Meeting Report

Old Challenges and New Directions in Pediatric Rheumatology

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ABSTRACT. A symposium was convened April 2, 2005, by the Department of Pediatrics, University of British Columbia, Vancouver, Canada. The event was a tribute to Dr. Ross Petty on his retirement and in recognition of his contributions to the local and international community of pediatric rheumatology. Speakers were past and present fellows, local basic science and adult rheumatology colleagues, and pediatric rheumatologists from the Pacific North West. (J Rheumatol 2006;33:173–84)

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A symposium was convened April 2, 2005, by the Department of Pediatrics, University of British Columbia, as a tribute to Dr. Ross Petty (Figure 1) in the year of his retirement from the University of British Columbia. Held in recognition of his contributions to the local and international community of pediatric rheumatology, the symposium also incorporated the second annual meeting of Pacific North West pediatric rheumatologists. The speakers were specifically drawn from past and present fellows, local basic science and adult rheumatology colleagues, and our pediatric rheumatology colleagues from the Pacific North West.

The opening session by Ron Laxer provided a historical perspective of Canada's role in the evolution of our subspecialty, while in an editorial[1] in this issue of *The Journal*, Alan Rosenberg speculates on our future. The 4 thematic sessions of the meeting were: translational basic science (the "bench"), health services delivery, rare and unwanted diseases, and arthritis. Summaries of the presentations are provided either as personal commentaries and/or as referenced abstracted reviews.

CANADA AND THE EVOLUTION OF PEDIATRIC RHEUMATOLOGY

Ronald M. Laxer

Most people would agree that the 1976 meeting of pediatric rheumatologists in Park City, Utah, USA, was the watershed event for the development of pediatric rheumatology as a specialty. There were 5 Canadian pediatric rheumatologists at that meeting (Bram Bernstein, Jim Boone, Tony Russell, Rob Hill, and Ross Petty). Bill Gibson[2] and Rob Hill[3] in Vancouver, Jim Boone[4] in Toronto, and Hanna Strawczynski[5] in Montreal laid the foundation for what would become a Canadian powerhouse.

The development of Canadian pediatric rheumatology

Figure 1. Dr. Ross Petty.

really began with the recruitment of Ross Petty to Winnipeg, where he met and inspired both Kiem Oem and Alan Rosenberg to pursue academic careers in pediatric rheumatology. When Rob Hill recruited Ross to Vancouver with the assistance of The Arthritis Society in 1980, it led to the development of Canada's first formal training program in pediatric rheumatology. This training program has had a remarkable impact on the field, where its graduates (or descendants of its graduates) have developed academic programs in 8 academic centers in Canada!

Canadian contributions to the evolution of pediatric rheumatology have been made in many areas.

Clinical observation/clinical research. Many case reports and cases series have advanced the field. Some have expanded knowledge of the spectrum of disease[6-9], and others have led to basic science discoveries[10,11]. The recognition of the role of enthesitis in the pediatric spondyloarthropathies by Rosenberg and Petty in 1982 changed both pediatric and adult rheumatology dramatically[12]. Descriptions of psoriatic arthritis by Shore and Ansell[13], and subsequently the Vancouver group, led to new criteria for the disorder[14], and an important longterm followup study[15]. Canadians have contributed to the description of the macrophage activation syndrome in systemic juvenile rheumatoid arthritis (JRA)[16] and the development of prognostic indicators for this disease[17]. The work of Malleson, *et al* on idiopathic musculoskeletal (MSK) pain has assisted clinicians dealing with this challenging problem[18]. Lang and Finlayson demonstrated that sunshine is not the only factor responsible for the development of naproxen-induced pseudoporphyria[19].

Health services research. The development of the Juvenile Arthritis Quality of Life Questionnaire by Duffy, *et al* has provided a valid and responsive measure for use in clinical trials[20]. Feldman, *et al* have described important distinctions in the various quality of life measures in children[21], and described the clinical meanings of some of the functional outcome scores[22,23], conducting multicenter studies of functional outcomes in juvenile dermatomyositis (JDM) and validating the Childhood Health Assessment Questionnaire in JDM[24].

Epidemiologic observations. Two series studies have provided valuable information on the incidence of different pediatric rheumatic diseases[25,26]. Oen, *et al* have provided evidence for the possible role of an infection in the etiology of JRA[27], and working with Western collaborators, described the disease course and outcome of JRA, radiologic outcomes, and early predictors of these outcomes, as well as predictors of pain in a multicenter cohort[28-32]. These studies provide an important baseline for future cohort studies.

Treatment studies. Important Canadian contributions in the treatment of pediatric rheumatic diseases include the role of intravenous pulse methylprednisolone in JDM[33], the safety and efficacy of intraarticular steroid injections in JRA[34,35], the role of intravenous immunoglobulin in both systemic and polyarticular JRA[36,37], and most recently, the efficacy of leflunomide in the treatment of JRA[38,39]. Ongoing multicenter international trials of infliximab and anti-interleukin 6-MRA (monoclonal receptor antibody) in the treatment of polyarticular and systemic onset JRA, respectively, are being led by Canadians.

