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THE IOWA ORTHOPAEDIC JOURNAL

VOLUME 20, 2000

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2000 • Volume 20

INSTRUCTIONS TO AUTHORS

Any article relevant to orthopaedic surgery, orthopaedic science or the teaching of either will be considered by *The Iowa Orthopaedic Journal* for publication. Articles will be enthusiastically received from alumni, visitors to the department, members of the Iowa Orthopaedic Society, residents and friends of The University of Iowa Department of Orthopaedics. The journal is published annually in May or June. The deadline for receipt of articles for the 2001 journal is February 1, 2001.

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1. The **original manuscript complete with illustrations**. The corresponding author must be clearly identified with address and telephone number. Manuscripts of accepted articles will not be returned.
2. A **bibliography**, alphabetical and double-spaced, or references made in text only. Refer to bibliographies in *The Journal of Bone and Joint Surgery* and follow the style exactly.
3. **Legends** for all illustrations submitted, listed in order and typed double-spaced.
4. **Illustrations**
   a. *Black-and-white glossy prints* of photographs. Give *magnification* of photographs.
   b. *Original* drawings or charts.
   c. Color illustrations cannot be used unless, in the opinion of the journal, they convey information not available in a black-and-white print. If color is desired, please send both color and black-and-white prints.

Preparation of manuscript: Manuscripts must be typewritten, double-spaced with wide margins. Write out numbers under 10 except percentages, degrees, or numbers expressed in decimals. A direct quotation should include the exact page number on which it appeared in the book or article. All measurements should be given in SI metric units. In reporting results of surgery, only in rare instances can cases with fewer than two years' follow-up be accepted.

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EDITORS' NOTE

The University of Iowa
Department of Orthopaedics

It is with great pride that we are able to bring you the 2000 edition of the *The Iowa Orthopaedic Journal*. This year's edition marks the twentieth anniversary of the IOJ's existence. We are proud to carry on this rich tradition that reflects the hard work and dedication of our faculty, residents, alumni and other contributors. With each passing year, the pressures and time constraints placed upon us make devoting time to writing and research even more difficult. As such, we are extremely grateful for the contributions put forth by the authors represented in this issue.

The past year has been an exciting time in our department. The first biennial Reginald R. Cooper Orthopaedic Leadership Conference afforded us the opportunity to appropriately honor our retiring chairman. The meeting featured lectures by several respected leaders in the world of orthopaedics, several of which have been included in this year's journal. We hope you find them both informative and thought-provoking. As well, we entered a new era of leadership in The University of Iowa Department of Orthopaedics, as Dr. Joseph A. Buckwalter became the department's fourth chairman on July 1, 1999. Dr. Buckwalter's vision and guidance promise to maintain and further develop Iowa's strong orthopaedic tradition.

We are also excited to be bringing this year's edition into the information age. As you are probably aware, many of the traditional print journals have become available via electronic media. In joining this growing trend, we will be making this issue available on the internet. By accessing our departmental web page, interested readers will be able to browse the IOJ in full text form. We hope you find this useful and would appreciate your feedback on this new endeavor.

We have elected to dedicate the journal to Dr. David Murray, chairman of the Department of Orthopaedics at SUNY-Syracuse. An alumnus of The University of Iowa, Dr. Murray is a tremendous example of the many Iowa alumni who have made an impact on orthopaedics at both the local, national and international level after training in Iowa City. We are happy to feature him in this year's issue.

Finally, we would like to thank the efforts of the many people who have made the twentieth edition of the IOJ possible. Our faculty advisors, Drs. Buckwalter and Callaghan, have given us tremendous support and direction. In addition, we thank Mr. Paul Etre and Ms. Kay Redlinger for their administrative assistance, Ms. Laura Cole for her exemplary secretarial skills, and Ms. Diane Thomas of The University of Iowa Printing Department for her help in presenting this publication in a timely fashion.

We hope you enjoy this year's edition, and we welcome your comments and criticism.

Gregory N. Lervick, M.D.
José Morcuende, M.D., Ph.D.
Peter D. Pardubsky, M.D.

BONFIGLIO EDUCATIONAL ENDOWMENT FUND

In honor of Dr. Michael Bonfiglio's distinguished career, the University of Iowa Orthopaedic Department initiated a campaign for the Bonfiglio Orthopaedic Education Endowment in 1994. This serves as permanent recognition of Dr. B.'s commitment to the department and provides a variety of educational materials and activities for the fellows, residents and students. The new department Education Center was dedicated to Dr. Bonfiglio in September 1995 at the Iowa Orthopaedic Alumni Meeting. It includes a collection of microscopic slides and imaging studies, computers, educational computer software and literature-search capabilities, audiovisual equipment and educational programs.

The goal is to raise enough funds so that the Bonfiglio Endowment will support the center's educational endeavors. In this way, the center will enhance training opportunities for medical students, orthopaedic residents and fellows, clinicians and allied health care personnel for years to come.

Gifts and pledges to the Endowment should be directed to the Bonfiglio Educational Endowment Fund and qualify as charitable contributions.

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DEPARTMENT
OF
ORTHOPAEDIC
SURGERY
THE UNIVERSITY OF IOWA
RESEARCH

Department of Orthopaedics

Todd McKinley
1999-present

R. Kumar Kadiyala
1998-present

Leon Grobler
1996-1999

Brian Adams
1993-present

Charles Saltzman
1991-present

John Callaghan
1990-present

David Tearse
1989-present

Ernest Found
1987-present

Lawrence Marsh
1987-present

Curtis Steyers
1985-present

James Nepola
1984-present

Fred Dietz
1984-present

James Weinstein
1983-1996

Barbara Campbell
1982-1984

Charles Clark
1980-present

William Blair
1980-1997

William Pontarelli
1980-1984,
1999-present

Joseph Buckwalter
1979-present

Thomas Lehmann
1978-1987

Stuart Weinstein
1976-present

Mike Mickelson
1976-1981

Richard Brand
1974-present

Arthur Steindler
1912-1949

Theodore Willis
1917-1918

Joseph Milgram
1926-1932

Ernest Freund
1932-1936

Thomas Waring
1932-1939

James Vernon Luck
1936-1939

Ignacio Ponseti
1946-present

Eberly Thornton
1946-1952

Robert Newman
1948-1956

Michael Bonfiglio
1950-1995

Carroll Larson
1950-1978

Adrian Flatt
1956-1979

Reginald Cooper
1962-present

Howard Hogshead
1964-1965

Maurice Schnell
1964-1965

Richard Johnston
1967-1970,
1998-present

Donald Kettelkamp
1968-1971

Gerald Laros
1968-1971

Richard Stauffer
1970-1972

John Albright
1971-present

Doug Mains
1972-1973

Bruce Sprague
1972-1979

The University of Iowa
College of Medicine

2000 GRADUATING SENIOR RESIDENTS

Lisa M. Coester, M.D., M.B.A.
Lisa was born in Norman, Oklahoma and grew up in Texas and Arizona. She earned a B.S. in animal health science in 1986, and an M.B.A in 1990, both from the University of Arizona. She received her M.D. from the University of Southern California in 1995. After residency, Lisa and her husband Bill will be moving to Cedar Rapids, Iowa (not far from their horsefarm), where she will join the Physicians' Clinic of Iowa as a general orthopaedist.

Matthew B. Dobbs, M.D.
Matt was born in Dallas, Texas and raised in Rome, Georgia. He received a B.S. in Biology from the University of Notre Dame where he also played collegiate tennis. He earned his M.D. from the University of Iowa in 1995. This summer Matt, his wife Christina Gurnett, and son Ellison, will move to St. Louis, Missouri for a pediatric orthopaedic fellowship with Dr. Perry Shoenecker at the St. Louis Shriner's Hospital.

David K. Sneller, M.D.
David was born and raised in Sioux Center, Iowa. He attended Central College where he earned a B.A. in Biology with a Chemistry minor in 1991. He received his M.D. from the University of Iowa in 1995. This summer David, his wife Neila, and their daughter Ellen will move to Ames, Iowa, where he is joining the McFarland Clinic to practice general orthopaedics.

Mark J. Spoonamore, M.D.
Mark was born and raised in Savoy, Illinois. He received a B.S. in Biology at the University of Illinois, Champaign in 1991 and an M.D. from the University of Illinois at Chicago in 1995. Next year Mark will travel to Los Angeles, California, where he will complete a spine surgery fellowship at the University of Southern California.

Dennis P. Weigel, M.D.
Dennis was born in Wells, Minnesota and grew up in Earlham, Iowa. He received a B.A. in Chemistry from Central College in 1991 and an M.D. from the University of Iowa in 1995. This summer, Dennis, his wife Karin, and daughter Sydney will be moving to Alexandria, Minnesota, where Dennis will join Alexandria Orthopaedic Associates and practice general orthopaedics.

NEW ORTHOPAEDIC FACULTY

The past two years have brought many changes to the Department of Orthopaedic Surgery at the University of Iowa. In addition to naming our fourth chairman, Dr. Joseph A. Buckwalter, several new faculty have joined our department.

Todd O. McKinley, M.D.
Dr. McKinley was born and raised in Osage, Iowa, a rural farming community. He enjoyed the benefits of growing up in Iowa, with an emphasis on family, school and community activities. His passions during his youth included wrestling and spaceflight. He studied Aerospace Engineering at the University of Minnesota and subsequently went into industry, working for the McDonnell Aircraft Company in St. Louis, Missouri. He met his wife Sara in St. Louis and married one month prior to starting medical school at the University of Minnesota. With a background in structures, orthopaedics was a natural choice. He completed his residency training at the University of California at Davis under the direction of Michael Chapman. Following residency, he applied to the Mission Specialist Astronaut program and was a finalist candidate, but was not selected. He did a research fellowship studying trabecular bone mechanics at Davis, followed by a trauma fellowship at the Shock Trauma Center in Baltimore under the direction of Andrew Burgess. He and his wife Sara have two boys: Owen, age ten and Paul, age seven. They are grateful for a chance to return to the Midwest and be part of the University of Iowa Department of Orthopaedic Surgery.

William R. Pontarelli, M.D.
Dr. Pontarelli is a "returning" new faculty member at the University. He previously served as a faculty member in Orthopaedics and organized the trauma service. He has previously received the M4 Teacher of the Year Award from the College of Medicine, and he has continued to teach over the past 15 years in private practice in Iowa City. He returns to the Department of Orthopaedic Surgery with a strong interest in outcomes research. Furthermore, Dr. Pontarelli was the faculty member responsible for originating the *Iowa Orthopaedic Journal* in 1980, when he was first with the department.

R. Kumar Kadiyala, M.D., Ph.D.
Dr. Kadiyala was raised in West Lafayette, Indiana. He received a B.S. in Chemistry from Purdue University in 1984 (summa cum laude) and attended Stanford University, where he enrolled in the Medical Scientist Training Program Fellowship. Upon completion of his M.D. and Ph.D. in 1991 he entered the Harvard Combined Orthopaedic Program in Boston, Massachusetts for residency training. He followed his residency training with a fellowship in adult reconstructive surgery with Dr. Donald T. Reilly at Beth Israel Deaconess Medical Center in Boston. He also completed the Harvard Hand and Upper Extremity Fellowship with Dr. Barry P. Simmons at Brigham and Women's Hospital, also in Boston. His diverse list of publications includes physical chemistry, immunology, and upper extremity topics. His orthopaedic interests include all clinical problems involving the adult and pediatric upper extremity including brachial plexus, shoulder and elbow pathology. His research interest involves healing, regeneration, and specificity of peripheral nerve repair. Dr. Kadiyala is pleased to return to the Midwest after years of study in the Bay Area and Boston.

DR. DAVID G. MURRAY DEDICATION

We are happy to dedicate this year's edition of *The Iowa Orthopaedic Journal* to Dr. David G. Murray of the SUNY-Syracuse Department of Orthopaedics. Dr. Murray is a native Iowan, born and raised in Ames. He attended college at Cornell University in Ithaca, NY, where he was a member of Phi Beta Kappa and graduated in 1951. He subsequently obtained his medical degree from Washington University in St. Louis, Missouri, in 1955. He then spent one year each in Vancouver, BC, Canada, the US Navy Medical Corps and the Department of General Surgery at SUNY-Syracuse, before returning to Iowa to do his orthopaedic residency in Iowa City.

Dr. Murray was highly respected as a resident training at the University. It was during this time he worked closely with one of his mentors—Dr. Ignacio Ponseti. Dr. Ponseti recalls that Dr. Murray was ". . . very respectful of, and dedicated to, his patients. He was always extremely well-read and well-prepared, whether it be in conferences, clinic or the operating room. He came from a very strong family, and one could see early on that he had the makings of a fine orthopaedist." In addition to his daily duties, Dr. Murray was very active in the orthopaedic biochemistry lab during his training years.

Upon completion of his orthopaedic training, Dr. Murray returned to Syracuse as an Assistant Professor of Orthopaedic Surgery, which was at that time a division of the general surgery department. In 1966, the hospital created a separate department of orthopaedics, and Dr. Murray was named its first chairman, a position he held until 1986. He was later recruited back to the chairmanship in 1990 and will be retiring "again" later this year.

To all who know him, Dr. Murray is a gentleman in the truest sense of the word. He is a fine example of the many alumni of the Iowa Department of Orthopaedics who have distinguished themselves in academic orthopaedics after training in Iowa City. In addition to his research, teaching and patient care duties, Dr. Murray has devoted much time throughout his career to numerous orthopaedic, medical and surgical organizations, often serving in a position of leadership. He is a past president of the American Academy of Orthopaedic Surgeons, the Orthopaedic Research and Education Foundation (OREF), the Knee Society, and the American College of Surgeons. He has authored numerous articles and book chapters on a variety of topics, most often in the area of total joint replacement. He was an honored guest at The University of Iowa Johnston Lectureship in Hip Reconstruction in 1998. There, many of the current faculty and residents were privileged to meet him and hear him speak.

Dr. Murray's devotion to both patient and profession is a source of inspiration to his students and colleagues alike. We would like to salute Dr. Murray as an exemplary alumnus of The University of Iowa Department of Orthopaedics, and we wish him the very best in his coming retirement.

DEPARTMENT OF ORTHOPAEDIC SURGERY
2000-2001 LECTURESHIPS AND CONFERENCES

Carroll B. Larson Shrine Memorial Lecture
May 12-13, 2000
Perry L. Schoenecker, M.D.
Shriners Hospital
Washington University
St. Louis, MO

Senior Residents' and Fellows' Day
June 2-3, 2000
James F. Kellam, M.D.
Carolinas Medical Center
Charlotte, NC

Scott J. Mubarak, M.D.
University of California- San Diego
Medical Center
San Diego, CA

Fifth Biennial Johnston Lectureship
In Hip Reconstruction
October 20-21, 2000
Daniel J. Berry, M.D.
Mayo Clinic
Rochester, MN

James G. Andrews, M.S.
Mechanical Engineering
University of Iowa

Donald L. Bartel, Ph.D.
Cornell University
Ithaca, NY

Edmund Y.-S. Chao, Ph.D.
Good Samaritan Hospital
Baltimore, MD

Roy D. Crowninshield, Ph.D.
Research and Development- Zimmer
Warsaw, IN

Dwight T. Davy, Ph.D.
Case Western Reserve University
Cleveland, Ohio

Kwan Rim, Ph.D.
Samsung Advanced Institute of Technology
Suwon, KOREA

Sports Medicine Symposium
December 1-2, 2000
Peter Fowler, M.D.
Fowler Kennedy Sports Medicine Clinic
University of Western Ontario
London, Ontario
Canada

J. Richard Steadman, M.D.
Steadman Hawkins Sports Medicine Foundation
Vail, CO

Senior Residents' and Fellows' Day
May 18-19, 2001

MELODIE DELZELL WARTH 1956-1999

In May of 1999, the Department of Orthopaedics lost one of our most respected and loved nursing staff, Melodie Delzell Warth, in a motor vehicle accident. Melodie was truly one in a million, and the opportunity to honor her in this journal is most appropriate, as she had a special respect and concern for our orthopaedic residents. She loved to help the residents learn. She treated them with respect as young adults who were learning not only orthopaedic surgery, but also about how to treat the orthopaedic patient. Her skills as an OR nurse, combined with her patient teaching skills made her the nurse every resident hoped to have one day. Her bubbly spirit, joy of life, friendship and concern for others have impacted us all, and will forever. We miss her every day personally and professionally. Our thoughts are with her husband Ed and her children Luke and Ali.

Department of Orthopaedics
1999-2000

First Row (L to R): Charles R. Clark, Joseph A. Buckwalter, Reginald R. Cooper, John P. Albright

Second Row (L to R): Stuart L. Weinstein, William R. Pontarelli, Jay D. Keener, Peter D. Pardubsky, Joseph G. Khoury, Curtis M. Steyers, R. Kumar Kadiyala

Third Row (L to R): John J. Callaghan, Erin E. Forest, Rola H. Rashid, Karen E. Evensen, Lisa M. Coester, David H. Allmacher, Brian R. Wolf, Gregory N. Lervick, Christopher D. Sliva, Jay C. Albright

Fourth Row (L to R): Fernando De Maio, Matthew B. Dobbs, Steven A. Herbst, David K. Sneller, Jose A. Morcuende

Fifth Row (L to R): J. Lawrence Marsh, Frederick R. Dietz, Daniel C. Fitzpatrick, Robert C. Greenberg, Stephen L. Knecht, Todd O. McKinley, Dennis P. Weigel

Not Pictured: Ignacio V. Ponseti, James V. Nepola, Charles L. Saltzman, Brian D. Adams, Ernest M. Found, Mark J. Spoonamore, Michael R. O'Rourke, Andres R. Ayoob, Goeffrey F. Haft, Mark L. Hagy, Aimee S. Kaplach

DAMAGE CONTROL MECHANISMS IN ARTICULAR CARTILAGE: THE ROLE OF THE INSULIN-LIKE GROWTH FACTOR I AXIS

James A. Martin, Ph.D.
M. B. Scherb, B.S.
Lois A. Lembke, M.S.
Joseph A. Buckwalter, M.D., M.S.

ABSTRACT

Articular chondrocytes maintain cartilage throughout life by replacing lost or damaged matrix with freshly synthesized material. Synthesis activity is regulated, rapidly increasing to well above basal levels in response to cartilage injury. Such responses suggest that synthesis activity is linked to the rate of matrix loss by endogenous "damage control" mechanisms. As a major stimulator of matrix synthesis in cartilage, insulin-like growth factor I (IGF-I) is likely to play a role in such mechanisms. Although IGF-I is nearly ubiquitous, its bioavailability in cartilage is controlled by IGF-I binding proteins (IGFBPs) secreted by chondrocytes. IGFBPs are part of a complex system, termed the IGF-I axis, that tightly regulates IGF-I activities. For the most part, IGFBPs block IGF-I activity by sequestering IGF-I from its cell surface receptor. We recently found that the expression of one binding protein, IGFBP-3, increases with chondrocyte age, paralleling an age-related decline in synthesis activity. In addition, IGFBP-3 is overexpressed in osteoarthritic cartilage, leading to metabolic disturbances that contribute to cartilage degeneration. These observations indicate that IGFBP-3 plays a crucial role in regulating matrix synthesis in cartilage, and suggest that cartilage damage control mechanisms may fail due to age-related changes in IGFBP-3 expression or distribution. Our investigation of this hypothesis began with immunolocalization studies to determine the tissue distribution of IGFBP-3 in human cartilage. We found that IGFBP-3 accumulated around chondrocytes in the pericellular/territorial matrix, where it co-localized with fibronectin, but not with the other matrix proteins tenascin-C and type VI collagen. This result suggested that the IGFBP-3 distribution is determined by binding to fibronectin. Binding studies using purified proteins demonstrated that IGFBP-3 does in fact bind to fibronectin, but not to tenascin-C or type VI collagen. Finally, we investigated the metabolic effects of fibronectin and IGFBP-3 in a chondrocyte culture system. These experiments showed that fibronectin enhanced the inhibitory effect that low concentrations of IGFBP-3 had on matrix synthesis. Taken together, these observations confirm that IGFBP-3-fibronectin interactions affect the IGF-I axis, and they indicate that IGF-I is stored in the chondrocyte territorial matrix through binding to a complex of IGFBP-3 and intact fibronectin. This arrangement may play an important role in cartilage damage control mechanisms. The local increase in matrix synthesis following injury could result from damage-induced IGF-I release from such pools. An age-related failure to organize this system may contribute to degenerative disease.

INTRODUCTION

The proteoglycan- and collagen-rich cartilage extracellular matrix (ECM) is well-adapted for resisting mechanical stresses imposed by weight bearing and joint motion: proteoglycans (aggrecan) serve to resist compression, while type II collagen fibers lend tensile strength.[41,65] This complex structure is actively maintained by ECM-synthesizing chondrocytes which replace components lost to mechanical wear and tear or injury.[12,53] Chondrocytes control the rates of synthesis and turnover of matrix proteins, stabilizing the existing ECM (maintenance and repair) or forming a new ECM with a different composition (remodeling). Maintenance and repair activities replace worn or damaged ECM components, while remodeling expands or strengthens the matrix. Together, these activities counter the effects of daily wear and tear and support cartilage adaptation to changing patterns of joint use.[11,12,47,49,54,72,82] Permanent structural damage may be done when cells fail to keep pace with matrix losses, a situation that can lead to the

Iowa City Veterans Affairs Medical Center and University of Iowa Department of Orthopaedic Surgery, 01013 John Pappajohn Pavilion, University of Iowa College of Medicine, Iowa City, IA 52242

degenerative joint disease, osteoarthritis (OA).[38] The strongly age-related incidence of OA suggests that this failure to control and repair damage to the cartilage ECM is an age-dependent phenomenon;[54] however, precisely how repair efficiency declines with aging is not clear.

The demand for new matrix components in cartilage depends, in part, on patterns of joint use. Animal models show that cartilage tolerates chronic, vigorous exercise, but undergoes important structural changes to maintain stability. These include increased thickness, stiffness and proteoglycan content.[47,49,72] An initial increase in ECM turnover implies that both matrix loss and matrix synthesis rates are induced by mechanical stress.[75] Several laboratories have demonstrated modest (~1.5-fold) stimulation of proteoglycan and/or type II collagen synthesis following exposure to cyclic stress *in vitro*.[46,78] While the cell signaling mechanisms mediating these effects are still unknown, it has been widely assumed that stress stimulates ECM synthesis directly *via* stress-dependent signaling mechanisms. However, other lines of evidence indicate that chondrocytes respond to ECM depletion or damage.[54] These data show ECM synthesis in organ culture is stimulated by culture-induced proteoglycan depletion,[78] by proteolytic digestion of the matrix,[75] or by mechanically induced ECM damage.[54] Again, the specific mechanisms mediating the stimulatory effects have not been elucidated.

ECM synthesis in cartilage is tightly regulated by cytokines, such as interleukin-1b (IL-1 β) and tumor necrosis factor alpha (TNFα), which inhibit matrix synthesis,[40,79,81] and by growth factors such as insulin-like growth factor I (IGF-I), transforming growth factor beta (TGF-β), and bone morphogenic proteins (BMPs) which stimulate synthesis.[62,64,79,81] IGF-I is the major endogenous inducer of matrix synthesis in normal adult cartilage.[25,52,62,79,81] IGF-I alone is capable of maintaining matrix stability in cartilage organ cultures,[52] and IGF-I can reverse some of the damage to cartilage caused by cytokine treatment.[80] These studies indicate that IGF-I is vital for cartilage integrity. Unfortunately, because osteoarthritic chondrocytes lose IGF-I responsiveness,[27,29,45] IGF-I treatments do not reverse OA.[12] Interestingly, the actions of IGF-I in OA cartilage do not appear to be limited by the concentration of IGF-I itself, which is actually higher in OA than in normal cartilage; rather, as described below, it appears that other factors curtail the bio-availability of IGF-I.[27,63,77]

The IGF-I found in articular cartilage is derived from synovial fluid or is secreted by chondrocytes.[25,34,55,63,79] IGF-I stimulates overall protein synthesis, cell division, glucose uptake and oxidation, and synthesis and secretion of collagen type II and aggrecan.[25,55,62,79,81] Protein and ECM synthesis in bovine and ovine cartilage is stimulated 2-4 fold by physiologic doses of IGF-I.[25,54,62,79] IGF-I levels are determined in part by IGF-I synthesis. Growth factors and cytokines found in the synovial compartment have been shown to affect IGF-I expression; however, activities are also controlled by regulation of IGF-I receptor density,[77] or by processes that limit the bio-availability of IGF-I once it is secreted.[25,26,55,67,69,76]

The activity of secreted IGF-I is regulated by a class of extracellular proteins, the IGFBPs which bind IGF-I with an affinity equal to that of the cell surface IGF-I receptor. These proteins are important systemic regulators of IGF-I activities and also act on a tissue-specific basis.[3,17,2] Peptides derived from IGFBPs directly affect cell metabolism,[7,8,68] but the principle mechanism of action for most IGFBPs is to sequester IGF-I in the extracellular space, making the growth factor unavailable for binding cell surface receptors.[23,61] Thus, an apparent loss of IGF-I sensitivity is observed even though the total number of IGF-I binding sites in the tissue increases.[13,27,45,55,56,57,67] Like IGF-I itself, IGFBPs are secreted by chondrocytes. Of the six genetically distinct IGFBPs described thus far, at least 3 (IGFBP-3, -4, -5) are expressed by human articular cartilage chondrocytes.[26,27,70,77] Although IGFBPs have been found to potentiate IGF-I action in some cell types,[28] only inhibitory actions have been shown in chondrocytes. Weak chondrocyte IGF-I responses have been associated with excessive IGFBP-3 expression in aging, in wasting syndromes[35,56] and in OA.[27,29,55,77] Increased IGFBP-3 levels in human synovial fluid are associated with expression of the OA/Rheumatoid marker, C-reactive protein (CRP).[29] IGFBP expression is stimulated by IGF-I, IL-1, prostaglandin E2, and TNFa[26,58,69,74,76] and inhibited by TGF-b.[23]

IGFBPs are themselves subject to complex regulation.[3,17,23] Though their physiologic significance is unclear, post-translational modifications such as phosphorylation[24] and glycosylation[2,30] affect IGF-I binding activity. IGF-I binding affinity is reduced by specific proteolytic cleavage of IGFBPs, a mechanism that has been shown to regulate IGF-I availability in many tissues.[1,2,4,5,6,40,48,50,59,60] Proteinases that target IGFBPs include intracellular cysteine proteinases such as cathepsin D[9,22] and extracellular proteinases including MMPs,[31,32] plasmin[8,16] and unidentified serine proteinases,[1,6,66] which cleave IGFBPs into fragments with reduced affinity for IGF-I.[4,5,6] Finally, IGFBP distribution in a tissue can be regulated by specific interactions with selected ECM components, including heparan sulfate proteoglycans.[7,43,44,33,71,73] Studies in our laboratory suggest that fibronectin, a quantitatively minor glycoprotein of the cartilage ECM, plays such an IGFBP-bind-

ing role. Cartilage-specific fibronectin isoforms[10,14,15,20] play important roles in regulating metabolism in normal and OA cartilage.[11] Numerous studies have demonstrated that fibronectin expression is increased in OA.[10,18,19,20,42,51] Proteolytic fragments of fibronectin, which are abundant in OA synovial fluid, strongly induce cartilage proteoglycan degradation.[39]

We propose that most cartilage IGF-I is held in an inactive pool by macromolecular complexes composed of IGF-I, IGFBPs, and matrix proteins which act together to link matrix disruption and matrix synthesis by controlling the bio-availability of IGF-I. Moreover, we predict that physical and/or enzymatic ECM disruption stimulates proteolysis of IGFBPs, resulting in the release of IGF-I from the pool. The studies summarized below present three lines of evidence that fibronectin and IGFBP-3 are part of this damage control mechanism which regulates matrix synthesis in cartilage: (1) Striking colocalization of fibronectin and IGFBP-3 was observed in immunohistological studies of human tibial plateau cartilage, whereas other matrix proteins such as tenascin-C and type VI collagen, that are similarly enriched in the pericellular\territorial matrix,[21,41] did not colocalize with IGFBP-3. These data suggest a physical interaction between fibronectin and the binding protein. (2) Binding assays with purified proteins showed that IGFBP-3 does indeed bind to fibronectin, but not to tenascin-C or type VI collagen, supporting our interpretation of the immunohistologic data. (3) Fibronectin strongly affected the physiologic activities of IGFBP-3, altering its effects on proteoglycan synthesis in a chondrocyte culture system.

MATERIALS AND METHODS

Human cartilage blocks were harvested from the central regions of 5 tibial plateaus obtained as surgical discards from patients (aged 37, 52, 67, 77, 84 years) undergoing total joint replacement for degenerative joint disease. Only cartilage which appeared grossly normal was used. The blocks were cryoembedded and sectioned. Ten mm-thick frozen sections were placed on gelatin-coated slides and fixed for 5 minutes in 3.5% paraformaldehyde freshly prepared in phosphate buffered saline (PBS). One slide was stained with the sulfated glycosaminoglycan-specific stain, Safranin-O,[41] to confirm normal cartilage morphology. The remaining slides were then washed repeatedly with PBS and blocked with 1% bovine serum albumin (BSA fraction V) in PBS with 0.5% Tween-20 (PBST) for 30 minutes. Mouse monoclonal antibodies against fibronectin (clone HFN7.1, Developmental Studies Hybridoma Bank), type VI collagen (clone 5C6, Developmental Studies Hybridoma Bank), and tenascin-C (Clone EB2, ICN), were applied at ~10 μg/ml IgG. The rabbit anti human IGFBP-3 polyclonal antibody (Upstate Biotechnology) was applied at the same time at a 1:50 dilution. The sections were incubated with primary antibodies overnight at 4° C. The sections were washed in PBST and blocked in 10% normal goat serum for 30 minutes before the addition of secondary antibodies. Secondary antibodies consisted of a goat anti-mouse Cy2 conjugate (Jackson Immunoresearch) and a goat anti-rabbit Cy5 conjugate (Jackson Immunoresearch). These were diluted 1:400 and applied to the sections. The slides were incubated for 1.0 hour at ambient temperature. Isotype controls in which purified mouse IgG or rabbit serum (diluted 1:200) replaced the primary antibodies were included on every slide. After several PBS washes the slides were mounted using Aquamount (Lerner Laboratories) and imaged on a Biorad scanning confocal laser system using a Nikon microscope and 20X objective. Two images of the same section were recorded using an excitation wavelength of 488 nm and a 515 nm cutoff filter (for Cy2) and an excitation wavelength of 630 nm with a cutoff of 670 nm (for Cy5). Semi-quantitative image analysis was performed to determine the extent of overlap between individual stains. Paired images representing double stains for IGFBP-3 and fibronectin, IGFBP-3 and tenascin-C, and IGFBP-3 and type VI collagen were first thresholded, then combined using Boolean operators "and" and "or" (Scion Image). The areas covered when the images were combined using either the "and" or "or" functions were determined and the ratio of "and" to "or" calculated. These ratios, which are a measure of colocalization, were determined for all 5 individual samples. These data were pooled for statistical analysis.

A novel diffusion assay was developed to study interactions of selected ECM proteins with IGFBP-3. Purified proteins (200 nM) including bovine plasma fibronectin (ICN), human collagen type VI (Chemicon), bovine heparan sulfate proteoglycan (HSPG) (Sigma), and human tenascin-C (Chemicon) were mixed with 1% molten low-melt agarose (FMC Bioproducts) in Dulbecco's Modified Eagle Medium (DMEM) buffered with 10 mM HEPES. Purified IGFBP-3 at 200 nM (R&D Systems) and ^{125}I-IGF-1 at ~5.0 nM (ICN) were added and multiple 10 ml aliquots of molten agarose were dotted on culture dishes and allowed to solidify. The agarose dots were pre-incubated for 1.0 hour at 37° C to allow intermolecular protein binding to occur. The dots were then overlaid with 100 ml DMEM and incubated at room temperature. The medium was removed at various time points (1, 5, 10, 20, 30, 60, 120, and 180 minutes) and the agarose dots extracted in 7.7 M urea. ^{125}I-IGF-I CPM was quantitated by liquid scintillation

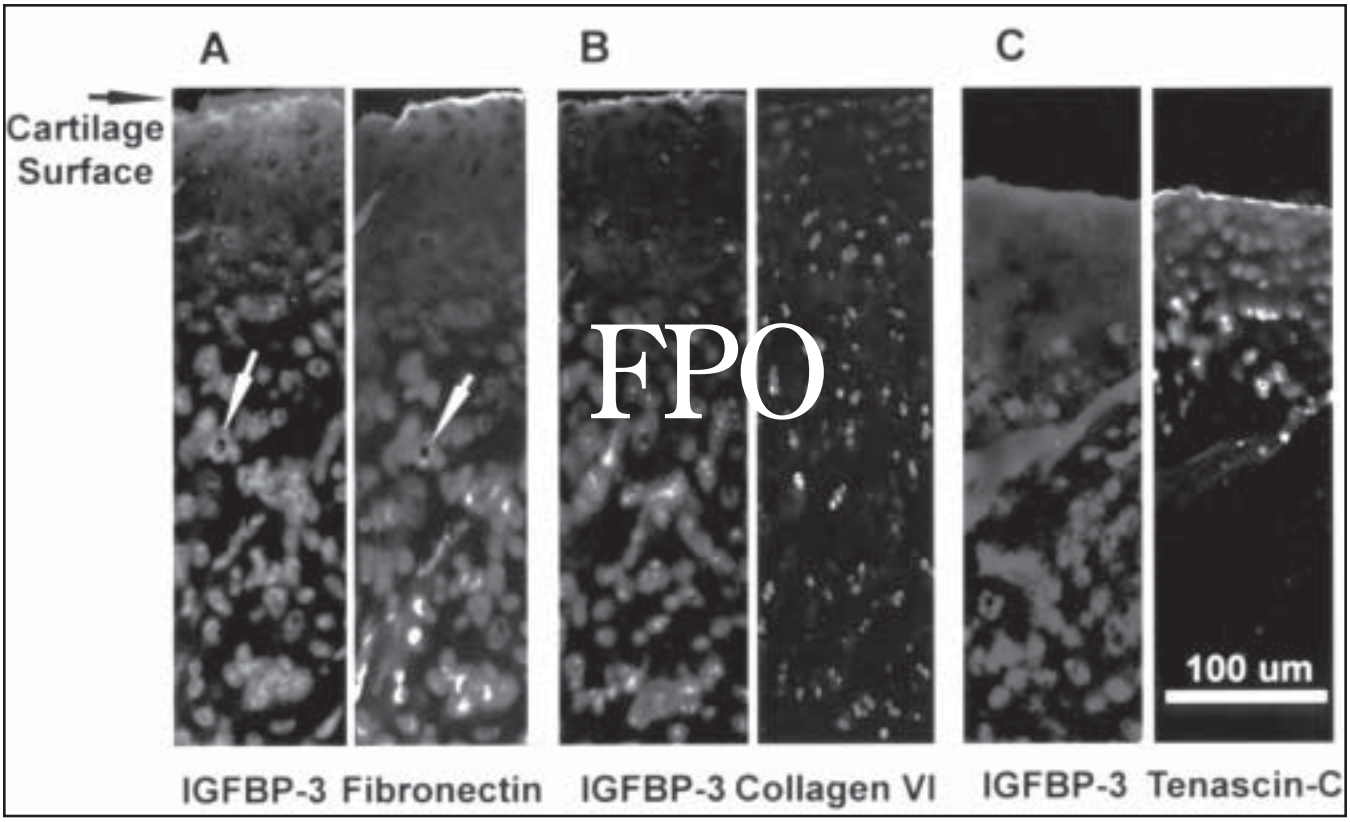

Figure 1. Tissue Distributions of IGFBP-3, Fibronectin, Type VI collagen, and Tenascin-C
Cartilage sections were double-stained with a polyclonal antibody to IGFBP-3, and monoclonal antibodies against fibronectin (A), type VI collagen (B), or tenascin-C (C). Positive immunofluorescence staining for IGFBP-3 is red and staining for matrix proteins is green. Sections are oriented with the cartilage surface up. White arrows in A indicate the pericellular/territorial matrix around a chondrocyte which stains positively for both fibronectin and IGFBP-3.

counting and IGFBP-3 was assayed by immunoblot in both the medium and agarose extracts. Ratios of extract (agarose dot) to total (agarose + medium) ^{125}I-IGF-I and IGFBP-3 were calculated for each time point. These data were plotted and fitted with exponential decay curves (Microcal Origin) to determine the $t_{1/2}$ for protein retention in the agarose dot. Each experiment included controls consisting of ^{125}I-IGF-I without additional proteins and ^{125}I-IGF-I with IGFBP-3.

Cultures of rat articular chondrocytes were used to determine the effects of fibronectin on IGFBP-3 activity. Chondrocytes were isolated from cartilage pooled from the tibial plateau and femoral condyles of 6-8 one-month-old Sprague Dawley rats. The cartilage was digested overnight in DMEM with 10% fetal calf serum containing 0.5 mg/ml each type IA collagenase (Sigma) and dispase (Life Technologies) and antibiotics. The digestion was filtered through 40 mm nylon mesh and the cells counted on a hemocytometer in the presence of 0.04% trypan blue. Greater than 90% of the isolated chondrocytes were viable. The cells were pelleted and resuspended in alginate (Kelco) to a concentration of 2 x 10^7 cells/ml as described.[36] The suspension was split into two fractions and rat plasma fibronectin (Life Technologies) was added to one fraction to a final concentration 10 µg/ml. An equal volume of the solvent (0.01 M acetic acid) was added to the other fraction. Each fraction was again divided into 4 equal fractions and IGFBP-3 was added from a freshly reconstituted 50 µg/ml solution to final concentrations of 0.01, 0.10, or 1.0 µg/ml. The 0.01 M acetic acid solvent was added to make an equal percentage (2%) of 0.01 M acetic acid in all fractions. Alginate beads were formed as described[36] and were placed in 96-well tissue culture plates (1 bead per well) in 200 µl DMEM/10% FCS containing 50 µCi/ml carrier-free $^{35}SO_4$ (Amersham). The cultures were incubated overnight at 37° C in a humidified chamber with 5% CO_2. The whole cultures (beads and medium) were extracted by adding 200 ul 8 M 2X extraction buffer (guanidine-HCl with 100 mM sodium acetate, 100 mM 6 amino hexanoic acid, 20 mM EDTA and 4% Triton X 100, pH 6.8) to each well and incubating overnight at 4° C with shaking.[37] The extractions were passed over Sephadex G-50 (Pharmacia) columns to remove free $^{35}SO_4$. Column eluates were mixed with scintillation cocktail and counted in a Beckman LS 3801 liquid

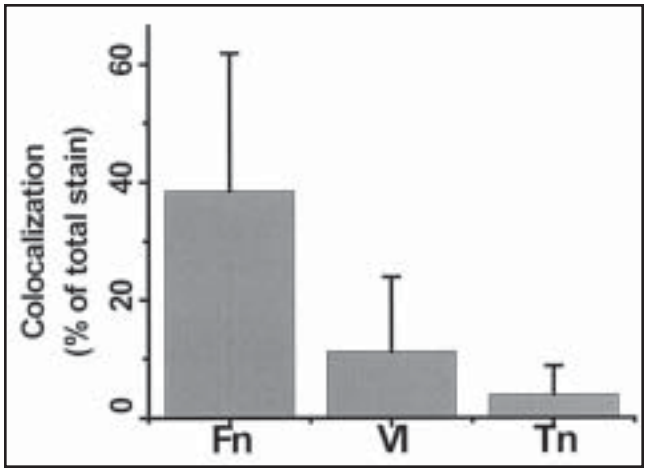

Figure 2. Colocalization Analysis
IGFBP-3 and matrix protein double stains were analyzed. Colocalization for IGFBP-3 and fibronectin (Fn), IGFBP-3 and type VI collagen (VI), IGFBP-3 and tenascin-C (Tn) was determined. Means and standard deviations are shown for analyses of cartilage from 5 different donors. The value for IGFBP-3/fibronectin is significantly greater than the values for IGFBP-3/type VI collagen and IGFBP-3/tenascin-C ($p<0.05$).

scintillation counter. The means and associated standard deviations for 6 replicate wells for each dose group (CPM/bead) are presented as a function of IGFBP-3 concentration in Figure 4. Chondrocytes from at least one bead per dose group were not extracted but instead were recovered from the bead and counted on a hemocytometer in the presence of trypan blue. Viability averaged 88% and there were no significant differences attributable to IGFBP-3 or fibronectin treatments.

