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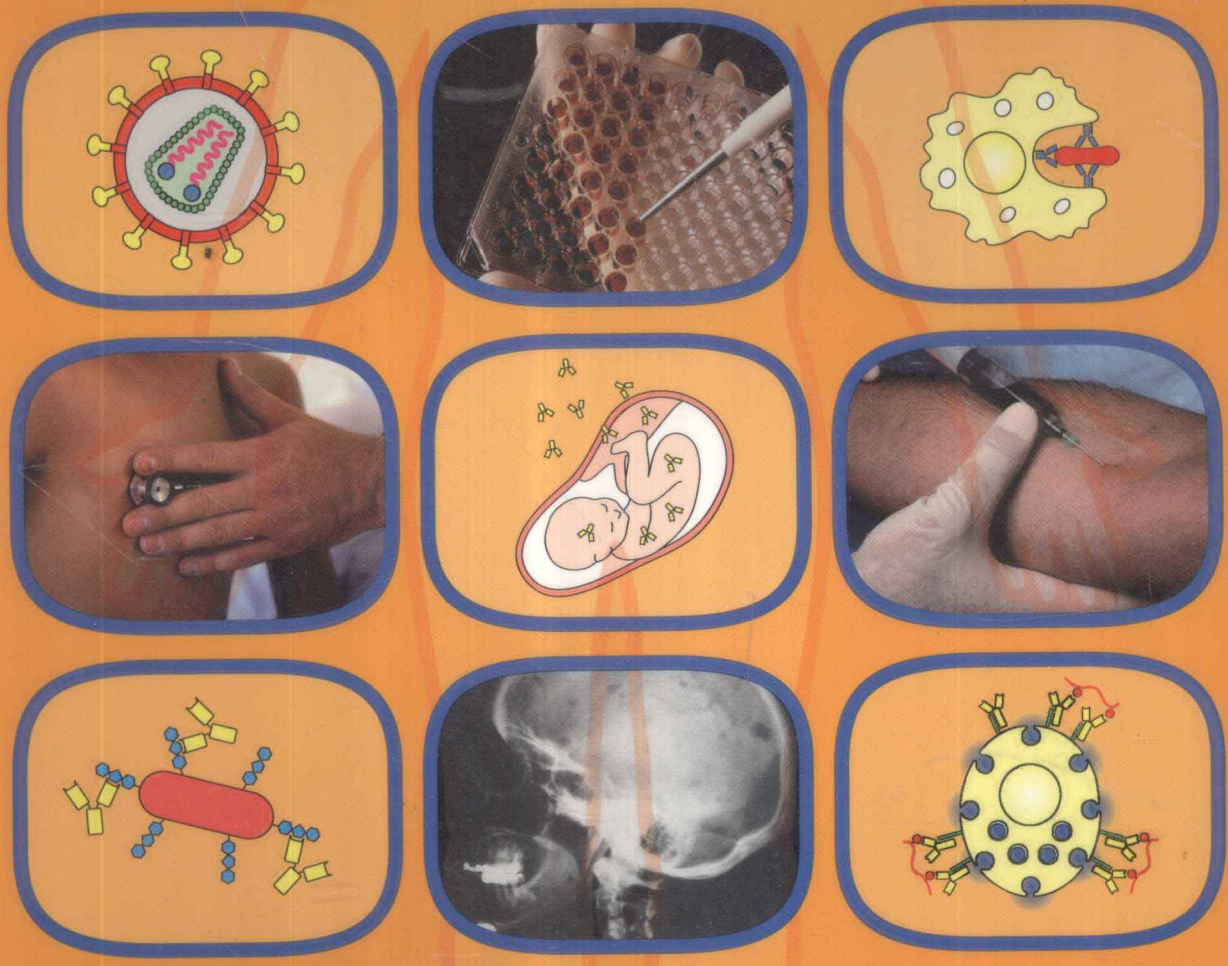
A CLINICAL COMPANION



THIRD EDITION

FRED ROSEN • RAIF GEHA

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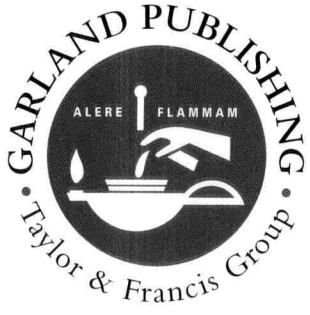

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Preface to the third edition

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 third 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. Fundamental mechanisms of immunity are illustrated with 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 revision 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 what has been learned from the case.

The color-coded table at the beginning of each case refers the reader to the relevant topics in the fifth edition of *Immunobiology: The Immune System in Health and Disease* by Charles A. Janeway, Paul Travers, Mark Walport, and Mark Shlomchik. In that edition of *Immunobiology*, the cases dealt with in our text are now indicated by a marginal icon—the caduceus. As another new feature, the Garland Science website (http://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 Power Point-ready format.

We are grateful to Dr. Robertson Parkman of the Los Angeles Children's Hospital for the MHC class II deficiency case, to Dr. Henri de la Salle of the Centre Régional de Transfusion Sanguine in Strasbourg, France for the MHC class I deficiency case and to Professor Michael Levin of St Mary's Hospital, London for the interferon-γ receptor deficiency case. We are also greatly indebted to our colleagues Drs. David Dawson, Susan Berman, Lawrence Shulman, and David Hafler of the Brigham and Women's Hospital, to Dr. Razzaque Ahmed of the Harvard School of Dental Medicine, to Drs. Ernesto Gonzalez and Scott Snapper of the Massachusetts General Hospital and to Drs. Peter Newburger and Jamie Ferrara of the Departments of Pediatrics of the University of Massachusetts and the University of Michigan 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, and Rima Rachid in constructing several case histories. In the course of developing these chapters, we have been indebted for expert and pedagogic advice to Mark Walport, Jan Vilcek, George Miller, Ten Feizi, Fenella Woznarowska, Michael I. Colston, Anthony Segal, Peter Parham, Emil Unanue, Leslie Berg, Christopher Goodnow, Hugh Auchincloss, Anthony De Franco, John J. Cohen, Cox Terhorst, Fred Alt, Jennifer Puck, Luigi Notarangelo, William Murphy and Alistair Coles.

