

The Journal of the



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3 *Editorial*
Issues in Pediatric Rheumatology

4 *Pediatric Rheumatology*
Classification for Childhood Arthritis

9 *CRA News*

12 *Controversy*
Viscosupplementation

Consultants

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*The mission of the CRAJ is to encourage
discourse among the Canadian
Rheumatology community for the
exchange of opinions and information.*

Issues in Pediatric Rheumatology

Canadian physicians have played a leading role in the development and advancement of rheumatology as a clinical and academic discipline. Shining examples include the development of the rheumatic disease unit concept, prospective clinical studies in lupus, therapeutic studies in rheumatoid arthritis, fibromyalgia, and spondyloarthropathies, to name but a few areas in which Canadians have led the world.

Canadian pediatric rheumatologists have maintained these outstanding traditions and contributions. As a group, Canadians have played leadership roles academically and in administrative areas on the international scene. Physicians from around the globe have come to Canada to train in pediatric rheumatology over the last 15 years.

Pediatric rheumatology is a unique specialty. While the diseases in children may have similar names to their counterparts in adults, the clinical manifestations are frequently very different.

The clinical expression of disease may be altered by a developing immune system, a growing musculoskeletal system, and the social and/or developmental stages of the child. Management requires an understanding of how pharmacologic agents are handled at various stages of development.

Of even more importance is an ability to understand and appreciate the impact of psychosocial factors on disease expression, coping mechanisms that children and families use to deal with chronic diseases, and factors that affect compliance with treatment.

Physicians trained in the specialty of pediatric rheumatology are in the best position to diagnose and direct the management of children and adolescents

afflicted by a disease from within the wide spectrum of rheumatic diseases. Pediatric rheumatologists are uniquely positioned to educate medical students, post-graduate trainees and allied health professionals to ask the research questions that must be answered for the benefit of their patients. They can develop research protocols that are necessary to advance the knowledge of pediatric rheumatology, and provide the best comprehensive care in a multidisciplinary fashion for children with rheumatic diseases.

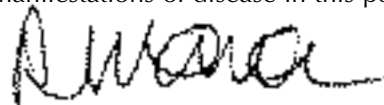
Health care in Canada is supported by the Canada Health Act, which is applicable to every Canadian citizen. The principles of the Canada Health Act are:

- **Public Administration** (government funded);
- **Comprehensiveness** (access to basic health services);
- **Universality** (equal health care coverage);
- **Portability** (no barriers between provinces); and
- **Accessibility** (access to the same quality health care).

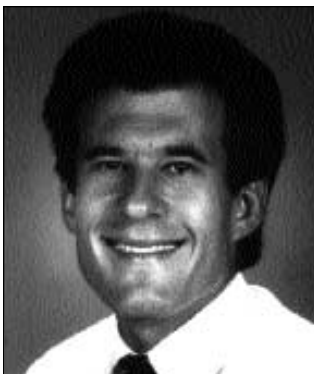
These principles should be applied to the care of every patient. We are fortunate in this country to have experienced and well-trained physicians in each province with expertise in pediatric rheumatology in each province. All children and adolescents with rheumatic diseases must have access to the diagnostic and management expertise of the entire pediatric rheumatology team, which should assume the responsibility for directing the long-term management of these patients and working with the patient's primary care physician.

Distance must not be an issue. Just because a child lives in an area without a pediatric rheumatologist nearby is not an excuse for that child to miss the opportunity to be seen in consultation by a pediatric rheumatologist, who can subsequently collaborate with local pediatricians, family physicians, allied health professionals and adult rheumatologists to provide the very best treatment.

Beginning with this issue, the Journal of the CRA will highlight a variety of important topics in pediatric rheumatology. We hope this will stimulate the readership to learn more about pediatric rheumatology and the manifestations of disease in this population.



Ronald M. Laxer



Ronald M. Laxer, MD, FRCPC
Dr. Laxer is Professor of Pediatrics and Medicine, Vice-Chairman for the Department of Pediatrics, University of Toronto. He is also Associate Pediatrician-in-Chief of The Hospital for Sick Children, Toronto, Ontario.

A New Classification for Childhood Arthritis

The heterogeneity of childhood arthritis was recognized by George Frederic Still in his sentinel paper published in 1897.¹ Since that time, classifications have been devised to recognize and rationalize this clinical heterogeneity. To a considerable extent, these efforts have been useful in helping identify patient groups for the purposes of communication and investigation both in the clinic and in the laboratory.

COMPARISON OF CLASSIFICATIONS

The American College of Rheumatology (ACR) recognizes three types of chronic childhood arthritis: pauciarticular, polyarticular, and systemic-onset juvenile rheumatoid arthritis (JRA).² **The European League Against Rheumatism (EULAR)** recognizes, in addition, children with juvenile ankylosing spondylitis and juvenile psoriatic arthritis. EULAR reserves the term juvenile rheumatoid arthritis for those children with polyarthritis and rheumatoid factor.³ Thus, the two pre-eminent classifications of childhood arthritis in current use describe different patient populations.

