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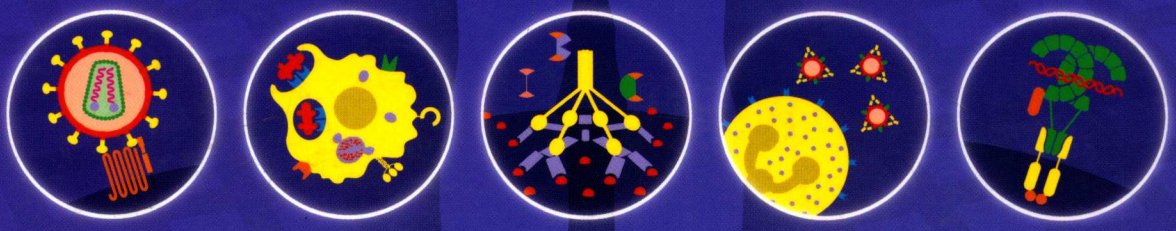
CASE STUDIES IN IMMUNOLOGY

A CLINICAL COMPANION

6TH EDITION



RAIF GEHA • LUIGI NOTARANGELO

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Raif Geha • Luigi Notarangelo

Harvard Medical School

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Preface

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 the past 215 years, the basic science of immunology has shed light on the pathogenesis of immune-mediated diseases. Conversely, the investigation of diseases of the immune system, particularly of genetically inherited primary immunodeficiency diseases, has provided valuable insights into the functioning of the normal immune system.

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 sixth edition, we have added 10 new cases that are representative of key aspects of immune system development and function, as revealed by specific forms of primary immunodeficiencies and by common diseases with interesting underlying immunologic mechanisms. These cases include DiGeorge syndrome, familial hemophagocytic lymphohistiocytosis, Chediak–Higashi syndrome, hyper IgE syndrome, ataxia telangiectasia, WHIM syndrome, severe congenital neutropenia, recurrent herpes simplex encephalitis, juvenile arthritis, and Crohn's disease. New concepts, such as the genetic control of myeloid development, the mechanisms of lymphocyte-mediated cytotoxicity, chemokine-mediated control of leukocyte trafficking, the biology and function of T_H17 cells, and type 1 interferon-mediated control of viral infections, are also discussed in the book. We have also revised several cases to add newly acquired information about these diseases and novel developments in immunological therapeutic intervention. The cases illustrate fundamental mechanisms of immunity, as shown by genetic disorders of the immune system, immune-complex diseases, immune-mediated hypersensitivity reactions and autoimmune and alloimmune diseases. They 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 in Boston, Massachusetts. Names, places, and times have been altered to obscure the identities of the patients; other details are faithfully reproduced. The cases are intended to help medical students and pre-medical students learn about basic immunological mechanisms and understand their importance, and particularly to serve as a review aid, but we believe they will be useful and interesting to any student of immunology.

Each case is presented in the same format. The case history itself is preceded by an introduction presenting basic scientific facts needed to understand the case. The case history is followed by a brief summary of the disease under study and discussion of the clinical findings. Finally, several questions and discussion points highlight the lessons learned. These questions are not intended as a quiz but rather to shed further light on the case.

We are grateful to Dr. Peter Densen of the University of Iowa for the C8 deficiency case material, Dr. Sanjiv Chopra of Harvard Medical School for the case on mixed essential cryoglobulinemia, and Dr. Peter Schur of the Brigham and Women's Hospital for the rheumatoid arthritis case. We also thank Dr. Jane Newburger of the Boston Children's Hospital for the case on rheumatic fever and Dr. Eric Rosenberg of the Massachusetts General Hospital for the AIDS case. We thank Drs. Lisa Stutius Bartnikas, Arturo Borzutzky, Janet Chou, Ari Fried, Erin Janssen, and Andrew Shulman of Children's Hospital Boston for the cases of hyper IgE syndrome, Chediak–Higashi syndrome, ataxia telangiectasia, DiGeorge syndrome, systemic-onset juvenile idiopathic arthritis,

