Marker Proteins in Inflammation

Marker Proteins in Inflammation

Proceedings of the Symposium
Lyon, France, April 22-25, 1981

Editors
Robert C. Allen · Jacques Bienvenu
Philippe Laurent · Robert M. Suskind

Walter de Gruyter · Berlin · New York 1982

Editors
Robert C. Allen, Ph. D., Professor of Biochemistry
Department of Laboratory Animal Medicine and Pathology
Medical University of South Carolina
171 Ashley Avenue, Charleston, South Carolina 29403, USA

Jacques Bienvenu, M. D.
Biochemical Laboratory, Hôpital Jules Courmont
69310 Pierre Bénite, France

Philippe Laurent, M. D.
Department of Immunology, Institut Pasteur de Lyon
55 Rue Pasteur

Robert M. Suskind, M. D.
College of Medicine, Department of Pediatrics
University of South Alabama

CIP-Kurztitelaufnahme der Deutschen Bibliothek

Marker proteins in inflammation: proceedings of the symposium Lyon, France, April 22-25, 1981/ed. Robert C. Allen ... - Berlin; New York: de Gruyter, 1982.
ISBN 3-11-008225-5
NE: Allen, Robert C. [Hrsg.]

Library of Congress Cataloging in Publication Data

Main entry under title: Marker proteins in inflammation.
Proceedings of the First International Symposium on the Marker Protein of Inflammation sponsored by the Group d'étude et de recherche sur les marqueurs de l'inflammation (G.E.R.M.I.) Bibliography: p. Includes index.
1. Inflammation--Congresses. 2. Blood proteins--Diagnostic use--Congresses.
I. Allen, R. C. (Robert Chadbourne), 1924- . II. International Symposium on the Marker Protein of Inflammation (1st: 1981: Lyon, France) III. Groupe d'étude et de recherche sur les marqueurs de l'inflammation (France) [DNLM: 1. Inflammation--Physiopathology--Congresses. 2. Proteins--Physiology--Congresses.
QZ 150 M345 1981]
RB131.M35 1982 616'.0473 82-9939
ISBN 3-110-08625-5 (Germany) AACR2

Preface

The First International Symposium on the Marker Protein of Inflammation was held in Lyon, France from April 22 to April 25, 1981, under the sponsorship of the "Groupe d'Etude et de Recherche sur les Marqueurs de l'Inflammation (G.E.R.M.I.)" (President: J.L. Touraine, Lyon) with Professor Frank W. Putman, distinguished Professor of Molecular Biology and Biochemistry, Indiana University as Symposium President.

Some 320 participants from 14 different nations attended this initial Congress. 46 papers and 92 posters were presented, the majority of which appear in this volume. This volume is divided into four sections and contains presentations made either as plenary lectures or posters. The manuscripts have been divided into four major sections entitled (I) The Inflammatory Response, (II) Acute Phase Reactants, (III) Malnutrition and the Immune Response and (IV) Posters, which are subdivided further by category.

Production of these proceedings has been made possible through the cooperation of the many authors, and we wish to thank all of them for their efforts. We also appreciate, in no small way, the efforts of the staff of Walter de Gruyter, Berlin, which led to the rapid publication of this volume.

The editors would also like to express their profound gratitude to Mrs. Sharon Fields, Mrs. Mae Jean Reeves and Miss Patricia A. Corcoran of the Department of Pediatrics, University of South Alabama, Miss Brenda Altman of the Department of Laboratory Animal Medicine, Medical University of South Carolina, and Mrs. Dominique Karsenty, Laboratory of Biochemistry, Hôpital Jules Courmont, Lyon, for their outstanding efforts in manuscript-retyping and secretarial assistance.

VI

The Convenors would also like to express their sincere appreciation for the outstanding efforts of Mr. A. Roullet who acted as Secretary-General of the meeting and was always present to help the speakers and attendees, no matter what the problem or request, and also for those of his Assistant, Miss Helene Bernon. We wish also to express our appreciation to Miss Daniele Ferreboeuf, Miss Maris-Alix Fournier and Mrs. Odile Damour for their help in the smooth running of the Symposium and in hosting the social events. We would like to thank Miss Debbie Impastato as well, particularly for her aid as an interpreter to those whose French was lacking. Also, her efforts as a tour and shopping guide in Lyon were much appreciated.

We would also like to express our sincere gratitude to the Mayor of Lyon, Dr. Maurice Carraz - Director, Institute Pasteur, Lyon - and Dr. Charles Merieux as hosts of the splendid social events, and to Monsieur Jacques Barrot - Minister of Health - for governmental support.

We also wish to thank the following exhibitors who helped make this Symposium possible: Beckman Instruments (France), Biolyon, Biomerieux, Boehringer-Mannheim (France), Laboratoires Fumouze, Helena (France), Hoechst-Behring, Hyland-Travenol, Immuno (France), Sebia, Compagnie Technicon.

R.C. Allen
Charleston, SC

J. Bienvenu
Lyon, France

P. Laurent
Lyon, France

R.M. Suskind
Mobile, Alabama

Contents

Section I
The Inflammatory Response

Progress in Plasma Proteins: Hallmarks of Health and Markers of Disease
F.W. Putnam 1

Plasma Proteins Implicated in the Inflammatory Response
L.M. Killingsworth 21

Acute Inflammatory Process
P. Laurent, J. Bienvenu 33

The Inflammatory Response
D.A. Willoughby, A. Sedgwick, J. Edwards 45

Relationships between Acute Non-Specific Inflammation and Non-Specific Defense Mechanisms of the Host
M. Pelletier, I. Florentin, D. Nolibe, M. Roch-Arveiller, J.M. Jadin, J.P. Giroud 49

The Role of Thrombocytes in Inflammation
J. Benveniste 57

Section II
Acute Phase Reactants

Clinical Usefulness of C Reactive Protein Measurement
P. Laurent 69

Control Proteins of the Alternative Complement Pathway: In Vivo Correlates of In Vitro Function
S. Ruddy 89

Plasma Fibronectin, its Biochemical and Biological Properties and its Pathological Changes in Man
I. Millet, P. Laurent 99

Interaction between C-Reactive Protein (CRP) and Platelets
B.A. Fiedel, R.M. Simpson, H. Gewurz 111

Interactions between CRP and Mononuclear Cells
K.K. James, C. Mold, H. Gewurz 131

Clinical Usefulness of Orosomucoid Determination
J. Bienvenu 139

Alpha$_1$ Acid Glycoprotein - Structure, Genetics and Biological Significance
P. Arnaud, E. Gianazza 159

Alpha$_1$-Antitrypsin Structure and Genetics
P. Arnaud, C. Chapuis-Cellier, E. Gianazza 171

Affinity-Immunodeletion (AID) Isoelectric Focusing on Ultra-Thin Gels and Staining with Silver Diamine Applied to the Marker Proteins of Inflammation
R.C. Allen, P. Arnaud 185

A Survey of the Measurement, Distribution of Values and Phenotypes of the Haptoglobins
O. Hever 197

Recent Findings on the Biological Role of Haptoglobin in Rats
R. Engler 209

Biochemical Aspects of Complement Activation
M.G. Colomb, J.C. Bensa, A. Reboul 215

The Acquired Abnormalities of the Complement System in the Acute or Chronic Inflammatory Response

F. Berthoux, B. Laurent, C. Genin, J.-C. Sabatier, R. Gonthier 231

Acute Phase Reactant Protein Profiles in Cancer: An Approach to Deciphering their Message

E.H. Cooper, J. O'Quigley 239

Plasma Protein Profile: A Model of Data for Interpretation with Special Reference to Inflammatory Conditions

J.C. Frot, P. Giraudet, H. Hofmann, F. Muller 253

Section III
Malnutrition and the Immune Response

Protein-Calorie Malnutrition-Clinical Biochemical and Immunological

R.M. Suskind 277

Complement, Orosomucoid, Transferrin, Retinol Binding Protein and Prealbumin in Malnutrition

F. Touraine, G. Gay, J.L. Touraine 341

Cellular and Humoral Immunity in Malnutrition

R.K. Chandra, S. Sahni, S. Chandra 347

Immune Deficit in Kwashiorkor

J.-L. Touraine, G. Gay 355

Inhibition of Cell-Mediated Immunity by Serum Abnormalities in Protein-Calorie Malnutrition

G. Gay, J.-L. Touraine 369

Host Resistance in Malnutrition

W.P. Faulk, V. Wallis, A.J.S. Davies 381

Usefulness of Prealbumin as Nutritional Indicator
Y. Ingenbleek 405

Section IV
Posters

A. Acute Phase Reactants in Neonates

A Comparative Study of the Sequential and Coupled Determination of CRP and Orosomucoid during Neonatal Infections
F. Bienvenu, C. Chantin, L. Sann 417

CRP and Neonatal Sepsis
R. Alt, D. Willard, J. Messer, P. Métais, C. Goester 421

Characterization of a C2 Derived Oligopeptide with Biologic Activity
M. Lopez-Trascasa, M. Moisy, E. Pirotzky, Y. Blouquit, C. Blanc, A. Sobel 423

Direct Quantitation of the Complement C3 Split Product C3d in Plasma in Immunopathological Disorders
I. Brandslund, B. Teisner, S.-E. Svehag 424

Variations of Orosomucoid Levels in New-Born Twins
B. Capolaghi, O. Baubin, C. Grasmick, C. Marchal, P. Roos 427

Complement Levels in Infants of Diabetic Mothers over the First Month of Life
A.-M. Freyria, A. El Mohandes, T. Raffin, J.-P. Lamelin, B. Salle, J.-L. Touraine 429

B. Protein Status in Clinical States

Protein-Status and Malnutrition, Preliminary Results of a Prospective Study of 177 Patients
J. Jouquan, M. Garre, J.F. Menez, P. Youinou, J.F. Morin, J.M. Boles, Y. Pennec, G. Le Menn 437

Research of Relationship between Protein and Folic Acid Deficiencies

J.M. Boles, P. Youinou, M. Garre, D. Lhostis, J. Morin, J. Jouquan, G. Le Menn, C.H.U. Morvan 438

The Measurements of Plasma Proteins in Patients with nutritional Deficiency

G. Levy, G. Francois, M.-C. Liechtensteger, J.-P.Ardissone, J. Romette, J. di Costanzo, B. Mallet 439

Value of Plasma Prealbumin in the Early Recognition of Protein-Energy Malnutrition in Sahelian Children

A. Froment, L. Monjour, F. Bourdillon, A. Fribourg-Blanc, J.M. Kyelem, E. Gouba, M. Gentilini 440

Visceral and Muscular Proteins in Anorexia Nervosa: An Example of Severe Malnutrition in Industrialized Countries. Effects of Renutrition

J.L. Richard, J. Bringer, L. Monnier, J. Mirouze 442

C. Protein-Calorie Malnutrition and the Immune Response

Effects of Protein-Calorie Malnutrition on the Cell-Mediated Immune Response in Mice

G.-A. Conge, P. Gouache, P.-H. Langrange, D. Lemonnier 447

Effects of Early Under- and Over-Nutrition on the Immune Response in Mice

S. Wade, D. Lemonnier, F. Bleiberg, J. Delorme, P. Chappuis 450

D. Inflammatory Proteins in Patients with Cancer

Plasma Transferrin Level: A Preoperative Prognosis Indicator in Esophageal Cancer Patients

J.-P. Alibeu, C. Arvieux, C. Alibeu, V. Danel, R.Sarrazin 455

Usefulness of a Protein Profile as an Indicator for a Gastrostomy in Patients with Advanced Head and Neck Cancer