In spite of this, both classifications are often used interchangeably, resulting in confusion about the results of clinical, epidemiologic, genetic and other basic research, and confounding collaboration in clinical trials. Furthermore, neither classification provides definitions of many of the categories, particularly psoriatic arthritis, for which the Vancouver criteria⁴ are often employed, and juvenile ankylosing spondylitis, for which the criteria of the European Spondylitis Study Group are used.⁵

The Classification Taskforce of the Pediatric Standing Committee of the **International League of Associations for Rheumatology (ILAR)** has proposed a new classification based on the recommendations of an international group of pediatric rheumatologists.^{6,7} The goals of the taskforce were to define distinct, homogeneous categories of idiopathic childhood arthritis that would “facili-

table 1
COMPARISON OF CLASSIFICATION OF CHILDHOOD ARTHRITIS

ACR(2)	EULAR (3)	ILAR (7)
<i>Juvenile Rheumatoid Arthritis</i>	<i>Juvenile Chronic Arthritis</i>	<i>Juvenile Idiopathic Arthritides</i>
Systemic	Systemic	Systemic
Polyarticular	Polyarticular	Polyarticular RF Negative
	Juvenile Rheumatoid Arthritis	Polyarticular RF Positive
Pauciarticular	Pauciarticular	Oligoarticular - Persistent - Extended
	Juvenile Psoriatic Arthritis	Psoriatic Arthritis
	Juv. Ankylosing Spondylitis	Enthesitis-Related Arthritis
		Other Arthritis

tate research in immunogenetics and other basic sciences, epidemiology, outcome studies and therapeutic trials”.

Space does not permit complete discussion of the exclusions that are an integral part of the classification criteria and are essential to the precise application of this classification system. They are particularly important to the categories of oligoarthritis, and enthesitis-related arthritis, and the reader is referred to their full description.⁷

Like its predecessors, the ILAR classification is an onset classification based on the clinical characteristics of disease during the first six months after onset. This classification is also based largely on clinical criteria rather than laboratory parameters. Unlike its predecessors, the ILAR classification relies heavily on the presence of family history of psoriasis or HLA-B27—associated diseases to permit or prevent inclusion in any specific category.

A limited number of studies suggest the criteria are workable (although more complicated than the ACR or EULAR criteria) and they will yield patient groups of greater clinical homogeneity. Whether or not their application will lead to a clearer understanding of the etiology, pathogenesis, therapeutic responsiveness and prognosis of the childhood arthritides is yet to be seen and awaits the results of studies of histocompatibility antigens and other investigations currently under way.

It is the intention of the taskforce to undertake ongoing evaluation of these criteria and to modify them as necessary.

Continued on page 5



Ross E Petty, MD, PhD, FRCPC
Dr. Petty is a professor and the head of the Division of Rheumatology, Department of Pediatrics, University of British Columbia and British Columbia's Children's Hospital.

Letters to the Editor

Dear Editor,

I read Dr. Glen Thompson's letter with interest and learned many facts about the contemporary activities of the CRA, but as an old-timer, I feel I must, for the sake of historical accuracy, correct one small point.

You speak of Metro Ogryzlo's concept of the Rheumatic Disease Unit (RDU) changing rheumatology four decades ago. As a contemporary and a good friend of Metro's, I have the greatest admiration for him and I realize that he made an important contribution to the development of the RDU, but it was by no means his original idea.

The inspiration for the RDU as I recall, came from Philip Hench during World War II. He was developing one in the U.S. as a joint tri-service facility. He demonstrated what he was doing to Wallace Graham who came back and started such a tri-service unit at the RCAF Station, St. Thomas, Ontario. Shortly after the end of the war, the unit was transferred to a DVA division in the Toronto East General Hospital. Metro and I were the first civilian residents under Dr. Graham and Dr. Almon Fletcher, relieving Drs. Bill Hurlburt and Alan Traynor, who were still in uniform and anxious to get their release.

The unit was transferred to Sunnybrook Hospital as soon as quarters were finished there, and later a parallel unit was opened in the Toronto Wellesley Hospital. After his training was completed, Metro was on staff (I think of the two units) and assumed the direction of the Wellesley Unit when Wallace Graham died at a young age.

Metro did a great deal over the years to advance the original concept of the RDU, but you will see that the idea was established well before he joined the resident staff at the East General.

Henry A. Sims, BA, MD, FRCPC

The Journal of the Canadian Rheumatology Association welcomes your letters to the editor. Your comments, criticisms and frustrations will be published here.

Go ahead, we can take it!

Please address your letters to
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Toronto, Ontario, M5T 2S8

One such revision of the originally proposed criteria has already taken place, resulting in deletion of the category of probable systematic arthritis, recognition of two subsets of oligoarthritis (persistent and extended), and establishing a category (other arthritis) for children who fit no other category or who fit more than one category.⁷

To date, except for the promulgation of the classification and the classification criteria, very little has been accomplished.

The conflicting language of the ACR and EULAR classifications can hopefully be laid to rest, but the process will only fully achieve its goal when the above outlined aims are realized.

