

SPECIAL ARTICLE

A History of Pediatric Immunology

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ABSTRACT

Immunology has played a prominent role in the history of medicine. Pediatric immunologists have focused on immune aberrations in pediatric disorders, particularly those involving host defense mechanisms. These efforts have paid rich dividends in terms of fundamental knowledge of the immune system and major therapeutic advances, including 1) i.v. immunoglobulin therapy, 2) hematopoietic stem cell transplantation, and 3) gene therapy. Pediatric immunology as an organized discipline emerged in the early 1950s, when pediatricians and their basic scientist colleagues began to focus on clinical and basic research related to immunodeficiency. Since then, key organizations and infrastructure have been developed to support this research and the clinical care of immunodeficient patients. We review

here the evolution of contemporary pediatric immunology, particularly in North America, from its roots in 19th-century Europe to its current expression as one of the fundamental scientific and clinical disciplines of pediatrics. (*Pediatr Res* 57: 458–467, 2005)

Abbreviations

ADA, adenosine deaminase
APS, American Pediatric Society
CGD, chronic granulomatous disease
IVIG, intravenous immunoglobulin
SCID, severe combined immunodeficiency disease

Immunology touches every pediatric subspecialty. Most closely aligned to allergy and rheumatology, immunology also has close ties to infectious diseases, hematology, and nephrology. Furthermore, each other specialty has its autoimmune diseases, relies on immunologic tests for diagnosis, and uses immunosuppressive drugs or i.v. immunoglobulin (IVIG) treatment; yet there are only a handful of patients, those with a primary immunodeficiency, to whom no other specialist lays claim. Because these patients are fairly rare, a practicing pediatrician who devoted his practice to primary immunodeficiency would probably starve. Furthermore, no separate board for pediatric immunology exists, although the American Board of Allergy and Immunology, while emphasizing allergy, now has considerable emphasis on clinical immunology and immunodeficiency. This article details the scientific advances as well as the individuals and the organizations involved in the development of the specialty of pediatric immunology.

FOUNDATIONS OF PEDIATRIC IMMUNOLOGY

Variolation and vaccination. Conventional wisdom traces the birth of immunology to 1798, when Edward Jenner (1749–

1823) of Gloucestershire, UK, inoculated (vaccinated) material from the cowpox sores of milkmaid Sarah Nelmes into the arms of several teenage boys. One boy, James Phipps, was subsequently exposed to smallpox and found to be fully protected (1).

A less well-known event, termed the “Royal Experiment,” preceded Jenner’s work by several decades. During the smallpox epidemic of 1721, Caroline, Princess of Wales (daughter of King George I), was understandably concerned that her 3-y-old daughter Mary would become infected. She had heard the rumors from China and Turkey and reports by Cotton Mather of Boston and Lady Mary Worthley Montagu, wife of the British Ambassador to Constantinople, that suggested that cutaneous inoculation of a small amount of material from a smallpox lesion (*i.e.*, variolation) would protect against smallpox. Princess Caroline ordered safety and efficacy tests on six prisoners and five orphan children (including smallpox challenge of the inoculated prisoners). Only then did she allow Dr. Charles Maitland to inoculate Mary (2).

19th-century immunology. A detailed history of immunology has been published (3), and only a summary is provided here. Rudolf Virchow’s 1859 treatise on cellular pathology provided the first formal theory for the cellular basis for disease as opposed to disturbances of the humors (blood, phlegm, black bile, and yellow bile) that had reigned for 2000 y. In the

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1870s, Louis Pasteur (1822–1895) and Robert Koch (1843–1910) established the germ theory of disease.

Pasteur used this knowledge to develop attenuated germs to vaccinate against fowl cholera, anthrax, and rabies (and the rabies virus was as yet unseen) (4). Koch also tried to develop a tuberculosis vaccine but instead developed the tuberculin test (1891). He showed that passive transfer of tuberculin sensitivity could be accomplished with cells but not serum.

The cellular theory of immunity advanced in 1884 by the Russian zoologist Elie Metchnikoff (1845–1916) represented a major conceptual revolution. The inflammatory reaction had been previously considered deleterious to the host, despite frequent reference through history to “laudable pus” (3). Metchnikoff was the first to propose an active host defense, which depended on engulfment and killing of pathogens by phagocytic cells (5). This formed the basis of his theory that began with amoeboid cells from starfish larvae and water fleas and moved to blood and tissue macrophages and microphages (neutrophils), thus demonstrating Darwinian evolutionary development (6).

In 1888, George Nuttall, an American PhD student in Göttingen, confirmed the finding by Metchnikoff that frog leukocytes killed anthrax bacilli. Nuttall also observed that bacilli were killed equally well outside the phagocytes (7) and that this bactericidal activity was destroyed by heating. In the next year, Hans Buchner also showed that cell-free serum would kill bacteria, and he coined the term *alexin* (“I defend”) for this humoral factor (3) (later renamed *complement* by Paul Ehrlich).

