VOLUME 2

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Encyclopedia of Medical Immunology

Autoimmune Diseases

Springer Reference

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L–Z

With 227 Figures and 121 Tables

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Introduction

The concept of an encyclopedia derives from the Greek words for gathering together or "encircling" knowledge and learning. Indeed, Diderot and the French encyclopedists of the mid 18th century aimed to bring together all of the world's knowledge in one giant publication. Our ambitions today are more modest but "encapsulating" existing knowledge of a defined topic is still a reasonable basis for decision making in the present and planning for the future. The Encyclopedia of Medical Immunology follows in the encyclopedist tradition. At the present time, however, progress is proceeding at such a rapid pace that a static volume, no matter how extensive, could never do justice to this dynamic subject. Thus our present encyclopedia is based on the concept that articles will be linked to current research and updated on a regular basis. The reader needs to gain an understanding of medical immunology not only at the date of publication, but on a continuing basis.

The immune system, as a vital component of normal physiology, participates in establishing and maintaining the well-being of the host. Its core responsibility is to prevent or control infection and malignancy. Immune functions can be divided into constituative and adaptive. Inherited innate immunity takes its origins from most primitive cellular functions of recognition and nutrition. In animals, it evolved through invertebrates as a group of formed barriers and a system of cells and cell products for promptly dealing with harmful invaders or preventing clonal amplification of malignant cells. In vertebrates, in addition to innate immunity, an adaptive immune system provides a more focused and potent response, but one that requires more time to mobilize. It utilizes a novel system of hypermutation and recombination to provide a sufficiently broad repertory of receptors to recognize and eliminate, in principle, any potential microbial invader. In establishing and maintaining such a wide repertory of recognition structures, the adaptive immune system inevitably recognizes many epitopes on molecules within the body of the host. Thus, the same protective effector mechanisms of the healthy immune system, if out of control, can produce harm in the form of the immune mediated disorders described in these Volumes.

The most frequent disorders of the immune system are deficiencies. If the immune system fails to perform its core function of protection, infectious or malignant disease can follow. Most of these immune failures result from germ line inheritance of mutations in genes regulating the innate or adaptive

immune systems. The most frequent sign of an immune deficiency disease is infection due to one or more of the myriad microorganisms that inhabit the human environment.

A second group of immune-related illnesses results from loss of normal immunologic homeostasis. The regulatory devices that normally limit immune responses are inadequate. The failure may result from deficiencies, either inherited or acquired, of the overall regulatory machinery. Rather than a decrease in homeostatic regulation, immune disease can result from augmented immune responses. Powerful adjuvants, providing the non-antigen-specific signals, may overcome even normally functioning immune regulation.

Both types of immune-mediated disease are considered in our encapsulated knowledge. Allergies result from exposures to foreign substances that are harmless in the majority of individuals. As a group, allergic diseases affect at least 10% of the population and appear to be increasing over time in many populations. In contrast to an exaggerated response to foreign antigens, autoimmunity is the consequence of the "forbidden" recognition of some antigens in the host's body. Like allergic disease, autoimmune disease represents an uncontrolled immune response. Because allergic and autoimmune diseases can occur in different organ systems in the body, they can differ greatly in their clinical presentation, even though they share many genetic and regulatory features.

The goal in all medical immunology is to alleviate or prevent illness. If a disease is related to an inadequate immune response or to an overwhelming challenge, an intervention in the form of vaccination is a historically proven approach. Preventive vaccinations may be the most successful public health measure of the 20th century. New vaccines directed to oncoming newly emerging infectants or subtypes remains a major goal of current immunologic research. Potential adverse effects of vaccines also require constant attention. These days vaccines are being tested as a way of limiting or reducing malignant tumors.

Immunotherapy is a more modern success story as biological agents such as monoclonal antibodies and receptor-blocking ligands are increasingly available for control of diseases due to immunological derangement.

The need for an Encyclopedia of Medical immunology is compelling. Our encyclopedia is divided for convenience into the four subject areas discussed above: Immune deficiency diseases, allergic diseases, autoimmune diseases and vaccines. Each of these areas has significant and immediate relevance to medical practice and public health. Each is a growing area of research.