J.-F. Gillette, J. Susini, J. Oglobine, R.T. Saracino 457

Acute Phase Reactant Proteins and Cancer

L. Israel, R. Edelstein, R. Samak, F. Pontet, F. Rousselet, P. Giraudet 460

Plasmapheresis in Cancer Patients and Acute Phase Reactant Proteins

L. Israel, R. Samak, R. Edelstein, J. Baudelot, F. Pontet, F. Rousselet, P. Giraudet 462

Prognostic Value of the Macrophage Component of an Inflammatory Reaction Induced by Skin Abrasion in Cancer Patients

L. Israel, R. Samak, M. Samak, R. Edelstein 465

Nutritional Markers in Advanced Large Bowel Cancer

J.C. Hall, J. O'Quigley, G.R. Giles 467

Effects of Acute Phase Reactant Proteins on PHA-Induced Lymphocyte Blastogenesis

R. Samak, L. Israel, R. Edelstein 469

Effects of Acute Phase Reactant Proteins on Monocyte Chemotaxis in Vitro

R. Samak, L. Israel, R. Edelstein, M. Samak 471

E. Protein Changes in Other Clinical States

Evaluation of Inflammation Proteins, Cardiac Enzymes and Myoglobin in Myocardial Infarcts

C. Maurice, O. Vernet, J.C. Rymer, M. Roncato, M. Paris, M. Leclerc 477

Human Serum Perchlorosoluble Glycoproteins in Myocardial Infarct

M. Succari, M.-J. Foglietti, F. Percheron 480

Elevated C-Reactive Protein Levels in Sarcoidosis Patients

J.-F. Mornex, J. Brune, J.-P. Revillard, C. Vincent 483

Determination of Plasma Fibronectin Concentration in Pulmonary and Circulatory Failure

J. Labrousse, J.M. Coulaud, J.P. Salmona, A. Tenaillon, J. Lissac, P. Beyne, J. Rapin, A. Jacqueson, D. Allard, H. Jerome 486

Protein, Alpha$_1$ Antitrypsin, Lysozyme in Broncho-alveolar Lavage Liquid in Case of Sarcoidosis

J.-J. Buneaux, H. Gosselin, F. Buneaux, P. Leclerc 489

Macrophage Phagocytic Activity and Lysozyme Concentration in Bronchoalveolar Lavages

S. Guibaud, A. Simplot, A. Plumet, J.C. Guerin 491

Determination of Human Serum Complement Using the Hemolytic Radial Immunodiffusion Micromethod during Ventilatory Tests of Allergenic Provocation in Asthmatics

F. de Massia-Castex, M. Bastide, J.-M. Bastide, Ch. Seignalet, F.-B. Michel 493

Inflammation Markers in Patients with Pulmonary Pathology

N. Biot, A. Revol, R. Harf, Y. Pacheco, M. Perrin-Fayolle 496

Usefulness of C-R P /C4 - 1 Index of Detection and Prognosis of Septic States in the Burn Patients

P. Laurent, J. Marichy 497

Assessment of Appropriate Laboratory Measurements to Measure Crohn's Disease Activity

C. André, L. Descos, F. André, F. Paille, S. Perrin 503

Assessment of Appropriate Laboratory Measurement to Measure Ulcerative Colitis Activity

L. Descos, C. André, F. André, F. Paille, S. Perrin 505

Diagnostic and Prognostic Value of the Plasma Variations of Prealbumin and Transferrin in the Post-Operative Period of Gastrointestinal Tract Surgery - Preliminary Results

J.F. Zazzo, D. Vauzelle, A. Abella 507

Serum C-Reactive Protein Assay in Renal Transplantation
J.-P. Revillard, M. Laville, C. Vincent, J. Traeger 509

Relation between the Quantity of Serum Lysozyme and the Amount of Succinatedehydrogenase (SDH) and Alpha-Glycerophosphate-Dehydrogenase (alpha-GDPH) on Activated Lymphocytes Membranes as a Possible Index of the Immune Response after Human Renal Transplantation
K. Metodiev 511

Study of Some Markers of Inflammation (C Reactive Protein, Haptoglobin, Orosomucoid) in Chronic Inflammatory Articular Rheumatic Diseases
F. Bertrand, X. Herbeuval, P. Paysant, G. Faure, A. Gaucher 513

Levels of Serum C9 Complement Factor in Various Chronic Inflammatory Articular Rheumatic Diseases
P. Montagne, G. Faure, M.-Ch. Bene, A. Gaucher, J. Duheille 516

Modifications of "Inflammatory Proteins" (Transferrin, Orosomucoid, Coeruloplasmin, Alpha-1-Antitrypsin in Human Gonadotropin Induced Ovulation
S. Ferrand, F. Touraine, H. Dechaud, B. Claustrat, C. Quincy, J.M. Thoulon 518

Changes of Distribution of Glycosylated Forms of Human Orosomucoid and Alpha-2-HS Glycoprotein during Inflammation and Pregnancy: Study by Isoelectric Focusing and Crossed Immuno-Affinity Electrophoresis
I. Nicollet, J.-P. Lebreton, M. Fontaine, M. Hiron 520

Variation of C Reactive Protein in Serum Following Severe Skull Trauma
C. Goester, G. Férard, A. Bourguignat 524

Studies on some Blood Proteins in Medullary Patients
B. Sallier, G. Pilonchery, J. Depassio, P. Minaire, A. Revol 528

The Prostaglandin Induced Acute Phase Response and its Failure in Scleroderma
J.T. Whicher, M.F.R. Martin, P.A. Dieppe, L. Marshall 535

F. Acute Phase Reactants in Rodents

Serum Amyloid P Component in the Rat: Isolation, Characterization and Original Features
M. Pontet, M. d'Asnières, R. Engler, J. Escaig 541

Transcortin (CBG) Actitivities, Endogenous Corticosterone Levels and other Serum Parameters in the Course of the Acute Inflammatory Reaction of the Rat
L. Savu, H. Zouaghi, Ch. Lombard, E.A. Nunez 544

Secretion of 3 Proteins during Experimental Inflammation in Rats
F.N. Dinh, J. Davy, M. Appel, G. Durand, J. Féger, J. Agneray 547

Identification of Intracellular Acute Phase Proteins in the Liver of Mice by Crossed Immunoelectrophoresis
H.-B. Oh, T.C. Bøg-Hansen 550

Studies on the Mechanism of the Prostaglandin Induced Acute Phase Response; its Failure in Endotoxin Tolerant Animals
J.T. Whicher, J. Unwin, A. Bell, P. Southall 552

G. Proteinase Inhibitors

Inhibition of Formation of the Human Amplification C3 Convertase by Fluid Phase Polycations
F. Maillet, M.D. Kazatchkine 557

Determination of the Degree of Desialylation for Orosomucoid and Alpha$_1$ Antitrypsin. Application to Rheumatoid Polyarthritic Sera
M. Bordas, N. Serbource-Goguel, D. Biou, J. Féger, G. Durand 558

Proteinase Inhibitors Controlling Biologic Activity of Lymphoid Tissue Cells

F. Baranova, A. Berman, L. Popova, Y. Zaretskaya 561

Binding of Alpha-1-Antitrypsin Specific Antibodies to Human Lymphocytes: A Flow Cell Microfluorometry Study

J. Bata, G. Cordier, J.-P. Revillard 563

Suppression of Antibody-Dependent Lymphocyte Mediated Cytotoxicity by Human Alpha-2 Macroglobulin

G. Cordier, J.-P. Revillard, M. Latour 565

H. Methodology

Protein Evaluation of Populations in Intertropical Regions

A. Fribourg-Blanc, P. Druilhe, L. Monjour, B. Carme, D. Richard-Lenoble, M. Gentilini, P. Carnevale, J.F. Trape, J.F. Molez, E. Bois 569

Immunophelometric Quantitation of C.R.P. - Importance of Samples Storage

H. Bernon, J. Bienvenu, M. Perouse de Montclos, A. Roullet, P. Laurent 573

Pre Albumin Titration Using a Rate Nephelometer. Critical Study. Applications in Nutrition and Oncology

J. Oglobine, M. Meslin, C. Bouchet, R.T. Saracino, J.-F. Gillette, J. Susini 575

Plasma Fibronectin: Its Dosage in Clinical Biology

M.-L. North, Y. Dudt, M. Schwartz, J.-P. Cazenave, S. Rabinovitch, B. Audhui, P. Ciret 579

Quantitative Immunoelectrophoretic Methods

R. Guinet, S. Gabriel 582

Protein Profile in Surgical Intensive Care

M.C. Diemert, J. Galli, A. Galli, F. Baud, F. Rouillon, P. Glaser 586

Section I
The Inflammatory Response

PROGRESS IN PLASMA PROTEINS: HALLMARKS OF HEALTH AND MARKERS OF DISEASE

Frank W. Putnam
Department of Biology, Indiana University
Bloomington, Indiana 47405, USA

Introduction

In recent years great progress has been made in knowledge of the plasma proteins and of their role in health and disease (1-4). The advances include better methods for identification and isolation, ultrasensitive and precise techniques for quantitation, better knowledge of their metabolism and of their interaction with each other and with cell surfaces. Complex cascades of enzymatic reactions such as blood coagulation, complement action, fibrinolysis, and kinin formation are being dissected and reassembled on a molecular basis. The intricate interactions of these cascades are being delineated, and their myriad pharmacologically active products--both proteins and peptides--are being discovered. The periodic table of the immunoglobulins is now probably complete with the recent determination of the structure of human IgD in my laboratory (5). The complete amino acid sequences and in a few cases even the three-dimensional structures of a number of human plasma proteins are already known, and much more is on the way. Gene sequencing is revealing startling new discoveries such as the phenomenon of skipping genes and may be on the verge of deciphering the mechanism of genetic control of expression and regulation (6-8).

Many of you on the symposium committee, speakers on the program and others in the audience have been participants in

Marker Proteins in Inflammation

this parade of progress. Some in basic research, others in laboratory medicine and clinical research. Our program will assemble and integrate the many diverse themes I have referred to into a holistic view through our three topic sessions: 1) Protein Profile in Malnutrition; 2) Protein Profile in Inflammation, and 3) Future Trends on Acute Phase Proteins.

My purpose today is to give you an overview of recent progress in plasma proteins, to relate this progress briefly to the three major themes of the Symposium, and then to illustrate the highlights of some of our current work on human IgD as it relates to the themes of the Symposium.

Progress in Plasma Proteins

According to an exhaustive survey made in 1975 (1, 2), about 86 human plasma proteins had been described, but the function was known for only about a dozen (see Table I, Ch. 2 of Ref. 1). Today, about 100 have been purified and the function is known for about 40 including many trace proteins. In 1975 there was a scarcity of structural data on human plasma proteins (see Table II, Ch. 2 of Ref. 1); in 1981 there are probably more amino acid sequence data on human plasma proteins in press or ready for publication than were extant in 1975. To use immunoglobulins as an example: In March 1965, when we reported our first sequence data for a Bence Jones protein (9), the world's literature then contained a total of only about 50 amino acid residues of immunoglobulin sequence. By 1979 even before DNA sequencing began, about 47,500 residues had been published. The rate has been increasing exponentially since the advent of the commercial automatic protein sequencer and is doubling every three years, and DNA sequencing will soon shorten the doubling time. However, it is not the rate of accumulation of data that I want so much to emphasize but rather the pace of increase of molecular understanding of antibody specificity, structure, and genetic control.