Laboratory research. Canadian pediatric rheumatologists have also made important contributions to laboratory research. These have included the work of Petty, *et al*[40,41] and Rosenberg, *et al* [42] in the areas of antinuclear antibodies and uveitis, Oen, *et al* in immunoregulatory cells in JRA[43], Isacovics and Silverman in neonatal lupus[44], the role of cytokines in JRA[45] and Kawasaki disease (KD)[46,47], and most recently Yeung and colleagues, who investigated interactions of cytokines and endothelial cells in an animal model of KD[48].

Training. Canadian centers have played an important role in training Canadian and international fellows. Trainees from over 20 countries have studied in the programs in Vancouver, Toronto, and Montreal. There are now 4 generations of Canadian pediatric rheumatologists who have "evolved" since Ross Petty began his first training program in Vancouver in 1980 (Figure 2).

The Canadian Pediatric Rheumatology Association (CPRA) began in 1986, and 2 important multicenter studies have evolved from this group[26,49]. More recently, a multicenter Canadian Institute of Health Research (CIHR) 5 year grant was awarded to this group to study an inception cohort of children with juvenile idiopathic arthritis (JIA).

Creative professional activity. The development of the

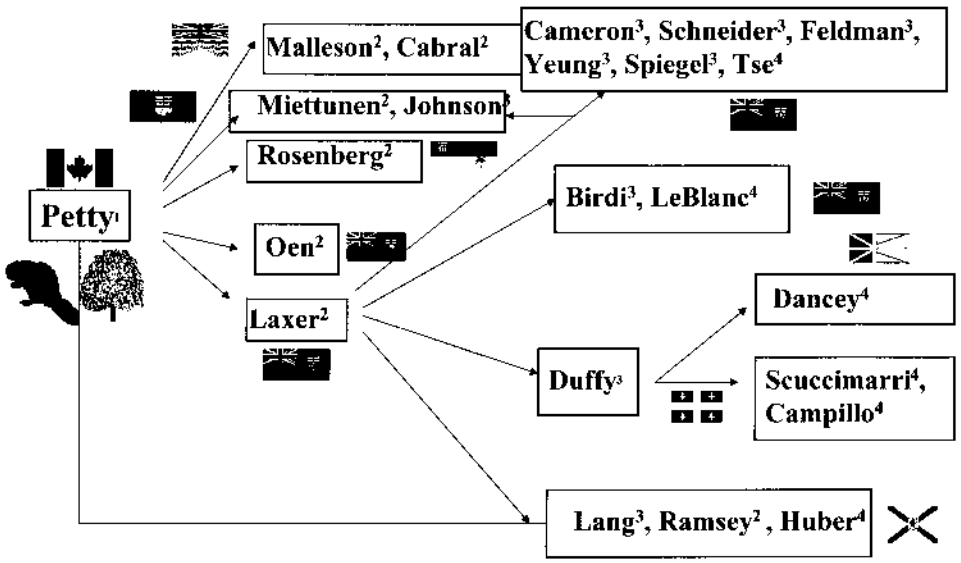

Figure 2. Current Canadian pediatric rheumatologists who have trained in the Canadian system, starting with the Vancouver Training Program under Ross Petty. Superscripts represent the "generation" of trainee emanating from Ross Petty. The flags represent the different Canadian provinces in which these academic pediatric rheumatologists are now practicing.

Rheumatology Bulletin Board by Peter Dent in 1995 was a major step in improving the care of children worldwide. There are currently over 300 subscribers to this bulletin board, which provides a key source of continuing education, transmission of information regarding clinical dilemmas, current practice, research activities, governmental affairs, and employment opportunities.

The nomenclature of chronic childhood arthritis remains an issue of debate in which Canadians have played a prominent role, both in developing criteria for the new classification and in leading discussion around appropriate nomenclature and classification[50,51].

The bible of our specialty, *The Textbook of Pediatric Rheumatology*, is now entering its 5th edition, with contributions from multiple Canadian pediatric rheumatologists[52]. Canadian pediatric rheumatologists also serve on the editorial boards of *The Journal of Rheumatology*, *Arthritis and Rheumatism*, and *Arthritis Care and Research*, and have co-chaired the most recent and will co-chair the next Park City pediatric rheumatology meetings.

Summary. Canadian pediatric rheumatologists have been world leaders in our academic mission, are known to provide excellent clinical care, have attracted the best and brightest trainees and disseminated knowledge widely, and have created new knowledge through the scholarly approach to clinical care and through collaborative research. All this remains the legacy of a master of the field, Dr. Ross Petty.

