As orthopedic surgeons, we are constantly looking for the best surgical treatment option to apply for a given cartilage lesion based on the size, location and etiology of the defect as well as on the age of the patient. As doctors, however, we must also be cognizant of the nonoperative options and alternatives to surgery that can be used alone, or in combination with surgery. We continue to be faced with patient pressure to look for alternatives to surgery.

There is, for example, a growing interest in using nutritional supplements that are administered orally or injected into the joint. There is a huge market supporting them. Yet many nutritional supplements are not reimbursed by insurance, and it is important that the money spent by the patient is worthwhile. When considering the efficacy of vitamins, minerals or antioxidants for preventing or treating cartilage problems including arthritis, (continued on page 7)

President's Message
Barry R. Tietjens, FRACS, New Zealand, 2001-2003 ISAKOS President

Today in Auckland the sun is shining and the sky is clear blue. On the water, yachts from around the world are competing to determine who will challenge New Zealand for the America's Cup in February. We are very fortunate to live in a beautiful, safe country.

In September we were deeply saddened to learn of the tragic death of Sandy Kirkley in a small plane crash. Sandy had been an inspirational leader of the ISAKOS Scientific Committee. In her flourishing career, she had made friends all around the world where everyone was impressed by her commitment to scientific excellence. I was honored that Nicola Maffulli agreed to assume leadership of the Scientific Committee. Sandy’s legacy will be the Scientific Committee’s monograph titled Methodology for Clinical Trials in Orthopaedic Surgery, which is due for completion before the ISAKOS Congress in Auckland. At the congress, Peter Fowler will deliver the Sandy Kirkley Memorial Lecture.

In November I traveled to Florence for the ISAKOS Knee Committee Workshop on PCL Reconstruction. This is the second workshop led by Paolo Aglietti, Chairman of the ISAKOS Knee Committee. Once again, the meeting was an outstanding success with contributions from 21 surgeons and one scientist, representing 13 countries. The important issues were intensely debated and consensus was reached in the congenial spirit of international cooperation that is the hallmark of our society. A book and CD-ROM will be produced from the workshop, containing all the workshop presentations together with consensus statements from the chairman of each workshop session. These books and CDs will be presented to everyone who attends the ISAKOS Congress in Auckland.

The continuing work of the Arthroscopy, Orthopaedic Sports Medicine and Upper Extremity committees will also be presented in Auckland. All arrangements are in place for the congress. At that time we will welcome the first ISAKOS Exchange Traveling Fellows representing SLARD, our South American regional partner. The South American group will be making a three-week visit to the Asia Pacific region to coincide with the ISAKOS Congress. John Bartlett and his program committee have constructed an outstanding scientific program for the congress with a truly international faculty, bringing us the best of current knowledge.

I look forward to seeing you all in Auckland in March.
Announcements From the ISAKOS Office

Review the List of Presidents
The ISAKOS Web site contains a comprehensive list of international, regional and national societies that relate to ISAKOS specialties. Please help us to keep the societies’ contact information and presidents listings current. Many people use it as a resource. The office depends on your help to keep the information accurate and timely. Simply e-mail the ISAKOS office with any changes.

Pay Your Dues Today Online
ISAKOS has a new online dues payment system that is fast, easy and secure. Visit the ISAKOS Web site today to review your member balance and ensure that you continue to receive the journal in 2003. Remember, you must be current with your 2003 ISAKOS dues if you wish to register as an ISAKOS Member at the congress.

Include Your Educational CD-ROM in the ISAKOS Multimedia Center
ISAKOS is establishing an educational library of instructional CD-ROMs and DVDs for use by its members. We would like to include your CD-ROM or DVD in the ISAKOS Multimedia Center at the ISAKOS Congress in Auckland. Please send your CDs to the ISAKOS office by February 15 if you would like your media included in the Auckland catalogue.

Review the Bylaws
There are several proposed changes to the current ISAKOS bylaws, and they will be voted on at the first business meeting of the 2003 congress in Auckland. Visit the ISAKOS Web site today to review the changes prior to your vote.

ISAKOS Committees
If you are interested in becoming a member of an ISAKOS committee for the 2003-2005 term, please contact the ISAKOS office by e-mail at isakos@isakos.com or fax +1 (925) 314-7922. Please indicate in which committees you are interested. You must be an active member in good standing to become an ISAKOS committee member.

Associate Members
The Membership Committee will review all associate member applications for promotion to active status at the 2003 Congress in Auckland. If you are an associate member who wishes to be eligible for active status, you must have at least one sponsor recommendation on file. Please ensure your sponsor has submitted your recommendation.

ISAKOS Thanks 2003 Congress Sponsors
ISAKOS thanks the following companies for their generous donations to the ISAKOS Congress. Their sponsorships have made the congress more accessible and affordable to our attendees. It would be impossible to have an international congress without their support.

PLATINUM SPONSORS

Linvatec
Linvatec Corporation, a leading manufacturer of arthroscopic instrumentation, medical imaging, and power surgical equipment, offers a diverse line of products critical to the orthopaedic/arthroscopic surgeon.

