The History of Pediatric Rheumatology

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ABSTRACT

The care and study of children with rheumatic diseases began slowly in the 19th century, with the most attention centered on rheumatic fever. Other rheumatic diseases of children received little attention until the 1940s. Rheumatic diseases taken together remain a significant cause of chronic illness in children throughout the world. A number of other conditions that masquerade as rheumatic diseases in children also demand recognition and management. Although ultimate causes and cures of childhood rheumatic diseases remain elusive, advances in therapy have improved the outlook for affected children, and advances in

biomedical research are adding to our basic understanding of the disease process involved. Pediatric rheumatology has become a well-organized, although underpopulated, specialty that enhances recognition and care of affected children and contributes to basic research knowledge in infectious disease, immunology, and genetics. This review focuses most prominently on the early history of pediatric rheumatology and its development as a specialty. The recent burgeoning of new biomedical science and new means of treatment will be better told in the historical perspective of years to come. (*Pediatr Res* 58: 997–1007, 2005)

Pediatric rheumatology is one of the newest and least populated of the pediatric subspecialties, having come slowly into being only after the Second World War. As Eric Bywaters, one of its fathers, commented in 1976 at the First American Rheumatism Association (ARA) Conference on the Rheumatic Diseases of Childhood in Park City, Utah: “Pediatricians can no longer cover the whole field of pediatrics, and have had to develop their own subspecialties. Pediatric rheumatology is one of the latest arrivals and one of the smallest, although I would say not premature. I think I can say I saw it arrive, although I cannot specify its birthday or place” (1).

EARLY STUDIES

Aside from what we now call rheumatic fever, rheumatic diseases were not recognized as a problem in children until the late 1800s. Indeed, pediatrics itself was a relatively new field in the late 1800s; children were usually considered to be small adults. As late as 1957, Charles Short, Walter Bauer, and William Reynolds commented in their definitive book *Rheumatoid Arthritis* that, “We adopted the generally accepted principle that rheumatoid arthritis is the same disease in adults and children, with certain minor differences” (2). The realization that rheumatic diseases in children differ in many important aspects from rheumatic diseases in adults was mentioned by Still in his classic article of 1897 (3), but this concept was not pursued until interest in these diseases increased after the 1940s.

Pediatric rheumatology is closely linked to the field of immunology, and the rheumatic diseases often referred to loosely as “autoimmune” conditions. Definitions of rheumatoid factors, the lupus erythematosus cell phenomenon, antinuclear antibodies, immunologic deficiency syndromes, and concepts of autoimmunity have all been vital to its development. Pediatric rheumatology has important links to other clinical specialties including orthopedics, ophthalmology, rehabilitation medicine, nephrology, gastroenterology, cardiology, infectious disease, and dermatology. Pediatric rheumatology is also notable for its close working relationships with allied health professions including physical and occupational therapy, nursing, social service, and psychology.

SCOPE OF THE SPECIALTY

One fundamental problem in defining rheumatology is the difficulty of defining the scope of diseases included. An English physician, Sir Thomas Barlow, noted in the late 1800s that, “The fundamental difficulty in discussing rheumatism consists in defining what we mean by it” (4). Indeed pediatric rheumatologists see a wide variety of patients. The diseases traditionally considered as rheumatic include rheumatic fever, juvenile rheumatoid arthritis (JRA, also referred to as juvenile idiopathic arthritis or simply juvenile arthritis), the spondyloarthropathies, systemic lupus erythematosus (SLE), dermatomyositis, scleroderma, the vasculitis syndromes, and a number of rarities. Prominent involvement of the musculoskeletal system and chronic or recurrent inflammation of connective tissues characterize all of these conditions.

All of the rheumatic diseases are recognized primarily on the basis of clinical findings, with limited help from laboratory

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tests. Other children with unexplained fevers, rashes, and various musculoskeletal complaints also confront pediatric rheumatologists, making the matter of accurate differential diagnosis extremely important. Indeed, a good pediatric rheumatologist must be an excellent clinician with an expert knowledge of the rheumatic diseases as they affect children, a basic understanding of the complicated laboratory work involved, and a broad acquaintance with the various conditions that can mimic rheumatic diseases. A good pediatric rheumatologist must also be skilled in the difficult tasks of caring for children with severe acute illness and children with disabling chronic illness.

HISTORICAL ASPECTS, 1800–1950

There is essentially no mention of rheumatism or rheumatic conditions in children before 1800. George Frederic Still, in his *History of Pediatrics* (5), commented “It seems strange that rheumatism finds no place in any work on diseases of children before the 19th century, although it was known and studied in adults.” The earliest reference that Still found was from 1810, when rheumatic nodules were mentioned in a child of “nearly 15 years.” The only earlier acknowledged reference is that of Thomas Phaer (or Phayr) from Wales, who in 1545 produced *The Boke of Chyldren*, in which he included a section describing “styffness of the lymmes,” a condition that he considered to result from exposing children to the cold (6).

Rheumatic fever. Rheumatic fever or, as it was called, “acute rheumatism” has been known since ancient times as a disease that affected young adults and sometimes children. During the 1800s, it was recognized that the arthritis was usually transient and migratory, and associations with heart disease, subcutaneous nodules, chorea, and sore throat were noted (2,4,5,7). The observation that acute manifestations of the disease, including arthritis, could be relieved by salicylates in various forms dates back to the 1700s when an English minister, the Reverend Edmond Stone, noted that his parishioners with “the ague” (which probably included some persons with acute rheumatism) improved when they ingested the bark of the willow tree (*salix*, Latin for willow) (8).

Observers of acute rheumatism in the 1800s acknowledged that not all arthritis was related to what we now call rheumatic fever, but that conditions such as tuberculosis or pyogenic arthritis were also possible explanations (7).

The association of rheumatic fever with streptococcal sore throats was established in the 1930s (9). Rammelkamp, Wannamaker, and colleagues showed in the 1940s that prompt penicillin therapy of streptococcal pharyngitis could prevent the subsequent appearance of rheumatic fever, and that prophylaxis of patients after a first attack of acute rheumatic fever could prevent subsequent attacks (10). A decline in the prevalence of rheumatic fever in the industrialized world began in the 1930s, antedating the arrival of penicillin and suggesting that improved socioeconomic conditions with better nutrition and less crowded living conditions also played a role in disease occurrence (11–13).

Chronic arthritis. Chronic arthritis in children, which differed from the acute rheumatism of rheumatic fever, was

described between 1864 and 1900 by several authors [Cornil (Paris, one case in 1864) (14), Bouchet (Paris, six cases in 1875) (15), Garrod (London, one case in 1876) (16), Lewis-Smith (New York, one case in 1876) (17), Moncorvo (a Brazilian who described one case he had seen in Paris plus eight cases from the literature, 1880) (18), West (London, two cases in 1881) (19), Garrod (London, two cases in 1890) (20), and Marfan (Paris, 1896) (21)].

The landmark description of chronic arthritis in children occurred in 1897, when George Frederic Still, while a registrar in pediatrics and pathology at the Hospital for Sick Children, Great Ormond Street, London, described 22 children with chronic arthritis and commented that most had a disease that differed from chronic arthritis as described in adults (3). Still postulated that more than one condition was responsible. A number of his patients had what we would now call systemic-onset JRA: he described the fever and many of the other systemic complaints of this condition, as well as the chronic arthritis that ensued. Being a pathologist, he described autopsies on some patients, noting that there was less actual destruction of cartilage and joints than one might expect, and postulating that much of the joint deformity was related to tissue contractures from lack of joint mobility. In retrospect, this observation made a good case for the use of physiotherapy in treatment of juvenile arthritis.

Still became one of the best-known pediatricians of his day and authored six books and some 108 papers during a long and productive career in pediatrics, but he said little more about chronic arthritis in children. Indeed, this field fell fallow, aside from a description of 12 cases and a review of the literature by Kuhns and Swaim of Boston in 1932 (22). Not until the 1940s did interest revive in rheumatic conditions of children other than rheumatic fever.

Early arthritis centers. During the first half of the 20th century, a few units were established for care and convalescence of children with rheumatic fever. These included, for example, The House of the Good Samaritan in Boston, Irvington House in New York State, and La Rabida in Chicago. A few similar units for children with physical disability were created such as Rainbow Babies Hospital in Cleveland and Children’s Orthopedic Hospital in Seattle.

