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To all those investigators who paved the way for our present understanding of inflammation and its regulation, and to our wives, secretaries, and others without whose loyal support these chapters would not have been written

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Preface

Callimachus, the Alexandrian poet, once wrote: "A big book is a big evil." On the whole, we must agree with this view. This two-volume work is therefore a compromise between trying to lessen this evil while still doing justice, with an adequate review, to the tremendous outlay of effort and ingenuity expended by physicians, chemists, and experimental biologists through the years in seeking new drugs to treat arthritis and other severely debilitating chronic inflammatory diseases.

This treatise is a review of the current status of antiinflammatory research from the laboratory to the clinic. It is directed toward the student and investigator concerned with the design of new and better agents and with their critical evaluation in the laboratory and in man. Emphasis is given to factors which could lead to new and better agents.

One of the advantages of having a multiauthored volume is to introduce a variety of viewpoints. Authors have been encouraged to express their personal opinions. Inevitably there is a certain amount of duplication and even contradiction among some of the individual contributions. Some of the reviews are the first generally available in English. We hope they may provide a suitable foundation and appropriate stimulus for the preparation of more evenly balanced, second generation surveys at some time in the future. Certainly this present offering owes much to its antecedents, the reviews and literature surveys which have accumulated over the past twenty years. A list of some of the more recent reviews can be found in Volume I following the Introduction for the benefit of those who wish to read the earlier literature not detailed in the succeeding chapters.

The work is divided into three parts, presented in two volumes. The first part, comprising one chapter only, discusses the medical background and describes the current therapy for the more prominent inflammatory diseases. The chemistry of diverse types of compounds with antiinflammatory activity

is then surveyed in the remaining chapters of Volume I, comprising the second part. The last four of these chapters deal with gold compounds, corticosteroids, colchicine, allopurinol, and some natural antiinflammatory agents, including their special pharmacology as well as chemistry. The more general biological properties of antiinflammatory (and immunosuppressive) agents are then discussed in the third part which comprises this volume. Two of the chapters are devoted to the clinical assessment of these agents in man and the concluding chapter to some aspects of metabolism related to the design and evaluation of antiinflammatory drugs.

Regrettably, it has not been feasible to include any systematic discussion of topical antiinflammatory agents other than the steroids. The inadequacy of current assays has necessarily obscured the possible utility of such agents as dimethyl sulfoxide or glycyrrhetic acid derivatives, to mention but two types of locally active agents, as "leads" in developing new drugs to treat rather localized inflammatory states. Several topics have inevitably received less attention than they deserve. To those investigators whose work has been undervalued or, worse still, ignored, we offer our regrets and apologies.

Whatever merits this treatise possesses lie with the contributing authors, each of whom found time amidst a full and active schedule to share his insights and enthusiasm with us and cheerfully accepted the thankless burden of authorship. For its shortcomings, only the editors are responsible.

We would like to acknowledge our gratitude to Riker Laboratories, Inc., for assisting us in many ways, to Rosemary Baatz for preparing the Subject Index, and to the staff of Academic Press for their patience, encouragement, and ready assistance in translating this book from a nebulous concept into concrete reality.

While this work was in preparation we were saddened to hear of the death of C. V. (Steve) Winder (1909–1972) who contributed greatly to our present understanding of the pharmacological control of inflammation. Through his life and his work he was an inspiration to many who knew him.

ROBERT A. SCHERRER
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Chapter 1

Introduction and Background to the Regulation of Inflammation and the Immune Response

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> To cure degenerative diseases will require pharmacological sharpshooting—in the technical sense, the use of drugs with a very high specificity of action.
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> Drugs have been successful in knocking out microbes because high specificity is not essential to that task. [Here] the targets are organisms whose physiology differs from that of man; there is therefore, a reasonable probability that a drug damaging to microbes will not seriously damage the human body. But in degenerative disease the target is some abnormal process of the patient's own body. Generally physicians do not know precisely what process is at fault; even if they did, they would still face the delicate task of correcting the deranged process without disrupting other, normal processes on which life depends [W. Modell *et al.* (1967)].

I. THE COST AND BENEFIT OF INFLAMMATION AND ITS THERAPY

Because this is a book primarily concerned with drugs and their development, no apologies need be made here for neglecting to include in this volume any systematic survey of the biology of inflammation, especially as experimentally induced in small laboratory animals. Fortunately there are now available some excellent treatises on this subject (see Section XIII) and it continues to receive much attention from experimental pathologists around the world. A few notable laboratories are making outstanding contributions to our current knowledge of the nature of, and interplay between, various component factors that determine both the onset and sustenance of the immune response in animals and man. To be regretted, however, is the comparatively scanty literature dealing with the "other half" of the subject of inflammation—particularly its remission or natural regulation—and, with the more theoretical and comparative aspect of why it is generally manifest to a lesser degree in lower forms of life. Although we know that the immune response may be quite well developed in reptiles and fishes, these lower forms seem to be altogether less responsive to powerful irritants, such as Freund's adjuvants or histamine, than the higher forms of animals. In terms of a cost : benefit ratio, it is sometimes hard to comprehend as (presumably) being of benefit to the host, the more catastrophic tissue injury at higher body temperatures that accompanies attempts to remove, via the phenomenon we call inflammation, the irritant or inflammagen in warm-blooded animals. Even if we accept the axiom that nature is blind and indiscriminate in her dealings, it is sometimes still hard to accept or indeed explain the crippling inflammatory diseases as being merely manifestations of the same life-preserving mechanisms that ensure the survival of the individual in the face of the continual threat of parasitism and possible loss of the purity of "self." In a delightful article, Lewis Thomas (1971) has given a fascinating insight into inflammation as a means to counterbalance a natural trend to symbiosis —a powerful force that has evolved to balance another of equal thrust.

