

REPORT FROM THE ROSS PETTY PEDIATRIC RHEUMATOLOGY SYMPOSIUM:

Old challenges & new directions in pediatric rheumatology

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Introduction

On April 2nd, 2005, the 2nd Annual Meeting of Pacific Northwest Pediatric Rheumatologists (PNPR) convened in Vancouver, British Columbia to honor Ross Petty at the time of his retirement from his position as Division Head. The PNPR chose a stellar group of pediatric rheumatologists and scientists to present a varied and impressive set of topics to an appreciative audience of over 100 pediatric and adult rheumatologists. This report summarizes briefly some of these presentations. The Journal of Rheumatology plans to publish the talks in a more complete form in the future.

I The History and Contributions of Canadian Pediatric Rheumatologists

Ron Laxer of Toronto described in detail the many contributions of Canadian pediatric rheumatologists over the last 45 years. As he noted: "When you're the best, it's not bragging".

A. *The early years*

Pediatric rheumatology in Vancouver was begun with the formation of the Arthritis Society by Patty Clark, a mother of a child with polyarticular JIA. Canadians were well represented at the seminal Park City I meeting in 1976. Canada was represented by Rob Hill, Jim Boone, Bram Bernstein, and Ross. Contributions by Canadian pediatric rheumatologists to the medical literature in the last 45 years have been extraordinary. At a time when treatment of JIA consisted mostly of aspirin and corticosteroids, Gibson set a standard of practice with the team approach for JIA including PT/OT with his article in 1962. Shortly thereafter, Robert Hill began the first juvenile idiopathic arthritis clinic in Vancouver. Jim Boone set up a similar clinic in Toronto in 1965 shortly followed by establishment of a clinic in Montreal.

Meanwhile, Ross was beginning his medical training at the University of Michigan in Ann Arbor and making the crucial decision to become a pediatric rheumatologist rather than a neonatologist or endocrinologist. He trained with the wonderful team of Jim Cassidy and Donita Sullivan. After two years and with the help of the Arthritis Society, he traveled to London to work

with Dr. Barbara Ansell for 2 years followed by a PhD dissertation on antigen-antibody specificity. He then took his current position in Vancouver in 1972 and began developing the rheumatology center.

B. Contributions in the literature, academics, center development, and training.

There have been many contributions to pediatric rheumatology over the years by Canadian pediatric rheumatologists with some seminal pediatric articles. The articles number over 30 and are too numerous to enumerate here.

Canadians have made more contributions other than published manuscripts:

- 1) Established Pediatric rheumatology as a pediatric subspecialty in Canada.
- 2) Three training programs for fellows certified and producing fellows regularly.
- 3) Trained over 20 pediatric rheumatologists who practice outside of Canada
- 4) Established the Canadian Pediatric Rheumatology Collaborative Group,
e.g., 5,10,15 year outcome of JIA- Oen, Malleson, et al
- 5) Headed the ILAR Nomenclature group -Petty et al
- 6) Recently published an A&R article on use of nomenclature in JIA/JRA-Ciaran Duffy et al
- 7) Began and maintains the internet pediatric rheumatology bulletin board -Peter Dent (1996)
- 8) Petty and Cassidy textbook-now in 4th edition
- 9) Journal of Rheumatology began a pediatric section; subsequently Arthritis & Rheumatism has followed suit.
- 10) Ciaran Duffy is co-chair of Park City VI
(Reporter's Note: Several Canadians have been instrumental in establishment and development of the Pediatric Rheumatology Online Journal)

In summary, Canadian pediatric rheumatology has been essential to the development and leadership of pediatric rheumatology in many areas.

II New Paradigm of Science: Discovery science, not just hypothesis driven science.

John Schrader

Genomics is now transforming the nature of science. We have the DNA of mammals and mice and humans as well as pathogens. We understand and utilize better genes, control elements, maps, and markers. Humans have only a small number of genes, approximately 27,000. This number of genes is not much more than the number of genes of a fruit fly. The difference between the fruit fly and us is the number of proteins we make, somewhere between 150,000-300,000 proteins! So proteomics may be a major advance in science.

