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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 constitutive 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 (e.g. 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

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Editors-in-Chief
Preface

The rapid change in immunology is both exciting and intimidating. The number of papers identified as of April 2014, in PubMed by the search term “allergy” has increased 16,668 since January 2013 and by 4,084 since January 2014. How is anyone to stay abreast?

This volume of the Encyclopedia of Medical Immunology, “Allergic Diseases”, has been assembled with the assistance of worldwide leading and emerging experts in the field of allergy and immunology. It is a living document as the growth of the science is much too rapid for textbooks to keep pace. The editors identified the major areas of allergic diseases that are likely to prompt questions and have engaged section editors to craft entries to answer these questions. Most of these are disease- or organ-focused, but others apply to general concepts, such as anaphylaxis, pharmacology, allergen immunotherapy, and insect allergy. The editors anticipate the addition of other sections and additional entries as this volume expands.

The value is that the extensive knowledge of allergy and allergic diseases is distilled into a compendium that is searchable. The breadth of clinical science and active research in the field is reflected in the volume’s range of topics, from IgE to contact dermatitis, from allergen immunotherapy to asthma, from insect hypersensitivity to rhinitis.

The editors wish to thank the outstanding section editors and the authors of the individual submissions for saying “yes” when asked to participate in this initiative. This is a group effort, and they should receive the credit.

The editors are confident you will find this volume an excellent “go-to source” for questions related to allergic diseases and a useful reference that meets your immediate and future needs.

We acknowledge the invaluable efforts of Ms. Geeta Gehi and the publisher for their assistance in making this effort a success.

June 2014

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Editors
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.
Editors

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Dennis K. Ledford was born and grew up in East Tennessee and was the valedictorian of his high school class. He attended college at Georgia Institute of Technology, Atlanta, Georgia. He graduated magna cum laude with a degree in chemical engineering and was selected for membership in Tau Beta Pi, the engineering honor society. He received his medical degree from the University of Tennessee Health Science Center. Dr. Ledford is a member of Alpha Omega Alpha Honor Medical Society (AOA), being selected as a third year student at the University of Tennessee, and he received the outstanding student of medicine award, graduating first in his class. He remained in Memphis for the completion of his internal medicine residency and served as chief medical resident for Dr. Gene Stoller at the City of Memphis Hospitals. A fellowship in rheumatology and immunology followed at New York University and Bellevue Hospital in New York. A fellowship in allergy and immunology at the University of South Florida completed his education. Dr. Ledford remained in Tampa at the University of South Florida (USF), joining the faculty and achieving the rank of professor of medicine in 2000. Dr. Ledford received the honor of being named the USF Morsani College of Medicine Mabel and Ellsworth Simmons Professor of Allergy in 2012. He is
actively involved in the pediatric and internal medicine allergy/immunology training programs and established and was the prior program director of Clinical and Laboratory Immunology at the University of South Florida.

Dr. Ledford has contributed in a variety of areas to the USF Morsani College of Medicine. He is a current member of the Professionalism Committee and is a faculty member of the Professionalism Education Task Group. He is the Past President of the Medical Faculty and served as President from 2012 to 2013. He has served on the medical student selection committee and was chair of the committee for two separate terms. He is the current director of the USF Allergy and Immunology Clinic at the Morsani Center for Advanced Health Care.

Dr. Ledford received the outstanding teacher award from the USF medical house staff, the outstanding medical volunteer of the year award in Hillsborough County, and the Governors’ Community Service Award from the American College of Chest Physicians. He has served on the American Board of Allergy and Immunology as secretary/treasurer and leader of the Maintenance of Certification initiative. He is a past president of the Florida Allergy, Asthma and Immunology Society, past member and vice-chair of the Residency Review Committee for Allergy/Immunology of the Accreditation Council of Graduate Medical Education, an associate editor of *The Journal of Allergy and Clinical Immunology*, editorial board member for *Annals of Allergy, Asthma and Immunology* and *The Journal of Allergy and Clinical Immunology: In Practice*, and a past contributing editor for *Allergy Watch*. He is a contributor to *UpToDate*.