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An Interview With Dr. Hugh Smythe

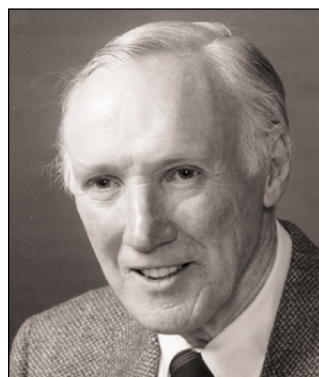
The Journal of the CRA is looking at the history of rheumatology in Canada through the eyes of its elders. We will reflect on the history of this specialty by interviewing the most experienced members of our community.

Q *Dr. Smythe, what encouraged you to choose rheumatology as a career when so little was known about the specialty?*

In fact, much was known within the specialty. In 1950, rheumatology had already entered one of its most dramatic periods of discovery and program development. The rheumatoid factor and LE cell test had been developed and the stunning therapeutic effects of cortisone had just been described. The links between streptococcal infection and rheumatic fever had firm laboratory support and antibiotics were rapidly being discovered, which would forever change the impact of infectious agents.

Major research units had been developed in the U.S. and U.K., and a special feature was the openness of the international community. Debate was often fierce, but was free and special efforts were made to attract and include a new generation. The international collaborations developed during the second world war and by the Marshall Plan, were strongly paralleled in the rheumatology community. The World Congress of the International League Against Rheumatism was awarded to Toronto, and held in 1956.

However, none of this was visible to us undergraduate students. Rheumatology was represented by one lecture, and the few patients to be found on the teaching wards were so badly deformed that it was clear the new therapeutics would be of little value and, therefore, of little interest.



Hugh Smythe, MD, FRCPC

Dr. Smythe is a professor at the University of Toronto and a Rheumatologist at the Toronto Hospital, Western Division.

Given that background, why did I choose Rheumatology? The short answer is Sunnybrook. The brilliant team of clinicians/teachers/researchers had developed at Sunnybrook with the best post-graduate learning environment I have experienced. The tone of Grand Rounds and the clinical pathological conferences was set by a sign stating “Where all think alike, no one is thinking”.

In contrast to the lack of development of rheumatology in the major general teaching hospitals nationwide, there was recognized to be a strong need for a major treatment unit for veterans with various forms of arthritis. At Sunnybrook, there was a 90-bed ward for patients, plus a 12-bed clinical investigation unit where metabolic balance studies could be performed. The treatment model was that of the sanitarium; patients with active disease would be kept in hospital until their disease was under control.

The average length of stay in this unit was (can you believe it?) about 6 months. In addition, veterans claiming or receiving pensions were followed as outpatients on at least an annual basis. All research were available, from the time of enlistment.

As a resident, I was pushed (willingly) to compare the heart disease in patients with spondylitis and other diseases and was able to establish the unique clinical and pathologic features of spondylitic heart disease. We soon moved on to the mechanisms underlying the excess risk of cardiac involvement in patients with gout and mechanisms possibly linking vascular disease with the overproduction of uric acid.

My intent in all this detail is to underline another feature of rheumatology that is almost unique amongst subspecialties. Within rheumatology, you must use all of the hard-won skills of general medicine. You need not, indeed cannot, abandon cardiology, neurology, endocrinology, renal physiology, infectious diseases or dermatology.

While all of this was happening at Sunnybrook, nothing comparable was being developed for non-veteran patients. Precisely the same staff members and residents functioned within the Toronto General Hospital, but the evolution of a rheumatic disease program in this major teaching hospital had specifically been reversed in 1949, in the interest of general medical wards. The focus was on undergraduate

training in preparation for community practice. It was specifically stated that the activities of staff rheumatologists at Sunnybrook were outside the sphere of interest of the Chairman of the Department of Medicine at the university. At the Toronto General, few referrals to rheumatologists came from colleagues inside the Department of Medicine and virtually none from Orthopedic Surgery. Nevertheless, a pressure for change was developing and received strong support from The Arthritis Society and the McLaughlin Foundation.

When I was first invited to join the staff of the Toronto General Hospital, I was offered a post in neurology. The chairman and my wife were equally surprised when I chose rheumatology instead.

Q *What was the state of rheumatology when you first started?*

There were many opportunities and a few problems. Money was certainly one of them. I had received support from the Arthritis Society while training, but none was available for junior staff investigators. There was no National Health Insurance Plan and I looked after most of my patients in the Arthritis Clinic and the teaching wards for free.

Nevertheless, I was allowed to use the office of the department chairman for a half day per week for my consulting practice and referrals came quickly. I was also appointed to the staff of Sunnybrook Hospital, serving on a general medicine ward, as well as the Arthritis Service. I was granted funds and space to do studies in uric acid metabolism, studies which led to a fruitful collaboration with Fraser Mustard on platelet turnover and the effects of diet, smoking, sulfinpyrazone and later, the effects of acetylsalicylate on platelet economy.

I was flattered and stimulated by invitations to join the Communications Committee of the American Rheumatism Association and similarly joined the Board of Directors first of the Ontario Division and then the National Board of the Arthritis Society.