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. Angela Bennett, Mark Ditzel, Sarah Gibbs and Matthew McClements have painstakingly organized the text and figures and without their vital work this book would not have come into being.

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 fifth edition of *Immunobiology* by Charles A. Janeway Jr., Paul Travers, Mark Walport, and Mark Shlomchik. 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.

Photograph acknowledgements

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CONTENTS

CASE 1 Congenital Asplenia

The role of the spleen in immunity.

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.

Topics bearing on this case:
Circulation of lymphocytes through secondary lymphoid tissues
Toxoid vaccines
Hemagglutination tests
T-cell help in antibody response

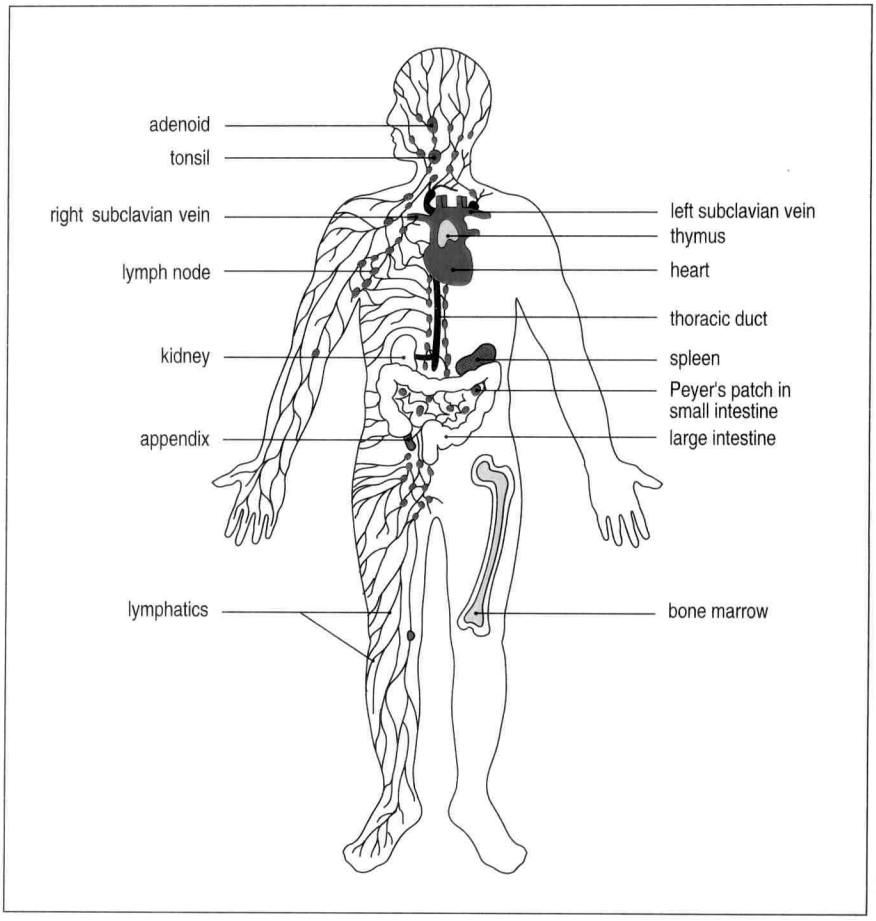
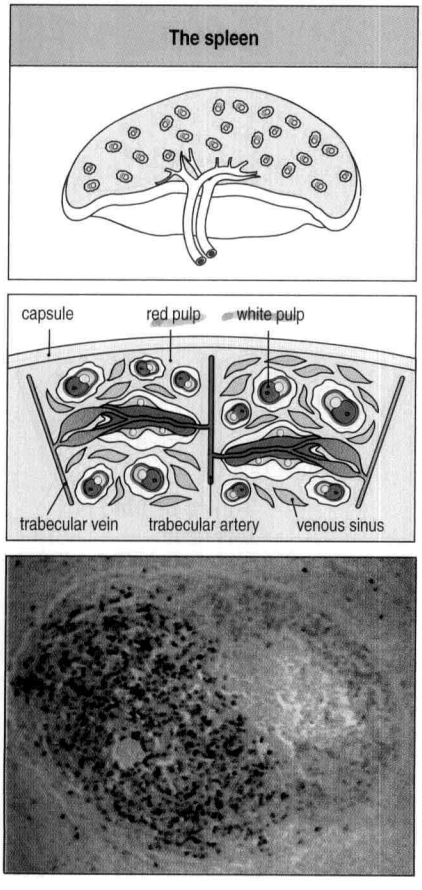


Fig. 1.1 The distribution of lymphoid tissues in the body. Lymphocytes arise from stem cells in bone marrow, and differentiate in the central lymphoid organs (yellow)—B cells in bone marrow and T cells in the thymus. They migrate from these tissues through the bloodstream to the peripheral lymphoid tissues (blue)—the lymph nodes, spleen, and mucosal-associated lymphoid tissues such as tonsils, Peyer's patches, and appendix. These are the sites of lymphocyte activation by antigen. Lymphatics drain extracellular fluid as lymph through the lymph nodes and into the thoracic duct, which returns the lymph to the bloodstream by emptying into the left subclavian vein. Lymphocytes that circulate in the bloodstream enter the peripheral lymphoid organs, and are eventually carried by lymph to the thoracic duct where they reenter the bloodstream.