A GLIMPSE INTO THE FUTURE FROM THE "BENCH"

Discovery Science: the Promise of Proteomics

John Schrader

Clinical science has always been driven by observation and intuition. Most discoveries have had their roots in experience and observation and the painstaking collection of data: the formation and testing of hypotheses came later. Proteomics and genomics are simply powerful tools that are greatly accelerating the gathering of data and the correlation of biological and clinical observations with genetic and molecular changes. The sequencing of the human genome provided a comprehensive list of the 27,000 or so human genes and enabled the explosion of databases that are linking clinical conditions with differences in specific genes and their expression. One of the surprises of deciphering the human genome was just how few human genes there are: humans thus have less than 2 times more genes than much simpler organisms like fruit flies. We now recognize that the additional complexity of humans in part reflects that each human gene gives rise to 5 or 10 proteins. This results from gene splicing and the fact that primary polypeptides are modified by cleavage or addition of chemical groups including sugars and phosphates, generating multiple forms of each primary gene product. New technological developments in mass spectrometry and bioinformatics now enable the generation of lists of the global changes in levels of different proteins in tissues or body fluids in a particular patient sample. Comparisons can be made of urine, synovial fluid, and plasma obtained from healthy control populations or patients.

There are intriguing indications that differences in the spectrum of proteins and their modifications will enable diseases to be broken down into subcategories. Every physician is aware of the great limitations in our ability to accurately

classify disease and thus to prescribe treatment and predict outcomes. Heterogeneity within current classifications of disease prevents identification of those patients who will benefit from aggressive therapy — it also clouds our thinking on etiologies and potential cures.

Pediatric arthritis clearly has a great unmet need for better classification and thus management of disease. Proteomic analyses of synovial fluid or plasma are beginning to identify protein profiles characteristic of different clinical states.

The promise of proteomics in illuminating the classification, treatment, and causes of arthritis will only be realized if there are strong, bidirectional interactions between clinicians and bench scientists. Accurate documentation of clinical conditions, histories, treatments, and collection of high-quality specimens is as critical as technological advances in mass spectrometry and bioinformatics. Building mechanisms that foster personal relationships between imaginative and well trained clinicians and bench scientists is essential.

The Role of Innate Immunity in Rheumatic Disease
Stuart Turvey

Autoimmunity results from a failure of the normal mechanisms maintaining immunological self-tolerance. Our immune system has 2 components — the innate and the adaptive immune systems. The innate immune response precedes and empowers the adaptive immune response. Phylogenetically ancient, innate immunity allows the host to differentiate self from pathogen. It provides a sophisticated first line of defence against infections, initiating a protective inflammatory response within minutes.

Our understanding of innate immunity accelerated in the mid-1990s when the Drosophila protein Toll was shown to be critical for defending flies against fungal infections. This opened the way for the description of similar proteins, called Toll-like receptors (TLR), in mammalian cells. The human TLR family consists of 10 receptors that are critically important for innate immunity. TLR allow for recognition and response to diverse microbial epitopes on pathogens — pathogen-associated molecular patterns, or PAMP — enabling the innate immune system to discriminate among groups of pathogens and to induce an appropriate cascade of effector adaptive responses. Intracellular signaling pathways triggered by TLR culminate in the activation of nuclear factor-κB and other transcription factors, driving the production of proinflammatory cytokines and other protective immunological responses[53].

It seems likely that the inflammatory response causing autoimmune diseases arises from the same molecular pathways involved in fighting infection, including the TLR pathway. Indeed, the TLR pathway is highly effective in producing a range of proinflammatory cytokines implicated in autoimmunity, including tumor necrosis factor-α (TNF-α), interleukin 6, and interleukin 1ß.

Evidence is emerging defining a role for TLR in the pathogenesis of autoinflammatory diseases. For example, the immune complexes found in individuals with systemic lupus erythematosus (SLE) are enriched with unmethylated CpG motifs and hence stimulate secretion of proinflammatory cytokines through TLR9[54]. Kawasaki disease, a condition linked to infection with a vast array of microbes, is associated with excess production of TNF-α[55]. An intriguing (and testable) hypothesis is that excessive TLR signaling, producing large quantities of proinflammatory cytokines, underlies the pathogenesis of KD.

As the role for TLR in rheumatic disease is better defined, selective targeting of TLR might be useful therapeutically[56]. Today we have the tools to target some of the cytokines produced by TLR signaling. Novel future targets include individual TLR, enzymes in the common signaling pathway (such as IRAK-4), or even blockade of the protein–protein interactions in the signaling cascades. But we must interfere with the finely tuned immune system with caution and humility, since all the consequences of our manipulations are impossible to predict.

Maternal Microchimerism in Pediatric Autoimmune Diseases *Anne Stevens*

During pregnancy, maternal and fetal cells commute between mother and fetus, leading to maternal microchimerism (MMc) in the child and fetal microchimerism (FMc) in the mother. MMc and FMc are hypothesized to play a role in autoimmune diseases that resemble graft-versus-host disease (GVHD)[57]. However, microchimerism is also a normal outcome of pregnancy. Determining how MMc or FMc may become pathogenic is an active area of research.