In 1947, shortly after the end of World War II, the Canadian government presented to the people of Great Britain an English war hospital it had founded, and a unit was founded for the care of children with rheumatic diseases. The gradual decline of cases of rheumatic fever and the realization that children also had other rheumatic conditions changed the direction of this new unit. The Canadian Red Cross Hospital subsequently became a referral unit for children with JRA and a broad array of other rheumatic diseases from all over England. This hospital was fondly referred to as “Taplow,” the name of the idyllic English village nearby (23). Professor Eric Bywaters became head of the Medical Research Council Rheumatism Unit established at Taplow, and was later joined by a young colleague, Dr. Barbara Ansell. This unit at Taplow represented perhaps the first concerted effort to devote a center and professional careers to the practice and study of pediatric rheumatology. Taplow became a center for the training of fellows

from many countries in both adult and pediatric rheumatology. (North American pediatric rheumatologists who worked at Taplow included John Baum, James Cassidy, Chester Fink, Virgil Hanson, Ross Petty, Jane Schaller, and Patience White.) The hospital established immunology and pathology units with vital research resources and important ancillary services for children in physical and occupational therapy, surgical therapy, ophthalmology, and residential schooling. From 1947 to 1985, Taplow was a center for the development of knowledge about childhood rheumatic diseases and their appropriate therapy.

In 1952, Elizabeth Stoeber and her colleagues similarly transformed a sanatorium for children with tuberculosis into a center for childhood rheumatic diseases in Garmish-Partenkirchen, Germany (24).

THE HISTORY OF SPECIFIC RHEUMATIC DISORDERS, 1940–1970

Chronic arthritis. Between 1940 and 1960, several publications addressed chronic arthritis in children (25–35). The condition was generally considered a single entity and confusion remained about its relationship to adult rheumatoid arthritis, the various disease manifestations, relationship to the newly described rheumatoid factors, and appropriate nomenclature. The condition was widely referred to as Still's disease in honor of George Frederic Still, occasionally as the Fanconi Wissler syndrome, acknowledging that Fanconi had also recognized this condition, as JRA (particularly in the United States), and as juvenile chronic polyarthritis (particularly in England).

Ankylosing spondylitis. Ankylosing spondylitis has been recognized from antiquity, a type of arthritis that differed from rheumatoid arthritis in its involvement of the axial skeleton, its predilection for males, and its familial occurrence. Ankylosing spondylitis was not well described in children until the 1960s [Jacobs, 1963 (36); Schaller, Bitnum, and Wedgwood, 1969 (37); Ladd, Cassidy, and Martel, 1971 (38)]. Subsequently it was recognized that ankylosing spondylitis and its related spondyloarthropathic syndromes (Reiter's syndrome, reactive arthritis, and some cases of the arthritis of inflammatory bowel disease) had been often lumped with JRA when they began in childhood, their link to spondyloarthropathies overlooked because the classic axial skeletal complaints often did not evolve until adulthood, or perhaps never at all.

Lupus erythematosus. Systemic lupus erythematosus (SLE) was well described clinically during the 1800s (39). The name "lupus" (Latin, wolf) described the cutaneous lesions of lupus that could ulcerate and eat away at the patient, as would a carnivorous animal. The description of the lupus erythematosus cell by Hargraves and colleagues in 1948 (40) led to the subsequent discovery of antinuclear antibodies (41) and better understanding of the disease as one where immune complex deposition played a major role in tissue pathology and disease manifestations.

Although we now recognize that about 20% of cases of lupus begin during childhood years, childhood lupus was rarely described before the 1950s. Systemic lupus in children was considered a disease with a high fatality rate. Early papers include those of Zetterstrom and Berglund, 1956 (42); Gribetz

and Henley, 1959 (43); Cook, Wedgwood, Craig, Hartmann, and Janeway, 1960 (44); Jacobs, 1963 (45); Peterson, Vernier, and Good, 1963 (46); Hagge, Burke, and Stickler, 1967 (47); Hanson and Kornreich, 1967 (48); Robinson and Williams, 1967 (49); and Meislin and Rothfield, 1968 (50).

Dermatomyositis. Dermatomyositis, a condition predominantly affecting striated muscle and skin, was well described in children in the 1950s [Wedgwood, Cook, and Cohen, 1953 (51); Pearson, 1962 (52); Banker and Victor, 1966 (53); Hanson and Kornreich, 1967 (48); Sullivan, Cassidy, Petty, and Burt 1972 (54)]. The disease, when untreated, had a fatality rate as high as 50%, the main causes of death being gastrointestinal vasculitis and swallowing or respiratory dysfunction. Calcinosis was known as a long-term complication, and there was a high rate of crippling in children who survived the active phase of disease.

Vasculitis. Schonlein-Henoch vasculitis has been recognized as a childhood condition since descriptions of the rash by Schonlein and the nephritis by Henoch in the 1800's. This vasculitis of small vessels was described in children by Wedgwood and Klaus in 1955 (55); Bywaters *et al.* in 1957 (56); Allen *et al.*, 1960 (57); and Vernier *et al.*, 1961 (58). Bywaters pointed out the association of streptococcal infection with some cases. The nephritis of Schonlein-Henoch was somewhat controversial; some observers thought it was potentially dangerous and required treatment, while others recognized its generally benign and transient nature in children. Other forms of vasculitis such as polyarteritis nodosa and Wegener granulomatosis were rarely described in children (59).

Kawasaki disease. Following World War II, Kawasaki disease emerged as a seemingly new condition, although suspiciously resembling a rare syndrome described in the 1940s as infantile polyarteritis (60,61). Tomisaku Kawasaki, a young academic general pediatrician in Tokyo, described 50 children he saw between 1961 and 1967 with what we now call Kawasaki disease, and recognized that this was a distinct condition. Kawasaki published his first papers in 1967 in Japanese (62); his first report in English appeared in 1974 (63). Kawasaki disease has now been recognized in nearly every country of the world as a febrile disease accompanied by a distinctive form of vasculitis with a predilection for medium- and large-sized vessels, notably the coronary vessels.

Scleroderma. Scleroderma, a disease of fibrosis of the skin and internal organs, is rare in children. Cutaneous forms of scleroderma (morphea, linear scleroderma) were well described in children in the 1960s [Chazen *et al.*, 1962 (64); Kass *et al.*, 1966 (65); Winkleman *et al.*, 1971 (66)]. Systemic scleroderma with fibrosis of internal organs was not considered a condition of childhood.

DEVELOPMENT OF PEDIATRIC RHEUMATOLOGY AS A SUBSPECIALTY, 1970–2004

Early organizations. The organization of pediatric rheumatology as a subspecialty blossomed in the 1970s, spurred by a realization that the rheumatic diseases in children were distinct from those in adults, the burgeoning of immunology and new technology, and the advent of modern drug therapy. Before that

time, the International League Against Rheumatism (ILAR) and the American Rheumatism Association (ARA) existed without sections addressing childhood rheumatic diseases. Children with rheumatic diseases were generally considered as small adults, to be consulted on by adult-oriented specialists.

In 1971, the American Rheumatism Association established a "JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association." Its members were (in alphabetical order) Jack Bass of Columbus, Ohio, Earl Brewer of Houston, James Cassidy of Ann Arbor, Chester Fink of Dallas, Jerry Jacobs of New York, Milton Markowitz of Hartford, Jane Schaller of Seattle, and J. Sydney Stillman of Boston.

The purpose of this JRA Criteria Subcommittee was to gather the few pediatricians who were focusing on pediatric rheumatology to see whether they could agree on the classification of juvenile rheumatoid arthritis. After many vigorous discussions, this group produced the first criteria for the classification of juvenile rheumatoid arthritis in 1973 (67). Much of the difficulty, in retrospect, was the difficulty of establishing criteria for a condition which includes more than one entity.

In 1975, the few American specialists in pediatric rheumatology prevailed upon the American Rheumatism Association to form a Council on Pediatric Rheumatology. The members were (in alphabetical order) John Baum of Rochester, NY, Earl Brewer of Houston, James Cassidy of Ann Arbor, Chester Fink

of Dallas, Virgil Hanson of Los Angeles, Jerry Jacobs of New York, Joe Levinson of Cincinnati, Jane Schaller of Seattle, and J. Sydney Stillman of Boston.

In 1975, another important event took place with the organization of the Pediatric Rheumatology Collaborative Study Group to encourage pediatric studies of the new nonsteroidal antiinflammatory agents that were appearing on the market. The chair of this group was Earl Brewer; its members included most of the members of the Council. These new drugs were being labeled "not to be used in children because not tested," which led to considerable consternation in the pediatric rheumatology community inasmuch as these agents were being widely touted in adult medicine. The Pediatric Rheumatology Collaborative Study Group established protocols for safety, efficacy, and controlled studies of drugs in children with rheumatic disease, and published the results of its first drug trial in 1977 (68).