Nonetheless, as I will outline later, we still have much to learn about the biological effector functions of the Fc domain, such as the site and mechanism of complement fixation, cytotropic reactions, and binding to cells. And these are the antibody functions that are critical to many inflammatory processes. Whole systems of plasma proteins besides the immunoglobulins have been thoroughly investigated. Much progress has been made with the coagulation proteins especially the serine proteases, the antiproteases, and the complement system. The mechanisms of transport of metal ions, heme, drugs, and organic ligands are being elucidated, and the importance for human health of the interaction and competition of these processes is being clarified. As we shall see in this Symposium, inflammation is involved in many of these processes.

Despite the parade of progress in plasma proteins much remains to be learned. As yet, we know the function of less than half of the 100 or more readily detectable plasma proteins, and we are hardly aware of the hundreds of lesser components, some of which may have important physiological roles. C-reactive protein is the prototype of the acute phase reactant. Yet serendipity led to its discovery 50 years ago through the lucky accident that it forms a specific precipitate with the C polysaccharide of pneumococcus, and this was observed in the leading laboratory for study of pneumococcal polysaccharides. Still today we are only beginning to learn the biological function of CRP. How many such marker proteins remain to be discovered? In previous reviews I have listed a dozen alpha and beta glycoproteins in search of a function (1, 4). Conversely, I could name a dozen other proteins that were isolated, characterized, and named before their function was discovered and then found to be already known under another name related to their function. One example is fibronectin, the plasma form of which was long known as "cold-insoluble globulin". The role of this cell surface glycoprotein in cellular interactions remains to be clarified, and we look forward to

Dr. Laurent's discussion of fibronectin.

Theme 1 - Protein Profile in Malnutrition

Although plasma protein represents only about 2% of the tissue protein mass, the ease of sampling and of analysis early led to many studies of changes in total plasma proteins in severe human malnutrition or as the result of protein depletion in experimental animals. This early work has been rather critically reviewed by Garrow (10) who emphasized three aspects: 1) the interaction of plasma protein levels and tissue protein stores, where the greatest effect is on liver, 2) the diagnostic value of plasma proteins as a measure of nutritional stress, and 3) dynamic changes in plasma protein metabolism. However, in recent years the emphasis has focused on two more significant phenomena that are the subject of the first theme of this Symposium, i.e. 1) general and specific effects of malnutrition and concurrent infection on humoral and cellular immunity, and 2) specific effects on the plasma protein profile such as characteristic decreases in certain proteins other than the general indicator, serum albumin.

An important question to ask is whether the effect on the plasma protein profile caused by malnutrition or marasmus, or more generally by protein-calorie malnutrition, is mainly a general change in profile or whether there is some specific and significant effect, for example on the immune response. Last year this question was the subject of an entire symposium on nutritional deficiency, immune responses, and infectious illness that was chaired by Dr. Chandra (11). At our Symposium, he, together with Drs. Page Faulk, Touraine, and Gay will lead the discussion on our first theme--Protein Profile in Malnutrition. In this matter it is difficult to separate the individual roles of malnutrition, infection, and socio-cultural status. We will look forward to their efforts to dissect the effects of these conditions both on cell-mediated immunity

(CMI) and on humoral immunity and to seek to identify the ways in which specific nutritional deficiencies may alter CMI responses.

In contrast to the current indication of possible specific effects of nutritional deficiencies on the CMI response, is the apparently benign effect on humoral immunity. In the absence of severe infection, serum IgG, IgA, and IgM levels are usually normal or somewhat increased; though, to be sure, serum IgE may be elevated and complement levels decreased (12). Thus, current interest centers on specific effects on the plasma protein profile, notably the profound deficit of transferrin in kwashiorkor, as well as the decline in ceruloplasmin, β-lipoproteins, and in other proteins to be discussed by Touraine.

Theme 2 - Protein Profile in Inflammation

The terms "acute-phase proteins," "acute-phase reactants," and AP-proteins or AP-reactants have traditionally been used to denote plasma proteins whose concentration increases significantly in the acute phase of inflammatory processes, and often in pregnancy, cancer, and various diseases (13). Originally the AP-proteins represented an uncharacterized group consisting mainly of α-glycoproteins with two characteristics in common: the presence of carbohydrate and synthesis in the parenchymal cells of the liver. These are not very clear distinguishing features because all typical plasma proteins except immunoglobulins are synthesized in the liver, and virtually all plasma proteins are glycoproteins except for albumin, retinol-binding protein, and notably C-reactive protein - the archtype of AP-reactants. Much of the early literature dealt with seromucoid, an α-glycoprotein fraction of plasma which contains α_1-glycoprotein (orosomucoid) as its major component. As summarized in Table I, in recent years the principal AP-reactants have been isolated and well characterized. In most

TABLE 1. Properties of Acute-phase Reactants of Human Plasma

Protein	Symbol	Molecular Weight	pI	Carbohydrate content (%)	Amount in normal plasma (mg/100 ml)	Sequence
α_1-Acid glycoprotein (orosomucoid)	α_1S	40,000	2.7	41.4	55-140	complete
α_1-Antitrypsin	α_1AT	54,000	4.8	12.4	200-400	advanced
Ceruloplasmin	Cp	135,000	4.4	8.0	15-60	half-done
C-reactive protein	CRP	$(21,500)_{5-6}$	?	0	<1	complete
Haptoglobin (type 1-1)	Hp	86,000	4.1	16.4	100-200	complete
Fibrinogen	-	341,000	5.5	2.5	200-450	complete

cases even their amino acid sequence has been determined. New quantitative immunochemical methods have facilitated their individual measurement. Their biochemical and biological properties have been thoroughly investigated, and the results of these studies will provide a major theme for this Symposium on Markers of Inflammation.

Biochemical properties of the acute-phase reactants. In study of Table I and Fig. 1, one is struck by the heterogeneity of the characteristics of AP-reactants. Though a significant carbohydrate content is said to be a characteristic, C-reactive protein (CRP) is devoid of carbohydrate, whereas orosomucoid (α_1-acid glycoprotein; α_1S) has about 41%, about the highest of any plasma protein. Though most are α-globulins, fibrinogen is not. The AP-proteins are unrelated in amino acid sequence, and polypeptide chain structure. Likewise, they differ in their known biological functions; two (ceruloplasmin, Cp; and haptoglobin, Hp) are transport proteins, one is a protease inhibitor (α_1-antitrypsin, α_1AT), one a coagulation factor (fibrinogen), and two have unknown or yet to be defined functions (α_1S and CRP). The molecular weights span

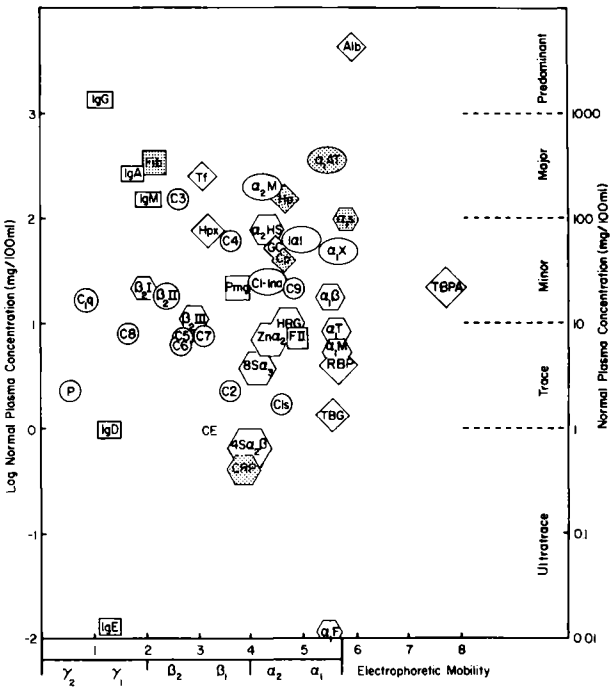

Fig. 1. Scatter diagram of the approximate normal mean concentration of some 50 human plasma proteins. The concentration is plotted to a logarithmic scale (ordinate), and the protein is located by its mobility at pH 8.6. The proteins are denoted by standard symbols (1-4). The five classes of immunoglobulins are at the left of the diagram and are enclosed in rectangles. Components of the complement system and properdin pathway are enclosed in circles, antiproteases in rectangles, albumin and specific binding proteins in diamonds, and a series of miscellaneous alpha and beta globulins in hexagons. Modified from Putnam (14). AP-reactants are cross-hatched.

an eight-fold range. The isoelectric points vary. Perhaps most important, the normal concentration range varies from almost zero for CRP to values up to 200 to 400 mg/100 ml for fibrinogen and α_1-antitrypsin, which are about the third and fourth most abundant plasma proteins. Whereas most AP-reactants double or so in concentration at the height of the inflammatory process, CRP undergoes an exponential increase of almost 100-fold. In the rat, two AP-reactants (α_1-AP globulin and α_2-AP globulin) can be induced by trauma and inflammatory

agents, but their counterparts in human plasma are not clear. They may be related to the human pregnancy-associated glycoproteins described by Bohn (15); he designated the pregnancy-associated proteins as β_1AP (acute phase) glycoprotein and α_2AP (acute phase) glycoprotein and has shown that they both bind steroid hormones. One is reminded that the biosynthesis of the major acute phase proteins of plasma is modulated by the action of known hormones on the liver, and some are affected by oral contraceptives.

Table I lists only the so-called classical acute phase reactants in human plasma; it omits lesser-known human AP-reactants such as the pregnancy-associated glycoproteins (15) and also the α-AP globulins inducible in the rat by trauma or injection of irritants. There may indeed be other trace proteins similar to CRP (e.g. some carcinofetal antigens) that may yet qualify as AP-reactants. The remarkable thing is how much we know about the physical properties and structure of the AP-reactants listed in Table I and how little we understand their function in the acute phase response. Complete amino acid sequence data is available for all AP-proteins listed in Table I except for α_1-antitrypsin, for which the structural study is far advanced, and ceruloplasmin, for which we have already reported half the sequence (564 residues) (16, 17). Again excluding α_1AT, all these proteins have been crystallized, but no crystallographic structures have yet been reported. Genetic polymorphism has been identified in all cases except CRP, and specific deficiencies have been found for all but orosomucoid. How these factors influence the acute phase response in the affected individuals is not known.

With all this knowledge of the biochemical properties of the acute phase proteins, it is surprising how little we know of even the physiological functions of some of them, such as orosomucoid, CRP, and the pregnancy-associated glycoproteins; this is in addition to our lack of understanding of their role

in the acute phase response. However, though we may not know all their individual functions, the acute phase response in general seems beneficial in that its roles appear to be to prevent a spread of local inflammatory tissue damage and to induce repair processes. This role may be mediated by interaction of one or more of the AP-proteins (or their cleavage products) with leukocytes or other cells involved in immune and phagocytic processes. In this regard, we will have special interest in the interaction of CRP with lymphocytes and platelets to be described by Gewurz and Fiedel. How can we reconcile these diverse characteristics as common to a single process - probably only by looking at the site of the inflammation and the biosynthetic and metabolic processes. This is one of the aims of this Symposium. In conclusion, we can say that unlike the complement system, or immune complexes, or vasoactive polypeptides and lymphokines, the AP-reactants are markers of inflammation, not mediators of inflammation.