By bringing together these different areas in one comprehensive publication, the encyclopedia illustrates and emphasizes the fundamentals of the immune response. For immunity to play its part in good health, it must maintain homeostasis within itself and with all other physiologic systems. The challenges to maintaining immunologic good health are both internal and external. In the face of changes in the environment, including climate, infectious agents and industrial exposures, human survival places a need for constant recalibration of the immune system. Internally, the effects of aging,

hormonal changes, the microbiome and life cycle events (eg. puberty, pregnancy) also require readjustment of immunologic homeostasis. Interventions are designed to restore immunologic balance, to repair innate or induced deficiencies and to strengthen immune responses.

As Editors-in-Chief, we trust that the users will find this "encirclement" of a body of knowledge will prove helpful for decision making in promoting immunologic health and reducing immunologic disorders.

June 2014

Ian R. Mackay
Clayton, Victoria, Australia
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Preface

The immune system is the sensory organ that perceives and responds to dangerous alterations in tissue. The major alerts to the immune system are pathogen-associated molecular patterns (PAMPs) expressed by microbes and damage-associated molecular patterns (DAMPs) expressed by stressed or injured tissue. These triggers bind to membranes and cytosolic pattern recognition receptors (PRPs) and galvanize the immune system into action. An immune response begins with activation of an innate immune response and progresses to an adaptive immune response, which is the locus of immune memory. Interestingly, the response may also be communicated to the brain, which can contribute to the regulation of peripheral inflammation and immune responses.

During lymphocyte ontogeny and in the course of any immune response, there is a risk of the generation and/or activation of autoreactive lymphocytes that may cause an autoimmune disease. Development of autoimmune disease is regulated by the complement of genetic risk and protective alleles as well as by exposure to known and unknown environmental insults.

The encyclopedia will introduce the reader to processes of immune activation and quiescence that is required for self-tolerance. Both infectious and non-infectious mechanisms of immune activation are addressed. Moreover, tissue-specific immune function and immune pathologies are addressed in detail.

All authors are experts in their field, and all entries include a bibliography that provides further reading material. This encyclopedia is the first line in learning about specific immune mechanisms in health and disease. It has been designed to be useful to the new learner and to the expert alike.

June 2014

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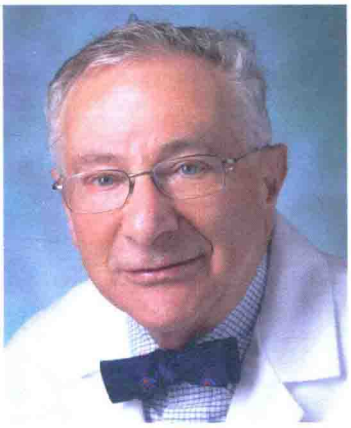
Photo credit:
Australian Academy of Science

Ian R. Mackay's research career, mostly directed to autoimmunity, began in 1956 in the Clinical Research Unit (CRU) of the Walter & Eliza Hall Institute and Royal Melbourne Hospital (RMH), Melbourne, Australia. It comprehended associations between disorders of immunological function and clinical expressions in diseases of obscure causation. Research laboratories in the Hall Institute and supervision of a 27-bed general medical ward in the adjacent RMH encouraged one to think of autoimmunity holistically rather than via any single disease. A particular interest in autoimmunity and liver and a collaboration with D Carleton Gajdusek pointed to autoimmune responses in causation of two major entities, chronic active hepatitis and primary biliary cirrhosis (PBC). The detection of autoimmune reactivity of a monoclonal plasma paraprotein was a key element in Burnet's formulation of the Clonal Selection Theory of Acquired Immunity. Mackay's later return to PBC in the molecular era (1980s) in research with M Eric Gershwin resulted in cloning and identification of the gene for the disease-associated "mitochondrial" autoantigen of PBC, the E2 subunit of pyruvate dehydrogenase complex (PDC-E2). In autoimmune hepatitis, levels in serum of transaminase enzymes were found to reflect ongoing hepatocellular damage, so providing a monitor of efficacy of immunosuppressive drugs prednisolone and azathioprine and, in the 1960s, the first long-term treatment trial established their benefit. This drug combination remains today as the standard therapy for autoimmune hepatitis.