MMc occurs in up to 100% of cord blood samples and has also been found in fetal and newborn tissues. Longterm MMc was first discovered in multiple cell lineages in the peripheral blood of healthy subjects as old as 49 years. MMc was found at higher levels in the target organs and blood in juvenile dermatomyositis and systemic sclerosis (SSc)[57]. We have identified MMc in the hearts of infants who died of neonatal lupus[58]. The level of MMc correlated with disease, but whether the maternal cells instigated or perpetuated the inflammatory disease or were helping to regenerate injured tissue after injury occurred is not known. Knowing that circulating stem cells have multilineage plasticity, we demonstrated that maternal cells can differentiate into cardiac myocytes in hearts of infants. MMc could therefore act as allogeneic target cells to the host immune system. Only one functional study for MMc has been reported[59]. Maternal T lymphocytes from JDM patients react to the child's cells *in vitro* by producing interferon-α (IFN-α). Thus, maternal T lymphocytes may be pathogenic under some circumstances.

HLA alleles influence the risk for autoimmune disease and also for MMc. For example, HLA compatibility

between mother and child has been associated with increased risk for SSc in the mother. Because MHC Class II compatibility between donor and recipient is important in human GVHD as well as in SLE-like GVHD in mice, we studied HLA compatibility between male SLE patients and their mothers[60]. Compared to controls, SLE patients had increased bidirectional compatibility (identical alleles) with their mothers at HLA-DRB1. In subjects carrying the SLE-associated HLA alleles DR2 or DR3, the odds ratio was even greater and extended to DQA1 and DQB1.

Thus, the genetic basis for autoimmune disease may involve not only genes of the patient, but also genes of microchimeric cells that may interact with the patient's immune system. Microchimerism may also derive from a twin. Considering the persistence of FMc and MMc, even an older sibling or grandmother could contribute. Any of these donor cells could be involved in an *in vivo* mixed lymphocyte reaction leading to chronic inflammatory disease in the patient.

Are We Closer to Understanding Kawasaki Disease?

Rae Yeung

Kawasaki disease is the most common cause of vasculitis affecting children. Although the inflammatory response is found in medium and small vessels throughout the body, the most common site of end organ damage is the coronary arteries. The resulting coronary artery lesions have made KD the leading cause of acquired heart disease in children in the developed world[61]. KD is unique among coronary vessel disease with its propensity to aneurysm formation. Many gaps still exist in our knowledge of the etiology and pathogenesis of KD, making preventive measures and improvements in therapy difficult. The mechanisms involved in coronary artery damage are not understood, and cardiac tissue is not available from children with KD, thus necessitating a disease model.

We have refined a murine model of KD, which utilizes a gram-positive bacterium, *Lactobacillus casei*, cell wall extract (LCWE) to promote development of coronary arteritis in young mice. LCWE-induced coronary arteritis in mice reflects human KD in its time course, pathology, susceptibility in the young, and response to intravenous immunoglobulin therapy. We have characterized a novel superantigen within LCWE[62,63]. We found a vigorous T cell response to LCWE with all the hallmarks of a classic bacterial superantigen; more importantly, superantigenic activity correlates with the development of coronary arteritis in mice. The immune response is characterized by a T-helper 1 predominance. We have identified critical roles for IFN-γ and TNF-α, not only in the systemic inflammatory response, but also in local inflammatory disease at the coronary artery[48]. The proinflammatory effects of IFN-γ and TNF-α are synergistic under most physiologic circumstances, but we have identified divergent roles for these 2 cytokines in the pathogenesis of coronary inflammation. IFN-γ participates in and regulates the immune response to LCWE, but is not necessary for induction of coronary disease. Conversely, IFN-γ participates in the inflammatory response and is absolutely necessary for the development of coronary disease. Ablation of TNF-α activity totally abolishes both inflammation and vessel wall damage. TNF-α-dependent lymphocyte recruitment and upregulation of proteolytic activity are 2 of the critical elements involved in disease development. Elastin breakdown is the hallmark of aneurysms. We have evidence that localized production of the proinflammatory cytokines IFN-γ and TNF-α is linked to production of elastolytic matrix metalloproteinases associated with development of coronary artery lesions. Improved understanding of the mechanisms involved in development of coronary artery disease has tremendous potential to influence treatment and longterm outcome in children affected by KD.

HEALTH SERVICES: THE CHALLENGES

Barriers to Care in Pediatric Rheumatology Care — UK, USA, and Globally

Helen Foster and Helen Emery

Early and appropriate intervention improves the outcome for children with rheumatic disease. There is a recent trend to earlier and more aggressive intervention, with evidence emerging that this approach reduces joint damage. Standards of care in the UK advocate that children with suspected JIA be referred to an experienced multidisciplinary team within 4 weeks of onset of symptoms (http://www.arma.uk.net).

We have investigated access to care for children with JIA in the UK and USA, and our work shows that delay in receiving specialist care is common and is likely to be a global problem. As a consequence, many children with JIA have unmet needs, resulting in a major impact on their quality of life. A delay results in a prolonged interval to interventions such as joint injections and methotrexate (MTX), which, coupled with lack of physical therapies, results in functional disability, potential for joint damage, and impaired longterm outcome. The reasons for delay are multifactorial and include organizational (e.g., availability of specialist teams, geographic factors, financial constraints imposed by contracts, and healthcare providers); social patterning (e.g., public awareness of arthritis in children, family experiences, and expectations), and disease factors (e.g., variability, and sometimes subtlety, in the clinical presentations of rheumatic disease in children)[64]. The pathways of care to pediatric rheumatology care are complex; many children present to general pediatrics, orthopedics, and emergency rooms, and referral to pediatric rheumatology is often overlooked[65,66]. Our work suggests that a major barrier to care is lack of knowledge about rheumatic disease in children and awareness of the need for referral to an experienced multidisciplinary team. Further, poor musculoskeletal clinical skills among doctors to whom these children present are common; evidence shows poor performance in the MSK

assessment of children, with many trainee doctors lacking confidence in their ability to assess the MSK system[67].