Beginning in 1890, von Behring and Kitasato demonstrated that a heat-stable factor(s) found only in the serum of an immunized animal could neutralize the toxins of tetanus and diphtheria, either *in vitro* or *in vivo* if injected into a susceptible animal before toxin injection (8). These observations framed the argument for a humoralist explanation of immunity, in opposition to Metchnikoff’s cellularist theory.

Pfeiffer’s observation in 1895 that immune serum lysed cholera vibrios reinforced the humoralist’s view (9), as did Ehrlich’s side-chain concept that tied together antigen, antibody, and complement (3). Another strong humoralist argument was the successful treatment of diphtheria by passive administration of animal antitoxin, thus rescuing thousands of children from “the strangling angel of death.”

Emil von Behring was awarded the first Nobel Prize in Medicine in 1901. His citation read, “For his work in serum therapy, especially its application against diphtheria, by which he has . . . placed in the hands of the physician a victorious weapon against illness and death” (3).

Immunology 1900–1950. When Metchnikoff defined phagocytosis, he conceded to serum the minor role of merely modifying the phagocyte. The humoralists, in contrast, attributed host defense against infection solely to serum. These opposing views were reconciled by Wright and Douglas in 1903 who established 1) that phagocytosis of pathogenic bacteria could not occur without serum; 2) that this effect was achieved by modification of the microorganism rather than the phagocyte; and 3) that immunity developed in the serum, not in the phagocyte (10,11).

They coined the term *opsonin* for this phagocytosis-promoting factor, derived from the Greek “to cater, prepare food for” (10). Whether this serum effect was accomplished by specific antibody alone or in conjunction with a nonspecific, heat-labile serum activity, namely complement, was not clear until 1933, when Ward and John Enders (later to receive the Nobel Prize for isolation of poliovirus) demonstrated that ingestion of pneumococci occurred slowly in the presence of heated immune serum but was greatly accelerated by fresh, nonimmune serum (12). Optimal opsonization of pneumococci was later shown to require antibody and the complement system through C3 (13).

Much of the immunologic focus in the first half decade of the 20th century was the delineation of various types of antibody and their use in diagnosis and therapy (14). Key observations included the experimental production of anaphylaxis in dogs reinjected with marine toxins (Portier and Richer, 1902), inflammation produced by antigen-antibody interaction in the skin (Arthus, 1903), and the description of serum sickness (Pirquet and Schick, 1906) (3,14).

Wasserman used antibody and complement fixation for the serodiagnosis of syphilis (1906). Pediatrician Oscar Schloss used skin tests to document food allergies (1911) (15), and Robert Cooke and Arthur Coca in 1921 demonstrated that hay fever and some cases of asthma were due to allergic antibodies that could be identified by skin testing. Cooke also described blocking antibodies, the basis for allergy immunotherapy. Prausnitz and Kustner demonstrated passive transfer of allergy antibodies in 1922. Diphtheria immunization was instituted, first with toxin-antitoxin mixtures in the early 1900s and later with formalin-modified toxins (*i.e.* toxoids) in the 1920s.

Other than Koch’s study on tuberculin reactivity, most early studies on cellular immunity involved tissue transplantation. It was recognized as early as 1905 that autologous skin grafts were tolerated, allogeneic skin grafts (unrelated human) were usually rejected, and skin xenografts (different species) were always rejected. In the 1920s, it was observed that skin grafts from an identical twin were well tolerated. Subsequent studies using tumor cell grafts and inbred animals established that the closer the blood relationship between donor and recipient, the more likely the take.

Histologic studies of skin-graft rejection identified the presence of lymphocytes in 1922. It was also shown that X-irradiation would slow down graft rejection. The need for skin grafts in burn patients during World War II accelerated research in transplantation. Peter Medawar’s studies on graft rejection included the observation that leukocyte injections from a donor (*i.e.* sensitization) could accelerate rejection. The description of the HLA antigens in 1957 was a major finding that accelerated the entire transplantation field.

Other important studies included the first description of an autoimmune disease, paroxysmal cold hemoglobinuria, in 1904 by Donath and Landsteiner; they identified in a patient with paroxysmal cold hemoglobinuria a serum factor that lysed the patient’s own red cells in the cold. ABO blood groups were identified in 1900, and Rh blood groups were identified in 1940.

EARLY PEDIATRIC IMMUNOLOGY

To chart how these seminal studies influenced pediatric thought and practice, we used the annual programs of the American Pediatric Society (APS) as summarized by Faber and McIntosh in 1966 (16). We include not only the outstanding advances but also the thinking that, in retrospect, was completely in error.