RESULTS

Double immunofluorescence studies showed that IGFBP-3 was concentrated in the pericellular/territorial matrix around chondrocytes where it appeared to colocalize with fibronectin. Typical sets of double-stained fluorescence images taken using a 10X objective (Figure 1) showed that whereas the matrix proteins fibronectin (A, green), type VI collagen (B, green), and tenascin-C (C, green) were all concentrated in the pericellular/territorial matrix, only fibronectin showed an overall tissue distribution similar to IGFBP-3 (red). This relationship was found to hold true at higher resolution: 3-dimensional reconstructions done using a 63X objective confirmed IGFBP-3/fibronectin colocalization (not shown). Semi-quantitative analysis of cartilage samples from 5 different individuals confirmed this subjective impression (Figure 2). These data represent the extent of colocalization or overlap between red and green stains. Kruskal-Wallis one way analysis of variance with Dunn's method for multiple comparisons indicated that the IGFBP-3 co-localized with fibronectin

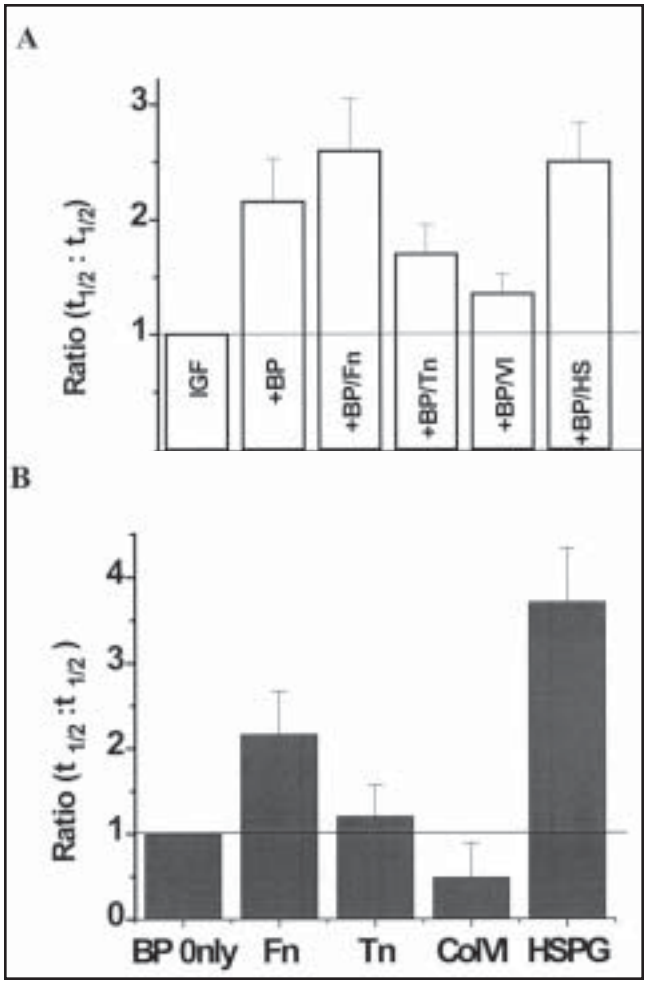

Figure 3 *In Vitro* Diffusion Assays
(A) ^{125}I-IGF-I diffusion. The $t_{1/2}$ for diffusion from agarose dots to medium was determined for ^{125}I-IGF-I alone (negative control) and the $t_{1/2}$ values with added matrix and IGFBP-3 were normalized to this value. The histogram shows the means and standard deviations (error bars) of these ratios from triplicate assays. The following combinations of proteins were tested: ^{125}I-IGF-I+IGFBP-3 (+BP), ^{125}I-IGF-I+IGFBP-3 +fibronectin (+BP/Fn), ^{125}I-IGF-I+IGFBP-3+tenascin-C (+BP/Tn), ^{125}I-IGF-I+IGFBP-3+type VI collagen (+BP/VI), ^{125}I-IGF-I+IGFBP-3+heparan sulfate proteoglycan (+BP/HS). (B) IGFBP-3 Diffusion. The $t_{1/2}$ for diffusion from agarose dots to medium was determined for IGFBP-3 only (without matrix proteins) and the $t_{1/2}$ for IGFBP-3 in the presence of matrix proteins was normalized to this control value. Means ± standard deviations (error bars) of three independent assays are shown. The following combinations of proteins were tested: IGFBP-3+fibronectin (Fn), IGFBP-3+tenascin-C (Tn), IGFBP-3+type VI collagen (colVI), IGFBP-3+ heparin sulfate proteoglycan (HSPG).

to a significantly greater extent than colocalization with either type VI collagen or tenascin-C ($p<0.05$).

IGFBP-3 interactions with selected ECM proteins were determined in an agarose diffusion assay. Purified proteins including fibronectin, collagen type VI, heparan sulfate proteoglycan, and tenascin-C were mixed with molten agarose. Purified IGFBP-3 and ^{125}I-IGF-1 were added and multiple 10 ml aliquots of the

mixtures were dotted on culture dishes and overlaid with DMEM. The negative control for ^{125}I-IGF-I diffusion experiments consisted of ^{125}I-IGF-I alone without additional proteins. The negative control for IGFBP-3 diffusion consisted of IGFBP-3 without the addition of matrix proteins. DMEM was removed at subsequent time points and the ^{125}I-IGF-I quantitated by liquid scintillation counting of the medium and agarose extracts. IGFBP-3 was assayed by immunoblot in the same medium and agarose extracts. The ratios of the ^{125}I-IGF-I and IGFBP-3 remaining in the agarose dot to the total present in both phases were calculated for each time point. These data were normalized to controls, plotted, and fitted with exponential decay curves to determine the $t_{1/2}$ for protein retention in the agarose dot. Data from three independent assays are shown in Figure 3. ^{125}I-IGF-I diffusion data indicated that, as expected, IGFBP-3 increased the $t_{1/2}$ of ^{125}I-IGF-I in agarose: The mean for ^{125}I-IGF-I alone was 14.2 minutes +/- 6.5 minutes (SD), whereas the mean for ^{125}I-IGF-I in the presence of IGFBP-3 alone was 30.7+/- 17.9 minutes (~2-fold longer). Although the binding protein retarded ^{125}I-IGF-I diffusion in both the presence and absence of matrix proteins, matrix proteins did affect $t_{1/2}$: While tenascin-C and type VI collagen reduced the retardation observed with IGFBP-3 alone, both fibronectin and heparan sulfate proteoglycan enhanced the effect. To determine if this might be due to IGFBP-3-matrix interactions, we performed assays for IGFBP-3 on the same medium and extracts used for ^{125}I-IGF diffusion studies. These immunoblot data (Figure 3B) show that IGFBP-3 diffusion was slowed by fibronectin or HSPG ($t_{1/2}$=2-4 fold greater than IGFBP-3-only). In contrast, both type VI collagen and tenascin-C had very modest effects.

A chondrocyte culture study was performed to determine the effects of fibronectin on matrix synthesis activity in the presence and absence of IGFBP-3 (Figure 4). Fibronectin and IGFBP-3 were incorporated into the alginate matrix and the cells were cultured in medium with $^{35}SO_4$ and varying doses of IGF-I. $^{35}SO_4$ incorporation was determined as a measure of matrix synthesis activity. Consistent with previous observations[57], we found that fibronectin itself stimulated anabolic activity in the absence of added IGFBP-3. IGFBP-3 clearly inhibited $^{35}SO_4$ incorporation both in the presence and absence of fibronectin; however, there were substantial fibronectin-related differences in the IGFBP-3 dose response. The means for fibronectin-treated and untreated controls were significantly different by one-way analysis of variance ($p<0.05$) at all IGFBP-3 doses except the 0.1 mg/ml dose. Only the highest IGFBP-3 doses (0.1 and 1.0 mg/ml IGFBP-3) consistently inhibited $^{35}SO_4$ incorporation in fibronectin-free cultures whereas, in the presence of fibronectin the lowest (0.01 mg/ml) dose was inhibitory. Interestingly, incorporation was stimulated by 1.0 mg/ml IGFBP-3 in the presence of fibronectin, but not in its absence. This result may be due to fibronectin-dependent enhancement of the stimulatory effects of IGFBP-3 fragments contaminating the IGFBP-3 preparation.[8]

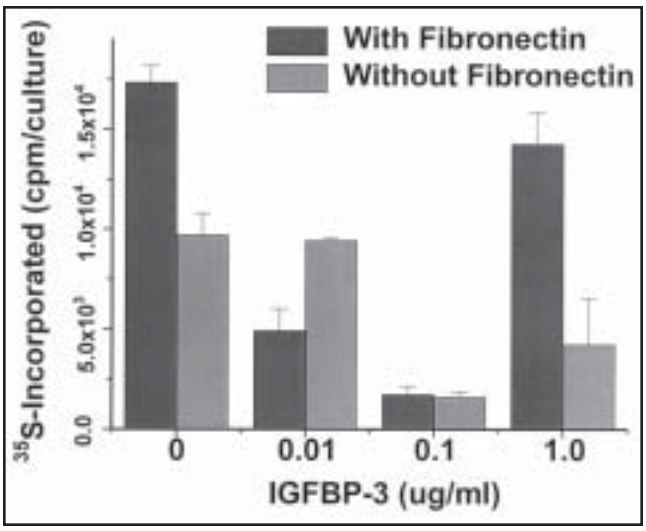

Figure 4. Effects of Fibronectin and IGFBP-3 on ^{35}S-sulfate Incorporation in Chondrocyte Cultures.
Chondrocytes were cultured in ^{35}S-sulfate-containing medium with IGFBP-3 at the indicated doses (0-1.0 ug/ml), with or without added fibronectin. Means and standard deviations (error bars) of ^{35}S-sulfate incorporation (counts per minute per alginate bead) from 3 independent assays are shown. The differences between the fibronectin-treated and control means were significant at 0, 0.01, and 1.0 ug/ml IGFBP-3 ($p<0.05$), but not at 0.10 ug/ml.

DISCUSSION

Our studies confirm that IGFBPs are part of the cartilage system for regulating IGF-I availability and support the hypothesis that IGF-I is stored in the matrix as part of a damage control mechanism. We observed striking colocalization of IGFBP-3 with fibronectin in the pericellular/territorial matrix. This relationship was not observed with tenascin-C or type VI collagen, suggesting that the colocalization with fibronectin was not merely incidental, but was due to specific binding between fibronectin and IGFBP-3. Evidence for such an interaction was sought using purified proteins in a cell-free *in vitro* diffusion assay. These data indicated that IGFBP-3 binds to fibronectin, and heparan sulfate proteoglycan, a protein which had previously been shown to bind IGFBP-3. Consistent with the colocalization data there was no evidence of binding to tenascin-C or type VI collagen. Finally, we sought physiologic evidence that fibronectin affects cellular re-

sponses to IGF-I in the presence of added IGFBP-3. These cell culture studies showed that fibronectin significantly altered matrix synthesis activity, particularly when IGFBP-3 was present. Taken together these findings suggest that IGF-I, IGFBP-3, and fibronectin form a strategically placed growth factor pool. We propose that this spatial arrangement maintains a constant, low level of bioavailable IGF-I in normal cartilage, consistent with the minimal need for synthesis activity. Moreover, we postulate that proteinases activated during the initial response to mechanical or chemical insult degrade IGFBP-3 and fibronectin, destabilizing IGF-I binding. This results in a rapid rise in available IGF-I around chondrocytes at the damaged site without the need for an immediate increase in local IGF-I synthesis. The resulting burst of IGF-I-driven matrix synthesis is limited to the damaged site and persists until the local ECM, and its associated IGF-I storage pool, is re-established.

Although aberrant IGF-I responses almost certainly contribute to osteoarthritis, the mechanisms of IGF-I action in normal cartilage must be understood first before events leading to degenerative disease can be recognized. The long-term goal of this effort is to develop strategies to improve the effectiveness of IGF-I as a pharmacologic agent against cartilage degeneration, perhaps by combining IGF-I and IGFBPs. Another important goal will be to determine whether disturbances in the IGF-I axis are related to aging processes, or to environmental factors such as mechanical stress, which might be avoided in at-risk individuals. These studies will also contribute to the design of engineered cartilage implant materials by identifying the molecules that regulate the IGF-I pathway.

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TRANSFORMING GROWTH FACTOR BETA ONE (TGF-β1) ENHANCEMENT OF THE CHONDROCYTIC PHENOTYPE IN AGED PERICHONDRIAL CELLS: AN IN VITRO STUDY

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ABSTRACT

Background

Perichondrium is recognized as a tissue with chondrogenic potential yielding cells which can be used for osteochondral repair. Factors which influence the proliferative ability and chondrocytic phenotype of such cells include age and presence of specific growth factors, i.e. TGF–β1. The present in vitro study assessed proliferation and markers of chondrocytic phenotype in cells extracted from the rib perichondrium of four- to five-year-old aged rabbits, and assessed the effects of exogenously added TGF–β1 on those cells.

Methods

Assays included ^{3}H-thymidine incorporation (cell proliferation), ^{35}S-sulfate incorporation (proteoglycan synthesis) and quantitative RT-PCR for determination of type II collagen gene expression.

Results

The results demonstrated that addition of TGF–β1 to the culture media stimulated thymidine incorporation and proteoglycan synthesis up to four- and five-fold, respectively, in aged perichondrium-derived cells. Moreover, the exogenous addition of TGF–β1 to the culture media resulted in an up-regulation of transcriptional expression of the type II collagen gene.

Conclusions

In summary, the present study has demonstrated that exogenously added TGF–β1 can stimulate proliferation and chondrocytic phenotype in aged perichondrium-derived cells in vitro.

INTRODUCTION

The repair of articular cartilage injuries remains a challenge, with several current therapeutic modalities based on the grafting of chondrocytic tissues[1,27] or the implantation of cells capable of generating a cartilage-like matrix.[5,33] One such tissue, perichondrium, is recognized as having chondrogenic potential[14,19,28,32] and one from which cells with a chondrocytic phenotype can be isolated for implantation into osteochondral defects.[7-9] Among the factors that may influence the success of repair models utilizing chondrocytic cell transplantation is the age of the donor tissues. Specifically, parameters important to chondrocytic phenotype that are influenced by age include rate of cell proliferation, rate of proteoglycan synthesis and type II collagen gene expression.[10,25,26] These parameters are also known to be affected by certain members of the growth factor family of regulatory proteins. In particular, TGF–β1 has been reported to influence the proliferation of a variety of cell types including articular chondrocytes,[16,17,30] osteoblasts[12] and periosteum-derived cells.[11,18] TGF–β1 has also been shown to stimulate proteoglycan synthe-

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sis,[23,24,30,31] induce type II collagen production in chondroblasts[31] and periosteum-derived cells,[3,4,21] and stabilize the chondrocytic phenotype in such cells.[3]

In a previous study, we demonstrated that markers of the chondrocytic phenotype, i.e. proteoglycan synthesis and type II collagen gene expression, were enhanced by the addition of TGF–β1 to explant cultures of mature perichondrium-derived cells.[13] The primary goals of the present in vitro study were to assess proliferation, proteoglycan synthesis and type II collagen gene expression in cells extracted from aged rabbit perichondrium, and to determine if those parameters may be susceptible to modulation by the addition of TGF–β1.

MATERIALS AND METHODS

Cell Preparation and Culture System

Six aged rabbits four to five years old were sacrificed according to the animal subjects protocols at UCSD and used for preparation of six individual primary perichondrium cell cultures. Using sterile procedures the costal ribs were dissected, adhering tissue was removed and the perichondrium layer was isolated. The perichondrium was then washed three times in sterile buffered salt solution containing antibiotics and incubated overnight in 0.1% collagenase (CLS-2, Worthington Biochemical, Freehold, NJ) solution at 37° C under 5.0% CO_2. The collagenase digest was passed through a sterile 0.45 micron filter and the remaining cells and tissue debris were further digested with 0.1 μg/ml hyaluronidase (Sigma) and trypsin (Irvine Scientific) for two hours. This digest was then passed through an 80 micron filter to isolate the cells. Primary cell cultures were established on 100 ml tissue culture plates by incubation in α-MEM (α-modified Earl's medium) containing 10% FBS and antibiotics at 37°C under 5% CO_2. Culture media was changed every two to three days and the cultures were maintained until 100% confluency was achieved. The cells were then trypsinized and counted prior to passaging onto 6 - well (35 mm) plates at 0.5 x 10^5 cells per well.

^{3}H-Thymidine Incorporation Assay for Cell Proliferation

Passaged cells were kept in α-MEM supplemented with 10% FBS and antibiotics for 24 hours. After this period the medium containing 10% FBS was removed and replaced with medium containing 0.5% FBS. After a 12 hour incubation, TGF–β1 was added to separate cultures at concentrations of 0.1, 0.5, 1.0, 5.0 and 10.0 ng/ml (n=6 for each TGF–β1 concentration) and incubation was continued for 48 hours. Cell cultures containing only 0.5% FBS served as untreated controls. The cultures were then pulsed with ^{3}H-thymidine (2 μCi/ml of media) and incubated for 12 hours. The medium was then removed and the plates were washed twice with cold sterile phosphate buffered saline (PBS) before the cells were released by digestion with trypsin-EDTA. After centrifugation, the cell pellets were washed twice more with cold PBS to remove any remaining unincorporated tritium. The cell pellets from individual wells were lysed by adding 1.1 ml of 1 N NaOH and incubating at 60° C for two hours. One hundred μl of cell lysates were then added to 10 ml of scintillation cocktail (Fisher) and neutralized by addition of 20μl of 6N HCl. Radioactivity was counted in a model 6800 liquid scintillation spectrometer (Beckman Instruments). The remaining one ml of cell lysate from each well was used for DNA measurement as described by Amiel et al.[2] After trypsinization, the numbers of viable and dead cells were counted manually with a hemocytometer using trypan blue staining. There were no differences in cell viability among the different wells of different groups; therefore, thymidine incorporation was normalized to DNA content in each well. The relative cell proliferation (^{3}H-thymidine incorporation) rates are thus expressed as cpm/μg of total cellular DNA.

^{35}S-Sulfate Incorporation Assay for Proteoglycan Synthesis

Passaged cells (0.5 x 10^5 cells per well in 6-well plates) were kept in α-MEM supplemented with 10% FBS and antibiotics for 24 hours at 37° C and then treated with TGF–β1 at concentrations of 0.1, 0.5, 1.0, 5.0 ng/ml (n=6 for each TGF–β1 concentration). After four days the cells were made quiescent by replacing 10% FBS with 0.5% FBS and incubating for 24 hours. ^{35}S-sulfate (20 μCi /ml of media) was then added to the cell cultures and incubation was continued for four hours. The medium was then removed and the plates were washed twice with cold sterile phosphate buffered saline (PBS) before the cells were released by digestion with trypsin—EDTA. After centrifugation the cell pellets were washed twice with cold PBS to remove unincorporated ^{35}S-sulfate. The cell pellets from individual wells were lysed by adding 1.1 ml of 1 N NaOH and incubating at 60°C for two hours. One hundred μl of cell lysates were then taken for quantitation of radioactivity by liquid scintillation spectrometry. The remaining one ml of cell lysates from each well was used for DNA measurement. The relative rates of proteoglycan synthesis (^{35}S-sulfate incorporation) are expressed as cpm per μg of total cellular DNA.

Collagen Gene Expression By Reverse Transcription Polymerase Chain Reaction (RT-PCR)

Passaged cells were plated at 4 x 10^5 cells per 100 mm diameter tissue culture plate. After 24 hours of incubation at 37°C, the cells were treated with TGF–β1 at concentrations of 0.1, 0.5, 1.0, 5.0 ng/ml (n=6 for each TGF–β1 concentration). After four days of incubation, 10% FBS was removed and replaced with 0.5% FBS and the cells were allowed to incubate for another 24 hours. Total cellular RNA was then extracted using the acid guanidinium-thiocyanate-phenol-chloroform extraction procedure.[6] To ensure that PCR amplification of contaminating genomic DNA would not affect the data, total extracted RNA was treated with RNase free DNase (RQ1, Promega, Madison WI). Five micrograms of total RNA were converted to cDNA using oligo(dT) and MMLV reverse transcriptase (Promega, Madison, WI). First strand cDNA for type II collagen was then amplified by polymerase chain reaction. In order to monitor the quality of the RNA preparation and to normalize the reverse transcription RT-PCR protocol, the glyceraldehyde-6-phosphate dehydrogenase (GAPDH) housekeeping gene was also subjected to RT-PCR in all extracts. Ten microliters of the reverse transcription solution was then taken for PCR in a total reaction volume of 50 µl: 5 µl of a 10x Mg-free PCR buffer, 2.5 mM $MgCl_2$, 5 units taq DNA polymerase (Promega), and 20 picomoles of each primer. PCR primers specific to selected coding regions of GAPDH (5'-TCCATGCCATCACTGCCA-3' & 5'-CATACCAGGAAATGAGCT-3') and type II collagen (5'-GACCCCATGCAGTACATG-3' & 5'-GACGGTCTTGCCCCACTT-3') were constructed (Retrogen, San Diego CA) based on the published sequences for those genes (36). PCR was performed using a DNA thermal cycler (GeneAmp PCR System 2400, Perkin Elmer, Norwalk, CT). For GAPDH and type II collagen transcripts a cycle profile consisted of 25 sec at 94°C for denaturation, 30 seconds at 58°C for annealing and 30 seconds at 72°C for extension. Following electrophoresis on 1% agarose gels containing ethidium bromide for visualization, photodocumentation and the Image Tool Analysis Program (NIH image version 1.6, Natl Inst of Health USA, http://rsb.info.nih.gov/nih-image/) were used to quantitate PCR products. PCR was performed for 12-32 cycles at two-cycle intervals in order to determine the linear range of PCR amplification. The midpoint of linear amplification, 20 cycles, was calculated from a linear regression curve of log mean density vs. cycle number. This number of cycles was subsequently used for all PCR reactions. Integrated band density values for the type II collagen gene were then normalized to GAPDH. All treatment groups of passaged cells (n=6 for each concentration of TGF–β1 + 0.5% FBS control) were analyzed in triplicate for a total of 18 RT-PCRs for each group. Absolute numbers of type II collagen gene transcripts were determined as previously described[15,29] from a standard PCR curve derived from a 20-cycle amplification of serially diluted solutions of a plasmid (pGEM T-vector) containing the type II collagen PCR insert. Results are expressed as number of type II collagen transcripts per microgram of total RNA.

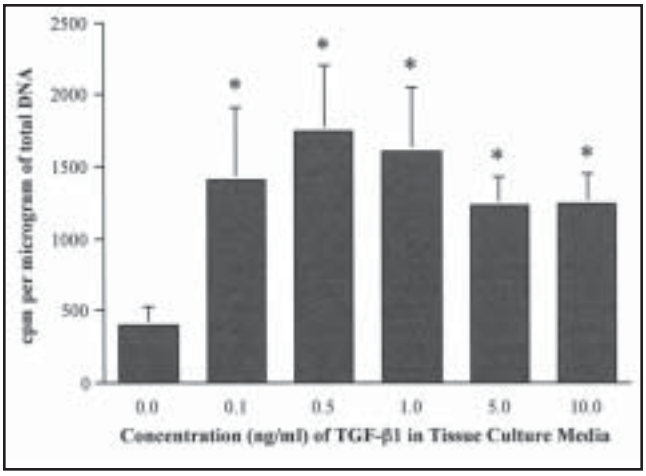

Figure. 1. The effect of TGF-β1 on 3H-thymidine incorporation in cultured aged perichondrium - derived cells. Each column represents the mean ± standard deviation of six cultures. Asterisk (*) refers to statistical significance of $p < 0.05$ relative to the 0.0 ng/ml TGF-β1 control.

Statistical Analysis

Statistical significance was determined by analysis of variance (ANOVA) and all data are presented as mean ± standard deviation.

RESULTS

Effect of TGF-β1 on Thymidine Incorporation

The results of experiments exploring the effect of TGF–β1 on ^{3}H-thymidine incorporation by aged perichondrium cells are illustrated in Figure 1. Treatment of aged cells with TGF–β1 caused a significant ($p < 0.05$) increase in ^{3}H-thymidine incorporation over the entire range of growth factor concentrations applied, i.e. 0.1 - 10.0 ng TGF–β1 per ml of tissue culture media. TGF–β1 stimulation reached a peak at a concentration of 0.5 ng/ml where the incorporation rate was approximately four times greater than in untreated cells; an apparent plateau occured between a concentration of 5.0 and 10.0 ng/ml.

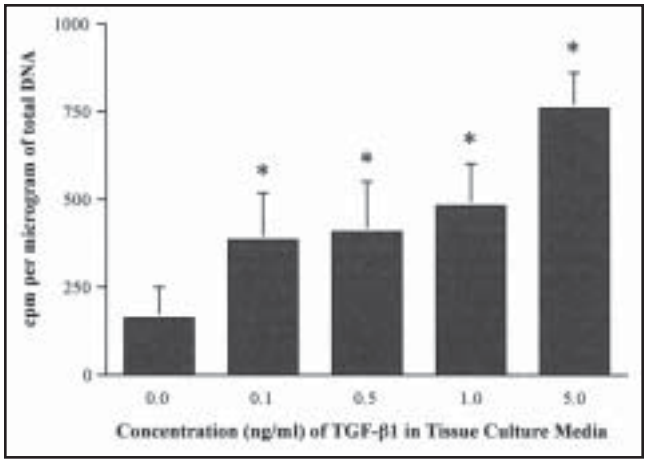

Figure 2. The effect of TGF-β1 on 35S-sulfate incorporation in cultured aged perichondrium - derived cells. Each column represents the mean ± standard deviation of six cultures. Asterisk (*) refers to statistical significance of $p < 0.05$ relative to the 0.0 ng/ml TGF-β1 control.

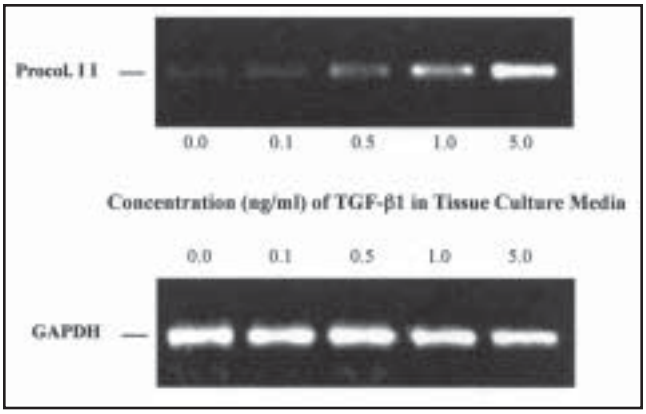

Figure 3. Representative result for RT-PCR of RNA extracted from TGF-B1 treated cultured aged perichondrium - derived cells. Top: Type II collagen; Bottom: GAPDH.

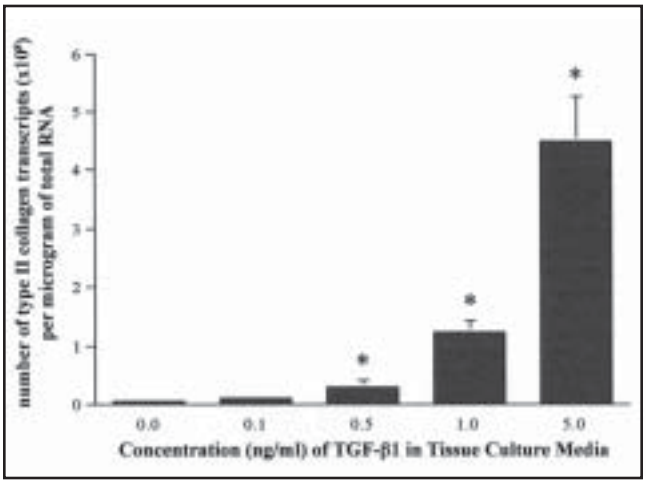

Figure 4. Results of quantitative image analysis following RT-PCR of type II collagen mRNA after extraction of total RNA from TGF-β1 treated cultured aged perichondrium - derived cells. Each column represents the mean ± standard deviation of six cultures. Asterisk (*) refers to a statistical significance of $p < 0.05$ relative to the 0.0 ng/ml TGF-β1 control.

Effect of TGF-β1 on Proteoglycan Synthesis

Figure 2 shows the relative rates of *in vitro* proteoglycan synthesis (^{35}S-sulfate incorporation) in aged perichondrium cells treated with TGF–β1. This figure shows that, relative to untreated controls, ^{35}S-sulfate incorporation into aged cells was stimulated by addition of TGF–β1 to the culture media. This effect was significant ($p < 0.05$) over the entire range of growth factor concentrations tested. The greatest ^{35}S-sulfate incorporation was achieved with the addition of 5.0 ng/ml of TGF–β1

Effect of TGF-β1 on Type II Collagen Gene Expression

PCR products for GAPDH were uniformly expressed in all groups (Figure 3). A typical result for RT-PCR of type II collagen mRNA is shown in the top panel of Figure 3; this figure clearly shows that the type II collagen band intensity was increased in aged perichondrium cells after treatment with TGF-β1. Type II collagen-specific transcripts were quantitated as number of type II collagen transcripts per μg of total RNA, and the results are illustrated in Figure 4. Relative to untreated controls (0.5% FBS), the level of transcription of the type II collagen gene in aged perichondrium-derived cells was significantly ($p < 0.01$) up-regulated with the addition of TGF–β1 to the culture media at concentrations ranging from 0.5 to 5.0 ng/ml. The greatest effect of the growth factor was observed at a concentration of 5.0 ng/ml.

DISCUSSION

The present *in vitro* study has demonstrated that addition of TGF–β1 to cultured aged perichondrium-derived cells can stimulate cell proliferation and enhance the chondrocytic phenotype, i.e. proteoglycan synthesis and type II collagen gene expression. To our knowledge this is the first study to report such effect of a specific growth factor, i.e. TGF–β1 on aged perichondrial cells. Several studies have reported on age-related changes in proliferative ability and phenotypic expression in various cell types derived from such tissues as bone marrow and periosteum. For instance, O'Driscoll[26] reported an age-related decline in chondrocytic mark-

ers in periosteum-derived cultured cells and suggested that such decline might be caused by a reduction in the pool of chondrocyte precursor cells. In a similar study, Nakahara[25] showed that that periosteal cells with osteochondrocytic potential could be liberated from human donors up to the age of 22 years, but that the population of such cells decreased thereafter. With regard to the osteochondrocytic potential of human bone marrow cells, it has also been suggested that there is a difference between young and aged human donors in terms of the ability of such cells to undergo terminal osteochondral differentiation[29] and in an *in vivo* study, Cohen and Lacroix reported that the osteochondrocytic potential of autogenous periosteal grafts in rabbits varied considerably depending on age.[10]

In a previous *in vitro* study carried out in our laboratory[13] we reported that exogenous addition of TGF–β1 to media containing 0.5% fetal bovine serum resulted in a marked increase of tritiated thymidine uptake by mature (eight to ten months old) perichondrium-derived cells with optimum proliferative effects at 0.1 ng/ml. The present study showed that thymidine incorporation in aged perichondrium-derived cells was similarly increased by TGF–β1 over a wide range of growth factor concentrations, i.e. 0.1 to 10.0 ng/ml of media. This study also showed that proteoglycan synthesis (^{35}S-sulfate incorporation) in aged perichondrium-derived cells was stimulated by TGF–β1 over a similar concentration range, while phenotypic expression of the chondrocytic collagen phenotype, i.e. type II collagen, was dramatically increased in aged cells treated with TGF–β1. The exact mechanisms of such effects remain to be elucidated, but since growth factor activities are mediated through their respective receptors, it is likely that those receptors undergo age related changes in number and/or responsiveness to growth factors. Further studies to explore the relationships between age and growth factor effect and mediator responsiveness would be appropriate.

Balance between cell proliferation and chondrocytic potential is important with regard to utilizing TGF–β1 in clinically related studies such as bioengineered cartilage repair. In this regard, TGF–β1 has been demonstrated to exhibit duality in its effects on chondrogenicity. It has been reported, for instance, that TGF–β1 can stimulate synthesis of cartilage-specific type II collagen in rat mesenchymal cells,[22,31] while, at relatively higher concentrations, this growth factor inhibited synthesis of type II collagen in vitro in articular chondrocytes.[20] In the present study, ^{35}S-sulfate incorporation and type II collagen gene expression were increased over a concentration range of 0.1 to 5.0 ng/ml of TGF–β1. This concentration range was also effective for increasing cell proliferation rates.

In conclusion, the present study has demonstrated that exogenously added TGF–β1 had a strong morphogenic effect and stimulated the chondrocytic phenotype in aged perichondrium-derived cells *in vitro*. These results are encouraging with regard to enhancing the repair of osteochondral defects in the aged using autologous transplantation of aged perichondrium-derived cells.

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OPEN REDUCTION AND CEMENTATION FOR FEMORAL HEAD FRACTURE SECONDARY TO AVASCULAR NECROSIS: PRELIMINARY REPORT

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ABSTRACT

Current treatment for femoral head avascular necrosis has shown good results in early stages of disease, but are not as impressive after progression to collapse. We treated 19 patients (20 hips) with Stage III avascular necrosis (AVN) by open reduction augmented by methylmethacrylate cementation. Follow up ranges from 6 months to 2 years (average=8.7 months). We followed patient progress with pre- and post-operative Harris Hip Scores, Womac Osteoarthritis Index and a Health Status Questionnaire (SF36). All patients realized immediate post-operative pain relief and improvement in function. Harris Hip, Womac Osteoarthritis Index and SF36 physical health scores improved significantly from 54.0 to 79.5 ($p<0.05$), 54.3 to 29.8 ($p<0.05$) and 28.4 to 42.4 ($p<0.05$), respectively. Three patients had a conversion to total hip arthroplasty. Cementation is technically simple, burns no bridges and enables patients a rapid recovery. The long term results, in regards to progression of disease and secondary arthritis, are unknown.

INTRODUCTION

Avascular necrosis (AVN) of the femoral head is characterized by disruption of normal blood flow with subsequent bone death. Frequently, this results in collapse of the normal spherical head contour with progression to degenerative arthritis. AVN is a common and devastating problem for adults between the ages of twenty and fifty years. Unfortunately for this population, there are few therapeutic options for end-stage disease. For patients who are greater than fifty years of age, THA has the most predictable long-term result for their disease. However, in the younger population, total joint replacement is sub-optimal secondary to the high rate of complications in this age group.[1,2]

The Ficat staging system, based on radiographic findings and clinical symptoms,[3] was modified by Hungerford[4] to include MRI diagnosis in stage 0. In stage 0, the MRI shows evidence of AVN despite normal radiographic findings in an asymptomatic patient. In stage I, the patient has pain with MRI changes, but no radiographic findings. Stage II has radiographic findings that are subcategorized. In stage IIA, the changes include sclerosis and cyst formation, and in IIB a crescent sign. In stage III, there is loss of the spherical shape (collapse) of the femoral head. In stage IV, radiographic changes include joint space narrowing and acetabulum involvement.

In early stages of the disease, the goal is to prevent collapse. Conservative therapy such as crutch ambulation or bed rest for Ficat early-stage (I and II) disease leads to collapse in 65 to 90% of patients within five years.[5,6,7] Once collapse occurs, the goal is to prevent further collapse and possibly restore femoral head sphericity.

Current surgical treatment modalities have shown good results in early-stage disease, but are not as impressive in stage III and IV.[4,8,9,10,11,12,13,14,15,16] Bone grafting techniques predictably halt progression to collapse in early stages, but have been less successful at joint restoration once collapse occurs. We present a modification of treatment for stage III AVN by open reduction and cement fixation (cementation).

Materials and Methods

This study represents the first report of hips undergoing cementation for Ficat stage III AVN of the femoral head from August 1997 to August 1999. The treatment protocol for AVN at our institution is dependent

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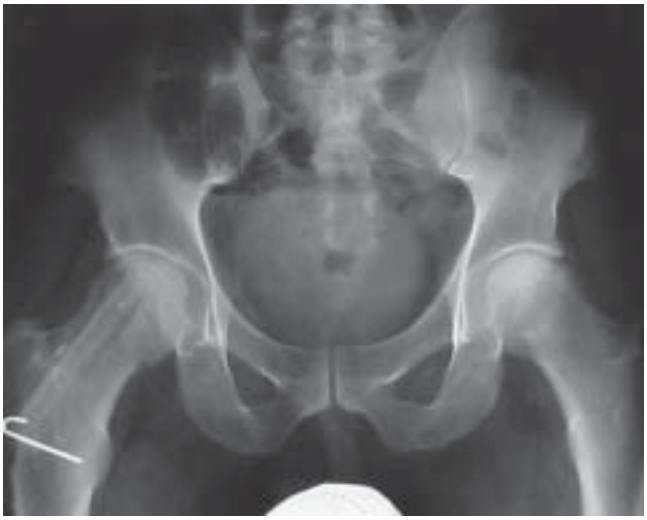

Figure 1. Radiograph shows a patient who has undergone a free fibula graft on the right hip for early stage disease and who has stage III AVN on the left.

upon Ficat stage. Stage I is treated by core decompression, stage II by free fibular bone grafting and stage IV by arthroplasty. The senior author (SSK) treated 19 patients (20 hips) with Stage III avascular necrosis by open reduction and augmentation by methylmethacrylate (cementation). Figure 1 represents a radiograph of a patient with Ficat stage II on the right (after free fibular grafting) and stage III on the left.

The population consists of 14 males and 5 females with an average age of 39.1 years (25-51) and an average weight of 200 lbs. The disease was associated with steroid use in 10 patients, alcohol consumption in 5 and trauma in 2, with 2 being idiopathic. Follow-up ranges from 6 months to 2 years (average=8.7 months). Failure in this study is defined as the need for conversion to THA.

The indication for operation was pain at presentation, physiologic age of less than 50 and Ficat Stage III AVN of the femoral head diagnosed by plain x-ray. All patients were initially evaluated by a surgeon qualified to perform free fibular bone grafting and were referred if there was evidence of collapse.

We followed patient progress pre- and post-operatively with Harris Hip Scores[17], the Womac Osteoarthritis Index[18] and a Health Status Questionnaire (SF36)[19]. Harris Hip scores are physician administered and represent a functional result. Patient administered scores include the SF36, which provides both a physical and mental health score, and the Womac Osteoarthritis Index (WOI), an indication of pain, stiffness and lower-extremity function. A lower numerical result in the WOI indicates an improvement.

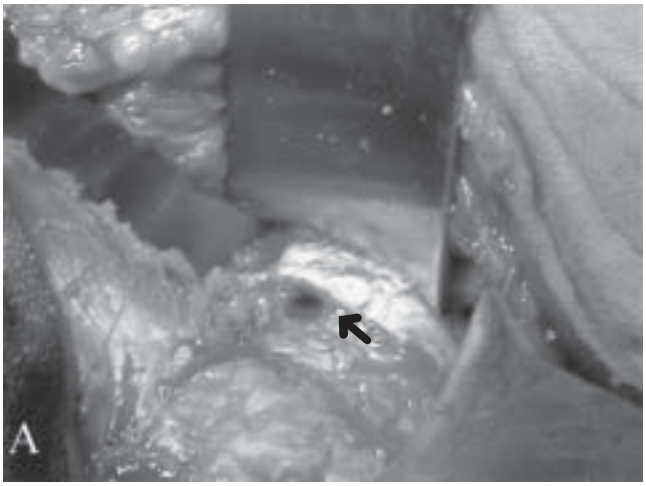

Figure 2A. A small burr hole is drilled at the base of the cartilage that allows for debridement of necrotic bone and access for the cement. Note the cartilage deformity. See arrow.

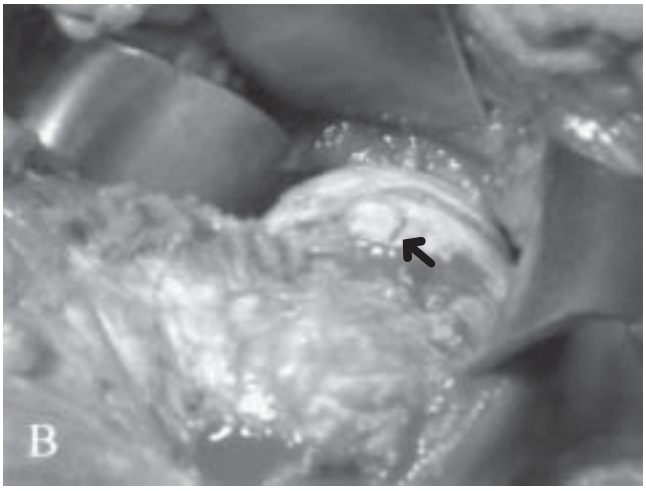

Figure 2B. A small bone dowel from the greater trochanter is used to plug the hole. Note that the cartilage deformity has been reduced. See arrow.

Operative Procedure

The procedure is performed in the lateral decubitus position. An approximately 20 cm incision is made centered over the greater trochanter. The anterior one third of the abductors are detached and a T-shaped capsulotomy is performed at the base of the femoral neck. This allows either anterior dislocation or subluxation of the femoral head and visualization of the pathologic area of articular cartilage. Next, a 6-mm hole is created in the neck at the junction of the articular cartilage (Figure 2a). This allows access for the cement and debridement of dead bone. The collapsed segment is elevated and reduced using a joker. High viscosity cement, Surgical Simplex, P (Howmedica Inc., Rutherford, NJ, Pfizer Hospital Products Group), was used in ten cases and low viscosity cement, Osteobond,

(Zimmer Inc., Warsaw, Indiana), was used in ten. The cement is pressurized by injection into the femoral head. The hip is reduced and the cement is allowed to harden with contouring and molding of the femoral head by the acetabulum. A small bone dowel graft taken from the greater trochanter is placed in the entry hole (Figure 2b). The absence of free cement is verified radiographically (fluoroscopy) and visually. Post-operatively, the patients are allowed partial weight bearing for 6 weeks.

RESULTS

All patients realized immediate post-operative pain relief and improvement in function. Despite improvement, 3 patients developed symptoms that subsequently required THA.

Pain

At most recent follow-up, 16 of 20 hips had improvement in pain, 3 reported no change (2 converted to THA) and 1 reported worse pain (converted to THA). Pre-operatively the majority of patients reported moderate, severe or disabling pain, while post-operatively the majority of patients reported mild, slight or no pain. Pre-operatively, 18 of 19 patients used pain medications, 12 of which required narcotics. At most recent follow-up, 9 patients were still needing pain medications with only 4 requiring narcotics.

Gait

At least half of the patients reported improvement in gait and the distance they were able to walk. Pre-operatively, 2 reported no limp, 4 slight, 10 moderate and 4 severe. Post-operatively, 7 had no limp, 6 slight, 6 moderate, and 1 severe. Pre-operatively, 10 used no support devices, 3 used a cane for long walks, 4 used a cane full time and 3 used a crutch. Post-operatively, 9 needed no support devices, 6 used a cane for long walks, 4 used a cane full time and 1 used a crutch. Pre-operatively, 3 could walk an unlimited amount, 7 could walk six blocks, 6 could walk two to three blocks and 2 were confined to indoor walking only. Post-operatively, 9 could walk an unlimited amount, 4 could walk six blocks, 4 could walk two to three blocks and 3 were confined to indoor walking only.

Activities of daily living

Improvements were observed in ADL's. Pre-operatively, 5 reported ease with putting on socks and shoes and 15 reported difficulty. Post-operatively, 15 reported ease with putting on socks and shoes while 5 had difficulty. Pre-operatively, 3 reported no difficulty using stairs, 8 used a banister, and 8 used any method. Post-operatively, 3 reported no difficulty using stairs, 4 used a banister and 13 used any method.

Physician administered scores (Harris Hip)

Physician administered scores indicated significant improvement in function. Mean Harris Hip scores improved from 54.0 to 79.5 ($p<0.05$). Pre-operatively, 17 hips were rated poor (Harris Hip score < 70, pain), 3 were rated fair (Harris Hip score 70-79, slight or moderate pain) and none were rated good or excellent. Post-operatively, 6 were rated excellent (Harris Hip score > 90, minimal or no pain), 5 were rated good (Harris Hip score 80-89, slight pain), 2 were rated fair and 7 rated poor.

