Fundamental and Clinical Aspects of Internal Medicine

CLINICAL RHEUMATOLOGY

A Series of Volumes for the Postgraduate Course
The University of Miami School of Medicine

Edited by

John H. Talbott, M.D.

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THE UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
Department of Internal Medicine
William J. Harrington, M.D., Chairman
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GENERAL PREFACE

Four years ago the Department of Internal Medicine of the University of Miami School of Medicine inaugurated an annual series of postgraduate courses entitled "Fundamental and Clinical Aspects of Internal Medicine". The first course, prompted by many requests from area physicians and medical societies, was timed to precede by one to two weeks the initial recertification examination of the American Board of Internal Medicine.

Among the teaching materials developed for this course was a group of booklets designed to follow closely the lecture presentations of subject matter judged to be of most pertinence to internists qualified for certification. Since the course was intensive and of only two weeks duration, we realized that the material to be presented had to be carefully selected, with assumptions made concerning content presumed to be already well known and also concerning material that would not in our judgment be needed by a competent general internist, although of great importance to the subspecialist.

The course has now been given each of the past four years. Its quality has been widely noted, and many physicians both from the United States and other countries have become annual registrants. Accordingly, it was felt that the course booklets might find a wider appeal if they were professionally produced and distributed by a publisher. This objective has been concluded by an agreement with Elsevier North-Holland to publish the series of volumes.

It should be stressed that these volumes are not intended to be comprehensive. They will not cover subject matter in the breadth ordinarily found in standard textbooks, but rather will supplement standard works. In order to be useful for the review course, the books will be inexpensive, and will be updated periodically, to maintain currency with advances in their respective areas.

We acknowledge the immeasurable help of our staff coordinator, Mrs. Arlene Gunn, and the secretarial staff of the divisions who contributed in the preparation of these volumes.

JOSE S. BOCLES, M.D.
WILLIAM J. HARRINGTON, M.D.

PREFACE TO THIS VOLUME

For several years the members of the Faculty of the Symposium on Rheumatology, sponsored by the Postgraduate Division of the Department of Internal Medicine of the University of Miami School of Medicine, have prepared manuscripts on their respective subjects prior to presentation. The contents of each chapter were revised and updated annually and reviewed by the Editorial Committee before distribution. The final draft of the most recent contributions forms the basis for these current presentations.

The Symposium on Rheumatology was designed primarily for its value in teaching postgraduate students, irrespective of age or stage of professional career. However, it is believed that the merits of this book will overlap into undergraduate instruction as well, particularly when the Rheumatic Diseases are included in an Introduction to Medicine course. Since the book provides a concise description of the clinical aspects of all of the important rheumatic diseases, with particular emphasis on the various forms and subleties of clinical findings and the vagaries of treatment, such an application seems self-evident.

Except for gout and osteoarthritis, and a smattering of information regarding deforming arthritis (rheumatoid arthritis) and its variants, most of the information contained in this book was born in this century. In fact, many of the diseases as well as the terms, have been discovered or coined in the past few decades. Furthermore, although some of the usual as well as unusual conditions (for instance, ochronosis) probably existed 4 or 5,000 years ago, even the names in association with joint diseases are recent. Thus, the terms Reiter's Disease, Polymyalgia Rheumatica, Chondrocalcinosis, Whipple's Disease, Systemic Lupus Erythematosus, Eosinophilic Fasciitis, and certain types of Necrotizing Vasculitis, etc., are relatively recent. By the same token, the diagnostic procedures and tests for the various types of joint disease are new. Thus, the RA factor, the several histocompatibility antigens but especially the B27, and the significance of the complement system, all extremely valuable in the diagnosis of specific types of joint disease, have been discovered in our time.

The references listed after each subject have been selected because of their comprehensive nature or contemporary pertinence. Extended bibliographies in the chapters on the complement system and inflammation and the mediators of the inflammatory process are justified because of the many recent advances in these areas.

For the student who wants additional information, expanded discussions of various features of the Rheumatic Diseases may be found in the following:

1. Hollander, JL, and McCarty, DJ, eds: Arthritis and Allied Conditions, 8th ed. Philadelphia, Lea & Febiger, 1972, 1593 pp.
2. Rodnan, GP, McEwen, C, and Wallace, SL, eds: Primer of Rheumatic Diseases, 7th ed. JAMA 229: 661–812, 1973.

The Arthritis Division is deeply indebted to Mr. and Mrs. William L. McKnight for their continuing support of the several Division activities, including the preparation of this volume.