Antibody Therapy

Diphtheria was the dominant topic of the first 14 meetings of the APS beginning in 1889. At the first meeting (held 1 d in Washington, DC, and 1 d at the newly opened Johns Hopkins Hospital and attended by 25 people), diphtheria-preventive measures by avoidance of contact, cleanliness, nasopharyngeal gargles, sprays, and daily inspections were proposed.

By 1895, diphtheria equine antiserum was available and reported to decrease the mortality to an extremely low 17%. Its prophylactic use at Boston Children's Hospital also prevented nurses and newly admitted patients from contracting the dreaded disease from the current diphtheria patients.

In 1897, an APS committee reported that a multicenter survey indicated that the mortality from laryngeal diphtheria that was treated with intubation and antitoxin was 28% compared with a mortality of 70% with intubation alone. Its effectiveness prompted a report that antitoxin administration once or twice per school year served as a successful preventive measure. The i.v. use of antitoxin in severe cases was reported in 1922.

In 1916, the value of the Schick test (intradermal injection of a small amount of diphtheria toxin) to determine immunity to diphtheria was reported, and its repeated use served as an alternative immunization strategy to the toxin-antitoxin method introduced by von Behring in 1913. By 1927, widespread toxin-antitoxin immunization was under way, but the many adverse effects of the horse serum component led to the development of toxoids in 1928.

The success of antibody therapy in diphtheria led to the use of serotherapy in other disorders. In 1908, the use of meningococcal antiserum for meningitis was reported to reduce the mortality from 75 to 37% and with fewer sequelae in the survivors. This treatment was used extensively over the next 35 y, including its use intrathecally, intracisternally, and intraventricularly.

In 1925, George Dick confirmed that a streptococcal toxin caused scarlet fever, and in 1929 he reported that streptococcal antitoxin shortened its course and decreased its complications. In 1933, placental extracts were reported to have antibodies to diphtheria, scarlet fever, measles and polio. In 1935, human serum was preserved by lyophilization (freeze drying) and was claimed to be of value in the prevention and therapy of multiple diseases, including rheumatic fever, impetigo, measles, chicken pox, and scarlet fever.

In 1939, type-specific antisera were used for the treatment of pneumococcal pneumonia, and in 1940, antisera were used in pertussis. In 1942, Hattie Alexander administered *Haemophilus influenzae* antisera in conjunction with sulfa to successfully

treat 37 cases of *H. influenzae* meningitis, heretofore a nearly always fatal disease.

Hypersensitivity Disorders

In 1896, one patient died immediately after the injection of diphtheria antitoxin (anaphylaxis), and two patients died several days after the injections (probable serum sickness). Descriptions of other disorders as a result of aberrant immunity included nephritis after influenza (1890), childhood pernicious anemia (1917), and dermatomyositis (1918).

Other Immunologic Observations

In 1917, permanent cutaneous anergy to tuberculin was observed in terminal tuberculosis, and transient anergy was described in scarlet fever and measles. Blackfan and Diamond (1934) discussed the role of the monocyte and lymphocyte in different stages of tuberculosis.

In 1935, elevation of the antistreptolysin titer was reported in acute glomerulonephritis, thus implicating the *Streptococcus* in its etiology.

In 1939, experimental encephalomyelitis was produced in monkeys by injections of brain antigens, emphasizing the risk for rabies and polio vaccines derived from brain tissue or tissue culture.

In 1949, Alexander reported that antibody to pertussis was absent in newborns for ~6 mo but was always present in adult serum. In 1950, Hodes reported that the polio-neutralizing antibody in milk differed in size and specificity from that of the blood.

Therapeutic Misadventures

Thymic irradiation. The attitude toward the thymus bears some examination. In 1903, Koplik described congenital laryngeal stridor as a result of an enlarged thymus; in one case, the thymus weighed 20 g on postmortem examination. In 1907, John Howland described status lymphaticus, a disorder characterized by fever, convulsions, coma and rapid death, and a thymic gland exceeding 10 g. This and other reports led to the widespread use of thymic irradiation in cases of stridor or other respiratory problems.

As early as 1909, doubts were cast on this association after a report of an infant who died with a very large thymus (28 g) but without laryngeal compression. In 1914, it was reported that thymectomy in dogs had no adverse effects, leading to the conclusion that the thymus was of no physiologic importance.

By 1917, aided by the widespread use of x-rays to document thymic enlargement, thymic irradiation was so widespread that it was deemed mandatory, particularly in the preoperative period, as a way to avoid lawsuits. The x-ray diagnosis of laryngeal compression as a result of thymic enlargement was questioned again in 1920 on the basis of fluctuations in its shape during respiration. Edith Boyd (17), a pathologist, pointed out in 1927 that the thymus does not obstruct the larynx and demonstrated that chronic but not acute illness leads to thymic atrophy, so infants who die suddenly will have larger thymic glands than infants who die after a prolonged illness.