Patient administered scores (Womac and SF36)

Significant improvement was observed in patient administered scores. Womac scores improved (lower scores indicate improvement) from 54.3 to 29.8 ($p<0.05$). The SF36 scores improved in physical health from 28.4 to 42.4 ($p<0.05$) while mental health scores showed no significant change (56.6 to 55.8). Overall satisfaction for having the operation was reported in 14 of 19 patients (Table 1).

Complications

There were no complications of deep vein thrombosis or wound infection. Of the 20 hips that were operated on, 3 required conversion to THA.

DISCUSSION

The etiology of avascular necrosis (AVN) can be classified into two categories; arterial compromise and high intraosseous pressure. Arterial supply may be compromised by femoral neck fracture or by arterial thrombosis (e.g. hemoglobinopathy such as sickle cell disease). High intraosseous pressures obstruct blood flow when pressure in the femoral head rises above the capillary pressure. Steroid use and ethanol abuse are examples which are thought to increase marrow celluarity and fat, subsequently increasing intraosseous pressures[20]. Trauma, steroid use, and ethanol abuse account for more than 90% of the cases of AVN[21].

Current treatment for AVN is dependent upon etiology and stage of disease. The goal for treatment in stage I is to decompress the femoral head pressure before progression to stage II, which is characterized by formation of reactive bone. The goal in stage II is to reconstitute the dead bone before progression to stage III, which is characterized by fracture and collapse. The goal in stage III is to restore head sphericity and pre-

Hip #	Age	Date of Surgery	Hip	Follow-up (months)	Etiology	Pre-op HH Score	Post-op HH score	Post-op Pain	Post-op Medication	Post-op Limp	Post-op Support	Overall Satisfation
1	42	8/9/97	R	20	steroids	60	84	improved	none	same	cane, full-time	yes
2	45	1/20/98	R	14	steroids	49	45	same	oxycodone	same	cane, long walks	no
3	26	4/10/98	L	12	steroids	73	94	improved	none	same	none	yes
4	47	6/2/98	L	12	steroids	66	86	improved	none	improved	cane, long walks	yes
5	51	7/24/98	R	THA (6)	steroids	68	57	worse	NSAIDS	same	cane, full-time	no
6	47	7/31/98	L	THA (6)	EtOH	50	48	same	NSAIDS	same	cane, long walks	no
7	41	9/1/98	R	6	steroids	45	76	improved	acetominophen	improved	none	yes
8	41	9/11/98	L	6	EtOH	49	99	improved	none	improved	none	yes
9	48	9/11/98	L	6	trauma	32	57	improved	codeine	improved	cane, long walks	no
10	25	10/2/98	L	6	steroids	75	94	improved	none	improved	none	yes
11	48	10/2/98	L	6	idiopathic	59	82	improved	none	improved	cane, long walks	yes
12	28	10/27/98	R	6	EtOH	39	80	improved	acetominophen	improved	none	yes
13	35	10/27/98	L	6	steroids	23	61	improved	none	improved	cane, full-time	yes
14	43	10/30/98	L	6	EtOH	37	70	improved	none	same	cane, long walks	yes
15	43	11/6/98	R	THA (6)	steroids	49	33	improved	oxycodone	worse	crutch	no
16	43	11/6/98	L	6	steroids	58	87	same	none	same	none	yes
17	26	12/18/98	R	6	steroids	73	91	improved	none	improved	none	yes
18	41	12/29/98	L	6	idiopathic	69	96	improved	NSAIDS	same	none	yes
19	46	1/12/99	L	6	trauma	46	53	improved	propoxyphene	same	cane, full-time	yes
20	30	1/26/99	L	6	EtOH	59	97	improved	none	improved	none	yes

Table 1. Summary of findings. Legend: THA=total hip arthroplasty, HH=Harris Hip

vent further collapse before progression to stage IV, which is characterized by degenerative changes.

Comparing the results of treatment options reported in the literature presents difficulties. Many studies had small patient populations[22], as did ours. The criteria for success among the studies varied from a good functional result[23] to the lack of radiographic progression or the need for a subsequent operation[14]. The statistical methods varied with the use of survivorship analysis versus crude survivorship[13,24]. Follow-up rates varied, not only in percent follow-up, but also in number of years[25]. Finally, different classification systems were used including the Ficat[3], Marcus[26] and Steinberg[27]. Even among the same classification system, Smith et al have shown that there is poor interobserver reliability and fair intraobserver reproducibility[28].

The most common reported therapeutic options for management of avascular necrosis include observation, core decompression, rotational femoral osteotomy and bone grafting (non-vascularized and vascularized). These approaches are effective for early-stage disease before collapse of the femoral head contour.

Core decompression in stage I disease has been shown to be successful in 75%—100% of patients.[3,4,13,14,24,29,30] In stage II disease (pre-collapse), the success rate decreases to 34—83%.[3,4,14] Core decompression is sub-optimal treatment for stage III disease (femoral head collapse) with success rates reported from 0 – 60%.[4,10,13]

Proximal femoral osteotomy is effective for late stages of disease, especially in select populations. In stage II, success rates range from 56%—89%.[23,31,32,33] For stage III disease, success rates range from 56—87%.[23,31,32,33] The effectiveness of femoral rotational osteotomy is dependent on the amount and location of femoral head involvement. Unsatisfactory results are observed with increasing femoral head involvement, advanced osteoarthritic change and the inability to rotate the collapsed segment to a non-weight bearing area.[31]

Non-vascularized bone grafting has been used for stage II and III disease. Rosenwasser et al reported on non-vascularized, cancellous bone grafting for stage II and III femoral head AVN. At a mean of 12 years, success was seen in 7 of 9 stage II patients and in 4 of 5 stage III patients.[25] Lee and Rehmatullah followed 10 stage II hips treated with non-vascularized bone grafting. At 3.5 years follow-up, they reported success in 7 patients.[22]

Vascularized bone grafting is the gold standard for preventing collapse in stage II and preventing progression in stage III disease. In stage II disease, vascularized bone grafting has been shown to be successful in 83 - 100% of patients.[10,11,13,16,34] In stage III disease, after femoral head collapse, the success rate decreases to 36—81%.[10,11,13,16,34]

Our microvascular surgeon limits vascularized free fibular bone grafting to stage II disease and refers young, stage III patients who would otherwise be candidates for total hip arthroplasty. His results have been extremely good in stage II disease, but not in stage III. The inability to restore head sphericity and prevent further collapse could account for some of the failures seen with vascularized free fibular bone grafting in stage III disease.

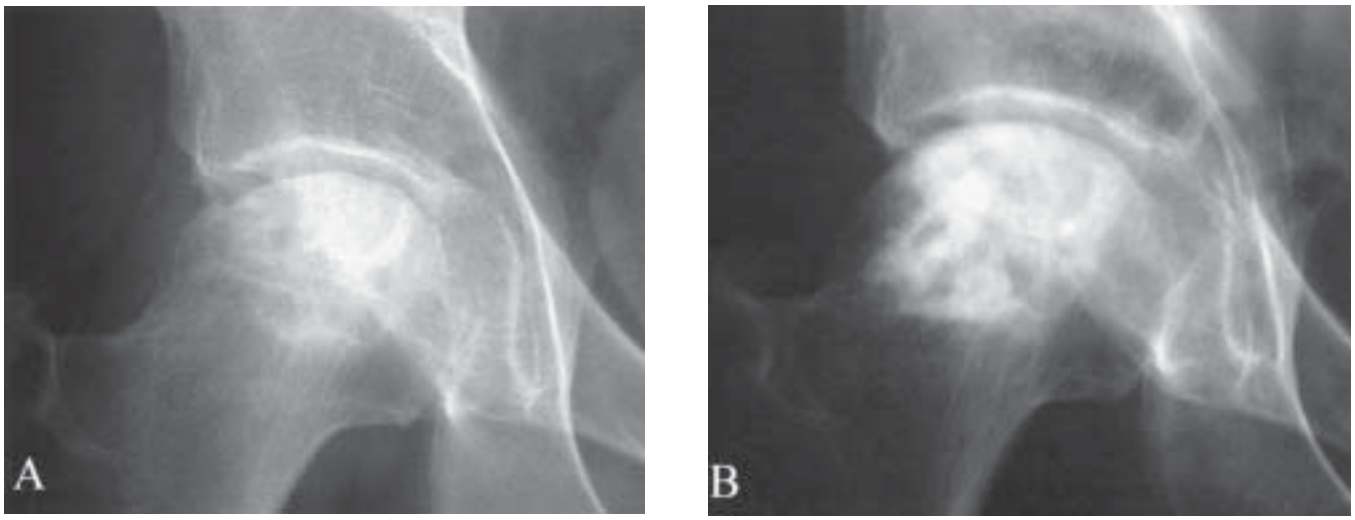

Figure 3. Pre- and post-operative radiographs demonstrating collapse (A) and restoration of femoral head sphericity with cementation (B).

An improvement in the treatment of stage III disease could possibly be accomplished by open reduction and cement augmentation. Ideally, permanent cement fixation would restore femoral head sphericity and prevent further collapse (Figure 3). Using cement under subchondral bone to support the collapsed segment could potentially avoid the loss of fixation seen with the remodeling of bone grafts. We are encouraged by the published clinical and basic science success rates with using methylmethacrylate to support cartilage; however, we remain concerned about animal study results.

Ewald et al[35] looked at cementation of the femoral head in the canine model. All dogs in this study walked with normal gaits for the entire experimental period of 2.5 years, but histological studies confirmed degenerative changes in the cemented hips. This study involved an aggressive surgical procedure with amputation and coring of the femoral head and complete replacement of the cancellous bone with cement. Six of the thirteen dogs were excluded; three secondary to death and three for dislocation. Of the remaining seven dogs, five had well reduced hips. It is not possible to attribute the degenerative changes in these canine hips to the stiffness of methylmethacrylate. Despite complete filling of the femoral head with cement, mechanical testing in this study showed that the cemented hips were not significantly stiffer (5%) than the control. It was suggested by Ewald et al that the arthritic changes may be a result of the change in mechanical properties and loss of trabecular architecture. We minimize these changes by only debriding and reducing the collapsed segment.

There are clinical reports that endorse the use of methylmethacrylate to support cartilage. Giant Cell tumors of bone have been successfully treated by curettage of the lesion (to subchondral bone) followed by packing of the cavity with methylmethacrylate. Pals and Wilkins followed 10 consecutive cases for thirty-six months with 8 patients having excellent functional results and 2 with fair results (scored on the Musculoskeletal Tumor Society rating system)[36]. Persson and Wouter reported on 6 patients, all of whom had excellent functional results at 2 year follow up[37]. Malawer and Dunham reported on 25 patients, all less than 21 years old, who underwent cryosurgery for benign bone tumors with an average follow-up of 60.8 months. Thirteen patients had bone grafts, 8 had polymethylmethacrylate with or without bone graft and 4 had no reconstruction. Excellent or good functional results were reported in 96% of the cases[38].

There are other centers using cement to stabilize femoral head fractures secondary to AVN. Hernigou et al[39] have injected low viscosity cement into the femoral heads of 16 patients with AVN secondary to sickle cell disease. They describe reducing the collapsed segment with a pin, then injecting into the junction of the living and necrotic bone until the collapse of the articular cartilage has been corrected. Fourteen of 16 patients were still improved (some reported slight pain) at a mean follow up of 5 years. Another study reported treatment of 13 patients with a similar cement inflation technique. At a range from 6 months to 3 years, 12 of 13 patients realized immediate post-operative symptom relief and were doing well.[40]

Our procedure differs from other studies in that we use an anterior-lateral approach versus anterior or posterior. In reducing the collapsed segment, we drill a 6-

mm burr hole, reduce the collapsed segment (from below), and then inject with a cement gun equipped with a 6-mm tip. In other procedures, if reduction is performed prior to cementation, a pin is used for reduction (through the articular cartilage and into the fracture line). For injecting cement, a small cannula or syringe has been previously described.

The modifications made with our technique have had variable success. We used high viscosity cement for the first four cases before changing to a low viscosity cement (ten cases). After noting failures, we resumed using high viscosity cement for the final six cases. Potential early problems may have included over debridement and packing of the femoral head. Wide debridement may compromise the vascularity of the surrounding healthy bone. Also, it is uncertain whether or not violating the sclerotic rim has an effect on further progression and collapse. Catto has shown that after collapse, re-vascularization ceases in the necrotic segment[41]. It can be postulated that a larger cavity filled with higher pressures of methylmethacrylate will not only cause increased pressures on the surrounding bone, but will also create an exothermic reaction that would not be favorable. In our earlier cases, the femoral head was dislocated anteriorly, which also could have compromised vascularity. By using a distraction device, we now perform this technique without dislocation.

Despite the early problems seen with cementation, we are optimistic for our procedure. Cement has the potential to maintain reduction and sphericity, without the potential for resorption and collapse as seen when bone grafts remodel. Cement will never be as physiologic as cancellous bone, especially in regards to stiffness and remodeling. The long term results in regard to progression of disease and secondary arthritis is unknown. The possible indication for this procedure is a young patient with Ficat stage III disease who has active, unresolved disease.

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HIGH DENSITY POLYETHERURETHANE FOAM AS A FRAGMENTATION AND RADIOGRAPHIC SURROGATE FOR CORTICAL BONE

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ABSTRACT

Background

Although one of the most important factors in predicting outcome of articular fracture, the comminution of the fracture is only subjectively assessed. To facilitate development of objective, quantitative measures of comminution phenomena, there is need for a bone fragmentation surrogate.

Methods

Laboratory investigation was undertaken to develop and characterize a novel synthetic material capable of emulating the fragmentation and radiographic behavior of human cortical bone.

Result

Screening tests performed with a drop tower apparatus identified high-density polyetherurethane foam as having suitable fragmentation properties. The material's impact behavior and its quasi-static mechanical properties are here described. Dispersal of barium sulfate ($BaSO_4$) in the resin achieved radio-density closely resembling that of bone, without detectably altering mechanical behavior. The surrogate material's ultimate strength, elastic modulus, and quasi-static toughness are within an order of magnitude of those of mammalian cortical bone. The spectrum of comminution patterns produced by this material when impacted with varying amounts of energy is very comparable to the spectrum of bone fragment comminution seen clinically.

Conclusions

A novel high-density polyetherurethane foam, when subjected to impact loading, sustains comminuted fracture in a manner strikingly similar to cortical bone. Moreover, since the material also can be doped with radio-opacifier so as to closely emulate bone's radiographic signature, it opens many new possibilities for CT-based systematic study of comminution phenomena.

INTRODUCTION

Bone surrogates usefully serve a number of niche purposes in orthopaedics. Manufactured plastic anatomic replicas of skeletal members are widely used for student teaching, for motor skill development, and as visual aides for patient communication. They hold obvious advantages over natural bone in terms of durability, reproducibility, versatility (e.g., whole-joint models including ligaments, menisci, etc.), and economy. Recently, patient-specific stereolithographic plastic bone replicas generated from CT data have proven valuable in planning complex surgical procedures[10]. In laboratory settings, biomechanically realistic whole-bone models made from fiberglass laminates or from acrylic/epoxy are widely used for purposes of implant design and construct strength testing[6]. At the intrinsic tissue level, a large number of *ad hoc* research protocols[18]— and now even several consensus testing standards[3]— utilize surrogate materials specifically developed to mimic bone's local interaction with orthopaedic devices (e.g., screw purchase, suture holding strength,[5,9,17] etc.)

Another potential use of surrogates is to help systematically investigate aspects of bone behavior which are otherwise difficult to study. One seemingly fertile area is the phenomenon of comminution in high-energy fractures. Complex fragmentation patterns in high-energy fractures typically defy classification by conventional measures[11], despite recognition that comminution

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severity correlates with tissue-level energy absorption, and hence with treatment outcome. A surrogate material with bone-like radiographic properties, and which mimics bone's tendency to shatter into ever smaller pieces with increased impact energy, would be useful for developing objective digital image analysis techniques to quantify the morphology and displacement of comminuted fragments.

Taking this possibility a step further, it may even be feasible to quantify the energy responsible for a given fracture. A means to do so would be to draw upon the principles of engineering fracture mechanics, in that the energy absorbed in propagating a crack through a solid medium is equal to the medium's fracture energy per unit surface area (a measurable material property) times the total surface area liberated[1]. For a given comminuted fracture, in principle one could use image analysis of CT-apparent fragment margins to measure liberated surface area, and hence estimate energy delivery. Developing the necessary computer programs would be aided by having bone-fracture-mimicking surrogate material amenable to controlled-energy impacts. This paper describes the composition and characterization of a novel surrogate material that is being utilized to facilitate the development of objective, quantitative measures of comminution phenomena.

MATERIALS AND METHODS

Foam composition and radio-opacification

Various types of fracturable materials (acrylics, ceramics, brittle foams) were screened for fracture patterns consistent with those of bone, using a drop tower test. Of these materials, the most promising were dense, closed-cell foams created by mixing polyetherurethane resin with methyl diphenyl diisocyanate. That class of foams' cell size and texture can be controlled with a silicon surfactant. It was found that pulverization tendencies (i.e., the propensity to produce powder rather than discrete fragments) were less for glucose-based (versus sucrose-based) foams, and that powdering also tended to decrease with increased density. We judged that clinically realistic fragment morphology occurred for a density of about 640 kg/m^3. To adjust the radiographic appearance of the material, finely sieved anhydrous $BaSO_4$, a clinically familiar radio-opacifying agent, was dispersed throughout the foam in concentrations ranging from five to twenty-five weight-percent. Specimens were examined radiographically using a Toshiba Express/XS CT scanner (Toshiba, Tustin, CA) at 120 kVp and 250 mAs. The Hounsfield number (H) was sampled at five locations in each of four transverse CT slices ranging from 1 mm to 10 mm in thickness (1mm, 2mm, 5mm, 10mm). A best-fit curve was then determined for this data.

Drop tower testing

Next, parametric drop tower testing was conducted at various input energies and with differing mass/velocity combinations. Specimens with twenty-percent $BaSO_4$ concentration* were machined to uniform hollow cylinders (19.69 mm OD, 11.11 mm ID, 69.22 mm height). During testing, a flat platen was placed on top of test specimens to ensure even distribution of the impact load. For one set of test specimens (n=6 per group), five distinct energy levels (ranging from 2.73 x 106 to 9.63 x 106 J/m3) were delivered, all with the same impact velocity (6.24 m/s) but with different drop masses. The minimum energy level was based on a pilot test group which had shown that an input energy of 2.23 x 106 J/m3 reliably produced small cracks, but was insufficient to cleave the specimens into separate fragments. In a second set of drop tests (n=8 for each of five groups), all groups received the same energy input of approximately 4.66 x 106 J/m3, but impact velocities differed (3.46 to 6.92 m/s).

Specimen preparation

To further characterize the foam surrogate, its mechanical properties were compared to those of bovine cortical bone via quasistatic four-point bend testing and by pendulum impact testing. All bovine specimens were machined from three tibiae that had been obtained from a local slaughterhouse and fresh frozen to –20° C. During all phases of specimen preparation, the bones were continually hydrated with saline. Tibiae were first rough-cut into curved longitudinal beams using a bandsaw. The long axis of the specimens was made roughly parallel to the long axis of the bone. Bone samples were then milled to their final dimensions within 0.25 mm. Foam samples were also milled.

Four-point bend testing

An MTS Bionix 858 Servohydraulic Test Machine (MTS Corporation, Eden Prairie, MN) with a 2500 N load cell was used to perform four-point bending tests on the foam. Standard four-point bend fixtures (span separation of 38.1 mm (1.5 in) for the foam and 25.4 mm (1.0 in) for the bone) were used. The crosshead

*This specifically fabricated foam has been designated Grade FR7140 Last-A-Foam® (General Plastics Manufacturing Co., Tacoma, WA)

Figure 1a. Hounsfield Balanced Impact Test Machine. The pendulum on the left (outer pendulum) is slotted in the middle (and has the impaction platens) such that the pendulum on the right (inner pendulum, with the specimen) can swing through it. The white dashed line indicates the location of the impact plane.

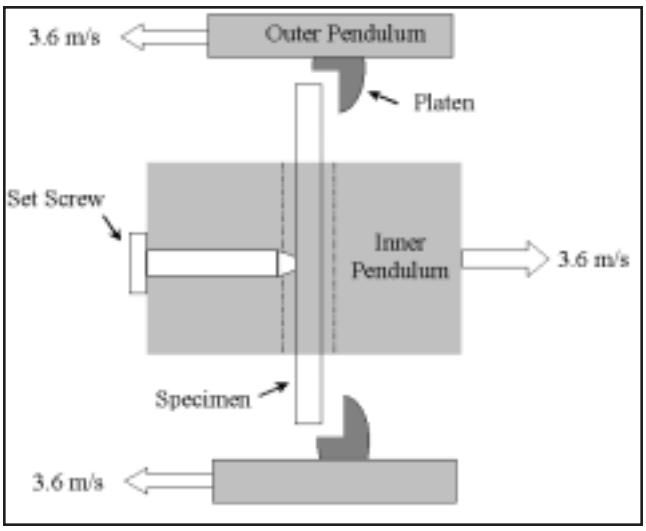

Figure 1b. Top view of "impact plane" just before the instant of specimen contact in the dual pendulum apparatus.

speed was set in such a manner as to produce a strain rate of 0.00017 s^{-1}. Span-to-depth ratio (unsupported length to bone thickness) was 16:1, as recommended by ASTM standards.[2] Flexure specimen dimensions were 139.3 x 12.7 x 7.14 mm for the foam (n=6), and 101.6 x 12.7 x 4.76 mm bone (n=5). From the recorded load-deflection curve, Young's modulus (E) was calculated according to:

$$E = \frac{5\ c^3[P/y]}{121}$$

where c = span distance between the inner contacts, I = cross-sectional area moment of inertia, and P/y = slope of the load-deflection curve.

Pendulum impact testing

The test apparatus (Hounsfield balanced impact tester (Figure 1a)) consisted of two cast iron pendulums, simultaneously released from height. The test specimens traveled in a slot on one pendulum, and, at the lowest point in the swing (Figure 1b), percussed against two flat points on the other approaching pendulum. The energy lost to the specimen during this three-point bending impact loading event, manifest by reduced pendulum upswing, was registered on a dial scale. For our impact tests, the impact velocity was 7.2 m/s. Speci-

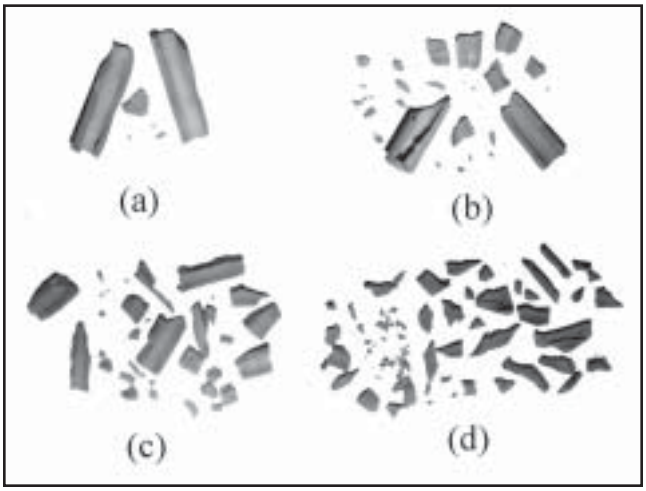

Figure 2a-d. Foam surrogate fragmentation increases monotonically with input energy from drop tower tests. Input energy in this series ranges from 2.73 x 10^6 J/m^3 to 9.63 x 10^6 J/m^3.

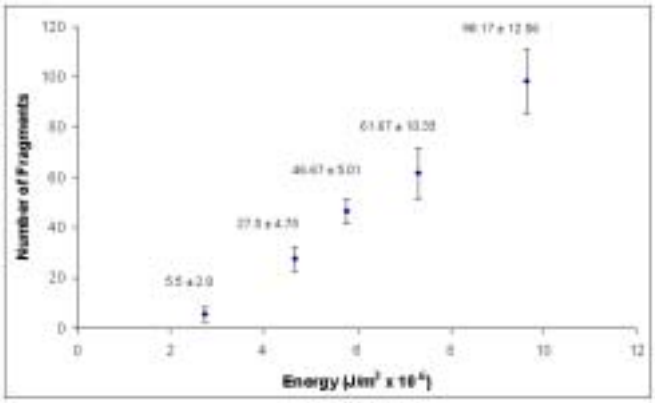

Figure 3. Fragment count for different energy levels in drop tower impacts to the surrogate material. (Constant velocity, varying drop mass).

men dimensions were 45.72 x 13.72 x 5.97 mm (n=8 per group), and they were positioned such that impact was transverse to the (anatomic) longitudinal direction. Results for bone and foam were compared with an unpaired, homoscedastic t-test.

RESULTS

Fracture patterns obtained from drop tower tests confirmed that, as is seen in clinical bone fracture cases, polyetherurethane foam is fracturable into ever-larger numbers of irregular fragments with increasing energy input (Figure 2 and 3). As energy input increases, fragment size decreases, number of fragments increases, and 'sharpness' of fragments increases.

The surrogate closely replicates the CT signature of natural bone at clinically relevant scan parameters. Hounsfield number varied in direct proportion to percentage of $BaSO_4$. This relationship was very well characterized by a linear regression equation ($R^2 = 0.9999$):

$$H = 99.497 \times (\% BaSO_4) - 427.6$$

Foam containing twenty percent $BaSO_4$ appeared in the CT scans as 1555 ± 28 H, as averaged over all thicknesses.

In pendulum impact testing (Table I), the foam's energy absorption capacity was marginally higher than that of cortical bone. (The foam, as would be expected, exhibited far less variability than natural bone.) The foam material was an order of magnitude lower than cortical bone in terms of bending modulus and ultimate strength (Table I). The foam's quasi-static toughness (Table I), computed from a stress-strain curve, was halfway between the values reported for cortical bone and regressed for cancellous bone[14].

Table I.
Four-point bend and pendulum impact test results

	Foam	Cortical Bone
Absorbed Energy	0.071 ± 0.009 J/mm²	0.106 ± 0.048 J/mm²
Young's Modulus	0.795 ± 0.030 GPa	13.69 ± 4.25 GPa
Quasi-static Toughness	4.00 ± 0.24 MPa	21.17 ± 3.48 MPa
Ultimate Strength	27.34 ± 1.74 MPa	222.00 ± 39.53 MPa

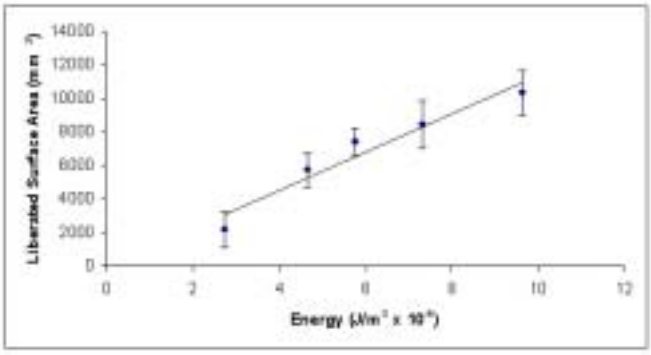

Figure 4. Estimated interfragmentary surface area increases in proportion to input energy in foam surrogate specimens.

A first-order approximation of surface area can be obtained from fragment counts with the simplifying assumption of identical size and nominally spherical morphology for the foam fragments produced by each specimen. Plotted in that idealized manner, data in Figures 4 and 5 are reasonably consistent with the theoretically suggested linear proportionality between energy and interfragmentary surface area. Linear regression of the data from the constant velocity series yields the line of best fit depicted in Figure 4, with an R^2 value of 0.937. In the series with constant energy input, analysis of variance demonstrates no significant dependence of liberated surface area solely on mass ($p=0.240$) or impact velocity ($p=0.124$).

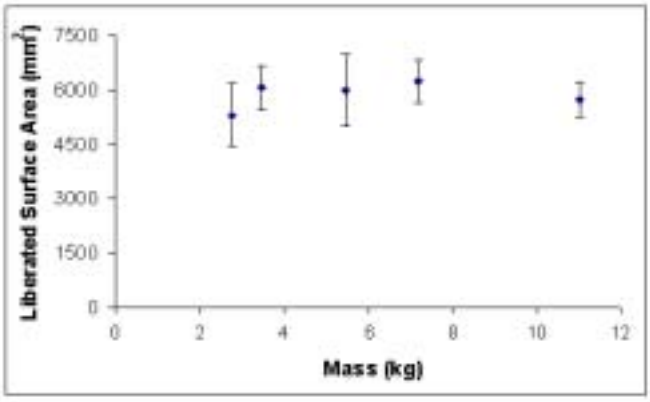

Figure 5. Approximate foam surface area liberated with constant energy input for various mass/velocity combinations. Analysis of variance shows no statistically significant effect of mass (p=0.240) on liberated surface area if energy is constant.

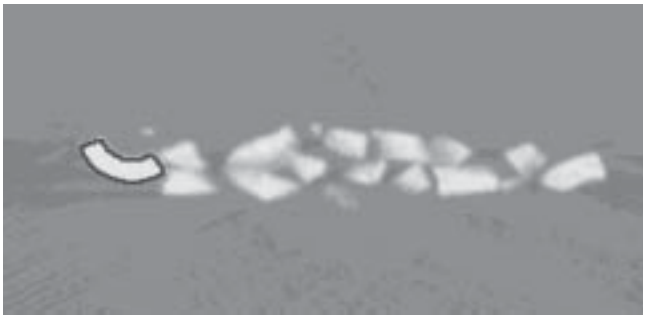

Figure 6a

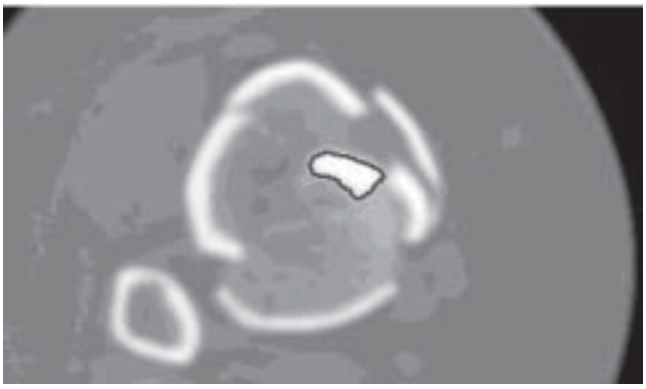

Figure 6b

Figure 6. Delineated perimeter, an index of interfragmentary surface area, is shown in (a) a foam surrogate CT slice and (b) a tibial pilon fracture CT slice.

DISCUSSION

Predicting the force and energy necessary to cause bony fracture has been a topic of interest to biomechanists and orthopaedists for over a hundred years.[13] With this new surrogate foam as a study vehicle, the reverse can now also be contemplated – examining a fractured bone and measuring the energy it absorbed.

Radio-opacification

There is appreciable variation in CT Hounsfield number for natural cortical bone, the reported range being from +1000 to +2000 H.[8] When doped with twenty percent $BaSO_4$ the foam falls at the midpoint of this range. If needed, the foam's radiodensity can be modulated to span the entire range from cortical to cancellous bone.

An added benefit of this novel surrogate material is that it is easily machinable. Thus, highly precise geometrical objects can be produced from the foam, for example for computer model validation purposes. Alternatively, as needed, the foam can be fabricated into irregular (e.g., anatomic) shapes by means of pressurization molding.

Mechanical testing

The present four-point ultimate bending strength of bovine cortical bone (222.00 ± 39.53 MPa) compares well with the results of Martin and Boardman[12] for plexiform bovine tibial bone (230.5 ± 17.7 MPa). The present elastic modulus and ultimate strength are also similar to values previously reported by Behiri et al[4]. Compared to these typical cortical bone data, the polyetherurethane surrogate material is an order of magnitude lower in bending modulus and ultimate strength. The foam's quasi-static toughness is about halfway between cortical and cancellous bone fracture toughness[14]. In the four-point bend test, the foam exhibited about one-fifth the toughness of bovine cortical bone. However, it should be recognized that the present data for cortical bone stiffness, strength, and quasi-static toughness were collected for transversely loaded rectangular specimens, and therefore would tend to be overestimates of direction-averaged values that might more directly correspond to comminuted fractures.

Because the surface area to volume ratio is minimized for a sphere, estimates of liberated surface area based on spherical morphology are subject to a greater degree of underestimation as fragment number rises. This effect is consistent with the concave downward nature (apparent relative to the fitted regression line) of the trend in Figure 4.

In the pendulum impact test, there was much better repeatability in the values obtained for the polyetherurethane than in the values obtained for bone. Under these moderately high speed impact conditions, the surrogate exhibited a fracture toughness which was only slightly lower (p=0.065) from that of bone, unlike the order-of-magnitude difference prevailing quasi-statically. Obviously, both the bone and the polyetherurethane foam are viscoelastic materials, and therefore exhibit strain rate dependent mechanical properties. Establishing similarities and differences in strain rate dependency of the foam, versus that of bone, is an inviting subject for future study.

Our current use for the foam surrogate is as a gold standard (phantom) calibration material for development of CT-based image analysis routines for fragment perimeter identification (Figure 6). Besides aiding in classifying comminution for clinical injury description, we are working toward establishing an explicit linkage between interfragmentary surface area and energy absorption.

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ANTIBIOTIC BEAD PRODUCTION

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ABSTRACT

We are reporting a practical technique for the production of antibiotic beads for use in combating musculoskeletal infections. The technique utilizes bead molds with tobramycin powder mixed with polymethylmethacrylate on twisted wire strands to produce strands of 25 beads of various sizes. These beads are gas sterilized and available for use "off the shelf" in a manner that is much more efficient than traditional production by hand on the back table in the operating room. Our technique was also utilized at a second institution to demonstrate its efficacy at another site.

INTRODUCTION

Antibiotic beads have gained wide acceptance in orthopedics in the treatment of a variety of skeletal infections due to their ability to provide high concentrations of antibiotic at the site of infection while avoiding the complications associated with systemic toxicity.[8,11] Traditionally, beads have been made by hand in the operating room on the back table during the case. This is a time consuming and cumbersome process, and is an inefficient use of resources. The antibiotic is not uniformly distributed, the bead size and shape is inconsistent and the beads are not well attached to the wire. In addition, the methylmethacrylate monomer, known to be toxic to musculoskeletal tissue, is still present for the first two hours after mixing the beads.[12,13] Prefabricated beads are less expensive and easier to use. They allow for more uniform delivery of the antibiotic and are of better quality and consistency than hand made beads (Figure 1). Although the FDA has approved the use of antibiotics in beads, these beads are not commercially available because no company has been approved to sell the combined product. The purpose of this article is to outline and illustrate our technique, and provide practitioners with all the information required for the production of these beads using molds. We report the evaluation of our technique at the University of New Mexico in terms of improvements in quality, efficiency and cost of bead production with molds compared to traditional methods. We also report experience using these techniques at another institution.

MATERIALS AND METHODS

The first step in the prefabrication of antibiotic beads is obtaining bead molds. We utilized the metal casted teflon coated molds commercially available from the University of Vermont (Figure 2).[3] Each mold will make two chains of 25 beads that are 6.4 mm in diameter. The materials are then assembled (Table 1). Beads are

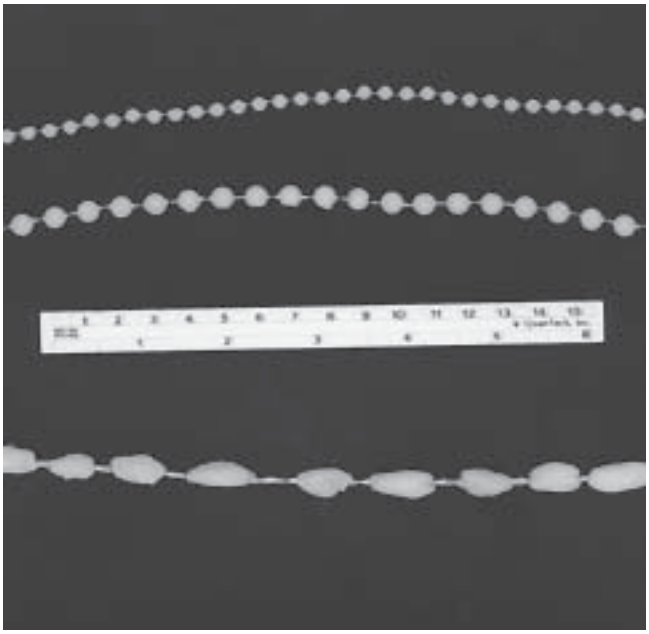

Figure 1. The 6.4 mm diameter and 5.0 mm diameter mold produced beads are compared to the typical hand made beads.

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TABLE 1
MATERIAL FOR BEAD PRODUCTION

Antibiotic bead mold:
University of Vermont, Instrument & Model Facility
280 East Ave
Burlington, VT 05401-3462
Phone: (802) 656-2976
Fax: (802) 656-8561

Sizes:
6.4mm beads- 25 beads/strand- $990/mold
4.0mm beads- 40 beads/strand- $1040/mold

1 package polymethylmethacrylate (40g)
2-1.2g vials Tobramycin (Nebcin) powder
26- gauge wire
2-10cc syringes
1-20cc syringes
5 specimen cups
1 plastic bowl
Gloves
Hand drill to twist wire
Scale
Scoopla (small stirring rod)
Suture Kit
1-18 gauge filter needle
Laboratory scale

Table 1. The materials for bead production

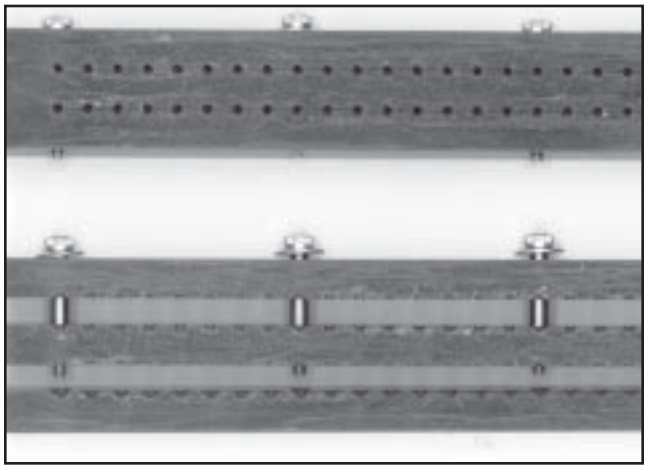

Figure 2. The black, forged metal, teflon-coated bead molds for the 6.4mm diameter beads are shown. This mold produces two chains of 25 beads.

TABLE 2
METHOD FOR BEAD PRODUCTION

1. Twist two strands of 26- gauge wire x 50 turns using the hand drill.
2. Place the twisted wire in the bead mold and tighten the mold.
3. Mix one package of bone cement with 2.4g Tobramycin in a plastic bowl.
4. Weigh 5 equal portions of 8 grams mixture into specimen cups.
5. Draw up monomer into a 20cc syringe using the filter needle. Remove needle.
6. Add 4cc of monomer to 8g of powder mixture (one specimen cup), and mix for 20 seconds.
7. Pour this mixture into two 10cc syringes (plungers out).
8. Replace the plungers and inject the mixture into each cavity of the mold sequentially by applying light pressure (takes about 2 minutes).
9. Once filled, remove excess cement by running a tongue depressor along the top of the mold.
10. Place mold on its side and leave it for 15 minutes.
11. Gently remove the beads from the mold, and remove the flashing using the tweezers.
12. Place each strand of beads in a peal pack and gas sterilize.
13. Repeat the procedure for each remaining specimen cup.
14. Use as needed.

**Steps 6 through 8 should take no longer than 5 minutes.
**Makes 10 bead strands total.

Table 2. The method of bead production

made in a clean vacuum hooded environment by the formula described in Table 2. Two strands of 26 gauge wire are twisted together fifty turns using a hand drill and placed in the slots of the mold. One 40 gram packet of sterile methacrylate monomer powder is mixed with two vials of tobramycin powder (1.2 grams each), and then divided into five equal, eight gram portions utilizing a laboratory scale, and placed into specimen cups. The monomer is aspirated into a 20cc syringe using an 18 gauge filter needle. Four milliliters of monomer is

mixed with the eight grams of powder mixture for 30 seconds and placed in two 10cc syringes. The liquid is then sequentially injected into each hole in the bead mold with gentle pressure. Excess cement is removed by scraping the tongue depressor along the top of the mold, and the molds are allowed to set for twenty minutes. The beads are subsequently taken from the molds and flashing is removed. When the process is complete, each bead chain is placed in a sterile peal pack and gas sterilized using ethylene oxide gas. The sterile packets are opened in the operating room for use as they are needed.

To determine the efficiency of this bead production method we compared the cost and time of our bead production method with traditional hand methods. We compared the total cost of the components of each technique and the amount of time to use each technique. The bead production method described was the end result of attempting over twenty different techniques for antibiotic bead production using molds. The cost of production included the mold, antibiotic powder, polymethylmethacrylate, wire, syringes and gas sterilization. The time included time to assemble the materials, production of the beads and sterilization time. The costs of the traditional method included the antibiotic powder, polymethylmethacrylate, wire, and cost of the operating room. The time included time to assemble the materials, and production of the beads. We also investigated the potential for this technique to be used at another institution.

RESULTS

This method was successful at the routine production of tobramycin impregnated polymethylmethacrylate bead chains. The cost of bead production with molds was eighty dollars per chain. The cost of bead production by traditional methods was two hundred and seven dollars per chain. The cost savings were the result of improved efficiency through marked reduction in wasted material. Eight chains were produced per batch of cement with prefabrication while hand-made technique averaged 1.5 chains/batch. Prefabricated beads were made in batches in a laboratory setting with economies of scale in set-up costs and marked reduction in cost compared to the operating room production of hand made beads. This cost efficiency was ten times greater than the increased cost of packaging, sterilization and storage of prefabricated beads. The time to make one chain with molds averaged twelve minutes. The time to make one chain by traditional methods was twenty-eight minutes. This represents a thirty percent improvement in cost, and a thirty-five percent reduction in time. When sterile unused cement was scavenged from arthroplasty cases and utilized in bead production, cost savings were increased to fifty-five percent. In addition to the quantitative advantages of bead production with molds, there were also distinctive qualitative advantages. The beads were vastly more uniform and more firmly attached to the wire. The antibiotic appeared to be more evenly distributed within the beads, and there also appeared to be less debris. The bead size was more appropriate for the majority of wounds than the hand made beads, which tended to be too large. Using the molds we were able to produce ten bead chains from one batch of cement. The hand made method produced only two bead chains.

