Immuno-globulins

Biologic Aspects and Clinical Uses

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Ohio State University College of Medicine
and
Division of Medical Sciences
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Preface

The National Research Council, organized in 1916 by the National Academy of Sciences at the request of President Woodrow Wilson, has as one of its principal functions the promotion of the effective application of science and engineering for the benefit of society. Within the Council, the Division of Medical Sciences has responsibility for promoting the application of medical science for this purpose. In this respect, the Division has a longstanding interest in basic and developmental research on human blood and blood products and has maintained a series of scientific advisory committees to assist with its undertakings in the field. This function is currently vested in the Committee on Plasma and Plasma Substitutes.

In the early 1960's, this Committee was called upon to evaluate the current and proposed uses of what was then referred to as "gamma globulin," for which therapeutic efficacy was supported by valid data. Many of the originally proposed uses of gamma globulin in the prevention and treatment of infectious diseases had been obviated by vaccines, the sulfonamides, and the antibiotics. The Committee found that gamma globulin was used principally in the prevention and amelioration of measles and viral hepatitis and in the management of hypogammaglobu-

linemia, but that its use in measles might decline if a vaccine then under study became available.

It was evident that both basic and applied research on gamma globulin had lagged in the 1950's. However, enthusiasm was developing in the study of the physicochemical nature of immunoglobulins as an area of basic research, and, although it was premature to consider the possible application of the data from these early research efforts, the Committee felt that there was an inherent promise of useful application. It therefore determined to review the field later. In 1967, the Committee, noting the rapid progress that was being made, particularly in the field of immunoglobulin physicochemistry, proposed that a meeting be held before the close of the decade to review the status of this research. In so proposing, the Committee pointed out that the work was being done principally by persons in basic research fields having specialized interests and viewpoints. In the normal course of events, the emerging data would be published in a variety of scientific journals, and its application in medical practice would be delayed and piecemeal. The Committee was of the opinion that a meeting and a publication for the purpose of acquainting clinicians with the research and the researchers with the potential clinical application of their work would expedite the flow of scientific and technical information from the laboratory to the bedside.

Dr. Charles L. Dunham, Chairman, Division of Medical Sciences, invited the Ohio State University College of Medicine to conduct such a meeting, and Dr. Richard L. Meiling, Dean of the College, accepted the invitation with enthusiasm. As mutually agreed, the Division established a National Research Council committee to plan the scientific program, and the College assumed responsibility for all other tasks related to the planning and conduct of the meeting. The meeting, attended by over 150 scientists and medical practitioners from the United States and abroad, was held March 31 through April 2, 1969, in Columbus, Ohio.

The emphasis of this conference on the biology of immunoglobulins, rather than their immunochemistry (as in the previous conference, held in October 1962), reflected the growth of immunology in the intervening eight years. Once it had been learned what, in a broad sense, immunoglobulins were, it was reasonable to ask how they behave, what they do, and how they could be used in solving medical problems. This conference tried to summarize some relevant facts along these lines. The cellular

aspects of immunology, only briefly alluded to here, may well form the basis of another conference eight years hence.

These proceedings contain the reports of all but one of the authors who contributed to the conference. The contributions have been arranged, not necessarily in the order of their presentation or overall importance, but rather to cover areas of common interest, beginning with scientific essays on the classes of immunoglobulins and closing with more general discussions of the standardization and surveillance of immunoglobulins and their uses.

Each author has emphasized his own interests to create a variegated, slightly opinionated, but readable account of his particular field. The presentations are not overburdened with the experimental details that often tend to narrow scientific reporting, but instead are brief overviews of a broad, complex, and at times frightfully confused field of endeavors. Although details often change, broad lines of thought appear immutable, by virtue of the scientific approach that we follow.

The conference appears to have served its purpose well, and the information it produced should be helpful in defining steps that should be taken to increase the value of immunoglobulins in preventing and alleviating human disease.

ROBERT L. WALL, M.D., *Chairman*
Conference on Biologic Aspects
and Clinical Uses of Immunoglobulins

A NOTE ON THE NOMENCLATURE OF HUMAN IMMUNOGLOBULINS

Because the study and application of the human immunoglobulins are expanding rapidly, their nomenclature is often inconsistent. Most of this volume reflects an attempt to impose a degree of needed consistency. The main points of the nomenclature used here are:

1. The symbol Ig (usually) or γ followed immediately by a capital letter (A, D, E, G, M) is reserved for chemically pure proteins.
2. The word "immunoglobulin" is used chiefly to indicate the normal distribution of the proteins IgG, IgA, IgM, and so on, as they occur in serum.
3. Cohn's fraction II+III (which is 95% IgG, but also contains notable amounts of IgA, IgM, and albumin), the material used clinically for prophylaxis and therapy, is called "gamma globulin."
4. A gamma globulin preparation with known antibody activity is referred to as an "immune globulin."
5. Immune globulins are sometimes called "antibodies"; the serum from which an antibody (or an immune globulin) is derived can be called either an "immune serum" or an "antiserum."
6. Immunoglobulin chains are designated by the symbols κ and λ for L chains and γ, α, μ, etc., for H chains.

