THE IOWA ORTHOPAEDIC JOURNAL VOLUME 19, 1999

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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 2000 journal is February 1, 2000.

Articles published and their illustrations become the property of the journal. *The Iowa Orthopaedic Journal* is listed in the *Index Medicus*, therefore articles previously published will not be accepted unless the content has been significantly changed.

When you send an article it is essential that the following items be submitted:

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.

Preparation of illustrations: Number all figures and indicate *top* plainly. Write the author's name on the back of each illustration. Send prints unmounted; paste or glue will damage them. Drawings, charts, and lettering on prints usually should be done in black; use white backgrounds. Put dates or initials in legends, not on prints. Make lettering large enough to be read when drawings are reduced in size. When submitting an illustration that has appeared elsewhere, give full information about previous publication and credit to be given, and state whether or not permission to reproduce it has been obtained.

Printed on acid-free paper effective with Volume XV, 1995.

EDITORS' NOTE

The University of Iowa
Department of Orthopaedics

It is a privilege to bring you this, the nineteenth edition of *The Iowa Orthopaedic Journal*. Once again, our mission is the education of our readers in hopes of providing better patient care. From its inception, this journal has provided a forum somewhat different from other periodicals; providing a wide variety of articles including those of historical and ìphilosophicalî interest, clinical and basic science studies, general review manuscripts, and case reports. We greatly appreciate the numerous authors who contributed time and effort to enhance this edition. In a time of increased clinical, research, and administrative demands on physicians and scientists, it is of paramount importance to continue to place equal emphasis on education.

Each edition of *The Journal* has honored one person who has been instrumental in the advancement or orthopaedics at the University of Iowa. This year, we have chosen our chairman, Dr. Reg Cooper. During the last 26 years he has guided the growth and development of the Department of Orthopaedic Surgery at the University of Iowa leading it to a preeminent position among orthopaedic departments. He has also made major contributions to basic research as well as multiple professional and scientific organizations. As a resident under Dr. Cooper, one quickly learns to appreciate his very effective and memorable teaching style which combines knowledge, intellect, and humor. He teaches the value of critically evaluating even the most widely accepted opinions and practices. He has and will continue to positively affect the careers of many orthopaedic residents.

The assembly of the "finished" product involves many steps. The solicitation of articles and advertisements, editing of manuscripts, and organization of the distribution is the responsibility of the residents. However, we could not have completed this project without the help of many others. We thank our faculty advisors, Drs. Buckwalter, Cooper and Clark for their guidance. We also appreciate the secretarial support of Ms. Laura Cole and Ms. Linda Croy, and the expertise of Diane Thomas who was instrumental in the assembly of the finished product.

We hope that you will enjoy and benefit from our efforts, and we welcome your comments and criticism.

Matthew B. Dobbs

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.

Address:

Bonfiglio Educational Endowment Fund
The University of Iowa Hospitals and Clinics
Department of Orthopaedic Surgery, JPP
200 Hawkins Dr.
Iowa City, IA 52242-1088


DEPARTMENT
OF
ORTHOPAEDIC
SURGERY
THE UNIVERSITY OF IOWA
RESEARCH

Department of Orthopaedics

R. Kumar Kadiyala
1998-present

Leon Grobler
1996-present

Arthur Steindler
1912-1949

Brian Adams
1993-present

Theodore Willis
1917-1918

Charles Saltzman
1991-present

Joseph Milgram
1926-1932

John Callaghan
1990-present

Ernest Freund
1932-1936

David Tearse
1989-present

Thomas Waring
1932-1939

Ernest Found
1987-present

James Vernon Luck
1936-1939

Lawrence Marsh
1987-present

Ignacio Ponseti
1946-present

Curtis Steyers
1985-present

Eberly Thornton
1946-1952

James Nepola
1984-present

Robert Newman
1948-1956

Fred Dietz
1984-present

Michael Bonfiglio
1950-1995

James Weinstein
1983-1996

Carroll Larson
1950-1978

Barbara Campbell
1982-1984

Adrian Flatt
1956-1979

Charles Clark
1980-present

Reginald Cooper
1962-present

William Blair
1980-1997

Howard Hogshead
1964-1965

William Pontarelli
1980-1984

Maurice Schnell
1964-1965

Joseph Buckwalter
1979-present

Richard Johnston
1967-1970

Thomas Lehmann
1978-1987

Donald Kettelkamp
1968-1971

Stuart Weinstein
1976-present

Gerald Laros
1968-1971

Mike Mickelson
1976-1981

Richard Stauffer
1970-1972

Richard Brand
1974-present

John Albright
1971-present

Bruce Sprague
1972-1979

Doug Mains
1972-1973

The University of Iowa
College of Medicine

1999 GRADUATING SENIOR RESIDENTS

R. Dow Hoffman, M.D.
Dow was born in Columbus, Indiana, and later moved to Jacksonville, Florida. He earned a B.S. in chemistry at the University of Florida in 1990, and an M.D. at Duke University in 1994. Next year, Dow and his wife Rhonda will be moving to Naples, Italy, where Dow will begin a three-year assignment as an orthopaedist in the United States Navy.

Darron M. Jones, M.D.
Darron grew up in Iowa Falls, Iowa, with his parents and a younger sister. He graduated from Iowa State University in 1990 with a degree in zoology. He then moved across the state to The University of Iowa where he obtained his M.D. in 1994. After completing residency training, Darron, his wife Julie, and their son Samuel, will be moving to Salt Lake City, Utah, for a fellowship in sports medicine at the Orthopaedic Specialty Hospital under the direction of Dr. Lonnie Paulos.

Sean B. Kaminsky, M.D.
Sean was born in Lexington, Kentucky, but grew up in the Tampa/Clearwater area a few miles from his wife Kristen. He graduated from Emory University in 1990 with a degree in Economics, and from Emory Medical School in 1994 with his M.D. After completing his residency training, Sean, Kristen, and toddler son Harrison will be moving to Georgia for his Shoulder Reconstruction and Sports Medicine fellowship at the Hughston Clinic.

Joff G. Thompson, M.D.
Joff grew up in Grand Forks, North Dakota. He received a B.A. in biology in 1990 from Boston University, and an M.D. in 1994 from Duke University School of Medicine. He and his wife, Maria, have a one-year-old son, Andrew, and are expecting another child in June. This summer, Joff and his family will be moving to Bend, Oregon, to start a general orthopaedic practice with the Bend Orthopaedic and Fracture Clinic.

Paul A. Watson, M.D.
The youngest of six sons, Paul was born in Armonk, New York, and graduated from Byram Hills High School in 1987. He received a Magna Cum Laude Bachelor of Arts in Biology from Harvard University in 1990. He then went to McGill University for Medical School in Montreal, Quebec, Canada. Next year, Paul will be joining three previous Iowa graduates, Dennis Colles, Craig Mohler, and Tom Wuest in Eugene, Oregon, doing general orthopaedics.

DEPARTMENT OF ORTHOPAEDIC SURGERY
1999-2000 LECTURESHIPS AND CONFERENCES

Carroll B. Larson Shrine Memorial Lecture
March 4-6, 1999
George H. Thompson, M.D.
Case Western Reserve University
Cleveland, OH

Senior Residents' and Fellows' Day
May 20-22, 1999
Scott D. Boden, M.D.
Emory Spine Center
Decator, GA

Peter G. Trafton, M.D.
Brown University School of Medicine
Providence, RI

First Biannual Reginald R. Cooper Orthopaedic Leadership Lectures
May 21, 1999
Robert C. Leach, M.D.
Boston University
Waltham, MA

Newton C. McCollough III, M.D.
Shriner's Hospital
Tampa, FL

Thomas Nelson, B.S., M.P.A.
Smith, Bucklin and Associates
Chicago, IL

Augusto Sarmiento, M.D.
The Arthritis and Joint Replacement Institute
Coral Gables, FL

Clement B. Sledge, M.D.
Harvard Medical School
Boston, MA

Michael Bonfiglio Iowa Orthopaedic Alumni Meeting
September 24-25, 1999
Michael Simon, M.D.
University of Chicago
Chicago, IL

James Heckman, M.D.
University of Texas
San Antonio, TX

Sports Medicine Symposium
December 3-4, 1999
Louis U. Bigliani, M.D.
Columbia Presbyterian Center
New York, NY

Senior Residents' and Fellows' Day
May 19-20, 2000

REG COOPER

Joseph A. Buckwalter, M.D.