and Crohn's disease, respectively; Dr. Jolan Walter of the Massachusetts General Hospital for the case of hemophagocytic lymphohistiocytosis; Dr. Anna Virginia Gulino of Ospedale Sant'Eugenio in Rome, for the case of WHIM syndrome; and Dr. Itai Pessach of Children's Hospital Boston for the case of severe congenital neutropenia. 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; to Drs. Peter Newburger and Jamie Ferrara of the Departments of Pediatrics of the University of Massachusetts and the University of Michigan; to Dr. Robertson Parkman of the Los Angeles Children's Hospital; to Dr. Fabio Facchetti, Dr. Lucia Notarangelo, and Dr. Antonio Regazzoli of the Spedali Civili of Brescia, Italy; to Henri de la Salle of the Centre régional de Transfusion Sanguine in Strasbourg, France; and to Professor Michael Levin of St. Mary's Hospital, London, for supplying case materials. Our colleagues and trainees 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, John Lee, and Lilit Garibyan 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, Talal Chatila, John J. Cohen, Michael I. Colston, Anthony DeFranco, Peter Densen, Ten Feizi, Alain Fischer, Christopher Goodnow, Edward Kaplan, George Miller, 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 sixth edition.

A note to the reader

The main topics addressed in each case correspond as much as possible to topics that are presented in the eighth edition of *Janeway's Immunobiology* by Kenneth Murphy. 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 sections on recognition of antigen, pink for the development of lymphocytes, green for the adaptive immune response, purple for the response to infection and clinical topics, and orange for methods.

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The images from Case Studies in Immunology, 6th Edition, are available on the Instructor Site in two convenient formats: PowerPoint® and JPEG. They have been optimized for display on a computer. The resources may be browsed by individual cases and there is a search engine. Figures are searchable by figure number, figure name, or by keywords used in the figure legend from the book.

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Contents

CASE 1 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 more than 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. 1.1). 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's 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.

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. 1.2).

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.

This case was prepared by Raif Geha, MD, in collaboration with Ari Fried, MD.

Topics bearing on this case:
Humoral versus cell-mediated immunity
Effector functions of antibodies
Effector mechanisms of humoral immunity
Actions of complement and complement receptors
B-cell maturation
Methods for measuring T-cell function

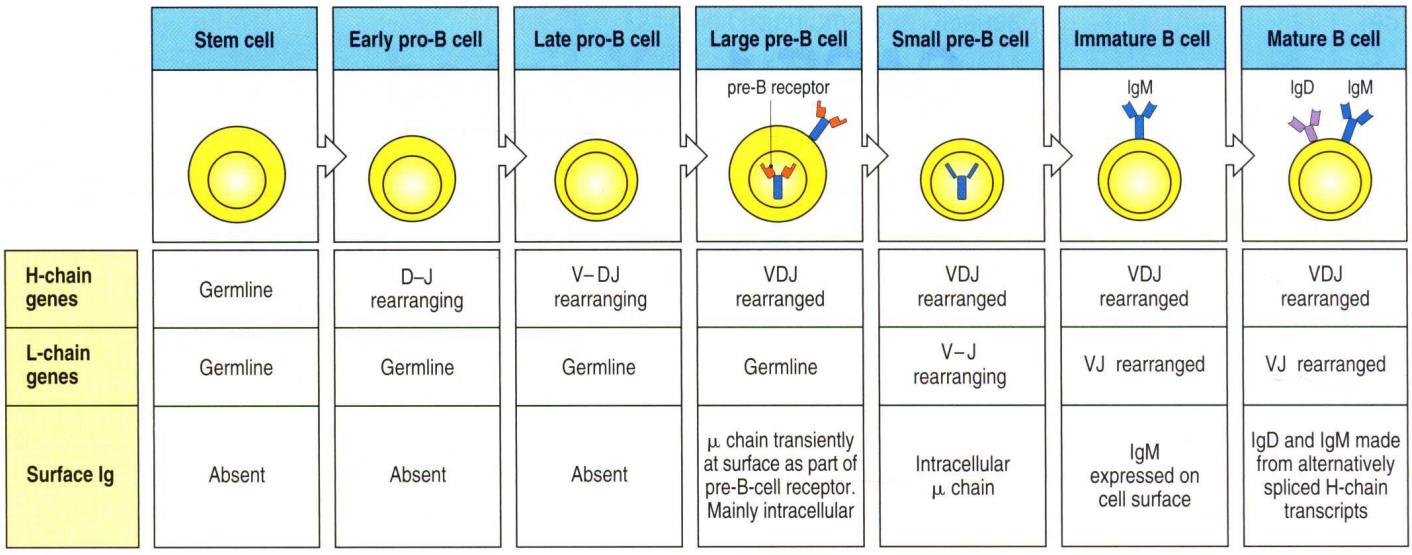
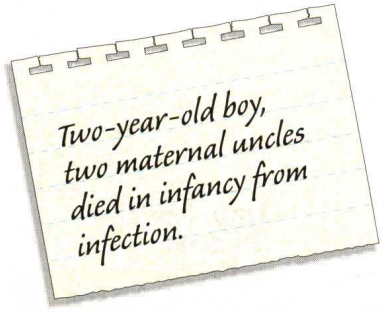