To overcome these barriers is a major challenge and is likely to require a multifaceted approach. In the UK, USA, and elsewhere, provision of pediatric rheumatology services is inadequate, and there is a need to raise the awareness for early referral to specialist services. Dr. Emery has focused on improving the knowledge of doctors in clinical practice, through an educational program to facilitate early recognition of JIA and referral to specialist teams. Dr. Foster has focused on improving clinical skills to facilitate early diagnosis, and has validated a MSK screening examination tool for children to be taught to all medical students as part of their core teaching. Further work is required to identify other barriers to care and develop interventions to facilitate access to specialist services for all children with rheumatic disease, and ultimately improve the longterm outcome.

RARE, UNDER-RECOGNIZED, OR UNWANTED DISEASES

What the Dermatologist Thinks We Miss! Pediatric Rheumatology Presenting to the Dermatologist

Julie Prendiville

Many pediatric rheumatologic disorders have cutaneous manifestations. Some, such as the rash of dermatomyositis, are very characteristic, whereas others are less specific, particularly in early or evolving disease. Four conditions in which the clinical presentation may cause diagnostic difficulty are discussed.

Neonatal lupus syndrome masquerading as neonatal infection. Neonatal lupus syndrome (NLS) is characterized by a transient lupus dermatitis and variable systemic manifestations including thrombocytopenia, neutropenia, hemolytic anemia, hepatitis, hepatosplenomegaly, and pneumonitis. We diagnosed NLS in an infant with multisystem disease and widespread skin lesions at birth. The clinical findings together with abnormal neuroimaging and radiographs showing frayed distal femoral metaphyses initially suggested a diagnosis of congenital intrauterine infection. Central nervous system (CNS) involvement is not a well recognized manifestation of NLS. We performed computerized tomographic (CT) imaging and/or brain ultrasonography (US) in 10 further infants presenting with lupus dermatitis. Nine of these 11 infants had abnormal neuroimaging studies[68]. Cerebral US findings included subependymal cysts (n = 4), echogenic white matter (n = 3), and echogenic lenticulostriate vessels (n = 3). CT imaging revealed decreased attenuation of the cerebral white matter (n = 6), basal ganglia calcification (n = 2), and ventriculomegaly (n = 2). There was no clinical evidence of neurologic disease. Awareness of neuroimaging abnormalities in NLS may avoid confusion with congenital viral infection. The potential for neurologic sequelae is unknown.

Rash of systemic JIA (sJIA). The typical rash of sJIA is an erythematous urticarial eruption that flares during febrile episodes and is absent or minimal when the patient is afebrile. It may be asymptomatic or intensely pruritic, with linear lesions at sites of pressure or excoriation. We observed this characteristic rash in 3 adolescents, and a similar more persistent eruption in 2 further patients, who presented with fever and systemic inflammatory disease[69]. All 5 adolescents had arthralgias and transient arthritis but none developed a sustained arthritis. The clinical findings met the diagnostic criteria for adult onset Still's disease (AOSD). We believe the same inflammatory disorder as sJIA can occur in the absence of a persistent arthritis and be indistinguishable from AOSD. The distinctive rash is a helpful diagnostic feature in a child or adolescent presenting with fever of unknown origin.

The spectrum of severe aphthous stomatitis and Behçet's disease in children. Behçet's disease (BD) is another disorder for which there is no specific clinical feature or diagnostic test, and the diagnosis depends on classification criteria[70]. We have followed a number of children with severe recurrent oral and/or genital/perianal ulceration. Some progressed over months or years to develop the required international classification criteria for diagnosis of BD, whereas others with identical oral and/or genital/perianal lesions did not. One child had periodic fevers and oral ulceration; a diagnosis of PFAPA (periodic fever with aphthous stomatitis and adenopathy) was excluded by the severity of the oral ulceration and development of genital ulcers during one episode. Ocular disease was rare, observed in 2 patients only. We believe that severe recurrent aphthous stomatitis and BD belong to a spectrum of disease in which there may be (1) oral or genital/perianal ulceration, (2) oral and genital/perianal ulceration, or (3) BD fulfilling the international classification criteria.

Fibroblastic rheumatism in a child with evidence of Bartonella infection. Fibroblastic rheumatism is a rare disorder characterized by multiple cutaneous nodules and an erosive arthritis[71]. We diagnosed this condition in a child who visited a petting zoo and had high antibody titers to *Bartonella henselae* and *Bartonella quintana*[72]. Although the significance of this association in a single case is uncertain, we believe Bartonella infection should be considered in patients with this unusual condition.