Figure 1. Dr. Reginald Cooper. Faculty member of the University of Iowa Department of Orthpaedic Surgery since 1963 and chairman of the Department from 1973 to 1999. Dr. Cooper, a distinguished leader in the specialty of orthopaedics, served as president of the Orthopaedic Research Society, chairman of the board of trustees of the Journal of Bone and Joint Surgery, chairman of the Medical Advisory Board of the National Shriners Hospitals for Crippled and Burned Children, chairman of the orthopaedic Residency Review Committee and president of the largest orthopaedic professional and scientific organization, the American Academy of Orthopaedic Surgeons. During his years as chairman of the University of Iowa Department of Orthopaedic Surgery, Dr. Cooper directed the growth of the department from eight faculty to 18 faculty and the expansion and development of specialty services including joint replacement, pediatric orthopaedics, trauma, sports medicine, orthopaedic oncology, hand and microvascular surgery, spine surgery and foot and ankle surgery. Under Dr. Cooper's leadership the department has received national and international recognition for excellence in patient care, teaching and research.

Only a few physicians make major contributions to basic research, professional and scientific organizations and the development of an academic department. Reg Cooper is one of these uncommon individuals (Figure 1). His research helped clarify the ultrastructure of bone, tendon and ligament, the physeal abnormalities associated with disturbances of skeletal growth and the effects of immobilization and re-mobilization on skeletal muscle[4-8, 14]. Dr. Cooper and his co-workers were the first to define the changes in ligament insertion structure and strength caused by decreased physical activity15. His service with the National Institutes of Health, the American Orthopaedic Association, the American Board of Orthopaedic Surgery, the Orthopaedic Research Society, the Shriners Hospitals for Children, the Journal of Bone and Joint Surgery and the American Academy of Orthopaedic Surgeons has strengthened the specialty of Orthopaedics. During the last 26 years he has guided the growth and development of the Department of Orthopaedic Surgery at the University of Iowa leading it to a preeminent position among orthopaedic departments. Over the same period he has contributed significantly to the advancement of the University of Iowa College of Medicine and the University of Iowa Hospitals and Clinics (Figure 2).

Figure 2. Photograph from a November, 1974, press conference held to announce the gift from Roy J. Carver that led to the construction of the University of Iowa Hospitals and Clinics Carver Pavilion. The Orthopaedic Department moved from the Children's Hospital, the location of the Orthopaedic service starting in 1919, to the Carver Pavilion in 1979. From left to right, Dr. Sidney Ziffren, Chair of Surgery in 1974, Roy J. Carver, John Colloton, Director of University Hospitals and Clinics in 1974, and Reginald Cooper.

Please address correspondence to Joseph A. Buckwalter, 01013 Pappajohn Pavilion, Department of Orthopaedics, University of Iowa College of Medicine, Iowa City, IA 52242, Phone (319) 356-2595, FAX (319) 356-8999, email: joseph-buckwalter@uiowa.edu

WEST VIRGINIA TO IOWA

The story of Reg's journey to becoming a leader in the specialty of orthopaedics, a loyal Iowan and an integral part of the University of Iowa for more than 40 years begins in Dry Fork, a small community deep in the hills and hollows of rural West Virginia. His father taught in a one-room school for several years and then ran the country store in Dry Fork. His mother, who graduated with a teacher's degree, chose to be a home maker. Reg's grandfather, a physician, provided the medical care for people living in the immediate area. In addition to the country store, Dry Fork had a post office, a two-room school and a hard surfaced road. No more than 25 people lived in or near Dry Fork, and most of the people who stopped at the country store and collected their mail at the post office lived in areas not served by the United States Postal Service.

Reg was born in Elkins, West Virginia, the town with the nearest hospital. He attended the two-room school in Dry Fork and then moved on to high school in Harmon, West Virginia. In his spare time he helped in the country store and played the guitar in a square dance band. After graduating from high school with his class of 12 students, he attended Potomac State College in Kaiser, West Virginia, from 1948 until 1950. He was accepted at West Virginia University in Morgantown in 1950, and after graduating from the University, he entered the Medical School in Morgantown. In 1953, he transferred to the Medical College of Virginia in Richmond where he completed his medical education in 1955.

Reg's grandfather delivered Jackie Smith (the future Jackie Cooper) and her twin sister in the Smith family home. Jackie and her family lived in Tucker County, several miles from Dry Fork where her father worked in the coal mines and she attended a one-room school. Her family picked up their mail at the Dry Fork post office and she knew Reg and his family through visits to the country store and church activities. When Jackie was 14, Reg approached her after a church meeting and offered to walk her home, a distance of nearly three miles. This walk along the country roads was their first date. After finishing high school, Jackie attended Glenville State Teacher's College in Glenville, West Virginia, and graduated with a teaching degree. During college she taught in a one-room school and after graduation she taught in the Richmond school system. In 1954, when Reg was in his final year of medical school, Reg Cooper and Jackie Smith married. They are now approaching their 50th wedding anniversary and have four children: Pam, an attorney in Rochester, Minnesota, Doug, an orthopaedic surgeon, in Marshalltown, Iowa, Chris, a pediatric urologist who will be joining the faculty at the University of Iowa, and Jeff, a hospital administrator at Loyola of Chicago. Thus far, they have four grandchildren.

One of Reg's rotations during medical school included the care of children with neuromuscular disorders. He found the problems presented by these patients challenging. This experience led him to develop a strong interest in the causes of neuromuscular diseases in children and in finding ways to improve the function of these patients. He was particularly impressed with the benefits of orthopaedic treatments, including surgical procedures and braces. One of his classmates, William Bell, shared Reg's interest in neuromuscular disorders and they frequently studied together and discussed approaches to the diagnosis and treatment of patients with neuromuscular diseases. In their last year of medical school, Reg and William Bell wrote to the University of Iowa for information concerning postgraduate medical education at Iowa. Based on the brochure sent to them by the University of Iowa Hospitals they applied for internships at Iowa, and both of them were accepted.

Following Reg's graduation from medical school, Reg and Jackie packed their belongings in the back seat of a black 1948 Chevrolet, made a brief visit to Dry Fork, and then started the long drive to Iowa. They arrived in Iowa City for the first time in June of 1955 with $36.85, their car, their clothes and a few dishes, pots and pans. Reg started a rotating internship at the University of Iowa Hospitals and Clinics in July of 1955 and Jackie began working as a teacher at the University of Iowa Hospital School. William Bell started his internship at the University of Iowa the same year. He became a widely respected pediatric neurologist, and, like Reg, spent his entire career at the University of Iowa.

ORTHOPAEDIC RESIDENCY AT IOWA

Reg completed a year of General Surgery residency in 1957, and was accepted into the orthopaedic residency at the University of Iowa. Two other General Surgery residents from the University of Iowa, Robert McCoy and Ralph Cotton, joined him as Orthopaedic residents. After signing a contract for his first year of orthopaedic residency, Reg learned that his salary would be $75 per month. He initially considered this amount insufficient and expressed his concern to Dr. Carroll Larson, the chairman of Orthopaedics. Dr. Larson explained that although the salary might seem low the residents would not be expected to pay tuition as they did at other outstanding Orthopaedic residencies. He added that he probably could find other people who would be happy to accept the position. Reg decided not to pursue the issue.