JOHN H. TALBOTT, M.D.
Coordinator for Teaching
Arthritis Division

CONTENTS

CLINICAL RHEUMATOLOGY

THE COMPLEMENT SYSTEM AND INFLAMMATION

DUANE R. SCHULTZ, Ph.D.

Activation of the complement (C) proteins in plasma and other biologic fluids represents an important amplifying system for producing tissue damage in many of the connective tissue diseases (1–8). Thus, the majority of these diseases have at least one feature in common: an *immunologically induced inflammation* in which C is one of the major effectors.

There are two major C pathways, the classic pathway and the alternative or properdin pathway. The classic pathway utilizes nine components in a cascade of enzyme–substrate reactions (C1, C4, C2, C3, C5, C6, C7, C8, C9), whereas the alternative pathway bypasses the early-acting C1, C4, and C2 steps but activates C3, C5, C6, C7, C8, and C9 to achieve the same final results. It is the mechanism of C3 activation that differentiates the two pathways. Several C inactivators found in normal plasma (e.g., C1, C3, and C6 activators) and at least two divalent cations, i.e., calcium and magnesium in the classic pathway and magnesium in the alternative pathway, comprise the complement system (Fig. 1 and 2).

Additional factors control the biologic activities of the pathways. The anaphylatoxic fragments that originate from native C3 and C5, as well as bradykinin from the kallikrein system, are controlled by a normal plasma enzyme with carboxypeptidase-B–like activity, called the anaphylatoxin inactivator. A single cleavage of the COOH-terminal arginine of these phlogistic peptides is the mechanism of action (9). In addition, the chemotactic properties of the fragments C3a and C5a, and $C\overline{567}$,[1] are inactivated by two factors with enzymatic activity in normal human plasma. The factors are unlike the anaphylatoxin inactivator (10).

[1]Activated C components may be designated with a bar over a number or letter (eg, $C\overline{4b2a}$) or by a lower case letter (eg, B→Ba + Bb).

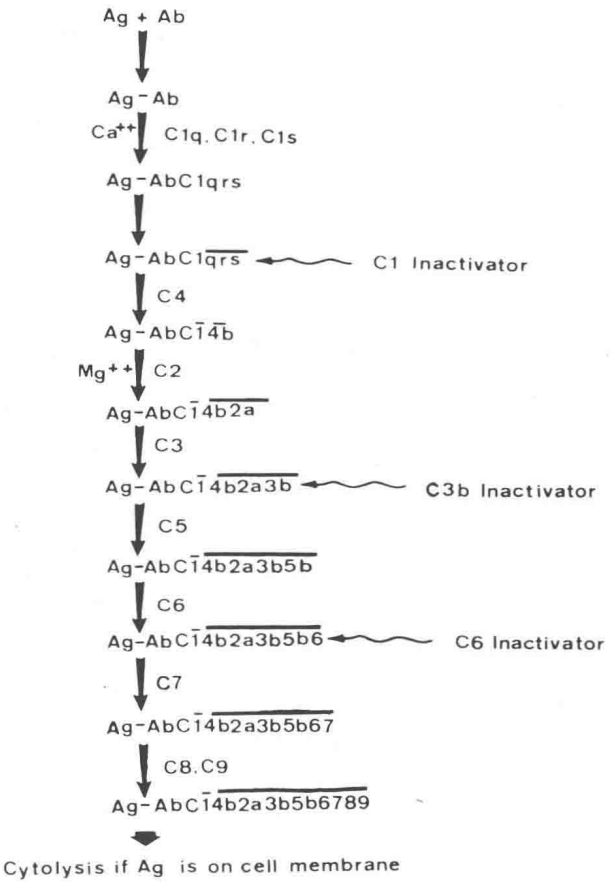

FIGURE 1. The components, inactivators, and metal cations which are involved in the classic complement pathway. A bar over a letter or number (eg, $\bar{C1}$) indicates that the component is activated. C, complement component; Ag-Ab, antigen–antibody complexes.

Immunoglobulins have an important role in the activation of both C pathways. Characteristically, the plasma and other biologic fluids of patients with diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) often contain antibodies to a number of self-antigens. Immunochemical studies of RA have concentrated on antiimmunoglobulins, just as those of SLE have centered on antibodies directed against various autologous nuclear components from, for ex-