In 1976, the Council on Pediatric Rheumatology, co-chaired by Jane Schaller of Seattle and Virgil Hanson of Los Angeles, organized a landmark conference on childhood rheumatic diseases, held in the unlikely setting of a partially built new ski resort in Park City, UT (Fig. 1). This international meeting was perhaps the real beginning of organized pediatric rheumatology. Some 50 invitees including pediatric rheumatologists, leading adult rheumatologists, immunologists, and geneticists, and orthopedists and physiatrists gathered for a week of papers

Figure 1. (A) Park City I, 1976: The Council on Pediatric Rheumatology deliberates. From the left lower corner: John Baum, Rochester; Sydney Stillman, Boston; Chester Fink, Dallas; Jerry Jacobs, New York; Virgil Hanson, Los Angeles; Lynn Bonfiglio, Executive Director American Rheumatism Association; Joe Levinson, Cincinnati; Jane Schaller (standing), Seattle; Earl Brewer (the host for Park City), Houston; Jim Cassidy, Michigan. (B) Park City I, 1976: Co-chair Virgil Hanson of Los Angeles opens the first Park City conference. (C) Park City I, 1976: The group deliberates, small in size and rough in surroundings. John Baum speaking; identifiable in first rows: Milton Markowitz, Connecticut; Chester Fink; Earl Brewer; Gerald Rodnan, Pittsburgh; behind him, Barbara Ansell, UK; behind her, Eric Bywaters, UK; Jim Cassidy, Michigan. (D) Park City I, 1976: The whole group, plus a few accompanying persons, gathered outside one of the several accommodations.

and discussions of the whole field of pediatric rheumatology. In 1976, we could count no more than 30 pediatric rheumatologists in the entire United States. The proceedings of this conference presented the state of knowledge of childhood rheumatic diseases in 1976 (69).

The following year, the European Union Against Rheumatism and the World Health Organization jointly sponsored a workshop on nomenclature and classification of arthritis in children in Oslo, Norway (70), marking the beginning of an association of European pediatric rheumatologists (Fig. 2). A number of United States pediatric rheumatologists also attended this meeting.

Current organizations. The old Council on Pediatric Rheumatology has become the Section of Pediatric Rheumatology of the American College of Rheumatology (<http://www.rheumatology.org/sections/pediatric/>). The American Academy of Pediatrics has also developed a Section on Pediatric Rheumatology (www.aap.org/sections/rheumatology). These two organizations together conducted the Fifth Park City Conference, Pediatric Rheumatology 2003: Park City and Beyond, this time held at Snowmass (71). This Fifth International Conference was attended by more than 500 pediatric rheumatologists and related professionals. The American College of Rheumatology Section on Pediatric Rheumatology now includes more than 200 professionals, at least 14 of whom belong to an expanding assembly of MD-PhDs.

Board examinations. United States boards in pediatric rheumatology were first established in 1992 under the American Board of Pediatrics; the specialty was defined as requiring prior certification by the Board of Pediatrics. As of December 2003, there were 192 diplomats in pediatric rheumatology certified by the American Board of Pediatrics, representing 1.2% of all pediatric subspecialists. Pediatric rheumatology is 13th in size among the 16 pediatric subspecialties; only neurodevelopmental disability, sports medicine, and medical toxicology have fewer diplomates.

Distribution of pediatric rheumatologists. According to the latest available statistics (2002), 63% of pediatric rheumatologists were in full-time academic and 6% in part-time academic pediatric rheumatology. None was in full-time private rheumatology practice. Six percent of pediatric rheumatologists practiced academic pediatric rheumatology and academic pediatric general pediatrics. An additional 13% of pediatric rheumatolo-

gists were in private practice of both pediatric rheumatology and general pediatrics. As of 2003, 47 fellows were training in pediatric rheumatology, only 10 of whom were in the final third year of training (72).

The vast majority of pediatric rheumatologists practice in academic and children's hospital centers. The difficult patients seen by pediatric rheumatologists often require the team services and other pediatric specialist consultations that are available only in such centers. Furthermore, education of medical students and residents about childhood rheumatic diseases is important for all who will enter related or general fields of practice. It is of concern that a study in 2000 found that 45 of 125 medical schools in the United States had no pediatric rheumatologist on their faculties and 45 additional medical schools had only one pediatric rheumatologist who was often not full-time at the institution. These statistics suggest that a number of referral children's hospitals in the United States do not have an available pediatric rheumatologist (73). An update of these figures in 2003 indicated little improvement: 135 pediatric rheumatologists were working full-time in academic pediatric rheumatology, but 48 U.S. medical schools still did not have a pediatric rheumatologist (74). Recent studies have again demonstrated that a significant number of children suffer from rheumatic diseases and related conditions (75) and that a significant number of these children are being cared for by adult rheumatologists who often feel uncomfortable treating children younger than the teenage years (76,77).

A recent study of pediatric subspecialty care undertaken by the American Academy of Pediatrics indicated that the pediatric subspecialty workforce faces strong competitive market pressures based on cost-containment and that support for additional subspecialists in many areas seems to be diminishing (78). This is a concern, given the finding that physicians being trained in primary care and other specialties such as adult rheumatology are too often being trained in medical schools and training centers where there is not a pediatric rheumatologist available for either education or consultation.

ADVANCES IN THERAPY

The Pediatric Rheumatology Collaborative Study Group, currently based in Cincinnati, remains well organized and

Figure 2. (A) The Oslo Conference, 1977: Our European counterparts hard at work. Conference luminaries Eric Bywaters, Taplow, and Philip Wood, Birmingham. (B) The Oslo Conference, 1977: A lighter moment: Jane Schaller, Seattle; Lenox Holt, UK; Barbara Ansell, UK.

active, and has conducted and published a number of important studies on the use of antirheumatic agents in children.

Corticosteroids. The advent of modern drug therapy for rheumatic diseases began in 1949 with the observation by Hench and his colleagues at the Mayo Clinic, that corticosteroids were remarkably effective in suppressing rheumatoid arthritis in adults (79). Adverse effects of corticosteroids were not noted until later. Other agents used at that time included antimalarials, gold salts, phenylbutazone, and salicylates.

Nonsteroidal antiinflammatory drugs. In the 1970s, a number of new nonsteroidal antiinflammatory agents appeared, and at that time the Pediatric Rheumatology Collaborative Study Group was first organized. Early studies defined standard methodology for design, conduct, and analysis of drug trials in children with rheumatic diseases (80). A series of papers then described standardized drug trials of a number of the new nonsteroidal antiinflammatory agents that were appearing in the 1970s. These studies included tolmetin (1977) (68), meclofenamate (1982) (81), proquazone (1982) (82), pirofen (1982) (83), ketoprofen (1982) (84), aspirin and fenoprofen (1982) (85), and liquid ibuprofen (1990) (86). In general, these nonsteroidal agents were found to be relatively safe in children (although gastric irritation was reported) and to be convenient if infrequent dosage schedules could be used, but would offer little therapeutic advantage.

Slow-acting antirheumatic drugs. The Collaborative Study Group then moved on to the study of the so-called slow-acting antirheumatic drugs, attempting in 1987 to define characteristics of responders and nonresponders to these agents (87). In 1986, studies of hydroxychloroquine and penicillamine in severe juvenile rheumatoid arthritis did not show their efficacy when compared with placebo (88). A controlled study in 1990 (89) showed that the oral gold therapy was not effective when compared with placebo; subsequent results of a 5-y extension trial did not change this finding (90).

In 1992, a controlled trial of showed low-dose methotrexate to be effective in resistant JRA (91). The results of these studies of the traditional "slow-acting" agents were that methotrexate came to be the second line agent of choice in juvenile arthritis, that the use of penicillamine and oral gold were virtually abandoned, and that antimalarials were probably used much less frequently. Although there was not a controlled study of parenteral gold conducted, the use of this agent also lessened after the demonstrated efficacy of low-dose methotrexate.

Intravenous immune globulin. Two subsequent studies addressed the efficacy of intravenous Ig in the treatment of systemic JRA (92) and of polyarticular JRA (93). The results did not indicate great efficacy, although some individual patients improved.

Biologics. A new class of therapeutic agents that target specific components of the inflammatory and immune systems such as cytokines or immune cells appeared in the 1990s. These agents represent a major breakthrough in therapy of both children and adults with rheumatic diseases, particularly for those with chronic arthritis, although the follow-up periods are still relatively short and the agents remain very expensive. Two studies have addressed the safety of etanercept (which targets tumor necrosis factor, a cytokine) in children with severe JRA

over a short term (94) and a somewhat longer term, and have demonstrated the remarkable efficacy of this agent over follow-up times of several years (95). Other biologic agents are also currently under study by the group.

Other studies. Other studies of the Pediatric Collaborative Study Group include validation of criteria for disease activity and damage in juvenile myopathies (96), defining an international consensus for measuring disease activity and damage in both juvenile systemic lupus erythematosus and juvenile dermatomyositis (97), and drafting criteria for clinical remission in juvenile arthritis (98). The last two studies cited were conducted in collaboration with the counterpart European organization PRINTO.