The public was so convinced of the value of thymic irradiation that Brenneman in 1927 stated that until the matter was settled, "I shall continue to have all children with symptoms suggestive of thymic enlargement examined and treated roentgenologically." It was not until the report of Duffy and Fitzpatrick in 1950 (18) that thyroid cancer in children might be associated with thymic irradiation did this practice cease. Waldo Nelson, in his *Textbook of Pediatrics* (6th edition) in 1954, stated, "In neither instance (respiratory obstruction and sudden death) are there substantial data to justify a significant causative role to the thymus gland."

Tonsillectomy. The tonsils were to the surgeon what the thymus was to the radiologist, aided by the cooperation of the pediatrician. Widespread tonsillectomy was started around 1912 on the basis of the theory that focal infection accounted for almost all of the ills of childhood. The practice was questioned by several pediatricians, who pointed out the serious risks of tonsillectomy, but this did not slow down the rush to the surgical suite during this period. In 1951, Faber showed that tonsillectomy in monkeys increased the likelihood and severity of encephalitis after experimental polio vaccination and led to the recommendation of postponing tonsillectomy during polio season.

Other dubious treatments. One prospective APS member in 1900 suggested that diphtheria antitoxin be given orally so as not to hurt the child. He was subsequently denied membership. Chest irradiation was recommended for the treatment of pertussis (1924), convalescent serum was thought to be of therapeutic benefit in polio (1932), and hyperpyrexia was advocated for chronic arthritis (1934).

PEDIATRIC IMMUNOLOGY AND IMMUNODEFICIENCY SINCE 1950

Pediatric immunology as a subspecialty can largely be traced to the description of the primary immunodeficiency disorders in the early 1950s. The study of these "experiments in nature" have had a symbiotic relationship to the entire field of immunology: the clinicians use current immunologic techniques to define the disease followed by the basic scientists' studies to define the underlying immunopathogenesis.

The birth of immunodeficiency is usually given as 1952, when Odgen Bruton (19) reported the first case of agammaglobulinemia, later known as X-linked agammaglobulinemia. However, clinical descriptions appeared several years earlier of neutropenia by Schultz in Munich in 1922 (20), ataxia-telangiectasia by Syllaba and Henner of Paris in 1926 (21), mucocutaneous candidiasis by Thorpe and Handley in Philadelphia in 1929 (22), and the Wiskott-Aldrich syndrome by Wiskott of Germany in 1937 (23). Even before these reports, a strain of guinea pigs with an undefined autosomal recessive complement deficiency was reported in 1919 (24).

Cellular immunodeficiency. In 1950, Glanzmann and Rinker (25) of Berne, Switzerland, identified two related infants with "lymphozytophthise," characterized by candidiasis, lymphopenia, and a rapidly fatal course. The next year, Donohue of Canada described a similar case (26). In 1958 Hitzig *et al.* from Zurich (27) and Tobler and Cottier (28) from Berne

reported four similar cases with a concomitant absence of γ -globulin. Two of the cases were related to the Glanzmann cases, suggesting a hereditary disorder.

This disease, originally termed Swiss-type agammaglobulinemia, was renamed severe combined immunodeficiency (SCID) in 1975 at the first World Health Organization committee meeting on primary immunodeficiency. It soon became evident that SCID was heterogeneous in terms of its clinical manifestations, basic defect, and heredity, as first exemplified by the delineation of X-linked SCID in 1963 (29), autosomal-recessive forms of SCID in 1971 (30), and the adenosine deaminase (ADA)-deficient form of SCID in 1972 (31).

Antibody immunodeficiency. Rosen (32) described the discovery of X-linked agammaglobulinemia. Colonel Bruton at Walter Reed Army hospital, using the new Tiselius electrophoretic apparatus, discovered that an 8-y-old boy with recurrent pneumococcal infections had no detectable γ -globulin. He consulted Charles Janeway of Boston, who had three similar cases; the four were presented at the Society for Pediatric Research meeting in 1952, followed by Bruton's publication a few months later. One of these boys was later shown to have a hyper-IgM syndrome (33). Shortly after Bruton's report, Sanford *et al.* (34) described a 39-y-old woman who had agammaglobulinemia and had been well as in infant, suggesting an acquired illness, now termed common variable immunodeficiency.

Selective IgA deficiency was described in the early 1960s (35,36), although the physiology of IgA and epithelial surface antibody was not defined until years later. Pearay Ogra, a major contributor to the field, demonstrated that the mucosal IgA response in patients with a double-barrel colostomy was largely confined to the barrel exposed to live polio vaccine and not to the unexposed segment (37). Several reports in the 1940s suggested that tonsillectomy predisposed to polio and should be avoided in the summer polio season. Ogra showed that the mucosal antibody response to polio vaccine in nasopharyngeal secretions was markedly blunted after tonsillectomy/adenoidectomy compared with the response before surgery (38).