Missing in Action: Sjögren's Syndrome in Children and Adolescents *Lori B. Tucker*

Sjögren's syndrome (SS) is a systemic autoimmune disease that primarily affects the exocrine glands, resulting in symptoms of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia)[73]. There are 2 types of SS; primary SS (pSS) and secondary SS (sSS), in which patients have another rheumatic disease such as rheumatoid arthritis or systemic lupus erythematosus. SS has always been described as rarely occurring in childhood, with only about 130 cases report-

ed[52]. In the Pediatric Rheumatology Clinic at the B.C. Children's Hospital in Vancouver, we noted that we diagnosed 7 children with pSS from 2001 to 2004, and therefore wondered if, in fact, pSS is more common than previously recognized in children.

Parotid gland enlargement, or recurrent episodes of parotid gland swelling, is a common feature of pSS and sSS. Recurrent parotid swelling is not a rare condition in childhood; children with this problem may be referred to the pediatric otolaryngologist, but less frequently to the pediatric rheumatologist. The differential diagnosis for recurrent parotid swelling includes: mumps, acute bacterial parotitis or sialadenitis, recurrent acute sialadenitis, chronic sialadenitis (secondary to infections such as tuberculosis or actinomycosis), calculi, sarcoid, or SS.

How is the diagnosis of pSS made? Classification criteria have been developed to assist in the accurate diagnosis of SS in adults. The revised European Consensus Study Group (ECSG) criteria[74] require patients to have at least 4 of the following 6 criteria: ocular symptoms, oral symptoms, ocular signs (by Schirmer's test or Rose Bengal staining), lymphocytic infiltrates on lip biopsy, salivary gland involvement (by scintigraphy or sialography), and serum autoantibodies to anti-Ro, anti-La or both. These criteria do not function well for children presenting with pSS. In a review of the literature-reported cases of pSS in childhood, together with 7 cases followed at the B.C. Children's Hospital, only 39% of children diagnosed with pSS by expert opinion fulfilled the ECSG classification criteria.

Recently, Bartunkova, *et al* published proposed diagnostic criteria for juvenile pSS[75]. These proposed criteria include a broader range of clinical symptoms (in addition to oral and ocular symptoms, and other mucosal and systemic features) and laboratory abnormalities (in addition to immunologic abnormalities, abnormal lip biopsy and sialography, and other biochemical and hematologic abnormalities). Parotid gland enlargement or recurrent parotitis are included in these pediatric criteria; these are features more commonly seen in children and teens with pSS as compared with adults. Application of these proposed pediatric criteria to the reported cases of pSS and our Vancouver cases improved the diagnostic capability to 76%. Although the Bartunkova pediatric criteria for pSS improve the diagnostic utility, further studies need to be undertaken to examine which of the items in the criteria have the best performance for predicting the diagnosis of pSS.

Finally, it appears that pSS is probably underdiagnosed in childhood, related to the broad spectrum of disease manifestations and an indolent clinical course. Recurrent idiopathic parotitis of childhood is an important clinical clue to consider pSS as the diagnosis.

Juvenile Systemic Sclerosis: What Do We Know and How Will We Learn More About This Disease? *Ivan Foeldvari*

The data regarding prevalence of juvenile systemic sclerosis (JSSc) are based on case series or retrospective multinational surveys. About 10% of all patients with SSc develop the disease in childhood. The first large multinational retrospective survey[76] reported 135 patients from 34 centers worldwide. The mean followup was 5 years, the mean age of onset of disease was 8 years, and the survival rate after 5 years of the disease was 95%. Compared to survivors, more frequent vital organ involvement was seen in patients who died: pulmonary disease (75%/49%), renal disease (50%/10%), and CNS disease (38%/14%). In a second large retrospective multinational case collection, of 153 patients from 55 centers (Proceedings of the Second International Workshop of Juvenile Systemic Sclerosis, Padua, Italy, 2004), the organ involvement pattern was similar. In both groups renal involvement of around 10% was strikingly low, and pulmonary involvement was in the range between 40% and 50%. No patient in either group had CREST syndrome.

In a summary of case reports and case series published from 1966 to 1998, there were 51 cases with sufficient data for analysis. Twelve of the 51 patients died, 11 before 1990. The age of onset and the organ involvement pattern was similar to that found in the surveys. Of the patients reported in the survey or case reports who died, 80% did so within the first 4 years of the disease course.

Classification specific for JSSc to be used in prospective studies have been developed at the First and Second International Workshops on JSSc. The proposed classification criteria include one major criterion (sclerosis and induration) and several minor criteria, which represent the involved organ systems and are characteristic of JSSc. The patient fulfills the proposed classification criteria if one major criterion and 2 minor criteria are present.

Prospective studies of JSSc using the new proposed criteria, in the planning phase, aim to recruit a multinational inception cohort of patients for characterization and standardized assessment. A feasibility study showed that it is possible to recruit enough patients in 3 years[77].