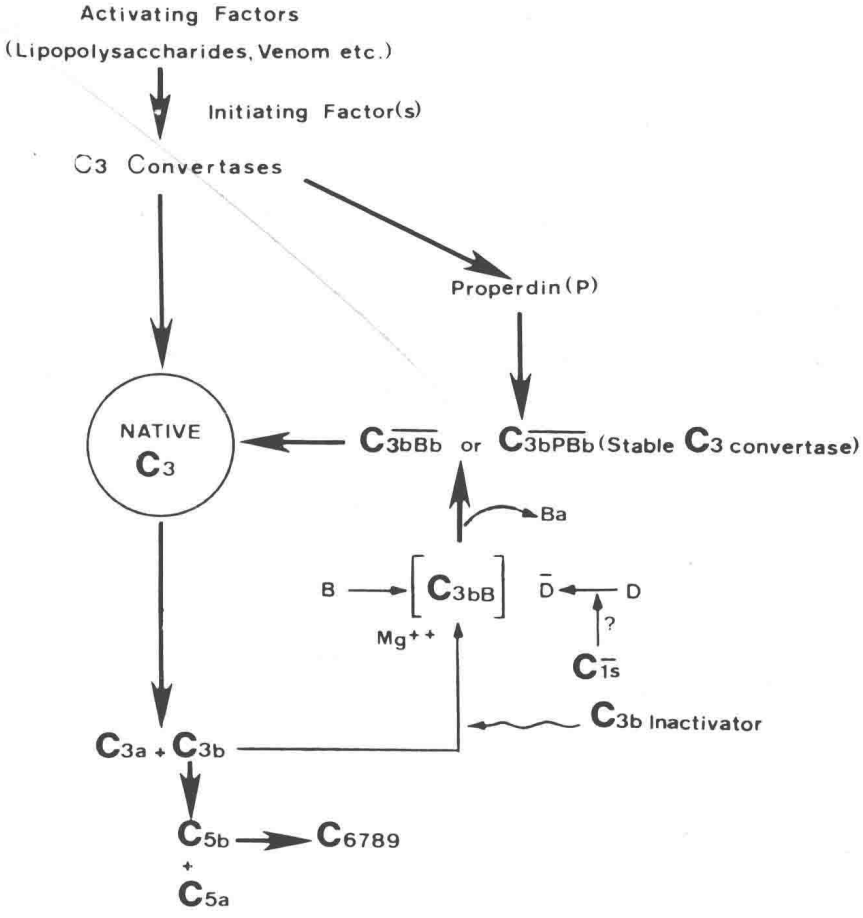

FIGURE 2. The properdin or alternative pathway for complement component activation.

ample, both DNA and RNA, blood cells, anticoagulants, and cardiolipin. These autoantibodies together with C may produce disease directly, as with the extravascular or intravascular hemolysis of red cells in autoimmune hemolytic anemia, or indirectly, as in the acute glomerulonephritis caused by circulating, soluble antigen–antibody complexes which become lodged in glomeruli. It seems likely that antigen–antibody complexes also play a major role in polyarthritis and some forms of chronic liver disease.

The immunoglobulin classes that most commonly activate the classic C pathway are IgG (subclasses IgG1, IgG2, IgG3; but not IgG4) and IgM (both 19S and 7S). In arthritis, rheumatoid factors (RF) are antibodies against the patient's gamma globulins, usually of the IgM class, but IgG and IgA have been described. The major specificity of the antibody is directed toward determinants on the patient's own IgG molecules. Because RF–IgG complexes may activate C, this reaction has phlogistic importance in the pathogenesis of RA. The reactive sites on these immunoglobulin molecules for C activation are on the Fc portion of the heavy chains (the fragment (F) of heavy chains which crystalizes (c) readily when separated from the native immunoglobulin molecule).

There are representatives of all the immunoglobulin classes which are capable of activating the alternative C pathway, provided they are in an aggregated state. In addition, certain bacterial lipopolysaccharides (endotoxins) and plant polysaccharides interact with serum components to generate factors that cleave C3 and C5 via the alternative C pathway. This pathway is also important in host resistance to microbial infection, and in causing lysis of erythrocytes in patients with paroxysmal nocturnal hemoglobinuria. Detailed discussions of autoimmune processes in RA and their role in pathogenesis are found elsewhere (2,11,12).

CLASSIC COMPLEMENT PATHWAY

The classic C pathway (Fig. 1) is initiated after macromolecular C1 (C1q, C1r, C1s held together with calcium) binds to antigen–antibody complexes via the C1q portion of the molecule. C1q has six binding sites for IgG and, probably, for IgM. Following the attachment, $C\bar{1}r$, probably through an internal rearrangement, proteolytically cleaves C1s (a serine protease) to an activated form. Although antigen–antibody complexes are perhaps the major mechanism for activating C1 in connective tissue diseases, other tissue and humoral enzymes such as trypsin and plasmin as well as lysosomal proteases are capable of this function. The C1q portion of C1 is of interest chemically because the six connecting strands on the molecule which terminate in six receptor sites have a composition similar to that of collagen. Fol-