The T- and B-cell paradigm. The role of the thymus in development of the immune system of experimental animals was delineated by Good (39) and Miller (40) in the early 1960s, in part stimulated by a patient who had agammaglobulinemia and thymoma [Good's syndrome (41)]. Further clinical and animal studies led to the description by Cooper *et al.* (42) of the two-limbed concept of the adaptive immune system. The key role of the thymus in T-cell development was further solidified in 1965 by the description of the DiGeorge syndrome of facial dysmorphism, heart disease, hypoparathyroidism, and thymic aplasia with T-cell defects (43). This dual scheme led to the realization that several immunodeficiency syndromes had defects of both antibody and cellular systems, *e.g.* Wiskott-Aldrich syndrome, ataxia-telangiectasia, and cartilage-hair hypoplasia.

Phagocyte disorders. Neutropenia, originally described as "agranulocytic angina" in 1922 by Schultz *et al.* (20), may represent the first recognized primary immunodeficiency. Kostmann in 1956 defined a congenital form of the disease as a cause of severe recurrent infections in infancy (44). Neutrope-

nia has subsequently been found to be associated with several other genetic immunodeficiencies, including X-linked agammaglobulinemia (45), common variable immunodeficiency (46), X-linked hyper-IgM syndrome (47), severe combined immunodeficiency (48), cartilage-hair hypoplasia (49), Griscelli syndrome (50), and WHIM syndrome (warts, hypogammaglobulinemia, infection, and myelokathexis) (51–53).

Two years after the description of agammaglobulinemia, Janeway, Gitlin, and colleagues described at the 1954 APS meeting five children with severe recurrent infections and elevated total immunoglobulin (54), indicating that absence of immunoglobulin is not the only predisposing cause of recurrent infection.

In 1957 Good and colleagues described four boys with a syndrome of widespread abscesses, hepatosplenomegaly, and draining lymph nodes caused by staphylococci or Gram-negatives rather than the pneumococci and other pyogens that typically infected agammaglobulinemic boys. They called the syndrome “fatal granulomatosis” (55).

The pathogenesis of the syndrome, eventually termed chronic granulomatous disease (CGD), was elaborated in 1966 by Quie and Holmes, who reported that CGD neutrophils could ingest bacteria normally but could not kill them (56,57). Baehner and Nathan found that CGD cells could not produce the bactericidal agent hydrogen peroxide, thus confirming that peroxide was essential for bacterial killing and, indeed, for survival (58). They also discovered that CGD phagocytes could not reduce nitroblue tetrazolium dye from yellow to blue, the basis for the NBT test for diagnosis for CGD (59). Pediatricians used CGD cells to elucidate the basis of oxidative killing (60,61), identified the genetic basis of X-linked CGD (62), showed that interferon- γ reduced serious infections in CGD (63), and created a national patient registry for CGD, the first such for an immunodeficiency disease in the United States (64).

Although the early discoveries of CGD and the biology of the phagocytosis-associated respiratory burst were made in the United States, subsequent research on phagocyte disorders and physiology has come prominently from European pediatric centers, especially in Zurich (Hitzig and Seger), Paris (Griscelli, Fischer, and Casanova), London (Soothill), and Amsterdam (Weening and Roos) (65,66). Other phagocyte disorders reported by pediatric investigators include the leukocyte adhesion defects (67–70), actin dysfunction (71,72), the chemotactic defect sometimes present in the hyperimmunoglobulinemia E syndrome (73), specific granule deficiency (74), Rac-2 deficiency (75), and leukocyte mycobactericidal defect (76,77).

Complement disorders. Pediatricians Rosen, Wedgwood, Colten, and Frank have been important investigators and mentors in this field. Even before Nelson’s demonstration in 1966 of the nine components of the classical pathway, Donaldson, Rosen, and colleagues reported the first inherited defect of the complement system, hereditary angioedema (78,79). Rosen and co-workers described C2 deficiency in 1966 (80), C3 deficiency in 1969 (81), and deficiency of factor I of the alternative pathway in 1970 (82).

West and colleagues reported a serum C3 lytic system in patients with membranoproliferative glomerulonephritis (83)

and subsequently showed that this nephritic factor (later shown to be an autoantibody to the alternative pathway C3-cleaving enzyme) promotes continuous activity of the alternative pathway with consumption of C3 (84). The discovery of C4-deficient guinea pigs allowed Frank and co-workers to study the complement system *in vivo* and its role in host defense and inflammation (85).