Theme 3 - Future Developments for Markers of Inflammation

I have already hinted at the third theme of the Symposium, that is, future trends in the study of markers of inflammation and their interaction with cells. Inflammation, immunity and hypersensitivity are linked at both the molecular and cellular levels. To achieve future developments we must learn more about the complex processes and interactions of the humoral immune response, the complement cascade, and cell-mediated immunity and its manifold mediators. I wish I had both the time and the insight to integrate for you the interplay of these complex processes. They involve interaction of at least four increasingly well defined plasma protein systems: the immunoglobulins, the complement cascade, and the coagulation and the kinin systems. The systems interact not only with each other but with a variety of cells: lymphocytes, leukocytes, platelets, macrophages etc. Some of these cells such as the lymphocytes are being elegantly classified into subsets

with different functions. Their products and activators are collectively known as the mediators of inflammation (18), and they include the anaphylatoxins, the kinins, the lymphokines, SRS-A, prostaglandins, lysosomal enzymes, proteases and protease inhibitors. Many workers now concentrate on the molecular and cellular biology of these systems in the hope of deriving a molecular model of inflammation comparable to that discovered for humoral immunity from intensive study of the structure and properties of the immunoglobulins. Success is coming most rapidly in unravelling the intricacies of the complement cascade. Since this is to be described by Colomb and Lackman, I will later limit myself to the highlights of newer knowledge of the immunoglobulin system, particularly as it affects inflammation.

Many new aspects of cell-protein interactions are developing rapidly. The specific interaction of antibodies and cells is being clarified through explicit information on the structure of Fc fragments and of Fc receptors on cells. The interaction of IgE with mast cells and basophils, which elicits acute immediate-type hypersensitivity, is a prime example of this. Sometimes a complex assembly process is required, as in the classical complement pathway and in the alternative pathway, both of which are being elucidated in elegant molecular detail. The nature of opsonins is still obscure, but study of the interactions of CRP with platelets and lymphocytes, of fibronectin, and of platelet-activating factor will help elucidate the basis of phagocytosis and cell adhesion.

Control mechanisms. Future directions must also focus on the control mechanisms for the synthesis and expression of markers of inflammation. We know too little about the physiological and genetic mechanisms that control the synthesis of plasma proteins especially those derived from cell surfaces. Nor do we have an exact idea as to the localization of synthesis of particular proteins in individual cells or groups of cells, or

to what extent there is independent control of synthesis of individual proteins. Are there substances released from cells in injury that activate protein synthesis by the liver? We do know that normal physiological control can involve responses to hormones that increase or inhibit synthesis or release of plasma proteins stored in parenchymal cells. Abnormalities may result from fluid and electrolyte changes induced by shock, burns, trauma, or stress. The changes may be both quantitative and qualitative, where quantitative refers to the increase or decrease of the major acute phase reactants and qualitative denotes the exponential increase in an inflammation marker such as CRP or a carcinofetal antigen such as alphafetoprotein. Trauma and tissue breakdown may release intracellular proteins, especially neutral and acid proteases, tissue-specific isoenzymes, lysozyme, etc. Since these inflammation markers are not true plasma proteins, I have referred to them as "passenger proteins" (1, 4). In addition, the triggering of enzymatic cascades such as those of coagulation, complement, and fibrinolysis can generate new components and bioactive peptides such as anaphylatoxins, kinins, fibrinopeptides, etc.

Biological Effector Functions of Antibodies as Illustrated by Recent Studies on Human IgD.

Structure and function of antibodies. I will use our recent findings on the structure of human IgD (5, 19) to illustrate some still unsolved problems of the multiple functions of immunoglobulins. By now, everyone is familiar with the principles of the structure of antibodies, which are exemplified by the model of IgD given in Fig. 2. Up to now, greatest emphasis has been placed on the nature of the antigen combining site and how this is determined by the structural variability of the V regions. There are two identical combining sites in the Fab region, each determined by the V regions of the light and heavy chains. Though the development of our knowledge of

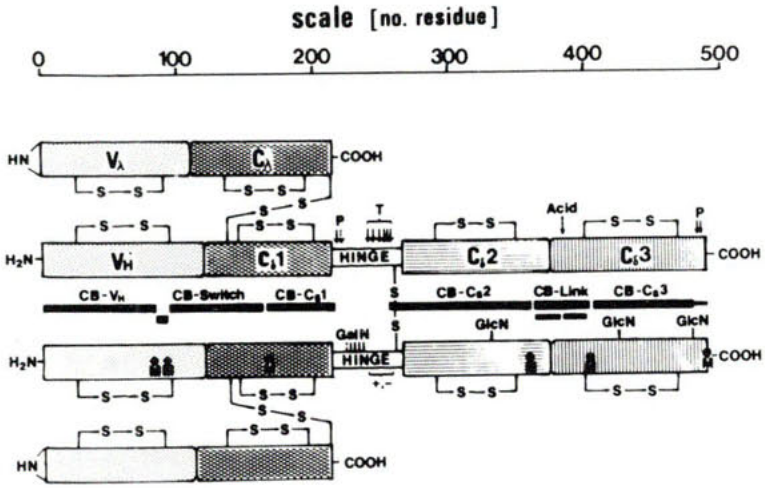

Fig. 2. Structural model of human IgD protein WAH. This IgD molecule has the basic four-chain structure of immunoglobulins. It has a λ light chain with a variable (Vλ) and a constant (Cλ) domain. The δ chain consists of one variable domain (V_H) and three constant domains (Cδ1, Cδ2, and Cδ3) with an extended hinge region located between the Cδ1 and Cδ2 domains. The meaning of other symbols is: M, methionine; CB, cyanogen bromide fragment; GalN, galactosamine oligosaccharide; GlcN, glucosamine oligosaccharide; P, pepsin; T, trypsin. Modified from Lin and Putnam (19).

antibody specificity is remarkable, I will restrict my discussion to the hinge region and the Fc portion of antibodies because it is through these that the ultimate biological effects of the antibody-antigen reaction are mediated.

It is important to recognize that antibodies are multifunctional and that the functions are located in different structural domains. Whereas the combining sites are in the Fab region, the hinge region is the fulcrum for conformational change after interaction of antigen and antibody. The first domain of Fc is the probable site of complement binding in complement-fixing Ig classes. In all Ig classes the principal

cytotropic effects are located in the last domain. Finally, there is a small tailpiece that is involved in membrane binding. This tailpiece differs in secreted IgM versus membrane IgM, and is coded for by separate DNA exons (7). The latter principle probably holds for IgA and IgD, but evidence for IgG is still lacking.

The hinge region. The structurally most unique portion of each Ig class is the hinge region. This raises questions both as to its origin and its functions. Only Ig classes having four domains in the heavy chain have a hinge region, namely IgG, IgA, and IgD, and in these cases the hinge is coded for by a specific discrete exon in the DNA. IgM and IgD have an extra C region domain but lack a hinge region. The hinge is the site of limited proteolytic cleavage to form Fab and Fc fragments and thus is the initial site of catabolism. IgG, IgA, and IgD exhibit great differences in susceptibility to cleavage to form Fab and Fc, and this difference is related both to function and catabolism. IgG is moderately resistant, whereas IgA - as the main antibody of mucous fluids - is necessarily highly resistant. In contrast, IgD is extraordinarily susceptible (19); this partially explains the low concentration of IgD in normal plasma and may be related to its principal role as a membrane receptor protein on the B lymphocyte.

The Fc region of IgD. Although all domains of all Ig light and heavy chains have a common structural polypeptide backbone known as the "immunoglobulin fold," the exact folding pattern differs from chain to chain and from domain to domain (20-22). Figure 3 gives a schematic spatial model of the IgD Fc region, which is divided into two domains, $C_\delta 2$ and $C_\delta 3$, and a final tailpiece (5). Since three-dimensional structures are not available for IgD, this schematic diagram is based on crystallographic structures for IgG and light chains. All immunoglobulin domains are arranged in a sandwich structure composed

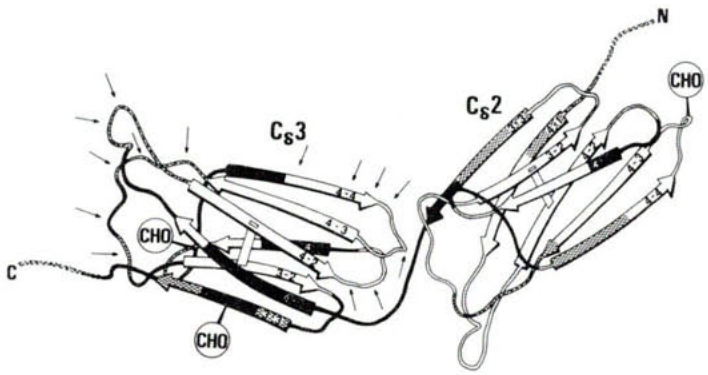

Fig. 3. Spatial model of the IgD Fc region adapted from a drawing of the Cλ domain of a light chain for which the three-dimensional structure has been determined (20). The β-strands are numbered according to Edmundson et al. (20). The shading on the α-carbon backbone indicates the extent of sequence homology as follows: open, highly conserved among all five chains; shaded, scattered but significant homology among all five chains; cross-hatched, high divergence among all five chains; solid, high homology among all heavy chains except the δ chain. The three glucosamine oligosaccharides attached to the Fc region of IgD are designated CHO, enclosed in circles. Arrows pointing to the Cδ3 domain indicate the clustering of proline residues at the carboxy terminus. From Lin and Putnam (5).

of two β-pleated sheets, one made up of four antiparallel segments of the chain and the other out of three segments of the chain (20-22). Because the amino acid sequences of each domain of each class of chain differ, the folding pattern also differs somewhat. The shading on the backbone in Fig. 3 indicates the extent of homology between the δ chain and the other four human heavy chains. It is apparent that the Fc region of IgD differs considerably from that of other Ig classes, and especially so in the last domain, $C_\delta 3$. Note that this has a high clustering of proline residues (indicated by the arrows) and also has two carbohydrates (CHO) lacking in other classes. We postulate that these unique structural features of the C-terminal domain of IgD are related to its function as a surface immunoglobulin on B cells.

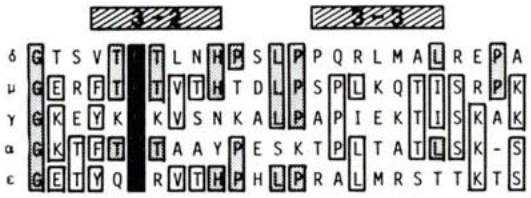

Fig. 4. Comparison of the amino acid sequence of the five classes of human heavy chains at the sequence proposed by Burton et al. as the binding site for Clq in the C 2 domain of human IgG. The C-terminal β-strands are designated 3-2 and 3-3. The sequence given for the Clq binding site in human IgG is Gly-316 to Lys-340. Homology based on Fig. 2 of Lin and Putnam (5). Sequences given in the one-letter code.

Binding of complement. From the point of view of phagocytosis, and the formation of inflammatory immune complexes, the failure of IgD to bind complement is important. Presumably, binding of Clq, the first component of complement, is determined both by the polypeptide chain conformation and the nature of the amino acid residues at the binding site. Burton et al. (23) have amassed strong though indirect evidence that the last two (C-terminal) β-strands of the C 2 domain, which are highly charged, are the binding site for the Clq in IgG. As indicated in Fig. 3 by the shading of these strands (designated 3-2 and 3-3), the heavy chains of all five Ig classes differ greatly in their 3-3 strands. The amino acid sequences for these strands are given in Fig. 4. In this stretch of 25 amino acids, the μ and γ chains (both of which bind Clq) have the greatest homology (10 identical residues), whereas the γ and δ chains have least (4 identical residues). Furthermore, the γ chain is highly charged (7 Lys and 2 Glu), as is the μ chain (2 Lys, 2 Arg and 2 Glu), and the δ chain least so (2 Arg, 1 Glu). Although crystallographic studies will be needed to verify the conclusion of Burton et al. (23), comparative structural study of this sort can be used to deduce the binding site for Clq in IgG and IgM and to understand the lack of Clq binding in other Ig classes.

