could rid itself of a microbial infection was by phagocytosis and intracellular destruction of organisms.

HUMORAL THEORIES

The humoral view of inflammation supported by Cohnheim argued for the initial response arising from the blood and tissue fluids (*Fig.* 1.4). We know from our present knowledge that these fluids do in fact contain complex enzyme cascade systems which are responsible for many features of inflammation (Chapter 2). These systems have close links to one another, each having products which affect other systems at some stage. The cascade of enzymes makes up an amplifying system producing a multiplicity of mediators duplicating several times the signs of inflammation so that, if one system fails, another can take over. Within these mediator-producing systems are also important moderating factors which ensure that the inflammatory response is normally self-limiting (Chapter 3). These controlling influences include enzyme inhibitors, enzymes which inactivate the mediators and suppression of cellular activities.

CELLULAR THEORIES

The alternative view to humoral inflammation was that of Metchnikoff, who maintained that the cells which appeared during the inflammatory process were the chief protection of the body against microbial infection (*Fig.* 1.5). So whilst Cohnheim suggested that it was the blood vessels which first responded to the inflammatory stimulus, Metchnikoff insisted that it was the circulating phagocytic leukocytes which provided the initial response.

With our present knowledge, it seems difficult to imagine that either view is not of the greatest importance, since they are so inter-related (*see* Chapter 7). For example, complement components cause the release of histamine from mast cells, increase vascular permeability and attract various kinds of leukocyte to perform their functions at the

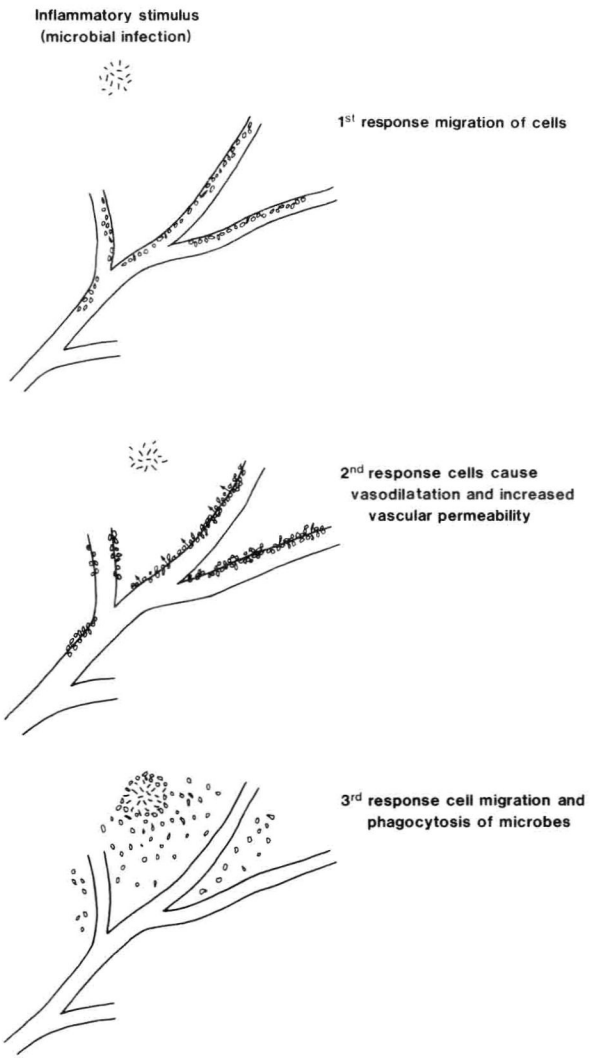


Fig. 1.4. The humoral basis of inflammation. Cohnheim supported the view that the initial inflammatory response resided in the blood vessels. Although the concept of chemically mediated effects was not then appreciated, his view was that the vessels responded to the stimulus by dilating and increasing their permeability. These procedures allowed for the circulating white cells to escape into the tissues to phagocytose the microbes.