Beginning in the late 1960s and into the 1980s, discovery of complement-deficiency states served as natural experiments that allowed explosive growth in knowledge of complement biology. Pediatric centers were prominent in these discoveries, including the discovery of genetic deficiency of the complement components C1q (86) and C1rs (87), defective alternative pathway activity in sickle cell disease (88,89), subnormal complement activity in newborn infants (90–93), predisposition to pneumococcal bacteremia in C2-deficient individuals (94), C3 deficiency in dogs (95), many aspects of the genetic basis of complement component synthesis (96), deficiency of the control protein C4 binding protein (97), and the role of complement in the induction of antibody responses (98,99).

Genetic diagnosis. Since these early descriptions, >100 clinical syndromes have been identified. The gene responsible for SCID ADA was identified and cloned in the early 1980s (100), and in the 1990s, genes were identified and cloned for many other immunodeficiencies, including X-linked SCID (101), X-linked agammaglobulinemia (102,103), and ataxia-telangiectasia (104). Subsequently, the genes for 30 or more immunodeficiencies have been identified (105). The yet undefined disorders are heterogeneous (*e.g.* common variable immunodeficiency, selective IgA deficiency, IgG subclass deficiency), so a single gene defect probably will not be found.

The ability to identify gene defects in the primary immunodeficiency diseases has permitted heterozygote detection, prenatal diagnosis, delineation of genetic variants, and gene therapy. The presence and the function of several of these genes were unknown at the time of their discovery, so these experiments in nature provided enormous insights into the normal development of the immune system. Rosen (32) and Hitzig (106) have provided detailed accounts of the discovery of the immunodeficiencies.

Pediatric HIV infection. Shortly after the 1982 Centers for Disease Control report of AIDS among young adult patients, AIDS was described in infants who received HIV-positive blood components, vertically infected from the mother, or by breast milk transmission (107–111). Because these infants mimic primary immunodeficiency patients, several pediatric immunologists have focused on pediatric HIV, assuming leadership roles in the National Institutes of Health pediatric AIDS clinical trials centers (*e.g.*, Diane Wara, William Shearer) and the Pediatric AIDS Foundation (*e.g.*, Arthur Ammann, Catherine Wilfert).

The first antiviral agent zidovudine for AIDS was developed in 1986 and used in infants and children in 1987 (112). This led to the landmark trial of its use in the prevention of maternal-fetal transmission. Zidovudine given to mothers during pregnancy and delivery and to their newborn infants for 6 wk after birth reduced the rate of maternal-fetal transmission from 27 to 7% (113). Subsequent studies with other antiviral drugs and

widespread testing for HIV has virtually eliminated congenital HIV infection in the United States and other developed countries.

The HIV epidemic worldwide continues to escalate, without an effective vaccine in sight. Programs to decrease maternal-fetal transmission by the use of antivirals such as single-dose nevirapine (114) are under way in many developing countries.

Major Therapeutic Advances

IVIG. Bruton's 1952 paper not only described a disease but also described a treatment, weekly intramuscular injections of human immune globulin (IG), a product available since 1945 for the prophylaxis of certain infectious diseases, particularly hepatitis. To avoid these painful injections, Barandun and co-workers in Switzerland were the first to develop IG preparations for i.v. use (115). The first therapeutic trial of IVIG in the United States was completed in 1982 (116), which eventually led to the use of larger therapeutic doses of IG.

In addition, IVIG was found to be of benefit in several other disorders unrelated to immunodeficiency, notably immune thrombocytopenic purpura (117); Kawasaki disease 1984 (118); and neurologic disorders such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculopathy, and myasthenia gravis. Now >100 inflammatory and autoimmune disorders are treated with IVIG; several different mechanisms seem responsible for its benefits (119).

Bone Marrow Transplantation

The first successful bone marrow transplants using HLA-identical siblings were recorded in 1968 by Gatti *et al.* (120) in a child with SCID and Bach *et al.* (121) in a child with Wiskott-Aldrich syndrome. From then until 1980, many successes were reported but only for those with an HLA-identical sibling. Development of techniques to deplete mature T cells from the marrow by Muller-Ruchholtz *et al.* (122) in 1976 and Reisner *et al.* (123) in 1978 allowed the use of haploidentical donors (*e.g.*, parents) to treat SCID beginning in 1982 (124). Thousands of children have been cured of their lethal disorders since then by bone marrow or other hematopoietic stem cell transplantation.

Other options for transplantation in children without an HLA-matched donor use closely matched but unrelated bone marrow (125) or umbilical cord blood (126). The development of registries of HLA-matched bone marrow donors and stored cord blood has facilitated these efforts. The success of bone marrow transplantation in immunodeficiency has stimulated its use for other hematologic and metabolic disorders, as well as refractory autoimmune disorders.