Apart from this, I very much enjoyed my role as Team Physician for the Toronto Maple Leafs. At first, I was a junior partner to the team surgeon, ensuring warm friendships with surgical colleagues that might not have developed within the teaching hospital. The diagnostic challenges we faced influenced my reading and studies for later careers that were then totally unanticipated (and

unsought). Before returning to Toronto, I had spent a year in England, primarily with Bywaters and Ansell, but also with Professor Kellgren, whose work on referred pain was still evolving.

As a group of rheumatologists, our main challenge was to create facilities for non-veterans comparable to those which had proved so powerful at the veteran's hospital. Several efforts to develop facilities within the Toronto General were rebuffed. A treatment unit was opened at the Home for Incurables (renamed the Queen Elizabeth Hospital) but still remote from University Avenue. This experience taught us simply that an academic service must be centrally placed within major teaching hospitals to have any major effect.

Q *How has the practice of rheumatology evolved (academic or community settings) since you started?*

In 1961, the Arthritis Society (then the Canadian Arthritis and Rheumatism Society) prepared a submission to the Royal Commission on Health Services. There was, of course, broad input, but the task of drafting this submission fell largely on Edward Dunlop and myself. From the English, American and Sunnybrook models, we knew we wanted a strong focus on education and research as well as on treatment. However, the context as a national plan required a formulation that would be meaningful to donors and patients in every community across Canada. Ivory towers were not enough; a clear link between the proposed university-based Rheumatic Disease Units (RDUs) and diagnostic and treatment programs available to every Canadian had to be clearly visible. Edward Dunlop's genius lay in his ability to translate objectives and strategies into specific tactics stated in terms of places, times and dollars. He was very good at leverage. Every dollar raised and spent by the board of the Arthritis Society resulted in about \$20 newly available for the care of patients with arthritis. Due to the educational component, exemplary care of a patient in an RDU influenced the care of future patients because of the rapidly expanding family of rheumatologists, orthopedic surgeons, allied health professionals and researchers brought into the field.

Parallel with these events, the Wellesley Hospital was being rebuilt as a university teaching hospital. A special effort by the Arthritis Society Directors raised about 20% of the funds required for the rebuilding of the Wellesley

Hospital and ensured that a major RDU could at last be made available for non-veterans. Plans for rebuilding were being drawn in 1961. With the creation of a 40-bed ward, plus a metabolic study unit and a wing of research labs, plus a fellowship program and a major role in undergraduate and graduate training of physicians and allied health personnel, we could begin establishing what Met Ogryzlo later claimed would be “The best Arthritis Program in the world”. Hearing the budget figures, the distinguished treasurer of the Arthritis Society diffidently asked “How much would it cost for second best?”

The Wellesley unit first opened in rented space at Sunnybrook Hospital in 1964 and finally moved to its new home in November 1996. We did not forget our community commitment. Our colleagues in British Columbia were ahead of us, but I had the opportunity to join Phil Gofton in a study of the prevalence of ankylosing spondylitis among aboriginal people in Bella Coola. This led to collaborations to establish and perform blind readings of population survey films with John Decker and others in the United States as well as John Lawrence from England.

Wallace Graham, the Director for the Toronto Rheumatic Disease Program, died suddenly in 1962. At that time, he was the author of three of the chapters in Hollander’s Text Book on Arthritis. Met Ogryzlo took responsibility for the chapter on ankylosing spondylitis and I was asked to write the section on fibrositis.

This had not been an area of interest to me. I felt more confused after reading the literature and, in 1966, I attempted a fusion between the American concept of tension rheumatism and Kellgren’s studies on referred pain; recognizing that these two concepts were not obviously compatible. My own experience in acute musculoskeletal medicine, my knowledge of the extensive works on spinal pathology written by my friend Ian McNabb, and the epidemiological studies of Kellgren and Lawrence all pointed to the neck and low back as the source of referred pain.

Shortly thereafter, Harvey Moldofsky began working with us. He (and others) showed that the muscles in the regions of pain were electrically silent. Terms such as “tension rheumatism” or “tension headaches” are misnomers, as defined electrophysiologically. How this evolved is another story. In this account, it illustrates the easy collaborations which could develop within a framework in which there are large numbers of patients available to study, in a setting in which hypotheses are framed so that they may be challenged.

This brings us to the early 1970s, by which time rheumatology was still not a recognized subspecialty in Canada. There was great research productivity. The Journal of Rheumatology Publishing Company was formed in the fall of 1973. By 1976, RDUs were established in all of Canada’s medical schools and the rapid expansion of community rheumatology was well underway.

Q *How do you see the future of rheumatology evolving in Canada?*

The political momentum is changing and it is clear that Canadians wish to repair the damage to health care. Rheumatologists have certainly shown they care and wish to act in collaboration with their colleagues in solving problems both geographic and interdisciplinary. A deep concern is a loss of access to undergraduate students.

Q *What advice would you give to those following in your footsteps?*

Perhaps I can reduce it to three short statements:

- Give yourself time to become a really good doctor.
- Dare to be different.
- Make sure you enjoy what you are doing.

