IMMUNOLOGIC DISORDERS IN INFANTS AND CHILDREN

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PREFACE

Twenty-five years ago, the thymus was a mystery organ that was irradiated for respiratory stridor, organ transplantation was science fiction, a gamma globulin determination was a sophisticated research effort, the function of the lymphocyte was not known, and the immunodeficiencies were not yet discovered. Since then a bountiful harvest of immunologic information has been gathered by the combined efforts of physicians, biochemists, microbiologists, pathologists, and other scientists. A significant portion has relevance to human health and disease and has been collected under the heading of clinical immunology. This book is concerned with the clinical immunology of infancy and childhood.

Like other specialty fields, clinical pediatric immunology is primarily concerned with a specific group of related illnesses necessitating special investigative procedures—the primary immunodeficiency diseases. Unlike most other specialties, pediatric immunology widens its horizon to include such related areas as collagen diseases, infectious diseases, allergies, transplantation, and immunization procedures. Further, the field encompasses many aspects of endocrine, hematologic, renal, neurologic, gastrointestinal, and malignant diseases, and thus it is especially attractive to the physician who enjoys the entire scope of pediatric medicine. In sum, pediatric immunology has some relevance and contribution to the whole of pediatrics.

This book has been written by men and women from 18 universities in North America and Europe whose own careers have been devoted to some aspect of clinical immunology. Writing with both the specialist and the generalist in mind, the contributors have combined the basic knowledge of the immunologic system with clinical descriptions of immunologic disorders.

The book begins with the development and biology of the immune response and the components of the immunologic system (Part One), continues with a detailed exposition of the immunodeficiencies (Part Two), and concludes with a group of chapters detailing the immunologic aspects of various pediatric disorders (Part Three). Included in Part One is a review by Dr. Robert Good of the major experiments in nature which have served as the impetus for the advances in clinical immunology.

The terminology employed for the immunoglobulin classes, complement components, and immunodeficiencies is that recommended by the World Health Organization. The terminology for the primary immunodeficiencies has only recently been codified, and since many eponyms

are well established in the literature (e.g., Wiskott-Aldrich syndrome), we have added these to avoid ambiguity. Except in the section on immunodeficiencies (Part Two), no attempt has been made to present complete bibliographies. In the other sections, key references to summary and review articles are often used.

A suitable subtitle for a primarily American work on pediatric immunology might be "A Tale of Two Cities." The cities are not London and Paris in the 1830's but Minneapolis and Boston in the 1960's. The pediatric departments of the University of Minnesota and Harvard, under the leadership of Good, Janeway, and Gitlin, have provided much of the information in this volume and served as the training grounds for many of the contributors. Others, including the editors, have indirectly benefited by the stimulation from these centers. In 1833 Dickens stated that "It was the best of times, it was the worst of times." In 1973, it is the best of times for physicians concerned with the exciting and challenging aspects of immunologic disorders; for most patients, it is still the worst of times, because, with rare exceptions, therapy is unrewarding. The outlook should be bright; one large cloud is the diminution of support for the further exposition of this subject.

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Part Three

IMMUNOLOGIC ASPECTS OF PEDIATRIC ILLNESS

Part One

DEVELOPMENT AND FUNCTION OF THE IMMUNE SYSTEM

1

Crucial Experiments of Nature that have Guided Analysis of the Immunologic Apparatus

*Robert A. Good**

Real contributions toward understanding the nature of immunity and the relations of structure to function in the lymphoid system have been derived from analysis of a series of experiments of nature. For example, the science of immunology was dramatically launched when Jenner (1798, 1806) attempted to generally apply the observation that milkmaids who had had cowpox could not contract smallpox. His attempts to interpret this natural experiment introduced the principles of vaccination and active immunization and provided the first evidence that hypersensitivity may be associated with immunity. They represented the first use of an attenuated virus vaccine and even presented the first glimpse at viral interference. This legacy has proved a truly remarkable contribution, derived from the interpretation of a single experiment of nature.

Pasteur's discovery that cholera organisms grown at room temperature as an aged culture yield the starting material for an effective vaccine based on a culture of an attenuated organism also can be viewed as an interpretation of a natural experiment—a chance conjunction of a natural event and a uniquely prepared and concerned mind.

*Supported by grants from the National Foundation–March of Dimes, the United States Public Health Service (AI-08677, AI-00798, and NS-02042), and the John A. Hartford Foundation.