Dr. Ledford has served the American Academy of Allergy, Asthma, and Immunology (AAAAI) in a number of capacities. He was a prior governor of the Southeast Region of the State, Local, and Regional Allergy Societies of the AAAAI and chair and member of several committees and currently serves on the In-Service Training Exam Committee as a section leader. He has been a member of the board of directors and was President of the AAAAI from 2011–2012. He served on numerous task forces for the AAAAI and as chair of the International Collaboration in Asthma Allergy and Immunology. Dr. Ledford is currently the chair of the Steering Committee for the Allergy, Asthma and Immunology Education and Research Trust.

Dr. Ledford works with the division’s faculty in managing Academic Associates in Allergy, Asthma and Immunology and is chief of the section of allergy and immunology at Florida Hospital, Tampa. He has been selected as one of America’s best doctors consecutively for more than 20 years. Clinical responsibilities occupy the majority of his time, but he has developed research interests in severe, steroid-dependent asthma, allergen characterization, the association of gastroesophageal reflux disease and upper airway disease, and eosinophilic esophagitis. Dr. Ledford has been the principal investigator in more than 20 and coinvestigator in more than 160 clinical trials, authoring or coauthoring more than 120 publications. He has been married to Jennifer S. Ledford for 40 years and is blessed with three children, Keith, Michael, and Robert, and 10 grandchildren, Madelyn, Andrew, Isaiah, Ian, Lukas, Kaila, Annika, Grant, Ethan, and Miles.
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Richard F. Lockey director of the Division of Allergy and Immunology, Department of Internal Medicine, and professor of medicine, pediatrics, and public health, was named the Joy McCann Culverhouse Chair in Allergy and Immunology at the University of South Florida College of Medicine, Tampa, Florida, in 1997. He is a tenured physician at the University of South Florida Morsani College of Medicine’s Health Science Center. He is also the chief of the Section of Allergy and Immunology at the James A. Haley Veterans’ Hospital. In 2007, he was honored by receiving the additional title of University Distinguished Health Professor.

He joined the faculty of the University of South Florida College of Medicine in 1973, at which time he also became a staff member at the James A. Haley Veterans’ Hospital. He is board-certified in internal medicine and in allergy and immunology.

The Division of Allergy and Immunology, Department of Internal Medicine, is a widely recognized treatment, teaching, and research facility in the field of allergy, asthma, and clinical immunology. For example, in one publication, five clinicians named “best doctors” in America are members of the Division. Through the efforts of Dr. Lockey, the Division is endowed with more than US$14 million dedicated to teaching and research. The faculty in the Division work in the state-of-the-art Joy McCann Culverhouse Airway Disease Research Center, a molecular biology laboratory with three full-time basic scientists devoted to long-term treatments and even a cure for allergic and immunologic diseases and asthma. In addition, the Division’s Clinical Research Unit has participated in most of the major drug innovations for the treatment of allergic diseases and asthma over the past 40 years. The Division currently has approximately 50 members including six core clinical physicians, three PhDs, eight voluntary clinical faculty, and other healthcare professionals and support staff. It is closely associated with and collaborates in teaching, research, and clinical care with the Division of Allergy and
Immunology, Department of Pediatrics, at the University of South Florida College of Medicine, Tampa, Florida, and All Children’s Hospital, St. Petersburg, Florida.

Dr. Lockey received an undergraduate degree from Haverford College, Haverford, Pennsylvania, and a medical degree from Temple University School of Medicine, Philadelphia, Pennsylvania, where he was a member of the Alpha Omega Alpha National Medical Honor Society. After completing his internship in medicine at Temple University School of Medicine in 1966, he finished his residency in internal medicine in December 1968 and fellowship in allergy and immunology at the University of Michigan, Ann Arbor, Michigan, in December 1970, where he also attended the University of Michigan Rackham Graduate School and received a master’s degree in internal medicine. He was a major, U.S. Air Force, and served as chief of allergy and immunology at Carswell Air Force Base, Fort Worth, Texas, from 1970 to 1972.