The current membership of the Pediatric Rheumatology Collaborative Study Group comprises 170 pediatric rheumatologists at 93 separate clinical sites in North America. All told, this remarkable organization has contributed greatly to our knowledge of drug trials in children, to advocacy with the pharmaceutical industry and the government for the importance of testing drugs in children, and of studying pediatric efficacy, safety, or lack of the same in the drugs that have been commonly used to treat rheumatic diseases in adults.

OTHER CURRENT ORGANIZATIONS

The Childhood Arthritis and Rheumatology Research Alliance (CARRA; <http://www.carragroup.info/>) was formed in 2001 to create a multicenter organization that can support clinical trials and clinical research in pediatric rheumatology. This organization is currently centered at Stanford University, and has been focusing on establishing a scientific agenda and building the needed infrastructure. Collaborating organizations include the Arthritis Foundation, the American College of Rheumatology, and the National Institutes of Health.

The American Juvenile Arthritis Organization was formed by the Arthritis Foundation (AJAO; www.arthritis.org/communities/juvenile_arthritis/about_ajao.asp) in 1981 as a support and advocacy group for parents, allied health professionals, and pediatric rheumatologists.

The pediatric rheumatologists of Europe have formed an active European Pediatric Rheumatology Group (PRES; www.pres.org.uk/), as well as a Pediatric Rheumatology International Trials Organization (PRINTO; www.printo.it) to further research and studies of therapy in Europe. This group is collaborating actively with the Pediatric Collaborative Study Group of the United States.

The Myositis Association (www.myositis.org) has formed an active group of rheumatologists and advocates with major interests in childhood dermatomyositis. The organization is preparing a book, covering the inflammatory myopathies of childhood, for parents, the public, and other interested parties (98a).

PUBLICATIONS

A number of publications have now addressed pediatric rheumatology. Major pediatric textbooks did not include childhood rheumatic diseases aside from rheumatic fever until 1959, when the seventh edition of the Nelson *Textbook of Pediatrics*

included a chapter on childhood rheumatic diseases (under the designation of "Diseases of Mesenchymal Tissues"), authored by Ralph Wedgwood of Cleveland (99). Chapters in other pediatric textbooks followed, as did chapters in major rheumatology textbooks.

Several texts have been devoted solely to pediatric rheumatology: *Chronic Arthritis in Childhood*, Barbara Ansell (100); *Textbook of Pediatric Rheumatology*, James Cassidy and Ross Petty (101) (5th Ed.); and the *Differential Diagnosis of Childhood Arthritis*, Jerry Jacobs (102). A number of other publications, including *Clinics in Rheumatic Diseases*, have featured volumes on pediatric rheumatology.

In 2003, the first edition of an online pediatric rheumatology journal appeared, a child of the Sections on Pediatric Rheumatology of the American College of Rheumatology and of the American Academy of Pediatrics (www.pedrrheumonlinejournal.org).

PEDIATRIC RHEUMATOLOGY, 1970–2004

A number of advances in basic and clinical sciences over the past several decades have contributed to better understanding of the rheumatic diseases and better care for children with rheumatic diseases. Clinical and epidemiologic studies have resulted in better classification and delineation of rheumatic disease syndromes as they occur in children. This delineation of disease type has been particularly notable in JRA, as suggested in 1969 (103) and 1972 (104) by Schaller and Wedgwood and more recently by Petty and colleagues (105,106). Some syndromes seem almost unique to childhood, for example, the pauciarticular arthritis of early childhood associated with chronic iridocyclitis and antinuclear antibodies (107) and Kawasaki disease (63). Basic research in pediatric rheumatology has blossomed, with at least 10 National Institutes of Health–funded investigators in this field at present, and several National Institutes of Health Center and Training Grants focused on pediatric rheumatology. Substantial scientific contributions are coming from these endeavors, including basic mechanisms underlying the disease associations of HLA B27 (108) and HLA Class II antigens (109), the complex genomics of JRA (110), and dendritic cell biology in SLE (111).

Immunology. Advances in understanding human immunology have contributed to better understanding of the pathophysiology of rheumatic diseases, although this knowledge remains imperfect. The identification of immune complex disease as a basic mechanism in rheumatic diseases, particularly in systemic lupus, has furthered our understanding of tissue damage and has provided a useful mechanism for monitoring disease activity. Studies of the cytokines have enhanced our knowledge of mechanisms of inflammation, and opened the door for the creation of a number of new therapeutic "biologic" agents that target mediators of inflammation such as tumor necrosis factor and immune cells.

Genetics. The sequencing of the human genome represents an enormous step forward in science and offers promise for better future understanding of many crucial factors influencing rheumatic diseases: mechanisms of inflammation and immune

response, host-predisposition to disease, and pharmacogenomics and host responsiveness to drugs.

Histocompatibility typing has established that a genetic predisposition exists in a number of rheumatic diseases. The association is strongest for ankylosing spondylitis and the spondyloarthropathies, all of which are associated with HLA-B27. Associations have also been shown for adult-type rheumatoid factor–positive rheumatoid arthritis, pauciarticular JRA, SLE, and childhood dermatomyositis (112–114). However, in none of these conditions is HLA testing diagnostic, nor is it certain whether the HLA antigens or some linked factor explain the disease associations. Concerning other rare rheumatic syndromes of childhood, extensive studies have led to better understanding of the various febrile syndromes, a number of which are now recognized as single-gene diseases [*e.g.* familial Mediterranean fever (115), NOMID/CINCA (116)].

Imaging. Advances in imaging techniques including computer tomography, magnetic resonance imaging, and ultrasound have revolutionized the localization of organ involvement and tissue damage.

Epidemiology. Geographic and ethnic differences in prevalence of various rheumatic disease syndromes have also become apparent; in most instances it is not known whether these differences arise from a genetic or environmental basis, or combination of both. The spondyloarthropathies have a strong association with a genetic factor, HLA B27; these conditions are rare in populations with a low prevalence of B27 (*e.g.* Japan) and relatively common in populations of a high prevalence of this gene (*e.g.* the Haida population of the Pacific Northwest) (117).

Behcet syndrome is relatively rare in North America but relatively common in the countries such as Turkey and Iran (118). Kawasaki disease has been described most frequently in children of Japanese origin, even where there are mixed racial populations in areas such as Hawaii (119). The explanations for most of these geographic or ethnic diversities in rheumatic disease distribution remain to be found, but offer possible clues to basic disease mechanisms.

Differential diagnosis. Pediatric rheumatologists have become increasingly aware of the importance of accurate differential diagnosis in the evaluation and management of children with rheumatic complaints. Several observations have been made concerning infectious agents. Lyme arthritis, originally described in children thought to have pauciarticular juvenile arthritis, is now known to be caused by infection with a spirochete (120). Parvovirus, the virus causing Fifth disease, can be accompanied by arthritis in one or a number of joints (121). Influenza B infection can be followed by an acute transient "myositis" of the calf muscles (122). Childhood leukemia, and indeed any of the childhood malignancies, can be the basis for frank arthritis, sometimes with other systemic complaints also reminiscent of rheumatic disease (123).

Pain amplification syndromes. Pediatric rheumatologists everywhere are seeing an increasing number of children with either diffuse or localized musculoskeletal pain without apparent underlying organic disease. These pain syndromes are often labeled as reflex sympathetic dystrophy (pain generally localized to one limb or body part) (124), the fibromyalgia syn-

drome (diffuse pain syndrome) (125), or the chronic fatigue syndrome (126). Such conditions can be extremely disabling and usually have a strong psychological overlay. There is no ready explanation for their apparent increased prevalence. Management with restoration of function, attention to psychosocial issues, and a minimum of drug therapy is often difficult and time consuming.

Laboratory diagnosis. A number of basic laboratory studies are frequently used in the rheumatic diseases. Both rheumatoid factors, antibodies that react with immunoglobulin (127,128), and antinuclear antibodies, a family of antibodies that react with various antigens found in cell nuclei (40,41), were described in the 1940s. Both are useful in the classification of rheumatic diseases, but neither has proved to be a diagnostic test for any one disease.

The classic rheumatoid factors, IgM antibodies to IgG, are associated with adult-type rheumatoid arthritis. Antinuclear antibodies (ANA) are found essentially in all patients with SLE; their absence makes the diagnosis of SLE difficult to support. Some specific ANA are useful in disease classification: antibodies reacting with RNA for mixed connective tissue disease, antinuclear cytoplasmic antibodies for Wegener granulomatosis, antibodies to DNA in monitoring the activity of the immune complex disease of SLE. Positive tests for ANA are strongly associated with the iridocyclitis of JRA (107), but are also found in children with pauciarticular or polyarticular arthritis without eye disease, and children with dermatomyositis and scleroderma (129).