One possible goal of proteomics is to see what protein is present in one disease or which one is absent. It is also to see what patterns of proteins fits with what disease and stage of disease or response to therapy. Proteomics involves first isolating a protein, then cutting it into

peptides using trypsin, and analyzing the proteins by mass spectrometry yielding a unique protein fingerprint. The computer will remember the fingerprint of each protein portion. This expensive process of sample preparation, sample processing, sample analysis, and data analysis is all done by automated robots and computers.

The discovery science of proteomics can tackle even more complex patterns. Proteomics has the power to digest a large mass of proteins-tens of thousands of peptides, analyze them by mass spectrometry, and select out a target protein and then analyze that protein by itself.

How can proteomics be useful? First, it may be possible to associate proteins with diseases. One example might be the recent use of proteomic patterns to identify early ovarian cancer in 2002 in a proteomics-based work. In this study the authors prospective evaluated 100 patients by initially digesting serum proteins of each patient and performing proteomic computer analysis. Though controversial, this analysis appears to have been able to identify patients totally without ovarian cancer and patients who subsequently could be shown to have ovarian cancer in an early disease stage.

How else can proteomics be important? This discovery science may help us understand disease heterogeneity and classification problems, predict outcomes, and use the right medicine for the right patient at the right time. Current such projects include: 1) Proteomics with synovial fluid proteins at Harvard with orthopedic and rheumatology collaboration. The focus is initially on human proteins and the results will then be tested in animal models, an unusual paradigm; 2) Protein arrays for autoantibody profiling at Stanford.

The success of proteomics will depend upon optimizing collaboration from bench to bedside with a critical mass of excellent clinical scientists and scientific clinicians who are catalytic, credible, and connected. Each proteomic project will require authorities in both the clinic and bench with good communication skills in forums and meetings with a candid exchange of ideas and hypotheses, no matter how naïve. Cross-fertilization is critical with attitudes broadminded and catholic.

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3. Tilleman K, Deforce D, Elewaut D. Rheumatology: A close encounter with proteomics. *Rheumatology (Oxford).* 2005 May 31

III Innate Immunity and rheumatology

Stuart Turvey

Dr. Turvey began with a case presentation of a two year old with recurrent cervical adenitis whose brother had died of pneumococcal meningitis at age 5 years. All initial immunological tests were negative.

Dr. Turvey discussed that innate immunity is phylogenetically ancient and targeted mostly against most multicellular organisms. It is the quick responder with an immune response within hours. It involves neutrophils, macrophages, monocytes, NK cells, complement, and antimicrobial peptides. In contrast, the adaptive immune system is sexier but slower, taking days to have its full effect.

Toll mutations are a new focus. The Toll system is an ancient immune alarm system that empowers the adaptive response against most all bacteria. Toll mutations in fruit flies makes them susceptible to fungal infections. There are 10 Toll-like receptors in humans. Toll-like receptor 4 recognizes lipopolysaccharide. Toll-like receptor 5 recognizes flagella. Toll-like receptor 9 recognizes the unmethylated CpG motifs in bacteria. The Toll-like receptors activate cytokines, activate antigen presenting cells, induce maturation of dendritic cells, and have other functions. These receptors are critical for NFK-B signaling. Toll-like receptors serve as bridge from the innate to the adaptive immune system.

The two year old patient was found to be having a diminished Toll-cell response with a gene mutation of TLR4 that blunts Toll-like receptor signaling and affects PAMP activity. A TLR5 that recognizes flagella is associated with an increased susceptibility to Legionnaire disease. Toll-like receptors may be important in rheumatic disease, e.g., in molecular mimicry models-cross recognition of microbial and self epitopes. In SLE, autoantibodies and immune complexes containing DNA and unmethylated CpG motifs have been found. The immune complexes in SLE may stimulate secretion of proinflammatory cytokines through TLR9. CpG activation of TLR9 is dependent on acidification of endosomes.