Gene Therapy

After the description of ADA-deficient SCID, the benefits of enzyme replacement with polyethyleneglycol-conjugated bovine ADA (127) and the successful cloning of the ADA gene, gene therapy trials were initiated at the National Institutes of Health (128). Although successful gene transfer to the patients'

lymphocytes was accomplished, insufficient ADA was produced to correct the immunologic defect.

Alain Fischer and his group at the Hôpital Necker in Paris accomplished the first clinically successful gene therapy in X-linked SCID in 1999 (129). Subsequently, Aiuti and co-workers in Milan in 2002 reported successful gene therapy in ADA-deficient SCID (130). Two of the 12 children who were treated in Paris developed a lymphoproliferative syndrome after gene therapy, temporarily discontinuing further gene therapy trials (131).

Other Therapies

Cytokine therapy for the primary immunodeficiency diseases include the use of granulocyte colony-stimulating factor for neutropenic disorders, interferon- γ in chronic granulomatous disease and IL-2 in some cases of SCID. MABs, developed by Kohler and Milstein in 1963, were first used in immunology for diagnostic tools to quantify lymphocyte subsets (*e.g.* helper and suppressor T cells). The first therapeutic MAB, anti-CD4 (OKT4), was introduced in 1986 for immunosuppression, including for marrow transplantation. Several other therapeutic MABs are now available, including an respiratory syncytial virus antibody for respiratory syncytial virus prophylaxis and an anti-IgE antibody for severe allergies.

LEADERS

A suitable subtitle for this history might be "A Tale of Two Cities, Boston and Minneapolis," under the leadership of Charles Janeway (1909–1981) of Harvard and Robert Good (1922–2003) of the University of Minnesota. Nearly all of the practicing immunologists in North America can trace their lineages to these two pediatricians.

The founding fathers: Janeway and Good. Janeway of Boston, who studied protein chemistry with E.J. Cohn, was a co-discoverer of X-linked agammaglobulinemia in 1952. His younger associates included David Gitlin, Ralph Wedgwood, Walter Hitzig, and Fred Rosen, all of whom became leaders and mentors in the field. Rosen's trainees have included Richard Johnston, Raif Geha, Erwin Gelfand, and Robertson Parkman, whereas Wedgwood's trainees include Hans Ochs, Harry Hill, and Jane Schaller.

Good of Minneapolis, a student of Lewis Thomas, first suspected a relationship of the central role of the thymus when he reported a case of agammaglobulinemia with thymoma (now known as Good's syndrome) in 1954. He and his colleagues described CGD in 1957 and the functional defects underlying the disease in 1967. His animal studies on the role of the thymus gland along with those of JFAP Miller of the UK led him and his associates Ray Peterson and Max Cooper to delineate the role of the thymus and the two-compartment model of the immune system. His group also performed the first bone marrow transplant in 1968 on a child with SCID.

His remarkable career at the University of Minnesota, at Sloan-Kettering in New York, at the University of Oklahoma, and at the All Children's Hospital at St. Petersburg includes the training of an unmatched number of pediatric immunologists, including Max Cooper, Richard Hong, Arthur Ammann,

Micheal Blaese, Charlotte Cunningham-Rundles, and Richard O'Reilly. His list of "Good guys" includes some 300 individuals who have trained with him and helped him write his 2000+ papers.

Recognition. The John Howland award of the APS was awarded to Janeway in 1978 and to Good in 1987. Good and Max Cooper are members of the National Academy of Sciences.

Oscar Schloss (1933), Charles Janeway (1971), Richard Johnston (1997), and Rebecca Buckley (2000) served as presidents of the APS. Rebecca Buckley also served as President of the American Academy of Allergy, Asthma and Immunology in 1979.

The annual E. Mead Johnson Award for Research in Pediatrics has gone to a number of pediatric immunologists (Table 1). The 10 such awards from 1970 to 1986 are one measure of the spectacular expansion of knowledge of pediatric immunology. David Gitlin (recipient in 1956) and Jonathan Gitlin (recipient in 1998) are the only father-son pair to have received the award.

The outstanding achievement award of the Immune Deficiency Foundation has been awarded regularly since 1992 (Table 2), most recently to Alain Fischer for the first successful gene therapy.

DIVISIONS AND CENTERS

Although the study of immunodeficiency accelerated in the 1960s, the relative rarity of these disorders did not require separate divisions of immunology in most pediatric departments. Immunology divisions were first established at Minneapolis under Good, at Boston under Rosen, and at Seattle under Wedgwood. With increases in National Institutes of Health funding and the growth of pediatric departments and children's hospitals, divisions of immunology were created in many departments, usually aligned with allergy or less commonly with rheumatology or infectious diseases.