Serum complement studies are useful in following the activity of the immune complex of SLE, but are not diagnostic of any disease (130,131). The rare deficiency states of components of the complement system may be associated with rheumatic disease syndromes, particularly SLE (131,132).

The antiphospholipid antibodies are directed against negatively charged phospholipids, and have been associated with various rheumatic diseases, notably SLE (lupus anticoagulants) and Sjogren syndrome. These antibodies may also occur with infectious diseases and malignancies, or in the absence of disease. They are associated with an increased risk of hypercoagulability, stroke, and fetal loss, and their presence raises the question of anticoagulation or coagulation therapy (133).

CURRENT PROBLEMS AND CONTROVERSIES

Rheumatic fever. Rheumatic fever remains a major disease of children in the developing world, and to a lesser extent of poor children in the industrialized world (12,13). Preventing or treating the antecedent streptococcal infections of rheumatic fever involves addressing socioeconomic factors such as poverty, crowding, poor nutrition, and lack of access to adequate health care.

Efforts to find a suitable vaccine against streptococcal infections have not yet been successful, and adequate therapy of streptococcal pharyngitis remains crucial to control rheumatic fever (134). In the 1980s, outbreaks of rheumatic fever occurred in several parts of the United States, perhaps related to relatively asymptomatic streptococcal pharyngitis that was not recognized or treated (135,136). No convincing studies exist to

show that any form of antiinflammatory therapy during active rheumatic disease alters the long-term cardiac damage. When cardiac failure from valvular dysfunction has occurred, definitive therapy of valve replacement surgery is expensive and not available for most children in the developing world.

Although the role of antecedent streptococcal infection in causing acute rheumatic fever has been known for decades, extensive research has not yet fully elucidated the pathophysiologic mechanisms involved, or the matter of host predisposition to disease.

Chronic arthritis. Juvenile rheumatoid arthritis is now accepted as a syndrome of chronic arthritis with several different subgroups that probably represent different diseases. This concept was suggested by Schaller and Wedgwood in the late 1960s (103) and early 1970s (104,137). The occurrence of chronic iridocyclitis is virtually limited to a group of patients with early childhood onset of pauciarticular arthritis and frequent occurrence of antinuclear antibodies (107). This subgroup has an imperfectly understood associations with HLA DR5 and DR8 (112). The spondyloarthropathies, all associated with HLA-B27 (112,113), are now recognized within the spectrum of juvenile arthritis, and indeed account for most instances of pauciarticular arthritis beginning in later childhood, especially in males (137).

Classic IgM rheumatoid factors, the markers for seropositive adult rheumatoid arthritis, are restricted to a relatively small group of older children and adolescents with a severe form of polyarthritis that appears identical to classic adult rheumatoid arthritis and is associated with HLA-DR4 (138,139).

The other two generally accepted subgroups of juvenile arthritis are systemic onset disease, clearly delineated by its characteristic systemic complaints of high intermittent fevers and other system involvement, and rheumatoid factor-negative polyarthritis, a much less well characterized group (103,104,140).

Recently, the International League Against Rheumatism suggested the nomenclature "juvenile idiopathic arthritis" and proposed an even more complicated classification system for juvenile arthritis, differentiating the pauciartthritis of early childhood into two subgroups (persistent pauciartthritis and pauciartthritis that progresses to involve multiple joints), and adding categories for psoriatic arthritis and an undifferentiated arthritis group. Such detailed classifications may permit more accurate subgrouping, and thus provide a basis for better study of basic disease mechanisms (105,106).

Lupus erythematosus. Better recognition of children with systemic lupus and more aggressive therapy have improved the outlook. However, aggressive therapy is difficult and fraught with potential side effects. Corticosteroid therapy remains a mainstay, and intravenous cyclophosphamide is now the most commonly used regime to control severe disease (141). Ideal management requires the input of a pediatric rheumatologist or other specialist who is experienced in the control of this difficult disease in children and adolescents. The curious occurrence of a neonatal lupus syndrome associated with transplacental passage of maternal antibody to Ro/La from mothers with SLE or Sjogren syndrome (142), and of discoid lupus in mothers of sons with x-linked chronic granulomatous disease

(143) remain intriguing but poorly understood clues to lupus pathophysiology.

Dermatomyositis. Childhood dermatomyositis has been the focus of intensive study in several settings (144–146). A genetic predisposition to disease has been identified but is imperfectly understood. Extensive studies of pathophysiology have increased understanding of basic disease mechanisms of this condition, but cause and effect remain elusive. Magnetic resonance imaging of muscle has been accepted as a valuable tool for determining the extent of muscle involvement and to a certain extent the activity of disease. Therapy with a number of agents has been found to be effective, but no effective therapies have been found for the discouraging long-term complication of calcinosis.

Kawasaki disease and other vasculitis syndromes. Kawasaki disease remains essentially a childhood condition, and has now been recognized all over the world (147–149). In the United States, it is the most common cause of acquired heart disease in children. Despite much research effort, an understanding of basic disease mechanisms remains incomplete. The promising concept that Kawasaki disease is the result of a toxin produced by bacteria such as staphylococci or streptococci seems difficult to prove (150). Intravenous gamma-globulin has been found to be an effective tool in preventing coronary vasculitis, but we still do not understand its mechanism of action. Other forms of vasculitis, aside from Schonlein-Henoch, remain rarities in childhood (151).

Scleroderma. Scleroderma remains a rarity during childhood years. It is now accepted that the cutaneous forms are rarely if ever associated with involvement of internal organs. Systemic sclerosis is quite rare in childhood; Raynaud's phenomenon is often the harbinger of this disease. There have been no major research or therapeutic breakthroughs (152).

SUMMARY

Despite many recent advances in science, we are still left with an incomplete understanding of the pathophysiology of most of the rheumatic diseases, and hampered by our inability to prevent them or to predict accurately those patients at risk for severe disease. We have been successful at better defining diseases, and have made significant advances in therapy. Continuing emphasis on clinical, epidemiologic, and basic research is needed; a recent burgeoning of basic research in pediatric rheumatology holds promise for enhanced understanding and care of patients.

The scope of pediatric rheumatology has broadened to include pain syndromes, sports-related injury, musculoskeletal dysfunction, and overall fitness and musculoskeletal health. Cutbacks in health care, particularly in ancillary services such as physical and occupational therapy, pose problems for children with all kinds of chronic conditions including rheumatic diseases. Pediatric rheumatology has become a well-organized specialty area, and one that deserves preservation as a valid subspecialty that enhances both the recognition and the care of children with these difficult conditions.