In Kawasaki syndrome (KS), it is possible that multiple organisms may trigger or cause KS, increasing the likelihood that Toll-like receptors may play a role. Toll-like receptors can sense a wide spectrum of microbes and may generate large quantities of TNF-alpha. One possible model of KS, *Lactobacillus casei* arteritis, cannot be established in the C3H-HeJ mouse strain. Interestingly, this mouse strain does have a TLR defect.

Suggested References

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IV Maternal microchimerism in rheumatic disease

Anne Stevens

Maternal microchimerism is a process where cells from the mother pass into her fetus during pregnancy. These cells are usually tolerated well by the child's immune system and the cells may last for decades. The cells can be protective or damaging. This microchimerism has been detected in patients post-transplant and with rheumatic diseases.

The detection of male fetal progenitor cells in a mother with a rheumatic disease was first reported in 1996. These fetal cells were in the skin, kidney, spleen, and thyroid in multiple rheumatic diseases, especially scleroderma, lupus, primary biliary cirrhosis, thyroid, and Sjogrens syndrome.

How common is maternal microchimerism? All cord blood has some maternal cells and it appears that everybody has maternal cells for 40-50 years. Microchimerism has been found in half of systemic scleroderma patients compared to 20% of controls, noted in muscles in juvenile dermatomyositis, and in the heart tissue of neonates with neonatal lupus. Ann Reed has reported that 85% of juvenile dermatomyositis patients have microchimerism with CD4 and CD8 positive maternal cells (5-10% in controls). Could these cells be attacking the muscle in this illness?

Dr. Stevens noted that her research has shown that five percent of neonates with the SS-A/SS-B antibodies develop neonatal lupus. In these neonatal lupus newborns, maternal cells have been found in heart tissue of the AV node. These maternal cells in muscle cells express the sacrophage antigen. Also maternal cells can differentiate in renal, liver, and pancreas tissue and in the pancreas these cells can express insulin.

In SLE, the maternal microchimerism suggests a loss of tolerance of the host to these cells. In one study, microchimerism is only 19% in SLE patients while 40% in controls. Are SLE patients eliminating these cells from their blood and other tissues? A recent report of an increase of interferon-gamma and IL-4 produced by maternal cells in patients with SLE does suggest some loss of tolerance. Yet male microchimerism is increased in female patients who have SLE.

Dr. Stevens summarized by saying that maternal microchimerism is common in humans and these cells persist for decades both in blood and tissue. Maternal cells appear to be well tolerated by a child's immune system except in SLE. Male microchimerism in females with SLE is interesting and may turn out to have a role in the etiopathogenesis of SLE.

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other disorders. *Autoimmun Rev.* 2004 Aug;3(6):454-63

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V Views form the bench-Kawasaki Disease

Rai Yeung

Kawasaki disease (KD) is the #1 cause of acquired heart disease in children in most countries. Treatment has improved but is still inadequate. At Sick Children's Hospital in Toronto, there are 100-150 Kawasaki cases per year. As there are epidemics of KD, many experts believe that there is an infectious cause or trigger for KD.

Dr. Yeung described her rheumatology unit's interest in the *Lactobacillus casei* cell wall mouse model as a murine model for KD. In this model, the cell walls are injected intraperitoneally into the mouse at day 0 and a vasculitis develops with maximal disease at day 28. The arteritis (LCA) is most prominent in the coronary arteries and the aorta. Disruption of elastin is noted by day 42. This arteritis responds to immunoglobulin treatment just like KD.

This unit has demonstrated that a superantigen appears to be crucial to the development of LCA. If there is an absence of a superantigen, no disease occurs. If a superantigen is present, the LCA is expressed. The superantigen appears to cooperate with the Toll-like receptor in some models. Dr. Yeung noted that, in her opinion, it is unclear yet whether the TLR are crucial to LCA.

T cells and T-cell receptors may have an important role in LCA as the arteritis does not occur in C3h-HeJ mice which have a T-cell receptor VB 14 defect. Interferon-gamma (IF- γ) mRNA has been shown to be produced as early as day 3 in these LCA mice and as late as day 28 in the LCA coronary vessel wall. Yet IF- γ appears not to be essential to the development of LCA as the IF- γ knock-out mouse can still develop LCA.