GOLD SPONSORS

Smith & Nephew
Smith & Nephew, Inc., Endoscopy Division
A global leader within arthroscopy and an innovator in endoscopic surgery, Smith & Nephew, Endoscopy Division, designs, develops and manufactures endoscopic surgical instrumentation and techniques with the goal of reducing trauma and pain to the patient, reducing cost to the healthcare system, and providing better outcomes for surgeons.

SILVER SPONSORS

• Arthrex, Inc.
• Arthrotek
• Centerpulse
• Pharmacia/Pfizer
• Stryker Endoscopy
Pre-registration Deadline February 10
The deadline to pre-register for the congress is February 10, 2003. After February 10, you will be required to register on-site at the meeting in Auckland.

Simultaneous Interpretation to Spanish
Remember, all presentations held in the two concurrent general session rooms will be interpreted to Spanish, free of charge to all attendees.

Knot-Tying Manual Will Be Provided to All Congress Attendees
ISAKOS is proud to announce that it will be able to give every congress participant a knot-tying manual at the 2003 ISAKOS Congress in New Zealand. The booklet will be printed in color. All knots currently used in arthroscopic surgery will be covered.

We appreciate the cooperation and assistance of Mitek Worldwide, which has enabled us to produce this educational tool. We know how helpful a book like this can be for those just starting to perform arthroscopic procedures.

Special Congress Events

Welcome Reception at the Town Hall
This festive event will offer music, hors d’oeuvres and cocktails for all congress attendees. Attendance is included with the cost of registration. Dress is business casual, and guests are welcome. The Town Hall, built in 1911, is now home to both the New Zealand Symphony Orchestra and the Auckland Philharmonia.

Poster, New Member and Exhibit Reception
Join congress attendees and exhibitors as ISAKOS officially welcomes its newest members. This relaxed wine and cheese reception will be held in the foyers of the convention center, amidst the exhibits and electronic posters.

NEW! Free Lunchtime Workshops Will Offer Hands-on Education at Congress
ArthroCare, Bionx Implants, Inc., Centerpulse, Linvatec, Pharmacia/Pfizer, Smith & Nephew Endoscopy and Stryker Endoscopy will be offering lunchtime workshops and presentations to all ISAKOS attendees. Highlights include:

Arthroscopic Rotator Cuff Repair
James Esch, MD
Sponsored by Smith & Nephew Endoscopy
Attendees will be able to insert suture anchors arthroscopically into the humeral head of the shoulder model, pass suture through the rotator cuff of the shoulder model, and tie secure sliding knot arthroscopically in the shoulder model.

Clinical Experience and Surgical Technique in Rotator Cuff Fixation Using Bipolar Sports Surgery Devices
James Tasto, MD
Sponsored by Bionx
Attendees will hear a lecture about the clinical experience of Dr. Tasto, with the Bio Cuff Shoulder devices from Bionx Implants Inc. This lecture will include a demonstration of the technique as presented by Dr. Tasto.

Collagen Meniscus Implant - An Innovative Approach for Meniscus Regeneration
Rene Verdonk, MD; William Rodkey, DVM; J. Richard Steadman, MD; Paolo Bulgheroni, MD
Sponsored by Centerpulse
Attendees will study the treatment possibilities of irreparable meniscus injuries, as well as the concept and philosophy of collagensus implantation, US clinical results, selected Italian cases, and analysis of tissue regeneration.

Current Concepts in Meniscal Repair
Jens Buelows MD; Philippe Colombet MD
Sponsored by Smith & Nephew Endoscopy
Attendees will be able to discuss current options for meniscal repair including “all-inside” technique and perform a meniscal repair on sawbones model using the Fast-Fix® implant.

Live Surgical Demonstrations
ISAKOS is offering a series of live surgical demonstrations on cadavers, free to all attendees. All demonstrations will be interpreted to Spanish.

Monday, March 10
13:30-14:15
ACL Fixation
Don Johnson, MD, Canada
Sponsored by Linvatec

Tuesday, March 11
11:15-12:00
Arthroscopic Rotator Cuff Repair Including Use of Electroblade
James Esch, MD, USA
Sponsored by Smith & Nephew, Inc., Endoscopy Division

14:00-14:45
Shoulder Arthroscopy
Anthony Romeo, MD, USA
Sponsored by Arthrex

Wednesday, March 12
11:15-12:00
ACL Technique for Aggressive Rehabilitation Using DLSTG Graft and Patellar Tendon Demonstration
Stephen Howell, MD, USA, and Pier Paolo Mariani, MD, Italy
Sponsored by Arthrotek

13:30-14:15
Tibia & Femur Osteotomy
Giancarlo Puddu, MD, Italy
Sponsored by Arthrex

Thursday, March 13
11:15-12:00
Total Knee Replacement
Prof. Johan Bellemans, Belgium
Sponsored by Smith & Nephew Orthopaedics

13:30-14:15
Use of the ExoJet Fluidjet System for Contouring Articular Cartilage and Meniscal Tears. Comprehensive Arthroscopic Technique for Osteochondral Graft Transfer
Moises Cohen, MD, Brazil, and David Diduch, MD, USA
Sponsored by Mitek Worldwide
Innovative, Reproducible Approach to ACL Graft Tensioning
Don Johnson, MD
Sponsored by Linvatec
This hands-on workshop will allow the participants to:
• Learn this reproducible technique for ACL hamstring repair using the SE™ Graft Tensioning System.
• Gain an understanding of isometry and stress equalization of hamstring grafts.
• Practice tibial and femoral fixation with BioScrew® and XtraLok™ interference screws and the SE™ Graft Tensioning system.