Musculoskeletal Pain Syndromes: Are They Treatable and Should Pediatric Rheumatologists Treat Them?
David Sherry

Amplified musculoskeletal (MSK) pain syndromes are some of the most protean and disabling conditions of childhood. The pain can be associated with autonomic dysfunction (complex regional pain syndrome), be widespread (fibromyalgia) or in multiple sites, and can be intermittent or constant. An individual child can have multiple forms simultaneously. This disorder can be associated with other illnesses such as arthritis, it can occur after trauma or following surgery, or may be idiopathic. Adolescent girls are more prone to amplified MSK pain; rarely is it seen under age 7 years. These children are generally highly achieving, perfectionist, mature beyond their years, and internalize stress.

The average duration of pain before coming to our program is over 1.5 years. Distinct features include increasing pain over time, marked dysfunction, an incongruent affect (*la belle indifference*), and allodynia. The allodynia frequently has a highly variable border. Autonomic signs may not be present or may develop if the limb is moved or used. Conversion symptoms are not uncommon. Medical investigations reveal normal findings, and the child will either respond transiently or not at all to medical interventions. Side effects of medication are common.

Psychological distress is not uncommon even though the child and family seem to, on the surface, be coping well. Secondary gain is poorly appreciated in these families. Frequently emotional boundaries are blurred (enmeshment). The treatment we use is to stop further medical investigations and drug treatment and institute an intense, functionally directed, aerobic exercise program, up to 5 hours a day. Desensitization is paramount for those with allodynia. Our treatment team includes physical and occupational therapists, psychologist, education coordinator, music therapist, social worker, nurse, insurance coordinator, and physician. Our average treatment duration is 3 weeks and 80%–92% will resolve all pain and almost 100% will regain full function. Regarding relapse, only 15% need to be retreated by us (another 15% have recurrences that they treat by themselves). Other significant untoward outcomes include eating disorders, suicide attempts, other pain syndromes (headache, abdominal pain, tooth pain), and conversion syndromes including paralysis, blindness and pseudoseizure. Therefore, in addition to treating the pain and dysfunction with exercise therapy, the underlying psychological issues need to be recognized and addressed in most. Thus, both short-term and longterm benefits can be attained. The pediatric rheumatologist is ideally suited to diagnose and treat these children given our diagnostic skills, team leadership abilities, and frequent referral of children with MSK pain[78–81].

ARTHRITIS: WHAT NEXT?

Should We Believe the Results of Clinical Trials?

Alice B. Klinkhoff

From research, clinicians hope to find answers: Is a treatment effective and safe? Is it more effective than the best available alternative? Is there an optimum dose, and is it cost-effective? Are the results of clinical trials believable?

Clinical trial results are believable when the population studied is similar to those we treat in practice, and when the major sources of bias have been minimized in trial design, execution, and analysis. The largest source of bias relates to financial interest and influence of companies sponsoring clinical trials. The probability of a positive result in industry-funded trials is 68% compared with 35% in independently funded trials. Powerful influence of the sponsor results in delayed publication and nonpublication of negative trials and minimization of adverse reactions in published trial results. An example of the latter is the failure to identify infection as a side effect of treatment with biologics (the ERA, ATTRACT, and ARMADA trials, and a safety meta-analysis of 1897 infliximab patients). Explanations of such failures include "small sample size" or trial inclusion criteria that select patients with high disease activity but without significant comorbidity. There may be bias in the coding or interpretation of adverse reactions when they do occur.

In negative trials, it is important to look for type 2 error, the risk of missing a treatment benefit because the sample size is not large enough. For example, in a widely quoted trial of use of MTX in scleroderma by Pope, *et al*[82] all clinical endpoints favored MTX, but the results were not statistically significant. Unfortunately, with a sample size of 71 patients, the likelihood of missing a potential benefit is 50%. Simply stated, the results of negative trials with small sample size cannot be believed.

Consider the generalizability of the results: Do the results observed in trials apply to the patients we see in practice? According to Sokka and Pincus[83], the answer is often no; only 16% of patients with RA in 5 private practices in Nashville would have met inclusion criteria for ERA and only 5% for ATTRACT.

Finally, there are myriad ways that statistics can mask truth in data: incorrect statistical tests applied to subgroup analysis and post-hoc analysis, and handling of data of patients who do not complete the trial.

In conclusion, when evaluating the results of clinical trials, beware!

Search for the Magic Bullet (Quest for the Holy Grail) for Treatment of Juvenile Idiopathic Arthritis!

Carol Wallace

The treatment goals for JIA are to ameliorate acute symptoms, induce remission, and improve outcome. Preliminary definition of remission on-medication requires 6 months of inactive disease, and remission off-medication requires 12 months of inactive disease. Preliminary criteria for inactive disease requires no active arthritis, fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA, and no active uveitis; normal erythrocyte sedimentation rate or C-reactive protein; and inactive disease by physician global assessment[84]. The domains for outcome assessment include physical status (including disease activity, joint damage, visual impairment, and growth), functional abilities, psychosocial adjustment, and complications of the disease or its treatment. Eight recent studies of outcome for patients with JIA documented remission in 35%–73% with oligoarthritis followed for 5–26 years, in 24%–46% with polyarthritis followed for 7–26 years, and in 33%–76% with systemic arthritis followed for 5–26 years[85-92]. These results demonstrate limited efficacy of current treatments and the need to search for a magic bullet.