What about TNF- α ? KD kids have increased TNF- α levels and anti-TNF- α therapies such as infliximab have been used to treat KD with some success. TNF- α knockout mouse did not develop the LCA with no elastin breakdown. TNF- α dependent upregulation of migration molecules has been noted in this model as well.

Apoptosis does not appear to be increased in this model. Caspase-3 is not increased in LCA with no increased apoptosis at vessel walls. Elastin breakdown was investigated by looking at extracellular matrix regulation. MMP-9, a metalloproteinase, was found to be increased in the cardiac tissue level but not in serum. The MMP-9 knock-out mice injected with *L. casei* cell wall extract did have LCA inflammation but exhibited no elastin breakdown. Neutrophil elastin factor is currently being looked at. Interesting, high dose ASA, a staple of KD treatment since the 1970's, does have an effect on elastin. It also inhibits NF- κ B nuclear translocation, TNF- α cytokine pathways, and MMP-2 and MMP-9 metalloproteinases.

VI Barriers to care in pediatric rheumatology

A. The UK view-Helen Foster

The key questions are: How common is delay of diagnosis in pediatric rheumatology? Does it really matter? What are the barriers? What can be done to overcome barriers to treatment for patients with juvenile rheumatic disease.

It is essential to start with the fact that studies have shown that JIA is not a benign disease. Children do suffer. Joint damage and disability can occur and still often does. Children do not grow out of JIA and need early and aggressive treatment. In the 2001 article of Hull, et al, the standard of care was suggested to be that children with arthritis and likely JIA be evaluated by a multidisciplinary team at 6 weeks after the onset of the arthritis.

A prospective study of JIA in Northeast England recently reported data on 120 patients. The median age of the patients was 10 years old. Most had been recruited within a 12 mile radius. The median delay was 23 weeks with a range of 0-416 weeks. Eighty-three percent had a delay of more than 6 weeks.

There did not appear to be a single referral pattern problem. Patients tended to go through a morass of a referral tunnel of orthopedics, adult rheumatology, and other physicians before getting to a pediatric rheumatologist. Does this delay matter? Yes, it does. Most of these 120 children had prolonged active disease, missed school (mean of 14 days), and had a significant delay in starting aggressive treatment such as methotrexate. This delay has many fathers which involves organizational obstacles, social patterning issues, hospital and hospital contract barriers, and limitations of medicines and services.

One major barrier is the musculoskeletal exam skills of many physicians. Multiple studies have documented this deficit. Dr. Foster mentioned her recent study that showed that only 4% of pediatric inpatients in one hospital had a documented musculoskeletal exam. Even if the child was being evaluated for a limp, the documentation of this musculoskeletal exam was poor. In children being worked up for JIA, the documentation of the musculoskeletal exam was improved, but the laboratory workup and initial treatment was lacking. Much remains to be done to improve education of medical students and residents in the musculoskeletal exam. Dr. Foster has worked with a group in the UK that has developed the GALS musculoskeletal screening tool (gait, arms, legs, and spine) that will soon be taught to UK medical students. The pediatric component is in development.

In summary, Dr. Foster emphasized that a delay in referral of JIA patients appears to be very common and a significant problem. The problem and solutions may be multifaceted but the lack of physician musculoskeletal skills is critical. Better education is the key.

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joints': assessment of the musculoskeletal system is poorly documented in routine paediatric clerking. *Rheumatology (Oxford)*. 2004 Aug;43(8):1045-9.

B. Access to Care-The US view-Helen Emery

There are problems and obstacles. For example, the Arthritis Foundations appears to underestimate the juvenile arthritis/rheumatic diseases at only 300,000 children. Approximately one-third of US medical schools are without a pediatric rheumatologist to teach residents and medical students as well as care for children with these illnesses in their affiliated medical system. There are 202 board certified pediatric rheumatologists in the US, but more are needed. Obstacles to care include a lack of public awareness, the belief that there is not much to do for arthritis, the cost of care for children with a chronic illness, and a long waiting list to be seen at many pediatric rheumatology centers.