The first and last phrases are linked. If you are a good doctor, you can be flexible enough to change direction to take advantage of opportunities or overcome obstacles. If you are enjoying what you are doing, then you don’t mind taking time, even though immediate rewards may not be apparent.

Q *Would you choose to become a rheumatologist in 1999?*

First, I am not bright enough, so they probably wouldn’t let me in. Second, if I were bright enough, there are many alternative careers which I would equally enjoy. I like challenges, but perhaps there are not the first rate opportunities that were present 20, 30 and 40 years ago. Convince me otherwise practice managers, hospital presidents, medical politicians and ministry officials!

In rejecting (once again) one of my research applications, the reviewers for the Medical Advisory Committee of the Arthritis Society (of which I was then chairman) explained: “It is difficult to separate Dr. Smythe’s contributions from those of his colleagues”. This will serve nicely as my epitaph.

CRA AWARDS

Glen Thomson, president of the Canadian Rheumatology Association, presented the following CRA awards to recognize the outstanding achievements of CRA members at the annual CRA banquet held on Feb 26.

DISTINGUISHED RHEUMATOLOGIST AWARD

In recognition of a distinguished rheumatologist who has made an outstanding contribution to rheumatology in Canada, either through patient care and service or professional creative activity.

Awarded to André Lussier of Sherbrooke, Quebec. Dr. Lussier has recently retired and has been granted Emeritus membership in the CRA. He was the chair of the very successful PANLAR meeting held in Montreal in 1998.

DISTINGUISHED INVESTIGATOR AWARD

In recognition of a distinguished rheumatologist who has made an outstanding contribution to rheumatology in Canada in areas of teaching and research.

The award was presented to Dr. Nicholas Bellamy of the University of Western Ontario. Dr. Bellamy is known for his work in metrology. He has worked on developing instruments for measuring outcomes in arthritis research, including the WOMAC for the assessment of knee status and the AUSCAN for hand function. Dr. Bellamy has recently accepted a position in Australia.

YOUNG INVESTIGATOR AWARD

In recognition of a young Canadian Investigator who has contributed significant original research in Rheumatology.

The award was presented to Dr. Paul Fortin of Montreal, Quebec. Dr. Fortin is at McGill University in Epidemiology. He is recognized for his work in lupus, as well as in information databases.

The executive wishes to invite all members of the association to congratulate these members on their achievements.

For those wishing to propose nominations for the year 2000, please look to your dues announcement in the fall of 1999. If you have any questions, please do not hesitate to contact the Secretary-Treasurer.

WINTER WORKSHOP

The CRA Winter Workshop and Annual Meeting was held from Feb 24-27 at Chateau Lake Louise in Alberta. The Dunlop-Dottridge lecture was presented by Dr. Cornelia Weyand of the Mayo Clinic in Rochester, Minnesota. Her topic was "Vasculitis and the immune-deficient mouse model".

ANNUAL GENERAL MEETING

The Canadian Rheumatology Association continues to have significant success in organizing its Annual Meeting. The success is due in no small part to the support of our sponsors, including Diamond sponsors Searle Canada, Pfizer Canada Inc. and Merck Frosst Canada; Platinum sponsor Sanofi Canada; Gold sponsors Novartis Pharma Canada and Wyeth-Ayerst as well as Silver sponsors Schering Canada, Biomatrix Medical Canada and McNeil Consumers Products Canada.

Three additional motions were presented at the Annual Meeting:

- to establish a new category for members in training;
- the incorporation of the association;
- a motion to decrease annual dues was defeated.

The executive looks to its membership for direction in all these endeavors.

ARTHRITIS CARE

The Laboratory Centre for Disease Control of the Health Protection Branch of Health Canada has agreed to establish an arthritis/musculoskeletal division. In the recent budget, Paul Martin, Minister of Finance, specifically mentioned arthritis in his speech and the CAN/NCE has received positive reviews in a number of federal departments.

Arthritis care and research will experience renewed energy and increased funding if all members work with a single mind and message.

Viscosupplementation for Treating Osteoarthritis

Osteoarthritis (OA) is the most common problem faced by rheumatologists and orthopedic surgeons. Given current demographics, the prevalence of OA is going to at least double over the next two decades as baby boomers enter the OA years and life expectancies steadily increase. Thus, there will be ever-increasing pressure to develop and refine therapies that can be used to safely, effectively and economically manage OA.

Weight loss, physiotherapy, activity modification, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), bracing, intra-articular steroids and surgery have long been mainstays in the symptomatic management of OA. Unfortunately, no disease-modifying therapies have been forthcoming for OA to date. Recently, intra-articular injection of hyaluronan-based products has become available as a new method for managing human OA, especially knee OA. This form of therapy has been termed viscosupplementation. The purpose of this article is to briefly review the rationale, possible therapeutic mechanisms and clinical studies that address the use of viscosupplementation for the symptomatic treatment of human OA.

