case studies in immunology
A CLINICAL COMPANION
FIFTH EDITION

Congenital Asplenia

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The science of immunology started as a case study. On May 15, 1796 Edward Jenner inoculated a neighbor’s son, James Phipps, with vaccinia (cowpox) virus. Six weeks later, on July 1, 1796, Jenner challenged the boy with live smallpox and found that he was protected against this infection. During its 208 year history the basic science of immunology has been closely related to clinical observations and has shed light on the pathogenesis of disease.

The study of immunology provides a rare opportunity in medicine to relate the findings of basic scientific investigations to clinical problems. The case histories in this book are chosen for two purposes: to illustrate in a clinical context essential points about the mechanisms of immunity; and to describe and explain some of the immunological problems often seen in the clinic. For this fifth edition, we have added five completely new cases that illustrate both recently discovered genetic immunodeficiencies and some more familiar and common diseases with interesting immunology. We have revised other cases to add newly acquired information about these diseases. Fundamental mechanisms of immunity are illustrated by cases of genetic defects in the immune system, immune complex diseases, immune mediated hypersensitivity reactions and autoimmune and alloimmune diseases. These cases describe real events from case histories, largely but not solely drawn from the records of the Boston Children’s Hospital and the Brigham and Women’s Hospital. Names, places, and time have been altered to obscure the identity of the patients described; all other details are faithfully reproduced. The cases are intended to help medical students and pre-medical students to learn and understand the importance of basic immunological mechanisms, and particularly to serve as a review aid; but we hope and believe they will be useful and interesting to any student of immunology.

Each case is presented in the same format. The case history is preceded by basic scientific facts that are needed to understand the case history. The case history is followed by a brief summary of the disease under study. Finally there are several questions and discussion points that highlight the lessons learned from the case. These are not intended to be a quiz but rather to shed further light on the details of the case.

The Garland Science website (www.garlandscience.com) now provides instructors who adopt Case Studies with a link to Garland Science Classwire, where the textbook art can be found in a downloadable, web-ready format, as well as in PowerPoint-ready format.

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Levin of St. Mary’s Hospital, London for supplying case materials. Our colleagues in the Immunology Division of the Children’s Hospital have provided invaluable service by extracting summaries of long and complicated case histories; we are particularly indebted to Drs. Lynda Schneider, Leonard Bacharier, Francisco Antonio Bonilla, Hans Oettgen, Jonathan Spergel, Rima Rachid, Scott Turvey, Jordan Orange, Emanuela Castigli, Andrew McGinnitie, Marybeth Son, Melissa Hazen, Douglas McDonald and John Lee, and to Lilit Garibyan, third year medical student at Harvard Medical School, in constructing several case histories. In the course of developing these cases, we have been indebted for expert and pedagogic advice to Fred Alt, Mark Anderson, John Atkinson, Hugh Auchincloss, Stephen Baird, Zuhair K. Ballas, Leslie Berg, Corrado Betterle, Kurt Bloch, Jean-Laurent Casanova, John J. Cohen, Michael I. Colston, Anthony DeFranco, Peter Densen, Ten Feizi, Alain Fischer, Christopher Goodnow, Edward Kaplan, George Miller, Luigi Notarangelo, Peter Parham, Jaakko Perheentupa, Jennifer Puck, Westley Reeves, Patrick Revy, Peter Schur, Anthony Segal, Lisa Steiner, Stuart Tangye, Cox Terhorst, Emil Unanue, André Veillette, Jan Vilcek, Mark Walport, Fenella Woznarowska, and John Zabriskie.

Eleanor Lawrence has spent many hours honing the prose as well as the content of the cases and we are grateful to her for this. We would also like to acknowledge the Garland Science team for their work on the fifth edition.

A note to the reader

The cases presented in this book have been ordered so that the main topics addressed in each case follow as far as possible the order in which these topics are presented in the seventh edition of Janeway’s Immunobiology by Kenneth Murphy, Paul Travers, and Mark Walport. However, inevitably many of the early cases raise important issues that are not addressed until the later chapters of Immunobiology. To indicate which sections of Immunobiology contain material relevant to each case, we have listed on the first page of each case the topics covered in it. The color code follows the code used for the five main sections of Immunobiology: yellow for the introductory chapter and innate immunity, blue for the section on recognition of antigen, red for the development of lymphocytes, green for the adaptive immune response, purple for the response to infection and clinical topics, and orange for methods.