Along with the growth of divisions and National Institutes of Health support, many training programs were established in the 1970s, including those of Erwin Gelfand at Toronto, Max Cooper at Alabama-Birmingham, and Rebecca Buckley at

Table 1. E. Mead Johnson Award for Research in Pediatrics to Pediatric Immunologists

1955 Robert A. Good, University of Minnesota
1956 David Gitlin, Harvard University
1963 Richard T. Smith, University of Florida
1970 Joseph A. Bellanti, Georgetown University
1971 Fred S. Rosen, Harvard University
1974 E. Richard Stiehm, University of California, Los Angeles
1977 Arthur J. Ammann, University of California, San Francisco
1977 Micheal E. Miller, University of California, Los Angeles
1979 Harvey R. Colten, Harvard University
1980 R. Micheal Blaese, National Institutes of Health
1981 Erwin W. Gelfand, Hospital for Sick Children, Toronto
1982 Jerry A. Winkelstein, Johns Hopkins University
1986 Raif S. Geha, Harvard University
1997 Donald Y. M. Leung, National Jewish Hospital, Denver
1998 Jonathan D. Gitlin, Washington University, St. Louis
1999 Chaim M. Roifman, Hospital for Sick Children, Toronto

Table 2. Scientific achievement awards of the Immune Deficiency Foundation

1992 Robert A. Good
1993 Fred S. Rosen
1993 Max D. Cooper
1994 Rebecca H. Buckley
1996 Richard Hong
1996 E. Richard Stiehm
1997 Paul Quie
1998 Hans D. Ochs
2000 R. Micheal Blaese
2001 Mary Ellen Conley
2003 Alain Fischer

Duke. Currently, there are 87 training programs in allergy/immunology and 30 programs in immunology.

These training centers, along with the immunology group at the National Institutes of Health that includes Thomas Waldmann, Micheal Blaese, Warren Strober, and John Gallin, have developed clinical and research teams focused on immunodeficiency and related disorders. Simultaneously, pediatric immunology centers throughout Europe were developing, notably at the Zurich Children's Hospital under Walter Hitzig, at the Hospital for Sick Children in London under John Soothill, and at Hôpital Necker in Paris under Claude Griscelli and Alain Fischer.

ORGANIZATIONS AND MEETINGS

Because of the paucity of primary immunodeficiency patients, board certification of pediatric immunology has never been implemented. Many pediatric immunologists have received training and subspecialty certification in allergy. Furthermore, with the discovery of IgE, the immunologic basis for allergic disease could progress beyond skin testing described at the beginning of the century.

The American Academy of Allergy, founded in 1943, added Immunology to its name in 1982 and Asthma in 1995, resulting in its current name, The American Academy of Allergy, Asthma, and Immunology. Certifying examinations in allergy and immunology were begun in 1951, and the current conjoined pediatric-internal medicine board was established in 1971. Certifying and recertifying examinations are held every 2 y.

The meetings of the APS/Society for Pediatric Research have served as important venues for reporting immunologic observations. Clinical immunology has also become an important topic at the annual meetings of the American Association of Immunologists (founded 1920) and at the meetings of the Clinical Immunology Society (founded 1986). The biannual World Health Organization/International Union of Immunologic Scientists' meeting and the European Society for Immunodeficiency meetings are focused exclusively on primary immunodeficiency.

An expert committee of the World Health Organization has held frequent meetings since 1975 to codify and revise the classification of the primary immunodeficiencies. Fred Rosen has played a major role in chairing these meetings.

Texts detailing advances in the field have included Stiehm, Ochs, and Winkelstein's *Immunologic Disorders in Infants and*

Children, first published in 1973, with the 5th edition in 2004; and Ochs, Smith, and Puck's *Primary Immunodeficiency Diseases: A Molecular and Genetic Approach*, published in 1999.

FOUNDATIONS

Two foundations that focus on primary immunodeficiency have been established: the Immune Deficiency Foundation, founded in 1980 by Marcia and John Boyle, and the Jeffrey Modell Foundation, founded in 1986 by Fred and Vicki Modell. Their children, John Boyle and Jeffrey Modell, were cared for by immunologists Jerry Winkelstein of Baltimore and Charlotte Cunningham-Rundles of New York, respectively. Both foundations promote patient and physician awareness, support meetings and educational programs, conduct governmental lobbying, develop centers of excellence, and award research and training grants.

The Elizabeth Glaser Pediatric AIDS Foundation was founded in 1989 by the late Elizabeth Glaser, after her daughter Ariel became infected by breast feeding. Elizabeth had received an HIV-positive blood transfusion immediately after Ariel's birth (111). This foundation has played a role for pediatric AIDS similar to that played by the Immune Deficiency Foundation and the Jeffrey Modell Foundation for primary immunodeficiencies.

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