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.

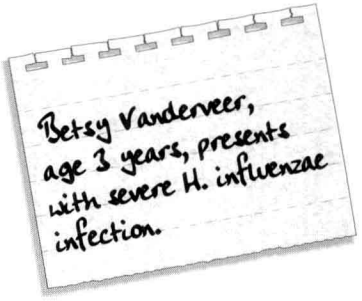
Fig. 1.2 Schematic views and light micrograph of a section of spleen. The spleen consists of red pulp (pink areas), which is a site of red blood cell destruction, interspersed with lymphoid white pulp. The center panel shows an enlargement of a small section of the spleen showing the arrangement of discrete areas of white pulp around central arterioles. The white pulp is shown in transverse section. Although the organization of the spleen is similar to that of a lymph node, antigen enters the spleen from the blood rather than from the lymph. Photograph courtesy of J.C. Howard.

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, diptheria, 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

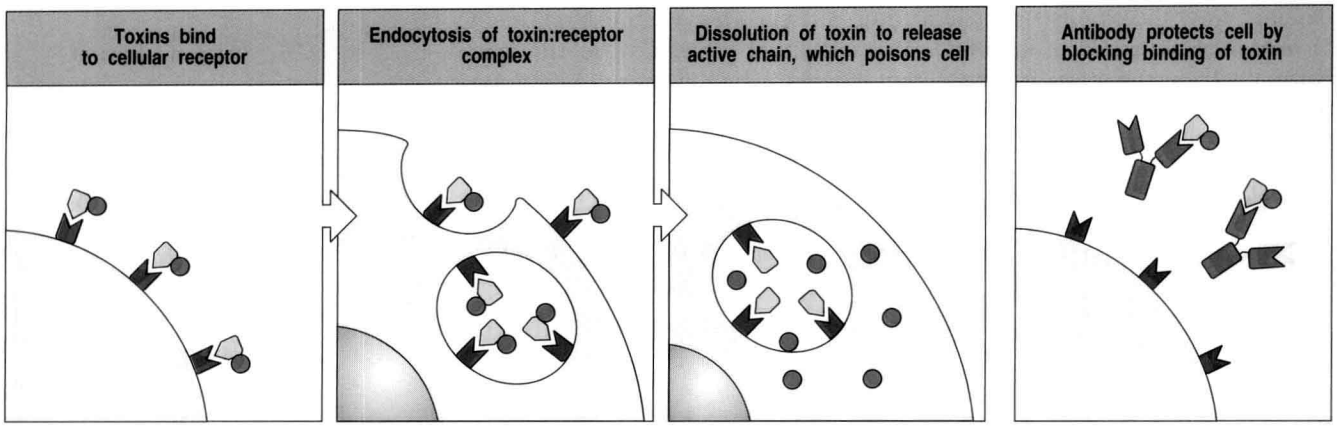
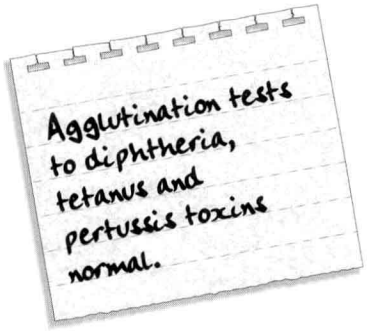


Fig. 1.3 Neutralization by antibodies protects cells from toxin action. Secreted bacterial toxins usually contain several distinct moieties. One piece of the toxin must bind a cellular receptor, which allows the molecule to be internalized. A second part of the toxin molecule then enters the cytoplasm and poisons the cell. In some cases, a single molecule of toxin can kill a cell. Antibodies that inhibit toxin binding can prevent, or neutralize, these effects. Protective antibodies can be generated by immunizing subcutaneously with toxoids. Toxoids are toxins rendered harmless by treating with denaturing agents, such as formalin, which destroy their toxicity but not their ability to generate neutralizing antibodies. In the case of the DPT vaccine, the killed *Bordetella pertussis* cells act as an adjuvant, which enhances the immune response to all components of the vaccine by delivering activating signals to antigen-presenting cells.



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 (Au^{198}), 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.

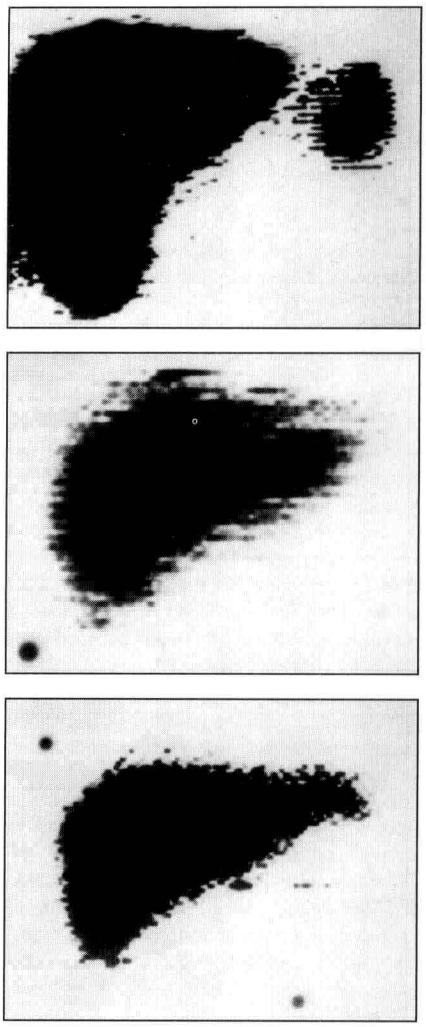


Fig. 1.4 A scintillation scan of the abdomen after intravenous injection with radioactive colloidal gold (Au^{198}) reveals that Betsy and David Vanderveer have no spleens. The top panel shows an abdominal scan of Betsy's mother. The large mass on the left is the liver and the small mass on the right is the spleen. The reticuloendothelial cells of both liver and spleen take up the labeled gold within 15 minutes after the injection. No spleen is seen in either Betsy (middle panel) or David (lower panel).