When Reg started the program in 1957 the Orthopaedic Department already had a more than 30 year history and enjoyed an international reputation for excellence in clinical care, research and teaching. Arthur Steindler started the first regular orthopaedic clinics at the University of Iowa Hospitals in 1912 and became the first chair of the newly established Department of Orthopaedic Surgery in 1927. Dr. Carroll Larson followed Dr. Steindler as chairman in 1950. In 1957 the faculty responsible for Reg Cooper's orthopaedic education consisted of four distinguished orthopaedic surgeons: Michael Bonfiglio, Ignacio Ponseti, Adrian Flatt and Carroll Larson. Dr. Bonfiglio was one of the leaders in the establishment of orthopaedic oncology as a specialty within orthopaedics and focused most of his efforts on studies of musculoskeletal pathology and the treatment of patients with bone tumors and necrosis of the femoral head. Dr. Ponseti had developed a biochemistry laboratory for the investigation of the causes of musculoskeletal deformities and dwarfism and was recognized as an international authority on the treatment of children with clubfeet, hip dysplasia and scoliosis. Dr. Flatt's extensive experience in hand surgery, his investigations of the biomechanics of the hand and wrist and his expertise in the treatment of patients with congenital and rheumatoid deformities of the hand had led to the development of a strong hand surgery program within the orthopaedics department. Dr. Larson had a well deserved reputation as an expert in hip surgery and the treatment of adults with back pain. These individuals expected a high level of basic scientific and clinical knowledge from the residents, an expectation that they reinforced at daily indications conferences where the residents presented clinical cases and were then questioned by the faculty. In addition to placing a strong emphasis on basic scientific and clinical education, the faculty encouraged the residents to conduct independent studies and write a thesis. Dr. Bonfiglio had developed a bone pathology laboratory and an extensive collection of bone specimens. Dr. Cooper developed an interest in bone pathology and conducted an investigation of giant cell tumors of bone. This work led to his receiving a Master of Science Degree.

UNIVERSITY OF IOWA FACULTY MEMBER

Following completion of his residency in 1960, Dr. Cooper entered the United States Navy and served in Pensacola, Florida until 1962. After leaving the Navy he began his career as a faculty member at the University of Iowa as an Associate in Orthopaedics. His interest in the pathology and structure of musculoskeletal tissues led him to seek a National Institutes of Health Research Fellowship at Johns Hopkins University in 1964 where his studies on immobilization, atrophy and regeneration of skeletal muscle and the structure of cortical bone led to classic articles that still are cited in many publications[1,5]. Following his research fellowship at Johns Hopkins, Dr. Cooper was appointed Assistant Professor at the University of Iowa Orthopaedic Department, in 1965. Shortly after his return to Iowa City, he established an electron microscopy laboratory in the Orthopaedic Department to continue the work he had started at Johns Hopkins.

During the year 1969, Reg joined Glen Edwards (Calgary, Alberta, Canada), Ashby Granthum (New York City), Robert Jackson (Toronto, Ontario, Canada), Vert Mooney (Downey, California), and Frank Wilson (Chapel Hill, North Carolina), as American British and Canadian Traveling Fellows[3]. This prestigious fellowship, established in 1948 by the American, British and Canadian Orthopaedic Associations, was designed to advance orthopaedic practice and research by promoting the exchange of ideas and life long interactions among orthopaedic surgeons. (Dr. Carroll Larson had been part the first group of American British and Canadian Traveling Fellows in 1948.) Dr. Cooper's group visited 22 orthopaedic programs in England, Scotland and Wales over a six week period, an experience that gave them an understanding of orthopaedic practice and research in the United Kingdom and led to many lasting friendships. Over the six weeks of travel the fellows came to know each other well. Frank Wilson discovered Reg's ". . . ironic sense of humor, along with the fact that anything was fair game for jest—except the University of Iowa[25]." Vert Mooney remembers:

> What stuck out about Reg was his ability to have sharp and insightful opinions about everything we saw and everyone we met. He was extremely frank with the ability to easily criticize the defects in various concepts and techniques, but he also easily praised a job well done. He could shift from the sharp edges of his personal opinions to a smooth and accommodating political role with extreme ease. — Maybe what surprised me most was how he could learn all that having grown up in West Virginia—after all, I grew up in Pittsburgh. — If he hadn't become an orthopaedic surgeon he should have run for Congress, Senate, or, . . . [19].

In 1971, Dr. Cooper was promoted to full professor, and in November 1973, he assumed the chair of the University of Iowa Department of Orthopaedic Surgery. The faculty at that time included Ignacio Ponseti, Michael Bonfiglio, Carroll Larson, Adrian Flatt, John Albright, and Bruce Sprague. At a faculty retreat in 1979, Dr. Cooper and the faculty consisting of John Albright, Richard Brand, Joseph Buckwalter, Ignacio Ponseti,

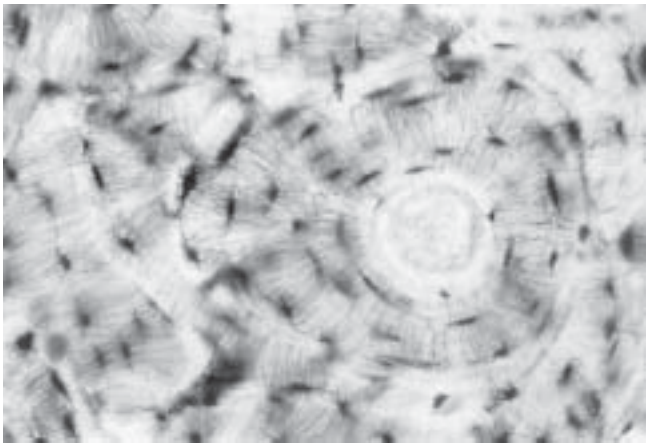


Figure 3. A light micrograph of Dr. Cooper's showing a transverse section through an osteon in cortical bone. Osteocytes with multiple fine cell processes are arranged circumferentially around the central canal of the osteon.

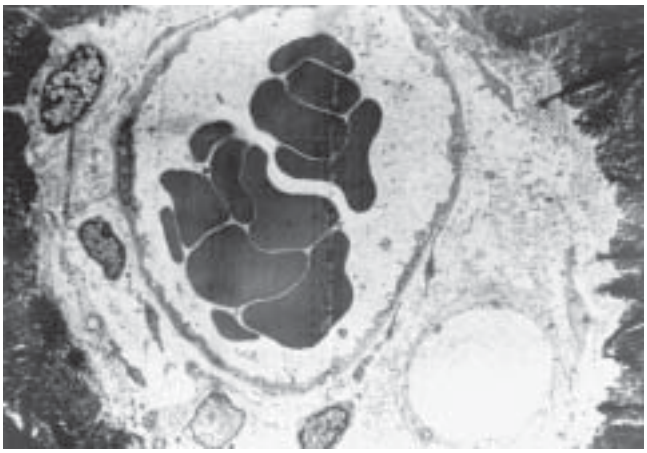


Figure 4. An electron micrograph of Dr. Cooper's showing the central canal of an osteon containing a blood vessel, a lymphatic vessel and undifferentiated cells.

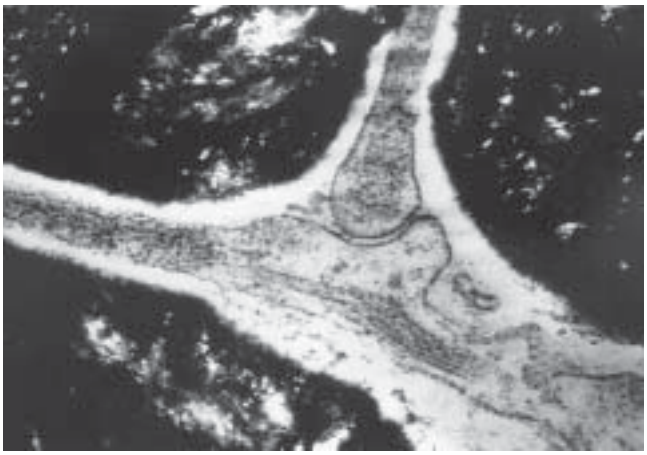


Figure 5. An electron micrograph of Dr. Cooper's showing contact between two osteocyte cell processes in cortical bone. The dark material is the mineralized matrix of cortical bone.