In the early 1960s, Mackay became sufficiently convinced of the reality of autoimmunity to compile with F MacFarlane Burnet the first authoritative text (1963). Thereafter, he made research contributions on numerous autoimmune diseases, thyroiditis, multiple sclerosis, myasthenia gravis, pemphigus, and gastritis. With "Reg" Strickland, gastritis was separated into Type A (autoimmune) and Type B (later, bacterial) gastritis, foreshadowing bacterial infection in peptic ulcer disease. Mackay became a major protagonist for the early development of the specialty of Clinical Immunology and with Senga Whittingham laid out specifications for the practice of this specialty. In the 1980s, the RMH drew on the CRU to establish an AIDS service, and observations made on human papillomavirus (HPV) infection in rectal swabs of homosexual men led to Ian Frazer's development in Brisbane of an HPV vaccine for prevention of virus-induced cervical cancer.

In 1987, Mackay relocated to the Department of Biochemistry, Monash University, where with Merrill Rowley an autoimmunity laboratory was established for further investigation of PBC, Type 1 (autoimmune) diabetes, and rheumatoid arthritis. The laboratory sought to identify in various autoimmune diseases molecular epitopes (auto-epitopes) using contemporary techniques including antibody screening of phage-displayed random peptide libraries. A notable achievement arising from collaborations at Monash with James Whisstock, Gus Fenalti, and others was the crystallization of both isoforms of glutamic acid decarboxylase (GAD) 65 and 67, revealing the 3D structure and "molecular positioning" of the reactive antibody epitopes of the autoantigenic 65kD isoform and differences from the non-autoantigenic 67 kD isoform. This work is ongoing.



Noel R. Rose received his basic training in microbiology at Yale University followed by PhD and MD degrees at the University of Pennsylvania and State University of New York at Buffalo. He was appointed to the faculty at Buffalo in 1951, where he began his research career. His early studies under the tutelage of Professor Ernest Witebsky searched properties of the organ-specific antigens that characterize the unique functions of normal and malignant cells. In the course of these investigations, he discovered that he could produce an autoimmune disease in the thyroid gland by immunization with the major thyroid protein thyroglobulin. Until that time, it was generally accepted that in only a few "privileged sites" in the body were such pathogenic autoimmune responses possible. These studies opened the modern era of research on the autoimmune diseases and set the direction of Rose's career since that time. In the 1960s, he investigated the requisite conditions for inducing autoimmune disease and the delineation of the basic immunologic and pathological processes. He included studies on other organs, such as the pancreas, as well as allergic diseases. In 1971, he and his colleagues discovered the first major gene that is responsible for susceptibility to autoimmune diseases and proved that it was a member of the major histocompatibility complex. At that time, he moved his laboratory to Wayne State University in Detroit, where he and his colleagues carried out detailed studies on the genes responsible for autoimmune disease of the thyroid gland. He also performed early experiments of the regulatory role of the thymus-derived lymphocytes and other studies related to unique enzymes of specialized cells, especially prostatic cancer. In 1981, Rose moved to Johns Hopkins University, where he created a department devoted to studies of immunity and infection. He directed much of his research to infectious agents and chemicals that induce autoimmune disease. A major effort was devoted to developing an experimental model of autoimmune heart disease produced in genetically prepared mice by infection with a virus that led work to the first identification of a well-defined antigen responsible for cardiac inflammation. Investigations on this model revealed a stepwise process that leads from infection to initial harmless autoimmunity to later life-threatening autoimmune disease.

In addition to his research, Rose has been deeply involved in the clinical practice of immunology. He directs a diagnostic immunology laboratory; he

serves as expert consultant to the World Health Organization and as director of the WHO Collaborating Center for Autoimmune Disorders. He chaired the first committee on clinical immunology of the American Association of Immunologists and was co-founder of the Clinical Immunology Society. He was editor-in-chief of the first six volumes of the Manual of Clinical Immunology co-sponsored by the American Association of Immunologists and the American Society for Microbiology.

Throughout his career, Rose has had the opportunity of working with a number of leading investigators including Pierre Grabar at the Pasteuer Institute, Paris; Henry Isliker at the Swiss Institute for Cancer Research; Sir James Gowans at Oxford University; and Sir Gustav Nossal and Ian Mackay at the Walter and Eliza Hall Institute in Australia. While at the Hall Institute, Rose was invited to prepare a book describing the broad area of autoimmune disorders. He joined with Mackay in producing the first volume of the book, *The Autoimmune Diseases*, which is now in its fifth edition.

At Johns Hopkins, he continues to teach in medicine and public health and directs an active research laboratory. He also heads the Center for Autoimmune Disease Research, which facilitates communication and collaboration among specialists in the different facets of autoimmune disease research.