RATIONALE

Hyaluronan (HA) imparts characteristics to normal synovial fluid that contribute greatly to joint homeostasis.¹ These properties include joint lubrication in low-load situations, shock-absorption during high joint loads, barrier and molecular exclusion effects, anti-nociceptive properties, anti-inflammatory effects and provision of renewed sources of HA for articular tissues. In OA, the molecular weight and concentra-

tion of HA in synovial fluid is diminished and its homeostatic properties are compromised.² The concentration is diminished on a dilutional basis and molecular weight appears to be decreased due to both increased degradation and aberrant synthesis of HA. The recognition that synovial fluid HA in OA is abnormal led to the proposition that removal of pathologic joint fluid in OA and replacement with products that restore the molecular weight and concentration of HA to normal levels can provide therapeutic benefit.³

POTENTIAL MECHANISMS UNDERLYING CLINICAL EFFICACY

There are at least four mechanisms whereby viscosupplementation may potentially ameliorate the symptoms of OA.⁴

1. **Restoration of synovial fluid elastoviscosity.**

Aspiration of pathologic synovial fluid and injection of HA-based products transiently restores the lubrication and shock-absorbing properties of synovial fluid. High-molecular-weight hylan is resident in synovial fluid and articular tissues substantially longer than low-molecular-weight hyaluronan products.⁵ The injected products move from synovial fluid to articular tissues in hours to days and even hylan is completely cleared from articular tissues in rabbits by 28 days. Given these relatively short residence times, there must be mechanisms other than transient restoration of synovial fluid elastoviscosity that account for the prolonged duration of symptomatic improvement that occurs for many patients.

2. **Anti-inflammatory effects.** HA-based products can influence activities of inflammatory cells in a non-specific, nonpharmacologic manner.⁶ Activities inhibited include phagocytosis, lymphocyte activation, cell migration and prostaglandin release.⁶⁻¹² The recent identification of cell membrane receptors that specifically bind HA suggests that some of these effects may be transduced through intracellular signaling pathways.^{13,14}
3. **Anti-nociceptive effects.** Intra-articular injection of HA-based products has been shown to ameliorate pain severity in a rat model of knee pain.^{15,16} There is evidence to support several different



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potential anti-nociceptive mechanisms, including inhibition of prostaglandin E and bradykinin synthesis in joint tissues, coating of articular pain receptors so as to insulate them from nociceptive molecules and entrapment of endogenous pain substances by HA molecules.^{15,16}

4. **Normalization of HA synthesis and degradation.**

Aspiration of OA synovial fluid containing many pro-inflammatory, degradative molecules and restoration of rheological properties with injection of HA-based products may help to inhibit the degradation of HA that typically occurs in OA synovial fluid. Additionally, it appears that viscosupplementation may help to restore synthesis of HA by type-A synoviocytes (hyalocytes) to relatively normal levels.¹⁷

Most of these studies have demonstrated efficacy for low-molecular-weight HA injections that is greater than that obtained with placebo as well as showing that five injections do better than three injections.

EFFICACY

There are a number of studies assessing the efficacy of low-molecular-weight HA products and high-molecular hylan for the treatment of human-knee OA. There are five low-molecular products available for human use: Artz® (Seikagaku, Japan), Hyalgan® (Fidia, Italy) Neovisc® (Stellar, Canada) Orthovisc® (Annika, USA) and Suplasyn® (Bioniche, Canada). Three of these are available in Canada: Neovisc®, Orthovisc® and Suplasyn®. The molecular weight of these products ranges between 500,000 and 1.2 million. The average molecular weight of HA in normal synovial fluid is 4.5 million. Most of the published clinical studies have assessed either Artz® or Hyalgan®. Most of these studies have demonstrated efficacy for low-molecular-weight HA injections that is greater than that obtained with placebo as well as showing that five injections do better than three injections.¹⁸⁻²² However, some studies have failed to demonstrate efficacy greater than placebo, or have only shown efficacy in a small subset of patients.²³⁻²⁵

In order to deliver HA-based products that have HA molecular weights similar to those seen in normal synovial fluid, hylans have been developed. Hylan is HA that has undergone cross-linking to create a high-molecular-weight product. There is one hylan that is available for treating human OA: Synvisc® (Biomatrix, USA). It has a molecular weight of six million. It is given in a series of three injections one week apart. Two placebo-controlled, double-blind studies have demonstrated significant improvement in Synvisc-treated patients compared to controls.^{26,27}

In a third study, Synvisc was compared to continuous NSAID therapy and was found to be as good as or better than NSAIDs.²⁸ In a retrospective study of a large heterogeneous OA population, 76% of patients responded to Synvisc and were either better or much better than baseline.²⁹

SAFETY

HA-based products have been used in veterinary and human medicine and surgery for 30 years and have an outstanding safety profile.³⁰ Intra-articular HA injections have a local adverse event incidence of about 3% per injection.^{28,29} There does not appear to be any difference in the incidence of local reactions between low-molecular-weight HAs and high-molecular-weight hylan.³¹ Most of these reactions are self-limited, lasting 24-48 hours. They typically consist of mild pain and swelling. Occasionally, more severe reactions occur that require analgesics, NSAIDs, arthrocentesis and/or steroid injection. On rare occasions, severe reactions occur that mimic a septic joint. White cell counts in excess of 100,000 may occur. Once infection is ruled out, these reactions usually respond to arthrocentesis and steroid injection. Joint sepsis after HA or hylan injection does not appear to be any more frequent than after any other type of arthrocentesis or injection.