Thomas Lehman, Michael Bonfiglio, Stuart Weinstein and Michael Mickelson determined that the future direction of the department should include development of nationally recognized expertise in the established and emerging orthopaedic clinical subspecialties. This decision guided the organization of the clinical services, resident and medical student educational programs and faculty recruitment. Over the next twenty years, Dr. Cooper directed the development of the department so that in 1999 the department includes 18 orthopaedic clinical faculty that provide nationally recognized clinical expertise in every orthopaedic subspecialty. In addition, the faculty includes emeritus faculty member Ignacio Ponseti, Dr. Thomas Brown who directs the Orthopaedic Biomechanics Lab, Dr. Jerry Maynard, who is also Chairman of Exercise Physiology, Dr. George El-Khoury, who has a joint appointment radiology, and Dr. Paul Strottman, who has a joint appointment in Internal Medicine.

SCIENTIFIC INTERESTS

Dr. Cooper's basic scientific contributions include studies of the ultrastructure of musculoskeletal tissues and the effects of immobilization on ligament insertions and skeletal muscle. During his fellowship at Johns Hopkins he developed techniques for the study of calcified cortical bone ultrastructure. Meticulous examination of cortical bone using these techniques formed the basis of his publication entitled "Morphology of the Osteon" (Figures 3, 4 and 5)[5]. In the course of these

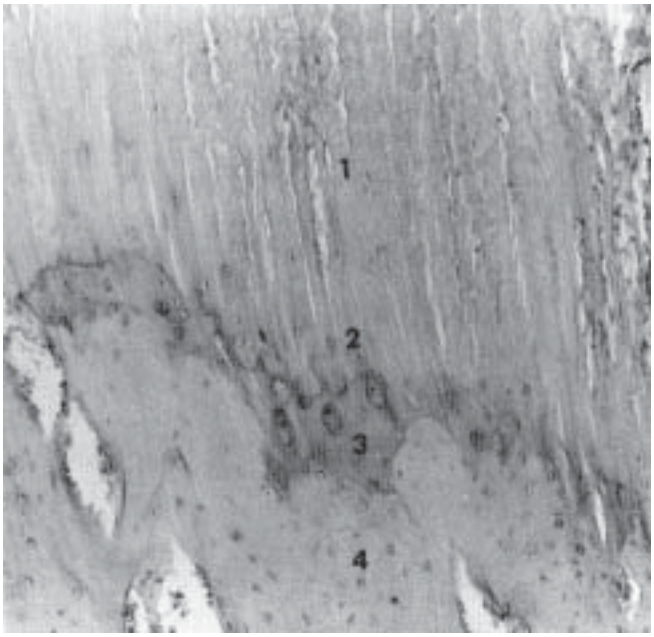


Figure 6. A light micrograph of Dr. Cooper's showing the four zones of tendon and ligament insertion: 1) tendon substance, 2) unmineralized fibrocartilage, 3) mineralized fibrocartilage, and 4) bone.

studies he also identified nerves in cortical bone, an observation which he reported in Science[2]. His work on tendon and ligament insertions described the four zones of these structures: tendon or ligament substance, unmineralized fibrocartilage, mineralized fibrocartilage and bone (Figure 6)[6]. This zonal organization, defined in Dr. Cooper's 1970 article, still forms the basis for the study of tendon and ligament insertions. Along with his colleagues, Drs. Laros and Tipton, Dr. Cooper studied the effects of limb immobilization on ligament insertions. These investigations showed that prolonged cast immobilization led to resorption of indirect ligament insertions and that restoration of the structure and strength of these insertions occurred slowly following an increase in activity[15]. Studies of atrophy and regeneration of skeletal muscle that Dr. Cooper started at Johns Hopkins University led to his winning the Kappa Delta Award in 1970 for outstanding orthopaedic research (Figures 7, 8 and 9)[1]. Examinations of growth plate ultrastructure conducted by Dr. Cooper and his colleagues led to significant advances in understanding of the structure and function of the growth plates as

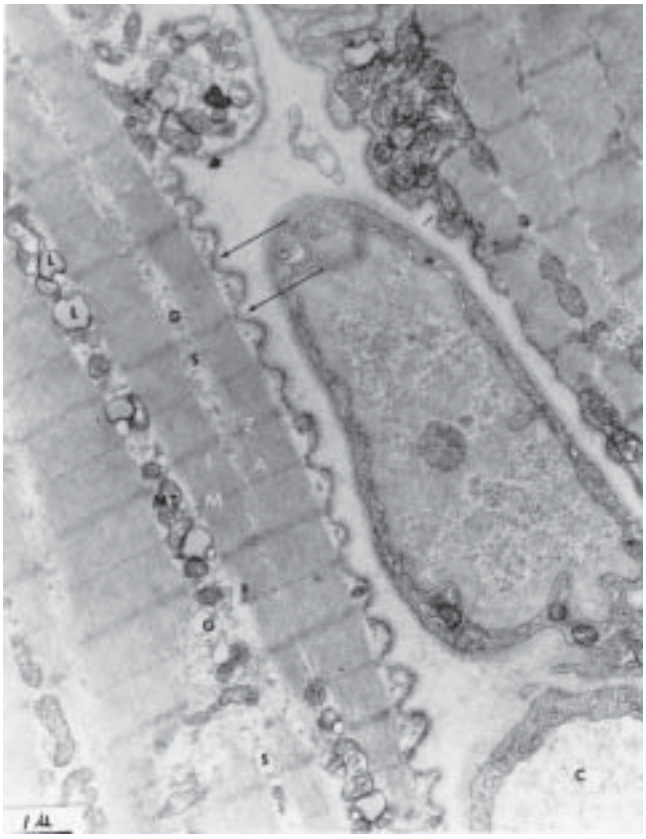


Figure 7. An electron micrograph of Dr. Cooper's showing normal skeletal muscle cells (myofibers) with well defined myofibrils and their Z, I, A and M bands. The mitochondria (MT), sarcoplasmic reticulum (S) and cell membranes (arrows) are intact.

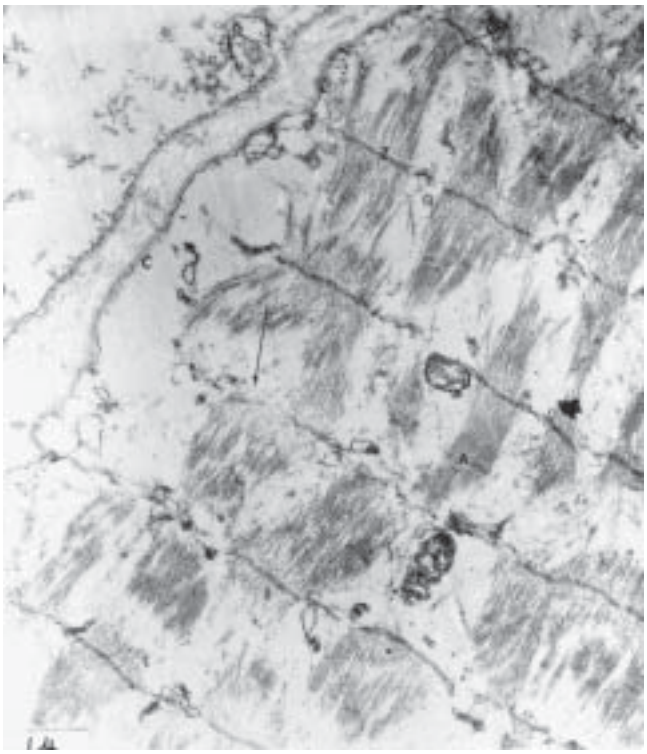


Figure 8. An electron micrograph of Dr. Cooper's showing skeletal muscle cells after immobilization of a limb in a cast for 14 weeks. The myofiber and myofibrils are disintegrating.