Fig. 1.1 The development of B cells proceeds through several stages marked by the rearrangement of the immunoglobulin genes. The bone marrow stem cell that gives rise to the B-lymphocyte lineage has not yet begun to rearrange its immunoglobulin genes; they are in germline configuration. The first rearrangements 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.

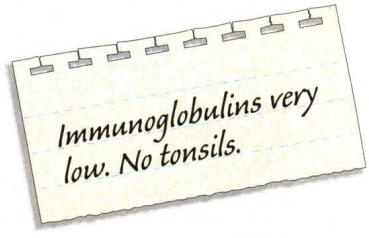
The case of Bill Grignard: a medical student with scarcely any antibodies.



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 had two sisters who were well; one had 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 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}).



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 tall (height and

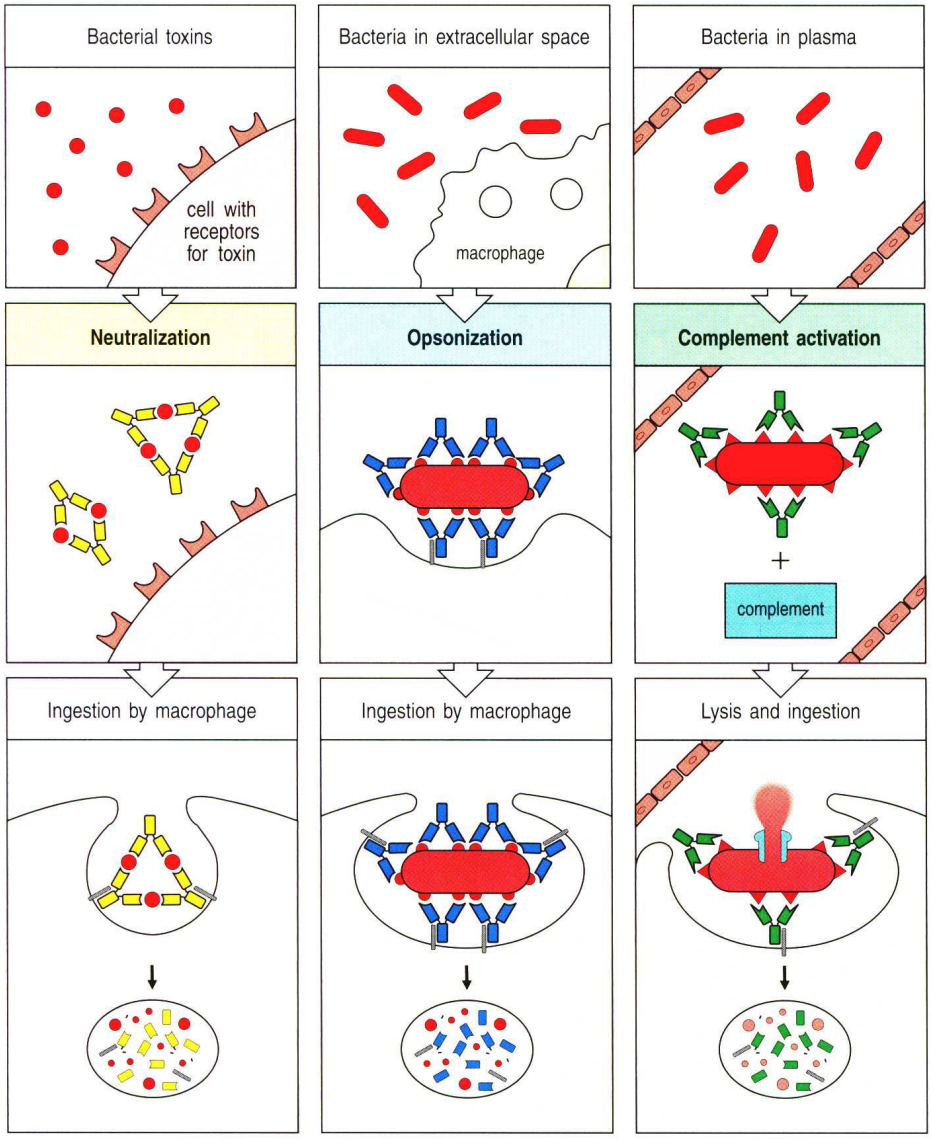


Fig. 1.2 Antibodies can participate in host defense in three main ways. The left-hand column shows antibodies binding to and neutralizing a bacterial toxin, preventing it from interacting with host cells and from causing pathology. Unbound toxin can react with receptors on the host cell, whereas the 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-hand 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.

weight 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).

Flow cytometry (Fig. 1.3) 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 against the B-cell marker CD19 (normal 12%) (Fig. 1.4).

T-cell proliferation indices in response to phytohemagglutinin, 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}, and serum IgA and IgM were undetectable.

Complete absence of B cells.

Bill was started on a preparation of gamma globulin rendered suitable for intravenous administration. He was given a dose of gamma globulin intravenously 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 eventually entered medical school. Except for occasional bouts of conjunctivitis or sinusitis, which respond well