Dedication

This fifth edition is dedicated to Fred Rosen (1935-2005). Fred dedicated his career of more than 50 years to the investigation and care of patients with primary immunodeficiency disease. Above all, he loved to teach and he did so superbly, aided by an encyclopedic knowledge of immunology, an incisive intelligence, an incredible memory, and charisma combined with an aura of authority. Fred had an enormous influence on many generations of both basic and clinical immunologists. This book is his brainchild and his contribution to it will be sorely missed.
Case 1  Congenital Asplenia
Case 2  Chronic Granulomatous Disease
Case 3  Leukocyte Adhesion Deficiency
Case 4  Hereditary Angioneurotic Edema
Case 5  Factor I Deficiency
Case 6  Deficiency of the C8 Complement Component
Case 7  Hereditary Periodic Fever Syndromes
Case 8  Interleukin 1 Receptor-associated Kinase 4 Deficiency
Case 9  X-linked Hypohydrotic Ectodermal Dysplasia and Immunodeficiency
Case 10  X-linked Agammaglobulinemia
Case 11  X-linked Hyper IgM Syndrome
Case 12  Activation-induced Cytidine Deaminase (AID) Deficiency
Case 13  Common Variable Immunodeficiency
Case 14  X-linked Severe Combined Immunodeficiency
Case 15  Adenosine Deaminase Deficiency
Case 16  Omenn Syndrome
Case 17  MHC Class I Deficiency
Case 18  MHC Class II Deficiency
Case 19  Multiple Myeloma
Case 20  T-Cell Lymphoma
Case 21  Interferon-γ Receptor Deficiency
Case 22  Wiskott-Aldrich Syndrome
Case 23  X-linked Lymphoproliferative Syndrome
Case 24  Autoimmune Lymphoproliferative Syndrome (ALPS)
Case 25  Immune Dysregulation, Polyendocrinopathy, Enteropathy X-linked Disease
Case 26  Toxic Shock Syndrome
Case 27  Acute Infectious Mononucleosis
Case 28  Mixed Essential Cryoglobulinemia
Case 29  Rheumatic Fever
Case 30  Lepromatous Leprasy
Case 31  Acquired Immune Deficiency Syndrome (AIDS)
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The adaptive immune response occurs mainly in the secondary lymphoid tissue—the lymph nodes, the gut-associated lymphoid tissue, and the spleen (Fig. 1.1). Pathogens and their secreted antigens are trapped in these tissues, and presented to the naive lymphocytes that constantly pass through. Microorganisms that enter the body through the skin or the lungs drain to regional lymph nodes where they stimulate an immune response. Microorganisms and food antigens that enter the gastrointestinal tract are collected in the gut-associated lymphoid tissue. Microbes that enter the bloodstream stimulate an immune response in the spleen.

Congenital Asplenia

The role of the spleen in immunity.

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Topics bearing on this case:
- Circulation of lymphocytes through secondary lymphoid tissues
- Toxoid vaccines
- Hemagglutination tests
- T-cell help in antibody response
The spleen is organized to accomplish two functions (Fig. 1.2). In addition to being a secondary lymphoid organ, it acts as a filter of the blood to remove aged or abnormal red cells and other extraneous particles that may enter the bloodstream, including microorganisms. The lymphoid function of the spleen is carried out in the white pulp and the filtration function by the red pulp. Many microorganisms are recognized directly and engulfed by the phagocytes of the red pulp. Others are not removed efficiently until they are coated by antibodies generated in the white pulp. In experimental animals, an immune response (as measured by antibody formation) can be detected in the white pulp of the spleen approximately 4 days after the intravenous injection of a dose of microorganisms. The clearance of antibody- and complement-coated bacteria or viruses by the phagocytic cells of the red pulp of the spleen is very rapid. Rapid clearance from the blood is important as it prevents these bacteria from disseminating and causing infections of the meninges (meningitis), the kidney (pyelonephritis), the lung (pneumonia), or other distant anatomical sites.
Bacteria enter the bloodstream all the time, such as when we brush our teeth or when we have a local infection, for example of the skin or middle ear. Normally these bacteria are disposed of efficiently by the spleen. When, for one reason or another, the spleen is not present, serious, even fatal, infections occur.

**The case of Susan Vanderveer: a fatality because of an absent spleen.**

Mr and Mrs Vanderveer owned a farm in the Hudson Valley in lower New York State. They were both descended from Dutch settlers who came to the Hudson Valley in the mid 17th century. There were multiple consanguineous marriages among their ancestors, and Mr and Mrs Vanderveer were distantly related to each other. At the time of this case, they had five children—three girls and two boys. Their youngest daughter, Susan, was 10 months old when she developed a cold, which lasted for 2 weeks. On the 14th day of her upper respiratory infection, she became sleepy and felt very hot. Her mother found that her temperature was 41.7°C. When Susan developed convulsive movements of her extremities, she was rushed to the emergency room but she died on the way to the hospital. Post-mortem cultures of blood were obtained, and also from her throat and cerebrospinal fluid. All the cultures grew *Haemophilus influenzae*, type b. At autopsy Susan was found to have no spleen.

At the time of Susan’s death her 3-year-old sister, Betsy, also had a fever of 38.9°C. She complained of an earache and her eardrums were found to be red. She had no other complaints and no other abnormalities were detected on physical examination. Her white blood count was 28,500 cells μl⁻¹ (very elevated). Cultures from her nose, throat, and blood grew out *Haemophilus influenzae*, type b. She was given ampicillin intravenously for 10 days in the hospital and was then sent home in good health. Her cultures were negative at the time of discharge from the hospital. She was seen by a pediatrician on three occasions during the following year for otitis media (inflammation of the middle ear), pneumonia, and mastoiditis (inflammation of the mastoid bone behind the ear).