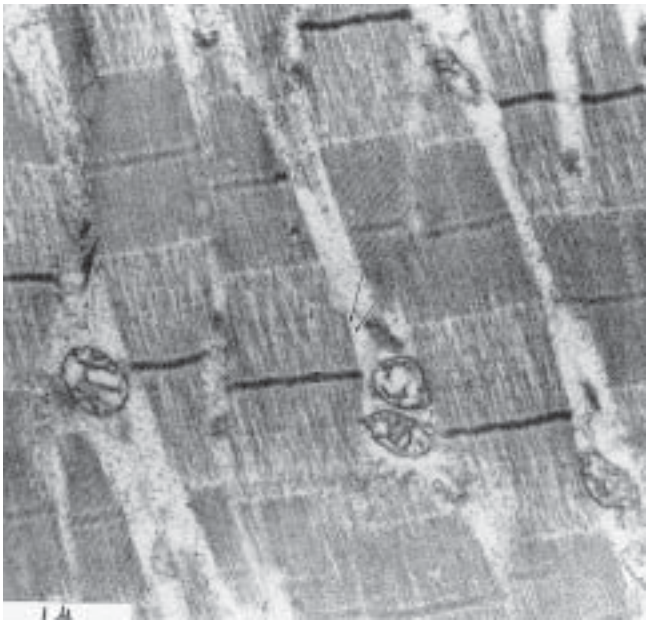


Figure 9. An electron micrograph of Dr. Cooper's showing regeneration of myofibrils and mitochondria three weeks after release of a limb from cast immobilization.

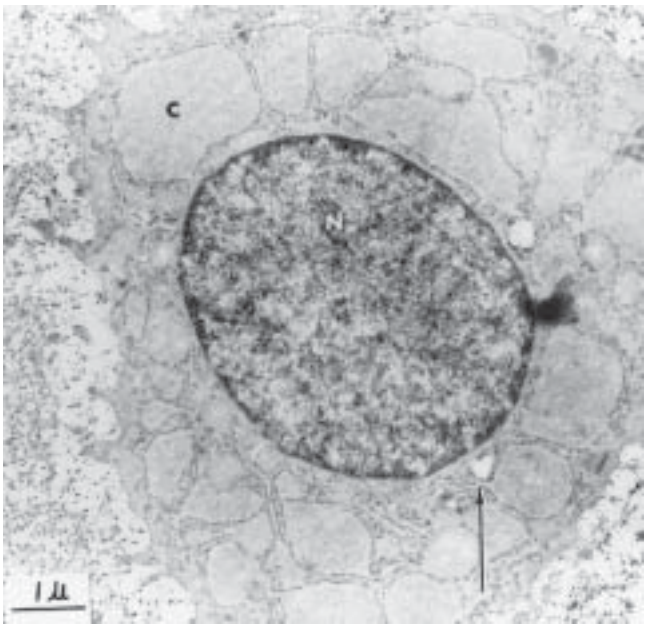


Figure 10. An electron micrograph of Dr. Cooper's showing an iliac crest chondrocyte from a patient with metaphyseal dyostosis. A granular material fills and distends the chondrocyte endoplasmic reticulum. Dr. Cooper and his co-author Dr. Ponseti concluded that the abnormality responsible for metaphyseal dyostosis resulted in the storage of this granular material.

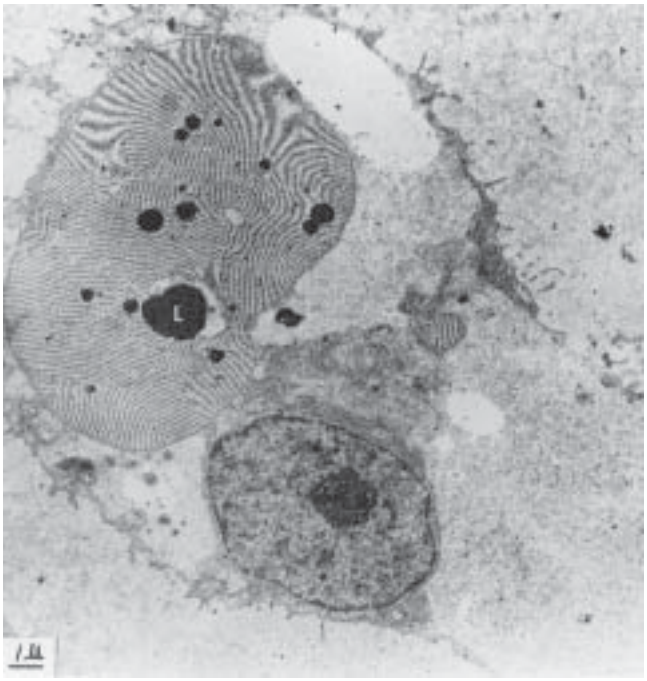


Figure 11. An electron micrograph of Dr. Cooper's showing accumulation of lamellar material in the endoplasmic reticulum of a growth plate chondrocyte from a patient with pseudoachondroplastic dwarfism.

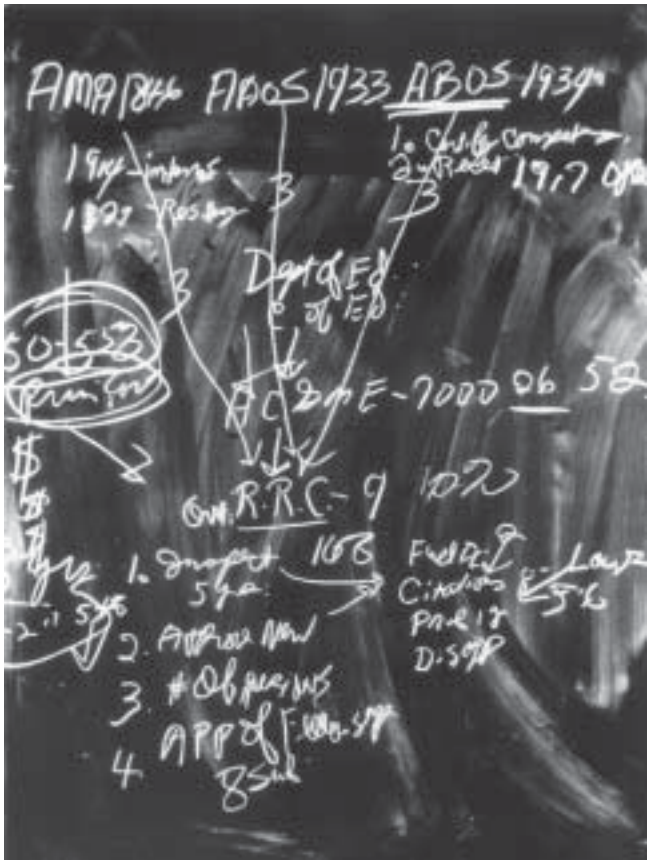
well as identification of growth plate abnormalities in skeletal dysplasias and dwarfism (Figures 10 and 11)[4,7,8,16,17].