At the turn of this century, von Pirquet (1905) taught us that not all immune reactions function for the benefit of man when he discovered and developed the concept of allergy from the interpretation of two natural experiments. He recognized that in the incubation period of infections and immunity to infectious diseases, resistance to disease and the very expression of many diseases after a period of incubation are both functions of host immune reactions (1911). His studies of serum sickness, an illness which he clearly related to the immune reaction of the body against the foreign serum which had been injected earlier, launched studies of the nature of immunologic injury which have only recently culminated in the understanding of certain forms of immunologic damage. These concepts have been resolved at the molecular level through signal contributions by Ishizaka and Campbell (1958), Germuth (1957), and Dixon et al. (1958, 1962).

Prausnitz and Küstner (1921), studying Küstner's own allergy to boiled fish protein, interpreted another major experiment of nature and provided evidence of the passive transfer of reaginic allergy and the persistent fixation of reaginic antibody in tissues. The potential value of desensitization or immunization, perhaps the first form of immunodeviation, was also a legacy of this early interpretation. Of course, we now have IgE and a molecular definition of reaginic antibody.

Here, once again, crucial experiments of nature—two patients with an unusual form of myeloma (Johansson and Bennich, 1967; Ogawa et al., 1971)—paved the way for the molecular analysis of reaginic sensitivity.

PLASMA CELLS IN IMMUNITY

Bing and Plum's study of agranulocytosis (1937) associated plasmacytosis with the production of globulins. In turn, Kolouch's (1938) concern with the plasmacytosis that he observed at autopsy in the marrow of a patient who had succumbed to subacute bacterial endocarditis led to the experimental association of plasma cell response with both antigenic stimulation and antibody production. This experimental analysis of an insight derived from the interpretation of a natural experiment led to further experimentation by Bjoerneboe and Gormsen (1943) which related extensive and intensive antigenic stimulation to extreme hypergammaglobulinemia and fantastic plasma cell accumulations, and which closely linked plasma cell accumulations with gamma globulin production. This finding finally culminated in Fagraeus' classic demonstration (1948) that in tissue explants the plasma cell–rich tissues synthesized antibody in vitro, while lymphocyte-rich, plasma cell–poor tissues did not. This succession was finally complete when Albert Coons and associates (1953, 1955a, 1955b), using Coons' new immunofluorescent technique, showed that plasma cells and their precursors were immunoglobulin-producing cells.

MOLECULAR IMMUNOBIOLOGY

The extraordinary romance of molecular immunobiology, indeed the very establishment of a firm molecular basis for all of humoral immunity, has been entirely dependent on the study of myeloma proteins (Edelman et al., 1961, 1969). The remarkable discovery of Kunkel and his students (Slater et al., 1955; Kunkel et al., 1951), that all myeloma proteins possess antigenic relationships to one another and to normal gamma globulins but can also be readily distinguished from one another and from normal gamma globulins by immunochemical and physicochemical analysis, represented a crucial step.

While the foregoing contains only a few cogent examples, I believe it can be effectively argued that virtually every major advance in the development of immunobiologic knowledge has been initiated by the interpretation of a critical natural experiment. Such experiments of nature are frequently encountered in the course of the care and analysis of sick people.

DISCOVERY OF AGAMMAGLOBULINEMIA

One of the milestones in the development of immunobiologic understanding was Bruton's discovery of a new disease that he called agammaglobulinemia (1952). His discovery and investigation and the subsequent analysis of large numbers of immunodeficient patients in Boston and Minneapolis, in this country, and in England, Switzerland, and other regions throughout the world have raised many critical questions and placed in focus much of the developing understanding of the lymphoid system and its function.

It is not within the scope of this summary to detail all of these contributions. May it suffice for the present brief review to point out that from the study of such patients major critical questions have been raised concerning: (1) the role of plasma cells and germinal centers in antibody synthesis (Good, 1954b, 1955a, 1955b; Gitlin, 1959); (2) the critical role of the thymus in the development and maintenance of the immune response (Good, 1954a; MacLean et al., 1956, 1957; Good et al., 1962a; Jeunet, 1968); (3) the relationship of autoimmunity to deficiency of immunologic function (Good et al., 1957; Fudenberg et al., 1962; Janeway et al., 1953; Wolf et al., 1963): (4) the surge of autoimmune phenomena with aging (Teague et al., 1971; Yunis et al., 1972); (5) the role of immunosurveillance in the body economy (Thomas, 1959; Burnet, 1970; Good, 1967; Gatti and Good, 1971); (6) the crucial role of the local immune system in the bodily defense (Tomasi, 1967) and in the prevention of the development of autoimmunity (Hong et al., 1969); and (7) the molecular basis of the transport of molecules across the epithelium in the local antibody system (Hong et al., 1969; South et al., 1966; Tomasi et al., 1968).

These and many other immunologic issues have been placed in clear focus by the questions derived from the study of patients with