Innovative Solutions in Shoulder Arthroscopy
Alex Castagna, MD; Stephen J. Snyder, MD
Sponsored by Linvatec
This hands-on workshop will allow the participants to:
• Become more proficient in arthroscopic knot tying techniques.
• Perform arthroscopic Bankart/SLAP repairs using Mini-Revo® and Ultrafix® Knotless Minimite® anchors.
• Perform arthroscopic rotator cuff repair using Super Revo®/UltraSorb™ and the Spectrum® suture passing system.

New Directions in Pain Management for Orthopaedic Surgery
Faculty To Be Announced
Sponsored by Pharmacia/Pfizer
The potential for coxibs to be used in the treatment of surgical pain will be explored fully by leading physicians during the Pharmacia/Pfizer-sponsored symposium to be held on Tuesday March 11, 18.00–19.30, at the Carlton Hotel, Auckland. The symposium will enable you to learn more about emerging trends in orthopaedic surgical pain management and provide you with the opportunity to engage with other specialists in discussion of this important topic.

A welcome dinner reception will be held at 17.30 and continue with coffee and desserts following the symposium.

New Frontiers for ACL Fixation
Lonnie E. Paulos, MD
Sponsored by Stryker Endoscopy
Attendees will be able to describe femoral fixation for hamstring ACL reconstruction, and discuss the advantages of absorbable ACL fixation.

PCL Reconstruction Techniques & Clinical Results
Moderator: David McGuire, MD; Faculty: Pascal S Christel, MD; Pier Paolo Mariani MD, PhD
Sponsored by Smith & Nephew Endoscopy
Attendees will be able to discuss technical aspects of PCL reconstruction procedures including approach, graft choice, fixation option and tunnel placement. They will also

Shoulder Instability Treatment: Use of Thermal Capsulorrhaphy as an Adjunct to Labral Repair
Moderator: Joe DeBeer, MD; Faculty: Anthony Miniaci, MD; Andrew Wallace, FRCS
Sponsored by Smith & Nephew Endoscopy
Attendees will be able to identify the correct indications for the use of thermal capsulorrhaphy in the shoulder. They will discuss the
treatment technique and how to avoid potential complications, as well as the rehabilitation protocol required to achieve good outcomes.

Techniques of Bionx, Bioabsorbable Sports and Trauma Fixation Devices in Knee
Gert Kristensen, MD
Sponsored by Bionx
Attendees will hear a lecture on the Contour Arrow, meniscus repair device and Smarth Nail, trauma and osteochondral fragments repair device from Bionx Implants Inc. This lecture will include a demonstration of the techniques as presented by Dr. Kristensen.

TOPAZ: Minimally Invasive RF Treatment of Tendinosis
James Tasto, MD
Sponsored by ArthroCare
Are you satisfied with your current treatment options for tendinosis? If not, please come by our workshop to learn more about TOPAZ, a new, minimally invasive, radiofrequency (RF) treatment for chronic tendinosis. James P. Tasto, MD, from the University of California San Diego, will present his research and clinical experience with TOPAZ.

Free Instructional Course Lectures in Auckland

**Tuesday, March 11, 2003, 07:00-08:30**
ICL #01: Basic Science and Clinical Use of Cell Therapy in Articular Cartilage Repair
Chair: Lars Peterson, MD
Faculty: Scott Gillaghy, MD, Bert Mandelbaum, MD, Anders Lindahl, Wayne Genoff and Carl Winialski

ICL #02: Computers in Clinical Practice
Chair: Don Johnson, MD
Faculty: Vladimir Bobic, MD, Nicola Mathalli, MD, MS, PhD, FRCR and Ronald Selby, MD

ICL #03: Issues in ACL Surgery
Chair: Peter Fowler, MD, FRCR
Faculty: Charles Brown, Jr., MD, Bart Klos and Philippe Negret, MD

ICL #04: Current Concepts in Posterolateral Instability of the Knee
Chair: Rolf F. Lav Paule, MD
Faculty: Lars Engbreten, MD, PhD, Steinar Johansen, MD and Fred Wentorf, MS

ICL #05: Clavicle Fractures and Dislocations
Chair: Ulrich Bossh, MD
Faculty: Eugene Wolf, MD, Stephen Snyder, MD and Reinhard Fremmery

**Wednesday, March 12, 2003, 07:00-08:30**
ICL #06: Sports Specific Outcomes in ACL Surgery
Chair: Joane Harlow, MD
Faculty: Suzanne Werner, Stephen Howell, Lars Engbreten and Jean-Claude Parmet

ICL #07: Emerging Technologies in Knee Surgery
Chair: Masahiro Karosaka, MD
ISAKOS Initiative Will Increase Member Services in Education

Barry R. Tietjens, FRACS, New Zealand, 2001-2003 ISAKOS President; Per A. Renström, MD, PhD, Sweden, 2001-2003 ISAKOS 1st Vice-President; John A. Bergfeld, MD, USA, 2001-2003 ISAKOS 2nd Vice President

As described in the Summer 2002 newsletter, ISAKOS is embarking on an ambitious program to increase member services in education. Bringing together suppliers, local organizations and our members, ISAKOS will create an international framework for the exchange and dissemination of information in arthroscopy, knee surgery and orthopaedic sports medicine that will benefit each member, partner and patient.