This antibiotic bead production technique was utilized at a second institution to investigate its general potential applicability. Texas Tech University in El Paso, Texas had previously used hand made antibiotic bead technique. The second site purchased the bead molds and after two demonstrations of the technique were able to effectively produce the beads and incorporate them into clinical practice. This required cooperation among the Department of Orthopedics, the operating room, pharmacy and sterile processing.

DISCUSSION

At the University of New Mexico, the most common indications for the use of antibiotic beads are for open fractures, large infected wounds, chronic osteomyelitis, infected nonunions and secondary nailing after external fixation.[1,2,6,9] They have also been successfully used in the treatment of traumatic gun shot wounds and contaminated bowel wounds.[10] One example of the use of antibiotic beads is that of the antibiotic bead pouch technique in the initial treatment of an open fracture.[4,7] In this technique, the wound is irrigated and debrided, and skeletal fixation is achieved by standard orthopedic procedures. A chain of antibiotic beads is placed in the wound, especially in the dead space of bone loss. The wound is covered with a semi-permeable opsite, which prevents fluid leaking and desiccation while allowing oxygen to pass. An overflow drain to gravity only is placed to prevent the opsite from detaching from the skin and is removed after 36 hours. Beads are removed once a nice vascular bed develops typically at four days. At that point, assessment is made to determine the need for a bone graft or soft tissue coverage.[5]

Because antibiotic beads have historically been produced by the orthopedic surgeons themselves, pharmacy involvement has been minimal. With the new methods available for bead production, pharmacy intervention could help to further minimize the obstacles associated with antibiotic bead production.[3]

Molds are available to make beads in three sizes: 6.4 mm, 4.0 mm, and 3.2 mm.[3] It was very difficult to inject the cement into the small opening for the 3.2 mm beads, so we abandoned this technique. The 6.4mm beads are the most appropriate for the vast majority of indications, although the 4.0mm beads were useful in the hand and selected small wounds elsewhere in the body. The molds can be re-coated with teflon if wear occurs. We have used molds more than two hundred times and have not yet needed re-coating.

The shelf life of prefabricated antibiotic beads has been reported to be in excess of one year in pharmacokinetic studies by Walenkamp[14] and in Septopal beads sold commercially in Europe. Based upon the method of sterile processing and packaging that we utilized, we identify a six month shelf life on the peal pack. We did not perform a comparison of the elution characteristics of prefabricated beads to those made in the operating room, nor is this a comparison of clinical efficacy of these two techniques.

There are a variety of other techniques across the country for using molds. Another type of mold that is available is the plastic, disposable bead mold which can be purchased from the University of Minnesota. These molds consist of two plastic molded half domes which clamshell together and are secured by stainless steel sliding channels. A longitudinal slot accepts 0-prolene suture or 20-gauge stainless steel wire. Three chains of 25 beads are produced with each mold. Although these are less expensive molds ($55/mold), we encountered a variety of insurmountable problems when using them. It was very difficult to get the cement into the molds at just the right consistency, which often resulted in the premature consolidation of the cement. Often the two half domes were not well attached to each other or to the wire. Significantly more cement was required for each mold due to the excess amount of flashing and the large increase in wasted material. It was difficult to keep, or insure that the wire was in the track, which resulted in beads that were not centered or were not even attached to the wire.

Molds could also be used in the operating room. We found this technique less reliable and less efficient in both cost and time. We also attempted to make our own molds using a variety of designs. None of them were as good or efficient as the molds purchased and described in our technique.

SUMMARY

Antibiotic beads can be produced by acquiring commercially available, forged metal teflon coated molds with the materials and methods described in this article. This bead chain production method resulted in significant savings of cost and time with improvement in bead quality. This method is recommended to the orthopedic surgeon currently using the traditional handmade technique in the operating room.

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BLOOD MANAGEMENT AND PATIENT SPECIFIC TRANSFUSION OPTIONS IN TOTAL JOINT REPLACEMENT SURGERY

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Andrew I. Spitzer, M.D.**

ABSTRACT

Strategies for blood management in the perioperative period of total joint replacement are changing with the better understanding of blood loss and blood replacement options in this population. The preoperative, intraoperative and postoperative options for blood management are outlined. Rationale for patient specific options are described.

INTRODUCTION

In this new millennium, the medical community in general and the orthopaedic surgeon specifically, have more scientific information available concerning the blood loss that occurs during and following total joint replacement of the lower extremity. In addition, better scientific data is available regarding the risks and benefits of various blood management options for patients. Also, newer pharmacologic and blood salvage options have been and are being developed. Finally, the medical community has obtained better data concerning the relationship of patient factors (including age, gender, comorbidities and hemoglobin levels) contributing to the blood management needs in the perioperative period. This paper will explore the various blood management options available for the orthopaedic surgeon and his or her patients when performing or undergoing total joint replacement. The preoperative planning of blood management needs will be outlined.

Blood Loss Following Total Hip or Total Knee Replacement Surgery

The blood loss associated with primary and revision total hip replacement and primary unilateral and bilateral total knee replacement has been extensively studied. In primary hip surgery the blood loss is 3.2 $\pm$ 1.3 units[141] and 4.07 $\pm$ 1.74 grams of hemoglobin.[24] Eighty seven per cent of patients lose less than 5.8 grams. In revision hip surgery the blood loss is approximately 4.0 $\pm$ 2.1 units. In primary knee replacement the blood loss ranges from 1000 to 1500 cc and averages 3.85 $\pm$ 1.4 grams of hemoglobin.[24,71,101] 87% of patients lose less than 5.25 grams of hemoglobin. Blood loss has been reported to be even higher in cementless knee replacement.[57] In the perioperative period for bilateral total knee replacement the reported blood loss is 5.42 grams $\pm$ 1.8 gram[24,71] with 87% of patients losing less than 7.22 grams. Blood loss may be greater for the second knee[21] and alterations in coagulation have been noted. Transfusion rates of 2.0 $\pm$ 1.8 units for primary total hip replacement and 2.9 $\pm$ 2.3 units for revision hip replacement have been documented.[8] The rates for knee replacement are not well studied but are estimated at 1 to 2 units for primary surgery and 3 to 4 units for revision surgery.

Several studies have documented the risk factors associated with the need for transfusion.[15,20,21,71,75,96,107,118,148] Preoperative hemoglobin level is a major predictor of the risk for transfusion following total joint replacement.[9,15,32,37,40,43,55,71] Patients with a preoperative hemoglobin of less than 10 grams have a 90% chance of needing a transfusion, those with 10 to 13.5 gram level a 40-60% chance and those with greater than 13.5 grams a 15-25% chance. Other associated risk factors include blood volume, weight, age (patients less than 65 years with a hemoglobin greater than 13.5 had 3% risk of transfusion if they didn't autodonate blood),[55] estimated blood loss, aspirin use, female sex, comorbidities, thrombocytopenia and bilateral total knee replacement.

In a study of a large number of patients (9482) undergoing total hip and knee replacement, 46% (57% hip, 39% knee) required a transfusion. The wasting rate of autologous units was 61% and 45% (highest in primary surgery and revision knee surgery.) Nine per cent of patients who autodonated blood required allogeneic transfusion (8% primary THA, 21% revision THA, 6% primary TKA, 11% revision TKA). The transfusion rate for patients with a hemoglobin of 10 to 13 (34% of all patients) was 57%. In this group, 33% of patients undergoing total hip replacement and 23% undergoing total knee replacement required allogeneic transfusion even though they donated autologous units. Predictors of allogeneic transfusion were baseline hemoglobin less

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TABLE 1.
Allogeneic Transfusion Risks

COMPLICATION	RISK PER UNIT
Minor allergic reactions	1:100
Bacterial Infection	1:2500
Viral Hepatitis	1:5000
Transfusion related lung injury	1:5000
Hemolytic Reaction	1:6000
Hepatitis B	1:63,000
Hepatitis C	1:103,000
HIV/AIDS	1:500,000
Anaphylaxis	1:500,000
Fatal Hemolytic Reaction (ABO incompatibility)	1:600,000
HTLV I/II Infection	1:641,000
GVHD	RARE
Immunomodulation	UNKNOWN

TABLE 2.
Comparative Mortality Risks

One pack per day of tobacco	1:200
Influenza	1:5000
Automobile deaths	1:6000
Frequent flying academic physician	1:20,000
Leukemia	1:50,000
Birth control pills	1:50,000
Tornadoes in Midwest	1:445,000
Floods	1:455,000
Earthquakes in California	1:558,000

than 13 grams and lack of autologous blood donation. Complications of allogeneic transfusion included infection and fluid overload ($p \leq .001$) and increase in length of stay ($p \leq .01$).

Options for Blood Management in the New Millennium

Allogeneic transfusion is a potential option for blood replacement in all patients. The risks of allogeneic transfusion are listed in Table 1 and comparative mortality risks are listed in Table 2. Other risks of allogeneic transfusion include clerical error (1:20,000-24,000), bacterial contamination, infection, immunomodulation, increase length of stay, and increased cost.

The goal of a blood management program is to reduce exposure to allogeneic blood, reduce the overall need for transfusion, eliminate transfusion related complications,[5,15,18,19,25,38,39,46,69,74,81,99,123,130,142] reduce cost, and develop a global strategy for blood management which is individualized and based on risk.[24,27,46,71,77,78,104,107,125] In addition, if possible, the blood management program should improve medical and functional outcome. Along this path recent investigators have evaluated postoperative vigor[72] in relationship to facilitated recovery, shortened length of stay, improved short term and long term physical function.

Strategies have been developed to reduce transfusion and the complications of transfusion during and following total hip and knee replacement. Practice guidelines include good hemostatic technique, preoperative autologous blood donation, intraoperative and postoperative blood salvage, acute normovolemic hemodilution, unit by unit transfusion based on individual needs and pharmacologic intervention when indicated. Blood loss can be reduced[103] by preoperative, intraoperative, and postoperative measures. Preoperatively anti-platelet agents and anticoagulants should be eliminated when possible, bleeding history should be obtained, appropriate laboratory screening (CBC, platelets, coagulation studies, and bleeding time if indicated) should be performed, and a rationale approach to predonated autologous blood donation should be instituted considering preoperative risk factors and estimates of blood needs.[9,55,78,81,107] Intraoperatively blood loss can be minimized by proper anesthetic techniques, pharmacologic intervention and surgical technique. Anesthetic techniques[124,129] include hypotensive anesthesia, regional anesthesia[23,31] and euthermia.[121,122] Pharmacologic techniques include topical agents (thrombin, fibrin glue, collagen, Gelfoam, Avitene, epinephrine sponges and bone wax) and systemic antifibrinolytics (Desmopressin,[67] Aprotinin,[56,66,98,140] tranexamic acid[11-13,62,63] and E-aminocaproic acid[92]). Postoperative measures include reduced phlebotomy, careful anticoagulation, nutrition, wound compression, and potentially avoiding continuous passive motion[84,112,151] and drains.[2,10,53,64,111,116,117,119] In addition, arbitrary transfusion triggers should be avoided.[25,44,46,106,135,136] The surgeon should transfuse for symptoms instead and assess the patient for his or her physiologic risk from anemia. Hemoglobin levels as low as 8 are tolerated in the elderly without consequences[23] and between 7 and 9 even in patients in critical care units without acute cardiac disease.[60] Blood should be transfused unit by unit as needed. Patients with known cardiac disease and risk factors for morbidity from anemia[25, 83,136] should be transfused earlier. Lower hemoglobins can be accepted in women due to lower hemoglobin starting point.[46]

Specific Alternatives to Allogeneic Transfusion

Preoperative autologous blood donation continues to be the current standard alternative to accepting allogeneic transfusion during and following total joint replacement.[1,17,47,50,126,137,139,143,147-149] Typically 1 or 2 units are obtained for primary joint replacement, 3 to 5 units for bilateral total joint replacement and 4 to 6 units for revision total joint replacement. The technique is indicated for patients with a hemoglobin greater than 11 and a hematocrit greater than 33. Units are drawn at 5 to 7 day intervals with the last unit drawn at least 3 days prior to surgery. Maximizing the time between the last unit and surgery increases the starting hemoglobin. Each unit removes about 500 cc or 9% of the blood volume of the average 70 kilogram man, hence supplemental iron should be provided. Contraindications include infection, unstable cardiovascular diseases and unacceptable anemia. Risks and complications[47,81,113] include the poor endogenous erythropoietin response in patients with mild anemia leading to an increase in preoperative anemia,[68,73,82] poor tolerance in the elderly to the donation process, bacterial contamination, wastage of unused blood[9,15,33,40,47,55,75] and potential increased risk of transfusion and allogeneic blood exposure.[9,27,55,126,138]

Preoperative autologous donation decreases hemoglobin by 1.2 – 1.5 grams/dl. The advantages of this technique include the reduction in perioperative allogeneic blood exposure[6,15,126] hence eliminating the risks of allogeneic blood transfusion.[19,58] Recent studies have also demonstrated a potential reduction in the risk of postoperative deep venous thrombosis in total knee[3] and total hip procedures.[8]

An alternative or adjunct to preoperative autologous blood donation is perioperative blood salvage. Intraoperative blood salvage has been shown to be beneficial in cases involving more than 1000 cc of blood loss.[42,80,92,122,124,132,144] Sixty per cent of intraoperative blood loss[124] can be salvaged and 400 to 500 cc of salvaged blood is required for reinfusion. The blood cells that are salvaged are altered (by irrigation, air, cement) and careful washing is important to avoid coagulopathy.[88,100,143] It is not cost effective in primary arthroplasty if preoperative autologous donation is used. Postoperative salvage and reinfusion drainage systems are also available using washed or unwashed and filtered cells.[14,22,26,28,29,36,41,51,54,59,61,76,86,87,127,128,131,145,146,148,150] Postoperative wound drainage is collected and reinfused. Complications of unwashed reinfusion have included hypertension, hyperthermia, upper airway edema, coagulopathy[100,133], febrile reaction, transfusion of byproducts of hemolysis and intraoperative contaminants[133] and even death. Blood can only be collected for 4 to 6 hours thus limiting reinfusion to 500 to 1000 cc. The advantages of this technique are that significant amounts of blood can be retrieved and reinfused. Postoperative blood salvage can reduce allogeneic blood transfusion exposure if no autologous blood is available,[7,75,105] and further reduce allogeneic exposure when autologous blood is available.[150]

Another option for avoiding allogeneic blood transfusion is normovolemic or hypervolemic hemodilution.[30,47,93,95,109,110,122] With acute normovolemic hemodilution blood is collected immediately preoperatively by the anesthesiologists and stored for reinfusion postoperatively. The volume removed is repleted with crystalloid and colloid. Hypervolemic hemodilution is performed without phlebotomy only using crystalloid. The rationale for this approach is that blood that is lost at surgery will have a lower hematocrit and that the cells and blood that is retransfused is healthier. Indications, as with the other described techniques, are in cases with expected significant blood loss (such as total joint replacement). The patient must be healthy enough to tolerate acute anemia. Risks include the time consuming nature of the procedure and the procedure is contraindicated in patients with coronary artery, renal, pulmonary and hepatic disease.[30] The advantages of this technique[24,47,122] include reduction in perioperative allogeneic blood exposure[110] (particularly if combined with other autologous blood use strategies[109]), reduced cost (no inventory or testing costs, no patient costs associated with procurement), and the reduced risk of clerical error (blood never leaves the room).

The other option in blood management is to increase hematopoiesis with pharmaceutical intervention. This has routinely been done by administering iron to those patients donating blood. However a much more effective way to increase hematopoiesis is the administration of erythropoietin alpha, a recombinant human erythoropoietin.[16,32,34,35,43,45,49,52,65,79,89-92,94,120,134,138] Erythropoietin stimulates the differentiation of progenitor cells to become dedicated to the red blood cell line. The recombinant form mimics the physiologic action of endogenous erythropoietin glycoprotein hormone. In this technique, weekly injections (600 units/Kg) are given preoperatively on day 21, 14, and 7 as well as on the day of surgery. Alternately, the drug can be given daily for 10 days (300 units/Kg) followed by 4 days postoperatively. Adequate levels of iron must be maintained.[34,48] The technique is presently indicated for patients with hemoglobin levels of 10 to 13, those unable or unwilling to undergo preoperative autologous blood deposit, bilateral and revision cases and patients that are Jehovah's Witnesses.[102,134] The advantages of this approach are that it augments the number and quality of preoperative autologous deposited units[45,108,114,115,] and

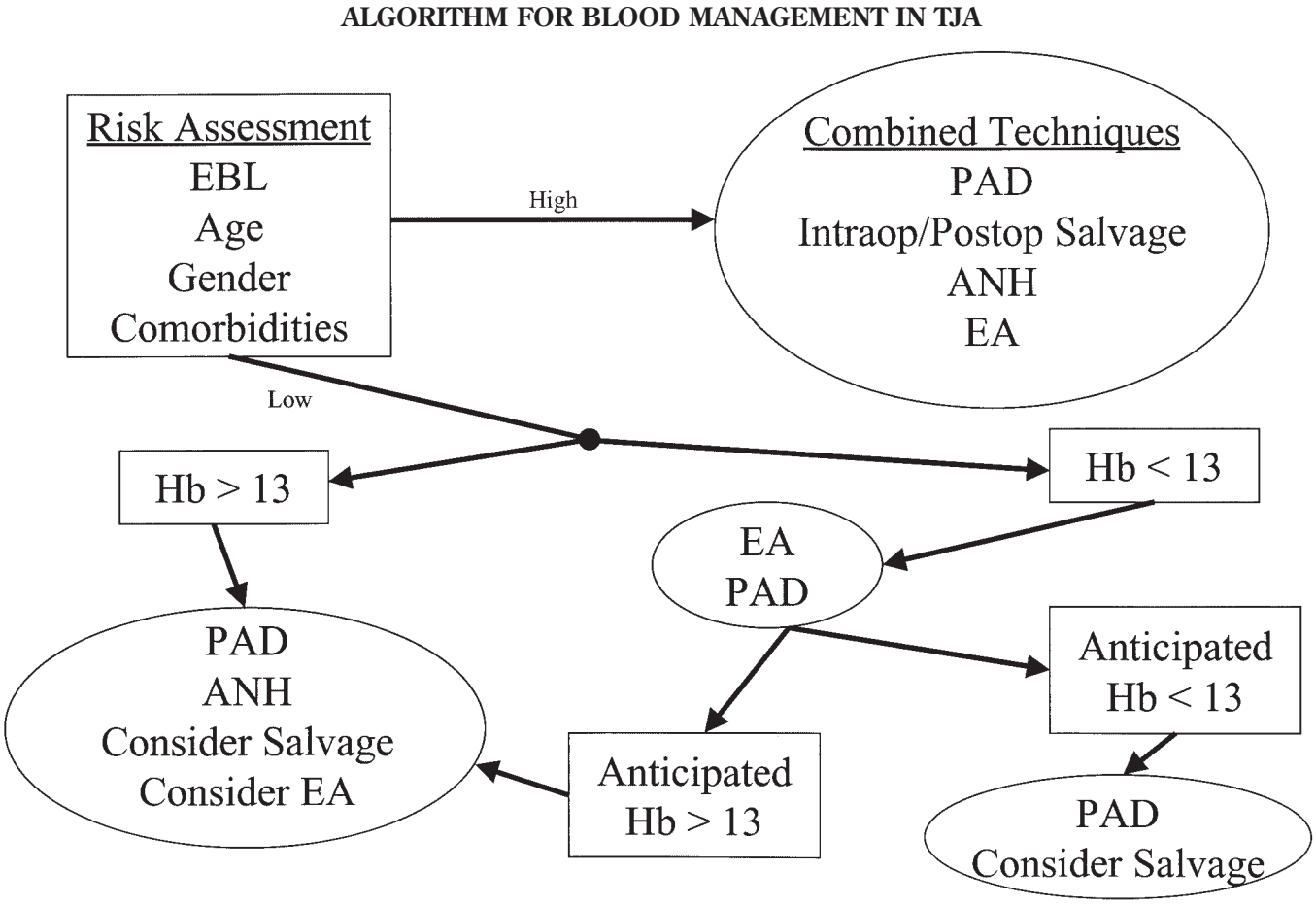

Figure 1. Proposed algorithm for blood management in total joint replacement. (Estimated Blood Loss, EBL; Preoperative Autologous Donation, PAD; Acute Normovolemic Hemodilution, ANH; Erythropoietin alpha, EA; Hemoglobin (gm/dl), Hb)

maximizes perioperative hemoglobin,[138] particularly in comparison to matched populations of autologous donors. Preoperatively, postoperatively, and at discharge, hemoglobin levels were higher in the erythropoietin alpha group compared to the preoperative autologous donation group. Recently, it has been shown to improve postoperative vigor.[72] Especially in patients with preoperative hemoglobin levels of 10 to 13 grams it significantly reduced transfusion risk (16 versus 45%). In this study hemoglobin level was directly proportional to readiness to resume activities of daily living and muscle strength. Improved hemoglobin enhanced the postoperative recuperative power (vigor and functional ability) and ability to participate in early intensive rehabilitation, thereby minimizing length of stay.[97] Other advantages of erythropoietin alpha are that it stimulates an accelerated response to anemia[4] and significantly reduces allogeneic blood exposure even in revision and bilateral surgery. The disadvantages of the drug are that it is injectable and expensive.

Patient Specific Transfusion Options

With all of the data available today concerning the blood loss associated with primary and revision total joint replacement, as well as the costs, benefits, and risks associated with the various blood management options and a better understanding of patient specific factors (such as the individual's blood volume and preoperative hemoglobin status), orthopaedic surgeons can better outline and implement blood management strategies for their patients. Although costs of allogeneic blood and autologous donation are hospital specific, autologous blood donation is considered more expensive and is bundled into the DRG of the procedure (Medicare part A) without additional reimbursement.[152] In addition, wastage has been documented in up to 80 percent of cases.[9,15,33,40,55,75]

When developing a cost effective strategy for blood management it should be based on patient risk. The goal should be to minimize morbidity to the patient including minimization of preoperative and postoperative

anemia, transmission of disease from transfusion and avoiding other morbidities from allogeneic or autologous transfusion. In addition, maximum functional outcome and postoperative vigor should be maintained and cost should be minimized. Waste and inappropriate use of technology should be avoided. Utilization of resources should be tailored to the documented needs of the patients.

Individual patient risk of transfusion should be assessed. Transfusion trigger should be determined based on the minimum hemoglobin that is acceptable given the patient's health, age and risk factors. The estimated blood loss should be determined (and this is probably surgeon and anesthesia dependent). The acceptable blood loss which will avoid transfusion trigger should be determined. Starting hemoglobin and patient weight and blood volume (males 65 to 70 cc blood/kg lean body weight, females 55 to 65 cc blood/kg lean body weight) are the important factors in this determination. An acceptable risk of allogeneic exposure should be chosen.

Algorithms for blood management in total joint replacement (Figure 1) have been developed.[9,24,27,40,47,55,71,77,78,81,85,104,107,125] The goal is to minimize transfusion by instituting institutional guidelines for transfusion,[6,44,69,70] reducing transfusion triggers, utilizing aggressive strategies to reduce blood exposure and blood loss, and using marrow stimulants such as erythropoietin. Patients are categorized as high risk for transfusion (i.e. difficult revision surgery) or low risk (i.e. routine primary hip or knee replacement). If a patient is low risk and has a hemoglobin above 13 grams, he or she and the surgeon may decide on predeposit autologous donation, normovolemic hemodilution, intraoperative and postoperative salvage or erythropoietin alpha. If the patient is low risk with a preoperative hemoglobin less than 13, the options include erythropoietin alpha or autologous donation (if the patient's hemoglobin is greater than 11). Since the need for transfusion in patients with a hemoglobin of 10 to 13 grams is high even with predeposit autologous blood we consider erythropoietin alpha (33% for primary hips and 23% primary knees). If following this therapy the anticipated hemoglobin is still less than 13, intraoperative salvage or additional autologous blood donation (if the hemoglobin is above 11) can be considered.

SUMMARY

In summary, total joint arthroplasty results in significant blood loss. Patients undergoing total joint replacement are at significant risk for transfusion. There has been a paradigm shift to reducing the need for its inevitability and to improving perioperative blood management to maximize hemoglobin and positively impact early and long term outcome. This requires preoperative risk assessment, preoperative preparation, optimizing operative technique, and proper postoperative management as outlined in this manuscript.

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DIFFERENCES IN MEN'S AND WOMEN'S MEAN ANKLE LIGAMENTOUS LAXITY

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ABSTRACT

The incidence of ligamentous ankle injuries is known to be one of the most common athletic injuries that exists. Recently, there has been a great deal of interest regarding the increased risk of female ligamentous injury, such as the anterior cruciate ligament, lateral ankle sprains and others. The purpose of this study is to evaluate whether or not normal lateral ankle ligamentous laxity is similar in male and female athletes. This study selects 22 male and 27 female college athletes who have had no significant ligamentous ankle injuries requiring medical treatment. They were placed on a Telos ligamentous stress device and stressed to a level of 15 daN. Radiographs were then obtained to determine talar tilt at this level of ankle stress. Results were compared between men and women showing that there was a statistically significant difference. Women had a much greater ligamentous laxity of the lateral ankle than men.

INTRODUCTION

The degree of ankle ligamentous laxity is important in determining treatment of the injured ankle, and measuring talar tilt angle is one way to determine this laxity. In order to determine whether or not laxity is excessive, it is necessary to establish normal talar tilt. Attempts to determine normalcy have been made, but these attempts have failed to examine possible differences in talar tilt between men and women.

Recent literature has begun to look at differences between injury patterns in men and women. In a study by Arendt, Agel, and Dick, collegiate women basketball and soccer players were shown to tear their anterior cruciate ligaments at a significantly higher rate than college-aged men participating in the same sports.[2] A study by Gray and colleagues examined 76 female and 151 male basketball players over a 30-month period. They found that 19 female basketball players ruptured their ACL's, while only 4 male basketball players did the same.[4] Zelisko, Noble, and Porter looked at all of the injuries sustained by one men's professional basketball team and one women's professional basketball team over two consecutive seasons. They found that the frequency of all of the women's injuries was 1.6 times that of men. They also found that the most frequently injured body part in the athlete was the ankle for both the men and women.[6]

Research on ankle talar tilt has established norms for men and women as a combined group. Cox and Hewes examined the talar tilt of 202 midshipmen's ankles (404 ankles) at the U.S. Naval Academy. All subjects had no previous ankle injuries in order to establish a normal tilt range. One hundred ninety-one males and 11 females made up this subject group, but they were not put into separate categories. Results of this grouped study revealed that 365 ankles had 0 degrees of tilt, 32 ankles had 1-5 degrees of tilt, and 7 ankles had greater than 5 degrees of tilt.[3]

Ahovuo, Kaartinen, and Slatis looked at 63 patients' ankles (30 men, 33 women) in which the men and women were again put into the same group. Results showed that of the uninjured ankles, 43 had a talar tilt of less than 5 degrees, 11 had tilts of 5-10 degrees, and 2 had tilts of greater than 10 degrees. These results established a normal talar tilt of 5 degrees or less.[1]

Research by Rubin and Witten examined talar tilt of the ankles categorizing patients as having normal ankles, ankles with old or recent sprains, and ankles with other abnormalities. They found that among the normal ankles 56% had tilts of 3 to 23 degrees. Again there was no comparison of the differences in the talar tilts of normal ankles of men and women.[5]

The purpose of this article is to present new information on the normal talar tilt differences between male and female athletes who have had no history of ankle sprains serious enough to warrant missing a practice or game, or causing need for any medical treatment.

MATERIALS AND METHODS

Twenty-two male and twenty-seven female athletes from a NCAA Division III University, with no previous history of significant ankle ligamentous injury requiring medical care, were used in this study. The Telos stress device was used to stress the lateral ligament of the ankles. The subjects' were sitting on the ground while their ankles (one at time) were placed in the Telos

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	Right Foot		Left Foot		Combined	
	Males	Females	Males	Females	Males	Females
Mean	1.18	2.96	0.95	3.44	1.07	3.20
Standard Deviation	1.53	3.37	1.46	3.17	1.48	3.25
Sample Size	22	27	22	27	44	54
Degrees of Freedom	21		21		43	
Test Statistic Value	-245		-3.64		-4.3	
p-Value	0.023		0.0015		0.0001	
90% Confidence	Means Are Not Equal		Means Are Not Equal		Means Are Not Equal	
95% Confidence	Means Are Not Equal		Means Are Not Equal		Means Are Not Equal	
99% Confidence	Means Are Equal - -		Means Are Not Equal		Means Are Not Equal	
	Means may be equal— (Hypothesis that Means are Equal not rejected)					

Table 1.

machine. The involved knee was at approximately a 20 degree flexed angle, the heel was placed firmly against the middle part of the foot holding device, the involved ankle was at 15 degrees of inversion in the Telos machine, and the cushion of the pressure device was placed at a distance of five centimeters above the medial malleolus. The pressure device was set at 15 daN. X-rays were taken of the anterior ankle joint in AP position and the talar tilt angle was measured.

RESULTS

Means and standard deviations were figured for both males' and females' right feet, left feet, and the combined totals. A two-tailed hypothesis test was used with the null hypothesis H_o: Mean of males (Mm) is equal to the Mean of females (Mf). The second hypothesis is H_a: Mm not equal to Mf. When H_o is true, we treat the hypothesis test statistic as having a student's t distribution, but with degrees of freedom given by the minimum of Number of males less one (Nm-1) and Number of females less one (Nf-1) This approach biases the results towards rejecting the latter hypothesis (rejecting that the male and female means are unequal). This makes us even more confident that the significance decision is correct. The results are shown in table 1. The right foot statistics revealed that the means (Mm and Mf) were not equal with a confidence level of 95% (p-value=0.05), left foot means were not equal with a confidence level of 99% (p-value=0.01), and the combined means were not equal with a confidence level of 99% (p-value=0.01). The normal talar tilt mean for the right foot was 1.18 degrees for males and 2.96 for females. The left foot means for males was .95 degrees and for females 3.44 degrees. The combined means totaled 1.07 degrees for males and 3.20 degrees for females.

DISCUSSION

This study was conducted to examine the difference in normal ankle ligamentous laxity between men and women. Previous studies have not focused on gender differences. With recent focus on the significant differences in ACL ruptures between men and women, this study on ankle ligamentous laxity differences was necessary. Results revealed that women's ankles are normally more lax than men's. This finding of normalcy is important in determining abnormal laxity after injury and in determining the need for surgery due to this abnormal laxity. Since women's lateral ankle ligaments are normally more lax than men's, the abnormal range may need to be set at a higher talar tilt than men's abnormal range when considering surgical intervention. Further study as to whether increased normal lateral ankle laxity affects incidence of ankle injury is necessary. A study to evaluate the effect that the level of relaxin at certain times during the menstrual cycle has on ligamentous laxity in female athletes would be of value.

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IS BONE A TARGET-TISSUE FOR THE NERVOUS SYSTEM? NEW ADVANCES ON THE UNDERSTANDING OF THEIR INTERACTIONS

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ABSTRACT

Bone cells respond in specific ways to various hormones and growth factors, but the biology of skeletal innervation and its physiologic significance in bone metabolism is poorly understood. With the introduction of immunohistochemical staining techniques and new molecular biology tools, the knowledge in this field has significantly improved. In this review, we update current understanding of the effects of neuropeptides on bone metabolism, specifically vasoactive intestinal peptide (VIP) and calcitonin-gene related peptide (CGRP). In addition, new information concerning the role of growth factors, such as neurotrophins, is also discussed. There is strong evidence to suggest that bone can be a target of the nervous system. Further investigations in this field will allow us to answer questions related to pre-natal development, bone growth, fracture healing, osteoporosis, osteoarthritis or neoplasias of mesoderm origin.

INTRODUCTION

The importance of the nervous system on body homeostasis including the immune, endocrine and hematopoietic systems has been previously described.[3] It has also been suggested that organogenesis and tissue repair are under neuronal control. Although bone has some innervation, little knowledge concerning the neural influence on bone metabolism has been accumulated. However, it seems reasonable that neural control could also apply to bone tissue, and several clinical and experimental observations support this concept, including Charcot's neuropathy and the exhuberant callus formation after diaphyseal fractures on head injured patients.[6, 55]

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The lack of knowledge concerning the physiologic significance of bone innervation is mainly due to two reasons. One, the relatively few number of nerve fibers in bone compared with other tissues has been interpreted as the nervous system playing a minor role in the skeleton. Second, it has been very difficult to identify nerves in mineralized tissue. Methodologically, histologic studies to demonstrate nerves in bone have used routine staining techniques, such as gold chloride-osmic acid and silver staining, but these techniques provide limited morphological information.[14,98] In the last few years, the introduction of immunohistochemical and molecular biology have greatly expanded our knowledge in this field.

In this review, we will update the current understanding of the effects of neuropeptides on bone metabolism, specifically vasoactive intestinal peptide (VIP) and calcitonin-gene related peptide (CGRP). In addition, new information on the role of growth factors such as neurotrophins is discussed.

Anatomy and physiology of bone innervation

Anatomy. The distribution of nerves in bone, specifically those with neuropeptide-containing fibers, has been extensively studied. These nerves are most frequently found in metabolically-active bone. In contrast to local factors, neuropeptides in the sensory and autonomic nervous systems are synthesized in dorsal root or local sympathetic/parasympathetic ganglia and then transported along the axon by means of dense vesicles to their storage site in bone.[54]

The majority of nerves in bone are found along blood vessels. Both sensory and autonomic fibers have been demonstrated in the vessels of the periosteum, Volkmann's canals, bone marrow, osteochondral junction of the growth plate and the attachment of the synovial membrane.[8,12,42,46] The anatomy of the autonomic sympathetic vasomotor nerve supply of bone has also been extensively studied in rabbits. Adrenergic nerves profusely supply intraosseous vessels. These nerves probably contain neurotransmitter substances that function as a neuro-vaso-muscular synapse.[18] On the surface of the bone, peptidergic periosteal nerves are more numerous at the epiphysis than in the mid-shaft region

of bones. Additionally, neuropeptide-like molecules can be produced and/or released by many non-neuronal cells in bone, which act synergistically with nerve fibers, e.g., vasoactive intestinal peptide-like peptides (VIP) by mast cells and neuropeptide Y by megakaryocytes/platelets.[54]

Neuropeptides are not only present in bone under normal conditions; changes in neuropeptide-containing nerves in various pathological experimental situations suggest that they are actively involved in local disease processes such as bone growth, repair, and remodeling.[16,31,38,54,63,73,86] Moreover, clinical situations have shown that patients with neurologic disorders exhibit localized bone changes and altered fracture healing with excessive callus formation.[29,32,39]

Physiology . Although there are few nerve fibers in bone, their presence may represent sophisticated and specialized regulatory elements able to deliver time- and site-specific stimuli according to demand [54]. The distribution of different nerves during bone formation, combined with the observed effects of transmitters on bone metabolism *in vitro*, suggest that there is neuroendocrine regulation of bone physiology. This fact is crucial, not only for local bone physiology, but also for skeletal ontogeny and pathology.[6]

Essentially, bone nerves have been implicated in two different roles: as regulators of bony mechanical forces and as a source of trophic factors essential for structure and bone function. According to Wolff's law, different grades of physical activity are converted into changes in bone mass. In this case, bone nerves may represent the "organ" able to perceive mechanical strain and stresses, process this information and then transform this physical signal into cellular and biochemical responses.[54] The perception of stretch, pressure, and position of the bone nerves may contribute to the overall mechanism of coordinated movement of the limbs and bone modeling.[68]

On the other hand, bone is a living and continuously remodeling tissue. Neuro-related molecules appear to have trophic effects on normal bone metabolism. Recently, it has become more evident that at least some neural influences on bone may be mediated by neuropeptides released from the sensory nerve fibers and from the post-ganglionic autonomic nerve fibers. Release of neuropeptides from bone nerves seems to be related to the stimulation of those nerves. Non-stimulated nerves do not seem to release their peptides to any great extent, but under diverse situations of stress, the nerve terminals liberate neuropeptides resulting in significant local concentrations of these molecules.[54] In addition, during the ontogeny of sensory and autonomic nerves in the hindlimb of the rat, neuropeptide expression coincided with the mineralization process.[91,92] It has also been observed that the nerves are predominantly located in areas of high osteogenic activity, such as the periosteum and osteochondral junction of the growth plate.

It is widely known that bone cell physiology and repair is controlled by various systemic and local factors, and some of these molecules are deposited in the bone matrix and bound to different extracellular matrix components. Following bone resorption or fracture, growth factors are released into their surrounding environment, where they reach significant concentrations. It has been suggested that neuropeptides can affect the bone remodeling cycle in a similar fashion.[54] Several neuropeptides, such as substance P, neuropeptide Y, neurokinin A, VIP and CGRP, have been involved in bone physiology, but the best characterized at present are calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP). We will discuss in a subsequent section the effects of these molecules on bone.

Bone patho-physiology and the nervous system

Many morpho-functional studies indicate a role of the nervous system on bone physiology. We will describe the clinical processes in which an influence of the nervous system has been observed, including fracture healing,[64,73] bone growth,[16,31] sciatic denervation,[42] heterotopic bone formation,[104] arthropathies[33,94] and limb regeneration.[20]

1. Fracture healing. In animal models, fibular fractures failed to unite after removal of proprioceptive receptors by periosteal stripping.[1] In human samples with delayed union or nonunion of diaphyseal fractures, the most remarkable finding was the insufficiency or total lack of peripheral innervation. Although mechanical stability is considered the main factor underlying this situation, lack of neural control leading to a delayed fracture is an attractive hypothesis. Supporting these concepts are the observations that patients with neurologic disorders exhibit altered fracture healing and excessive callus formation.[21,29,39] In addition, Dyck et al[19] showed that patients with neuropathic arthropathy due to subclinical sensory neuropathy also suffer from recurrent long bone fractures.

This difference in healing may imply that in fractures with an abnormal nerve supply the sensory innervation does not recognize anomalous movement of the fracture and, with unstable fixation, nerves may mediate signals that lead to altered bone healing. Under conditions of altered nerve supply, Retief and Dreyer observed that connective tissue proliferation from the damaged bone is non-osteogenic and prevents healing of experimental cortical defects in the rat mandibulae.[81]

Other studies have shown that fracture calluses are bigger, less dense, and mechanically weaker compared with controls after sciatic section.[72] In addition, Becker showed that the time of denervation in relation to the time of fracture is a critical factor in the influence of denervation on the rate of healing in the rat fibula[4]. In paraplegic rats, the fracture callus showed delayed accumulation of calcium and incomplete maturation of woven new bone.[2]

2. Bone growth. The effect of division of peripheral nerves on longitudinal bone growth has been studied by a number of authors. Experimental studies have demonstrated controversial results ranging from a decrease in growth[51] to minimal change,[77] to stimulation of growth.[83] After sciatic denervation in rats, using measurements of bones exclusively innervated by the sciatic nerve (such as the metatarsals), Garcés and Santandreu showed that the denervated side grew about 3% to 5% less than on the control side.[31] Clinical cases of sciatic nerve injury in childhood indicate that limb denervation produces decreased growth of the foot.[26]

3. Denervation. A number of experimental studies suggest direct neuronal influence on local bone metabolism. In sympathetically denervated rats, quantitative autoradioagraphic analysis using ^{3}H-proline showed reduced osteoblastic activity, and morphometric analysis indicated an increased number of osteoclasts and increased resorption activity after sympathectomy.[40] Sensory denervation, on the other hand, was associated with a decrease in the number of osteoclasts [55].

How denervation influences bone metabolism is unclear. Some authors suggest that the bone response after denervation is not only due to a local effect, but also to a systemic response. Accordingly, some authors have shown that after neurectomy there is an alteration in bone mass of the contralateral femur compared to the sham-operated limb.[64] This supports studies that have found increased callus formation, a greater and more rapid healing response, and heterotopic ossification in patients with head injuries.[93] *In vitro* studies also seem to support these findings. Kurereret al demonstrated the possible existence of a circulating humoral factor. Sera drawn from patients with head injury and from paraplegic patients with heterotopic ossification have increased osteoblast activity *in vitro*.[57]

4. Heterotopic ossification. When heterotopic bone formation is induced by the implantation of demineralized bone matrix in the abdominal muscles of the rat, nerves immunoreactive to substance P, CGRP, neuropeptide Y, VIP and neurokinin A appear very early after implantation. Several days later, interleukin-1-positive nerves are also observed. Sensory and autonomic nerves could be seen among differentiating chondroblasts in the fibrous tissue developing around and also within the implants. These observations suggest participation of the nervous system in the early development of bone.[8,56] However, which cells are responding and through what mechanisms is still unknown.

5. Arthropathies. Many observations implicate the nervous system in the pathophysiology of arthritis. For example, there is a symmetric, neurotome-like involvement of joints in rheumatoid arthritis. In patients with hemiplegia who develop rheumatoid arthritis, the paralytic side shows little or no sign of joint inflammation.[33,94] It is known that antidromic stimulation of primary afferents evokes vasodilation and increased vascular permeability, resulting in extravasation of plasma proteins into the surrounding tissues. Sympathetic denervation has been shown to cause an increase in bone blood flow.[97] Because of this, CGRP is recognized as the most potent vasodilator among sensory neuropeptides.

6. Limb regeneration. During the process of limb regeneration in animals it has been observed that nerves supply trophic factors that act on mesenchymal tissues.[89] Experimentally, amputation of a newt arm coincident with excision of the fourth spinal nerve resulted in a significantly smaller limb with significant skeletal deficiencies in all four digits when compared to the unoperated control regenerate arm. In addition, like experimental fractures, the timing of denervation is crucial to limb regeneration. When this neurotrophic factor is depleted by denervation at the time of amputation, regeneration does not occur. If the denervation occurs several weeks before amputation, the limb will regenerate.[103] If the nerve is sectioned after the critical post-amputation period, regeneration occurs although the resulting limb is reduced in size.[90] These results suggest that the absence of available neurotrophic factors at the amputation stump may affect the limb regeneration process.

Neuropeptides Involved in Bone Metabolism

As cited previously, many neuropeptides have been found in bone, but the best studied are calcitonin-gene related peptide (CGRP) and vasoactive intestinal peptide (VIP). In this section, we will review their effects on bone.