Discussion and 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?

First you find out that Nicholas has had all his routine immunizations. He received DPT (diphtheria, pertussis, and tetanus antigens) and oral live poliovirus vaccine at ages 3, 4, and 5 months, and a booster of both before entering kindergarten. He was also given MMR (mumps, measles, and rubella live vaccines) at 9 months of age. At the same time, he was given Hib vaccine (the conjugated capsular polysaccharide of *Haemophilus influenzae*, type b; Fig. 1.5). His growth and development have been normal. He suffered a middle ear infection (otitis media) at age 24 months. Other than that he has had no other illnesses, except for a common cold each winter. You feel comfortable that he is protected against infection with *Haemophilus influenzae* from the Hib vaccine. However, your concern about the possibility of pneumococcal infection leads you to advise the surgeon to immunize Nicholas against pneumococcal capsular poysaccharides by giving him Pneumovax (a vaccine containing the major prevalent pneumococcal polysaccharides). You also advise prophylactic antibiotics, to be taken at a low dose daily but at higher doses when Nicholas has any dental work done, or any invasive surgical procedure.

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

The typhoid vaccine was given subcutaneously and a response was mounted in a regional lymph node. The sheep red blood cells were given intravenously, and, in the absence of a spleen, failed to enter any secondary lymphoid tissue where an immune response could occur.

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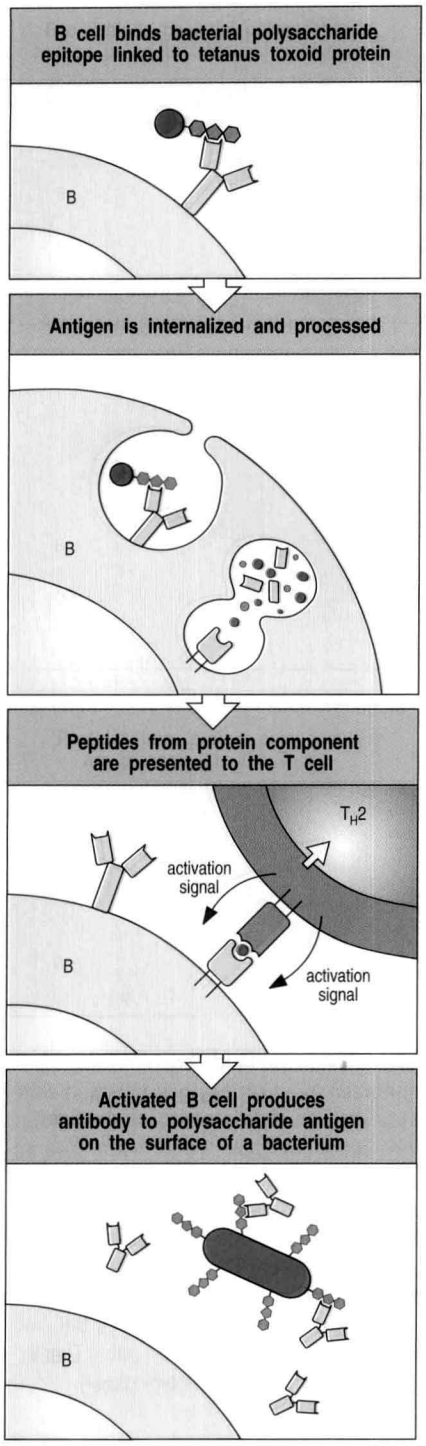


Fig. 1.5 *Haemophilus influenzae* b vaccine is a conjugate of bacterial polysaccharide with the tetanus toxoid protein, which enhances the immune response by allowing a polysaccharide-specific B cell to recruit T-cell help. The B cell recognizes and binds the polysaccharide, internalizes and degrades the toxoid protein to which it is attached, and displays peptides derived from it on surface MHC class II molecules. Helper T cells generated in response to earlier vaccination against the toxoid recognize the complex on the B-cell surface and activate the B cell to produce antibody against the polysaccharide. This antibody can then protect against infection with *H. influenzae* type b.

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?*

The defect is inherited as an autosomal recessive. The parents are normal but each carries this recessive gene. Furthermore, they are consanguineous, a setting in which autosomal recessive disease is encountered more frequently than in outbred people. Chance would predict that one in four (that is, two) of their eight children would be affected. Each pregnancy provides a one in four chance of the fetus' inheriting the abnormal gene from both parents. As it turned out, this happened in five of Mrs Vanderveer's eight pregnancies. Since Betsy married a normal man, all her children are heterozygous for the defect, like their maternal grandparents, and have normal spleens.

CASE 2 X-linked Agammaglobulinemia

An absence of B lymphocytes.

One of the most important functions of the adaptive immune system is the production of antibodies. It is estimated that a human being can make over one million different specific antibodies. This remarkable feat is accomplished through a complex genetic program carried out by B lymphocytes and their precursors in the bone marrow (Fig. 2.1). Every day about 2.5 billion (2.5×10^9) early B-cell precursors (pro-B cells) take the first step in this genetic program and enter the body pool of pre-B cells. From this pool of rapidly dividing pre-B cells 30 billion daily mature into B cells, which leave the bone marrow as circulating B lymphocytes, while 55 billion fail to mature successfully and undergo programmed cell death. This process continues throughout life, although the numbers gradually decline with age.