Over the next five years, ISAKOS will focus on:
• Hosting regional hands-on workshops and pertinent lectures in arthroscopy, knee surgery and orthopaedic sports medicine;
• Effectively utilizing online technology to offer members continuing education opportunities, including CME-accredited courses;
• Initiating special committee projects and traveling fellowships, and
• Bringing together the leaders of regional societies to collaborate in ways that enhance the overall profession while providing the best benefits to members in all parts of the world.

Since ISAKOS was founded in 1995 from the merger of the International Arthroscopy Association and the International Society of the Knee, our membership has grown 60 per-

Spotlight on Teaching Centers:
Sports Traumatology Center Koelliker – University of Turin • Torino, Italy

Our teaching center holds courses in arthroscopic surgery of the knee, including:
• ACL and PCL reconstruction;
• Medial and lateral (mini-invasive ligamentous plasty);
• Meniscal surgery (out-in and in-out techniques);
• Patellar surgery (mini-invasive proximal and distal realignment);
• Osteotomies around the knee (femoral and tibial); and
• Knee replacements.

We also offer courses in:
• Arthroscopic surgery of the ankle;
• Mini-invasive ligamentous plasty;
• Sports traumatology;
• Elbow and ankle overuse tendinopathies;
• Courses on one-day surgery (knee, shoulder and ankle); and
• Post-surgical rehabilitation.

The center is connected to the Faculty of Motor Sciences, and the Research Center of Sports Medicine of the University of Turin. Surgery takes place every Tuesday, Wednesday, Thursday and Friday morning in the Sports Traumatology Center located in the Koelliker Hospital.

Last year the Koelliker Hospital was ranked the best in northwestern Italy. Applicants may observe and, if allowed, scrub in. Applicants may follow each case before and after surgery, and during rehabilitation.

Applicants may review the documentation of every surgery and discuss it freely with the surgeon. They may also attend the annual International Congress held by the center. Applicants may be actively involved with research (prospective randomized studies). Low-cost accommodation near the center is available. In some special cases, no-cost accommodation may be available.

For more information, contact: Gian Luigi Canata, MD Corso Duca degli Abruzzi 30, 10129 Torino, ITALY Tel: +39 011 581 756 Fax: +39 011 580 5014 E-mail: canata@libero.it
cent, our biennial congress has been hailed by participants as a pre-eminent conference not to be missed, and our committees have tackled issues of international importance, including plans under way for developing international clinical standards, a complications registry, and an international dictionary of related terms.  

We have an accomplished record to build upon, and we have an exciting task before us.  

By providing high-quality opportunities to continually develop skills and foster the exchange of information internationally, ISAKOS will help propel our specialties in the global orthopaedic community toward greater achievement and even greater potential.  

Thanks to the interest of several major international firms, we are already off to a great start! To be successful we will need the support of all our members and industry friends. We invite you to learn more about this special initiative at the ISAKOS Fourth Biennial Congress in Auckland March 10-14, 2003, and join us in support of this exciting international effort.  

We look forward to seeing you there!

**Editor's Note**  
(continued from page 1)  

there is a paucity of information in the scientific literature compared with traditional medicine. We are constantly searching for more information to provide our patients, ourselves and our families. In light of these realities, I am grateful to Vladimir Bobic from Great Britain, a renowned cartilage expert who submitted an excellent summary on viscosupplementation for this newsletter  

Over the course of the past two years, I have been using intraarticular injections of hyaluronic acid for severe osteoarthritic knees where no other treatment can be applied other than the inevitable total knee. I also started to give some of the orally administered products, including monosaccharides and heteropolysaccharides (such as glucosamine, chondroitin sulfate and Hyaluronic acid), to my patients after mosaicplasty. Lars Peterson tells me that he is planning to do a study on glucosamine after ACI.  

But which drug to select? It is appropriate to look critically into the marketplace to enhance our treatment armament in a field that is full of veracity and benefit. We must carefully analyze the most beneficial approach to caring for cartilage defects. Cartilage repair alone may not be sufficient, osteotomies may be needed, and nutraceuticals or visco-supplementation may even be utilized.  

We shall carry on with this discussion in the next newsletter.

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**IN MEMORIAM**  

Alexandra (Sandy) Kirkley, MD, FRCS(C), MSc  
1962-2002

Peter J. Fowler, MD, Canada, 1995-1997 ISAKOS Past President

All of you will know that Sandy Kirkley and her husband Michael were killed in a small plane crash early in September 2002. This loss has been deeply felt not just here at our clinic and our university, but throughout the orthopaedic world. Most of you in ISAKOS will have met Sandy and witnessed first-hand her intelligence, integrity and commitment to orthopaedics and orthopaedic research. Many of you will, like us, have been privileged to share in the extraordinary energy and enthusiasm with which she lived her life.