Rheumatic disease in children and adults is one of the leading causes leading cause of disability in US. We recently began a study of lack of access to care for children with rheumatic disease at 4 pediatric rheumatology centers at Seattle, UCSF, Sacramento, and Stanford. The data collected included: months to first physician visit, distance traveled, costs, family identified obstacles, and CHAQ. The most impressive finding was that about ¼ of the children are ill more than 1 year before they get to a pediatric rheumatologist.

What can be done to get these kids into sooner? First of all, we need to Increase medical teaching skills. We should utilize tools such as the pediatric GALS screen (gait, arms, leg, and spine) in development. The observer evaluates a child walking, her hands and arm movement, and checks her legs and spine. This is a very simple and quick musculoskeletal screen which was developed for the education of medical students

Another approach is a yearly 4 hour seminars for local pediatric generalists. This can include a case-based diagnostic discussion, a show and tell, hands-on physical exam lab with patients, and a treatment discussion. The ACR Meet the Professor model for adult rheumatologists works well. A similar approach can be used to teach orthopedic residents. These efforts should be coupled with outcome measures-more calls, more referrals, and more appropriate referrals? Web-based educational program for general pediatricians, for example, through general pediatric organizations, may help as well.

To conclude, a delay in diagnosis is still too common and often appears universal. The biggest obstacle is a low awareness of both the public and physicians. We should work to educate all levels-medical students, residents, pediatricians, other professionals, and the general public. We do need more rheumatology fellows and faculty-The needed funding for these positions is another challenge and a subject for another talk.

VII Amplified musculoskeletal pain syndromes in children (AMPS)

David Sherry

You may often feel: Why me? But questions persist: Who are these kids-How to establish diagnosis? How to explain it to others? How do you treat these kids? First, you have to start with the fact that the pain is real and you must believe these kids-There are many different scenarios you can describe for these kids but in all of them, the kids suffer. In this process, though, it is important to keep an eye out for other diagnoses: JIA, tumor, lupus, and celiac disease .

We use the term reflex sympathetic dystrophy or pain amplification to describe these patients. They have RSD with and without overt autonomic dysfunction. The problems are quite variable and intermittent, with mixes of symptoms and signs. The disorders are seen more in females. They have increasing pain over time they may have started with a minor trauma. They develop allodynea/hyperaesthesia that worsens with rest, casting, and splinting. They have clearcut autonomic nerve dysfunction.

These patients are often accomplished athletes, dancers, and performers. Sometimes they have suffered multiple injuries. They usually appear mature but are pseudomature. They are achievers, people-pleaser, and perfectionists. They strive to meet other people needs, not their own needs. They often have la belle indifference, incongruent affects, even smiling with pain, and not unhappy to be in the situation they're in. Major life events often have occurred recently. These adolescents usually have a role model for pain in the family or among neighbors or friends.

You may sometimes think that you can negotiate with terrorists more easily than with some of the mothers of these children. The mother often speaks for the child. The mother and teen may exhibit enmeshment extraordinaire, each often finishing sentences for each other. The teen may even dress like the mother!

Physical findings often include severe swelling and edema in the involved extremity, particularly in the hand or foot. Color changes such as erythema and temperature changes may be present. There are often variable levels of pain, tenderness, and hyperaesthesia. Labs are usually normal and a bone scan usually reveals decreased uptake, if anything. Our working model for the pathophysiology of this pain amplification is a persistent reflex arc.

Our treatment program is simple. We discontinue all meds and discuss pain amplification. The critical treatment is 5 hours of physical or occupational therapy per day every day. A psychological evaluation is essential. Rarely behavioral modification is needed. In 103 patients with who have completed this exercise program, 69% have recovered without a problem, 31% had relapses. Of the 31% who relapsed, about half could treat themselves with the exercise program. 10% of the 103 patients had a chronic pain problem. These adolescents often had associated symptoms such as eating disorders, conversion disorder, depression and suicide attempts. The program should attempt to identify stress factors in the teen's life and help them start to develop individualization away from their family. Family counseling is crucial.