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Betty Diamond received an MD from Harvard Medical School in 1973. She performed a residency in Internal Medicine at Columbia Presbyterian Medical Center and then a postdoctoral fellowship in Immunology with Dr. Matthew Scharff at the Albert Einstein College of Medicine. She is currently Head of the Autoimmune Disease Center at the Feinstein Institute for Medical Research and on the faculty of the Albert Einstein College of Medicine.

Dr. Diamond's research has focused on the induction and pathogenicity of anti-DNA antibodies in Systemic Lupus Erythematosus. She received the Outstanding Investigator Award of the ACR in 2001, the Lee Howley Award from the Arthritis Foundation in 2002, and the Recognition Award from the National Association of MD-PhD Programs in 2004 and was elected to the Institute of Medicine in 2006. Dr. Diamond has served on the Scientific Council of NIAMS and the Board of Directors of the American College of Rheumatology. She is past president of the American Association of Immunologists.

Dr. Diamond's laboratory has demonstrated that a subset of anti-DNA antibodies cross-reacts with the NMDA receptor. These antibodies can mediate neuronal apoptosis in the hippocampus leading to a memory deficit or in the amygdala leading to a behavioral alteration. These antibodies are present in serum and cerebrospinal fluid and correlate with symptoms of neuropsychiatric lupus. These studies show that lupus antibodies can cause aspects of neuropsychiatric lupus in a noninflammatory fashion and create a paradigm for antibody-mediated changes in brain function in many conditions. With colleagues at the Feinstein Institute, she has generated a potential therapeutic to prevent neurotoxicity from these antibodies.

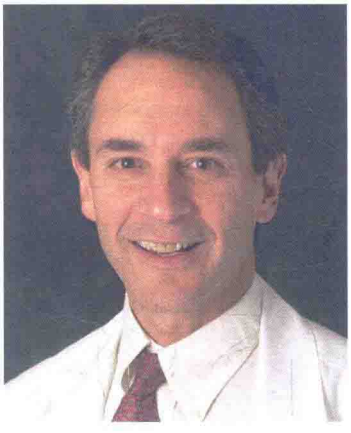
Anne Davidson, MBBS, The Feinstein Institute for Medical Research, NY, USA

Anne Davidson, received her MBBS degree from the University of Melbourne, Australia, and is a board-certified rheumatologist. She is currently an Investigator at the Feinstein Institute for Medical Research, New York, and Professor of Molecular Medicine at Hofstra North Shore-LIJ School of Medicine, New York, USA.

Dr. Davidson's research is focused on pathogenesis and therapy of SLE. She has worked extensively with mouse models of SLE, using newly discovered pathways of immune activation to determine the mechanisms of action of novel therapies for SLE. The results of these studies are then used to design mechanistic studies in the context of human SLE clinical trials. A main focus of the laboratory is to understand how B-cell tolerance is dysregulated in SLE. A second area of interest is to understand the mechanisms of inflammation within the SLE kidney, using a combination of systems biology and functional studies. She is a past recipient of the Dubois Award for SLE Research and the ACR Basic Science Distinguished Investigator Award.

Dr. Davidson is a member of the NIH study section PBKD and cochairs the grant review committee of the animal models subsection for the Lupus Research Institute. She is currently the Chair of the Scientific Advisory Council for the Rheumatology Research Foundation of the ACR.

Section Editors



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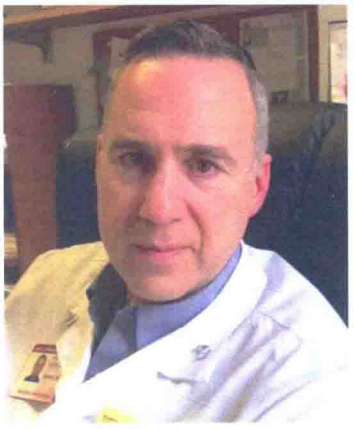

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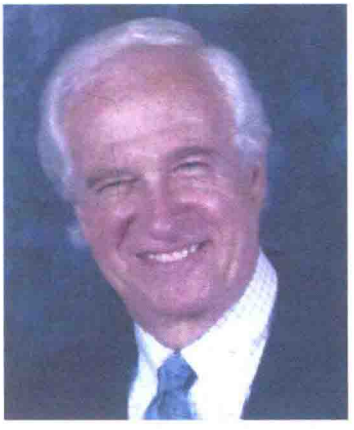

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