1. Calcitonin-gene related peptide (CGRP). CGRP is a 37 amino acid peptide produced by tissue-specific alternative processing of the primary RNA transcripts of the calcitonin gene. Two isoforms of CGRP, CGRP-I and CGRP-II, differ only in three amino acids.[54] The distribution of CGRP-positive nerve fibers has been widely described. During rat femur development, the number of CGRP-positive nerve fibers increased in the

metaphysis until the tenth postnatal day, when the animals started to use their limbs. After this period of time, innervation increases in the epiphysis but decreases in the metaphysis. In addition, CGRP-positive nerve fibers were more abundant in the epiphysis than in the metaphysis, and these nerve fibers ran along the epiphyseal trabeculae facing the growth plate.[38] Interestingly, Schwab et al., using immunohistochemistry staining, described the presence of CGRP-immunoreactive nerve fibers in the outer layer of articular cartilage and in contact with chondrocytes in the knee joints of newborn and adult rats.[87]

CGRP-innervation of bone has also been studied under different experimental situations. In sciatic-denervated rats, it has been shown that the number of CGRP-positive nerve fibers is markedly decreased along epiphyseal trabeculae facing the growth plate. Furthermore, the osteoclasts were localized in close contact with the bone surface and showed intense tartrate-resistant acid phosphatase activity. Additionally, the cartilage extracellular matrix almost disappeared from the epiphyseal trabeculae facing the growth plate. These results suggest that the high bone turnover at this site resulted in rapid absorption of mixed trabeculae with subsequent replacement by bone spicules without calcified cartilage.[38]

After a fracture, CGRP-immunoreactive fibers have been widely depicted. Periosteal CGRP-immunoreactive fibers showed dense ramifications and terminal sprouting after seven days. In addition to the periosteum, these nerve fibers were found in the middle of the callus interspersed with inflammatory cells. At days 14 and 21, many tortuous nerves were found in the periosteum, but not in mid-callus. Interestingly, mast cells have been observed in close proximity to CGRP-immunoreactive nerve fibers, especially at 21 days after trauma. Mast cells are powerful inflammatory mediator cells that may interact synergistically with the nerve fibers.[11]

CGRP-immunoreactive fibers have been shown to serve three functions. Acting on the vasculature, CGRP is the most potent vasodilator among sensory neuropeptides.[97] On bone cells, CGRP has been reported to stimulate osteogenesis,[5] either by activating stem cell mitosis or osteoprogenitor cell differentiation, or both.[88] Bernard and Shih reported that CGRP increased the number and size of bone colonies *in vitro*. This effect appeared to be dose-dependent. A similar finding was obtained by intravenous injection of CGRP 2 hours before bone marrow cells were harvested.[5]

The effect of CGRP on osteogenesis is mediated via $CGRP_1$ and $CGRP_2$ receptors which are distinct from calcitonin C receptors. The signal transduction mechanisms of calcitonin receptors have been extensively studied. It has been shown that CGRP receptors activate the cAMP or the protein kinase C (PKC) pathways.[54] These two transduction pathways required guanosine triphosphate (GTP)-binding proteins (G proteins) and led to opposite biological responses. Moreover, selective activation of one or the other pathway was cell cycle-dependent. Therefore, CGRP may induce different cell responses depending on their stage in the cell cycle. This type of modulation could be important in rapidly growing cell populations such as during embryogenesis, growth and tumor formation.[10]

Other authors have found a different mechanism of action not linked to the cAMP-signaling pathway. Data from Kawase et. al indicate that CGRP transiently increases in the intracellular pool of Ca^{2+}, in part by release of Ca^{2+} from intracellular stores.[50] This action is apparently not mediated via the cAMP-signaling pathway, because they are not replicated by forskolin. During bone resorption, CGRP inhibits osteoclastic function.[17, 47,75,85]

2. Vasoactive intestinal peptide (VIP). VIP is a ubiquitous 28 amino acid cleavage product of pre-pro-VIP, originally isolated from porcine intestine, that has been shown to be a potent activator of adenylate cyclase in many organ systems.[54] VIP-immunoreactive nerves are distributed in bones in a similar pattern to CGRP-related fibers. Several reports have shown that VIP-immunoreactive fibers are sympathetic in origin.[43] VIP-neurons could produce high VIP concentrations locally in bone, but unlike some other vascular structures, bone and periosteal vessels are not responsive to the vasodilatory effects of VIP alone.[44] These studies have suggested that vasodilation is probably not the primary action of VIP in bone.[43]

The prevalent function of VIP-immunoreactive nerves in bone seems to be the stimulation of resorption.[55] In experimental models inducing heterotopic bone formation, VIP-immunoreactive nerves have been found among differentiating chondroblasts in the fibrous tissue developing around, and also within, the implants.[8,56] In human osteosarcoma cell lines, osteoblasts respond to VIP by expression of specific cell surface receptors that also have been observed in bone organ cultures.[45,55]

The effects of VIP on bone are mediated by receptors coupled to two types of proteins belonging to the G family:[7,27,62] G_s protein and G_{plc} protein. VIP receptors linked to G_s protein stimulate bone resorption via a cAMP-dependent mechanism.[44] It has been shown that osteoblastic osteosarcoma cells respond to nanomolar concentrations of VIP with increases in cAMP, and whole mouse calvariae are resorbed under the influence of VIP.[44]

Although the effects on bone by neuropeptides trans-

ported by sensory and autonomic nerves is not totally elucidated, Vignery et al demonstrated that the neuropeptide CGRP increases both the accumulation of mRNA encoding IGF-I and the production of IGF-I peptide by osteoblasts.[101] Also, the neuropeptide VIP may take part in bone resorption by stimulating prostaglandin E_2.[80] Interleukin-1 (IL-1) immunoreactive nerve fibers have been seen at a late stage of heterotopic bone formation induced by allogenic bone matrix. The IL-1 immunoreactive nerve fibers stimulate release of prostaglandin E_2, which is known to promote bone resorption. IL-1 immunoreactive nerve fibers were also observed several days after immunoreactive-nerves to CGRP appeared. Both types of nerves have been related in the early development of bone.[7,56] These observations are important since they may lead to a better understanding of the interactions between nerves and bone function.

Neurotrophins and bone metabolism

The protein nerve growth factor (NGF) is a complex molecule that contains three different subunits. In neural tissues, it has been shown that NGF is an important factor required for the development and maintenance of peripheral sensory and post-ganglionic sympathetic nerves.[59] Moreover, during vertebrate development, survival and differentiation of many neurons depend on their target cells.

The role of NGF on target tissues has been demonstrated by studying the skin. The arrival of sensory fibers in developing mouse skin coincides precisely with the initiation of NGF synthesis in this area. This temporal association suggests that the arrival of sensory fibers might initiate NGF synthesis in their target tissues.[84] NGF also appears to evoke response in certain non-classical neural tissues, e.g. embryonic cartilage rudiments.[22] NGF, demonstrated by immunohistochemistry during craniofacial development in the mouse, appears in premuscular and precartilaginous mesenchyme as well as in the teeth. Cartilaginous expression of NGF supports the view that this molecule could play a role in the regulation of preskeletal differentiation.[61] Moreover, Frenkel et. al showed that NGF is not only present in chick embryo cartilage, but also in bone.[30] In accordance with the previous findings, more than twenty years ago, Varon and Bunge advanced that "it is possible that several of these responsive tissues are not 'physiological' targets of NGF but, rather, recognize it as an 'analog' of their own trophic agents."[99]

However, neurotrophins are also produced in the peripheral nervous system by non-neural target cells.[25] In the case of bone morphogenesis, bone-associated neurons have been considered to regulate bone differentiation through synaptic interaction between neuronal cells and bone forming cells.[41] Furthermore, Nakanishi et al[69] suggest that osteoblast-derived neurotrophins may support not only survival and differentiation of neural cells, but also the proliferation of osteoblasts themselves in bone tissue *in vivo*, finally leading to bone formation.

During bone proliferative phase and differentiation there is an increase in the level of NGF mRNA.[70] By addition of neurotrophin-3, Nakanishi et al[69] observed that bone cells became more elongated, condensed and overlapped, suggesting a stimulation of cell proliferation. Interestingly, it has been observed that the presence of neurons increased thymidine incorporation into non-neuronal cells by up to 400 %.[66] These results suggest that NGF could induce osteoblastic cell stimulation and may reflect the progressive interaction between bone cells and bone-associated neurons in the bone differentiation phase.[70]

The exact mechanism by which neurotrophins work on bone remains unknown, but several factors have been suggested. Proteoglycans are the binding site for many growth factors, and the binding of neurotrophin-6 to cell surface and/or extracellular matrix proteoglycans seems to protect neurotrophin-6 from proteolytic degradation.[35] In addition, it has been suggested that the anchoring of neurotrophin-6 to the proteoglycans might spatially restrict the action of this molecule and serve as an extracellular storage form, as has been shown for fibroblast growth factor (FGF) bound to heparan sulfate proteoglycans.[82,102] It remains to be established whether neurotrophin-6 requires the presence of heparin or a specific heparan sulfate proteoglycan for optimal biological activity, as is the case with the fibroblast growth factor.[74,107]

Yada et al[106] suggest that NGF acts on cultured osteoblastic cells by endogenous PGE_2. Other authors, however, have observed that cell lines from the osteoblastic lineage respond to the presence of $1,25(OH)_2$-D_3 by an increase in NGF mRNA levels.[49] On the other hand, Nakanishi et al have shown that addition of varied concentrations of TGF-ß to culture cells at the end of the monolayer stage enhanced the expression of neurotrophin genes[70]. TGF-ß is considered to control the expression of NGF mRNA in osteoblastic cells during osteogenesis, relevant to the stimulating effect of TGF-ß reported on osteogenesis of periosteal bone in vivo.[71]

The signal transduction of NGF has been studied using ^{125}I-NGF. When ^{125}I-NGF is added to bone cells in culture, osteoblastic cells display the properties of a low affinity NGF receptor.[49] Furthermore, Nakanishi et. al showed that neurotrophins, especially neurotrophin-3,

stimulated the proliferation of native non-neural osteoblastic cells via trkC.[69]. Signal transducible neurotrophin receptors have been identified as the trk protooncogens.[53,65,58] These receptors are selectively recognized by neurotrophins.[13,52,58] The expression level of trkC was higher during the growth phase than during the early differentiation phase. The co-expression of trkC and its ligand in the proliferating cell suggests that neurotrophin-3 plays an important role in the proliferation of osteoblastic cells in an autocrine manner. After activation of these receptors, NGF induces the expression of immediate-early genes, such as NGFI-A, c-myc, c-fos and c-jun in PC12 cells.[15,67,105] These immediate-early genes encode transcription factors that regulate the induction of late genes. Among immediate-early genes, overexpression of c-fos, c-jun and c-myc leads to cellular transformation, suggesting that these genes promote cellular proliferation. However, no evidence of NGF receptors or functional responses has been found in chick bone cells *in vitro*.[28]

NGF has also been noted in several physiologic and pathologic conditions. Sensory nerves also appear to be important in normal bone metabolism and in bone fracture repair.[47] Immunostaining for NGF was seen in skeletal muscle fibers, periosteal osteoprogenitor cells and superficial osteocytes in cortical bone. In addition, increased sensory and sympathetic innervation of fracture calluses has been reported in animal experiments.[37,47] NGF staining was almost complete in the whole tissues related with the fracture site, except in some chondrocytes and deep osteocytes in trabecular or cortical bone and osteoclasts. An important finding is that, in calluses, periosteal matrix stained heavily for NGF when juxtaposed to cartilage and less obviously when associated with new bone.[36]

It has been suggested that some cellular components of the fracture callus produce NGF which in turn increases the innervation.[37,72] NGF detected in chondrocytes and osteoblasts of embryonic chick skeletal tissue suggests that these cells may govern innervation in the embryo by synthesizing and secreting NGF.[30] Since fracture callus is initially composed of similar embryonal-like skeletal cells, it was therefore expected that cells of the callus could similarly contain NGF.[48] Grills et. al reported that most chondrocytes of the callus stained for NGF, indicating that NGF appears at a particular stage during chondrocytic differentiation in callus development.[36] Fibrous and cartilaginous matrices did not exhibit immunostaining for NGF, a finding similar to that in the embryonic chick study.[30] In addition, the presence of NGF in periosteal matrices contiguous to cartilage and new bone may also indicate that reinnervation of the periosteum (a highly innervated tissue) is important in fracture repair, as opposed to non-innervated cartilage or bone matrices.[43] This observation may also indicate that NGF, like some other growth factors (e.g., IGF-I), can be stored in certain matrices, and thus be made available for physiologic responses by release from such tissue.[79]

Eppley et. al observed that after producing nerve gaps in rat mandibular bone, nerve axon regeneration was induced by the topical administration of NGF.[23] This incidental finding suggest that bone formation was stimulated around the NGF-induced regenerating axons. Another important finding is the enhanced bone formation induced by NGF when it is specifically administered topically in areas of onlay bone grafts. It has been shown that NGF exhibited a beneficial effect on maintenance of onlay bone graft volume.[24] In addition, topical application of NGF to fractured rat ribs increases the stiffness and breaking strains of the bone callus, thereby suggesting stimulation of bone cells.[37]

Finally, another role of neurotrophins in the musculoskeletal system seems to be related to neoplastic processes. In fact, the implantation of mesenchymal tumors into chick embryos was the starting point for the discovery and investigation of NGF.[60] In Ewing's sarcomas, cells bear high-affinity receptors for NGF, and utilize signal pathways similar to NGF receptors on PC12 cells.[96] In addition, Fas/APO-1, a member of the NGF/TNF receptor superfamily, is expressed on the cell-surface of normal and malignant cells. It is known that Fas/APO-1 is associated with cell death induced by apoptosis, however, human osteosarcoma cell lines are resistant to the apoptosis-inducing effects of anti-Fas.[76] However, Thompson et al. found that the expression of human NGF receptors in non-neurogenic mesenchymal tumors was generally negative: 0 of 5 chondrosarcomas, 0 of 6 malignant fibrous histiocytomas, and 1 of 8 leiomyosarcomas.[95]

In summary, there is indirect evidence that strongly suggests that bone, and even cartilage, could be targets of the nervous system. Further research in this field will allow a better understanding of the basic mechanisms of neural control on skeletal cells, and could provide new pathways for the study of skeletal development and growth, fracture healing, osteoporosis, arthropathies or even neoplasias.

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TREATMENT OF IDIOPATHIC CLUBFOOT: AN HISTORICAL REVIEW

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ABSTRACT

Idiopathic clubfoot, one of the most common problems in pediatric orthopaedics, is characterized by a complex three-dimensional deformity of the foot. The treatment of clubfoot is controversial and continues to be one of the biggest challenges in pediatric orthopaedics. This controversy is due in part to the difficulty in measuring and evaluating the effectiveness of different treatment methods. We believe the heart of the debate is a lack of understanding of the functional anatomy of the deformity, the biological response of young connective tissue to injury and repair, and their combined effect on the long-term treatment outcomes. The aim of this review is not only to assess the different methods of clubfoot treatment used over the years in light of an evolving understanding of the pathoanatomy of the deformity, but to also clarify factors that allow a safe, logical approach to clubfoot management. Further research will be needed to fully understand the pathogenesis of clubfoot, as well as the long-term results and quality of life for the treated foot.

Initial Period of Serial Manipulations and Immobilization

Idiopathic clubfoot is one of the most commonly referred problems in pediatric orthopaedics and is characterized by a complex three-dimensional deformity. When clubfoot is analyzed from an historical perspective, it is difficult to ascertain if other types of foot deformity, for example equinovarus or metatarsus adductus, were included in the definition. However, we believe most experienced authors were able to differentiate it from the other foot deformities when they referred to a clubfoot, given the natural history of no improvement without treatment.

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Clubfoot was first depicted in ancient Egyptian tomb paintings, and treatment was described in India as early as 1000 B.C. The first written description of clubfoot was given to us by Hippocrates (circa 400 B.C.), who believed the causative factor to be mechanical pressure. He described methods for manipulative correction remarkably similar to current non-operative methods. Hippocrates understood two important principles in the treatment of clubfoot which succeeding generations have time and time again claimed as their own. He explained that the vast majority of cases can be successfully treated with serial manipulations, and that treatment should begin as early as possible before the deformity of the bones is well established. He also understood the inadequacy of restoring the foot to its normal position, but that it must be overcorrected and then held in this position afterwards to prevent recurrence.

Hippocrates treated clubfoot as soon after birth as possible. His technique involved repeated manipulations of the involved foot with his hands, followed by the application of strong bandages to maintain correction. There is no written account of the specifics of the actual manipulations, but there is mention of the importance of gentleness in correcting the deformity. When correction had been obtained by this method, special shoes were worn to maintain the correction and prevent recurrent deformity.

These techniques were apparently forgotten by subsequent generations. In the Middle Ages, the management of clubfoot and other deformities was the province of barber-surgeons, charlatans, and bonesetters, and minimal information is available concerning their practice. The next description of repeated stretching comes from Arcaeus, who in 1658 wrote a chapter on the treatment of clubfoot where he describes his stretching technique as well as two mechanical devices for maintaining the correction. The latter of these devices is similar to Scarpa's shoe, which will be discussed later.

In the mid 18th century, Cheselden, at St. Thomas' Hospital, treated clubfeet by repeated stretching using tape to maintain the improved position. From this time until 1803, when Scarpa published his historical *Memoir on Congenital Club-foot of Children,* the subject was apparently neglected.[17] The *Memoir* provides us with a

description of his concept of the deformity. He considered the talus to be normal both in position and shape, and that the deformity was due to a dislocation of the forefoot inward upon the head of the talus. His treatment involved forceful manipulation, not gentle stretching, and application of a complicated mechanical device, later known as Scarpa's shoe. His treatment method was never successful in other hands and for that reason was not widely accepted.

In the year 1806, Timothy Sheldrake published an essay entitled *Distortions of the Legs and Feet of Children*.[18] Sheldrake used bandages like Hippocrates, and claimed that most of his patients could be cured in two to three months. He also recognized that although an infant's foot might be cured, it should not be left free until the child was able to walk. He believed that half the disability was due to the ligaments and the other half to the muscles. In expressing an opinion as to the possibility of a cure, he said "that children taken at or within two months of birth a cure will be in every sense complete by the time they begin to walk. But the older the child is when treatment is begun so much longer will it be before a cure can be effected."[18]

Introduction of Percutaneous Achilles Tenotomy

In 1823, Delpech performed subcutaneous tenotomy of the Achilles tendon in two patients with acquired talipes equinovarus. Sepsis occurred in both patients and he did not repeat the operation. The high incidence of infection discouraged most surgeons from performing tenotomies. However, Stromeyer continued to practice the operation. In 1831, he subcutaneously divided the tendo-Achillis in several patients with no fever or other signs of infection. W.J. Little was a young British surgeon who acquired an equinovarus deformity due to poliomyelitis. He visited Stromeyer in Hanover, who successfully operated on him. In addition, Stromeyer taught Little how to perform the procedure and allowed Little to operate on several of the patients who came to his clinic. Little then returned to England where he introduced this procedure with great success. In his treatise, Little argues strongly against the mechanical theory of this deformity.[13] His view was that the deformity was due to abnormal muscular contractions during intra-uterine development. This was in contrast to Stromeyer, who believed the deformity was due to a deficiency of the internal malleolus.

Little also pointed out that although the medial ligaments cannot directly produce the deformity, stretching them can result in improvement. He believed that associated with the distortion of the foot there was a rotation of the thigh outwards, consequently affecting the entire extremity. From this line of thought arose the use of irons extending from the foot to the pelvis in the treatment of clubfoot.

For thirteen years after Little recorded his success with subcutaneous tenotomy, no work of note appeared in the literature. Subcutaneous tenotomy enabled many feet considered beyond correction to be remarkably improved. Rogers in 1834 and Dickson in 1835[6] were the first to perform subcutaneous tenotomy for clubfoot in the United States. In 1866, Adams was the first surgeon to draw attention to the error of dividing the Achilles tendon as the first stage in the correction of the deformity.

In order to further understand clubfoot deformity, Adams performed dissections on several stillborn infants with clubfoot and reported the results.[1] This report is especially interesting because it is the first to describe microscopic examination of the muscles in a patient with clubfeet. He found that they did not exhibit any abnormal structural conditions either to the naked eye or microscopically. He also examined the bones of several specimens and discovered the only one that exhibited any marked change was the talus, which tilted medially. He believed the alteration in the contour of the talus resulted from the altered position of the calcaneus and navicular. His observations of the articular surfaces of the tarsal bones in these specimens further supported this notion.

After discussing the evidence for and against the various theories of the causation of clubfoot, Adams stated he believed the muscles were the deforming force, and that anatomically, clubfoot is a dislocation of the talocalcaneonavicular joint. He emphasized that the talus can only assume its normal shape and position after the dislocation between it and the navicular and calcaneus has been reduced. He recommended early surgery to obtain anatomical reduction of the dislocation.

Adams condemned the use of Scarpa's shoe or other existing mechanical devices. He believed Scarpa's shoe was not constructed in accordance with the deformity it was supposed to correct. He did agree with Scarpa on the importance of correcting the varus element of the deformity before the equinus. However, after condemning the use of mechanical devices, he devised his own straight splint of turned sheet metal applied along the outer side of the leg.

In 1838, M. Guerin described the use of plaster-of-Paris in the treatment of congenital clubfoot, and was apparently the first to use it for this purpose. We will later discuss in further detail the current use of plaster cast techniques for the correction of clubfoot.

Introduction of Aseptic Surgical Techniques, Anesthesia, and Radiographs

With the exception of tenotomies, the operative treatment of clubfoot began with the introduction of aseptic technique and anesthesia. In 1867, Lister introduced antiseptic principles of surgery. Esmarch in 1873 described a flat-rubber bandage for expressing blood from a limb. The introduction of the pneumatic tourniquet to limb surgery by Cushing in 1904 was invaluable.[5] The introduction of radiography made possible the precise evaluation of deformities. The advent of anesthesia completed the surgical renaissance, and these advances set the stage for orthopaedic surgery to evolve from a specialty with much empirical craftsmanship into an important scientific discipline. However, in the case of clubfoot treatment, this evolution also allowed the development of more radical operations aimed to obtain a "perfect" foot.

In 1891, Phelps not only divided the Achilles tendon, but carried out a medial release of all soft tissues, elongation of the tibialis posterior and division of the medial ligament of the ankle joint and plantar fascia, abductor hallucis, flexor hallucis longus, all the short flexors and finally performed osteotomy of the neck of the talus and wedge resection of the calcaneus.[15] Duval (1890), Ogston (1902) and Lane (1893) all carried out similar radical procedures.

Elmslie (1920), however, considered these procedures too radical in their approach to the condition. He understood the resistance to correction to be largely due to the talonavicular capsule, the plantar fascia, the Achilles tendon, and less importantly the posterior tibial tendon.[8] Ober (1920) also agreed with Elmslie's approach.

Brockman (1930), in addition to releasing the medial ligaments and plantar fascia, divided the abductor hallucis, tibialis posterior and subsequently carried out elongation of the Achilles tendon to correct the equinus.[3] He noticed that the operated feet were left stiff and immobile and he eventually abandoned this procedure. He argued that widespread soft tissue release lead to the formation of extensive fibrous tissue. Steindler reported good results with this technique in only 45% of 91 operations.[19]

Elmslie, Ober, and Brockman all emphasized the importance of immobilization in a plaster-of-Paris cast until correction was established. These authors' operations all pursue the same end, namely correction of the adduction and inversion due to the soft tissue contracture. The Brockman operation is the most complete. These corrective procedures are all based on the notion that all elements of clubfoot must be corrected before correction of equinus is undertaken.

Tendon transfers first became popular in the 1920's. Dunn in 1922 described transfer of the tibialis anterior tendon in selected cases of clubfoot to prevent relapse.[7] However, he did not publish his results. In 1947, Garceau and Manning reported good results in a series of tibialis anterior transfer in 83% of 86 patients with recurrent deformity. Barr (1958) believed that the tibialis anterior tendon should not be transferred to a lateral insertion if peroneus longus is functioning, due to resultant muscle imbalance.[2]

During the same time period that many soft tissue surgeries were being performed, many surgical procedures on the skeleton of the foot were also being devised for treatment of clubfoot. Operations aimed at correction of the prominent talus were popular during the latter part of the nineteenth century. In 1872, Lund performed talectomy, not as a corrective procedure for the equinovarus deformity, but because it was prominent.[14] Unfortunately, this procedure resulted in a plantigrade foot. Agustoni in 1888 and Morestin in 1901 also attempted to improve the position of the foot through talectomy. Steindler reported good results in 1950 with removal of the ossific nucleus of all the tarsal bones.

Osteotomy and wedge resection of the tarsal bones was performed by Robert Jones in 1908.[11] He always obtained as much correction as possible by manipulation and plaster before considering any operation on bone, and when necessary, removed as little bone as possible. Denis Browne in 1937 disagreed and suggested that in all cases beyond the possibility of correction by casting, a "cresentic resection of the tarsus " below and in front of the ankle should be performed right away.[4] However, as Robert Jones wisely said in 1920, "There is not much to be said for the removal of large masses of bone. I have never seen a case of clubfoot when a good portion of bone has been removed where the foot has functioned well."[11] In fact there are very few indications for surgery on the bones of the foot to correct clubfoot deformity.

Interestingly, current trends contend that clubfoot is a surgical deformity where only mild cases can be corrected by manipulation and immobilization. This view is supported by the disappointing results obtained after prolonged manipulations and casting in the more severe cases. Interestingly, most publications on the surgical treatment of clubfoot emphasize that early alignment of the displaced skeletal elements results in normal anatomy of bones, joints, ligaments and muscles. However, there is still no unanimity about when surgery should be performed, how extensive it should be, or how to evaluate the results. Adding to the uncertainty is the lack of long-term follow-up of surgically treated cases.

We believe this lack of understanding has resulted in poor correction of the initial deformity accompanied by severe iatrogenic deformities. An immediate correction of the anatomic position of the displaced bones is, in fact, impossible. Any attempt to roughly realign the talonavicular, talocalcaneal, and calcaneocuboid joints requires wire fixation through the joint cartilage. Inevitably, the joint cartilage, as well as the joint capsules, are damaged and joint stiffness sets in. A few reports indicate that surgery is almost invariably followed by deep scarring, which appears to be particularly severe in infants. In addition, the average failure rate of clubfoot surgery is 25% (range 13% to 50%) and many complications can occur including wound problems, persistent forefoot supination, loss of reduction and recurrence, overcorrection of the hindfoot, dorsal subluxation of the navicular, and loss of normal motion of the ankle and subtalar joints.

Return to Serial Manipulations and Immobilization

It is striking when reviewing the history of clubfoot management to see how the same mistakes are made time and time again by the treating physicians. The mistakes are made because the treating physician consistently ignores what has already been learned by his predecessors and instead he is often misguided by new information or trends.

Hugh Owen Thomas (1834-1891) studied medicine at Edinburgh and University College, London. He developed the Thomas test for hip flexion contracture as well as the Thomas splint used in fracture treatment. In addition, he developed the Thomas wrench, a device used to forcibly correct clubfoot. The plane through which the correction occurred was never clear. Experts claimed that if properly applied, the Thomas wrench could easily detach the foot from a cadaver.

In 1894, Sir Robert Jones at the British Orthopaedic Society said that he had given up operative treatment in place of treatment by manipulation. He wrote that he had never met with a case in which treatment had been started in the first week where deformity could not be corrected by manipulation and bracing for two months. He also noted that the cure was only finally completed when the patient could walk. He accepted the view that the condition is due to pure mechanical causes. He expressed the view that tenotomy should only very rarely be necessary. Bone operations, he held, should never be performed without obtaining maximum correction by manipulation with the Thomas wrench. However, his claimed results could not be duplicated.

Denis Browne (1892-1967), a second generation Australian, became the father of pediatric surgery in the United Kingdom. He is best known in orthopaedics for his Denis Browne bar used to correct clubfoot; a similar abduction orthosis is still used today to maintain correction of the deformity.

Michael Hoke (1874-1944) was the first medical director of the Scottish Rite Hospital in Decatur, Georgia, and was instrumental in advocating manipulative treatment for clubfoot and holding the correction with plaster casts.

Kite then became the leading advocate of the conservative treatment of clubfoot for many years in the early and mid 1900's. Kite completed his orthopaedic training at Johns Hopkins and succeeded Michael Hoke as medical director of the Scotish Rite Hospital in Decatur, Georgia. He continued the meticulous clubfoot cast application and molding that he had learned from Hoke. Kite corrected each component of the deformity separately instead of simultaneously. He was able to correct the cavus and to avoid foot pronation, but correcting the heel varus took many casts. He recomended "getting all the correction by abducting the foot at the midtarsal joint" with the thumb pressing "on the lateral side of the foot near the calcaneocuboid joint."[12] However, by abducting the forefoot against pressure at the calcaneocuboid joint the abduction of the calcaneus is blocked thereby interfering with the correction of the heel varus. Therefore, it took many months and cast changes to slowly correct the heel varus and obtain a plantigrade foot. Due to the inordinate amount of time it took to obtain correction of the deformity, he lost many followers who sought quicker corrections via surgery.

It was through his attempt to understand the pathophysiology of clubfoot, as well as his ability to learn from the mistakes of his predecessors, that Ponseti developed his current method of treatment for clubfoot. His understanding of the anatomy of the tarsus of the normal foot and of the clubfoot was greatly enhanced by the work of Farabeuf's *Precis de Manual Operatoire*, first published in 1872.[9] Farabeuf described how in the normal foot when the calcaneus rotates under the talus, it adducts, flexes, and inverts. More precisely, as the foot goes into varus, the calcaneus adducts and inverts under the talus while the cuboid and the navicular adduct and invert in front of the calcaneus and the talar head, respectively. Farabeuf also explained that in the clubfoot deformity the ossification center of the talus responds to the abnormal pressures placed on it by the displaced navicular. In addition, he observed that while bony deformities in the infant with clubfoot were reversible, recurrences are high due to soft tissue contractures. In his time, clubfoot patients were rarely treated at an early age, so surgery was usually necessary to correct the deformity.

Huson in 1961 wrote his Ph.D. thesis entitled "A functional and anatomical study of the tarsus."[10] This work supported and advanced the ideas of Farabeuf. Huson demonstrated that the tarsal joints do not move as single hinges but rotate about moving axes. Furthermore, motions of the tarsal joints occur simultaneously. If the motion of one of the joints is blocked, the others are functionally blocked as well. Based on these concepts, Ponseti developed his treatment guidelines:

1. All the components of the clubfoot deformity have to be corrected simultaneously with the exception of the equinus which should be corrected last.
2. The cavus results from a pronation of the forefoot in relation to the hindfoot, and is corrected as the foot is abducted by supinating the forefoot and thereby placing it in proper alignment with the midfoot.
3. While the whole foot is held in supination and in flexion, it can be gently and gradually abducted under the talus, and secured against rotation in the ankle mortise by applying counter-pressure with the thumb against the lateral aspect of the head of the talus.
4. The heel varus and foot supination will correct when the entire foot is fully abducted in maximum external rotation under the talus. The foot should never be everted.
5. After the above is accomplished, the equinus can be corrected by dorsiflexing the foot. The tendo-Achilles may need to be subcutaneously sectioned to facilitate this correction.

When proper treatment of clubfoot with manipulation and plaster casts has been started shortly after birth, a good clinical correction can be obtained in the vast majority of cases. A plaster cast is applied after each weekly session to retain the degree of correction and soften the ligaments. After two months of manipulation and casting the foot often appears slightly overcorrected. As mentioned, the percutaneous tenotomy of the Achilles tendon is an office procedure and is done in 85% of Ponseti's patients to correct the equinus deformity. Open lengthening of the tendo Achilles is indicated for children over one year of age. This is done under general anesthesia. Excessive lengthening of the tendon must be avoided since it may permanently weaken the gastrocsoleus. Transfer of the tibialis anterior tendon to the third cuneiform is done after the first or second relapse in children older than two-and-a-half years of age, when the tibialis anterior has a strong supinatory action. The relapsed clubfoot deformity must be well corrected with manipulations and two or three plaster casts left on for two weeks each before transfer of the tendon. With appropriate early manipulations and plaster casts, surgery of the ligaments and joints should only be rarely necessary.

To provide patients with a functional, pain-free, normal-looking foot, with good mobility, without calluses, and requiring no special shoes, and to obtain this in a cost-effective way, further research will be needed to fully understand the pathogenesis of clubfoot and the effects of treatment, not only in terms of foot correction, but also of long-term results and quality of life. One thing that is definitely missing in the literature is a long term follow up study on surgically treated clubfeet. The authors of this paper are currently involved in a multi-center retrospective study to look at this group of patients.

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DIABETIC MUSCLE INFARCTION

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ABSTRACT

Diabetic muscle infarction is a rare complication of diabetes mellitus that is not clearly defined in the orthopaedic literature. This study is a descriptive case series of 7 new cases of diabetic muscle infarction and 55 previously reported cases in the literature. In the majority of patients, diabetic muscle infarction presents as a localized, exquisitely painful swelling and limited range of motion of the lower extremity. No cases affecting the muscles of the upper extremity have been observed. The onset is usually acute, persists for several weeks, and resolves spontaneously over several weeks to months without the need for intervention. Diabetic muscle infarction is a condition that should be considered in the differential diagnosis of any diabetic patient with lower extremity pain and swelling without systemic signs of infection. Magnetic resonance imaging is sensitive and specific enough to make the diagnosis. Muscle biopsy and surgical irrigation and debridement are not recommended since they are associated with complications. Pain management and activity restriction in the acute phase followed by gentle physical therapy is the treatment of choice. Recurrences in the same or opposite limb are common. Although the short-term prognosis is very good and the majority of cases resolve spontaneously, the long-term survival is uncertain in this patient population.

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INTRODUCTION

Diabetes mellitus is a common disease with a total number of cases estimated at 14 million in the United States. The most common diabetic complications seen in orthopaedic practice include neuropathy and vasculopathy (60-80%), diabetic foot ulcers and infections (2-3%), and neuropathic arthropathy (0.1-2.5%). Diabetic muscle infarction is a rare complication of diabetes mellitus that is not included in most standard orthopaedic texts. While previous reports have illustrated some of the clinical and imaging characteristics of this condition, the scarcity and widespread report of cases throughout different medical and surgical disciplines makes it difficult to determine its natural history and the most appropriate method of diagnosis and treatment [1-14, 16-28]. This study is a descriptive case series of 7 new cases and 55 previously reported cases of diabetic muscle infarction. We reviewed several controversial aspects of the diagnosis and management of this condition. We wish to call the attention of the orthopaedic community to this condition, so that unnecessary invasive diagnostic testing, biopsy and surgical debridement which may lead to further complications, can be avoided.

MATERIAL AND METHODS

We retrospectively reviewed the charts and imaging studies of seven patients with the diagnosis of diabetic muscle infarction without gangrene that were evaluated and treated in the Department of Orthopaedics at the University of Iowa Hospitals and Clinics. We also reviewed all the articles published on diabetic muscle infarction (MEDLINE database search). Data from the charts and the cases reported, when available, were obtained including age, gender, type of diabetes, insulin use and years of use, glucose control and systemic effects of the disease (nephropathy, neuropathy, retinopathy). Clinical data recorded include presentation, location and duration of the symptoms; previous injury or injections at the site; presence of concurrent infection; and systemic symptoms. Physical exam data recorded include area affected; presence of a mass and characteristics; pain with range of motion; skin changes; joint effusion; compartment tenderness; presence of aden-

opathy or gangrene. Laboratory results recorded include WBC count; hematocrit; Erythrocyte Sedimentation Rate; CK/LDH enzymes; and other tests if reported. Additional laboratory tests were also recorded including knee aspiration and blood/urine cultures. Imaging studies recorded include plain radiographs; ultrasound; vascular studies including doppler/venogram; bone/gallium scans; CT scan; and MRI. Surgical pathology data included the use and type of biopsy, surgical irrigation and debridement, and tissue culture results. Treatment type, response to treatment, complications, recurrences, follow-up and survival were also recorded.

RESULTS

There are remarkable similarities in the clinical presentation of the seven patients from this series and the reported cases as summarized on Table 1. Diabetic muscle infarction occurs most commonly in insulin-dependent patients (85%) who have poorly controlled diabetes mellitus and concomitant end-organ complications (nephropathy in 58%, neuropathy in 50%, and retinopathy in 45% of the patients). The average time of insulin use prior to the diagnosis was 14 years (range, 1 to 50). It occurs in an equal male/female distribution (53% and 47%, respectively) and the average age at presentation was 44 years of age (range, 19 to 81). Average follow-up was 16 months (range, 1 to 48 months).

The characteristic clinical presentation was a sudden onset of pain and swelling in the extremity with limitation of range of motion. The pain was usually excruciating, persisting during rest and increasing with activity. The most common anatomic locations were the thigh (75%), the calf (15%), or both (10%). No history of trauma or injections were observed in our cases or the reported cases. The presence of concurrent infections was reported in 2 cases (3%). Ninety-six percent of the patients had no systemic symptoms such as fever, chills, night sweats or weight loss. Two patients had low back pain and one patient had abdominal pain. The duration of the symptoms prior to clinical consultation was 4 weeks (range, 1 to 36 weeks).

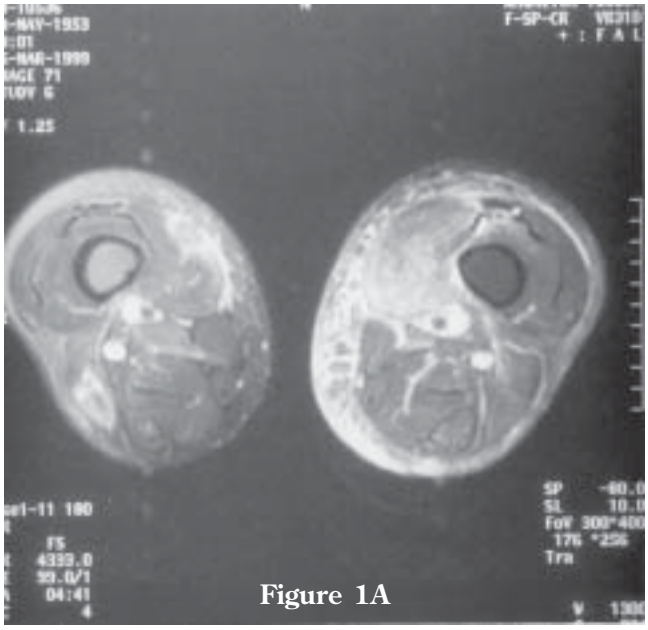
On physical exam, ninety-eight per cent of the patients had a localized, tender area with swelling and induration of the surrounding tissue. A palpable, firm, well-demarcated mass was observed in 32 patients (50%). In 5 cases (8%), there was skin redness but no induration. Knee joint effusion was reported in 2 cases (3%). No associated adenopathy, compartment syndrome or gangrene has been reported.

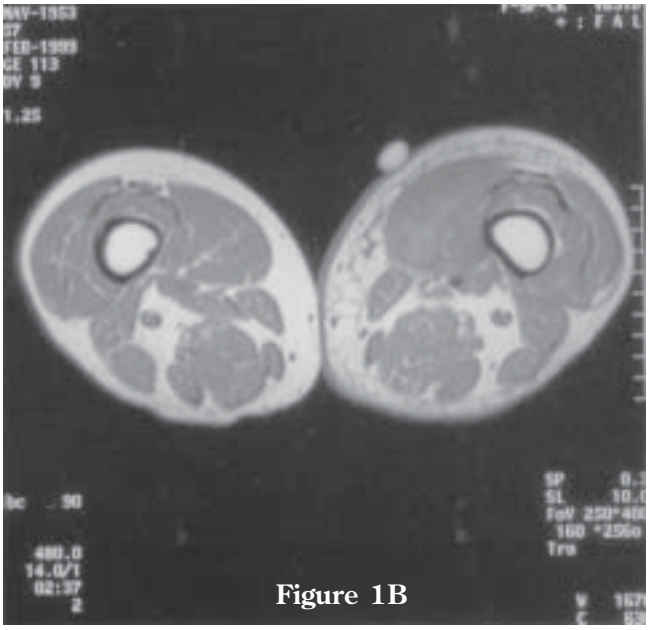
Laboratory evaluation demonstrated normal white cell count (79%), erythrocyte sedimentation rate (72%), and creatine kinase (85%). Anemia was observed in 10 cases (16%). Blood and joint aspiration cultures were negative.

Diagnostic imaging studies included MRI (76%), radiographs (35 %), vascular studies (34%), CT scan (29%), Tc99 bone scan (18%), and affected-area ultrasound (18%). Other studies included EMG/NCV studies (5 cases), angiography (3 cases), Ga 67 scan (2 cases), and a myelogram (1 case). Many patients had several tests performed (Table 1). MRI features included T1-weighted images demonstrating uniform, low-intensity signal enhancement of the affected muscle(s) with high contrast provided by the intermuscular fat planes. There are usually minimal changes of the subcutaneous tissues. T2-weighted images demonstrate high-intensity signal changes in the intra-and perimuscular tissues secondary to edema and hemorrhage. There is involvement of non-contiguous compartments and there are no bone marrow abnormalities (Figure 1). Gadollinium-DTPA contrast demonstrated linear areas of decreased signal intensity surrounded by rim-enhancement (+/- fluid collections). The muscles affected are described in Table 1. No cases of upper extremity muscles have been observed.

Needle biopsy was performed in 23 cases (45%), incisional biopsy in 17 cases (27%), and excisional biopsy 18 cases (29%). No biopsy was elected in 13 cases (21%). Four of the seven patients in our series had biopsies. The findings at the operation were consistent with what has been published in the literature. Briefly, there was edematous subcutaneous tissue and fascia. There was evidence of small pockets of edematous fluid deep to the fascia but no evidence of frank pus. The muscle was pale, felt woody and there was not responsiveness to pinching. Histologic examination showed skeletal muscle with areas of necrotic fibers surrounded by necrotic fibrous tissue, inflammatory tissue reaction, and hemorrhage (Figure 2). There were focal areas of intact muscle surrounded by abundant lymphocytic inflammation. Some of the areas showed collections of small atrophic fibers surrounded by fibrosis, and areas of muscle regeneration. Medium size arteries showed fibrinoid necrosis and others have a dense lymphocytic infiltrate in the media and intima. Occasionally, a superimposed infiltration of the subcutaneous tissues by polymorphonuclear leukocytes was also seen. Blood and tissues samples were examined for microorganisms. Gram stain demonstrated no white blood cells and no organisms. Aerobic, anaerobic, and fungus cultures were consistently negative.