Membrane binding site. Cloning and nucleic acid sequence analysis of mouse genes for IgM have shown that two mRNA's with different 3' ends encode membrane-bound (μ_m) and secreted (μ_s) forms of mouse IgM μ chains (7). Of great interest is the finding that the only apparent difference in predicted amino acid sequence in the two μ chains lies in the C-terminal tailpiece. The μ_s chain has a 20-residue hydrophilic segment after the last ($C_\mu 4$) domain similar to that we reported for the μ chain of human IgM (24). However, in the membrane-bound μ_m chain this is replaced by a 41-residue tailpiece containing a hydrophobic sequence that presumably enters the B cell membrane. Cloning and DNA sequencing of mouse tumor δ genes suggests that secreted and membrane-bound δ chains likewise may differ in their tailpieces (8). Our current work on the amino acid sequence of human IgD is directed towards answering this question (5). However, it is already clear that whereas the 20-residue tailpieces of the μ and α chains from secreted (plasma) IgM and IgA have high homology, they have no similarity to the short tailpiece of the human δ chain (Fig. 5).

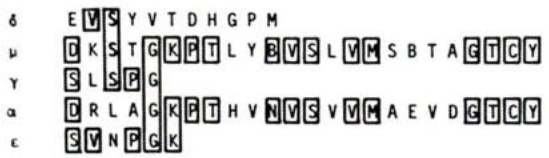

Fig. 5. Carboxy-terminal sequences of the 5 human heavy chains (5). For the μ chain the DNA coding segment (exon) for the last domain ends after the sequence GK (Gly-Lys). In the mouse (7) the last 18 residues (known as the tailpiece) are encoded for by a separate exon for the secreted μ chain. However, this is replaced by a 41-residue sequence in the membrane μ chain (7). A GlcN oligosaccharide is attached to the tailpiece of the human μ and α chains.

I have used these examples to illustrate the progress being made in elucidating the structural basis and genetic control of the four discrete parts of antibody molecules that are most involved in determining their biological effector properties and cytotropic interactions after their triggering by antigen-antibody combination; namely, the hinge region, the two Fc domains, and the tailpiece. Clearly, elucidation of these processes at a molecular level will contribute greatly to understanding the complex phenomena of inflammation that involve the humoral immune response, the complement cascade, and cell-mediated immunity.

Conclusion

Basic research on the structure, biochemical properties, and functions of the acute phase proteins and other markers of inflammation should be intensified. In my own laboratory we are doing this also for human ceruloplasmin for which we have just reported half the primary structure as well as evidence for a remarkable internal duplication (16, 17, 25). Much remains to be discovered by such approaches. However, the basic research must also be transferred to early applications in laboratory medicine and clinical research. As markers of inflammation, the acute phase proteins are of special interest, notably α_1-antitrypsin, orosomucoid, haptoglobin, and ceruloplasmin. Interactions of the humoral immune system and the complement cascade with each other and with lymphoid cells affect the inflammatory response, as do the products of such cells. Dissection at a molecular level of the biological activities of multifunctional plasma proteins is an important approach. This is illustrated by recent work on the structure and properties of human IgD.

Acknowledgements. Research referred to in the laboratory of the author was supported by Grants IM-2F from the American Cancer Society, CA08497 from the National Cancer Institute, and AM19221 from the National Institutes of Health (NIAMDD).

References

1. Putnam, F. W. (ed.): The Plasma Proteins, Second edition, Vol. 1, Academic Press, New York (1975).
2. Putnam, F. W. (ed.): The Plasma Proteins, Second edition, Vol. 2, Academic Press, New York (1975).
3. Putnam, F. W. (ed.): The Plasma Proteins, Second edition, Vol. 3, Academic Press, New York (1977).
4. Putnam, F. W.: in Trace Components of Plasma: Isolation and Clinical Significance (Jamieson, G. A., and Greenwalt, T. T., eds.) Alan R. Liss, Inc., New York (1976), pp. 1-24.
5. Lin, L.-C., and Putnam, F. W.: Proc. Natl. Acad. Sci. USA 78, 504 (1981).
6. Bernard, O., Hozumi, N., and Tonegawa, S.: Cell 15, 1133 (1978).
7. Rogers, J., Early, P., Carter, C., Calame, K., Bond, M., Hood, L., and Wall, R.: Cell 20, 303 (1980).
8. Tucker, P. W., Lin, C.-P., Mushinski, J. F., and Blattner, F. R.: Science 209, 1353 (1980).
9. Titani, K., and Putnam, F. W.: Science 147, 1304 (1965).
10. Garrow, T. S.: in Structure and Function of Plasma Proteins (Allison, A. C., ed.), Plenum Press, London · New York, Vol. 1, pp. 283-304 (1974).
11. Chandra, R. K.: Federation Proc. 39, 3086 (1980).
12. Stiehm, E. R.: Federation Proc. 39, 3093 (1980).
13. Koj, A.: in Structure and Function of Plasma Proteins (Allison, A. C., ed.) Plenum Press, London · New York, Vol. 1, pp. 73-125 (1974).
14. Putnam, F. W.: in Clinical Immunochemistry (Natelson, S., Pesce, A. J., and Dietz, A. A., eds.) Am. Assoc. Clin. Chem., Washington, D.C. (1978), pp. 45-66.
15. Bohn, H.: Arch. Gynaekol. 213, 54 (1972).
16. Kingston, I. B., Kingston, B. L., and Putnam, F. W.: Proc. Natl. Acad. Sci. USA 76, 1668 (1979).
17. Dwulet, F. E., and Putnam, F. W.: Proc. Natl. Acad. Sci. USA 78, 790 (1981).
18. Weissmann, G.: Mediators of Inflammation, Plenum Press, New York · London (1974).
19. Lin, L.-C., and Putnam, F. W.: Proc. Natl. Acad. Sci. USA 76, 6572 (1979).
20. Edmundson, A. B., Ely, K. R., Abola, E. E., Schiffer, M., and Panagiotopoulos, N.: Biochemistry 14, 3953 (1975).

21. Davies, D. R., Padlan, E. A., and Segal, D. M.: Annu. Rev. Biochem. 44, 639 (1975).

22. Amzel, L. M., and Poljak, R. J.: Annu. Rev. Biochem. 48, 961 (1979).

23. Burton, D. R., Boyd, J., Brampton, A. D., Easterbrook-Smith, S. B., Emanuel, E. J., Novotny, J., Rademacher, T. W., van, Schravendijk, M. R., Sternberg, M. J. E., and Dwek, R. A.: Nature 288, 338 (1981).

24. Putnam, F. W., Florent, G., Paul, C., Shinoda, T., and Shimizu, A.: Science 182, 298 (1973).

25. Dwulet, F. E., and Putnam, F. W.: Proc. Natl. Acad. Sci. USA 78, 2805 (1981).

PLASMA PROTEINS IMPLICATED IN THE INFLAMMATORY RESPONSE

Lawrence M. Killingsworth

Chemistry and Immunology Laboratories
Department of Pathology
Sacred Heart Medical Center
Spokane, Washington, U.S.A.

Introduction

The inflammatory response to tissue turnover or necrosis is accompanied by characteristic plasma protein changes. This acute phase response pattern is the most common abnormality seen in routine protein screening procedures such as electrophoresis. The protein changes are coordinated with the time course of the inflammatory process, and may be used to differentiate between acute, subacute and chronic pathological conditions. The intensity of the protein changes may or may not reflect the extent of tissue damage, and more research is needed on the clinical significance of the changes and the mechanisms which control the acute phase response.

Even though the acute phase pattern has been studied in a variety of diseases, it is not generally useful in establishing a differential diagnosis. This is due to the nonspecific nature of the inflammatory process. Detecting the presence of inflammation, however, and determining its progression is of clinical importance under many circumstances.

Postsurgical Acute Phase Response

The postsurgical acute phase response has been extensively

Marker Proteins in Inflammation

investigated, since surgery provides an excellent opportunity to study sequential protein changes with the time of trauma well established (1-7). Baseline studies can also be done, the amount of tissue damage can be estimated and complicating pathophysiological considerations can be kept to a minimum in a hospital setting.

After surgery, and in the absence of infectious complications, a well-characterized pattern of protein changes occurs. Increases are seen within 6 to 8 hours in C-reactive protein and α_1-antichymotrypsin, followed shortly by α_1-acid glycoprotein. These components reach maximum levels within 48 to 72 hours. By far the strongest response is seen with C-reactive protein, which can reach concentrations 10-fold higher than the presurgical level. Strong reactions by α_1-antitrypsin, haptoglobin and fibrinogen are observed at 24 hours. The negative reactants, prealbumin, albumin, α-lipoprotein and transferrin show decreases in the first few postoperative days. In the subactue phase, hemopexin, C3, ceruloplasmin and Gc-globulin show moderate increases. Immunoglobulins are usually non-reactive in the absence of infection or immune stimulation. α_2-Macroglobulin also shows no response and may serve as a control protein to monitor changes in hydrational status and blood volume. One exception to this finding is in bone surgery, where α_2-macroglobulin levels have been shown to decrease early in the postoperative period (3). Table 1 summarizes the postsurgical acute phase response.

Table 1

Post Surgical Acute Phase Response

Protein	6-8 hours	12 hours	1 day	2-3 days	1 week
prealbumin			↓	↓↓	↓
albumin			↓	↓	↓
α-lipoprotein				↓	↓
α_1-acid glycoprotein		↑	↑↑	↑↑↑	↑↑
α_1-antitrypsin			↑	↑↑	↑
α_1-antichymotrypsin	↑	↑	↑↑	↑↑↑	↑↑
α_2-macroglobulin					
ceruloplasmin					↑
haptoglobin			↑	↑↑	↑
hemopexin					↑
Gc-globulin					↑
transferrin			↓	↓↓	↓
C3					↑
fibrinogen			↑	↑↑	↑
Ig G					
Ig A					
Ig M					
C-reactive protein	↑	↑	↑↑	↑↑↑	↑

[Adapted from Killingsworth, L.M.: Critical Reviews in Clinical Laboratory Sciences. 11, 1-30 (1979)]

The most useful acute phase reactant for monitoring patients after surgery is C-reactive protein (5). It shows an early and dramatic increase which is followed by a predictable decreasing trend between the third and fourth postoperative days. Sequential determinationss of C-reactive protein to follow this trend provide a sensitive indicator of infectious complications.

Myocardial Infarction

As with surgical trauma, the time of onset of myocardial infarction can be documented in most cases. Thus, this disease process also lends itself to time course studies of the acute phase proteins (8-11). In addition to characterization of the typical pattern in myocardial infarction, some attempts have been made to correlate the extent of tissue injury with changes in the concentration of acute phase reactants.

The general pattern consists of three phases. C-reactive protein, α_1-acid glycoprotein, α_1-antitrypsin, α_1-antichymotrypsin, haptoglobin and fibrinogen show rapid increases which maximize at about 5 days with partial return to normal levels by 3 weeks. Prealbumin, albumin, transferrin, α-lipoprotein and IgG show rapid decreases, reach minimum levels at day 5 and return to normal in 3 weeks. Ceruloplasmin and C3 show moderate increases which maximize during the second week. Some slight changes can be observed with hemopexin, C4, α_2-macroglobulin and IgM. This overall pattern is similar to that observed in the postsurgical period, even though the time course is slightly longer. It is useful in interpreting protein results of a patient with suspected myocardial infarction, but its diagnostic value is limited by its nonspecific nature.

Johansson et al. (9) could find no correlation between maximal enzyme levels in myocardial infarction and the intensity of the acute phase response. Smith and colleagues (11), however, reported a quantitative relationship between enzymatic infarct size, as estimated by serial measurements of α-hydroxybutrate dehydrogenase, and the response of C-reactive protein, α_1-acid glycoprotein, haptoglobin and fibrinogen. They postulated that humoral factors originating from the site of infarction were probably responsible for evoking increased protein synthesis by the liver.