Topics bearing on this case:

- B-cell maturation
- Effector functions of antibodies
- Humoral versus cell-mediated immunity
- Effector mechanisms of humoral immunity
- Methods for measuring T-cell function
- Actions of complement and complement receptors

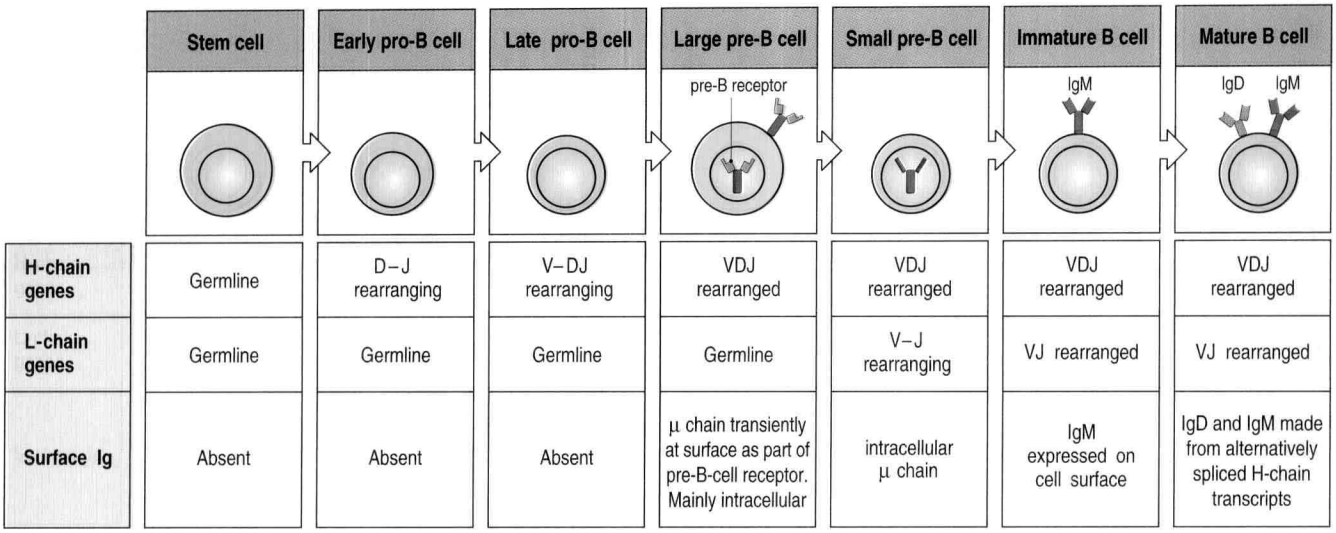
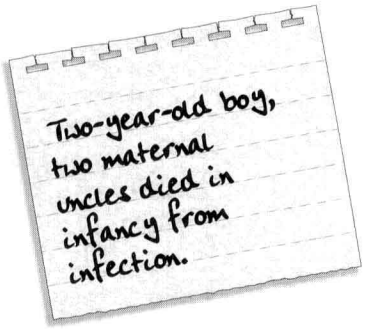


Fig. 2.1 The development of B cells proceeds through several stages marked by the rearrangement of the immunoglobulin genes. The bone marrow stem cell that gives rise to the B-lymphocyte lineage has not yet begun to rearrange its immunoglobulin genes; they are in germline configuration. The first rearrangements of D gene segments to J_H gene segments occur in the early pro-B cells, generating late pro-B cells. In the late pro-B cells, a V_H gene segment becomes joined to the rearranged DJ_H, producing a pre-B cell that is expressing both low levels of surface and high levels of cytoplasmic μ heavy chain. Finally, the light-chain genes are rearranged and the cell, now an immature B cell, expresses both light chains (L chains) and μ heavy chains (H chains) as surface IgM molecules. Cells that fail to generate a functional surface immunoglobulin, or those with a rearranged receptor that binds a self-antigen, die by programmed cell death. The rest leave the bone marrow and enter the bloodstream.

Mature circulating B cells proliferate on encounter with antigen and differentiate into plasma cells, which secrete antibody. Antibodies, which are made by the plasma cell progeny of B cells, protect by binding to and neutralizing toxins and viruses, by preventing the adhesion of microbes to cell surfaces and, after binding to microbial surfaces, by fixing complement and thereby enhancing phagocytosis and lysis of pathogens (Fig. 2.2).

This case concerns a young man who has an inherited inability to make antibodies. His family history reveals that he has inherited this defect in antibody synthesis as an X-linked recessive abnormality. This poses an interesting puzzle because the genes encoding the structure of the immunoglobulin polypeptide chains are encoded on autosomal chromosomes and not on the X chromosome. Further inquiry reveals that he has no B cells, so that some gene on the X chromosome is critical for the normal maturation of B lymphocytes.

The case of Bill Grignard: a medical student with scarcely any antibodies.



Bill Grignard was well for the first 10 months of his life. In the next year he had pneumonia once, several episodes of otitis media (inflammation of the middle ear) and on one occasion developed erysipelas (streptococcal infection of the skin) on his right cheek. These infections were all treated successfully with antibiotics but it seemed to his mother, a nurse, that he was constantly on antibiotics.

His mother had two brothers who had died 30 years prior to Bill's birth from pneumonia in their second year of life, before antibiotics were available. She also has two sisters who are well; one has a healthy son and daughter and the other a healthy daughter.

Bill was a bright and active child who gained weight, grew, and developed normally but he continued to have repeated infections of the ears and sinuses and twice again had pneumonia. At 2 years and 3 months his local pediatrician tested his serum immunoglobulins. He found 80 mg dl^{-1} IgG (normal 600–1500 mg dl^{-1}), no IgA (normal 50–125 mg dl^{-1}), and only 10 mg dl^{-1} IgM (normal 75–150 mg dl^{-1}).