Dr. Lockey has authored, coauthored, or edited over 650 publications including 14 books, 20 monographs, and numerous experimental papers, invited papers, editorials, and book chapters. He has been an invited speaker on more than 450 occasions for both national and international scientific conferences. He is a coeditor of *The Journal of Investigational Allergology and Clinical Immunology* and is on or has served on the editorial boards of a variety of peer-reviewed journals including *The Journal of Allergy and Clinical Immunology*. In 1987, he edited a special edition of *The Journal of the American Medical Association, Primer on Allergic and Immunologic Diseases*. He was a coeditor of the first American College of Physicians and American Academy of Allergy, Asthma, and Immunology Medical Knowledge Self-Assessment Program (MKSAP) in Allergy and Immunology published in 1992. He has published and coauthored articles in *Nature, JAMA*, and *The New England Journal of Medicine*.

Fellowships include the American Academy of Allergy Asthma and Immunology, the American College of Chest Physicians, and past fellow, American College of Physicians. He is also a member of the American Thoracic Society, European Academy of Allergology and Clinical Immunology, Clinical Immunology Society, American College of Occupational and Environmental Medicine, as well as the European Thoracic Society. He is a past member of the American Medical Association and is a current member of the Florida Allergy, Asthma, and Clinical Immunology Society.

Other professional honors include serving as president of the American Academy of Allergy, Asthma, and Immunology (1992–1993). Dr. Lockey is also a past Director of the American Board of Allergy and Immunology, the organization that oversees and examines physician candidates for certification as specialists in allergy/immunology. He was elected to the board of the World Allergy Organization in 1995 and served as its president from January 2010 until December 2012. Dr. Lockey has served as an associate on two World Health Organization (WHO) committees striving to promote the highest level of health for all people globally. Each committee has prepared a vital position paper. One document was entitled *Prevention of Allergies and Asthma* and the other *Allergic Rhinitis and Its Impact on Asthma*. He was
also a coeditor of a third project, the WHO position paper *Allergen Immunotherapy: Therapeutic Vaccines for Allergic Diseases* published in 1998. He was editor of the World Allergy Organization’s web page and the World Allergy Organization’s e-mail *News and Notes* from 2004–2009, which serves all physicians, particularly physicians in the specialty of allergy and immunology, throughout the world.

In 1992, Dr. Lockey received a “Certificate of Appreciation” from the Florida Medical Association in addition to being featured with Drs. Samuel C. Bukantz and Robert A. Good, mentors and colleagues, on the cover of the June/July 1996 special issue of *The Journal of the Florida Medical Association*.

Included among the numerous distinctions Dr. Lockey has received throughout his career are the Alumni Achievement Awards, Temple University School of Medicine, Philadelphia, PA, and McCaskey High School, Lancaster, PA. He has also received an award for Outstanding Leadership in Chapter Development and Patient Support from the National Asthma and Allergy Foundation of America, an appreciation award from the Asthma and Allergy Foundation of America, Florida Chapter, and the Team Physician Award for his services as a volunteer physician for the University of South Florida Athletics Department. He received a Special Recognition Award in 1993 and Distinguished Service Award in 1999 from the American Academy of Allergy, Asthma, and Immunology. In 2008, he was awarded the Distinguished Clinician Award from this same organization. He was awarded the Florida Academy of Sciences Medal for the year 2000 presented for outstanding work in scientific research, activities in the dissemination of scientific knowledge, and service to the community. He received the University of South Florida Distinguished Service Award in 2001 and is an honorary member of several societies. He was awarded the Southern Medical Association, Dr. Robert D. and Alma W. Moreton Original Research Award in 2012.

As Director of the Division of Allergy and Immunology, Dr. Lockey has helped train over 90 MDs in the specialty program of allergy and immunology and approximately 40 postgraduate PhDs or MDs from various parts of the world in clinical and basic research. Dr. Lockey continues to spend equal amounts of time caring for patients in basic and clinical research, particularly as it relates to allergic and immunologic diseases, and teaching at the University of South Florida College of Medicine and its affiliated hospitals. Dr. Lockey is married to Carol Lockey and has two children, Brian Christopher Lockey and Keith Edward Lockey, and is blessed with four grandchildren, Olivia, Benjamin, William, and Nicholas.
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