The tributes to Sandy have been fitting, and the countless messages of condolence we have received from you in the past three months have been heartfelt. On behalf of all of us here, I would like to thank you, for these have given us, and her family, great comfort during a truly terrible time.

ISAKOS is an organization Sandy believed in, supported and wanted to improve. She had yet to miss a congress. Since 1997 she had been a member of the Documentation Committee as well as Co-Chair and Head of the Clinical Trials Committee. There is no question that this is the area in which she would make her most valuable contributions. At the 2001 Congress in Montreux, she took on the symposium “Designing Outcome Studies.” As she was preparing for this and organizing her faculty, she asked me to participate along with herself and Bob Marx. I was flattered but confessed my fear that I would be of little use to her. My knowledge of this subject was embarrassingly poor. “Don’t worry,” she told me, “I’ll tell you what to say. I just want someone with white hair to say it.” It is no surprise that it turned out to be a very successful symposium.

In the past year she made it a personal mandate to work toward improving the scientific validity of research done by orthopaedic surgeons. To this end she spearheaded a collaborative effort among members of the ISAKOS Scientific Committee to create a reference manual on the topics of outcome tools and how to design, implement and run orthopaedic randomized clinical trials. Individual members would focus on his or her area of expertise, and the combined manuscripts would become a comprehensive and valuable resource. Nicola Maffulli and the Scientific Committee are continuing this work. We wish them success and look forward to a fine finished product.

I am pleased to tell you that Sandy and Michael’s young boys, Colin and Connor are both doing well in the care of their guardian family. They are recovering satisfactorily from their injuries, have returned to school and are adjusting to their new home. In our day-to-day lives, Sandy’s physical absence is a harsh reality. Our clinic has returned to what can be called “normal.” What we at first thought would be impossible to handle is being dealt with because Sandy’s indomitable spirit inspires and her great vision endures. We all know that ultimately, good patient care is at stake. And so we will carry on with her work.
The Indian Arthroscopy Society, founded in 1983, organized its official annual meeting in Coimbatore, India, on October 9-10, 2002. The society had already organized several meetings in the past. I had previously visited Coimbatore in 1995, when a small congress was organized by Dr. David Rajan. This year's congress took place in the GKNM Hospital, which boasts a nicely built and well-equipped convention room. One hundred and fifty orthopaedic surgeons attended the congress. The live surgery was performed in modern, air-conditioned theatres, with all the arthroscopic tools available to perform arthroscopic shoulder and elbow surgery.

This year's congress was also organized by Dr. Rajan, with cooperation from Dr. Joshi from Mumbai and Dr. Antao from Mumbai. As education chairman, I was invited and honored to officially open the congress on behalf of ISAKOS.

About 10 shoulder and elbow procedures were performed with a good connection from the theatre to the convention room. There were lively discussions between the surgeons, which followed lectures given by international and national faculty. There was ample exposure to arthroscopic knee surgery and ACL reconstruction, as well as a starting interest in shoulder and elbow procedures. The operative procedures I performed were collected by Dr. Rajan and his team and were all interesting cases of shoulder instability.

During the nightly social events, the hosts showed a great hospitality, providing some very interesting cultural activities. I witnessed a great interest in our Indian colleagues for the advancements in arthroscopic surgery. This annual meeting, which will undoubtedly be followed by other meetings in the future, contributed to the propagation of arthroscopic surgery on the Indian sub-continent.

The 6th Turkish Sports Traumatology, Arthroscopy and Knee Surgery Congress was a meeting of the Turkish Society for Arthroscopy, Knee Surgery and Orthopaedic Sport Trauma. The congress takes place once every two years and rotates between the three chapters: North in Istanbul, Central in Ankara and South in Antalya.

The meeting in Antalya addressed all fields of sports trauma and arthroscopy. Led by many international guests and a vast amount of research originating in Turkey, it gave an excellent opportunity to discuss, argue and often disagree on many controversial issues.

The congress, organized by Prof. Aydin, Prof. Pinar and Prof. Doral, along with many others, was outstanding. It was superiorly organized with an excellent scientific program and superior translation and technical back-up.

Turkey is slowly advancing to a leading position in the field of arthroscopic surgery and sports trauma.
Viscosupplementation for the Osteoarthritis of the Knee
Vladimir Bobic, MD, FRCSEd, United Kingdom, 2001-2003 Communications Committee

Osteoarthritis (OA) is a major cause of disability. Patients with OA have pain that typically worsens with weight-bearing and activity and improves with rest. Unlike the rheumatoid arthritis (RA) inflammation is usually mild and localized in the affected joint. Although the etiology of OA remains unknown, biomechanical stresses and biochemical changes in the articular cartilage, subchondral bone and synovial membrane, and genetic factors, are all important in its pathogenesis. In joints affected by OA, the synovial fluid’s capacity to lubricate and to absorb impact are typically reduced. These changes are partly due to a reduction in the size and concentration of hyaluronic acid (hyaluronan) molecules naturally present in synovial fluid. Medical management of OA of the knee is effective for many patients, but significant morbidity is common for those using non-steroidal anti-inflammatory medication (NSAIDs). Gastrointestinal toxicity has been a major problem for many patients on NSAIDs, especially for geriatric patients who need to take them for extended periods to treat chronic conditions. Although only a minority of patients using NSAIDs appear to develop serious GI problems, because of widespread usage it is estimated that there are at least 16,500 NSAID-related deaths each year in the United States among patients with osteo- and rheumatoid arthritis. Another 76,000 end up in the hospital. The economic burden of NSAID-associated gastrointestinal disorders is enormous, with an estimated cost of $500 million. Surgical treatment of the knee OA is effective but it is not appropriate for all stages of the disease or for all patients. It is also costly and not without risks. With increased understanding of the pathogenesis of OA, new therapies are being developed, one of which is viscosupplementation with hyaluronic acid. A new approach in the management of OA of the knee is to inject hyaluronan or derivatives of this molecule (hylans) into the joint. In recent years, the concept of viscosupplementation has gained widespread acceptance as a new treatment for the management of OA of the knee. The safety of this treatment has been well documented in numerous clinical trials, but controversy persists regarding efficacy and cost-benefit concerns.1