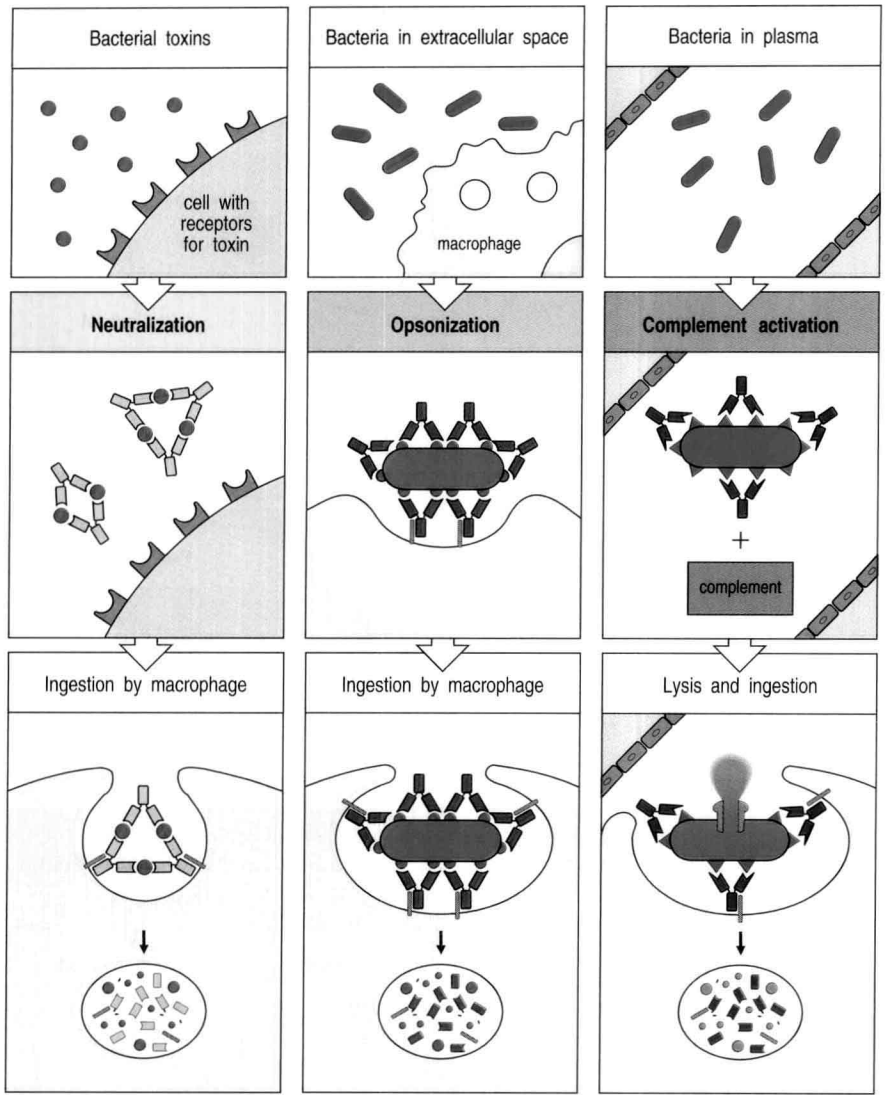


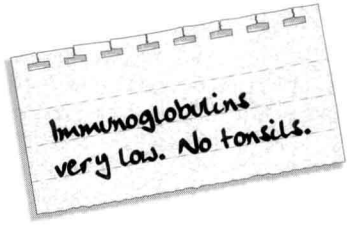
Fig. 2.2 Antibodies can participate in host defense in three main ways. The left column shows antibodies binding to and neutralizing a bacterial toxin, preventing it from interacting with host cells and causing pathology. Unbound toxin can react with receptors on the host cell, whereas the toxin:antibody complex cannot. Antibodies also neutralize complete virus particles and bacterial cells by binding to them and inactivating them. The antigen:antibody complex is eventually scavenged and degraded by macrophages. Antibodies coating an antigen render it recognizable as foreign by phagocytes (macrophages and polymorphonuclear leukocytes), which then ingest and destroy it; this is called opsonization. The central column shows the opsonization and phagocytosis of a bacterial cell. The right column shows the activation of the complement system by antibodies coating a bacterial cell. Bound antibodies form a receptor for the first protein of the complement system, which eventually forms a protein complex on the surface of the bacterium that favors its uptake and destruction by phagocytes and can, in some cases, directly kill the bacterium. Thus, antibodies target pathogens and their products for disposal by phagocytes.

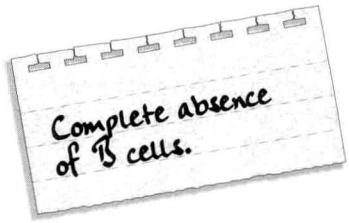
Bill was started on monthly intramuscular injections of gamma globulin; his serum IgG level was maintained at 200 mg dl^{-1}. He started school at age 5 years and performed very well (he was reading at second grade level at age 5 years) despite prolonged absences because of recurrent pneumonia and other infections.