INJECTION TECHNIQUE

Injection technique is critical. It is essential to ensure that the HA or hylan is injected intra-articularly. If the product is not injected into the joint space, efficacy is diminished and the incidence of local flare reactions increases. Prior to injection, it is also critical to aspirate as much pathologic OA synovial fluid as possible so that the injected HA-based replacement is not diluted.

CONCLUSION

It is clear that viscosupplementation has minimal morbidity compared to traditional OA therapies and that it is efficacious for the symptomatic amelioration of OA symptoms for prolonged periods (months to years) in many patients. The relative economic efficacy of viscosupplementation is currently being studied. There are also many other unresolved issues that require further study. These include determining the potential of viscosupplementation to be chondroprotective, clearly defining the relationship between molecular weight and the relative efficacy of the various HA products, establishing optimal dosing regimens, determining efficacy in

differing OA subpopulations, determining how to best incorporate viscosupplementation into current OA treatment algorithms, and exploring the potential for treatment of OA joints other than the knee. What is particularly encouraging is that HA-based therapy is proving to be safe and effective for many patients with knee OA, despite the fact that our experience with this approach is still in its infancy and there remain many unresolved issues requiring further study. Thus, as our experience grows and clinical studies provide new information, it is highly likely that the current clinical efficacy and safety of viscosupplementation can be further enhanced.

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Viscosupplementation: A Time to Re-evaluate

Viscosupplementation is defined as an attempt to restore the rheologic properties of synovial fluid in the arthritic joint by the injection of a hyaluronan-based material (fluid or gel) into the synovial joint. It is suggested that if the rheologic properties of synovial fluid (*i.e.*, viscosity and elasticity) are restored, the improved environment will be beneficial to synovial tissue and to (superficial layers of) articular cartilage. The benefit is the result of the restoration and re-establishment of adequate lubrication, protection from forces (shock absorption and tangential forces, for example) and the exclusion of inappropriate molecules.

Theoretically, it is suggested that the return of viscoelastic properties to synovial fluid facilitates tissue regeneration and enhances function of cartilage and synovial tissue. In addition, rheologically improved synovial fluid in the arthritic joint is thought to result in decreased pain through a positive influence on sensory receptors and nociceptors within the joint.¹

Since the 1960's, when the concept of viscosupplementation was first described for joints, a number of viscosupplements have been developed and studied.^{1,2} Hyaluronic acid (hyaluronan) has been used to give these viscosupplements their viscoelastic attributes.

Synovial fluid is a major-molecule hyaluronic acid (molecular weight of 3.5 to 5 million).¹ It was therefore logical to choose hyaluronic acid to form the foundation of synthesized viscosupplementary products. The source for these viscosupplements has been umbilical cord or rooster comb. More recently, newer viscosupplements have been purified and derived from organisms.³ Many of these products have had molecular weights of approximately 1 to 2 million or less.²

Studies over the past two decades have suggested these products (called devices in Canada) are beneficial to osteoarthritic joints, though this beneficial result has not been universally noted.^{2,4} Sodium hyaluronate has been studied and has demonstrated benefit in osteoarthritic knee joints.^{2,5} In all of these studies, multiple weekly injections (usually three, but sometimes as many as five to 10 injections) are required to achieve benefit.

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To attempt to more closely simulate synovial fluid molecular weight, the cross linkage of hyaluronic acid has resulted in the development of Hylan G-F 20.¹ The molecular weight of this viscosupplement is 6 to 7 million. The addition of this fluid-gel viscosupplement to osteoarthritic synovial fluid brings the rheologic properties of synovial fluid nearer to normal.

Carefully performed studies with this cross-linked material have shown a benefit comparable to other forms of treatment for osteoarthritis (OA).^{6,7} Rheologic properties alone based upon molecular weight may not, however, account for the benefits derived by these viscosupplementary products.⁸

For all these viscosupplements, the device, once injected into the synovial joint, remains there for a relatively short period of time.⁵⁻⁷ The reason for this remains unclear.

Viscosupplementation in animal models of osteoarthritis has resulted in less damage to articular cartilage.⁹ *In vitro* chondrocyte studies have demonstrated the positive influence on hyaluronic acid viscosupplements on chondrocyte synthesis.¹⁰ Moreover, potential anti-inflammatory benefits have also been suggested by *in vitro* studies.^{11,12}

TREATMENT FOR OSTEOARTHRITIS

Having noted the potential benefits of this form of treatment for osteoarthritis, the following statements may be made and verified in the literature:

1. In about 50 to 75% of osteoarthritis patients in clinical studies, some benefit occurs compared to placebo or to nonsteroidal anti-inflammatory drugs (NSAIDs).^{5-7,13}
2. Most of these benefits are subjective and use visual analogue scales or surveys of the patients and/or the physicians to evaluate patients, though some objective physical examination findings are sometimes used.^{5,7}
3. The benefit seems to occur most often in patients with early to moderate osteoarthritic changes. In most studies, less benefit is seen in those with severe radiologic changes.^{6,14}
4. In patients with large synovial effusions, less benefit is derived (a dilutional effect is suggested to potentially hamper the attainment of adequate rheologic benefit).¹⁴