REFERENCES

- Bywaters EG 1977 The history of pediatric rheumatology. *Arthritis Rheum* 20:145–152
- Short CL, Bauer W, Reynolds WE 1957 Rheumatoid Arthritis. Harvard University Press, Cambridge, p 30
- Still GF 1897 On a form of chronic joint disease in children. *Medico-Chirurgical Trans* 80:47–59; reprinted in *Am J Dis Child* 1978;132:195–200
- Goodhart JF, Still GF 1913 *The Diseases of Children*. J & A Churchill, London, p 777
- Still GF 1931 *The History of Paediatrics*. Oxford University Press, London, p 503
- Phaer T 1545 *The Boke of Chyldren*. London
- Still GF 1910 *Common Disorders and Diseases of Childhood*. Oxford University Press, London
- Stone E 1763 An account of the success of the bark of the willow in the cure of agues. *Philos Trans R Soc Lond* 53:195–200
- Schlesinger B 1930 The relationship of throat infection to acute rheumatism in childhood. *Arch Dis Child* 5:411–430
- Denny FW Jr, Wannamaker LW, Brink WR, Rammelkamp CH, Custer EA 1950 Prevention of rheumatic fever: treatment of the preceding streptococcal infection. *JAMA* 143:151–153
- Markowitz M, Gordis L 1972 *Rheumatic Fever*. WB Saunders, Philadelphia
- Kaplan EL 1993 The T. Duckett Jones Memorial Lecture. Global assessment of rheumatic fever and rheumatic heartdisease at the close of the century. Influences and dynamics of population and pathogens: a failure to realize prevention? *Circulation* 88:1964–1972
- WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease 2001 Rheumatic fever and rheumatic heart disease: report of a WHO Expert Consultation. WHO Technical Report Series No. 923, World Health Organization, Geneva
- Cornil MV 1864 [Report on the pathology of chronic articular rheumatism.] *Compte rendu Med Soc Bio Series (Paris)* 4:3–6
- Bouchet E 1875 [Practical treatise of illnesses in children.] JB Bailliere et fils, Paris
- Garrod AB 1876 *A Treatise on Gout and Rheumatic Gout*. Longmans, Green & Company, London
- Lewis-Smith JL 1876 *A Treatise on Diseases of Infancy and Childhood*. Henry C. Lea, Philadelphia
- Moncorvo CA 1880 [Chronic rheumatism of children and its treatment.] O Doin, Paris
- West C 1881 *Lectures on the Diseases of Infancy and Childhood*. Longman, Brown, Green and Longman, London
- Garrod AE 1890 *A Treatise on Rheumatism and Rheumatoid Arthritis*. Griffin, London
- Marfan AB 1896 [Treatise on Illnesses of Children.] Masson, Paris
- Kuhns JG, Swaim LT 1932 Disturbances of growth in chronic arthritis in children. *Am J Dis Child* 43:1118–1133
- Ansell BM, Bywaters EG, Spencer PE, Tyler JP 1997 Looking Back 1947–1985: The Canadian Red Cross Memorial Hospital, Cliveden, Taplow, England. Barbara M. Ansell, Buckinghamshire
- [Children's Clinic Garmish-Partenkirchen for children and youths.] (http://www.rheuma-kinderklinik.de/rpages/english/e_history.htm)
- Colver T 1937 The prognosis in rheumatoid arthritis in childhood. *Arch Dis Child* pp 253–260
- Coss JA, Boots RH 1946 Juvenile rheumatoid arthritis: a study of 56 cases with a note on skeletal changes. *J Pediatr* 29:143–156
- Schlesinger B 1949 Rheumatoid arthritis in the young. *Brit Med J* July:197–201
- Barkin RE 1952 The clinical course of juvenile rheumatoid arthritis. *Bull Rheum Dis* 3:19–20
- Sury B 1952 Rheumatoid Arthritis in Children: A Clinical Study. Andressen & Co., Copenhagen, Denmark
- Gauchat RD, May CD 1957 Early recognition of rheumatoid disease with comments on treatment. *Pediatrics* 19:672–679
- Edstrom G 1958 Rheumatoid arthritis and Still's disease in children: a survey of 161 cases. *Arthritis Rheum* 1:497–504
- Grokoest AW, Snyder AI, Ragan C 1957 Some aspects of juvenile rheumatoid arthritis. *Bull Rheum Dis* 8:147–148
- Norcross BM, Lockie LM, MacLeod CC 1958 Juvenile rheumatoid arthritis. In: *Ralibott JH, Lockie LM (eds) Progress in Arthritis*. Grune & Stratton, New York, pp 57–85
- Sairanen E 1958 On rheumatoid arthritis in children. *Acta Rheum Scand* 4:1–79
- Ansell BM, Bywaters EG 1959 Prognosis in Still's disease. *Bull Rheum Dis* 9:189–192
- Jacobs P 1963 Ankylosing spondylitis in children and adolescents. *Arch Dis Child* 38:492–499
- Schaller J, Bitnum S, Wedgwood RJ 1969 Ankylosing spondylitis with childhood onset. *J Pediatr* 74:505–516
- Ladd JR, Cassidy JT, Martel W 1971 Juvenile ankylosing spondylitis. *Arthritis Rheum* 14:579–590
- Talbot JH 1974 Historical background of discoid and systemic lupus. In: *Dubois EL (ed) Lupus Erythematosus*, 2nd Ed. University of Southern California Press, Los Angeles, pp 1–11
- Hargraves MM, Richmond H, Morton R 1948 Presentation of two bone marrow elements, the "tart" cell and the "LE" cell. *Mayo Clin Proc* 23:25–28
- Haserick JR, Lewis LA, Bortz DW 1950 Blood factor in acute disseminated lupus erythematosus. I. Determination of gamma globulin as specific plasma fraction. *Am J Med Sci* 219:660–663