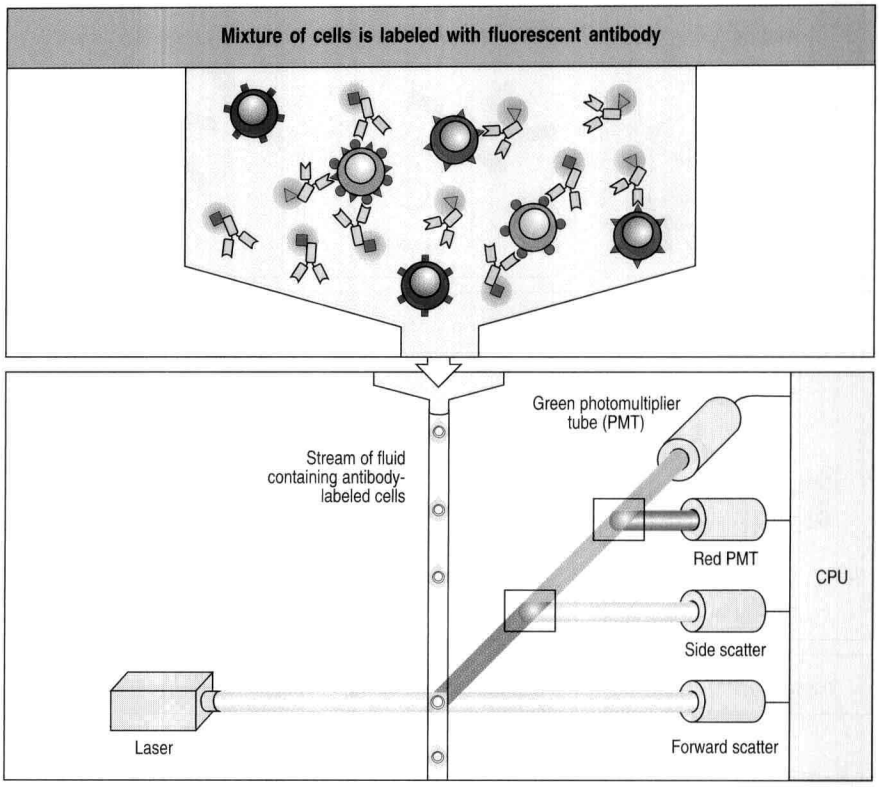
At 9 years of age he was referred to the Children's Hospital because of atelectasis (collapse of part of a lung) and a chronic cough. On physical examination he was found to be a well-developed, alert boy. He weighed 33.5 kg and was 146 cm in height (this height and weight is normal for his age). The doctor noted that he had no visible tonsils (he had never had a tonsillectomy). With a stethoscope the doctor also heard rales (moist crackles) at both lung bases.

Further family history revealed that Bill had one younger sibling, John, a 7-year-old brother, who also had contracted pneumonia on three occasions. John had a serum IgG level of 150 mg dl^{-1}.

Laboratory studies at the time of Bill's visit to the Children's Hospital gave a white blood cell count of 5100 μl^{-1} (normal) of which 45% were neutrophils (normal), 43% were lymphocytes (normal), 10% were monocytes (elevated) and 2% were eosinophils (normal).







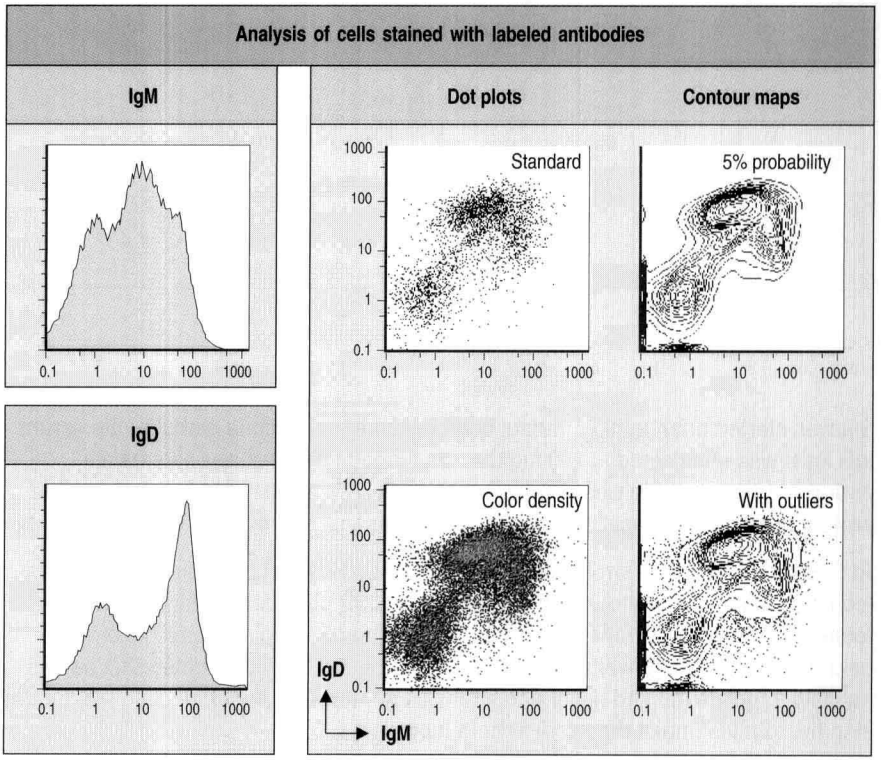


Fig. 2.3 The FACS™ allows individual cells to be identified by their cell-surface antigens and to be sorted. Cells to be analyzed by flow cytometry are first labeled with fluorescent dyes (top panel). Direct labeling uses dye-coupled antibodies specific for cell-surface antigens (as shown here), while indirect labeling uses a dye-coupled immunoglobulin to detect unlabeled cell-bound antibody. The cells are forced through a nozzle in a single-cell stream that passes through a laser beam (second panel). Photo-multiplier tubes (PMTs) detect the scattering of light, which is a sign of cell size and granularity, and emissions from the different fluorescent dyes. This information is analyzed by computer (CPU). By examining many cells in this way, the number of cells with a specific set of characteristics can be counted and levels of expression of various molecules on these cells can be measured. The lower part of the figure shows how these data can be represented, using the expression of two surface immunoglobulins, IgM and IgD, on a sample of B cells from a mouse spleen. The two immunoglobulins have been labeled with different-colored dyes. When the expression of just one type of molecule is to be analyzed (IgM or IgD), the data are usually displayed as a histogram, as in the left-hand panels. Histograms display the distribution of cells expressing a single measured parameter (e.g., size, granularity, fluorescence color). When two or more parameters are measured for each cell (IgM and IgD), various types of two-color plot can be used to display the data, as shown in the right-hand panel. All four plots represent the same data. The horizontal axis represents intensity of IgM fluorescence and the vertical axis the intensity of IgD fluorescence. Two-color plots provide more information than histograms; they allow recognition, for example, of cells that are 'bright' for both colors, 'dull' for one and bright for the other, dull for both, negative for both, and so on. For example, the cluster of dots in the extreme lower left portions of the plots represents cells that do not express either immunoglobulin, and are mostly T cells. The standard dot plot (upper left) places a single dot for each cell whose fluorescence is measured. It is good for picking up cells that lie outside the main groups but tends to saturate in areas containing a large number of cells of the same type. A second means of presenting these data is the color dot plot (lower left), which uses color density to indicate high-density areas. A contour plot (upper right) draws 5% 'probability' contours, with 5% of the cells lying between each contour providing the best monochrome visualization of regions of high and low density. The lower right plot is a 5% proba-bility contour map that also shows outlying cells as dots.