5. The efficacy response in some studies demonstrated equivalence, not superiority to, NSAIDs.^{5,7}
6. In a few studies, the response was equivalent to, but not better than, intra-articular corticosteroids.²
7. Though the onset of response for viscosupplements was slower than for intra-articular corticosteroids, the response to viscosupplementation was of longer duration in cited studies.²
8. A positive benefit (less pain, improved function) could, in some cases, last for months. Responses to as long as six months or more were seen in some studies (up to about 50% of the time).
9. Adverse effects consisted of local reactions in most cases (about 3% of patients). Most adverse reactions were mild, though occasionally, severe local flares could occur. Anaphylactoid reactions were extremely rare.^{5,7,14}
10. Local adverse reactions might occur, in part because of improper placement of the viscosupplement into tissues near the joint but not into the joint space itself.¹⁴
11. A series of injections are required for currently used viscosupplements.³⁻⁵
12. Repeated treatment may be successful in those who have responded initially. Moreover, even in those with local adverse reaction, if a beneficial result is seen with this series of injections, follow-up treatment with another series of injections may be similarly beneficial.¹⁴
13. In some cases, NSAIDs could be discontinued for periods of time.⁷

A few questions should be raised regarding synovial viscosupplementation examining the information gathered over the past 30 years, why does this form of therapy not relieve pain and improve function in a greater number of patients studied? When there is a benefit, what are the mechanisms that provide this benefit? Is articular cartilage metabolism actually improved when this form of therapy is utilized? Is there a role for viscosupplementation in OA?

The answer from the literature is clearly yes. What should be the place of viscosupplementation today, given the evidence? Should it be a first-line therapy given to all patients with osteoarthritis or should it be used selectively and as an adjunct in some patients

with OA? The following approach may be defended based upon the literature:

1. The physician should assess the osteoarthritic joint for a significant inflammatory component. If there is long-duration stiffness after immobility (> 30 minutes) and warmth, erythema and swelling (soft tissue and/or effusion), then the physician should consider an anti-inflammatory approach first. This would include the use of NSAIDs in appropriate anti-inflammatory doses (if there are no contraindications) and intra-articular corticosteroids (again, if there are no contraindications). The role of viscosupplementation as an adjunct to such an approach may be considered and should be further studied.

Is there a role for viscosupplementation in osteoarthritis? The answer from the literature is clearly yes. What should be the place of viscosupplementation today, given the evidence? Should it be a first-line therapy given to all patients with osteoarthritis or should it be used selectively and as an adjunct in some patients with osteoarthritis?

2. If there is an absence of inflammatory symptoms and signs, then an analgesic (*i.e.*, acetaminophen) in divided doses provides pain relief.¹⁵ Low-dose NSAIDs may be used as analgesics (if there are no contraindications). Viscosupplementation may be used as an adjunct for some of these patients if relief is suboptimal.
3. The degree of radiologic change should be evaluated. If it is mild to moderate, viscosupplementation is more likely to be successful than if the radiologic grade demonstrates severe damage.
4. The studies thus far confirm some benefit for the osteoarthritic knee and viscosupplementation should be confined to this site for the present. Further studies of hip and other joints should be completed with the same rigor as the knee studies before recommendations can be made for other osteoarthritic joints.

5. If NSAIDs are contraindicated where they would otherwise be required, the judicious use of intra-articular corticosteroids should be considered first. The presence of a large synovial effusion points to a significant inflammatory synovitis: anti-inflammatory therapy should be considered as the primary mode of treatment in such patients. The theoretical anti-inflammatory benefit of viscosupplements suggested in some *in vitro* studies might allow for this approach secondarily if intra-articular corticosteroids provide an inadequate response. There is a suggestion that aspiration of the joint should therefore be carried out to reduce the dilutional effect of the viscosupplement injected (theoretically improving the potential for benefit). Further studies should be carried out in this regard.

Other questions have been raised regarding viscosupplementation in OA. There is agreement that this form of therapy should be considered as an adjunct to treatment in OA.^{12,13} More studies are needed to determine

its potential for synergistic benefit subjectively and objectively.

The role for viscosupplementary devices to potentially deliver reparative biologics to articular tissues is intriguing.¹³ The theoretical benefit of having a viscosupplement closely matched in molecular weight to synovial fluid is suggested, yet recent studies demonstrate benefit from lower-molecular-weight viscosupplements.⁷

Further evaluation of the quality of response with better defined, objective, primary endpoints, perhaps including head-to-head studies of these viscosupplements may further clarify this dilemma.

Additional studies are required to more accurately demonstrate the mechanisms by which benefit is derived for patients with OA. Theoretical speculations should be supported by scientific evidence. The result may be a better understanding of the pathobiology of OA and the development of more effective treatment for these patients.

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