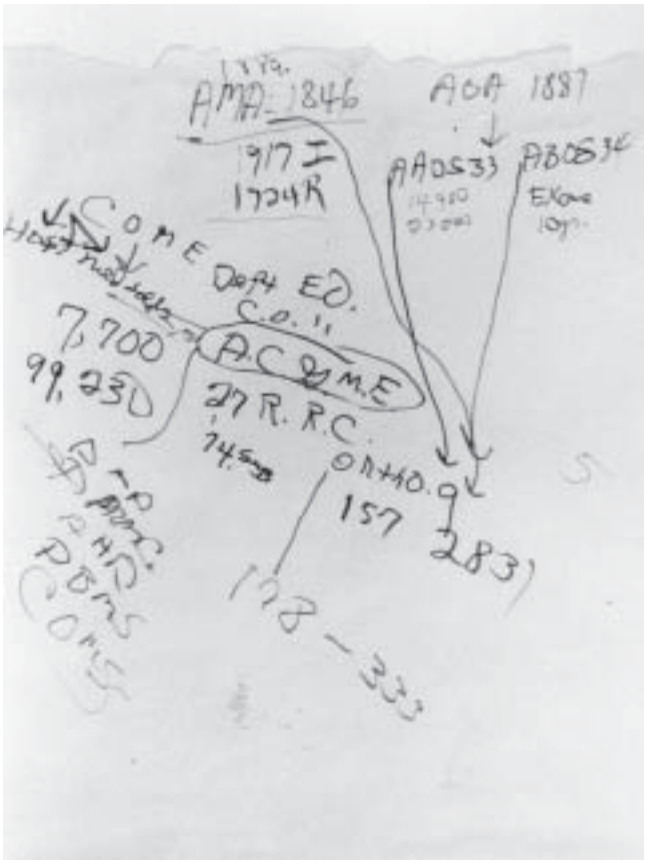
PROFESSIONAL AND SCIENTIFIC ORGANIZATIONS

Throughout his career Reg Cooper has enjoyed participating in and leading national professional and scientific organizations and has served these organizations in an exemplary fashion. More than most physicians, including those who have devoted themselves to service in professional and scientific groups, he has studied and tried to define the relationships among medical organizations and how they affect medical education, practice and research (Figures 12 and 13).

Organizations that have benefited from Reg Cooper's participation and leadership include the Orthopaedic Research Society, the Journal of Bone and Joint Surgery and the Shriners Hospitals for Children. His interest in basic research and contributions to the field led to his being elected President of the Orthopaedic Research Society in 1974[9]. He participated as a member of the Board of Trustees of the Journal of Bone and Joint Surgery from 1993 to 1995 and served as Chair of the Board of Trustees. He has devoted thousands of hours to the Shriners Hospitals for Children in various capacities including serving as Chairman of the Research Advisory Board and Chairman of the Medical Advisory Board. Newt McCullough, Director of Medical Affairs, for the Shriners Hospitals for Children noted that, ". . . Reg has performed these duties in a most devoted, diligent and effective manner and has been regarded with the highest respect and admiration by all of us those who work with him in the affairs of the Shriner's Hospital [18]." Dr. McCullough also has noted that Dr. Cooper has been, ". . . a major force in shaping programs for patient care, research and education for the Shriners Hospitals for Children and ensuring that they remain of high quality and are efficiently administered[18]." In addition to his leadership of the Orthopaedic Research Society, Journal of Bone and Joint Surgery, and the Shriners Hospitals for Children, Dr. Cooper has served on committees of the National Institute of Arthritis, Diabetes and Kidney Diseases and the American Orthopaedic Association, and as an examiner for the American Board of Orthopaedic Surgery.

Perhaps Reg's greatest contributions to an orthopaedic organization came during his more than 10 years of service to the American Academy of Orthopaedic Surgeons. He was chosen as chairman of the Academy's Examination Committee in 1978 and served in this capacity until 1982. During this time he ensured that the Orthopaedic In-Training Examination (an examination





Figures 12 and 13. Diagrams prepared by Dr. Cooper during lectures explaining the relationships among various medical organizations including the American Medical Association (AMA), the American Orthopaedic Association (AOA), the American Board of Orthopaedic Surgery (ABOS), the American Academy of Orthopaedic Surgeons (AAOS), the Orthopaedic Residency Review Committee (RRC) and others. Figure 12, diagram drawn by Dr. Cooper in 1986. Figure 13, a diagram drawn by Dr. Cooper in 1994.

taken annually by all orthopaedic residents in the United States) maintained a high level of quality and helped improve orthopaedic residency education. Members of the Academy recognized Dr. Cooper's exceptional intellect and administrative talent and elected him as Secretary of the American Academy of Orthopaedic Surgeons in 1981. He advanced to become Second-Vice President of the Academy in 1985, First Vice-President in 1986 and then President of the American Academy of Orthopaedic Surgeons in 1987. Following his year as president, Reg continued as a member of the Academy Board of Directors for three years. During his time as an Academy officer and member of the board of directors, the organization grew rapidly and its influence in American Medicine increased dramatically. Reg's depth of knowledge, decisiveness and quick mind made him one of the most confident and effective members of the Board. He identified people with talent and energy and promoted them to positions of responsibility within the Academy[11]. As president, he operated the Academy with exceptional efficiency. Before Board meetings, he routinely reduced agenda books of several hundred pages to less than ten. He disliked wasting time and moved meetings along with great dispatch. Reg could be counted on to interrupt long or repetitious presentations with a few clear concise comments that usually ended the presentations, but he also made sure that no question on the agenda was left undecided. He never hesitated to express his opinion on an issue facing the Academy or his opinion of some else's opinion. Exchanges between Reg Cooper and other Academy Board members including Clement Sledge (Harvard), Roby Thompson (University of Minnesota), Gus Sarmiento (Florida) and Charles Rockwood (University of Texas), clarified complex issues and provided entertainment for other members of the board. Dr. Sledge, a former president of the American Academy of Orthopaedic Surgeons who worked closely with Reg during their years on the Academy board of directors, noted that Reg frequently used his sense of humor to help the board of directors identify the flaws in a proposal. Dr. Sledge also noted that, "What distinguishes

Reg from just another good comedian is his intelligence and ability to cut through the layers of garbage to get to the core of an issue[22]." Those who worked with Reg during his decade of service to the Academy agree that he helped change the organization for better, and Dr. Charles Rockwood, also a former President of the American Academy of Orthopaedic Surgeons, described Reg as one of the "premier" Academy Presidents[20].

CHAIR OF ORTHOPAEDICS AT IOWA

During his years as chair, Dr. Cooper stressed that the primary mission of the department was "teaching exemplary patient care." He never tired of explaining that achieving this mission required providing the highest quality patient care, teaching medical students and residents the knowledge, values and skills that would make them excellent physicians and conducting research that improved understanding of the musculoskeletal system and the treatment of patients with musculoskeletal diseases and injuries.

He placed great emphasis on the residency program. Reg interviewed every prospective resident, and considered integrity, interpersonal skills, commitment to excellence and concern for patients as the most important factors in resident selection. He made the quality of resident education a high priority. When other orthopaedic departments rapidly expanded the number clinical fellowships and the roles of clinical fellows, Reg resisted this trend to insure that residents had the optimal educational opportunities. Iowa was among the first Orthopaedic Departments to accept residents directly after completion of medical school, instead of accepting them after one or two years of general surgery, and invested considerable effort in making the first post graduate year a well organized broad based educational program that now includes clinical experience in intensive care, plastic surgery, anesthesia, pediatric surgery, rheumatology and musculoskeletal radiology. This emphasis on the educational content and value of the first post graduate year in orthopaedics has gradually gained widespread acceptance, and in the last two years the orthopaedic Residency Review Committee and the American Board of Orthopaedic Surgery have changed their policies to require that all orthopaedic departments assume responsibility for the educational content and quality of the first post graduate year for individuals who will become orthopaedists. Understandably, Reg takes great pleasure from the accomplishments of people who completed their orthopaedic residencies at the University of Iowa.

His knowledge, intellect and quick wit make Reg Cooper an effective and memorable teacher. He has influenced the careers of medical students, orthopaedic residents, and faculty[12,13,21,24] and left them with lasting memories (Figure 14). Among his favorite expressions in clinical conferences are, "if it is not broken, don't fix it" and "when you have an acceptable reduction, quit!" He is remembered by generations of orthopaedic residents for his view on the consequences of beveling the tibia at the time of a below knee amputation. More than one resident, after reading standard texts, has made the mistake of suggesting that part of a below knee amputation might include beveling of the tibia, none of these individuals have forgotten that Dr. Cooper does not agree with this practice[21].