Treatment modalities reported include bed rest and analgesic in 94 percent of the patients, early ambulation in 25 per cent, and physical therapy in 43 percent. Other





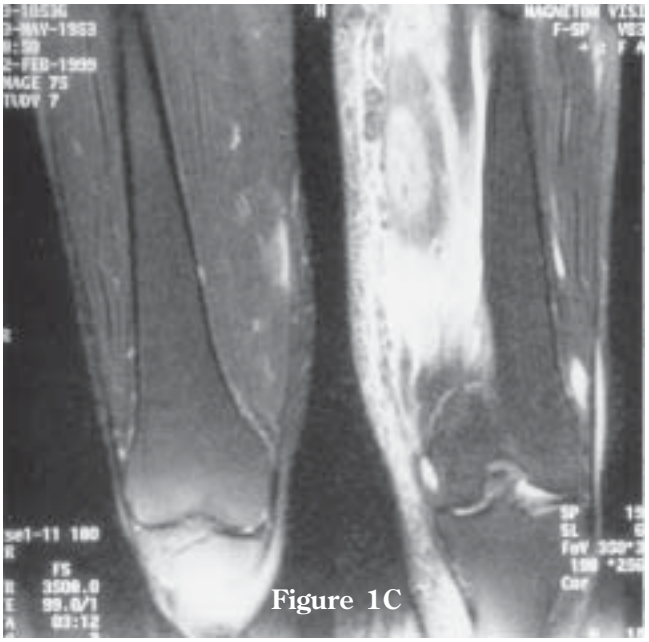


Figure 1. MRI examination performed 4 weeks after the onset of pain in left thigh. (A) Axial T2-weighted images demonstrating high-intensity signal in the intra- and perimuscular tissues of the left vastus medialis muscle secondary to edema and hemorrhage. Note minimal associated edema of the subcutaneous tissue. There is some involvement of the non-contiguous compartments as well as the vastus medialis muscle on the non-symptomatic right side. (B) T1-weighted images demonstrating uniform, low-intensity signal enhancement of the left vastus medialis muscle. There are no bone marrow abnormalities. (C) Coronal T2 weighted image demonstrating the extension of the abnormalities in the left vastus medialis muscle and also minimal changes on the non-symptomatic right side.

associated treatments included antibiotic therapy in 6 cases, anticoagulation in 3 cases and corticosteroids in 1 case. Clinical response demonstrated improvement of the symptoms in 82 percent of the patients at an average of 6 weeks (range, 3 to 14 weeks). There was recurrence of the condition in 21 per cent of the patients at an average of 20 weeks (range, 2 to 104 weeks). Ten patients (17%) were deceased.

Patients that had no biopsy or needle biopsy demonstrated no complications. Six patients that had aggressive physical therapy had recurrence of the symptoms. Patients that underwent excisional biopsy or surgical debridement had delayed wound healing (3 cases); a hematoma (2 cases); wound infection (1 case); nerve palsy (1 case); heterotopic ossification (1 case); and the need for blood transfusion (1 case).

DISCUSSION

Diabetic muscle infarction is an unusual complication of diabetes mellitus. The apparent rarity of this condition may make it difficult for clinicians and radiologists to become familiar with this entity, but diabetic muscle infarction is a distinctive illness that can be easily recognized. Angervall and Stener first described this condition as "tumoriform focal muscular degeneration" in two non-insulin dependent diabetic patients. Both patients were suspected of having a neoplasm prior to

TABLE 1
CLINICAL CHARACTERISTICS OF PATIENTS WITH DIABETIC MUSCLE INFARCTION

Author / year	Age (years) /Gender	Years diabetes	Systemic Complications	Symptoms (weeks)	WBC	Diagnostic tests	Biopsy	Recurrences	Follow up (mo)	Complications	Deceased	Muscles involved
Angervall and Stener (1965)	52 / M	10	K	4	NR	angiography	excisional	No	36	No	Yes	bcp
	23 / M	30	NR	4	NR	angiography	excisional	No	NR	No	No	vl / add
Levinsohn and Bryan (1979)	28 / F	NR	K	1	8900	radiographs /doppler / CT	excisional	Yes	24	No	Yes	quad
Reich et al. (1985)	54 / M	18	K,R,N	1	6700	radiographs/ ultrasound/ Myelogram/ Ga 67 / Tc99/ MRI	No	No	3	No	No	add
	29 / F	19	K,R,N	1	NR	CT /MRI	No	No	3	No	No	psoas / quad
Chester and Banker (1973 / 1986)	28 / F	15	K,R,N	4	8800	venogram	needle / excisional	Yes	24	Yes	Yes	quad x 2
	50 / F	10	K,R,N	4	11100	radiographs	needle / excisional	Yes	36	Yes	Yes	quad x 2
	34 / F	7	K,R,N	2	6100	radiographs/ venogram	needle / excisional	Yes	36	No	Yes	gs / quad
	34 / F	18	K,R,N	2	12000	Tc 99/ CT	needle / excisional	Yes	48	Yes	Yes	quad x2
	35 / F	6	K,N	4	NR	radiographs	needle	NR	NR	NR	NR	quad x2
	29 / F	19	K,R,N	3	11500	CT/ MRI	needle / excisional	Yes	36	No	Yes	quad
Ratlif et al. (1986)	57 / M	NR	NR	4	NR	radiographs/ ultrasound	excisional	No	NR	NR	No	vm
Grau et al. (1988)	75 / M	NR	NR	4	NR	CT	No	No	NR	No	NR	vm
Boluda et al. (1989)	64 / M	15	None	NR	NR	doppler / EMG / CT	No	No	12	NR	No	gs
Becker et al. (1992)	48 / F	10	NR	4	NR	CT / angiography	excisional	No	NR	No	NR	smb
Lauro et al. (1991) / Bahron and Kissel(1992)	29 / F	20	K,R,N	2	8000	radiographs/ venogram/ Tc 99 / MRI/ EMG	incisional	Yes	12	NR	Yes	smb / std
Barton and Palmer (1993)	42 / M	21	K	2	8000	MRI	excisional	Yes	47	No	No	vl x 2
Nunez-Hoyo et al. (1993)	28 / M	16	K,R,N	2	NR	doppler / CT / Tc99 /MRI	needle	Yes	12	No	No	vm / gs / vl x2
Rocca et al. (1993)	51 / M	5	NR	2	14500	doppler / CT	incisional	No	5	No	No	vl
Hinton et al. (1993)	29 / M	20	NR	7	9600	radiographs/ ultrasound / Tc 99/ MRI/ EMG	incisional	No	2	No	No	add / vm

TABLE 1 (continued)
CLINICAL CHARACTERISTICS OF PATIENTS WITH DIABETIC MUSCLE INFARCTION

Bodner et al. (1994)	46 / M	5	K,R,N	2	6000	doppler / EMG/ MRI	excisional	Yes	2	No	No	gs x2
Barohn et al. (1994)	19 / M	NR	NR	1	NR	EMG/ ultrasound / MRI / Tc 99	No	No	2	No	No	add / vl
Van Slyke et al. (1995)	25 / F	NR	NR	8	NR	MRI	incisional	No	2	No	No	pop / fhl / fdl
	55 / M	NR	K,R,N	28	8000	venogram/ MRI / doppler	excisional	Yes	12	No	No	vl / bcp
Kiers (1995)	47 / F	42	K,R	1	12600	venogram/ MRI	no	No	7	No	No	quad / sart
Bjornskov e t al. (1995)	35 / F	18	NR	2	NR	MRI	incisional	yes	NR	No	No	gra / add / quad
	48 / F	27	K,R,N	1	NR	venogram / MRI / Tc 99	incisional	yes	NR	No	no	gs / vm x 2 / vl x 2 / bcp / sart
Chason et al. (1996)	38 / F	NR	K,R	1	10900	radiographs / ultrasound	incisional	No	3	Yes	No	grac
	36 / M	NR	K,R	1	6000	radiographs / CT	incisional	No	6	Yes	No	rect fem
	42 / M	NR	K,R	3	12400	radiographs / MRI	incisional	No	24	Yes	No	vm
	43 / M	NR	K	8	8800	MRI	excisional	No	36	No	No	vl
Vande Berg et al. (1996)	28 / M	21	K,R,N	4	NR	radiographs/ doppler / CT / MRI	needle	No	3	No	No	gs
Umpierrez et al. (1996)	26 / F	20	K,R,N	6	5700	doppler/ MRI	needle / incisional	No	1	No	No	vl x2 / vl / gs
	31 / F	15	K,R,N	2	11200	MRI	incisional	Yes	4	No	No	vl x2 / gs
	65 / F	50	K,R,N	2	NR	radiographs/ doppler/ MRI	incisional	Yes	36	No	No	vl
Anonimus (1997)	81 / M	1	K,N	NR	6000	MRI	incisional	NR	NR	NR	NR	psoas /pect /add / obt int
Khoury e al. (1997)	28 / F	13	None	12	6000	doppler / MRI	No	Yes	5	No	No	quad x2 / bcp x 2 / sart /tens fascia
	63 / F	15	K,R	12	6000	CT / MRI	No	No	2	No	No	rect fem
Damron etal. (1998)	59 / M	12	R,N	3	6000	radiographs/ Tc 99 / MRI	incisional	No	28	No	No	quad / bcp
	31 / M	0	None	3	NR	radiographs / doppler / ultrasound / MRI	No	No	42	No	No	vm / sart
	48 / M	15	K,R,N	4	6000	radiographs / MRI	No	No	24	No	No	vm /vl / bcp
Aboulafia et al. (1999)	45 / F	8	K,N	3	12000	MRI / Ga 67	incisional	No	NR	No	NR	NR
	59 / F	15	N	4	12000	radiographs / MRI / Tc 99	needle	No	NR	Yes	NR	NR

TABLE 1 (continued)
CLINICAL CHARACTERISTICS OF PATIENTS WITH DIABETIC MUSCLE INFARCTION

Aboulafia et al. (cont.)	43 / M	17	N	6	6000	MRI	needle	No	NR	Yes	NR	NR
	40 / M	8	N	3	6000	MRI	needle	No	NR	No	NR	quad x2
	41 / M	5	N	8	6000	MRI	needle	No	NR	No	NR	NR
	32 / M	9	NR	12	NR	MRI	needle	No	NR	No	NR	gs
	39 / F	13	NR	7	NR	CT / MRI / Tc 99	incisional/ excisional	No	NR	No	NR	NR
	53 / F	16	NR	6	NR	CT / MRI / Tc 99	needle/ incisional	No	NR	No	NR	NR
	35 / F	1	NR	8	NR	MRI	needle	No	NR	No	NR	NR
	46 / F	9	NR	4	NR	CT / MRI	needle	No	NR	No	NR	NR
	40 / M	3	NR	4	NR	MRI	needle	No	NR	No	NR	NR
	43 / M	1	NR	8	NR	CT / MRI	needle/ excisional	No	NR	No	NR	vm
	36 / M	3	NR	3	NR	CT / MRI	needle	No	NR	No	NR	NR
	55 / M	20	NR	36	NR	CT / MRI	needle	No	NR	NR	NR	NR
Current Series (2000)	36 / F	23	K,R,N	8	8800	radiographs/ doppler / MRI	excisional	Yes	6	Yes	Yes	add /sat /rect fem / vm / vl /obt / glut med /glut min
	66 / M	30	K,R,N	6	10200	ultrasound / MRI	No	No	12	Yes	No	glut max / vm /add
	58 / M	7	K,N	4	9200	radiographs / ultrasound/ MRI	excisional	Yes	12	No	No	bcp
	45 / M	20	K,R,N	5	8500	Ultrasound / doppler / MRI	needle	Yes	24	No	No	vm / vm / sart x 2 / bcp
	34 / F	20	K,R,N	2	12700	Ultrasound / doppler / MRI	No	No	30	No	Yes	add / ham /quad x 2
	33 / M	17	K,R,N	2	14400	radiographs / ultrasound/ MRI	needle	Yes	16	No	No	gs / quad
	45 / F	14	K,R,N	5	9000	radiographs / MRI	No	No	56	No	No	quad

Abbreviations: Not reported, NR; nephropathy, K; retinopathy, R; neuropathy, N; quadriceps, quad; adductor, add; sartorious, sat; rectus femoris, rect fem; vastus medialis, vm; vastus lateralis, vl; obturators, obt; gluteus medius, glu med; gluteus maximus, glu max; gluteus minimus, glu min; biceps femoris, bcp; hamstrings, ham; gastrosoleus, gs; gracilis, grac; pectineus, pct; tensor fascia latta, tens fascia; popliteus, pop; flexor hallucis longus, fhl; flexor digitorum longus, fdl

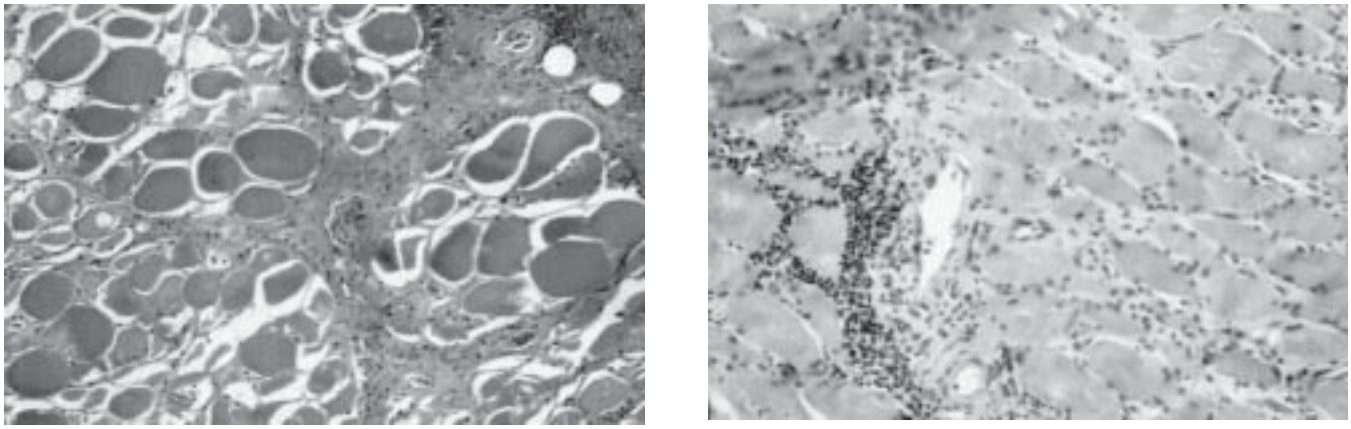


Figure 2. Representative histopathological findings of diabetic muscle infarction. (A) Skeletal muscle with areas of necrotic fibers surrounded by necrotic fibrous tissue and inflammatory tissue reaction. Scattered regenerating muscle fibers and marked endomysial edema are seen. Note thickening of the arteries and evidence of fibrinoid necrosis. (B) There are focal areas of abundant lymphocytic inflammation, but without evidence of concomitant vasculitis.

the biopsy. Pathologic examination of the muscle revealed no infection or tumor but a central area of hemorrhagic necrosis surrounded by muscle fibers in various stages of degeneration and regeneration, with hyalinosis and thickening of arterioles[2].

In a diabetic patient with painful swelling in the extremity, the differential diagnosis should include the conditions summarized in Table 2. Typically, diabetic muscle infarction presents as a localized, exquisitely painful mass associated with swelling and limited range of motion of the extremity. The onset is usually acute, persists for a few weeks, and there are no systemic signs of infection.

Vascular conditions and infections are the most common conditions to consider in the differential diagnosis. Deep venous thrombosis has been considered in almost every case of diabetic muscle infarction. The localized nature of the condition and the absence of distal edema or involvement of the lower portions of the limb will help in the diagnosis. However, vascular studies may be necessary to differentiate between the two. Primary hemorrhage into the muscle presenting with a localized, painful mass may mimic diabetic muscle infarction and may require imaging studies for the differential diagnosis. Pseudothrombophlebitis may present as a painful, swollen limb, but there is a typical history of arthritis, trauma, or recent exertion, and many of the patients will have a palpable cyst at the time of presentation. In arterial occlusion, the major blood supply of the limb is compromised and there may be absence of distal pulses with skin changes. A history of blunt trauma or recent strenuous activity can

TABLE 2
Differential Diagnosis of Diabetic Muscle Infarction

Vascular
Deep venous thrombosis
Hemorrhage
Pseudothrombophlebitis
Arterial occlusion
Post-traumatic false aneurysm
Infection
Cellulitis
Soft-tissue abscess
Pyomyositis
Necrotizing fascitiis
Osteomyelitis with soft-tissue extension
Parasitic infection
Neoplasia
Benign: lipoma, fibromas, leiomyoma
Malignant: liposarcoma, MFH
Inflammatory
Myositis: focal, nodular, proliferative
Rhabdomyonecrosis
Neurologic
Diabetic lumbosacral radiculoplexopathy (amyotrophy)
Bruns-Garland Syndrome

differentiate contusion, muscle strain or posttraumatic false aneurysm.

In a diabetic patient, and particularly one who is receiving insulin injections, local infections are not uncommon. Cellulitis is usually easily recognized, as it is superficial in nature. Soft-tissue abscesses and pyomyositis do result in pain, swelling and the development of a mass in the extremity. Fulminant conditions, i.e., necrotizing fascitiis, may be more difficult to differentiate especially at the early stages. However, patients will become rapidly ill and there may be evidence on physical exam of diffuse undermining of the skin. Occasionally, an osteomyelitis with adjacent soft-tissue involvement may present as a mass within the muscle. However, there are accompanying systemic signs of infection and characteristic radiographic features. Parasitic infections are extremely rare and the diagnosis may require imaging studies and biopsy.

The acute onset of the symptoms and the initial degree of pain are inconsistent with a primary soft-tissue neoplasm. Inflammatory myositis may present as a painful swelling of the extremity but creatine kinase elevations and proximal muscle weakness usually indicate the appropriate diagnosis. Neurologic syndromes may begin with an abrupt onset of lower extremity pain that ultimately will involve the opposite side. However, the pain is usually localized to the low back and buttocks and patients develop dramatic weakness and atrophy of the muscles[25].

Laboratory tests are helpful in the differential diagnosis, since the WBC, erythrocyte sedimentation rate, coagulation profile, and creatine kinase are usually normal, findings that help to distinguish diabetic muscle infarction from other entities. The failure of muscle enzymes to rise despite the presence of muscle necrosis is difficult to explain. It may depend upon when the CKs were obtained in the course of the disease (unclear for the cases reported in the literature) or to the limited amount of tissue involved. It is also possible that an elevated CK would be found more often if obtained within the first several days after the acute muscle infarct.

Different imaging modalities have been used to assess patients with painful swelling in the extremity. In the early reports, angiography was used and it showed atherosclerosis in the large and medium size arteries, but it has minimal value in the evaluation of these lesions today[2]. Standard radiographic films have been rarely helpful, except to exclude bony abnormalities or soft-tissue calcification. Radionucleotide studies using T99 or Ga67 demonstrate nonspecific accumulation of the tracer in the soft tissue[5,6,24]. Doppler ultrasound and venography of the lower extremity have been frequently performed, but they have been consistently negative. Ultrasonography has also been reported to show heterogenous, mass-like echogenic changes with loss of normal myofascial interfaces representing muscle swelling [12,28]. However, most of these studies are nonspecific and are probably unnecessary in the diagnostic work-up of patients suspected to have diabetic muscle infarction.

CT scan will show increased muscle size and lower attenuation due to edema and may help to exclude localized abscess, tumor or bone destruction, but it is of limited help in the evaluation of muscle pathology[11-13,17,21,24]. MRI more sensitively evaluates pathologic changes in the muscle and offers additional advantages over other conventional imaging studies. The MRI provides better anatomic definition than radionucleotide imaging, and greater sensitivity to biochemical alterations than CT scanning. MRI also allows evaluation of bone and bone marrow to rule out osteomyelitis. An additional advantage of MR imaging is the ability to perform venograms, excluding the presence of deep venous thrombosis.

MR imaging shows an increase in T2 signal in the affected muscle, most likely secondary to increase in tissue water. On T1-weighted images, the involved areas are isointense or hypointense relative to normal muscle. Perifascial and subcutaneous edema is a rather uncommon finding and, when present, is usually minimal. The relative absence of subcutaneous edema in patients with diabetic muscle infarction is helpful to differentiate it from cellulitis, in which subcutaneous swelling is the rule. Rarely, early pyomyositis can present with similar findings to diabetic muscle infarction, i.e., diffuse muscle abnormality without fluid collection[15,18]. In this situation, if there are clinical and laboratory findings suggestive of infection and a rim-enhancing lesion on MRI, pyomyositis should be considered. Gadolinium-enhancement is not necessary for the diagnosis of diabetic muscle infarction and should only be used if pyomyositis or soft-tissue/ muscle abscess is considered in the differential diagnosis [18].

The relationship between MRI abnormalities and symptoms is still controversial. MRI changes can resolve with the patient's clinical improvement and reappear with recurrence of symptoms[6,9,18,20,22,27]. However, abnormal MRI changes in muscle that do not appear to be clinically involved and that preceded clinical symptoms by up to 6 months have been observed[5,6,17]. Hence, while it has been suggested that MRI changes be closely related to the duration of the symptoms, larger series are needed to correlate these changes[27].

Biopsy may be needed in cases of diabetic muscle infarction in which the clinical presentation or imaging findings is atypical, or in which the recovery is delayed.

MRI may obviate biopsy by excluding pyomyositis, abscess, osteomyelitis or tumor. If confirmatory biopsy is needed, needle or incisional biopsy has been recommended since open biopsy has been associated with an increased risk of postoperative complications[4,13].

The treatment of choice of diabetic muscle infarction is analgesics and activity restriction in the acute phase, followed by gentle physical therapy until the resolution of the symptoms. In most cases, symptoms will resolve spontaneously without the need for surgical debridement. In very rare occasions, patients might not improve with this regimen and will benefit from surgical resection[1]. However, the complications reported in the literature appear to occur only when attempts have been made to excise the involved muscle and when physical therapy was begun early in the postoperative period. Banker and Chester described two patients who had excisional biopsy and early mobilization[4]. They developed hemorrhage and one required blood transfusion. In addition, the recovery period was prolonged because of repeated episodes of pain and swelling. In addition, when physical therapy has begun within the first few weeks after the diagnosis had been made, the symptoms were exacerbated[4,13,14,27]. Therefore, not only open biopsy, but zealous postoperative physical therapy should be discouraged.

Recurrences involving the original or contralateral limb have been observed in 21 percent of the patients. In all instances, the second event resolved rapidly. Although the short-term prognosis is very good and the majority of cases resolve spontaneously, the long-term survival is uncertain in this patient population. As many as half of the patients with diabetic muscle infarction have systemic end-organ complications. Seventeen per cent of the patients died between one and four years after the diagnosis had been made.

In summary, diabetic muscle infarction is a condition that should be considered in the differential diagnosis of any diabetic patient with lower extremity pain and swelling without systemic signs of infection. Magnetic Resonance Imaging is sensitive and specific for making the diagnosis. Muscle biopsy and surgical irrigation and debridement are not recommended, since they are associated with further complications. Pain management and activity restriction in the acute phase followed by gentle physical therapy are the recommended treatments.

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VOLAR PLATE ARTHROPLASTY OF THE THUMB INTERPHALANGEAL JOINT

William D. Engber, M.D.*

ABSTRACT

The fibrocartilaginous volar plate of the thumb interphalangeal joint is anatomically quite similar to the volar plate of the digital proximal interphalangeal joint. Due to this similarity, Eaton's technique of volar plate arthroplasty may also be utilized in fracture-dislocations of the thumb interphalangeal joint.

Fracture-dislocations of the interphalangeal (IP) joint of the thumb are uncommon injuries. As with most intraarticular fractures, obtaining a stable and congruous reduction is important. Unless a congruous reduction is obtained and maintained, a stiff, painful joint may develop and may predispose to posttraumatic arthrosis.

The treatment of digital fracture-dislocations is dependent on the size and degree of comminution of the intraarticular fragments. For small intraarticular fragments involving less than 25-40% of the articular surface, a stable closed reduction is usually possible[2]. With greater involvement of the articular surface, the treatment depends on the degree of comminution of the intraarticular fragment. For a single, large non-comminuted fragment, open reduction and internal fixation may be possible. If the large intraarticular fragment is comminuted, internal fixation may not be technically feasible. In this case, the treatment options are less clear. One option would be temporary pinning in a reduced position followed by early motion. Other options include mobile or immobile external fixation devices. Primary arthrodesis could be considered as a last resort.

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In 1971 Eaton[3] described a soft tissue arthroplasty for unstable dorsal fracture-dislocations of the proximal interphalangeal joint. In his procedure, the joint was approached volarly, the comminuted intraarticular fragments at the volar base of the middle phalanx were debrided, the joint was reduced, and the fibrocartilaginous volar plate was advanced into the volar defect in the articular surface of the middle phalanx.

In 1980 Eaton and Malerich[2] reported a long term follow-up study of 24 patients with volar plate advancement arthroplasties of the proximal interphalangeal joint. Their results were impressive with greater average range of motion (ROM) obtained when the procedure was done primarily (95°) than when done as a late reconstruction (78°). Other authors[4] have also obtained good results with this technique.

In an attempt to provide a stable, congruous reduction and to maintain mobility in fracture-dislocations of the interphalangeal joint of the thumb, Eaton's technique of volar plate arthroplasty was utilized. This report describes two cases of this injury and treatment, one pimary and one chronic, both with favorable results.

CASE REPORTS

Case 1

A 51-year-old factory worker sustained a hyperextension injury to his right thumb when a piece of wood "kicked out" of a table saw. X-rays showed a dorsal fracture dislocation of the IP joint (Figure 1A). He was splinted and referred. The joint was reducible but despite splinting in a flexed position the subluxation recurred. Three weeks after injury, a volar plate arthroplasty of the interphalangeal joint of the thumb was performed (Figure 1B). The K-wire across the IP joint was removed at three weeks and active range of motion was begun. Follow-up four years later (Figure 1C) showed a pain-free joint with an active ROM of 0° - 45° compared to the normal side of 0° - 65°. The patient continues to work in the factory.

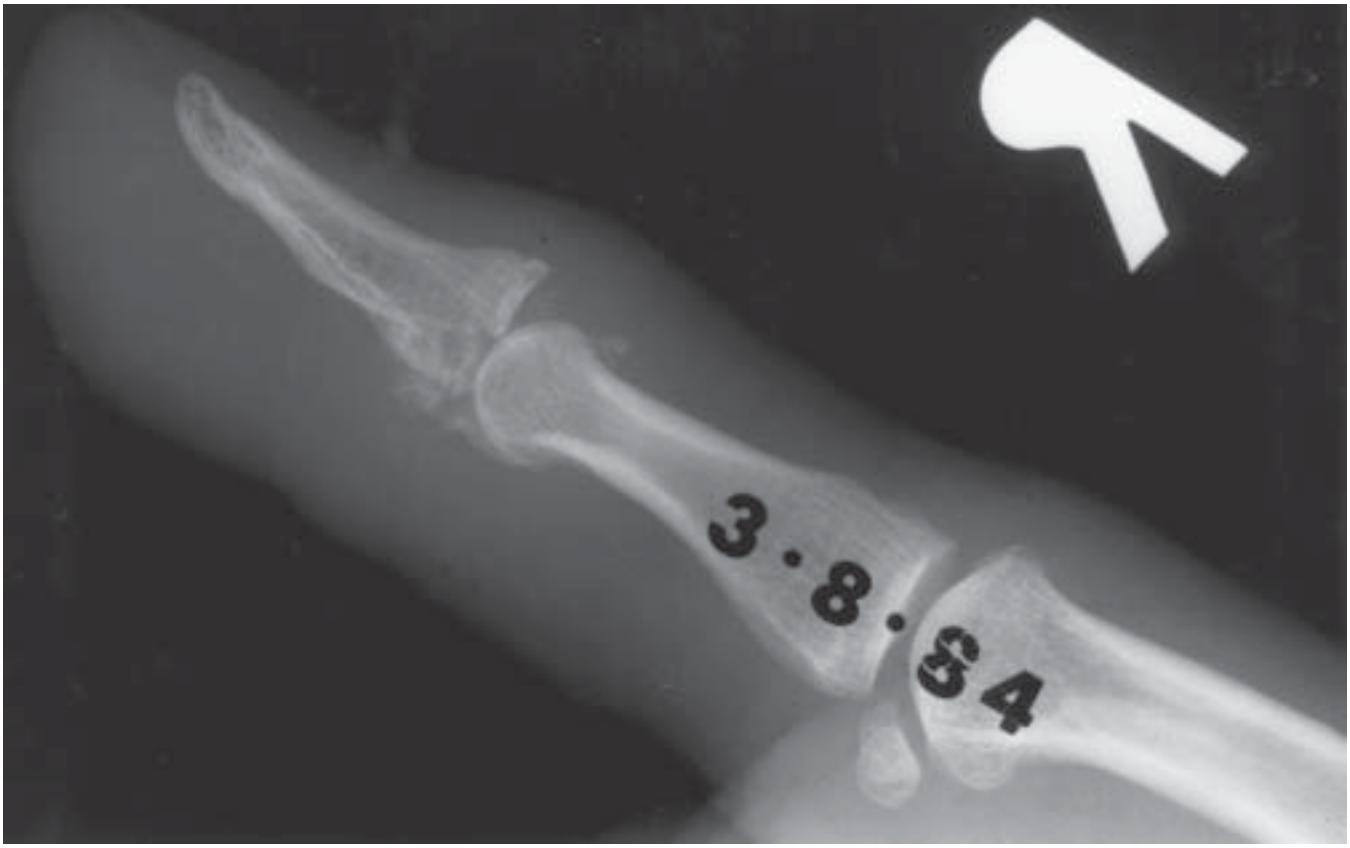

Figure 1A. Radiograph of dorsal fracture-dislocation of thumb interphalangeal joint.

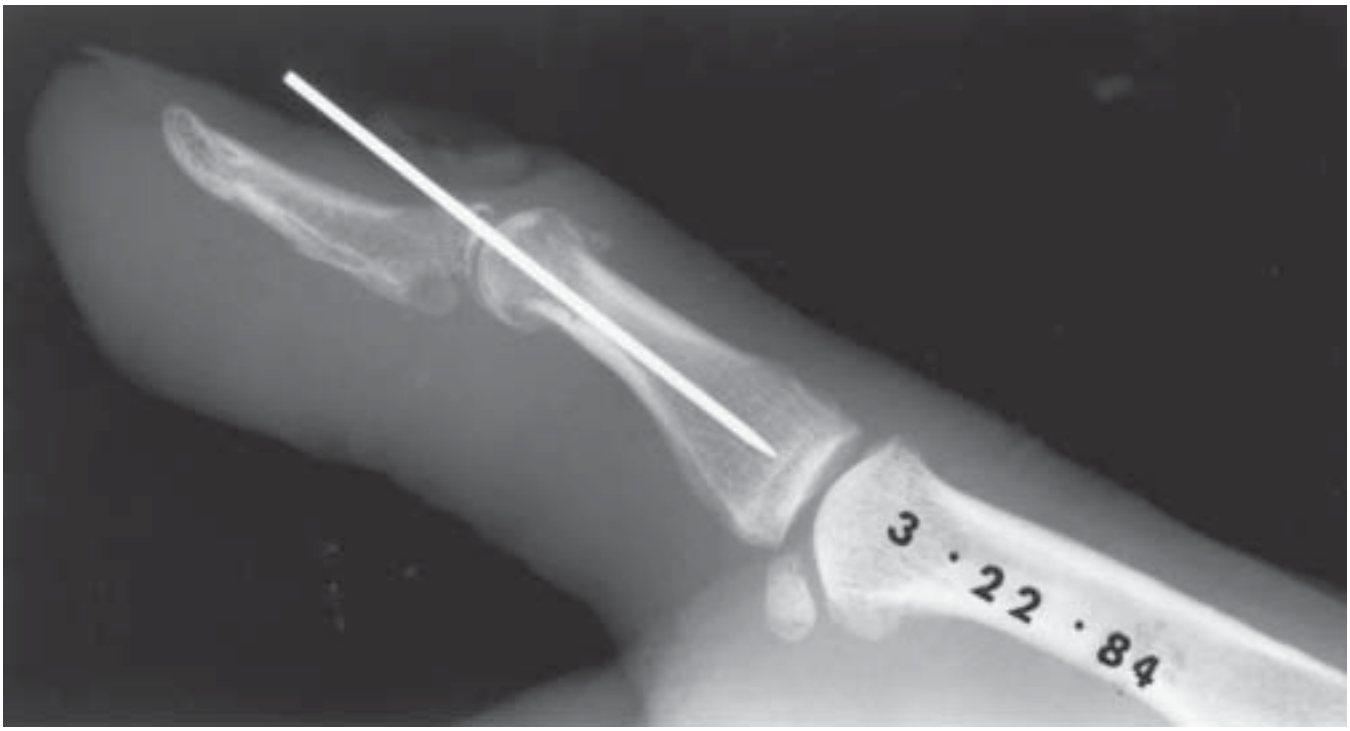

Figure 1B. Radiograph after volar plate arthroplasty.

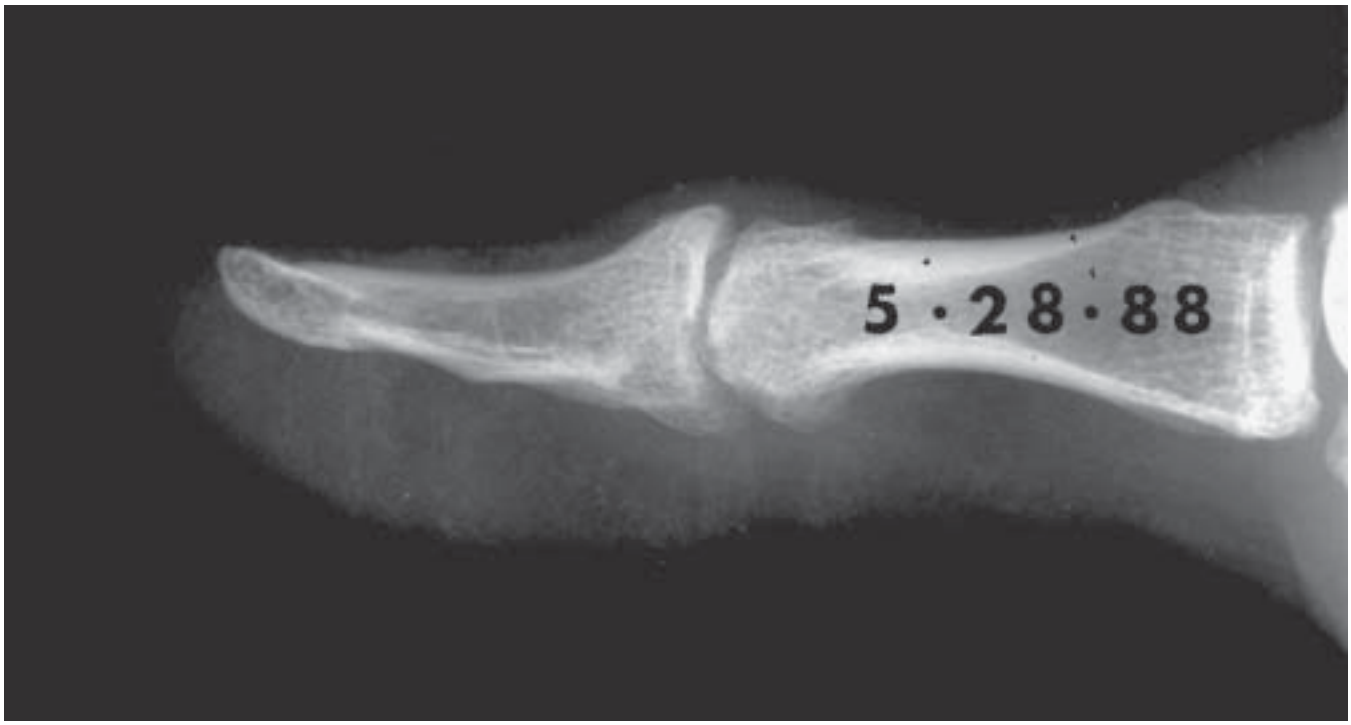

Figure 1C. Radiograph 4 years after volar plate arthroplasty of thumb interphalangeal joint.

Case 2

A 31-year-old laborer "jammed" his left thumb at work. X-rays showed a comminuted intraarticular fracture of the volar base of the distal phalanx. He was splinted for six weeks and started on active motion. Due to persistent pain, his physician recommended an arthrodesis. He was first seen by us seven months post injury and a volar plate advancement arthroplasty was recommended. Preoperatively he had a joint with painful crepitus and active ROM 15º - 45º. At eleven months post injury the procedure was done. The K-wire across the IP joint was removed at three weeks and active ROM was begun. At last follow-up, one year post surgery, he had a mobile, painless joint with an ROM of 10º - 55º compared to the normal side of 0º - 70º. He continues to be active and frequently bowls.

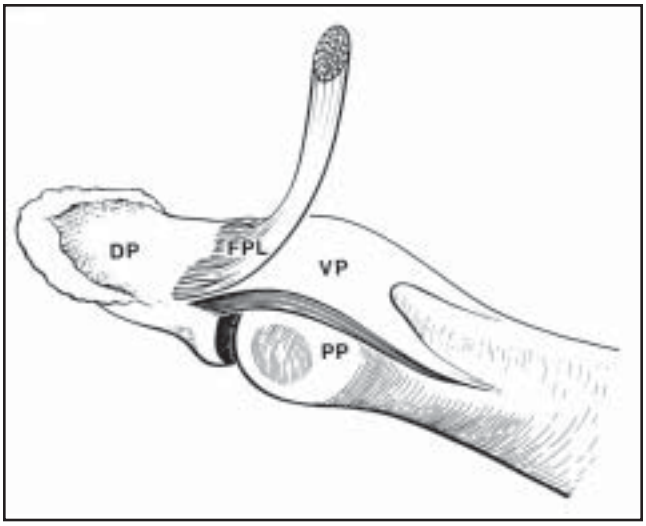

Figure 2. Schematic drawing of the volar plate (VP) at the thumb interphalangeal joint. The flexor pollicus longus tendon (FPL) is reflected distally.

DISCUSSION

Bower et al[1] have clearly reviewed the various anatomic descriptions of the proximal interphalangeal joint volar plate. Our surgical cases and cadaveric dissections of the volar pate of the thumb interphalangeal joint have shown it to be quite similar to the volar plate of the proximal interphalangeal joints (Figure 2). Distally the thumb's interphalangeal volar plate inserts on the volar base of the distal phalanx just proximal to the fan-like insertion of the flexor pollicus longus tendon. Sesam-

oid bones may be present in the volar plate just proximal to its thinner midline portion. The thick lateral structures or checkreins[5] merge volar-laterally with the fibroosseous canal of the flexor pollicus longus and dorsally with the periosteum of the proximal phalanx. Centrally the thumb's interphalangeal volar plate also becomes thinner and is loosely anchored to the periosteum of the proximal phalanx.

The anatomic similarity between the volar plates of these two joints would suggest that the Eaton volar arthroplasty would also be feasible at the thumb interphalangeal joint. Our clinical experience with two cases of thumb volar plate arthroplasty, one acute and one chronic, have been encouraging.

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STRESS FRACTURE OF THE HIP AND PUBIC RAMI AFTER FUSION TO THE SACRUM IN AN ADULT WITH SCOLIOSIS: A CASE REPORT

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ABSTRACT

Correction of adult scoliosis frequently involves long segmental fusions, but controversy still exists whether these fusions should include the sacrum. It has been suggested that forces associated with activities of daily living transfer the stresses to the remaining levels of the spine and to the pelvis. The case described here was a 43-year-old woman with scoliosis and chronic back pain refractory to non-surgical modalities. Radiographically, the patient had a 110 degree lumbar curve. An anterior and posterior fusion with Luque-Galveston instrumentation was performed. Six months postoperatively the patient returned with a 2-week history of right hip pain with no history of trauma. There was radiographic evidence of a displaced femoral neck fracture and pubic rami fractures. The femoral neck fracture was treated with a total hip replacement. Further surgeries were required to correct a lumbar pseudoarthrosis and hardware failure. We believe that this case provides evidence that fusion into the lumbosacral junction may distribute forces through the pelvic bones and hip resulting in stress and potential hardware complications, especially in patients at risk due to osteopenic conditions.

Correction of adult scoliosis often involves long segmental fusions into the lower lumbar spine and sacrum. However, inclusion of the lumbosacral joint in the fusion remains controversial. Following arthrodesis, forces associated with the activities of daily living transfer the stresses to the remaining unfused levels of the spine and pelvis, and may cause pseudoarthrosis, pedicle fractures, disc space narrowing, posterior facet hypertrophy and symptoms of mechanical back pain.[2-5,9-12] The purpose of this paper is to present a case illustrating that spinal fusion to the sacrum may distribute forces through the pelvic bones and hip, resulting in stress fractures and hardware complications.

CASE REPORT

A 43-year-old woman consulted the Department of Orthopaedic Surgery at the University of Iowa in 1988 for chronic back pain secondary to scoliosis which was diagnosed at the age of 18. The patient had back pain refractory to physical therapy and analgesic medication over the past 3 years. Her past medical history was significant for hypothyroidism with replacement therapy and varicose veins. She was recently diagnosed with probable Marfan's syndrome with elements of Ehlers-Danlos syndrome. The neurological exam was normal. Radiographically, the patient had an 18 degree left thoracic curve from T5 to T10 and an 88 degree right curve extending from T11 to L4. A kyphotic deformity at the cervico-thoracic junction was also noted. The lumbar curve measured 110 degrees, which corrected only to 90 degrees on lateral bending (Fig. 1). Due to progression and back pain, she was indicated for spinal arthrodesis and instrumentation. In August 1991, an anterior release and fusion, and posterior fusion with Luque-Galveston segmental instrumentation was performed concurrently (Fig. 2). There were no surgical complications, and postoperatively the patient was ambulating with a TLSO. The patient had significant pain relief over the next eight months, at which time the TLSO was discontinued. However, the patient began having discomfort at the iliac region. She was treated with non-steroidal anti-inflammatories and instructed to decrease her activity level. Six months later, the patient returned with a 2-week history of right hip pain with no history of trauma. There was radiographic evidence of a displaced femoral neck fracture and superior and inferior pubic rami fractures (Fig. 3-A). The femoral neck fracture was treated with a total hip replacement. The surgery was complicated by a transient femoral nerve palsy. (Fig. 3-B). The pubic rami fracture was treated non-operatively.