Introduction
The use of viscosupplementation is based on observation that there is a decrease in viscosity and elasticity of the synovial fluid in osteoarthritis and that the native hyaluronic acid in osteoarthritic knees has a lower molecular weight than that found in normal healthy knees. Replenishing the hyaluronic acid component of normal synovial fluid may play a role in supplementing the elastic and viscous properties of synovial fluid, which may help relieve the signs and symptoms related to osteoarthritis and improve function. In vitro studies of human synoviocytes from osteoarthritic joints have revealed that exogenous hyaluronic acid stimulates de novo synthesis of hyaluronic acid, inhibits release of arachidonic acid, and inhibits interleukin-1 induced prostaglandin E2 synthesis by human synoviocytes.4

Hyaluronic acid (HA) is a glycosaminoglycan that is composed of glucuronic acid and N-acetylglicosamine. It differs from other glycosaminoglycans in that it is unsulfated, also, it does not bind covalently with proteins to form proteoglycan monomers, serving instead as the backbone of proteoglycan aggregates. It is the only glycosaminoglycan that is not limited to animal tissues, being found also in bacteria. It serves as a lubricant and shock absorber in the synovial fluid, and is found in the vitreous humor of the eye. HA is not well absorbed orally, but has been widely used intraarticularly in the treatment of OA in animals and, more recently, in humans. HA is well tolerated with no demonstrable toxicity and few side effects. Because it is injected directly into the joint, its onset of action is rapid. Conversely, its route of administration does limit its therapeutic applications to some degree, and high cost is also a factor.1

Biochemistry
Glycosaminoglycans (GAGs) are carbohydrate polymers that are among the most abundant components of the ground substance of connective tissue throughout the body. GAG molecules are long, homogenous, unbranched polysaccharide chains that are formed by repeating disaccharide subunits. Hyaluronate is the most abundant GAG in synovial fluid. It is produced and secreted by synoviocytes. Hyaluronate is also prevalent in the extracellular matrix of articular cartilage, where it is produced by chondrocytes and where it forms the foundation for proteoglycan aggregates. The recurring disaccharide subunit of hyaluronate consists of N-acetylglucosamine and glucuronate. These sugar subunits are joined by glycosidic bonds. These bonds are extremely flexible in solution; therefore, hyaluronate has no defined tertiary structure. The carboxylate group on the glucuronate sugar is negatively charged. Thus, hyaluronate is a polyanion chain. The recurring electronegative charges along the chain repel one another and attract water molecules. Hence, hyaluronate has been likened to a “molecular sponge.” These properties account for the viscosity and elasticity of the hyaluronate macromolecule.

Pharmacology of Viscosupplementation
The notion of supplementing osteoarthritic synovial fluid with exogenous hyaluronate stems from the fact that the molecular weight and concentration of hyaluronate in osteoarthritic synovial fluid are reduced. This phenomenon diminishes the viscosity of osteoarthritic synovial fluid. Appropriate synovial fluid viscosity is believed to be critical for maintaining normal joint lubrication and is also believed to have chondroprotective effects. It is hypothesized that the reduced concentration and decreased molecular weight of hyaluronate in osteoarthritic synovial fluid renders articular cartilage more vulnerable to mechanical and enzymatic injury.

The goal of viscosupplementation is to increase the molecular weight and concentration of hyaluronate in articular joints so that the intra-articular milieu more closely resembles that of healthy synovial fluid. The mechanism of action by which viscosupplementation alleviates arthritic knee pain is a subject of debate. It has been proposed that exogenous viscoelastic sub-
stances act biomechanically by providing a “cushioning” effect. However, some authors have suggested that viscosupplements are eliminated from the knee too rapidly to exert a significant and lasting biomechanical effect. Indeed, the half-life of hyaluronate in sheep is less than 24 hours. In vitro research suggests that exogenous hyaluronate may stimulate endogenous production of additional hyaluronate by human synoviocytes. This could lead to more durable biomechanical consequences. Other studies suggest that hyaluronate supplementation has a direct anti-inflammatory effect on synoviocytes by inhibiting arachidonic acid release or by blocking prostaglandin-E2 production. It has also been suggested that exogenous hyaluronate inhibits damage mediated by oxygen free radicals and phagocytosis. Research has also found that hyaluronate may exert a direct analgesic effect on articular nociceptors. Possible mechanisms by which HA may act therapeutically include providing additional lubrication of the synovial membrane, and controlling permeability of the synovial membrane, thereby controlling effusions. Other possible, though less certain, mechanisms include: promotion of cartilage matrix synthesis and rearrangement of proteoglycans. One manufacturer has cross-linked hyaluronate chains in an effort to further enhance the molecular weight (and, hence, the viscoelasticity) of its product, Hylan G-F 20 (Synvisc™). A synthetic hyaluronic acid Arthrease™ is not cross-linked, but does have a high molecular weight. Arthrease™ has to be stored within a controlled temperature range of 2-8°C. It contains no animal protein and no residual cross linking reagents. Several studies have suggested that viscosupplements with higher molecular weights have greater therapeutic efficacy.6,7