However, regardless of what may have been the driving force that led to

the evolution of the highly developed inflammatory response in mammals, we must still ask whether it is sensible and realistic to try and modulate the overall inflammatory disease to a degree where we can expect less cost in terms of tissue injury or pain but still obtain the same degree of benefit, including natural protection from all other competing forms of life on this planet, even from neoplastic mutations of self." Recent experience with powerful immunosuppressants, used to mitigate destruction of allogenic tissue grafts, has clearly shown the fearful risk that this particular therapy entails, as it often permits the establishment of tumors in formerly resistant hosts. The story of King Pyrrhus is not merely legendary, although clearly based in history*; it is also a contemporary allegory for the ever continual dilemma in therapeutics: Does the likely benefit truly justify the risk (cost)?

Rephrasing this last question, we may ask: Will it ever be feasible to effectively suppress inflammation with yet more specific exogenous drugs than are currently available without paying the high cost that we do today using the corticosteroids, gold preparations, or immunosuppressive drugs? The optimists and pessimists will certainly be divided over the answer to this question. The pessimists may with some justification point to the history of drug research in this area. This can be summarized bleakly as the discovery of very effective but relatively toxic agents, such as cyclophosphamide, some highly ulcerogenic derivatives of phenylacetic acids, or some of those corticosteroids with potencies 2000 times or more of cortisol, so many of which cannot possibly be used routinely in the clinic because of the gravity of their adverse reactions. The optimists may take hope because in the natural order of things, there have evolved efficient inflammalytic mechanisms that ensure that we do not suffer chronic distress following brief exposures to venoms, surfeit of radiation, or excessive temperatures.

The progress of medicine and the art of therapeutics will be considerably enriched if we can and will only take the trouble to unravel the complexities of this marvelous homeostatic mechanism, placing due emphasis on the remission, rather than on the initiating events, of inflammation and concomitant healing. Progress in this direction may require novel experimental models but proven models of inflammation may still be of inestimable value if studied over different time spans than those normally scheduled. It is altogether appropriate that this introductory chapter should immediately follow in sequence Fisher's timely survey of some naturally occurring inflammatory regulators (see Volume I). None of these several natural products may actually be a "sufficient" inflammalytic agent in the genuine pathophysio-

*Pyrrhus (ca., 318–272 B. C.) was king of Epirus, now part of modern Albania. He fought the Romans at Heraclea in Southern Italy and soundly defeated the Roman consul Laevinus in 280 B.C., but only at the cost of such very heavy losses to his cavalry and army that this battle has been permanently memorialized as a "Pyrrhic victory" (see Plutarch's "Parallel Lives" and Polybius' "Histories," XVIII, 11).

logical context of chronic inflammation but some of them may be likely candidates for the role of endogenous regulators of the acute inflammatory response.

Turning aside from these polemical questions we shall briefly examine some of the known and conjectured mediators of inflammation and try and assemble a *dramatis personae* which play a real or imagined role in the tragic drama of debilitating inflammation. This is more than an academic exercise, for unless we attempt to do so we run the risk, by not identifying the heroes and heroines in this drama, of assuming all the identifiable participants to be villains and in our legitimate outrage, engaging in the practice of "overkill" with our therapeutic intervention.

II. LOCAL HORMONES AS INFLAMMAGENS AND MEDIATORS

We shall begin this overview by considering first the local hormones because they are indeed the first agents on the scene following a local injury. They are there first because they are formed or released *in situ* and their duration of action is usually mercifully brief. It is hard to believe that they are primarily responsible for the tissue injury of chronic inflammation, although they are undoubtedly very important in triggering the acute inflammatory state. We can arbitrarily divide these local hormones into two groups.

1. The acids, including the prostaglandins, heparin (from mast cells), the adenylates (cyclic AMP, ADP), and perhaps the lysolecithins, which promote membrane fusion phenomena; see Poole *et al.* (1970).
2. The bases, including histamine, serotonin, the kinins, the catecholamines.

Among the local hormones that act as alarm signals we can even include the various products formed when the complement system is activated and that do such astonishing things as bringing leukocytes to the scene, releasing histamine from its cellular stores, lysing cells, and promoting phagocytosis. We know from studies of the Arthus reaction in animals depleted of leukocytes by pretreatment with leukopenic drugs that complement activation in the absence of leukocytes causes surprisingly little tissue injury. This shows that local hormones are perhaps relatively innocuous in themselves and serve primarily as "alert mechanisms" rather than true effectors of tissue injury.

Nevertheless these local hormones are efficiently "turned off," either by rapid dilution within the extravascular fluids and removal in the lymph or inactivated by rather efficient, usually catabolic, enzyme systems. These enzymes are fairly ubiquitous and if not originally present within the extravascular mesenchymal tissues may be brought there by infiltrating plasma