Further justification for new treatments comes from

looking at disease course. Patients may move back and forth between active and inactive disease, both on and off medications. We examined disease course in 437 patients with oligo-, poly-, and systemic JIA from Pavia, Genova, and Seattle with a followup of 4–22 years (median 6.5)[93]. Remission on-medications occurred as follows: persistent oligo 60%, extended oligo 81%, polyarthritis rheumatoid factor (RF)-positive 65%, polyarthritis RF-negative 67%, and systemic 71%. There was a striking difference in the frequency of remission off-medications, from 68% of persistent oligoarthritis patients to 5% of patients with RF-positive polyarthritis. The majority of patients with persistent disease spent about two-thirds of their disease course with active disease. Overall, although 44% of patients achieved clinical remission, it lasted for a full year in only 28%, 2 years in 18%, and 5 years in 3% of patients.

Joint damage is another important outcome. Several small reports reveal the occurrence of joint space narrowing and erosions beginning in the first year of disease in a range of 2%–35% of patients with oligo disease, 13%–77% of patients with polyarticular disease, and 19%–75% of patients with systemic disease. Other adverse outcomes including complications of uveitis, growth delay, osteoporosis, organ involvement, surgery, amyloidosis, and death, also argue for a treatment change.

Earlier treatment of JIA may be more effective. Evidence from studies in adults with RA demonstrates that early treatment results in less joint damage; it may also be more cost-effective, and result in less exposure to medications. Data from 14 randomized clinical trials of DMARD in 1435 patients with RA revealed a significant difference in the response between patients whose disease was treated within 2 years compared to those treated later[94]. This effect is even more marked when anti-TNF medications are used. A recent study comparing infliximab with MTX versus MTX alone begun within the first year of disease revealed marked improvement in disease and marked decrease in joint erosions that persisted for another year after discontinuation of the infliximab.

There are many gaps in our basic understanding of JIA and currently used medications: Which medications are best? What are their optimal doses and routes of administration? MTX is the mainstay of treatment, corticosteroids clearly have a disease modifying effect demonstrated in RA, and anti-TNF medications show promise. As a magic bullet, I would suggest a starting combination of all 3 agents early in patients who we are increasingly able to predict will have a poor outcome. However, as important as the chosen treatment is the need to learn from what we do. If we all decide on a standard for treatment (either center, region, or country-wide) and collect all the elements necessary to document response, it would be possible to pool this information and begin the iterative process of finding the best treatment for JIA. This approach has been used very successfully to improve the outcome of childhood cancer.

Exercise Prescription — Are These Just "Buzzwords"?

Kristin Houghton

Children with juvenile idiopathic arthritis (JIA) have reduced physical activity levels and fitness compared to healthy children. Physical fitness includes cardiopulmonary or aerobic fitness, muscle strength and endurance, flexibility, and body composition. Aerobic fitness diminishes after adolescence and has a strong positive relationship with general health. Children with JIA have moderate impairments in aerobic fitness as measured by VO_2 peak. VO_2 peak is the gold standard for aerobic fitness and is equal to the product of cardiac output and mixed venous oxygen concentration. VO_2 peak may be limited by anemia, muscle atrophy, and deconditioning. Children with JIA also have high submaximal energy expenditures, suggesting increased metabolic demands for routine physical activity. Most studies show aerobic fitness is not significantly related to disease severity or activity, but may be related to disease duration. Increased physical activity levels and self-efficacy for exercise correlate with improved aerobic capacity, but a causal effect has not been established.

Children with JIA have generalized muscle weakness and muscle atrophy, most pronounced in muscles surrounding inflamed joints and often persisting even after clinical resolution of inflammation. Hypotheses include alteration of anabolic hormones and cytokines, protein energy malnutrition, motor unit inhibition from joint swelling and pain, and deconditioning. All cross-sectional studies fail to show a relationship between muscle strength and disease severity or activity. A longitudinal study showed decreased muscle strength and bulk in parallel with increased disease activity[95].

There is good evidence that children with JIA can participate in aquatic or land-based exercise programs without disease exacerbation. The literature suggests a minimum 6 week exercise program may lead to improved aerobic fitness; improved muscle strength and function; decreased disease activity; improved self-efficacy, energy level, and quality of life; and decreased pain and medication use, but a significant improvement in functional status has yet to be demonstrated. Aerobic capacity may be an important outcome measure for children with JIA.

The importance of exercise prescription in children with JIA is now well recognized, but research is needed to determine: response of tissue to mechanical loading in health and disease at various stages of growth and development; short and longterm effects of different exercise modalities on symptoms, disease activity, joint mobility, structural outcomes, bone mineral density, and quality of life; the most effective ways of increasing physical activity and fitness; and the most cost-effective ways to prescribe, monitor, and measure fitness in children with JIA.

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