Infectious Diseases

Ganrot (12) measured nine acute phase proteins in three acute infectious diseases: peritonsillitis, serous meningoencephalitis and influenza A. In each disease, α_1-antitrypsin, α_1-antichymotrypsin and haptoglobin and fibrinogen exhibited marked increases when compared to levels after recovery. The most pronounced changes were in peritonsillitis, however, and concentrations of C-reactive protein were from 3 to 10 times higher in this disease than in the other two studied.

Fischer and Gill (4) have also investigated a panel of acute phase proteins including α_1-acid glycoprotein, α_1-antitrypsin, haptoglobin and C-reactive protein in infectious diseases. They found that the highest levels of all four proteins were observed with bacterial infections. Viral infections resulted in relatively low levels of C-reactive protein and α_1-acid glycoprotein with moderate elevations in α_1-antitrypsin and haptoglobin.

Kindmark and Laurell (19, 20) assayed a panel of plasma proteins in patients with hepatitis A and hepatitis B. They showed that the general acute phase response was not present in the early stages of either disease, but that specific patterns for some acute phase reactants did occur. In hepatitis B, they found that α_1-antitrypsin was increased from the beginning with elevations persisting during the first month of illness. Values for α_1-acid glycoprotein clustered around the normal mean and haptoglobin levels were below the normal mean during the first month. Their results for hepatitis A revealed elevations in α_1-antitrypsin with levels of α1-acid glycoprotein above the normal mean for the first 10 days. Haptoglobin was also above the normal mean for the first two weeks after jaundice began. No significant differences between the two diseases were found for albumin, α-lipoprotein, α1-antichymotrypsin, ceruloplasmin, hemopexin, transferrin,

C3, C4 and C-reactive protein. The negative acute phase reactant, prealbumin, was shown to best reflect the clinical course of either disease.

Rheumatoid Arthritis

The rheumatic diseases constitute a variety of disorders which are characterized by both acute and chronic inflammatory episodes. This inflammation usually involves the connective tissues, but can be accompanied by systemic manifestations. Patients with rheumatic diseases frequently demonstrate plasma protein abnormalities. The most common abnormalities include those associated with the inflammatory response and those resulting from chronic stimulation of the immune system.

Rheumatoid arthritis is a chronic disease in which inflammation of the diarthrodial joints is often combined with a variety of extra-articular symptoms. Several groups of investigators have studied protein patterns in this disease (13-18). Though no distinct protein pattern is associated with rheumatoid arthritis, acute inflammatory patterns are commonly seen with α_1-acid glycoprotein, haptoglobin and C3 as the most consistently abnormal components.

Immunoglobulin increases are most often of the IgA class, with elevations in IgG and IgM occurring less often. No significant correlation has been shown between duration or stage of the disease and serum immunoglobulin levels.

Killingsworth and coworkers (17) determined nine plasma proteins on eighty-three patients with well-characterized rheumatoid arthritis. They showed that, of the proteins measured, the most sensitive indicator of disease activity was α_1-acid glycoprotein, though some patients without clinically detectable disease activity exhibited slight abnormalities in this protein.

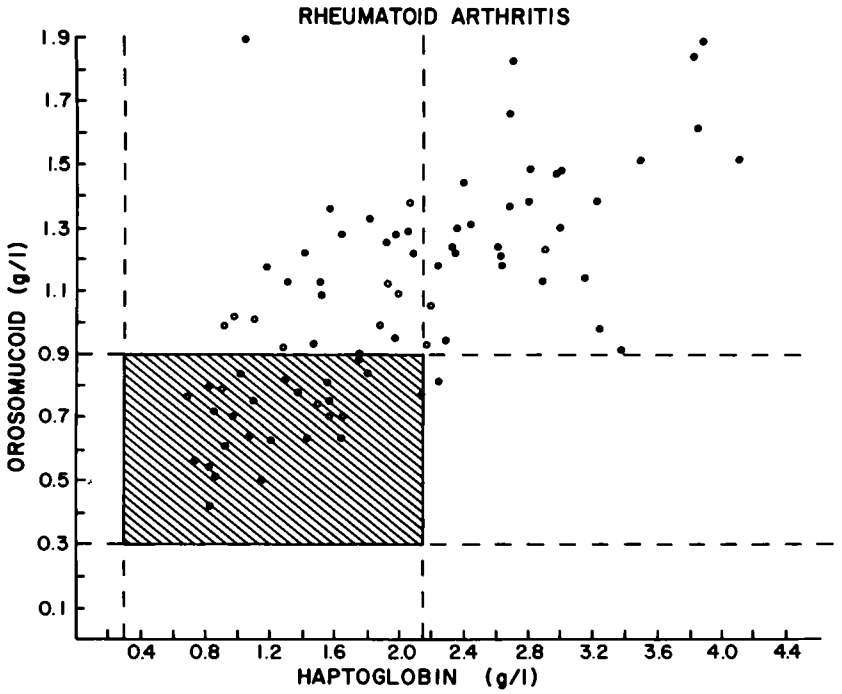

Figure 1. Comparison of α_1-acid glycoprotein (orosomucoid) and haptoglobin levels as indicators of disease activity in patients with rheumatoid arthritis.
Closed circles: active disease (65 patients)
Open circles: inactive disease (18 patients)

Other Disorders

Weeke and Jarnum (21) investigated patients with Crohn's disease and ulcerative colitis and found no significant differences between the protein patterns in the two diseases. Their

studies showed increased serum concentrations of α_1-acid glycoprotein, α_1-antitrypsin, α_1-antichymotrypsin, haptoglobin and hemopexin, with decreased levels of prealbumin, albumin, ceruloplasmin, α_2-macroglobulin and transferrin. They concluded that concentrations of the positive acute phase reactants reflected the amount of disease activity.

Fischer and Gill (4) have shown that tumors which are associated with tissue necrosis can bring about an atypical acute phase response. It can be characterized by low levels of C-reactive protein with marked elevations in α_1-acid glycoprotein and moderate increases in α_1-antitrypsin and haptoglobin. The authors emphasized, however, that this pattern was not diagnostic and would only be useful when interpreted along with the appropriate clinical data.

Active systemic lupus erythematosus can result in a wide variety of protein abnormalities (17, 22). The disease process can bring out a marked acute-phase response, often with normal or decreased haptoglobin due to in vivo hemolysis. Rather than acting as positive subacute phase proteins, complement components C3 and C4 are often decreased in concentration due to activation of the complement system by circulating immune complexes. Immunoglobulins are commonly involved, with a cathodal increase in IgG being a characteristic, but not diagnostic, finding.

In the cirrhotic process, the most dramatic findings are for immunoglobulins, but the acute phase reactants can also show abnormalities (23, 24). Of the positive acute phase reactants, α_1-antitrypsin is the most sensitive indicator for hepatocellular disease, while C-reactive protein, ceruloplasmin and fibrinogen are usually normal or slightly increased. Levels of α_1-acid glycoprotein are normal or decreased. Haptoglobin is usually normal, but can be decreased as a result of increased erythrocyte turnover. Complement component C3 is

usually normal, but advanced cirrhosis can lead to subnormal levels. The negative acute phase reactants, prealbumin, albumin, α-lipoprotein and transferrin show characteristic decreases, with prealbumin a sensitive indicator of hepatic function. Concentrations of α_2-macroglobulin can be elevated in cirrhosis, probably secondary to hyperestrogenism.

General Considerations

It should be noted that most of the commonly measured plasma proteins are either positive or negative acute phase reactants. These proteins also have fundamental biological functions in addition to their roles as indicators of the inflammatory response. In interpreting protein abnormalities, both the primary pathophysiological conditions and the secondary inflammatory status of the patient must be taken into account. This is best done when individual proteins are viewed in relation to the overall protein picture with a clear understanding of the patient's clinical status. Interpretation must be a synthetic, interactive process, involving the laboratory and the physician, with the ultimate goal of improved patient care.

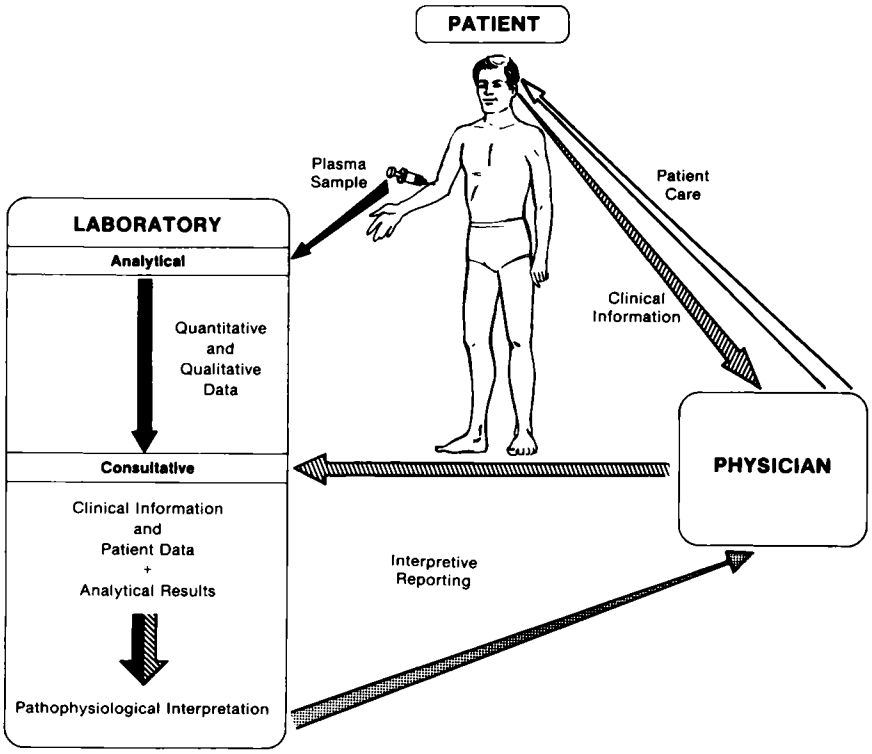

Figure 2. Interpretation of protein data: A synthetic, interactive process.
[Reproduced with permission from: Killingsworth, L.M.: Critical Reviews in Clinical Laboratory Sciences. 11, 1-30 (1979)]

References

1. Werner, M.: Clin. Chim. Acta 25, 299-305 (1969).
2. Aronsen, K.-F., Ekelund, G., Kindmark, C.-O., and Laurell, C.-B.: Scand. J. Clin. Lab. Invest. 29 (Suppl. 124), 127-136 (1972).
3. Dickson, I. and Alper, C.A.: Clin. Chim. Acta 54, 381-385 (1974).

4. Fischer, C.L. and Gill, C.W.: Acute phase proteins, in Serum Protein Abnormalities. Diagnostic and Clinical Aspects, Ritzmann, S.E. and Daniels, J.C., Eds., Little, Brown, Boston, 1975, Chap. 18.

5. Fischer, C.L., Gill, C., Forrester, M. and Nakamura, R.: Am. J. Clin. Pathol. 66, 840-846 (1976).

6. Killingsworth, L.M.: Crit. Rev. in Clin. Lab. Sci. 11, 1-30 (1979).

7. Gill, C.W., Bush, W.S., Burleigh, W.M. and Fischer, C.L.: Am. J. Clin. Pathol. 75, 50-55 (1981).

8. Owen, J.A.: Effect of injury on plasma proteins, in Advances in Clinical Chemistry, Vol. 9, Sobotka, H. and Stewart, C.P., Eds., Academic Press, New York, 1967, pp. 1-41.