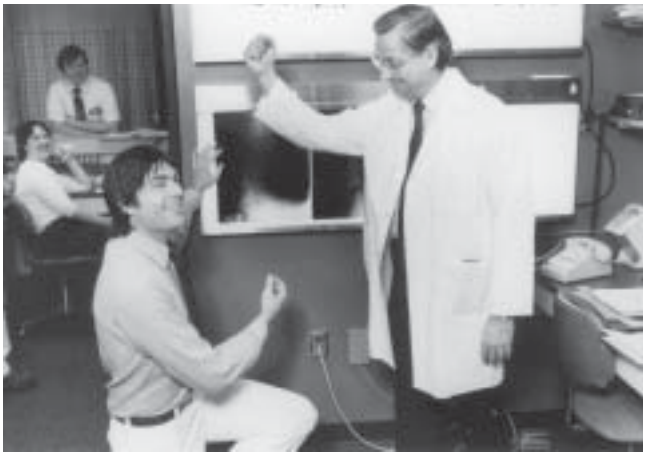


Figure 14. Dr. Cooper explaining to Dr. Richard Henderson the importance of first getting a resident's attention before trying to improve his education. Dr. Henderson, currently a Professor of Orthopaedics and Pediatrics at the University of North Carolina, credits Dr. Cooper with inspiring him to pursue a career as a teacher.

Dr. Cooper's most important and impressive accomplishment as chair of the Department of Orthopaedics has been the recruitment, development and retention of outstanding faculty. His success in these efforts has made him the envy of his peers[10,23]. During his years as chairman, he directed the expansion and development of clinical specialty services including joint replacement, pediatric orthopaedics, trauma, sports medicine, orthopaedic oncology, hand and microvascular surgery, spine surgery and foot and ankle surgery. National surveys have consistently ranked the clinical services provided by the Orthopaedic department among the best in the United States, and the faculty members who provide these services have received national and international recognition for their clinical expertise.

Dr. Cooper supported the academic interests of the faculty and departmental laboratories investigating the biology and biomechanics of the musculoskeletal system. The academic accomplishments of the faculty over the last 26 years document the success of these efforts. Five faculty members, including Dr. Cooper, have been

elected President of the Orthopaedic Research Society, two faculty members have served as president of the American Society of Biomechanics, four faculty members have won a Kappa Delta Awards for outstanding research, two faculty members have won the Bristol Myers/Zimmer Award for orthopaedic research, one faculty member, Dr. Cooper, served as President of the American Academy of Orthopaedic Surgeons, one faculty member has served as President of the oldest orthopaedic professional and scientific association, the American Orthopaedic Association, one faculty member is President-Elect of the American Orthopaedic Association, four faculty members have been selected as American, British and Canadian Traveling Fellows and one faculty member was selected as a member of the first group of Austrian, Swiss and German Traveling Fellows. Faculty members have served as President of the Pediatric Orthopaedic Society, the Cervical Spine Research Society and the Association of Bone and Joint Surgeons. Two faculty members have been Directors of the American Board of Orthopaedic Surgery and one was elected President of the American Board of Orthopaedic Surgery. Multiple faculty members have served as chairs of committees of the American Orthopaedic Association and the American Academy of Orthopaedic Surgeons and a faculty member has served as Chairman of the American Academy of Orthopaedic Surgeons Council on Research and Scientific Affairs. Three journals, the Journal of Biomechanics, the Journal of Orthopaedic Research, and Spine have selected University of Iowa Faculty members as their editors, two faculty members serve on the editorial board of the Journal of Bone and Joint Surgery, two faculty members serve on the Board of Consulting Editors for Research of the Journal of Bone and Joint Surgery and one faculty member is a deputy editor of Clinical Orthopaedics and Related Research. Even this incomplete list of faculty accomplishments in the last two and a half decades is unmatched by any other Orthopaedic Department, and most of the individuals responsible for these achievements started their faculty careers at the University of Iowa and have remained at Iowa.

The list of Reg Cooper's accomplishments, even when combined with the story of his journey with Jackie from Dry Fork, West Virginia to Iowa City, Iowa, do not capture his remarkable talents and effects on people and organizations. He never attempts to conceal his pride in and loyalty to the University of Iowa and the Orthopaedics Department, nor does he tolerate any effort to disparage the University or the Department. He has a powerful intellect combined with common sense, a quick wit, and a keen penetrating sense of humor that he enjoys using. His ability to effectively combine criticism with humor makes his points more memorable[22,25]. He approaches the most complex and contentious issues with authority. Once he has determined the correct position on such an issue, no one and no argument can easily dislodge him from that position, and anyone who intends to challenge his view should come well prepared. He identifies and articulates issues that most people do not consider before they accept a point of view or a plan of action. More than a few confident well respected orthopaedic surgeons, after arguing for the merits of a given surgical procedure, have found that Reg can raise questions that leave them wondering why they ever thought the operation was a good idea. In conferences, Reg rarely allows strongly expressed expert opinions of hip, knee, hand, foot, sports, spine, trauma, pediatric and tumor surgeons to go unchallenged, and usually emerges from such contests with at least a partial victory. As a result of such challenges, the participants and spectators, whether they agree with Reg or not, learn the value of critically evaluating even the most widely accepted opinions and practices. Talented people often put in their required time with an organization, make thoughtful comments and receive general approval from their peers, but leave no mark. Not Reg—his methods were not always diplomatic and the course was not always smooth, but he changed every organization he served. Few people he has worked with cannot recite at least one story of Reg reversing the firmly held views of a majority of the members of a group.

Scientific journals rank their influence by impact factors, numerical measures based on the number of times their articles are cited. No comparable measure of the influence of individuals on the specialty of orthopaedics exists: but, if a such measure did exist, Reginald Cooper's impact factor would rank high on the list for orthopaedic surgeons whose careers span the last four decades of the 20th Century. Although he has contributed important scientific observations and used his talents for the benefit of multiple professional and scientific organizations, his most important legacy is a strong and vital orthopaedic department that he has prepared well for the future.

REFERENCES

1. **Cooper, R.R.:** Alterations during immobilization and regeneration of skeletal muscle in cats. *J. Bone and Joint Surg.,* 54A:919-953. 1972.
2. **Cooper, R.R.:** Nerves in cortical bone. *Science,* 160:327-328. 1968.
3. **Cooper, R. R.; Edwards, G. E.; Grantham, S. A.; Jackson, R.W.; Mooney, V.;** and **Wilson, F. C.:** Visit of North American Traveling Fellows to Great Britain - 1969. *J. Bone and Joint Surg.,* 51A:1434-1444. 1969.
4. **Cooper, R. R.; Maynard, M.;** and **Ponseti, I. V.:** Pseudoachondroplastic dwarfism. *J. Bone and Joint Surg.,* 55A:485-495. 1973.
5. **Cooper, R. R.; Milgram, J.;** and **Robinson, R:** Morphology of the osteon. *J. Bone and Joint Surg.,* 48A:1239-1271. 1966.
6. **Cooper, R. R.;** and **Misol, S.:** Tendon and ligament insertion: a light and electron microscopic study. *J. Bone and Joint Surg.,* 52A:1-20. 1970.
7. **Cooper, R. R.; Pedrini-Mille, A.;** and **Ponseti, I. V.:** Metaphyseal dysotosis. *Lab. Invest.,* 28:119-125. 1973.
8. **Cooper, R. R.;** and **Ponseti, I.V.:** Metaphyseal dysostosis. *J. Bone and Joint Surg.,* 55A:485-495. 1973.
9. **Cooper, R. R.;** and **Shands, A. R.:** The Orthopaedic Research Society - its first twenty years. *Clin. Orthop.,* 106:285-289. 1975.
10. **Evarts, C. M.:** *Personal Communication*: 1999.
11. **Heckman, J. D.:** *Personal Communication*: 1999.
12. **Henderson, R.:** *Personal Communication*: 1999.
13. **Katz, R. P.:** *Personal Communication*: 1999.
14. **Laros, G.;** and **Cooper, R.R.:** Electron microscopic visualization of proteinpolysaccharides. *Clin. Orthop.,* 84:179-192. 1972.
15. **Laros, G.; Tipton, C.;** and **Cooper, R. R.:** Influence of physical activity on ligament insertions in the knees of dogs. *J. Bone and Joint Surg.,* 53A:275-286. 1971.
16. **Maynard, J.; Cooper, R. R.;** and **Ponseti IV:** Morquio's disease (mucopolysaccharidosis type IV) an ultrastructural investigation of epiphyseal plates. *Lab. Invest.,* 28:194-205. 1973.
17. **Maynard, J.A.; Cooper, R. R.;** and **Ponseti, I.V.:** A unique rough surfaced endoplasmic reticulum inclusion in pseudoachondroplasia. *Lab. Invest.,* 26:40-44. 1972.
18. **McCollough, N.C.:** *Personal Communication*: 1999.
19. **Mooney, V.:** *Personal Communication*: 1999.
20. **Rockwood, C.A.:** *Personal Communication*: 1999.
21. **Saterbak, A.:** I bevel. *Personal Communication*: 1998.
22. **Sledge, C.B.:** *Personal Communication*: 1999.
23. **Thompson, R.:** *Personal Communication*: 1999.
24. **Webber, K.A.:** *Personal Communication*: 1999.
25. **Wilson, F.:** *Personal Communication*: 1999.