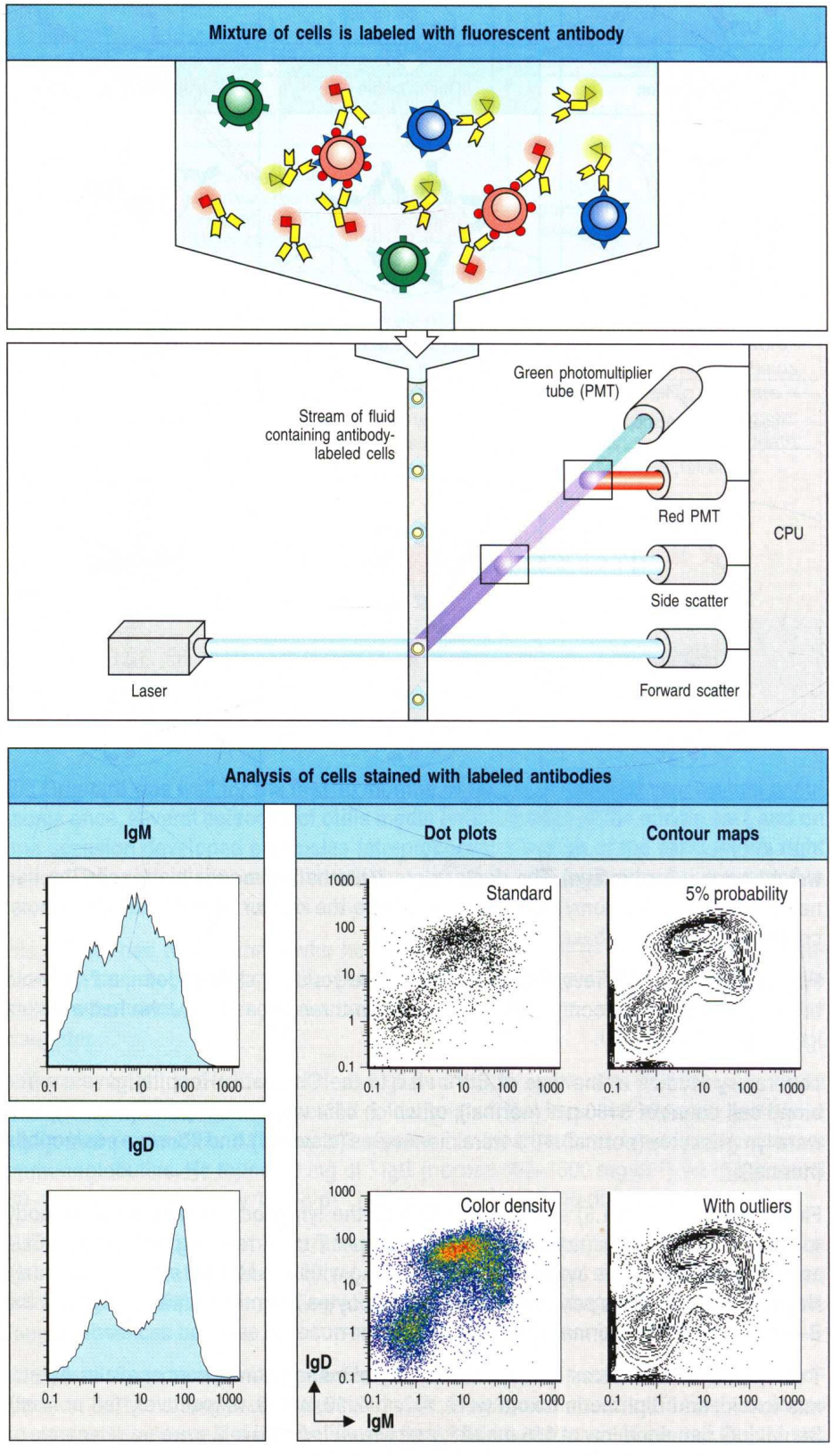


Fig. 1.3 The FACS™ allows individual cells to be identified by their cell-surface antigens and to be sorted. Cells to be analyzed by flow cytometry are first labeled with fluorescent dyes (top panel). Direct labeling uses dye-coupled antibodies specific for cell-surface antigens (as shown here), whereas 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 bottom 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 (such as 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 the 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; these 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 method 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% probability contour map that also shows outlying cells as dots.

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 of 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 these individuals 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 1000 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 Harvard Medical School during the Second World War. The five plasma fractions obtained are still called Cohn Fractions I, II, III, IV, and V. Cohn Fraction I is mainly composed of fibrinogen. Cohn Fraction II is almost pure IgG and is called gamma globulin. Cohn Fraction III contains the beta globulins, including IgA and IgM; Fraction IV, the alpha globulins; and Fraction V, albumin. Cohn Fraction II, or gamma globulin, is commercially available as a 16% solution of IgG. During the processing of the plasma some of the gamma globulin aggregates, and for this reason the 16% solution cannot be given intravenously. Aggregated gamma globulin acts like immune complexes and causes a reaction of shaking chills, fever, and low blood pressure when given intravenously. Gamma globulin can be disaggregated with low pH or insoluble proteolytic enzymes. It can then be safely administered intravenously as a 5% solution. In newer preparations, fractionation is followed by a further purification step using anion-exchange (DEAE) chromatography to get rid of trace contaminants. To decrease the risk of transmitting infection, the current commercially available products have several virus removal and inactivation steps incorporated into the manufacturing process.