Flow cytometry (Fig. 2.3) showed that 85% of the lymphocytes bound an antibody to CD3, a T-cell marker (normal); 55% were helper T cells reacting with an anti-CD4 antibody; and 29% were cytotoxic T cells reacting with an anti-CD8 antibody (normal). However, none of Bill's peripheral blood lymphocytes bound an antibody to the B-cell marker CD19 (normal 12%) (Fig. 2.4).

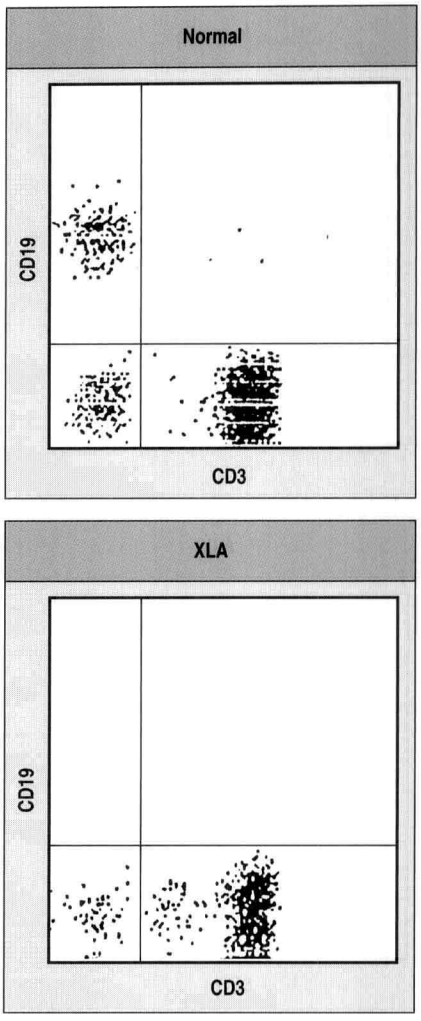


Fig. 2.4 Clinical FACS analysis of a normal individual (top panel) and a patient with X-linked agammaglobulinemia (bottom panel). Blood lymphocytes from a normal individual bind labeled antibody to both the B-cell marker CD19 and the T-cell marker CD3 (see top panel). However, blood lymphocytes from an individual with X-linked agammaglobulinemia such as Bill show only binding to antibodies against the T-cell marker CD3. This indicates an absence of B cells in these patients.

T-cell proliferation indices in response to PHA, concanavalin A, tetanus toxoid, and diphtheria toxoid were 162, 104, 10, and 8, respectively (all normal). Serum IgG remained low at 155 mg dl^{-1}, while serum IgA and IgM were undetectable.

Bill was started on a preparation of gamma globulin rendered suitable for intravenous administration. He was given a dose of gamma globulin intravenously so as to maintain his IgG level at 600 mg dl^{-1}. He improved remarkably. The rales at his lung bases disappeared. He continued to perform well in school and ultimately entered medical school. Except for occasional bouts of conjunctivitis or sinusitis, which respond well to oral antibiotic treatment, he remains in good health and leads an active life. He became skilled at inserting a needle into a vein on the back of his hand and he infuses himself with 10 g gamma globulin every weekend.

X-linked agammaglobulinemia.

Males such as Bill with a hereditary inability to make antibodies are subject to recurrent infections. However, the infections are due almost exclusively to common extracellular bacterial pathogens—*Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes,* and *Staphylococcus aureus.* An examination of scores of histories of boys with this defect has established that they have no problems with intracellular infections, such as those caused by the common viral diseases of childhood. T-cell number and function in males with X-linked agammaglobulinemia are normal, and they therefore have normal cell-mediated responses, which are able to terminate viral infections and infections with intracellular bacteria such as those causing tuberculosis.

The bacteria that are the major cause of infection in X-linked agammaglobulinemia are all so-called pyogenic bacteria. Pyogenic means pus-forming, and pus consists largely of neutrophils. The normal host response to pyogenic infections is the production of antibodies that coat the bacteria and fix complement, thereby enhancing rapid uptake of the bacteria into phagocytic cells such as neutrophils and macrophages, which destroy them. Since antibiotics came into use, it has been possible to treat pyogenic infections successfully. However, when they recur frequently, the excessive release of proteolytic enzymes (for example elastase) from the bacteria and from the host phagocytes causes anatomical damage, particularly to the airways of the lung. The bronchi lose their elasticity and become the site of chronic inflammation (this is called bronchiectasis). If affected males do not receive replacement therapy—gamma globulin—to prevent pyogenic infections, they eventually die of chronic lung disease.

Gamma globulin is prepared from human plasma. Plasma is pooled from approximately one thousand or more blood donors and is fractionated at very cold temperatures (–5°C) by adding progressively increasing amounts of ethanol. This method was developed by Professor Edwin J. Cohn at the

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