9. Johansson, B.G., Kindmark, C.O., Trell, E.Y. and Wollheim, F.A.: Scand. J. Clin. Lab. Invest. 29 (Suppl. 124), 117-126 (1972).

10. Scherer, R. and Ruhenstroth-Bauer, G.: Clin. Chim. Acta 66, 417-433 (1976).

11. Smith, S.J., Bos, G., Esseveld, M.R., Van Eijk, H.G. and Gerbrandy, J.: Clin. Chim. Acta 81, 75-85 (1977).

12. Ganrot, K.: Scand. J. Clin. Lab. Invest. 34, 75-81 (1974).

13. Claman, H.N. and Merrill, D.: J. Lab. Clin. Med. 67, 850-854 (1966).

14. Barden, J., Mullinax, F. and Waller, M.: Arthritis Rheum. 10, 228-233 (1967).

15. Veys, E.M. and Claessens, H.E.: Ann. Rheum. Dis. 27, 431-439 (1968).

16. Pruzanski, W., Russell, M.L., Gordon, D.A. and Ogryzlo, M.A.: Am. J. Med. Sci. 265, 483-490 (1973).

17. Killingsworth, L.M., Yount, W.J. and Roberts, J.E.: Clin. Chem. 21, 1921 (1975).

18. Watkins, J., Milford-Ward, A., White, P.A.E. and Swannell, A.J.: Serum protein profiles in rheumatoid arthritis, in Protides of the Biological Fluids, Peeters, H., Ed., Pergamon Press, Oxford, 1976, pp. 455-459.

19. Kindmark, C.-O. and Laurell, C.-B.: Scand. J. Clin. Lab. Invest. 29 (Suppl. 124), 105-115 (1972).

20. Kindmark, C.-O.: Plasma protein pattern in hepatitis A and B, in Protides of the Biological Fluids, Peeters, H., Ed., Pergamon Press, Oxford, 1976, pp. 431-435.

21. Weeke, B. and Jarnum, S.: Gut 12, 297-302 (1971).

22. Alper, C.: N. Eng. J. Med. 291, 287-290 (1974).

23. LoGrippo, G.A., Anselm, K., and Hayashi, H.: Am. J. Gastroenterol. 56, 357-363 (1971).

24. Hallen, J. and Laurell, C.-B.: Scand. J. Clin. Lab. Invest. 29 (Suppl. 124), 97-103 (1972).

ACUTE INFLAMMATORY PROCESS

P. LAURENT [+], J. BIENVENU [++]

Department of Immunology, Laboratory of Biology of Inflammation

[+]INSTITUT PASTEUR de LYON et du SUD EST
77, rue Pasteur, 69365 LYON cedex 2, France.

[++] Laboratory of Biochemistry
Hôpital Jules COURMONT-Sainte Eugénie
69310 PIERRE-BENITE, France.

Introduction

The description of the four cardinal signs : *Rubor et Tumor cum Calore et Dolore* - and later - *et function laesa*, of inflammation finds its origin in latin history (Celsus C.A.D. 178, and Galen C.A.D. 130). The inflammatory process involves a great number of events such as vascular, humoral, cellular phenomena which have for final aims the restoration *ad integrum* of tissue damage. The physiological and biological aspects of the inflammatory process were first described by Cohnheim (1839 - 1884) who stressed the local circulatory disturbances, and Mechnikoff (1845 - 1916) who stressed the phagocytic process during inflammation. The first line of the host's defense against injury is constituted by the inflammatory response, therefore it is not *a priori* a harmful response.

Vascular changes and humoral factors :

Rubor, calor et dolor are the consequences of several changes in the microvascular bed, of the blood composition and the connective tissue. These changes take place immediately following injury. The vascular effects are largely mediated through vasoactive amines, mainly histamine, serotonine (5 Hydroxy Tryptamine) and a number of factors derived from

Marker Proteins in Inflammation

the plasma kinin system, the fibrinolytic system and the complement system (1). These mediators act after a short period of ischemia (vasoconstriction) but are immediately followed by a slowing of the blood and stasis due to an increase of vascular permeability with exudation of plasma into the connective tissue. A persistent vasodilation occurs in 10 to 30 minutes of the initial lesion (2).

The vasoactive amines result from activation of cells like Mast Cells and Platelets (3). However, there are a great number of phlogistic substances derived from plasma components and the pivotal substance in the activation of these plasma systems is Hageman factor or factor XII (4), table 1. The homeostasis of these intricate systems is assumed by certain plasma proteinases inhibitors and chiefly C1 Inactivator, Antithrombin III, alpha 2 macroglobulin, and alpha 1 antitrypsin, table 2 (1, 5).

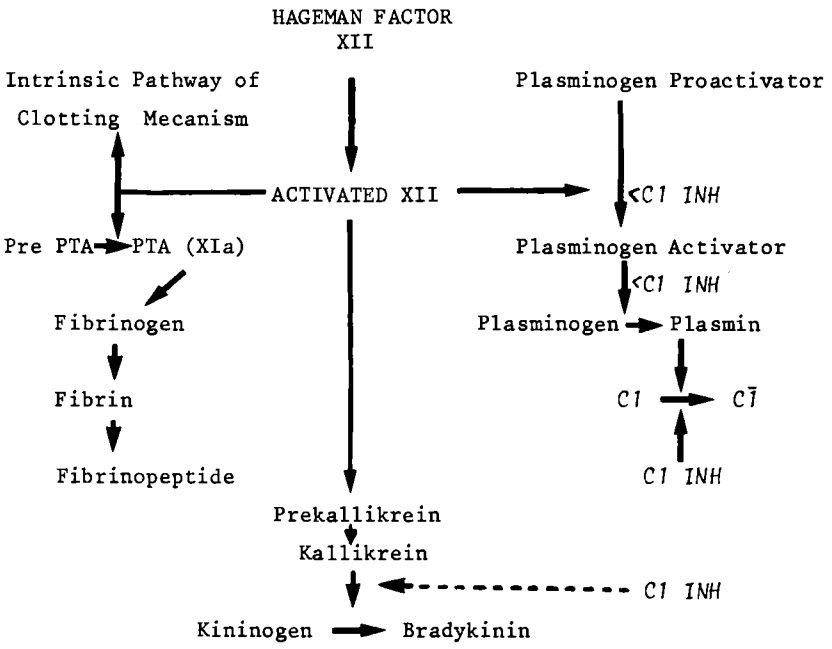

Table 1 : Interrelationship of the Hageman factor dependant initiation of coagulation, fibrinolytic system, kinin generation and plasmin activation. *C1 INH* = inhibitory effect.

PLASMA PROTEINASE INHIBITORS

C1 INH	AT III	α1 AT	α2 M
Factor XIa	Factor XIa		
Factor XIIa			
Factor XIIf			
Kallikrein	Kallikrein	Kallikrein	Kallikrein
Plasmin	Plasmin	Plasmin	Plasmin
C1 esterase	C1 esterase		
	Prekallikrein activator	Prekallikrein activator	
		Plasminogen activator	

Table 2 : effect of plasma proteinase inhibitors on the enzymes implicated in the vasoactive phenomena. C1 INH = C1 inactivator, AT III = antithrombin III, α1 AT = alpha 1 antitrypsin, α2 M = alpha 2 macroglobulin.

COMPONENT OR FRAGMENT	BIOLOGIC FUNCTION
C_2b	C_2 kinin = increased vascular permeability
C_3a	Anaphylatoxin = histamine release Lysosomal enzyme release
C_3b	Immune adherence of lymphocytes and phagocytes Opsonization Enhanced induction of antibody formation Enhanced ADCC Stimulation of B-Cell lymphokine production Triggers bone marrow release of leukocytes Activation of alternative complement pathway
C_3d	Immune adherence
C_4b	Immune adherence
C_5a	Anaphylatoxin = histamine release Chemotaxis of leukocytes (PMN, Monocytes, P.Eosino.)
C_5b	Opsonization of fungi
C_6	Promotion of blood coagulation
C_{567}	Chemotaxis of PMN leukocytes and Monocytes
C_{5-9}	Cytolysis

Table 3 : Biologic activities of components from activation of complement system.

The complement system is a group of several proteins normally present in the blood. The activation of this system by the classical pathway or alternative pathway induces the production of activated components which possess the biological properties and play a pivotal role in the inflammatory process, table 3 (6).

The prostaglandins represent a separate class of inflammatory mediator substances produced and secreted by platelets. Prostaglandins present in the blood are almost entirely produced by platelets during aggregation and blood clotting. The main prostaglandins are PGE2 and F_2 , the former act via the AMPc and the later probably by GMPc (7). Prostaglandins E2, E1, F1 and F2 are chemotactic for human blood PMN leukocytes. The main biological activities are summarized in table 4. The PMN can synthesize Thromboxane A2 and its stable metabolite Thromboxane B2 (8). The monocyte can synthetize prostaglandin E, which plays a role in the induction of collagenase secretion (3).

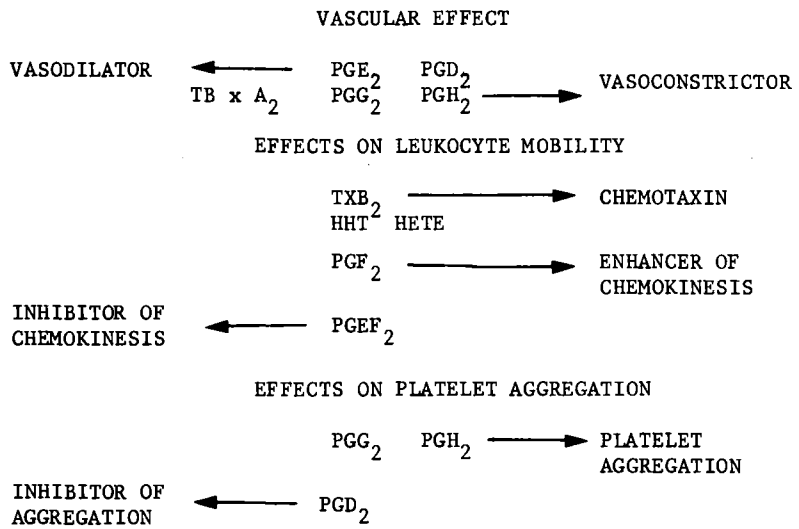

Table 4 : biologic activities of prostaglandins liberated by activated platelets.

The cellular response :

1) Platelet activation and aggregation :

Following injury of blood vessels, the immediate adhesion of circulating platelets, aggregation and release of a great number of intracellular substances make up the first step of the hemostatic process.
Thrombin, ADP, collagen, antigen-antibody complexes, arachidonate and certain bacteria and virus can induce platelet activation and aggregation (3).

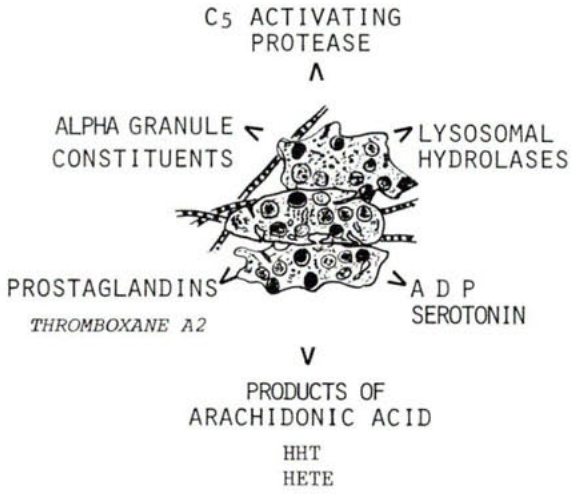

Table 5 : Intracellular inflammatory mediators released following activation and aggregation of platelets.