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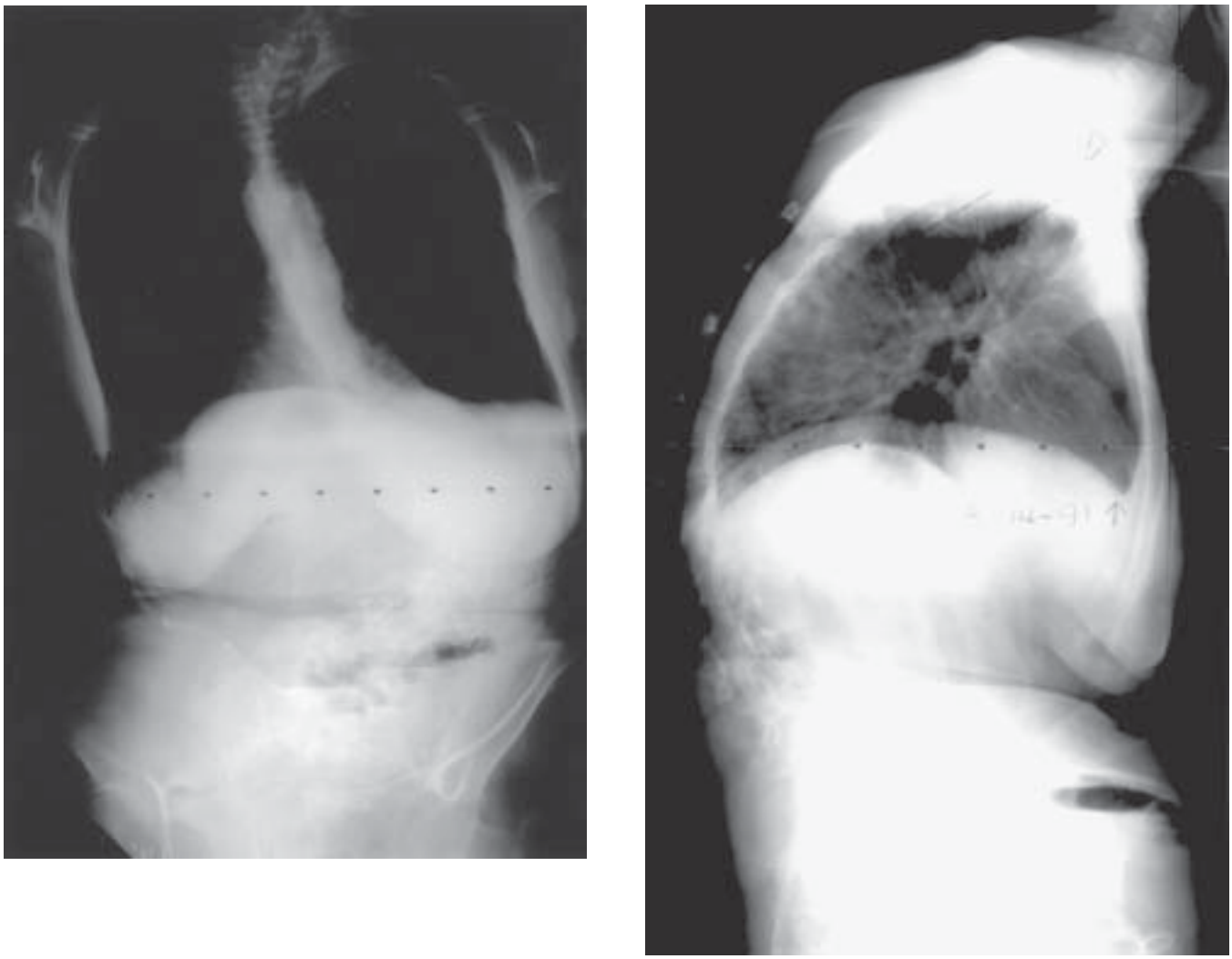
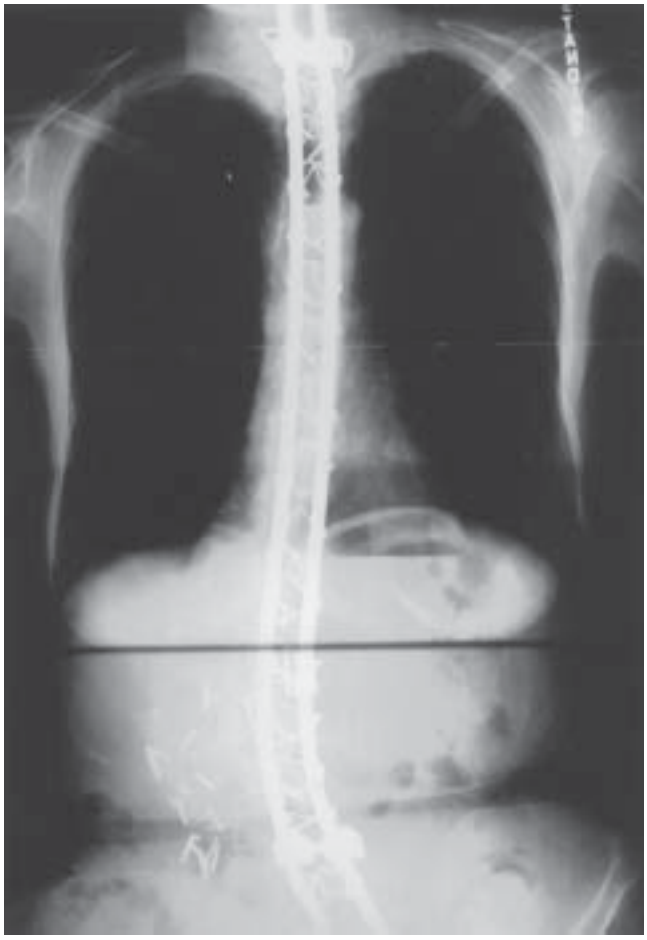


Figure 1. Preoperative standing postero-anterior and lateral radiographs of the spine.



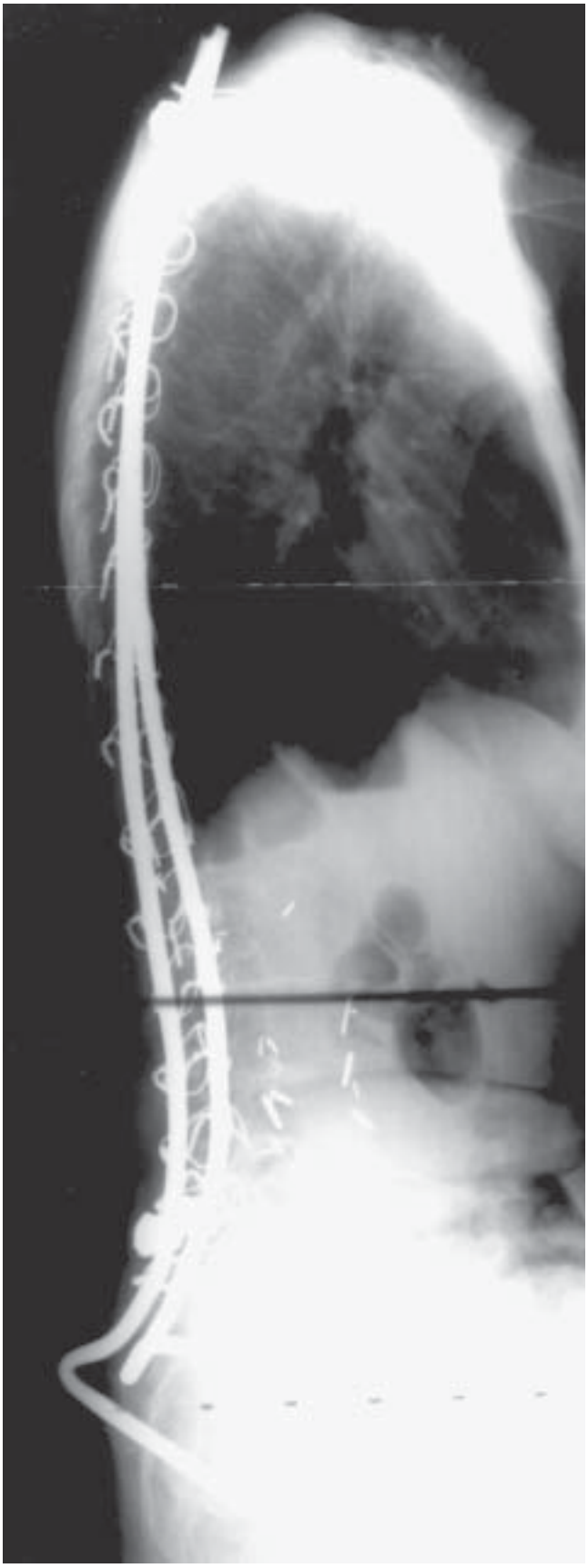


Figure 2. Postoperative standing postero-anterior and lateral radiographs after corrective surgery and fusion with Luque-Galveston segmental instrumentation up to the sacrum.

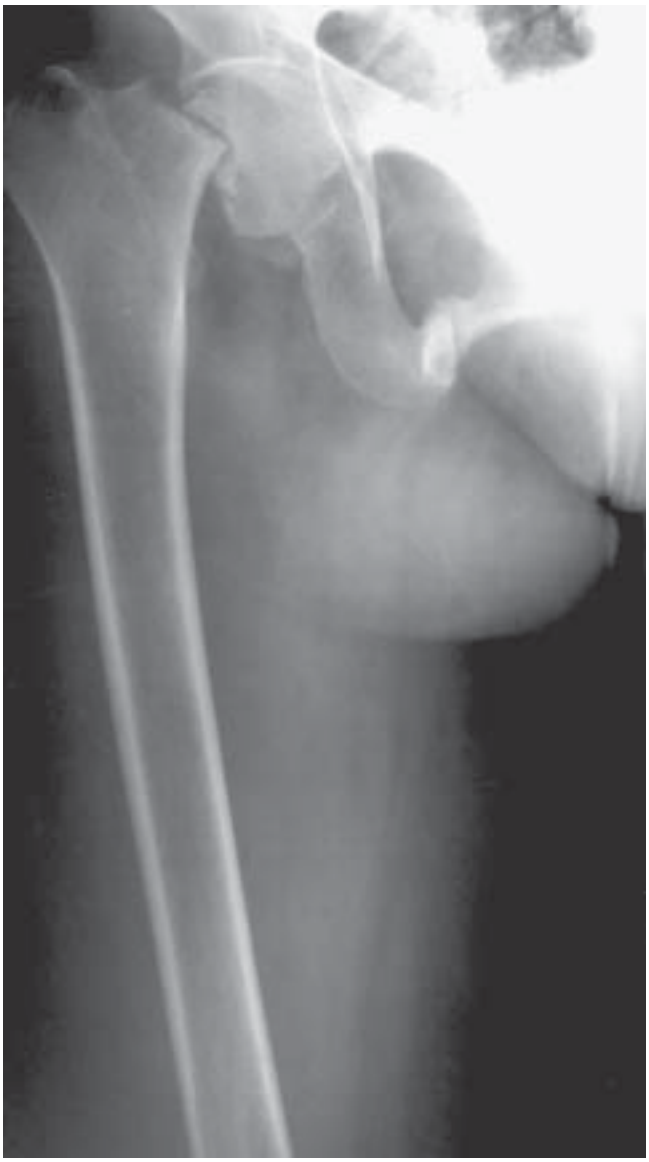


Figure 3A. Anteroposterior radiograph of the right hip demonstrating displaced femoral neck fracture.

Lack of lumbar lordosis was causing the patient difficulty with ambulation and a feeling of being "thrown forward" while walking. Therefore, spine revision surgery was performed to correct the position of the lumbar fusion. Several osteotomies through the fusion mass, which was found to be solid and without signs of pseudoarthrosis, followed by further bending of the Luque rods, achieved a significant increase in lumbar lordosis and a better gait pattern for the patient. The pubic rami fractures were healed by that time.

The patient underwent further spine revision surgery in July 1994 for a broken Luque rod related to pseudoarthrosis at the lumbosacral junction area. This was addressed with removal of the distal end of the Luque rod, insertion of VSP screws and TSRH hooks connected to short Luque rods and linking to the previous rods. Additional lordosis was obtained through the pseudoarthrosis. Extreme osteopenia was noted at that time. The patient was treated with a corset for 7 months. Skin breakdown over a prominent TSRH hook resolved with conservative treatment. When last seen in July 1995, all wounds were healed, the patient had no pain related to the spine, but still complained of a "pitching forward" sensation.

DISCUSSION

The management of the adult patient with progressive and painful scoliosis remains one of the most challenging problems for the spinal surgeon. When proper patient selection is made, adult scoliosis corrective surgery has been shown to improve patient self-reported health assessment and function.[1] However, specific considerations of adult scoliosis such as rigidity, associated degenerative disc and facet disease, and osteopenia make the surgery more complex. In addition, there is a higher incidence of complications when compared to similar surgery in adolescents.[4,6,7,8,11,12] Mortality is in the range of 0.7 to 5.6%, and the incidence of both minor and major complications ranges between 41 and 86%.[4,7,9,11]

Anterior and posterior combined procedures, as well as long segmental fusions into the lower lumbar spine when degenerative changes or instability are present, are frequently necessary.[2] When considering whether or not to extend a long fusion to the sacrum, the surgeon must take into account both the risks of complications resulting from arthrodesis or fixation of L5-S1 (12-70%) and the chances of iatrogenic instability or lumbosacral pain (75-90%).[2] If the fusion does extend to the sacrum, supplemental anterior fusion is recommended in most patients to minimize nonunion and to preserve the lordosis.[8] However, when a solid fusion mass is obtained, a stress riser may develop in the lower mobile

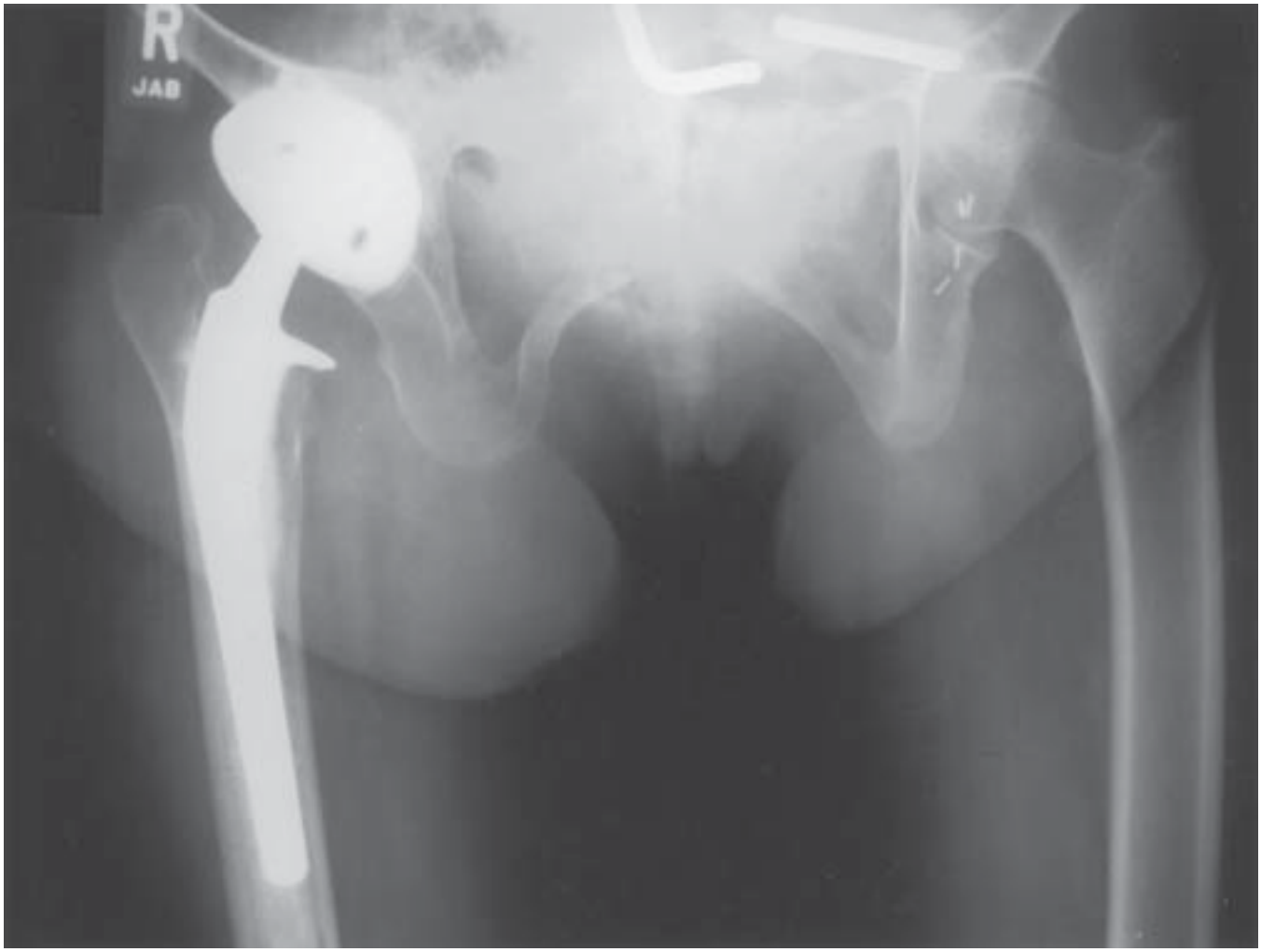


Figure 3B. Anteroposterior radiograph of the pelvis after total hip replacement. Note left side Luque rod fracture.

segments. Kostuik[4] noted a 49% loss of lordosis and 22% pseudoarthrosis rate in 45 patients fused to the sacrum. Knight[3] reported a case in which the dissipation of forces through the remainder of the spinal column resulted in a stress fracture of the pedicle of the lower fused vertebra.

In this case, although spinal fusion was initially achieved, there was a definite loss of lumbar lordosis. We believe that the lack of spinal flexibility, failure to restore the normal sagittal spinal contours and altered gait apparently concentrated the biomechanical stresses on the next mobile segment, in this case the pubic bones and the hip. These abnormal stresses, when coupled with the patient's osteopenia, caused stress fractures to occur in these structures. Subsequent hardware failure associated with pseudoarthrosis of the fusion mass required further surgeries. Although secondary procedures were successful in alleviating the stresses in the pelvis and hip, we believe this case provides evidence of the progression of stresses within an abnormal lumbar spine to more mobile segments.

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THE FUTURE OF ORTHOPAEDIC BASIC AND CLINICAL RESEARCH: WHERE HAVE WE BEEN? WHERE SHOULD WE GO? HOW DO WE GET THERE?

Clement B. Sledge, M.D.

CLINICAL RESEARCH

Clinical research in orthopaedics has been characterized by largely anecdotal reports, often of one surgeon's experience with a procedure. Fifteen years ago I did a survey of the English-language orthopaedic literature looking for controlled, prospective clinical trials; I found four—three of them were British! Of the four, only two looked at a disease and the efficacy of alternative treatments; the others examined a single treatment versus no treatment in the control group. Two papers emerged as representative of the "best" orthopaedic literature of the fifties and sixties. One compared surgery and cast-treatment for ruptures of the Achilles tendon. The other addressed the treatment of spinal tuberculosis in multiple centers around the world, examining different combinations of surgery and medical management. As good as those studies were, they would not meet the criteria for publication in a contemporary medical journal. Was that just a snapshot of the way things were back then? A search of the National Library of Medicine today using 'orthopaedics' and 'New England Journal of Medicine' as the search terms turned up only 10 articles and virtually all of those were written by non-orthopaedists. Admittedly, other MESH terms such as prosthesis, complications, etc, might have turned up more, but I believe the point is made: our clinical research doesn't meet the required level of science to be published in journals other than orthopaedic journals.

As a specialty we still tend to publish anecdotal, procedure-oriented articles that rely on data collected by the surgeon (and therefore biased). We do not control for factors known to influence outcomes such as racial, socioeconomic and educational levels. We now know that pre-operative functional level, health-care system and expectations play a major role in how well patients do following surgical treatment, but is that information included in our publications? Were those variables factored into the research protocol?

I realize that it is not always possible to conduct the same sort of clinical trial in surgery that one might carry out with a new medication; we can't do double-blind, cross-over studies of surgical procedures, but we can design controlled trials that take into account the factors known to influence outcome. We can design studies that are disease-oriented and patient-centered; that rely on information gathered from the patient and use validated clinical measurement instruments. We can describe the functional level of the patients before treatment and the possible influence of the health-care system and adjust for those variables.

For an example of the importance of these last two items, let me describe some findings of a multi-national study of knee replacement that my colleagues and I are currently conducting. In Japan, the average length of stay in the hospital after knee replacement is six weeks! All of the physical therapy that the patient will receive is given during that time, as there is essentially no infrastructure to provide outpatient treatment at home. Shouldn't we know that when we look at the results? In Australia, patients are at a higher functional level before surgery than patients in Great Britain have achieved at three months after surgery. We know from other studies that pre-operative functional status predicts final outcome. Shouldn't we have that information when we read papers reporting on knee replacement and other similar orthopaedic interventions? Without such information, how can we draw valid conclusions from the literature? How can we relate studies carried out in one country or with one group of patients to the needs and expectations of our own patients?

Although I am an advocate of evidence-based medicine, I am also a pragmatist. I realize two important shortcomings of the evidence-based approach; for most conditions, we don't yet have the evidence on which to base treatment. Additionally, I would accept the importance of the knowledge gained through experience. We denigrate it by the term "anecdotal" but it is an indispensable component of knowledge, especially in a surgical field. It is widely recognized in other fields. In law, for example, one expects to pay more for the senior lawyer; you are paying for experience. Both the young and the senior lawyer have access to the same library and to Lexus, but we accept the fact that experience, as distinct from recorded information, is valuable. As we accumulate the data necessary for evidence-based practice, let us use anecdote and experience, but always with a questioning mind.

BASIC RESEARCH

In brief, I would say "too little, too late." We lagged behind most of our colleagues in other surgical disciplines in terms of the number of young orthopaedists making a serious commitment to research. Our academic departments did not make a serious commitment to providing the essentials: support for research training, seed-money for young investigators and protected time for research done by the clinical faculty.

One can look at the history of basic research in clinical departments in 5 stages:

Stage 1. Orthopedists as part-time investigators
Stage 2. Post-residency research training
Stage 3. PhD's hired by departments
Stage 4. MD's and PhD's in team research
Stage 5. MD/PhD investigators

Stage 1 is, I believe, clearly over; research is too complex and funding is too competitive.

Stage 2 began 30 years ago and produced some notable successes—Drs. Cooper, Glimcher, Harris, for example—but it is no longer likely to succeed.

Stage 3 is either a successful paradigm or a dismal failure. The PhD hired so that the department can claim a "research unit" fails unless there is true collaboration with the clinicians. To succeed, this model requires both a PhD interested in working with clinicians and clinicians willing to learn enough to serve as "bridges" between the bench and the bedside. It requires a commitment on the part of both individuals; when the commitment is there, it is probably the most feasible and productive model and merges seamlessly into Stage 4 in which the clinician has a dedicated period of time each week for research, in collaboration with the PhD. This approach recognizes the competitive edge PhD's have in funding and the vital role of the clinician in maintaining relevance of the research. Stage 5 requires a time commitment that most clinically oriented individuals will not be able to meet. If the PhD is done during medical school, the training will no longer be current 5 years later when clinical training is complete. To do a PhD after clinical training requires both a sacrifice of time and money that will not be widely embraced.

THE FUTURE

We should recognize and acknowledge that "basic" and "clinical" research are not different entities, just different emphases; both require the same commitment by individuals within their departments. Both types of research must be integrated within their departments. Both types of research must be integrated into the clinical training program to the point that the trainee is as likely to ask "why" as "how." Clinical discussions should include both the research questions posed by the patient's condition and the unique characteristics of the patient that suggest certain treatments over others.

There must be more avenues for post-residency education with realistic integration of research and clinical careers. Not only must there be "protected" time for both basic and clinical research, but an environment must exist in which these activities are valued by the group.

I urge that we embrace clinical research with the same enthusiasm that we give to basic research. Let us invest it with the necessary money, time, and encouragement of our trainees. Let us look to the time when every department has a clinical epidemiologist, at least part-time, and every patient is entered into a prospective database. Let us create an environment where the most frequently asked question is what treatment to choose for a particular patient and why the chosen treatment will be best for <u>that</u> patient. Every patient must become part of a prospective database so that we may accumulate the documented experience that allows "anecdote" to become "evidence."

Finally there is the personal element: we need more department chairmen with the foresight of Carroll Larson of Iowa, 'Robbie' Robinson of Hopkins, Joseph Barr of Harvard, and your retiring chairman, Reg Cooper; individuals with the foresight to identify good people and support them as they acquire the skills to become the leaders of the next generation.

ACADEMIC MEDICINE AND INDUSTRY— THE ETHICAL DILEMMA

Augusto Sarmiento, M.D.

Without any pretense of humility, I can safely say that I lack the qualifications to intelligently discuss my assigned topic of ethics in the relationship between academic medicine and industry. I never had any special education in philosophy or any of its branches, including ethics. I suspect I was invited to speak on the subject because over the years I have, relentlessly and stubbornly, expressed concern over the degree to which industry has infiltrated the life of our profession.

I believe industry has gained significant control over the practice and education of the orthopaedist, and in doing so, it has jeopardized the foundations and perhaps the future of our discipline. This pervasive influence extends to the whole of medicine in varying degrees.

I am puzzled by the implication that the ethics that govern the relationship between academic medicine and industry is different than that between non-academic medicine and industry as suggested by the title given to my assigned presentation. Puzzled, but not surprised. By now we all have grown accustomed to society's supermarket approach to virtually every activity. We pick and choose what appears to be suitable and most convenient to our needs at any given time. This is why every social group, guild or trade has its own code of ethics, be it bankers, teachers, stevedores, dentists—you name it. Even the Mafia has its own code of ethics.

There is probably nothing wrong with this pattern because, in all fairness, societies at different times find it necessary to adopt new and different values. It is, however, a far cry from the traditional definition of ethics: the branch of philosophy that deals with universal principles of conduct. Universal, not individual or temporal.

I proceed with my assignment not knowing, however, the rules of the game that academia and industry are supposed to play by. I suspect that each has its own rules and plays the game accordingly. This is due to a great extent to the fact that industry is a business and it has customers. Medicine is a profession and has patients. It is hard to believe that one can equate the two groups without running into serious, profound philosophical conflicts.

That being the case, how does one define what is ethical or unethical in the interaction between the two partners. What is unethical in a particular conduct of the physician may be considered ethical in the conduct of the businessman, or vice versa.

What has happened over the years, and what has prompted my concern, is that industry has succeeded in making its values the values of the medical profession; or at least it has tried to accomplish that. It has been relatively easy for industry to do it because its overall influence in society has grown exponentially due to its greater financial resources. The adage, "he who pays the piper calls the tune" applies.

For quite some time medicine has been threatened with a loss of professionalism, and at times, it appears to have lost it almost completely. This development underscores the ethical concerns about medicine's relationship with industry. The commercialization of medicine has paved the way to the ethical dilemmas we face today.

Medicine failed to adapt to the changes brought about initially by the success of technology; subsequently, by the growing evidence that some type of universal health insurance is becoming a moral imperative; and finally, by the unexpected entrance of managed care. Those events have paralyzed the profession to the point where it appears unable to play a leadership role in the ongoing debate on health care delivery sweeping the world.

Because of this paralysis, organized medicine seems incapable either of articulating a credible position or dispelling the now deeply rooted perception that it simply represents a group of privileged people motivated exclusively by self-serving outcomes. A paper tiger no longer committed to the welfare of the sick, but dominated by an insatiable thirst for profit causing it to forget that professionals are individuals who subordinate their interests to the interests of those they serve.

By permitting medicine to become, in increasing degrees, a profit oriented business we have witnessed the erosion of the relationship between the profession and society. Limiting the relationship to nothing more than a commercial exchange is destroying the foundation of medicine. Medicine's inability or unwillingness to define its true mission and to recognize its important role in a changing society have contributed to the loss of professionalism among its members who remain uncertain about what their values and ethics should be. Loss of professionalism may be medicine's greatest challenge.

A discussion of ethics in medicine and particularly in reference to its relationship with industry is a most difficult subject. To unravel the complexity of the issue is a tall order.

Medicine's infatuation with technology, and the implied control of power that technology has given its members prompted them to forget the traditional traits of professionalism that made medicine, for a very long time, the most respected and influential profession in the world. The perception that physicians are simply sophisticated technicians has diminished their role in the public debate. Because of this, it is unlikely that, under the present circumstances, organized medicine will become a meaningful force in the body politics surrounding the important issue of health care delivery. Its rapid and continuous loss of autonomy seems inevitable. The medical profession is beginning to realize that the final decisions will increasingly be made through public debate, where it will not have an opportunity to participate.

Academic medicine, perhaps because of its acknowledged privileged position in medicine, is more likely to be targeted by industry in its efforts to implement its agenda. It is a logical and expected move. The fact that academic medicine is experiencing financial difficulties in maintaining and upgrading its educational and research activities makes it more vulnerable to alteration of its traditional values and ethics.

Industry, in order to gain access to the potential revenues that are derived from the use of their products, offers deans and professors involvement in ventures that in previous days would have made us question their appropriateness. ethics raises its head at the sight of such practices.

Is it wrong for a dean to accept an endowed chair if the donor demands the right to select the recipient of the chair? Acceptance of the proposal implies a break from traditional practices. Is it simply an inconsequential departure from tradition or an inappropriate, unethical action? I would say the latter. Obviously, others reason differently as they see such practices becoming common throughout the land. When I was confronted with such a situation at my own previous academic position, I came close to losing my job because of my refusal to accommodate the dean's donor.

Is receiving industrial grants for the financing and or construction of research or educational facilities in exchange for the use of the products manufactured by a given industrial concern unethical? Hardly. But is it right and appropriate to do it? I doubt it.

Some years ago a major distributor of orthopaedic equipment and implants, who I have known for a very long time, came to my office to propose to me what he called "a good deal". He offered to give me, under the table, 200 dollars for each implant of his that we were to use at the five affiliated hospitals. Pretending to be unhappy with the amount of money offered, I asked if the figure was negotiable and suggested 250 dollars. That's a deal, he said. Having then asked the distributor what made him think that I would accept such a shady proposition he apologized but closed the conversation with the remark, "But we do it all the time". Which means that a transaction that industry considers an ethical one in their business should also be ethical in the medical profession. The fact that "we do it all the time" speaks eloquently to the success that industry has had in imposing their ethics in medicine.

Shall we be concerned over such a trend or conclude that we need not worry about it?

Some years ago I witnessed several concerned Latin American orthopaedists complain that, in their respective countries, the practice of vendors giving hefty financial kickbacks to orthopaedic surgeons who used their products was becoming commonplace. It varied from 250 to 1000 dollars according to the country and the extent of the business the individual surgeons generated for them. In addition, traveling to national and international meetings was subsidized. One reason why such large amounts of money is offered is because in their countries the patient is responsible for purchasing the appliance directly from the vendor, who then overcharges in order to justify the dishonorable transaction.

More recently, I was told that the practice was so widespread that the size of the kickback was negotiated with several industrial firms in order to identify the most attractive incentive. This is being done abroad and with increasing frequency in our own country. Is it unethical to participate in such dealings? Unethical, if so many of our colleagues do it? I personally think it is unethical to indulge in such behavior. Many do not agree with me. It is, they say, an innocent business practice.

Is it unethical for a physician to become an official peddler of commercial products in exchange for the handsome revenues he or she receives? I do not know for certain. It is very likely that some who seek involvement in product development sincerely believe they have a responsibility to assist in the marketing of the product. They believe it is appropriate. Should they be called unethical because they profit by serving as paid agents of industry, and find themselves in a corporate situation that demands the defense of their products at all times and under all circumstances? Some of the so-called leaders in our profession are articulate salesmen for implants, and in that manner gained elevated posi-

tions while earning millions of dollars from their industrial sponsors. Is it unethical for those individuals to engage in commercial ventures to that extent? Not necessarily. I think it is possible to be involved in innovation and remain ethical. If properly conducted, entrepreneurial activities deserve admiration. Otherwise, they are unbecoming of a professional person.

Some nine or ten years ago the vice-president of a major orthopaedic manufacturing company visited my office and presented me with a velvet-lined box that contained a brand new prosthesis. He proceeded to tell me that his engineers had designed the implant according to my philosophy of hip surgery. His company wanted to dedicate it to me "in recognition for the contributions I had made to orthopaedics," particularly in hip surgery. They wished to call it the Sarmiento Total Hip Prosthesis. Before I had a chance to ask him how they had found out what my philosophy was, since I did not know I had one, he had reached into his coat pocket and produced a check made payable to me in the amount of $250,000. He added that royalties were negotiable.

When I indicated that I was annoyed by his assumption that I would accept my name being attached to an implant with which I had had nothing to do, he apologized profusely. We parted company after he returned the check to his coat pocket.

A few weeks later, I saw an ad in a major journal marketing the implant. When I inquired from the local vendor who the orthopaedist behind the implant was, he gave me the name of a fairly well-known surgeon! I am sure the implant represented his philosophy and therefore he was highly deserving of the fat check and handsome royalties!

Was it unethical for that surgeon to accept the large check and royalties? Ethical for me to reject the offer which I could have simply considered as having won the lottery? Was I simply an altruistic fool? Who knows.

I could spend the rest of the day sharing with you a myriad of examples that illustrate the deep inroads industry has made into our professional and personal lives. Examples that eloquently testify to the ubiquitous presence of a societal ethos that says "everything is OK," meaning that nothing is morally wrong. I could give details about the effective manner in which industry has gained control over the education of the orthopaedist and how his education is structured to a great extent to satisfy the marketing needs of industry. I have no time to venture into that experience.

My mother died recently as she approached her 99th birthday. During a visit home, one of my concerned relatives asked me to convince my mother that she should eat and exercise more. When I broached the subjects with the feeble, dear old lady she responded, "What for?" I was left speechless in the face of her profound philosophical reply. She had walked for nearly a century and did not feel that additional walking was necessary. What was it to be gained from exercising and eating more?

Walking down a busy street in Madrid some years ago my attention was drawn to a real-life bust of Don Quixote. He looked old and with his left hand he held a small candle. I was fascinated by the expression on his face. At first glance he appeared to be demented and staring vaguely into space. As I looked at it more closely, I began to see that his expression was more like that of a man intensely reflective. I could hear him say, "Who am I? Why am I in this predicament? Is it possible that these people around me are right in saying that I am crazy; that the enemies I valiantly fought, dressed in shiny armor, were only windmills? That my agile and elegant horse, Rocinante, was a decrepit old nag. That my beloved Dulcinea del Toboso was not a lady of distinction, but simply an uneducated waitress at the local inn?" The old man did not seem able to figure out the true meaning of the events in his chivalrous days.

I bring forth these two anecdotes simply to create an analogy with this discussion on ethics in academic medicine. What for? What difference does it make? Will things change because we address and debate them? It is hard to tell. There are powerful outside forces controlling events. We may not be able to influence them.

This year we celebrate the 100th anniversary of Friedrich Nietzsche's death. The iconoclastic philosopher that declared God dead; who chastised Christianity and blamed it for the perverse slave morality of the masses and exalted the virtues of the master morality of his envisioned Ubermensch, his superman.

The chances are that Nietzsche was wrong and that God is still alive. That the slave morality might prevail and the control of the world by the Ubermensch will not become a reality. That the pervasive Hollywood morality that now permeates through all aspects of society will not endure. That the words of Michael Douglas, in the movie Wall Street, "greed is good," will cease to be the expression depictive of the ethos of the times. That medicine, in a Phoenix-like fashion, might be able to rise again from the ashes of despair. That, from the abysm of frustration and suffocation that managed care has brought upon us and makes us feel like the chained slaves in Plato's Cave, one day we will see the non-reflected light of truth. That the eloquent words of Havel, president of the Czech Republic, "in the absence of a global revolution in the sphere of human consciousness, nothing will change for the better, and the catastrophe toward which the world is headed will be unavoidable,"

will prove to have been prophetic. That medicine will successfully rid itself of the cloth of superiority and once again don the mantle that depicts not only technical expertise, but also the image of a dedicated professional community.

Mythology says that in Pandora's empty box only hope remained. There is light at the end of the tunnel. Let's not give up.

BACK TO THE FUTURE?*

Newton C. McCollough III, M.D.**

During the 35 years which have elapsed since I finished my orthopaedic training, several trends have characterized the field of orthopaedic surgery. Among them are:

1. The trend from orthopaedic generalist to specialist;
2. The trend from comprehensive musculoskeletal care to procedural care; and
3. The trend from a research-based specialty to a practice-based specialty.

There is no question that the trends which we have experienced toward specialization and procedural care have produced enormous benefits for patients, and most certainly for orthopaedic surgeons. But has the pendulum swung too far in this direction? It is my belief that one should be a good doctor first, a good orthopaedist second, and an orthopaedic specialist third. You will be a better orthopaedist if you remain a good physician, and you will be a better specialist if you remain a good orthopaedist. In many ways, I think we have lost sight of our larger obligations as physicians who care for patients with musculoskeletal problems. This situation is now causing our specialty some problems.

The trend away from a research-based specialty toward a practice-based specialty is even more disturbing, and has a potentially chilling effect upon the future advances in orthopaedic care.

The title of this talk, "Back to the Future?", unlike the motion picture of the same name, is not intended to imply clairvoyance; rather, it raises the question: Might we find opportunities for the future of orthopaedics in the heritage of our past?

GENERALIST VS. SPECIALIST

Data obtained from the Academy's manpower and practice surveys clearly reveal a progressive trend toward specialization within orthopaedics. In 1982, 84% of practicing orthopaedic surgeons were self-described generalists, whereas by 1998, only 33% were classified as such. The proportion of orthopaedists with a specialty interest has increased from 33% to 37% in the last 10 years, while the true specialist now constitutes 30% of the total. Among orthopaedic surgeons under the age of 40, 38% considered themselves as generalists in 1988, compared to only 23% today[1,2,3,4].

The proportion of orthopaedists completing a specialty fellowship more than doubled between 1982 and 1998, from 19.6% to 42%[1,4]. More revealing is the fact that fully 59% of today's practicing orthopaedic surgeons under the age of 40 have completed formal fellowship training[4].

What can we conclude from all of this super specialization? Is it really needed or justified? Is it a cause for concern? Or does it reflect the desirable maturation of our specialty?

Ten years ago, I made the following observations[12].

> "We should be wary of over specialization and loss of our primary care patient base, lest office orthopaedics be lost to other medical and non-medical health care providers.
>
> More and more our residents are being taught by sub-specialists who serve as very effective role models for determining eventual practice patterns. We need a greater emphasis on orthopaedic medicine and rehabilitation in our teaching programs. Perhaps the time has arrived for a new sub-specialty—the sub-specialty of family orthopaedics."

More recently, Dr. Harold Dick, in his 1995 address to the American Orthopaedic Association, stated, "The orthopaedic surgeon of the future must be a generalist first and sub-specialist second. The reason is simple, that is what the managed care marketplace demands."[6]

The wise investor knows that over-specialization in the financial markets can be risky, depending upon the environment, and that a diversified portfolio is the key to steady growth. Is it possible that orthopaedics has become over-specialized, and that the managed care environment in which we find ourselves today has exposed that weakness?

In the mid 1980's, John Naisbett wrote a fascinating and insightful book called *Megatrends*. In his chapter describing the trend from an industrial society to an informational society, he makes the following statement,

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"We are moving from the specialist, who is soon obsolete, to the generalist who can adapt."[16] Elsewhere in the book he states, "The long-range perspective may signal the need to return to the ideal of a generalist education. If you specialize too much you may find your specialty becoming obsolete in the long run. As a generalist committed to lifelong education you can change with the times."[17]

These words were not written about orthopaedics, or medicine, but about business and industry. It seems to me, though, that this concept is valid for orthopaedics which, as a small specialty, has all too rapidly undergone super specialization, in various body parts and even procedures.

COMPREHENSIVE CARE VS. PROCEDURAL CARE

As a result of subspecialization, we have trended from comprehensive musculoskeletal care to more procedural care. Having reached that stage of life when one progressively becomes more of a consumer of health care, I know all too well that this trend is not confined to our specialty of orthopaedics, but is rampant among the specialties of internal medicine. The major adverse consequences of this trend are to exaggerate the importance of procedures to the totality of patient care, to diminish the importance and desirability of non-operative care, and all too often, to distance the doctor from the patient as a caring and involved physician. The procedure itself should not be the "be all" and "end all" for surgeon or internist; rather, it should represent an additional acquired skill to help people get well. Francis Peabody, Chief of Medicine at Boston City Hospital, said it best: "An essential quality of the physician is humanity, for the secret of patient care is in caring for the patient."

In the late 1980's, when the American Society of Internal Medicine was attempting to adjust the Medicare relative value scale in favor of internists, they promoted the term "cognitive physicians" for doctors in the specialties of internal medicine, and referred to surgeons as "proceduralists". The contrast emphasized their own value as "thinking doctors". Now, the internists have developed other terms for their own procedural colleagues, such as "interventional" cardiologists whom, we must assume, are still "cognitive".

But there is a message for us all in the unwelcome use of the word "proceduralist" and the inference that orthopaedists and others in surgery lack cognitive or non-operative skills. If this perception is shared by primary care physicians, it certainly can adversely affect patient referrals to surgeons. Most patients with musculoskeletal complaints do not need an operation—they need diagnostic evaluation, non-operative care, or rehabilitation. Many practitioners feel that referral of a patient to an orthopaedic **surgeon** consigns their patient to the knife, and that the surgeon's ability to perform an operation is frequently an indication to do one.

Charles V. Heck, who was Executive Director of the Academy for many years, recognized the use of the term orthopaedic surgeon as a problem. In his farewell address to the Academy fellowship in 1985, he recommended that "the name of the specialty be changed from 'orthopaedic surgery' to 'orthopaedics', and that its practitioners be referred to as 'orthopaedists, not 'orthopaedic surgeons'"[9].