The gene defect in X-linked agammaglobulinemia was identified when the gene was mapped to the long arm of the X chromosome at Xq22 and

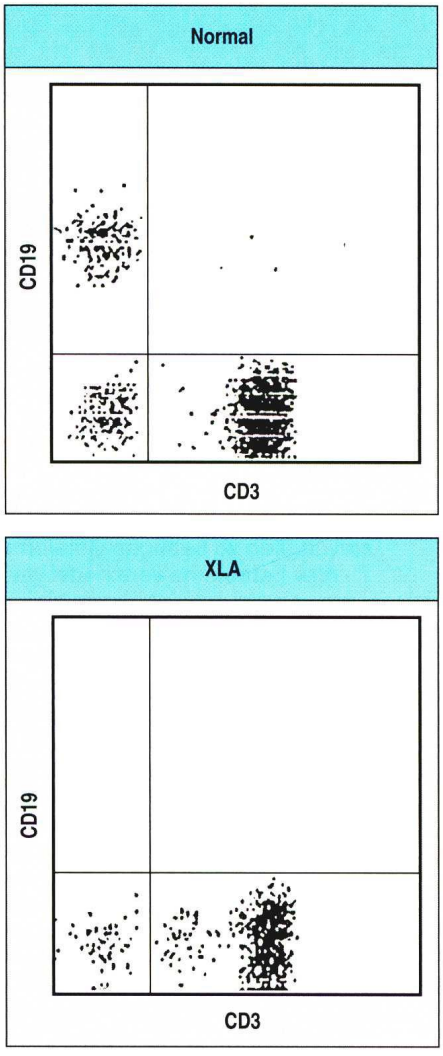


Fig. 1.4 Clinical FACS™ analysis of a normal individual (top panel) and a patient with X-linked agammaglobulinemia (XLA) (bottom panel). Blood lymphocytes from a normal individual bind labeled antibody to both the B-cell marker CD19 and the T-cell marker CD3 (see top panel). However, blood lymphocytes from an individual such as Bill with X-linked agammaglobulinemia show only binding to antibodies against the T-cell marker CD3. This indicates an absence of B cells in these patients.

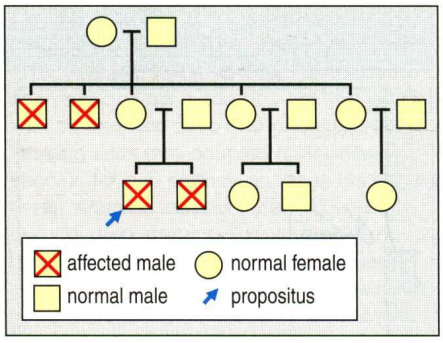


Fig. 1.5 Bill's family tree.

subsequently cloned. The gene, *BTK*, encodes a cytoplasmic protein tyrosine kinase called Bruton's tyrosine kinase (Btk), which is found in pre-B cells, B cells, and neutrophils. Btk is activated at different stages of B-cell development by the engagement of both the pre-B-cell receptor and the B-cell receptor. Btk is required to mediate the survival and further differentiation of the progenitor B cells in which successful rearrangement of their heavy-chain genes has occurred. It is also required for the survival of mature B cells.

Questions.