Anti-inflammatory Effect
Hyaluronic acid has both in vivo and in vitro effects on leukocyte function. These include inhibition of phagocytosis, adherence and mitogen-induced stimulation. These properties are dependent on the molecular size of hyaluronic acid. Intra-articular administration of hyaluronic acid reduces levels of inflammatory mediators, including prostaglandin and cyclic adenosine monophosphate, in the synovial fluid of patients with arthritis.3

Analgesic Activity
It seems that intra-articular hyaluronic acid modulates pain perception directly through inhibition of nociceptors or indirectly through binding of substance P - a small peptide involved in the transmission of pain signals.3

Chondroprotective Potential
There are some data from human and animal studies to suggest that viscosupplementation could have a chondroprotective effect. Llistrat et al suggest that repeated intra-articular injections of hyaluronan might delay the structural progression of osteoarthritis. However, the chondroprotective effect of hyaluronic acid remains unproved. More research is needed to evaluate whether or not viscosupplementation has disease-altering properties in addition to its apparent palliative characteristics.3,4

Clinical Effectiveness
Viscosupplementation is a proven adjunct to the treatment armamentarium of general practitioners and surgeons. A number of recent clinical trials have evaluated the efficacy and safety of intra-articular hyaluronic acid injections.4-9,30,31,32,33,34,13,15 The reports of these studies were among those presented to the Food and Drug Administration (FDA) in the course of the process that resulted in the release of this treatment modality. The American College of Rheumatology has included viscosupplementation in the treatment algorithm for osteoarthritis of the knee.4,5

VISCOSUPPLEMENTS

<table>
<thead>
<tr>
<th>Substance</th>
<th>Molecular Weight (daltons)</th>
<th>Treatment</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronate (Hyalgan™, Sanofi-Synthelabo)</td>
<td>500,000 to 730,000</td>
<td>1 injection per week for 5 weeks</td>
<td>purified from chicken combs</td>
</tr>
<tr>
<td>Hylan G-F 20 (Synvisc™, Genzyme Biosurgery)</td>
<td>6 million</td>
<td>1 injection per week for 3 weeks</td>
<td>purified from chicken combs</td>
</tr>
<tr>
<td>A synthetic hyaluronic acid (Arthrease™, DePuy Ltd, UK)</td>
<td>similar to healthy synovial fluid</td>
<td>1 injection per week for 3 weeks</td>
<td>bio-synthetic product</td>
</tr>
<tr>
<td>Hyaluronate in healthy synovial fluid</td>
<td>4 million to 6 million</td>
<td>-</td>
<td>natural</td>
</tr>
<tr>
<td>Hyaluronate in osteoarthritic synovial fluid</td>
<td>1 million to 4 million</td>
<td>-</td>
<td>natural</td>
</tr>
</tbody>
</table>

Cost-Effectiveness
In clinical trials of intraarticular hyaluronan preparations, pain relief among those who completed the study was significantly greater than that seen after intraarticular injection of placebo, and comparable with that seen with oral NSAIDs. In addition, pain relief among those who completed the study was comparable with greater than that with intraarticular glucocorticoids. Although pain relief is achieved more slowly with hyaluronan injections than with intraarticular glucocorticoid injections, the effect may last considerably longer with hyaluronan injections.16

The price for the course of HA ranges from approx. £200 to £300 in the UK. In our own experience on 104 patients, in Liverpool and Chester (with Hyalgan™, Synvisc™, Orthovisc™ and Arthrease™), from 1999 to 2002, the average duration of pain relief was seven months, but approximately 10 percent of patients did not experience any significant pain relief. We did not observe any significant complications. The only reported adverse effects were injection site pain in five patients (lasting less than 24 hours), and exacerbated knee effusion in two patients.
Safety

The risk of introducing infection into an OA joint is extremely low if standard aseptic technique is used. The lack of systemic side effects make the use of viscosupplementation an appealing option for the management of the knee OA. Extensive safety and toxicity tests were performed on Synvisc™ before the first clinical trials. Preclinical studies showed that Synvisc™ is nonantigenic, nontoxic, noninflammatory, and does not elicit foreign body reactions. Hyaluronan, from which hylan is derived, has been safely used in ophthalmic and orthopedic applications in millions of patients. There have been no systemic side effects attributed to Synvisc. No cases of anaphylaxis or anaphylactoid reactions have been reported in connection with Synvisc™ treatment. However, anaphylactic-like reactions have been reported following intra-articular Hylan™ injections.