David, Susan’s 5-year-old brother, had been admitted to the hospital at 21 months of age with meningitis caused by *Streptococcus pneumoniae*. He had responded well to antibiotic therapy and had been discharged. Another occurrence of pneumococcal meningitis at 27 months of age had also been followed by an uneventful recovery after antibiotics. He had had pneumonia at age 3½ years. At the time of Susan’s death he was well.

The two other children of the Vanderveers, a girl aged 8 years and a newborn male, were in good health.

All the Vanderveer children had received routine immunization at ages 3, 4, and 5 months with tetanus and diphtheria toxoids and killed *Bordetella pertussis* to protect against tetanus, diphtheria, and whooping cough, which are three potentially fatal diseases caused by bacterial toxins (Fig. 1.3). Serum agglutination tests were used to test their antibody responses to these and other immunogens. Samples of serum from both Betsy and David caused hemagglutination (the clumping of red blood cells) when added to red blood cells (type O) coated with tetanus toxoid. Hemagglutinating antibodies to tetanus toxoid were seen at serum dilutions of 1:32 for both Betsy and David, and were found at a similar titer in their 8-year-old sister. All three children were given typhoid vaccine subcutaneously and 4 weeks later...
samples of their sera were tested for the ability to agglutinate killed Salmonella typhosa. The results indicated a normal immune response. David had an agglutination titer of 1:16, Betsy 1:32, and their normal 8-year-old sister 1:32. All three children were given 1 ml of a 25% suspension of sheep red cells intravenously. David had a titer of 1:4 for hemagglutinating antibodies against sheep red blood cells prior to the injection. He was tested again 2 and 4 weeks later and there was no increase in titer. Betsy had an initial titer of 1:32 and her titer did not rise either. The 8-year-old normal sister had a preimmunization titer of 1:32. She was tested 2 and 4 weeks after the immunization, when she was found to have a hemagglutinating titer of 1:256 against sheep red blood cells.

All the children and their parents were injected intravenously with radioactive colloidal gold (198Au), which is taken up by the reticuloendothelial cells of the liver and spleen within 15 minutes after the injection. A scintillation counter then scans the abdomen for radioactive gold. The pattern of scintillation reveals that Betsy and David have no spleens (Fig. 1.4).

Asplenia and splenectomy.

The genetic defect causing asplenia has not yet been identified. The Vanderveer family is unusual in that three of their first four children were born without spleens. After the events described in this case, the Vanderveers had three more children. One of the boys and the girl were also born without spleens; the other boy had a normal spleen. This family provides us with an uncomplicated circumstance in which to examine the role of the spleen. The major consequence of its absence is a susceptibility to bacteremia, usually caused by the encapsulated bacteria Streptococcus pneumoniae or Haemophilus influenzae. This susceptibility is caused by a failure of the immune response to these common extracellular bacteria when they enter the bloodstream.
Surgical removal of the spleen is quite common. The capsule of the spleen may rupture from trauma, for example in an automobile accident. In such cases, the spleen has to be surgically removed very quickly because of blood loss into the abdominal cavity. The spleen may also be removed surgically for therapeutic reasons in certain autoimmune diseases, or because of a malignancy in the spleen. After splenectomy, patients, particularly children, are susceptible to bloodstream infections by microorganisms to which they have no antibodies. Microorganisms to which the host has antibodies are removed quickly from the bloodstream by the liver, where the Kupffer cells complement the role of the red pulp of the spleen. Antibodies to the encapsulated bacteria that commonly cause trouble with bloodstream infections persist for a very long time in the bloodstream of exposed individuals, even in the absence of a spleen (for reasons that are not fully understood). Adults who already have antibodies to these microorganisms are therefore much less vulnerable to problems of bacteremia than children who have not yet developed antibodies to these germs.

**Questions.**

1. Nicholas Biddleboy, a 5-year-old boy, had his spleen removed following a sledding accident, during which both he and his sled struck a tree trunk. In the emergency room of a nearby hospital, it was determined that his spleen had ruptured. The surgeon, following removal of a spleen that had indeed ruptured, calls you for an immunology consultation. What do you advise?

2. Why did David and Betsy have normal responses to the typhoid vaccine but not to the sheep red blood cells?

3. The Vanderveer family is unique in the medical literature. The parents, who were distantly related, were normal and had normal spleens. Five of their eight children were born without spleens. Of these, only Betsy subsequently had children—four boys and one girl. They are all normal and have spleens. What is the inheritance pattern of congenital asplenia in this family? According to Mendelian laws how many of the eight Vanderveer children would be expected to have no spleen?

**Figure Acknowledgments**

Fig. 1.2 bottom panel from *The Journal of Experimental Medicine* 1972, 135:200–219. Copyright 1972 The Rockefeller University Press.