Many others have alluded to the dangers of our specialty becoming too enchanted with the surgical aspects of care. Perhaps the first was Joel Goldthwait who, in 1933, in his paper entitled "The Backgrounds and Foregrounds of Orthopaedics"[7], remarked that,

> "In our special line of work, with the great interest in the operative side of the work, with the general indifference to the non-operative...one can but wonder if the basic ideals which justify our work have not been lost sight of. If we are to see only the operation...we cease to be true orthopaedic surgeons, but just surgeons doing bone and joint work."

In his closing paragraph he stated:

> "The opportunity is great, and if we choose operative work only, which is the easier, instead of the harder and more general, some other specialty or school will take this over."

Some 15 years later, shortly following World War II, a new specialty was born, focused initially on rehabilitation of neuro-musculoskeletal problems. It was the Specialty of Physical Medicine and Rehabilitation, and its founding was stimulated by Dr. Howard Rusk, an internist, who later established his world famous rehabilitation institute in New York, known as the Rusk Institute.

Prior to World War II and through the 1960's, it was the orthopaedist who provided the vast majority of rehabilitation for musculoskeletal problems. Our heritage from the founders of the specialty included the surgical and rehabilitative care of crippling diseases such as cerebral palsy, poliomyelitis, rheumatoid arthritis and infectious bone and joint disease.

Many orthopaedic surgeons were active in rehabilitation in the older days. In 1948, Henry Kessler, established what was perhaps the first rehabilitation institute in the country at West Orange, New Jersey, known as the Kessler Institute. When I met him there in 1969, he presented me with a book he had just written entitled, *The Knife is Not Enough*.

In 1952, Paul B. Magnuson, a leading orthopaedic surgeon of his day, began the work of founding a rehabilitation center in Chicago, which became the world renowned Rehabilitation Institute of Chicago. Following Dr. Magnuson's death, Dr. Clinton Compere continued to provide strong orthopaedic direction for the Institute, which was a leader in prosthetic and orthotic education. In 1953, Vernon Nickel became Chief of Surgical Services at Rancho Los Amigos Medical Center, and with Dr. Jacquelin Perry and other orthopaedists, developed a world famous orthopaedic rehabilitation program. Gus Sarmiento, inspired by all of these individuals, founded a rehabilitation center at Jackson Memorial Hospital in 1964, which grew to a 100 bed facility by 1978. He also founded the first Department of Orthopaedics and Rehabilitation in the country in 1972.

Even though rehabilitation has been a highly significant part of our heritage as orthopaedic surgeons, we have lost this important aspect of our specialty to physical medicine specialists. This has come about as a result of our neglect of comprehensive care and our seemingly insatiable fascination with technology. Dr. Vernon Luck addressed the Academy as its president 35 years ago on the subject of "Orthopaedic surgery—Shaping it for Permanence or Ending." Following up on Dr. Goldthwait's comments, he made a strong plea for the return of orthopaedic interest to non-operative and rehabilitative care, stating that ". . . the ominous alternative is to relinquish our leadership (in musculoskeletal care) and drift into the degraded status of surgical technicians, brought in at the beck and call of others of broader vision and deeper purpose."[11]

As we have trended more and more to specialty and procedural care, and away from general and comprehensive care, I would suggest that we are not only in the process of restricting our practice options in the field of musculoskeletal health, but we are abdicating our leadership role in many areas of this field to others. I do not believe we have too many orthopaedists, but we may have too many orthopaedic surgeons. Because of this, we are steadily losing our primary care base as more and more musculoskeletal disorders are being cared for by family practitioners, internists, neurologists, podiatrists and pediatricians.

The field of musculoskeletal health is enormous. The prevalence of musculoskeletal impairments in the United States is 124 per thousand population or 12.4% of the population.[14] For those 65 and older, the prevalence increases to 17.8%. Dr. Thomas Grogan of Los Angeles found that patients over 65 years of age consume four to five times more orthopaedic services than the population under age 65. The size of this population will more than double by 2030.[8]

Musculoskeletal conditions ranked as the second most frequent reason for office visits in 1996, nearly 95 million office visits in the United States.[15] Where did these patients go?

For new musculoskeletal problems, only 31% went to orthopaedic surgeons. Even upon referral, only 62% of musculoskeletal problems were sent to orthopaedic surgeons, while 9% were referred to family practitioners, 8% to neurologists and 7% to neurosurgeons.[15]

Thus, orthopaedists see only a portion of this huge population, and I believe that the first two trends which I have described are largely responsible for this fact. Some would argue that managed care is now responsible; however, I believe managed care is, in part, the result, not the cause of our over-specialization and focus on procedural care.

RESEARCH EMPHASIS VS. PRACTICE EMPHASIS

The third trend—that of a decreasing emphasis on research—is the most subtle trend, but one which has grave implications for the future of the specialty. Hurwitz and Buckwalter have recognized this in a recent editorial in the Journal of Orthopaedic Research entitled, "The Orthopaedic Surgeon Scientist: An Endangered Species?"[10]

There has been cause for alarm in the 1990's about orthopaedic research. Some of the warning signals are as follows:

The award rate for orthopaedic scientists from the National Institutes of Health decreased from 41% to 21% between 1980 and 1990, and the number of awards to orthopaedic surgeons as principal investigators has decreased from 63 to 50 during the same period. Only 37 orthopaedic departments had NIH funding in 1990.[5]

Of those orthopaedists taking fellowships, 11% had taken research fellowships, according to the Academy's 1982 survey, compared to 4% in 1988, 3.4% in 1994, and 3.1% in 1998.[1,2,3,4]

The Kappa Delta awards were established in 1950 to recognize, each year, the most outstanding orthopaedic research investigators. The first recipient of this award was Dr. Marshall Urist. During the 20 years from 1950 to 1970, 31 of the 34 awards, or 88%, were presented to orthopaedic surgeons as lead investigators. For the next 20 years, from 1971 to 1990, only 36 of the 68 awards, or 53%, were made to orthopaedic surgeons. Since 1990, only 13 of 27, or 48%, of the awards made by the Kappa Delta Sorority were made to orthopaedists.

Even our clinical outcomes research is being done by others-primarily by internists, epidemiologists and those in public health.

The Orthopaedic Research Society was founded in 1954. Its first president was Paul Colonna. Until 1982, each succeeding president was an orthopaedic surgeon. Since 1982, only eight of eighteen presidents of ORS have been orthopaedists.

No single one of these brief vignettes taken alone would be cause for great concern, but taken together, I believe they represent an ominous trend.

The root causes of this trend away from orthopaedic surgeon involvement in research are probably several. Among them are certainly the increasing emphasis on clinical practice income by faculties of academic medical centers as a result of managed care, and the lure of dollars which attracts orthopaedic residents and fellows to the world of private practice. Sources of funding for orthopaedic research have never been great and are becoming more scarce as the research budgets of academic health centers become tighter in response to the pressures of managed care.

A major reason for the dearth of orthopaedic clinician-scientists is the failure of most of our orthopaedic training programs to provide adequate research pathways. Training programs in general surgery, for example, much more commonly require or provide opportunities for up to 2 years of laboratory research during residency. An example of the difference that this makes is well illustrated by our Shriners Hospitals research program. Of 69 research projects submitted to our Research Advisory Board from our orthopaedic hospitals in a recent year, there were 31 physician principal investigators and of these, only 13 (41%) were orthopaedists. On the burn research side, of 99 grant submissions, 35 of the principal investigators were physicians, of whom 25 (71%) were surgeons.

Does our past then, really hold the key to our future? I believe it may, but many may disagree and say it is too late to reverse or slow these trends given the current managed care environment. Perhaps these are the thoughts of one who seeks to turn back the clock to an earlier time.

However, if it is true that we should reach back into our heritage in order to better realize the future for orthopaedics, how do we do that? As I see it, there are two pathways—one which is already being created by the marketplace in our changing health care delivery system. The second is one which we must create ourselves by changing the way we teach orthopaedics.

I believe there will be a gradual return of many practicing orthopaedic surgeons to primary musculoskeletal care, non-operative care and rehabilitation. This will occur because of the constraints being placed on the numbers of procedures we do by those who pay for health care. The economics of the new practice environment will gradually force more specialists into doing more primary care and more surgeons into doing more non-operative care. Academic orthopaedic departments would do well to consider the post-graduate educational needs of the specialist who wishes to return to more general work and consider devising educational modules to meet this need.

At the same time, a restructuring of the orthopaedic residency education program should probably occur to increase emphasis on general orthopaedics, geriatrics and rehabilitation, as well as providing adequate pathways for research. It seems to me that the best approach would be that suggested by Dr. David Murray, who, in his address to the Academy in 1982, said,

> "I foresee a reorganization occurring that will provide a basic year, three years of broad orthopaedic education, and a fourth year which is elective in any number of special interest areas including general orthopaedic surgery."[13]

This scheme would create general orthopaedists, or general orthopaedists with a special interest. The true specialist would add a sixth year of specialty training or fellowship, as occurs now. In order to achieve broad education in general orthopaedics, many academic medical centers would be well advised to add community based orthopaedists to their specialty based, full-time faculties.

In addition, there should be a finite research path in many more of our residency programs. As well, we need to teach the basics of outcomes research and other kinds of health services research at the residency level. There is a need for educator workshops in this area to "teach the teachers how to teach."

Are there really too many orthopaedists? Perhaps. There is much evidence to indicate that there are too many. I would suggest that the answer to this question is related directly to the scope of orthopaedic practice. In other words, it depends upon what we do. If the scope of orthopaedic practice can become more diversified to include primary musculoskeletal care, non-operative care and rehabilitation, as well as surgery; if the trend to specialization is moderated; and if we can create the proper incentives for the development of more orthopaedic scientists, then there will not be too many orthopaedists. I am suggesting that we need to return to our roots—in orthopaedic practice, as well as musculoskeletal research.

Izaak Walton wrote of the "Compleat Angler." Alfred Shands, in a tribute to Willis Campbell, founder of the Campbell Clinic referred to him as the "Compleat Orthopaedic Chirurgeon."[19] If and when we do go back to the future, we will have more Campbells, Steindlers,

Larsons, Ponsetis and Coopers—and that will be good for orthopaedics and for orthopaedic surgery.

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THE MISINFORMATION BOOM

Robert E. Leach, M.D.

The topic I have been asked to comment on concerns the present and future of orthopaedic information transfer. I will be speaking about printed journals and electronic publications present and future. If I were as lucky as Socrates I would feel a great deal better because he said, "My divine sign indicates the future to me." I have neither a divine sign nor any other way of being able to tell the future. Preparing for this talk I found virtually nothing in print which was of great value to me. Many writers have an opinion; most of which is based upon past experience or upon what they would like to see happen in the future. With that as a background, I will focus on some possibilities for what may happen in the next five years. Beyond five years I have no thoughts.

I termed this talk "The Misinformation Boom" because it seems to me that the possibilities of loading the electronic media with a great deal of misinformation of a non-peer reviewed type is potentially the most dangerous aspect of electronic publishing. By using that title it appears that I believe that the electronic publishing will do nothing positive. That is not the case. However, I am not presently as beguiled by electronic publishing as many others.

A good reason for having electronic publications as opposed to print publications would be to provide for a specific need within the orthopaedic community and to surmount some of the obvious problems we have with the present print journals. If there are a number of specific needs or one great problem, we must be close to having electronic publishing overtaking the print journals. So the question is, is there something better than conventional print journals and if so, in what ways would another type of publishing be of most help?

Let us take a look at that which is good and now provided by conventional paper printed journals. Journals are easy to read and are portable, and the expense of our orthopaedic journals is reasonable. However, in many of the narrower scientific fields, and in those with small circulations, the expense of a printed journal can be high. This is particularly so for libraries, since they try to stock many different journals. Printed journals provide an easy means of saving or archiving information for a long period of time. The low acid buffered papers presently available with our printing techniques give us journals which will be able to last for many centuries.

While ease of reading, portability, etc. are important for any journal, it is the material contained therein which is most important. The quality must be high. You must have authors who present good material and reviewers who provide competent peer review. Without competent peer review, sound editors and good copy editors you will not have top quality papers published by either the print or electronic media. Highest on everybody's reading wish list is good quality of the papers.

Are there problems with printed journals? Most would agree that the time it takes to get a particular paper into publication is a major problem. After an author has written the paper and sent it to a journal, that paper has to be set up, sent for review, reviewed, a decision made, sent back to the author for revisions (for there are always revisions), and copy edited and then reviewed by the author. It is then ready for publication and with most scientific orthopaedic journals of good quality, there will be a wait list for publication. This period of time from the author's initial submission to publication may range from six to eighteen months. Good material, which may be well known and accepted in the orthopaedic community through meetings, may take a while before getting into print. Another major problem for the printed journal is the lack of completely up to date bibliography because of the same problems. It may well be lacking the last few recently published references.

Does electronic publishing have the potential for solving both of these problems? Yes. The time to publication problem could potentially be solved in two ways. One, the decision may be made to not have it peer reviewed. One could simply publish the paper, which will cut down on the time enormously. Secondly, theoretically at least, there is no limit to the number of articles that could be published electronically as opposed to the usual printed journal, which has a specific number of articles that they usually publish. Since electronic journals might solve the two biggest problems, should we just get rid of printed material?

Let's examine the question of no peer review—or of the possibility of making peer review lightning fast. I believe non-peer reviewed papers would constitute a major danger for the field of medicine. Even with peer reviews we have many items which get into print early, which later prove to be incorrect. One must wonder what would happen with no peer review. In certain scientific fields, for instance in physics, I believe that they can get a type of peer review from their readers, even

an interactive type of peer review. Papers might be changed by interaction between readers and authors on the World Wide Web. I doubt this would work in the field of medicine, and patient care decisions are often made on the basis of reading journal material.

How about the possibility of finding reviewers who could do this in lightning fast time? Theoretically it means that the article would be received and a reviewer competent in that particular subject would be selected to do the review in twenty-four to forty-eight hours. The review could be put electronically online either to all the readers to judge both the review and the paper, or to the author, who would then theoretically change the paper. In this instance you would be asking a number of people to judge both the review and the paper. In the first instance, asking a particular reviewer, my assumption is that people now doing peer reviews would probably be the same people asked to do them for electronic publishing. There are not thousands of people out there competent in a particular area. Some people have suggested that pay might be helpful. I see no reason to believe that if you were to pay someone a small sum of money to peer review electronically published material that they would do it more quickly. Most reviewers are very busy; they do reviews to benefit their specialty, not to receive small amounts of compensation. If you pay a large amount, then the cost would be prohibitive. If you believe in peer review, it seems to me that there is a problem. You could depend upon an editor to do this, in which case you have a magazine dependent upon one person. Let's hope that Socrates or similar persons are available. To my way of thinking, in our field, if we do not solve the problem of peer review adequately, I believe problems will abound in electronic publishing.

It is of interest that the two major problem areas in printed journals (i.e. time to publish and an up-to-date bibliography) is of most concern to people doing research and writing papers. The majority of the usual readers of an orthopaedic journal are not doing research projects or publishing. They are reading the journals with the primary object of obtaining information with which to help their patients and to broaden their knowledge base. It is probable that the last minute bibliographic references are not as much valued to these readers. New information, at the earliest availability, is of interest to practitioners and research workers alike.

With regard to non-peer reviewed papers, one should look at the Internet to see how much material, and of what quality, is now being written primarily for the lay public by lay and other writers. There is much information out there. Many lay writers have medical knowledge ranging from nonexistent to minuscule to reasonable. Much of this material comes from a variety of health magazines and health organizations, which lends it a certain legitimacy. This is not the type of orthopaedic information I am primarily talking about, but it is another source of information which is available to our patients.

The use of websites by recognized medical organizations and even by individuals, such as is being done by Dr. Ponseti at the University of Iowa, is on the rise. When an individual such as Dr. Ponseti is writing about the clubfoot for the lay public and the profession, that can be of great value. The worry is that we will not always have such knowledgeable and esteemed individuals using the websites. We will not always be able to trust that information which lacks review.

The most common method of using the electronic media by reputable medical journals presently is to put abstracts or the entire content of a journal on the world wide web. Amongst the major journals now doing this are the *British Medical Journal, Lancet* and the *Journal of Bone and Joint Surgery*. Journals usually issue an introductory offer to encourage people to use this source of information. Then, the full text of the printed volume is made accessible to people who either take the print volume or a CD-ROM, and they usually pay an additional fee.

The editor of the *Journal of Bone and Joint Surgery*, the American volume, has recently stated that items already found on the CD-ROM of that journal, such as fuzzy-logic text searching, relevance ranked document retrieval, full indexing of all important text words and gray scale and color images will be available. There will also be links within the text to images, charts, graphs, etc. This is a great help to people doing research and those writing papers. It sounds somewhat less helpful to those who are reading the articles primarily for the knowledge to help take care of patients. Perhaps, we may have to distinguish between the electronic publishing concepts, which give us both a cutting edge and some fun tools, as opposed to those which will benefit most of our readers.

CD-ROMs have been out there for quite a while; they certainly give a concise way of being able to store information. They are presently available for many journals in orthopaedics and for a number of our major meetings. My impression is those which have the full text, slides, etc. for major meetings have not sold particularly well, but the people still prefer to go to the meetings for their information sources. This may not be so in the future. I doubt there will be a major change in the next half decade. With regard to the journals, which are on CD-ROMs, these have sold reasonably well but certainly are not as handy or as popular as the printed journals.

For this talk I have considered CD-ROMs and being online with full text to be a form of electronic publish-

ing. I do point out that these articles are handled as print journals with regard to time and peer review. They are then put on CD-ROM and then on the Web. This really represents an extension of the print process.

To me, it seems that Email, CD-ROMs and the world wide web now are used as forms of electronic communication. It is not pure electronic publishing in the sense of the Institute of Physics publishing group.

Perhaps of more value is the concept of abstract search engines now presently available, whereby you will be able to find abstracts dealing with virtually any topic. Also, the concept of a dynamic citation list, which would include both the usual references done in the printed text and a larger one of all bibliographic articles pertinent to the paper, is now coming. This could be continuously updated, probably automatically by title and keyword search. Both of these developments would greatly benefit authors, researchers and interested parties.

Make no mistake about it; there are remarkable plans afoot in the publishing industry. There is a library in Denmark, The National Technical Knowledge Center and Library, which is in the process of phasing out all print journals. They are going to put everything on the World Wide Web. The libraries believe that by doing this they can cut staff and save money. They believe that print journals cost too much money and that electronic journals will cost less and take up less archival space.

This question of cost is an interesting one. It is generally accepted that when work is performed somebody has to pay for it. Now, authors write and send their articles to journals where people who are paid work to get the papers into print. Subscribers pay to receive the journal. Advertisements in the journal by companies and organizations provide other sources of journal income and are usually a major consideration in the financial stability of any journal. As previously stated, some small specialty journals, particularly outside of medicine, have very high prices. Editors worry that with a price hike you could lose subscribers, despite the fact that the costs of publishing and postage have gone up astronomically during the past decade.

Who will pay for electronically published journals? At this point in time the only people who have been consistently able to make electronic publishing pay are those dealing with pornography. According to newspaper and magazine articles, that is a thriving industry. This is not so in other fields and other online endeavors. One would expect subscribers to pay a fee for an electronic journal, but this has not yet been very successful. There have been problems with people finding access without paying—hackers are out there. While libraries feel that electronic publishing will be cheaper in the long run, I am not sure why that would be so. If libraries become the major or sole source of these electronic journals, such as might happen in a medical school where students and staff use the library for its journals, certainly the electronic journals would then raise their prices for libraries.

What will advertisers do with electronic publishing? They have always worried about where advertisements are placed. In the non-subscription journals ads are placed throughout the pages of text in the hopes that readers will frequently notice them. In other journals, advertisements are put either at the beginning or the end. Will they be content with many of the ads that I now see online which do little to catch the eye and can easily be blinked off?

Presently in orthopaedics, many procedures and much of the equipment used has been a product of either funding from industry or actual work done by industry. Hip and knee implants and fixation devices for fractures are common examples. These companies have exerted tremendous financial resources to develop and push these products, and in many instances they have been a tremendous benefit to orthopaedic surgery. This marriage of industry, orthopaedic research and orthopaedic practitioners has helped us to make tremendous strides in the past thirty years. The other aspect of this is that peer reviewed journals and major organizations such as the Academy help to insure that the claims made by some of these companies and people who work with the instruments are reasonable and that the work is reviewed. With electronic publishing, it would be far easier for claims to be made and unsubstantiated results proclaimed.

While many industry driven designs and ideas have been very successful, there have been a variety of implants that have proven to be poor. Presently there are a number of procedures being advocated to regenerate joints that have small articular cartilage defects. Several of these procedures have received a major push from industries having a direct financial interest in these procedures. Would the internet provide the potential for having these procedures in print before being properly peer reviewed or prior to having had long-term follow-up? The lay public always believes that good medical ideas are too late to be printed. Those who have been in medicine for twenty years are aware that many ideas, which appear good, have later proven to be very poor. Peer review has played an important part in acting as a watchdog.

There is nothing to stop any particular person or company from setting up a website which will look as legitimate as any website of the American Academy of Orthopaedic Surgeons or the *Journal of Bone and Joint Surgery*. A new operative procedure could be proclaimed

on that website, and the next thing one would know is it would be all over the media. The public might assume that this is an accepted procedure and even put pressure on physicians to perform such surgery. One has to only remember the media frenzy that occurred following the first heart transplantation by Dr. Christian Barnard to realize the pressure that can come to bear with public acclaim and avid media.

There are other ideas to consider with regard to electronic publishing. A recent report states that the National Institutes of Health is considering serving as an electronic repository for all journals. They would have a webbed base network accessible to everybody, and people at the NIH see this as a simple extension of the National Library of Medicine public medical service which gives access to over 9 million full text articles on MEDLINE. One possibility is that the library would ask that the journals be a guarantor of peer review. If everything were to work through one library or even a number of libraries, we would certainly have a very different system. Instead of the journals that we often see in the laps of physicians who are going to major medical meetings, you would see everybody with a computer tapping into the NIH and wishing that the laptop screen were a lot bigger.

There are other considerations which should be mentioned with regard to electronic publishing. Some authors have been bothered by the so-called Ingelfinger rule, proposed by Dr. Franz Ingelfinger when he was the editor of the *New England Journal of Medicine*. He stated that a paper to be reviewed at the *New England Journal of Medicine* must be guaranteed, by its authors, that it is not being submitted elsewhere for concurrent review and publication. Most authors like a wide reading of their papers, which is why journals with high subscription rates are popular with authors. Most editors are aware of other journals in their particular jurisdiction, and keeping track of this Ingelfinger rule now is not too difficult. It is possible that with electronic publishing it would not be as easy to keep track of other publications. On the other hand, authors might be happy to have access to electronic journals that take papers, which are being concurrently published elsewhere.

Electronic publishing means that the receiving instruments may constantly need updating. During my life span, music has been delivered to the home via the radio, 78rpm phonograph records, 45rpm records, and finally 33s. We then went to tapes and on to discs, which have been further subdivided. Each of these changes necessitated a change in the apparatus for receiving the music. Some CD-ROMs have had major equipment changes since 1985, which have made certain CD instruments obsolete. With the lightning fast changes occurring in the computer industry, it is probable that updates on equipment would occur with expenses being a major problem. On the other hand, as equipment gets better we are able to do more things and have better material to read with graphs, etc.

There are other exciting possibilities out there. For instance, a company called E Ink, which derived a product from work done at MIT in Cambridge, Massachusetts, is using electrophoretic ink of microscopic colored capsules that change color when tiny electric current passes through it. The concept is to print a book with this ink and when after three years the material in the book is no longer pertinent, you could take the sheet out of the book, put it in the computer and zap it. This would produce a new black and white image of print different from that previously printed. In other words, the words would be arranged through this process. It sounds a bit like Star Wars, but it would certainly make the updating of books easier.

Trying to look ahead is difficult. Looking at electronic publishing, I have several obvious worries. It is conceivable that electronic publishing could play a role versus the printed journal similar to that which television has done to printed newspapers. Newspaper reading is down throughout the country. Many people get their news from television, a sound byte of 30 to 95 seconds. That may represent the present attention span of much of the population. This could happen in medicine, with doctors reading sound bytes of material rather than all the information, which they need. Reading a print abstract gives you some information but it is not enough to read an abstract and use that as a basis for treating patients. If electronic publishing starts to use sound bytes it presents a problem in the practice of medicine.

Perhaps the printed word will maintain a position similar to the position in which England now finds itself. In the middle of the 13th century when England was faced with the possibility of extinction, one of its statesmen said, "There will always be an England." He was correct, but it is an England much reduced in importance as compared to its former position on the worldwide scene. That may happen to the printed media, but in my opinion not for awhile.

My biggest personal worry is the question of adequate peer review of articles. Easy access by the public and the profession to electronically publish material might cause a problem, because most people seem to accept words on the screen or printed page as gospel.

Ann Morrow Lindberg said, "It is the wave of the future and there is no fighting it." Electronic publishing is a large wave of the future and I will not fight it. The question though is how it can best be used and whether it will coexist with the printed word, or whether it will eventually destroy the printed word.

At the present time, I am not convinced that most people would rather look at a small screen with the image presently available as opposed to reading a printed book or journal. One certainly could print out material that you are interested in, but if you do that a few times you would wonder why you did not have the printed journal. Where peer review is less important and work may be in progress and ongoing, electronic publishing will be quite successful. Whether this will be online or using so-called E print servers is immaterial. In my opinion, in the next five years the printed word will continue to be paramount for orthopaedic information. I believe the material that goes in the World Wide Web will be of primary value to researchers, people with a strong interest in a particular field and those who are writing articles. I think lay writers will be particularly interested but that it will be of less value to the majority of professional people who presently subscribe to a printed journal. As new technology becomes available, I believe that electronic publishing will become a stronger force, but the concepts of peer review must be mastered in a new environment for the protection of us all.

ORTHOPAEDIC PROFESSIONAL SCIENTIFIC ORGANIZATIONS WHAT SHOULD THEIR ROLE BE? HOW SHOULD THEY BE MANAGED?

Thomas C. Nelson

Let me begin by thanking Dr. Cooper and the Department of Orthopaedic Surgery at the University of Iowa for including me in the first series of Reginald R. Cooper Orthopaedic Leadership Lectures. I have had the privilege of working with many in this room, and I also have many great memories during my 26 years with organized orthopaedics. I look around this room, and see the proud traditions of the University of Iowa Department of Orthopaedic Surgery. I know that the future of orthopaedics is in good hands. I will predict, based on history, that in this room are future Presidents of several orthopaedic organizations, future chairs of orthopaedic residency programs and active participants in orthopaedic organizations. Iowa has a history of providing orthopaedic leaders and that will not change. I was fortunate to have been able to work with Dr. Cooper when he served as President of the Academy, Dr. Buckwalter when he was on the Academy Board of Directors as Secretary and later President of the American Board of Orthopaedic Surgery and Dr. Clark when he was a junior member on the Academy Board of Directors. I also served as Executive Director of the American Orthopaedic Society of Sports Medicine when Dr. Leach was President of AOSSM and Executive Director of the Academy when Doctors Sledge, McCollough and Sarmiento were Presidents the Academy. Since my professional life was shaped by over 26 years with the Academy and several orthopaedic specialty organizations, that will be the focus of my remarks. To begin, I believe we must revisit history to gain a perspective for today and the future. The Academy, as well as the orthopaedic specialty organizations, is far different than they were 30 years ago, 5 years ago, even last year. The changes in organized medicine during that time frame have had a dramatic impact on all organized orthopaedics. Some may argue it has been positive and others negative, but in my opinion this change has been inevitable.

History tells us that most orthopaedic organizations in the 60's and 70's were "good ol' boy clubs," organized for purposes of education, social interaction and opportunities to pursue the future with good times and good discussion.

The Academy, as well as all orthopaedic organizations, have as their purpose as stated in their by-laws, to "promote education, enhance learning, promote research, enhance educational interaction." In other words, have an annual meeting, learn, promote, educate, multiply, etc.

Having been in healthcare association management for over 30 years, I am struck by three watershed events which have dramatically changed the direction of all healthcare associations, and specifically orthopaedic organizations, forever. It changed their management style, changed their staffing needs, and changed their priorities, their directions and member expectations. In fact, in my opinion it is the latter, member expectations, which are driving healthcare associations today more than ever before. The question is, are those expectations realistic? Can a healthcare organization meet excessive expectations in the area of advocacy? Those are questions which need to be addressed. What were the events and how did they change healthcare associations? What will be their impact on the future?

First, the introduction of Medicare in the mid 60's. The passage of this law introduced health policy and advocacy into the healthcare vocabulary. Medicine fought the introduction of Medicare and lost this fight. Even if it turned out to be financially beneficial for a period of time, government was now directly involved in the funding of healthcare forever.

Second, the Hsaio Study in the early 80's. The changed the culture of organized medicine and officially began the splintering of healthcare into surgical and nonsurgical camps. Something that was unspoken prior to this became a verbal free-for-all.

Third, the failure of Clinton Healthcare Reform and the proliferation of managed care in the early 90's and today. Because Clinton's health system was defeated, policy makers, industry leaders and others identified managed care as the way to control healthcare costs. The results have been a new style of healthcare, which has changed the relationship between provider and patient.

These three events helped create a new culture within orthopaedics. Orthopaedic associations grew in the 70's, and had to expand their focus in the 80's because of the intervention of government or face being challenged by a membership who felt their leadership was out of touch with reality. These new political and policy threats were real, and an alarmed membership looked to their association to provide answers. They

wanted more than education. They wanted help in combating threats to their livelihood. For the Academy, this was new territory. Built on a foundation of education, which was appropriate, these watershed events have led all healthcare associations in general, and the Academy in particular, through some extremely painful times. I will review those activities in a minute, but first let me describe my thoughts regarding management of healthcare associations.

It has been my belief that all healthcare associations are built, for purposes of a simple description, on a three-legged stool. Resources are spent on three principal service or activity components.

One leg is education; historically, the foundation for healthcare associations. A second leg is research; always a critical component or activity, and one which sometimes receives more lip service than action. The third leg is advocacy; a new dynamic introduction in the 80's to the orthopaedic community, and now a significant activity in the Academy and all major healthcare associations.

Balancing expenditures and other resources in a way which meets the needs of its members can be difficult. 18,000 members of the Academy have different expectations. The challenge to the Board of Directors and staff is to listen, observe and be in front of the fast moving changes ahead of us as they relate to these three areas of activity. Unfortunately, when there is the perception that spending in one of the three areas is out of balance, the stool wobbles and there is a fear among some that the wrong organizational direction is underway.

The role of healthcare associations, today and in the future, has out of necessity expanded in order to deliver value to its members. The most challenging situation for associations in the future is to be able to afford the costs these new expectations bring to the organization. There are two principal revenue streams to associations—member dues and revenue from educational programs and services. Advocacy does not produce revenue, and it places significant stress on an organization to balance the resources needed to maintain that level stool.

What did each of these watershed events mean to organized medicine and organized orthopaedics specifically?

1. **Medicare**—Medicare refocused the efforts of the American Medical Association away from education to advocacy. Because of this new focus, beginning in 1965 and over the following years, specialty medicine had the opportunity to seize education as a way to grow and prosper, a way to significantly expand its budgets and meet the education needs of its members. The AMA, which once drew 60-70,000 physicians to its annual scientific program, saw their leadership role in education shrink as it turned its attention to health policy and politics. During the last 35 years the AMA has poured hundreds of millions of dollars into advocacy. Their membership has shrunk, and today they represent less than 35% of practicing physicians. Am I saying there is a connection between the AMA's focus with advocacy and a loss of membership? Yes, for a couple of reasons. First, as I said earlier, education and specialty medicine flourished as the AMA abdicated its role in education to the specialty organizations. Maybe this was inevitable, but it certainly escalated as the AMA refocused its commitment to the Washington scene and advocacy. Organized orthopaedics benefited from this refocus of the AMA, and the Academy's education programs expanded. They were the cornerstone of the Academy, both intellectually and financially, and they continue to be the dominant source of financial resources. Secondly, the growth of specialty societies and their economic windfalls from education made them much more independent both in attitude and action. The wheels of fragmentation of medicine were in motion, and there would be no turning back. All healthcare associations were on their way to enhanced financial strength because of the growth in education, and subsequent feelings of "we can do it better" began to come from all specialty societies. However, in the 70's and 80's that was not the spoken word.
2. **Hsaio Study**, in the early 80's—For the first time a "public" splintering of organized medicine occurred. Surgical organizations and non-surgical groups fought over the size of the dollars they should receive from government programs. Prior arguments over professional liability costs for high-risk surgeons paled in comparison to the open warfare that broke out in the 80's. Led by non-surgical organizations, surgeons' incomes were challenged as outrageous in some circles, as primary care physicians sought to expand their incomes and began to assert their rights as gatekeepers to the healthcare system. The Academy during these years began to significantly expand its resource allocation for advocacy. In fact, Dr. Reginald Cooper, as President of the Academy, led the first orthopaedic surgeons' workshop specifically called to address these issues. These and other similar activities began to increase organized orthopaedic activities in advocacy. It was these activities that began to drive organized orthopaedics to develop outcome tools and other similar instruments to enhance orthopaedic influence and position during these policy debates. The members expected it, and

the response was not inappropriate. They key was to balance orthopaedic resources in a way that did not diminish the education and research legs of our stool. The impact on organized orthopaedics was significant, as the Academy sought to find resources to be a "player" in the Washington policy arena. This also began the development of expanded orthopaedic education products beyond courses and an annual meeting to support growth in advocacy. Between 1983 and 1994 expenditures for orthopaedic advocacy grew from approximately $500,000 per year to in excess of $6 million per year. While that only represented 20% of the Academy operating budget, it represents an increase of substantial proportions. During this time, and possibly because of this new focus, orthopaedic specialty organizations such as AOSSM, AANA, POSNA and others saw new gains in education for their associations and likewise new dollars for their organizations. Sound familiar? It should, as history does have a tendency to repeat itself. This continues to be a risk within orthopaedics. Just as the AMA's focus on advocacy enhanced the Academy's treasury, helped fuel membership growth, and attendance at its programs the orthopaedic specialty societies are more than willing to pick up any slack in education from the Academy. Does this mean the Academy will decline?—not necessarily. Does it mean the orthopaedic specialty societies will grow and become increasingly independent?—maybe. Never underestimate the power of money to change attitudes. I am certain there are those who, in the 60's, felt the AMA would always be the dominant player in healthcare. In my opinion, while they are still a major player in Washington, they are but a shadow of their former selves. Partly because of fragmentation, and partly because of specialty organizations like the Academy representing the needs of its members in a way which better meets their expectations. By the year 2010 will that be the way of organized orthopaedics? You people will answer that question. I can predict with some certainty that by the year 2010 or sooner, events will test your alliances and allegiances.

3. **Clinton Reform—**The failures of Clinton Reform and the embracing of managed care in the 90's brought on the formation of expanded healthcare coalitions to combat this activity. In fact, from 1944 and through today, the Academy is a leader in the development and participation of these coalitions, which have been successful in representing the interests of physicians and orthopaedists in the debate. It has fought to meet the members' expectations in this area, but it has been at a cost.

First, healthcare organizations have historically found it difficult to work together. Partly, the issues drive this division and partly, the egos and independent attitudes of physicians keep medical organizations apart. You all want to be captains of the ship, and this is reflected when more than two groups try to work together. Not only are there external issues, but also you continue to argue within orthopaedics regarding direction and focus.

The concerns within organized orthopaedics today over organizational direction and advocacy are no different than it was in the early 80's, when education was "top dog". I continue to refer back to my 3-legged stool concept. Associations today are facing increasing pressures to maintain that delicate balance regarding resource allocation.

Dr. Sarmiento captures the mood of 1999 among many when in the most recent AAOS bulletin he wrote,

> "In spite of the reassuring words we have heard in recent months that the establishment of the parallel (c) (6) organization will not diminish the Academy's major commitment to education, I suspect that the move toward the trade union organization is inevitable and education might take a set back to lobbying. . . . Not only could the money available to education endeavors decrease, but the interest in education might diminish."

As usual, Dr. Sarmiento has eloquently stated a case for the legs of the stool being out of balance. I believe you could make a similar case in 1984 that education spending was excessive and could have led to the Academy not meeting the new needs of the members in health policy and advocacy as we headed toward some difficult times with healthcare reform on the horizon.

How medical society leadership and staff manage these different issues, balance the resources, maintain a level operating "stool" will determine the direction of organized orthopaedics as it faces an uncertain future. To thrive in the future the Academy and other orthopaedic specialty organizations must behave in a different way. Changing an operating culture that has been in existence since 1933 will be difficult. But to not modify the operating culture could challenge the Academy's survival as an organization.

Specifically, I believe the following are keys to that survival. First, the societies that survive will be those which have streamlined their decision making and implementation processes. Time is a luxury you don't have. Rapid response requires increased flexibility in both staff and membership structures. You must be able to pull together the right people, right now, if you are to have any chance of influencing the environment. You

must reexamine the cumbersome committee structures and a complex policy development process born during a time when the pace was slower and the stakes less critical. You must be willing to operate more effectively without a certain chain of command. Doing this could challenge the fundamental fiber of volunteer, individual membership organizations, using member participation in a bulging committee structure for the sake of involvement. However, to stand on that principal could well be the death note for organizations in a time when fast moving events require immediate responses.

Second, the strength for healthcare associations in the future lies in flexible coalitions, built with other groups who come together around specific issues. You cannot lock yourselves into monolithic alliances in which consensus is so elusive that nothing gets done. You must look for friends in new places, carefully considering what the vertical integration of healthcare will mean in terms of new clinical and administrative partners. Your coalitions may change depending on the issue. But you must make new friends and be willing to compromise in order for consensus to be developed. Failure here will also be to your disadvantage, if success is not achieved.

Third, medical societies must work hard to remain relevant to their members. There will be a scarcity of dollars in the future, and health care providers will choose more carefully among associations. You must pay special attention to your younger members who are usually under-represented on the policy making board of medical societies, but whose needs and interest form the foundation of your societies' futures. The context in which they practice medicine will be dramatically different from that of their older colleagues. Societies that fail to grasp this truth and continue to serve up "business as usual" will be left behind.

Fourth, you must be seen as credible players, as serious participants at the negotiating table. To accomplish this, you must reaffirm you and your members' commitment to quality patient care. Motivations of self-interest will be discovered and exposed, and you will lose your best, and perhaps only, ally—the patient. You must be well informed on the topics of the day and look for win/win solutions. Strident demands or threats will result in you being driven away from the venues where decisions are made.

These changes are also increasing the pressure and need for accountability among the staff leaders of your associations. Similar to changes in the operating culture of associations, there will need to be a new attitude among your executive leadership.

As medical executives I believe it is imperative that we grasp the magnitude of the changes unfolding around us. We must serve as the wide-angle lens that brings the big picture home to our members and their leaders.

As staff to organizations with these changing needs, we must redefine our role. I firmly believe that policy making should remain a member-driven activity. That is fundamental to the success of any healthcare association. Just like the balancing of resources on our 3-legged stool, staff must never become the policy maker and implementer. Crossing that line will result in the immediate decline of any association. However, I believe staff will be called upon increasingly to provide sophisticated analyses of the issues at hand. Further, staff will need to take the lead in planning and evaluation processes, which will ensure that resources are being deployed wisely and efficiently. Time commitments of the physician members are important, but you must take the time to be involved. Your predecessors did, and I do not accept the excuse of too busy as a crutch for not involving yourself in something as important as your future. The strength and effectiveness of the Academy, or any healthcare association, is only as strong as the involvement of its members. If you allow staff too much control and do not participate, be forewarned of the consequences.

The Sunbeam situation at the AMA, while certainly a failure of oversight, was not the total responsibility of staff. Physician leadership asked for more resources to cover the costs of increased advocacy at a time membership continued to decline. Staff responded, and the oversight on both sides was not effective. You do not need public disclosures of this kind in the future.

In the brave new world, our members and leaders will demand more of us. We, as senior staff executives, will and should be held accountable. We will need to be more creative in our thinking, more strategic in our planning, more frugal with resources, and more analytic in our background work. But most of all, we will need to be more visionary.

What a challenge this will be, but what an opportunity to create the new association capable of bridging the gap in healthcare reform. The partnerships for this new organization will be built with staff and members sharing the same vision. That may be one of the most difficult tasks on the horizon.

Leadership and staff must be certain they are leading the organization based on the events of today, not yesterday. That is true in education, research and advocacy. Today's healthcare association must be ahead of the changes unfolding around us.

The *Harvard Business Review* sums it up best:

"The root cause of nearly every one of the problems is not that things are being done poorly. It is

> not even that the wrong things are being done. Indeed, in most cases, the right things are being done—but fruitlessly. What accounts for this paradox? The assumptions on which the organization has been built and is being run no longer fit reality."

To accomplish this, the leadership of the successful healthcare association of the future must spend more time planning, and less time worrying about operations. They must do a better job of anticipating the events of the future and having in place programs to meet the needs of the members. They must do a better job of focusing on the activities of today and have the courage to delete popular programs because they are no longer relevant to today's healthcare organization. And most fundamental to all of this, they must listen to their members. Sometime we fail because we don't listen.

I want to close with a quote from Andrew Grove. To me it is a statement, which confronts business organizations, healthcare associations, all of us.

> "There is at least one point in the history of any organization when you have to change dramatically to rise to the next performance level. Miss that moment and you start to decline."

Prior to 1965, healthcare associations did not worry about those moments. Determining those moments, seizing the opportunities, responding in a way which directs the organization to a new performance level, exceeding the expectations of the membership and providing value to the member in education, research and advocacy; those are the challenges orthopaedic organizations face. You will face these challenges in the decades ahead. Will you be up to the task? Will you be able to say organized orthopaedics looked history in the eye and stayed together, stayed the course and delivered a balanced program to the orthopaedic surgeon so they had the tools to be effective? Did their organization give them the wherewithal to deliver high quality, cost effective orthopaedic care? Or will you fragment further and be a shadow of your former selves by 2010 or 2020?

Those, in my opinion, are serious questions, and the answers to those questions will take serious deliberation, solid and intuitive analysis, the course to compromise, and the ability to create win/win scenarios. You will drive the answers, the direction and the future of organized orthopaedics. I firmly believe honest and open debate will lead to the correct direction.

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