The team approach is essential to achieve these goals including nurses, social workers,

psychologists, educator, and particularly physical and occupational therapists. Everyone has to like these kids and believe their pain to work well in this program. It takes patience. These are good kids in real need and their pain is a red flag for significant problems.

The rheumatologist and the team are doing a real service in reducing pain and suffering, decreasing disability, decreasing the cost to health insurance and the medical system. Excellent cure rates are possible in the range of 90-95%. Much research remains to be done to delineate the pathophysiology of this syndrome and better treatment.

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VIII Beware of data from clinical trials

Alice Klinghoff

It is very important to be aware of the dangers and conflicts of clinical trials. For example, 70% of trials are commercial. In 25% there are financial relationships between the investigator and the commercial interest, and 60% of trials involve startup companies originating in a university with a very real financial interest.

There is also a tendency to highlight benefits and minimize risks in these trials. Especially worrisome are confidentiality agreements that prevent investigators from speaking out about certain side effects. One example might be that investigators and the drug companies emphasized that the major adverse reactions in anti-TNF- α medications were limited only to injection site reactions and minimized serious infections. Yet the FDA website noted early on problems with multiple infections with tuberculosis, histoplasmosis, atypical TB, and other infections.

Another clinical trial issue is a delay in publication of negative side effects, e.g., 1 positive trial and 5 negative trials on anti-depressants for teenagers and the positive trial was published first. Another example might be the usefulness of mycophenylate for arthritis.

One way of summarizing clinical trial pitfalls is BIAS. "B" is Beta error. This is the risk of missing a treatment benefit because the sample size is not large enough, e.g., methotrexate in scleroderma. "I" is for Integrity and for conflict of interest, e.g., the suppression of negative results or adverse side effects (Vioxx). "A" is for fraud and external validity, e.g., does this study apply to my patients? "S" is for statistics that lie and for \$ bias. Are the side effects systemically and completely reported? Consider the bias-is it the truth, the whole truth, and nothing but the truth?

IX The Future of Pediatric Rheumatology (PR)

Alan Rosenberg

“The future as it used to be needs new directions

The future is not as good as it used to be”

There has not been as much progress as Alan had hoped there would have been in PR. Causes are still not known. There has been some progress with more pediatric rheumatologists, much better treatment, and better programs. But there remains of much to be done with new progress into cause of diseases and prevention-Like Winnie the Pooh, we can love the anticipation of eating honey.

We need better clinical Care and education. Is our care cost-effective? Are all the treatment steps needed? Do we have underutilization or overutilization? Do our medications really work? Are we using the wrong members on our team for tasks. We should reappraise our treatments all the time and develop practice guidelines-debate, discuss, and improve them. We should go beyond biology by looking into psychosocial, family, environmental influences on disease. We must be always intolerant of an “idiopathic” status and go for real causes that make the idiopathic term anachronistic.

We have clearly established our niche but maybe have separated or isolate ourselves from adult rheumatologists too much. We need to work together and investigate how adult disease may start in childhood, teen years, even in utero. In our training and mentoring, we should examine carefully who we train. We should choose candidates that fit our needs and our ambitious agenda. We must anticipate scientific questioning and increase our collaboration with scientists in other disciplines-basic science colleagues, clinical researchers, rheumatologists, pediatricians, allied health professionals, and patients and families. We should continue advocacy-Make it special but broad in scope by developing pediatric rheumatology that in turn helps and cross-pollinates adult rheumatology, genetics and other specialties in collaboration with many disciplines.

Our research priorities should be determined by our patients and not by the outside agendas of others.-We can secure funding by an aggressive solicitation of funding for areas of genetics and biotechnology. We should continue our state-of-the art treatment regimens and outcome measures as tools to help children now, but strive for the causes of our diseases and how the cause changes the treatment and how psychosocial and environmental factors affect the cause and treatment.

We can achieve dramatic progress in the near future with these steps-much sooner than anyone imagines. We can survive without a Ross Petty in part because of the foundation that he has helped establish.

Reporter's note: The conference thus ended and was a great success and a fine tribute to an extraordinary leader of pediatric rheumatology.