2) Leukocytes emigration :

Concomitant modification of vasomotion, then occurs ; and thereafter the enhancement of vascular permeability, the migration of blood cells towards the connective tissue, notably polymorphonuclear leukocytes and monocytes. The chemotaxis of cells is preceded by adhesion to the endothelium of the microvessels involved in the inflammatory process (9).
For about 3 hours, the polymorphonuclear leukocytes dominate in the

focus of inflammation ; after a day or so the prevaling cell is the mononuclear, or macrophage, which is derived from the blood monocyte. This migration of cells is due to a great number of humoral factors. The crucial role of the complement system is to attract polymorphonuclear leukocyte (C5a, C567), but the chemoattractants are not limited to complement components or factors (10). Thus a number of bacteria such as *Staphylococcus albus, Salmonella typhi*...are chemotactic to polymorphonuclear leukocytes (1). Activated factor XII of the fibrinolytic system, some prostaglandins and some lymphokines can induce chemotaxis (3, 11, 12, 13). On the other hand, some lymphokines such as the macrophage inhibiting factor (MIF) exhibit an opposite effect in inhibiting cell mobility. The aim of cellular migration is phagocytosis by ingestion and digestion of particular matter, such as bacteria or damaged cells, etc... Once the inflammatory stimulus has been eliminated, the processes leading to restoration of normal tissue structure or to scar formation begin. The chronic inflammation focus may occur if the foreign substances are persistant. In the latter case, the typical focus of inflammation shows macrophage, lymphocytes fibroblasts and plasma cell (14).

Phagocytosis is influenced by a number of humoral factors such as opsonins. Immunoglobulins, complement and perhaps plasma fibronectin and some acute phase proteins (C.R.P.).

3) Release of lysosomal constituents :

The activation of polymorphonuclear leukocytes and macrophages during chemotaxis and phagocytosis leads to release of granule contents (15). These secreted products (lysosomes) appear to have important modulatory roles in the inflammation process. A large number of these substances possess an enzymatic activity such as collagenase, elastase, chymotrypsin like enzyme, cathepsin G (15).

The neutral protease released from human neutrophil leukocytes can act on kinin like peptides, plasmin derived substrates C3 and C5 (16).

The most important neutral protease which produces tissue and vascular injury is probably the elastase like enzyme. Some other substances can be released during cell activation. These include cationic proteins which can induce enhancement of vascular permeability, acid proteases like cathepsin D and slow reacting substances, which are implicated in tissue injury and inflammation (1).

The mechanisms of release of lysosomal constituents include cell lysis, the suicide sac (phagocytosis of uric crystals or silicate), regurgitation during phagocytosis, membrane pertubation by several concomitant stimulating agents, frustrated phagocytosis and IgG binding (15).

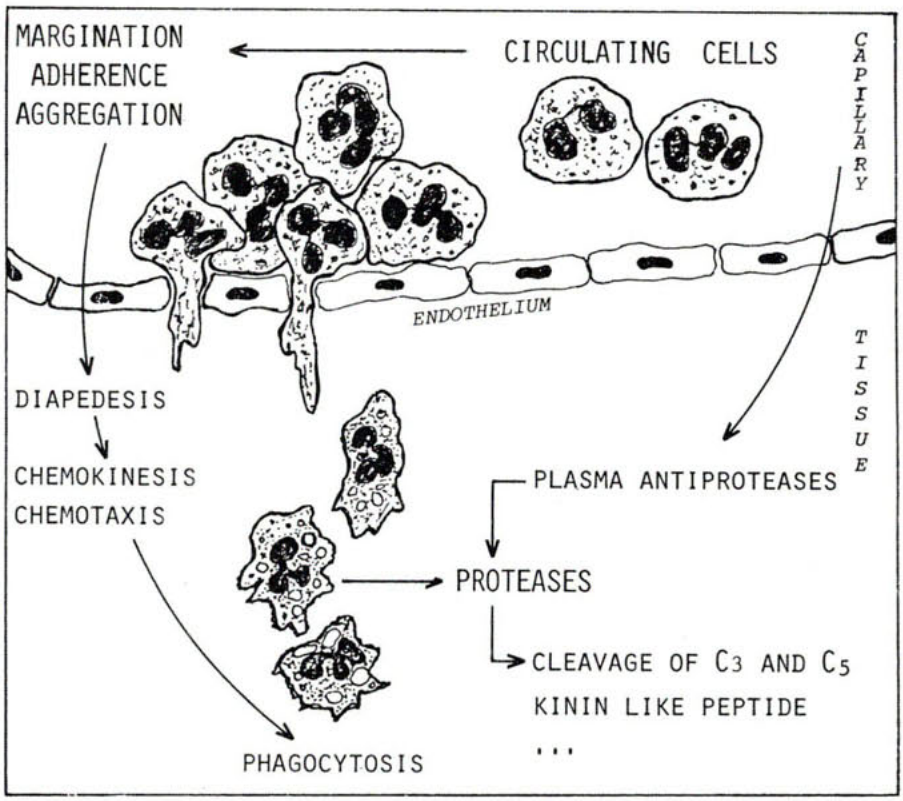

Table 6: activation and functions of polymorphonuclear leukocytes and release of lysosomal constituents (proteases)

The consequence of this release of enzymes is the high proteolytic activities in an inflammatory focus. But the protease-antiprotease interplay modulates these activities.

Consequences of early event in the interstitium

Although the blood vascular system seems to dominate the scene during the inflammatory response, it only proceeds to the extent allowed by the lymphatic vascular system in coordination with the surrounding interstitial area. The indispensable component of tissue homeostasis is provided by the lymphatic vascular system. Therefore the primary function of the lymphatics is to drain the interstitium of plasma proteins that have leaked from blood capillaries and return these components to the circulation. In addition to the drainage of escaped protein, the lymphatics are also essential for the continual migration of lymphocytes through out the body (17).

The accumulation at the site of the inflammatory focus of tissue debris, of activated plasma proteins, of products of cellular activation and cellular metabolism, induces a number of modifications in homeostasis. The ENDOPYROGENS coming from monocytes act on the hypothalamus and thermoregulation with a product derived from arachidonic acid (18). The COLONY STIMULATING FACTOR (CSF), protein synthetized by macrophage, stimulates the growth of granulocyte macrophage colonies. The SYNTHESIS INDUCTORS OF ACUTE PHASE REACTANT PROTEINS (APRP) have been not been precisely identified. They may be derived from leukocyte activation and increase the cellular activities of hepatocytes to produce the protein markers of inflammation.

CHANGES	PROTEINS	FUNCTIONS
+	alpha 1 antitrypsin	antiproteases
+	alpha 1 antichymotrypsin	
+	ceruloplasmin	copper transport oxidase
+	haptoglobin	hemoglobin transport
-	transferrin	binding iron
+	alpha 1 acid glycoprotein	immunoregulatory ? binding drugs
+	C-Reactive Protein	immunoregulatory opsonin
-	albumin	binding drugs
-	prealbumin	
+	fibrinogen	blood coagulation

Table 7 : Acute Phase Reactant Proteins (APRP) : the main proteins and their functions.

Among the APRP two groups are individualized by their changes in the blood during acute inflammation : the negative changes, and the positives changes after injury (table 7). Each APRP may have a specific biological function, some of which include the protease antiprotease interplay on clotting mecanism, on transport of copper, hemoglobin, iron etc. The more interesting role of certain APRP such as alpha-1-acid glycoprotein and CRP are that they enhance some immunological activities while suppressing others, and point to a immunomodulator role in immunopathologic mechanisms. Therefore these APRP can serve as an intermediate step between the early host response and the specific immune response.

References

1. Movat H.Z. : The acute inflammatory reaction - in Inflammation, Immunity and Hypersensitivity, Harper and Row, 1 (1979).
2. Wilhelm D.L., Masson B. : Br. J. Exp. Pathol. 41, 487, (1960)
3. Nachman R.L., Weksler B.B. : The cell biology of inflammation, G. Weissmann editor, Elsevier, 145 (1980)
4. Ryan G.B., Majno G. : Am. J. Pathol. 86, 185, (1977)
5. Bata J., Cordier G., Revillard J.P., Bonneau M., Latour M. : in transplantation and clinical Immunology, 11, 59, (1979)
6. Hugli T.E., Mûller Eberhard H.J. : Adv. Immunol. 122, 1134, (1978)
7. Tauber A.I., Kaliner M., Stechschulte D.J., Austen K.F. : J. Immunol. 111, 27, (1973)
8. Hamberg M., Svenson J., Samuelsson B. : Proc. Natl. Acad. Sci. USA 72, 2994, (1975)
9. Stossel T.P. : in Leukocyte Chemotaxis : Methods, physiology, and clinical implications, Gallin J.I., and Quie P.G. editor, 161, (1978)
10. Wright D.G., Gallin J.I. : in Leukocyte chemotaxis : Methods physiology and clinical implications, Gallin J.I. and Quie P.G. editors, 221, (1978)
11. Higgs G.A., Mc Call E., Youlten L.J.F. : Br. J. Pharmacol. 60, 539, (1975)
12. Stecher V.J., Sorkin E. : in Chemotaxis : its biology and biochemistry, Sorkin E. editor, Basel, S. Karger, 362 (1974)
13. Kaplan A.P., Goetzl E.J., Austen K.F. : J. Clin. Invest. 52, 2591, (1973)
14. Bainton D.F. : in the cell biology of inflammation, G. Weissmann editor, Elsevier, 1 (1980)
15. Ranadive N.S., Movat H.Z. : Tissue injury and inflammation induced by immune complexes, in Inflammation, Immunity and hypersensitivity, Movat H.Z. editor, Harper and Row, 409 (1979)
16. Janoff A. : Ann. Rev. Med. 23, 177, (1972)
17. Leak L.V., Burke J.F. : in the Inflammation Process, second edition, Zweifach B.W., Grant L., Mc Cluskey R.T. editors, Academic Press, 11, 163, (1974)
18. Fauve R.M. : Immunology 80, progress in Immunology IV, Fougereau M. and Dausset J., Academic Press, 739, (1980).

THE INFLAMMATORY RESPONSE

D.A. Willoughby, A. Sedgwick and J. Edwards
Department of Exp. Pathology
St. Bartholomew's Hospital
London, ENGLAND

In the past the acute inflammatory response has been extensively investigated. This is due to the well characterized nature of the vasoactive pharmacological agents involved, including histamine, 5-hydroxytryptamine, bradykinin and more recently the prostaglandins.

The metabolic pathway of prostaglandin synthesis from arachadonic acid has been hailed as one of the most important aspects of the action of the non-steroidal anti-inflammatory drugs. It has been shown by elegant studies from Vane's group that most of the non-steroidal anti-inflammatory agents are capable of inhibiting prostaglandin synthetase. Yet the prostaglandin family has been subsequently found to be capable of antagonising fellow members, i.e., PGE_2 is pro-inflammatory while $PGF_{2\alpha}$ is anti-inflammatory. Thus PGE_2 is capable of causing vasodilation or increased vascular permeability in certain species, of promoting chemotaxis of leukocytes, of causing histamine release and most important potentiating receptor sites for other mediators, such as those which promote pain.

If we consider the four cardinal signs of inflammation as described by Celsus:- heat, redness, swelling and pain, PGE_2 would seem to be adequately endowed to play an important role in these basic processes. It seems logical that inhibition of the formation of this fatty acid should give symptomatic relief in many inflammatory conditions. However it was shown experi-

Marker Proteins in Inflammation