Acknowledgments

When an invitation was received by the Ohio State University from Dr. Charles L. Dunham, Chairman, Division of Medical Sciences of the National Research Council, to host this conference, a "seed fund" contribution from the College of Medicine was made available to further the planning of the meeting. This in turn made it possible to receive a generous grant from the Office of Naval Research, Department of the Navy, necessary for the actual conduct of the conference, for which we are deeply grateful. Additional financial support for the conduct of the meeting, including its social aspects and accommodations for the European participants, was made available by generous contributions from Ortho Pharmaceutical Corporation, Pitman-Moore Biological Laboratories, Behringwerke A.G., Armour Pharmaceutical Co., Osterreiches Institut für Haemoderivate, American Association of Blood Banks, Lederle Laboratories, Hyland Division of Travenol Laboratories, Abbott Laboratories, Parke, Davis and Co., Merck Institute for Therapeutic Research, and Hoffman-LaRoche Inc. We express our appreciation for their understanding and generosity.

This volume itself could not have been made available except for a most generous grant (DADA17-69-G-9287) from the U.S. Army Medical Research and Development Command; that grant, entirely and ex-

clusively for support of the preparation and publication of this book, is gratefully acknowledged.

The content of the conference was established by a planning committee, which included Drs. Harlan D. Anderson, Marcel E. Conrad, John L. Fahey, Henry T. Gannon, Elvin A. Kabat, Robert B. Pennell, Fred S. Rosen, and Robert L. Wall.

Local planning for the conference was facilitated by the Center for Continuing Medical Education of the Ohio State University College of Medicine and the local planning committee, consisting of Drs. Samuel G. Murphy, Albert S. Klainer, and Robert L. Wall.

For valuable help and assistance during the conference, we are indebted to Dr. Robert B. Schweikart of the Center for Continuing Medical Education and his staff.

We are especially grateful to Dr. Ezio Merler, of the Laboratory of Immunology of Harvard Medical School, and Mr. Norman Grossblatt, editor for the Division of Medical Sciences of the National Research Council, for their anxious attention to the details of the scientific and literary content of this book.

RICHARD L. MEILING, M.D., *Dean*
Ohio State University College of Medicine

Contents

I
INTRODUCTION

CHARLES A. JANEWAY

The Development of Clinical Uses of Immunoglobulins: A Review

The history of the immunoglobulins is one of the mainstreams of the science of immunology over the last 30 years. Immunology had its first golden age in the late nineteenth and early twentieth centuries, when antibodies were discovered and first used in the treatment and prevention of disease, when complement was recognized by Ehrlich, and when the concept of allergy, which had been foreshadowed by the work of Koch, was elaborated by von Pirquet. For the first 25 years of this century, a great deal of quiet work went on, which led up to the biochemical era of immunology. Credit must be given to a biologist, my old teacher, Hans Zinsser, who, with Julia Parker, first described the specific soluble substance of the pneumococcus in the early 1920's. This set off the great studies at the Rockefeller Institute and at Columbia University by Avery, Heidelberger, and Goebbel, which led to the chemical characterization of the pneumococcal polysaccharides and the quantitation of their reactions with specific antisera—logical extensions of the pioneering studies of Landsteiner on the chemical nature of the specificity of antigens.

At about the same time, Felton introduced purification of antibody from type-specific antipneumococcal serum for therapeutic use by salt

fractionation; this was the conceptual forerunner of the purification of human gamma globulin. It was no accident that Dubos called immunology the science of pneumococcal polysaccharide in the late 1930's; the definition lost its meaning almost immediately with the introduction of sulfapyridine and penicillin. Felton's technique for preparing partially purified antipneumococcal antibody by salt fractionation had two major drawbacks: a long period was required for removal of the ammonium sulfate by dialysis, frequently permitting contamination and consequent pyrogenic reactions in clinical use; and the starting material was horse serum, much of whose antibody had a high molecular weight. With the introduction of antibody purified from rabbit antiserum, a preparation much more like human antibody in its physicochemical characteristics became available. But this preparation sometimes produced severe reactions when administered intravenously. One of Albert Sabin's first major contributions to medicine was to show that, if rabbit antibody were absorbed with Fuller's earth, the incidence of such reactions, presumably due to high-molecular-weight complexes, was diminished. Thus, the tremendous amount of work on the treatment of pneumococcal pneumonia with purified heterologous antibody during the 1930's by the Rockefeller Institute group and by White, Robinson, and Finland in Massachusetts provided an important background of knowledge for the development of human gamma globulin.

The first application of these techniques to human source material came in the 1930's, when Charles F. McKhann, a pediatrician, and Arda Green, a physical chemist, developed a globulin extract of ground human placentas as a source of human antibody for the prevention and modification of measles in susceptible children. Although the theory—that the placental tissue was probably the source of antibodies, was contaminated with tissue proteins and tissue breakdown products, and gave rise to occasional immediate reactions—was wrong, placental extract was an extremely useful therapeutic agent for several years.

In the late 1930's, Tiselius developed the technique of electrophoresis and was able to demonstrate, with Elvin Kabat, that the antibodies were associated with the gamma globulin fraction. At the same time, Edwin J. Cohn was developing a new system of plasma fractionation to meet his exacting standards for separation of proteins from mixtures in high purity and without denaturation so that their chemical and biologic