42. Zetterstrom R, Berglund G 1956 Systemic lupus erythematosus in childhood; a clinical study. *Acta Paediatr* 45:189-204
43. Gribetz D, Henley WL 1959 Systemic lupus erythematosus in childhood. *J Mt Sinai Hosp N Y* 26:289-296
44. Cook CD, Wedgwood RJ, Craig JM, Hartmann JR, Janeway CA 1960 Systemic lupus erythematosus. Description of 37 cases in children and a discussion of endocrine therapy in 32 of the cases. *Pediatrics* 26:570-585
45. Jacobs JC 1963 Systemic lupus erythematosus in childhood. Report of thirty-five cases, with discussion of seven apparently induced by anticonvulsant medication, and of prognosis and treatment. *Pediatrics* 32:257-264
46. Peterson RD, Vernier RL, Good RA 1963 Lupus erythematosus. *Pediatr Clin North Am* 10:941-978
47. Hagge WW, Burke EC, Stickler GB 1967 Treatment of systemic lupus erythematosus complicated by nephritis in children. *Pediatrics* 40:822-827
48. Hanson V, Kornreich H 1967 Systemic rheumatic disorders ("collagen disease") in childhood lupus erythematosus, anaphylactoid purpura, dermatomyositis, and scleroderma. II. *Bull Rheum Dis* 17:441-446
49. Robinson MJ, Williams AL 1967 Systemic lupus erythematosus in childhood. *Aust Pediatr J* 3:36-47
50. Meislin AG, Rothfield N 1968 Systemic lupus erythematosus in childhood. Analysis of 42 cases, with comparative data on 200 adult cases followed concurrently. *Pediatrics* 42:37-49
51. Wedgwood RJ, Cook CD, Cohen J 1953 Dermatomyositis. Report of 26 cases in children with a discussion of endocrine therapy in 13. *Pediatrics* 12:447-466
52. Pearson CM 1962 Polymyositis and dermatomyositis. *Bull Rheum Dis* 12:269-272
53. Banker BQ, Victor M 1966 Dermatomyositis (systemic angiopathy) of childhood. *Medicine (Baltimore)* 45:261-289
54. Sullivan DB, Cassidy JT, Petty RE, Burt A 1972 Prognosis in childhood dermatomyositis. *J Pediatr* 80:555-563
55. Wedgwood RJ, Klaus MH 1955 Anaphylactoid purpura (Schonlein-Henoch syndrome): a long-term follow-up study with special reference to renal involvement. *Pediatrics* 16:196-206
56. Bywaters EG, Isdale I, Kempton JJ 1957 Schonlein-Henoch purpura; evidence for a group A beta-haemolytic streptococci aetiology. *Q J Med* 26:161-175
57. Allen DM, Diamond LK, Howell DA 1960 Anaphylactoid purpura in children (Schonlein-Henoch syndrome): review with a follow-up of the renal complications. *Am J Dis Child* 99:833-854
58. Vernier RL, Worthen HG, Peterson RD, Colle E, Good RA 1961 Anaphylactoid purpura, pathology of the skin and kidney and frequency of streptococcal infection. *Pediatrics* 27:181-193
59. Fager DB, Bigler JA, Simonds P 1951 Periarthritis nodosa in infancy and childhood. *J Pediatr* 39:65-79
60. Munro-Faure H 1959 Necrotizing arteritis of the coronary vessels in infancy; case report and review of the literature. *Pediatrics* 23:914-926
61. Roberts FB, Fetterman GH 1963 Polyarteritis nodosa in infancy. *J Pediatr* 63:519-529
62. Kawasaki T 1967 [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children.] *Aterugi* 16:178-222
63. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H 1974 A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics* 54:271-276
64. Chazen EM, Cook CD, Cohen J 1962 Focal scleroderma. Report of 19 cases in children. *J Pediatr* 60:385-393
65. Kass H, Hanson V, Patrick J 1966 Scleroderma in childhood. *J Pediatr* 68:243-256
66. Winkelmann RK, Kierland RR, Perry HO, Muller SA, Sams WM 1971 Symposium on scleroderma. *Mayo Clin Proc* 46:128-133
67. Brewer E, Bass JC, Cassidy JT, Duran BS, Fink BS, Fink CW, Jacobs JC, Markowitz MM, Reynolds WE, Schaller JG, Stillman JS, Wallace SL 1973 Criteria for the classification of juvenile rheumatoid arthritis. *Bull Rheum Dis* 23:712-719
68. Levinson JE, Baum J, Brewer E Jr, Fink C, Hanson V, Schaller J 1977 Comparison of tolmetin sodium and aspirin in the treatment of juvenile rheumatoid arthritis. *J Pediatr* 91:799-804
69. Schaller JG, Hanson V (eds) 1976 Proceedings of the First ARA Conference on the Rheumatic Diseases of Childhood Park City, Utah, March 22-25, 1976. *Arthritis Rheum* 20:145-638
70. Wood PH 1978 Special meeting on nomenclature and classification of arthritis in children: proposed criteria for controlled clinical studies. *Scand J Rheumatol* 11:187-192
71. Pediatric Rheumatology: Park City and Beyond, Snowmass, CO, 2003 1:3-5 www.pedrhonlinejournal.org
72. American Board of Pediatrics (available at www.abp.org)
73. 2000 The future status of pediatric rheumatology in the United States: strategic planning for the year 2000. American College of Rheumatology Blue Ribbon Committee for Academic Pediatric Rheumatology. *Arthritis Rheum* 43:239-242
74. Cassidy JT, Athreya BH, Nelson AM, Lindsley CB 2003 The regional distribution of pediatric rheumatologists in medical schools in the United States-2002. *Pediatr Rheumatol Online J* (available at <http://www.pedrhonlinejournal.org/August/Pediatric%20Rheumatology/174.htm>)
75. Malleson PN, Fung MY, Rosenberg AM 1996 The incidence of pediatric rheumatic diseases: results from the Canadian Pediatric Rheumatology Association Disease Registry. *J Rheumatol* 23:1981-1987
76. Sherry DD, Wallace CA, Kahn SJ 1996 Pediatric rheumatology in adult rheumatology practices in Washington State. *Arthritis Rheum* 39:1218-1221
77. Mayer ML, Sandborg CI, Mellins ED 2004 Role of pediatric and internist rheumatologists in treating children with rheumatic diseases. *Pediatrics* 113:e173-e181
78. Stoddard JJ, Cull WL, Jewett EA, Brotherton SE, Mulvey HJ, Alden ER 2000 Providing pediatric subspecialty care: a workforce analysis. AAP Committee on Pediatric Workforce Subcommittee on Subspecialty Workforce. *Pediatrics* 106:1325-1333
79. Hench PS, Kendall EC, Slocumb CH, Polley HF 1949 The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis: Preliminary report. *Proc Staff Meet Mayo Clinic* 24:181-197
80. Giannini EH, Brewer EJ Jr 1982 Standard methodology for segment I, II and III Pediatric Rheumatology Collaborative Study Group studies. I. Design. *J Rheumatol* 9:109-122
81. Brewer EJ, Giannini EH, Baum J, Cassidy JT, Fink CW, Hanson V, Levinson JE, Schaller JG 1982 Sodium meclofenamate (Meclofen) in the treatment of juvenile rheumatoid arthritis. A segment I study. *J Rheumatol* 9:129-134
82. Brewer EJ, Giannini EH, Baum J, Fink CW, Hanson V, Jacobs JC, Schaller JG 1982 Proquazone (Biansan) in the treatment of juvenile rheumatoid arthritis. A segment I study. *J Rheumatol* 9:135-139
83. Bass JC, Giannini EH, Brewer EJ, Athreya B, Brandstrup NE, Goldsmith DP, Miller JJ, Pachman LM 1982 Pirofen (Rengasil) in the treatment of juvenile rheumatoid arthritis. A segment I study. *J Rheumatol* 9:140-143
84. Brewer EJ, Giannini EH, Baum J, Bernstein B, Fink CW, Schaller JG, Knee CM 1982 Ketoprofen (Orudis) in the treatment of juvenile rheumatoid arthritis. A segment I study. *J Rheumatol* 9:144-148
85. Brewer EJ, Giannini EH, Baum J, Bernstein B, Fink CW, Emery HM, Schaller JG 1982 Aspirin and fenoprofen (Nalfon) in the treatment of juvenile rheumatoid arthritis results of the double blind-trial. A segment II study. *J Rheumatol* 9:123-128
86. Giannini EH, Brewer EJ, Miller ML, Gibbas D, Passo MH, Hoyeraal HM, Bernstein B, Person DA, Fink CW, Alexander LA, Scheinbaum ML 1990 Ibuprofen suspension in the treatment of juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *J Pediatr* 117:645-652
87. Giannini EH, Brewer EJ, Kuzmina N, Alekseev L, Shokh BP 1988 Characteristics of responders and nonresponders to slow-acting antirheumatic drugs in juvenile rheumatoid arthritis. *Arthritis Rheum* 31:15-20
88. Brewer EJ, Giannini EH, Kuzmina N, Alekseev L 1986 Penicillamine and hydroxy-chloroquine in the treatment of severe juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind placebo-controlled trial. *N Eng J Med* 314:1269-1276
89. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Wallin B 1990 Auranofin in the treatment of juvenile rheumatoid arthritis. Results of the USA-USSR double-blind, placebo-controlled trial. The USA Pediatric Rheumatology Collaborative Study Group. The USSR Cooperative Children's Study Group. *Arthritis Rheum* 33:466-476
90. Giannini EH, Barron KS, Spencer CH, Person DA, Baum J, Bernstein BH, Kredich DW, Jacobs JC, Zemel LS, Gibbas D, Passo MH, Brewer EJ 1991 Auranofin therapy for juvenile rheumatoid arthritis: results of the five-year open-label extension trial. *J Rheumatol* 18:1240-1242
91. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, Fink CW, Newman AJ, Cassidy JT, Zemel LS 1992 Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. *N Eng J Med* 326:1043-1049
92. Silverman ED, Cawkwell GD, Lovell DJ, Laxer RM, Lehman TJ, Passo MH, Zemel LS, Giannini EH 1994 Intravenous immune globulin in the treatment of systemic juvenile rheumatoid arthritis: a randomized placebo-controlled trial. Pediatric Rheumatology Collaborative Study Group. *J Rheumatol* 21:2353-2358
93. Giannini EH, Lovell DJ, Silverman ED, Sundel RP, Tague BL, Ruperto N 1996 Intravenous immunoglobulin in the treatment of polyarticular juvenile rheumatoid arthritis. A phase I/II study. *J Rheumatol* 23:919-924
94. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Whitmore J, Finck B 2000 Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Eng J Med* 342:763-769
95. Lovell DJ, Giannini EH, Reiff A, Jones OY, Schneider R, Olson JC, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Lange M, Finck BK, Burge DJ 2003 Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. *Arthritis Rheum* 48:218-226
96. Lovell DJ, Lindsley C, Rennebohm RM, Ballinger SH, Bowyer SL, Giannini EH, Hicks JE, Levinson JE, Mier R, Pachman LM, Passo MH, Perez MD, Reed AM, Schikler KN, Smith M, Zemel LS, Rider LG 1999 Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies. II. The Childhood Myositis Assessment Scale (CMAS): a quantitative tool for the evaluation of muscle function. The Juvenile Dermatomyositis Disease Activity Collaborative Study Group. *Arthritis Rheum* 42:2213-2219
97. Ruperto N, Ravelli A, Murray KJ, Lovell DJ, Andersson-Gare B, Feldman BM, Garay S, Kuus W, Machado C, Pachman L, Prieur AM, Rider LG, Silverman E, Tsitsami E, Woo P, Giannini EH, Martini A; Paediatric Rheumatology International Trials Organization (PRINTO); Pediatric Rheumatology Collaborative Study Group (PReCSG) 2003 Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis. *Rheumatology (Oxford)* 42:1452-1459
98. Wallace CA, Ruperto N, Giannini E 2004 Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheum* 11:2290-2294
- 98a. Rider LG, Pachman LM, Miller FW, Bollor H, eds 2005 Myositis and Me: A Complete Family Guide to Juvenile Dermatomyositis and Other Inflammatory Myopathies. The Myositis Association, Washington, D.C.