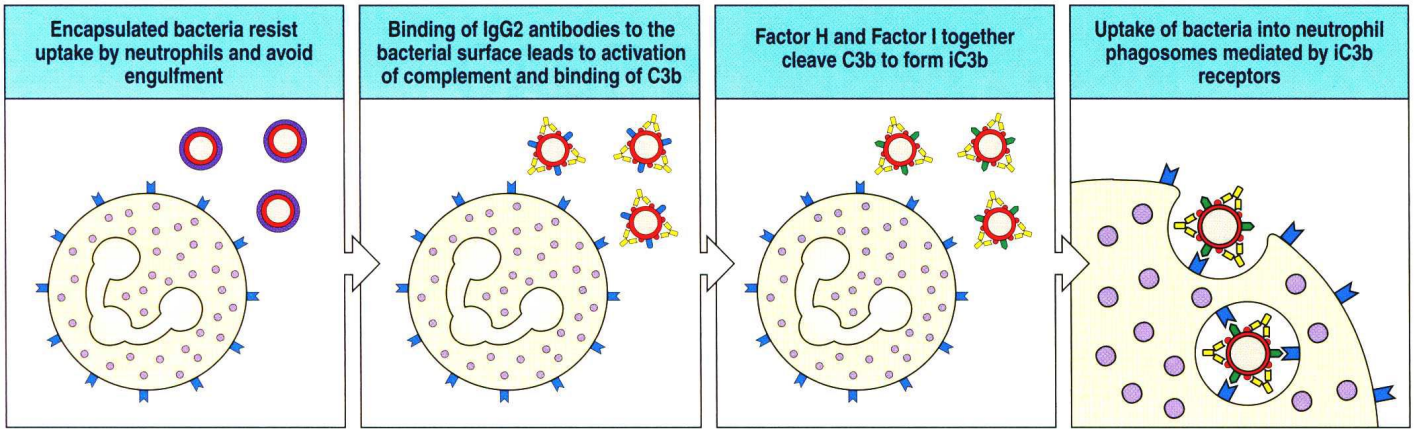
1 *Fig. 1.5 shows Bill's family tree. It can be seen that only males are affected and that the females who carry the defect (Bill's mother and maternal grandmother) are normal. This inheritance pattern is characteristic of an X-linked recessive trait. We do not know whether Bill's aunts are carriers of the defect because neither of them has had an affected male child. Now that the BTK gene has been mapped, it is possible in principle to detect carriers by testing for the presence of a mutant BTK gene. But there is a much simpler test that was already available at the time of Bill's diagnosis, which is still used routinely. Can you suggest how we could have determined whether Bill's aunts were carriers?*

2 *Bill was well for the first 10 months of his life. How do you explain this?*

3 *Patients with immunodeficiency diseases should never be given live viral vaccines! Several male infants with X-linked agammaglobulinemia have been given live oral polio vaccine and have developed paralytic poliomyelitis. What sequence of events led to the development of polio in these boys?*

4 *Bill has a normal number of lymphocytes in his blood (43% of a normal concentration of 5100 white blood cells per μl). Only by phenotyping these lymphocytes do we realize that they are all T cells ($CD3^+$) and that he has no B cells ($CD19^+$). What tests were performed to establish that his T cells function normally?*

5 *Bill's recurrent infections were due almost exclusively to* Streptococcus *and* Haemophilus *species. These bacteria have a slimy capsule composed primarily of polysaccharide polymers, which protect them from direct attack by phagocytes. Humans make IgG2 antibodies against these polysaccharide polymers. The IgG2 antibodies 'opsonize' the bacteria by fixing complement on their surface, thereby facilitating the rapid uptake of these bacteria by phagocytic cells (Fig. 1.6). What other genetic defect in the immune system might clinically mimic X-linked agammaglobulinemia?*



6 *The doctor noted that Bill had no tonsils even though he had never had his tonsils removed surgically. How do you explain this absence of tonsils, an important diagnostic clue in suspecting X-linked agammaglobulinemia?*

7 *It was found by trial and error that Bill would stay healthy and have no significant infections if his IgG level were maintained at 600 mg dl^{-1} of plasma. He was told to take 10 g of gamma globulin every week to maintain that level. How was the dose calculated?*

8 *Females with a disease exactly mimicking X-linked agammaglobulinemia have been found. Explain how this might happen.*

Fig. 1.6 Encapsulated bacteria are efficiently engulfed by phagocytes only when they are coated with complement. Encapsulated bacteria resist ingestion by phagocytes unless they are recognized by antibodies that fix complement. IgG2 antibodies are produced against these bacteria in humans, and lead to the deposition of complement component C3b on the bacterial surface, where it is cleaved by Factor H and Factor I to produce iC3b, still bound to the bacterial surface. iC3b binds a specific receptor on phagocytes and induces the engulfment and destruction of the iC3b-coated bacterium. Phagocytes also have receptors for C3b, but these are most effective when acting in concert with Fc receptors for IgG1 antibodies, whereas the iC3b receptor is potent enough to act alone, and is the most important receptor for the phagocytosis of pyogenic bacteria.