Unwanted Effects

In clinical trials, transient redness, local pain, warmth, and effusion, usually lasting up to three to four days, may occur. Occasionally, severe synovitis may occur requiring treatment with intra-articular corticosteroids.

Precautions

Patients should consult their doctor or surgeon if they have a history of hypersensitivities to hyaluronan preparations or are allergic to avian proteins, feathers and egg products. Intra-articular viscosupplements should not be given to patients with an infection or skin disease around the injection site, and should not be used if venous or lymphatic stasis is present in the leg, or if the joint is severely inflamed.

Market Analysis

The reimbursement of hyaluronic acid therapy varies greatly from market to market, particularly in Europe, and has become more important in some of these markets than efficacy or product reputation. Despite claims and reasonable clinical evidence from manufacturers of efficacy and specific product advantages, many end-users remain sceptical that hyaluronic acid viscosupplementation is truly an effective treatment for osteoarthritis of the knee. Therefore companies must increase physician and surgeon confidence through detailed clinical studies specifically designed to address these concerns.

The US will become the largest market for HA manufacturers and distributors, valued at $235 million in 2001, despite per capita usage of only 8.5 percent of that seen in Austria. The Austrian market is growing at a very slow pace, because of extremely high per capita usage. In contrast, the UK market is growing at a higher rate, but surgeon and GP scepticism, infrastructure problems, and lack of funds interferes with wider acceptance of viscosupplement therapy. In the UK there are additional difficulties with “evidence-based-medicine” approach of some NHS Trusts, which are unnecessarily restrictive, and in reality based on rationing policies. At the same time most orthopaedic surgeons recommend and use a wide range of expensive oral NSAIDs, a combination of intra-articular steroids and local anaesthetic injections, and arthroscopic debridements and washouts, without any restrictions.

As evident from the table below, the $563.9 million global market for hyaluronic acid is dominated by Japan and the US, with the European market accounting for a com-

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Design</th>
<th>Clinical Assessment Parameters</th>
<th>Conclusion</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listrat et al., 1997</td>
<td>3 injections of Hyalgan, every 3 months, for a year</td>
<td>Randomised, prospective</td>
<td>VAS (pain), Lequesne’s index (functional impairment), AIMS2 (quality of life)</td>
<td>This study suggests that repeated injections of hyaluronan might delay structural progression of the disease.</td>
<td>Industry-sponsored study. Small sample size</td>
</tr>
<tr>
<td>Adams et al., 1995</td>
<td>Hylan G-F 20 vs continuous NSAIDs</td>
<td>Randomised, single-blind, prospective, multicenter</td>
<td>VAS (pain)</td>
<td>Hylgan equivalent to continuous NSAIDs at 12-week follow-up</td>
<td>Industry-sponsored study</td>
</tr>
<tr>
<td>Wobig et al., 1999</td>
<td>Hylan G-F 20 vs a low molecular weight hyaluronate</td>
<td>Randomised, double-blind, prospective, multicenter</td>
<td>VAS (pain)</td>
<td>Hylan G-F 20 significantly better than low molecular weight hyaluronate at 12 week follow-up</td>
<td>Industry-sponsored study</td>
</tr>
<tr>
<td>Bellamy et al., 2001</td>
<td>Appropriate Care (according to ACR guidelines) with or without hylan G-F 20 injections</td>
<td>Randomised, prospective, multicenter</td>
<td>WOMAC, and SF-36</td>
<td>Results provide strong evidence for adoption of treatment with hylan G-F 20 in patients with knee OA. Good value for money.</td>
<td>Industry-sponsored study</td>
</tr>
</tbody>
</table>
paratively small level of sales. While Japan accounted for 47 percent of the global market value in 2001, nearly 86 percent of the total number of HA injections were administered in Japan. Low prices in Japan, and high prices in US, account for the discrepancy between comparative market values and comparative market volumes.

In France, the product is only reimbursed at 50 percent of the price, with only one product reimbursed in 2001. In Spain, the use of hyaluronic acid is very low, due to lack of reimbursement. In Italy, the market is fairly mature, with hyaluronic acid viscosupplementation first utilized in 1987 when Fidia launched Hyalgan to the market. Fidia’s product continues to dominate the market, which reached 345,000 injections in 2001. The largest HA market in Europe is Germany. The German HA market continues to exhibit impressive growth despite a relatively high market volume, forecasted to approach one million units sold in 2002. The young US market remains the fastest growing market, and in 2002 will become the highest value HA market in the world. Only three products currently competing on the US market are contributing to increased awareness and acceptance of hyaluronic acid among end-users and patients.

Conclusion

The economic costs of OA of the knee are enormous. If viscosupplementation does indeed reduce and defer the need for surgical procedures like arthroscopic knee washouts and debridements, and total knee replacements, the cost savings will be considerable. Even more important will be the diminution of the risks associated with anaesthetic and surgical procedures. However, three or five weekly injections are quite awkward for most clinicians and patients. One single injection, which lasts long enough, would be much more useful.

There is no doubt that viscosupplementation represents valuable addition to current treatments for osteoarthritis and an alternative treatment when other forms of medical treatment are contraindicated or have failed.

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A complete list of references can be found online at www.isakos.com/innovations/index.html.

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WINTER 2003
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