99. Wedgwood RJ 1959 Diseases of mesenchymal tissues. In: Nelson WE (ed) Textbook of Pediatrics. WB Saunders, Philadelphia, pp 915–929
100. Ansell BM 1980 Rheumatic Disorders in Childhood. Butterworths & Co., London
101. Cassidy JT, Petty RE 2001 Textbook of Pediatric Rheumatology, Churchill Livingstone, New York
102. Jacobs JC 1993 Pediatric Rheumatology for the Practitioner. Springer-Verlag, New York
103. Schaller JG, Wedgwood RJ 1969 Is juvenile rheumatoid arthritis a single entity? *Pediatr Res* 3:370–371
104. Schaller J, Wedgwood RJ 1972 Juvenile rheumatoid arthritis: a review. *Pediatrics* 50:940–953
105. Petty RE, Southwood TR, Baum J 1998 Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol* 25:1991–1994
106. Ramsey SE, Bolaria RK, Cabral DA, Malleson PN, Petty RE 2000 Comparison of criteria for the classification of childhood arthritis. *J Rheumatol* 27:1283–1286
107. Schaller JG, Johnson GD, Holborow EJ, Ansell BM, Smiley WK 1974 The association of antinuclear antibodies with the chronic iridocyclitis of juvenile rheumatoid arthritis (Still's disease). *Arthritis Rheum* 17:409–416
108. Colbert RA 2004 The immunobiology of HLA-B27: variations on a theme. *Curr Mol Med* 4:21–30
109. Patil NS, Pashine A, Belmares MP, Liu W, Kaneshiro B, Rabinowitz J, McConnell H, Mellins ED 2001 Rheumatoid arthritis (RA)-associated HLA-DR alleles form less stable complexes with class II-associated invariant chain peptide than non-RA-associated HLA-DR alleles. *J Immunol* 167:7157–7168
110. Thompson SD, Moroldo MG, Guyer L, Ryan M, Tombragel EM, Shear ES, Prahalad S, Sudman M, Kedache MA, Brown WM, Giannini EH, Langefeld CD, Rich SS, Nichols WC, Glass DN 2004 A genome-wide scan for juvenile rheumatoid arthritis in affected sibpair families provides evidence of linkage. *Arthritis Rheum* 50:2920–2930
111. Pascual V, Banchereau J, Palucka AK 2003 The central role of dendritic cells and interferon-alpha in SLE. *Curr Opin Rheumatol* 15:548–556
112. Nepom GT, Nepom B 1998 Genetics of the major histocompatibility complex in rheumatoid arthritis. In: Klippel JH, Dieppe P (eds) *Rheumatology*. Mosby, London, pp 5.7.1–5.7.1.2
113. Rubin LA, Amos CI, Wade JA 1994 Investigating the genetic basis for ankylosing spondylitis. *Arthritis Rheum* 37:1212–1220
114. Criswell LA, Amos CI 2000 Update on genetic risk factors for systemic lupus erythematosus and rheumatoid arthritis. *Curr Opin Rheumatol* 12:85–90
115. Samuels J, Aksentjevich I, Torosyan Y 1998 Familial Mediterranean fever at the millennium. Clinical spectrum, ancient mutations, and a survey of 100 American referrals to the National Institutes of Health. *Medicine* 77:268–297
116. Hull KM, Shoham N, Chae JJ, Aksentjevich I, Kastner D 2003 The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations. *Curr Opin Rheumatol* 15:61–69
117. Khan MA 1995 HLA-B27 and its subtypes in world populations. *Curr Opin Rheumatol* 7:263–269
118. Sakane T, Takeno M, Suzuki N, Inaba G 1999 Behcet's disease. *N Engl J Med* 341:1284–1291
119. Melish ME, Hicks RM, Larson EJ 1976 Mucocutaneous lymph node syndrome in the United States. *Am J Dis Child* 130:599–607
120. Steere AC, Grodzicki RL, Kornblatt AN 1983 The spirochetal etiology of Lyme disease. *N Engl J Med* 308:733–740
121. Nocton JJ, Miller LC, Tucker LB, Schaller JG 1993 Human parvovirus B19-associated arthritis in children. *J Pediatr* 122:186–190
122. Dietzman DE, Schaller JG, Ray CG, Reed ME 1976 Acute myositis associated with influenza B infection. *Pediatrics* 57:255–258
123. Schaller J 1972 Arthritis as a presenting manifestation of malignancy in children. *J Pediatr* 81:793–796
124. Sherry DD, Wallace CA, Kelley C, Kidder M, Sapp L 1999 Short-and long-term outcomes of children with complex regional pain syndrome type I treated with exercise therapy. *Clin J Pain* 15:218–223
125. Buskila D, Neumann L, Hershtman E, Gedalia A, Press J, Sukenik S 1995 Fibromyalgia syndrome in children—an outcome study. *J Rheumatol* 22:525–528
126. Viner R, Gregorowski A, Wine C, Bladen M, Fisher D, Miller M, Neil EI 2004 Outpatient rehabilitative treatment of chronic fatigue syndrome (CFS/ME). *Arch Dis Child* 89:615–619
127. Rose HM, Ragan C, Pearce E, Lipman MO 1948 Differential agglutination of normal and sensitized sheep erythrocytes by sera of patients with rheumatoid arthritis. *Proc Soc Exp Biol Med* 68:1–6
128. Waaler E 1940 On the occurrence of a factor in human serum activating the specific agglutination of sheep blood corpuscles. *Acta Pathol Microbiol Scand* 17:172–188
129. Sack, KE 2001 Evaluation of the patient: laboratory assessment. In: Klippel JH, Crofford LJ, Stone JH, Weyand CM (eds) *Primer on the Rheumatic Diseases*. Arthritis Foundation, Atlanta, pp 133–137
130. Frank M 1992 Detection of complement in relation to disease. *Clin Immunol* 89:641–648
131. Schur PH, Austen KF 1972 Complement in the rheumatic diseases. *Bull Rheum Dis* 22:666–673
132. Schaller JG, Gilliland GC, Ochs HD, Leddy JP, Agodoa LC, Rosenfeld SI 1977 Severe systemic lupus erythematosus with nephritis in a boy with deficiency of the fourth component of complement. *Arthritis Rheum* 20:1519–1525
133. Ravelli A, Martini A 1997 Antiphospholipid antibody syndrome in pediatric patients. *Rheum Dis Clin North Am* 23:657–677
134. Bisno AL, Gerber MA, Gwaltney JM Jr., Kaplan EL, Schwartz RH 2002 Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Clin Infect Dis* 35:113–125
135. Veasy LG, Wiedmeier SE, Orsmond GS, Ruttenberg HD, Boucek MM, Roth SJ, Tait VF, Thompson JA, Daly JA, Kaplan EL, Hill HR 1987 Resurgence of acute rheumatic fever in the intermountain area of the United States. *N Engl J Med* 316:421–427
136. Kaplan EL, Johnson DR, Cleary PP 1989 Group A streptococcal serotypes isolated from patients and sibling contacts during resurgence of rheumatic fever in the United States in the mid-1980s. *J Infect Dis* 159:101–103
137. Schaller JG, Ochs HD, Thomas ED, Nisperos B, Feigl P, Wedgwood RJ 1976 Histocompatibility antigens in childhood-onset arthritis. *J Pediatr* 88:926–930
138. Schaller JG, Hansen J 1982 Rheumatoid factor-positive juvenile rheumatoid arthritis: the childhood equivalent of classic adult rheumatoid arthritis. *Arthritis Rheum* 25:S18
139. Williams RA, Ansell BM 1985 Radiological findings in seropositive juvenile chronic arthritis (juvenile rheumatoid arthritis) with particular reference to progression. *Ann Rheum Dis* 44:685–693
140. Cassidy JT, Levinson JE, Bass JC, Baum J, Brewer EJ Jr, Fink CW, Hanson V, Jacobs JC, Masi AT, Schaller JG, Fries JF, McShane D, Young D 1986 A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. *Arthritis Rheum* 29:274–281
141. Lehman TJ, Onel K 2000 Intermittent intravenous cyclophosphamide arrests progression of the renal chronicity index in childhood systemic lupus erythematosus. *J Pediatr* 136:243–247
142. Buyon JP, Hiebert R, Copel J, Craft J, Friedman D, Katholi M, Lee LA, Provost TT, Reichlin M, Rider L, Rupel A, Saleeb S, Weston WL, Skovron ML 1998 Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. *J Am Coll Cardiol* 31:1658–1666
143. Schaller J 1972 Illness resembling lupus erythematosus in mothers of boys with chronic granulomatous disease. *Ann Intern Med* 76:747–750
144. Pachman LM 1995 Juvenile dermatomyositis. Pathophysiology and disease expression. *Pediatr Clin North Am* 42:1071–1098
145. Pachman LM 1995 An update on juvenile dermatomyositis. *Curr Opin Rheumatol* 7:437–441
146. Rider L, Miller F 2000 Idiopathic inflammatory muscle disease: clinical aspects. *Baillieres Best Pract Res Clin Rheumatol* 14:37–54
147. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS, Wilson WR, Baddour LM, Levison ME, Pallasch TJ, Falace DA, Taubert KA; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association 2004 Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 114:1708–1733
148. Kato H, Koike S, Yamamoto M, Ito Y, Yano E 1975 Coronary aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome. *J Pediatr* 86:892–898
149. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, Kazue T, Eto G, Yamakawa R 1996 Long-term consequences of Kawasaki disease: a 10-to-21-year follow-up study of 594 patients. *Circulation* 94:1379–1385
150. Meissner HC, Leung DY 2003 Kawasaki syndrome: where are the answers? *Pediatrics* 112:672–676
151. Ozen S, Anton J, Arisoy N, Bakaloglu A, Besbas N, Brogan P, Garcia-Consuegra J, Dolezalova P, Dressler F, Duzova A, Ferriani VP, Hilaro MO, Ibanez-Rubio M, Kasapcopur O, Kuis W, Lehman TJ, Nemcova D, Nielsen S, Oliveira SK, Schikler K, Sztajnbock F, Terreri MT, Zulian F, Woo P 2004 Juvenile polyarteritis: results of a multicenter survey of 110 children. *J Pediatr* 145:517–522
152. Kahaleh B 2004 Progress in research in systemic sclerosis. *Lancet* 364:561–562