HYPOTHESIS BASED RESEARCH: THE MATURATION OF ORTHOPAEDIC SCIENCE

Richard A. Brand, M.D.

"It is what we think we know that keeps us from learning."

Claude Bernard[1]

Surgery, as all of medicine, arose from empirical arts. Surgeons, pragmatic as a group, have always tended to believe and report what they can or potentially could directly sense (see, feel). Other branches of medicine, on the other hand, are more accustomed to dealing with the unseen: inadequate insulin throughout the body, micro-organisms buried somewhere within an organ. Perhaps in part owing to this fact, medical sciences accepted earlier hypothetical thinking: a search for biological explanation if you will, explanation of those things they could not directly observe. Whether or not this is the correct explanation, one needn't extensively survey medical and surgical literature to realize surgeons have typically described, rather than explained the results of their endeavors, and used either simple (and often simplistic) explanations for their observations. Recent events, however, suggest a "maturation" of approach in the "orthopaedic sciences." My arguments for maturation largely arise from the history and philosophy of science, and my thoughts emanate from those of others, although I accept sole responsibility for the synthesis.

Maturation requires recognition and acceptance of limitations. Engineering approaches have historically served to "explain" the locomotor apparatus owing to the obvious analogy with inanimate structures. Yet, if engineering has provided one of the greatest strengths of orthopaedic sciences, just as surely such analogies frequently mislead. Engineering, as surgery, arose from empirical endeavors. Mechanistic explanation wandered into engineering only in the 1700 and 1800's. (I hasten to add substantial introduction of mechanistic explanation ventured into surgical thinking nearly a century later). Numerical methods, the very foundation of engineering, worked extremely well for most structural purposes. I will therefore explore this limitation in some detail.

Department of Orthopaedic Surgery
The University of Iowa
Iowa City, IA 52242 USA

"Entia non sunt multiplicanda praeter necessitatem."
"The number of entities used to explain phenomena should not be increased unnecessarily."

Occam's Razor

William of Ockham (ca. 1280-1349)

William of Ockham (Ockegem) taught us to seek the simplest explanation consistent with observations. As a means to predict behavior, Occam's razor often applies in the physical sciences. One need only consider the example of Newtonian physics which predicts astonishingly well for phenomenon except at the speed of light and at the level of atomic particles. But in biology, which Elsasser notes is "unfathomably complex," (Elsasser, 1991) simple explanations rarely suffice owing to the almost inevitably elaborate chains of (causal) physical or chemical reactions underlying all biological responses. Simplistic explanations abound in the surgical sciences.

For example, "Wolff's Law" suggesting principal tensile and compressive stresses govern bone adaptation remarkably fails in predicting as readily as Newton's Laws succeed (Wolff, 1892). This is not to say seeking simple explanation is not an efficient means of advancing biological thought, only that *appropriately* simple explanations or hypotheses are most efficient. While Wolff's Law focused attention on the role of the mechanical environment on connective tissue adaptation, I would argue Wolff's simplistic law has done more harm than good, because for more than a century it diverted attention from the non-continuum nature of tissues and from temporal aspects of the mechanical environment likely more critical than merely load magnitude[2]. Perhaps more importantly, Wolff's writing seemingly confused prediction with explanation[3]. Owing to the pervasiveness of explicit or implicit mechanical (i.e., mathematical) explanation in orthopaedic sciences, I will explore this point in some detail, but imagine we had instead emphasized a "Roux's Law" based upon Wilhelm Roux's earlier and less restrictive teleological ("Zweckmässig") concept of "functional adaptation." (Roux, 1881)

In suggesting the most appropriately simple explanations, we must fundamentally understand science. "Science," as noted by the contemporary philosopher Robert Richards, "is not a disinterested examination of the structures of reality. Objective truths can be cap-

tured only in the thicket of cultural belief, refined experience, and honed intuition." (Richards, 1992) We never know how Nature works, we only develop explanations or models of how Nature works. In the sense all explanations are models, numerical models are like all others. However, in the sense numerical models do not address causal chains of events, they are distinct from current (molecular) biological models.

In particular, as scientific explanation of Nature, mathematics fails. Naomi Oreskes and her colleagues, compellingly argued in Science: "Verification and validation of numerical models of natural systems is impossible . . . The primary value of models is heuristic." (Oreskes, et al., 1994) That is, we can never prove the veracity or truthfulness and we can never prove the logical internal consistency in an open model system (i.e., one where all parameters are not identified and known in adequate detail). At best, we can confirm a model, meaning observations predicted by the model are consistent with those actually observed. This view is a far cry from that held by most of us accustomed to numerical models. If I do not entirely agree with her assessment of model utility, her assertion of impossibility of verification and validation is unquestionably correct.

Let me quote rather extensively from Whitehead: "Mathematics is thought moving in the sphere of complete abstraction from any particular instance of what it is talking about. So far is this view of mathematics from being obvious, that we can easily assure ourselves that it is not, even now, generally understood. " (Whitehead, 1925) Whitehead wrote this statement many decades ago, yet it is as true to day, as then. He continues: "For example, it is habitually thought that the certainty of mathematics is a reason for the certainty of our geometrical knowledge of the space of the physical universe. This is a delusion which has vitiated much philosophy in the past, and some philosophy in the present. This question of geometry is a test case of some urgency. There are certain alternative sets of purely abstract conditions possible for the relationship of groups of unspecified entities, which I will call geometrical conditions . . . . (Furthermore) . . . the certainty of mathematics depends upon its complete abstract generality. But we can have no a priori certainty that we are right in believing that the observed entities in the concrete universe form a particular instance of what falls under our general reasoning." Whitehead further commented, ". . . the equations of physics provide little or no basis for the layman's belief in causal connection as conceived by earlier philosophical discussions of the matter." The layman's intuitive view of causality, he realized, was somehow abandoned by many mathematicians, philosophers, and scientists. He continues, using a somewhat confusing double negative, "The criticisms of this rationalistic view of causal connection gradually undermined these convictions so that today it is not too much to say that they have been abandoned by a considerable number of philosophers and are in no way operative in the practice of scientists." Scientists, and I would add engineers and surgeons (as exemplified by Wolff, and more recently Pauwels and others), had somehow come to accept a seemingly magical connection between mathematics and causality[4], and, Whitehead believed, made a fundamental error. Whitehead understood mathematics was a creation of humans, not something inherent in Nature. We apply our abstract creation to Nature; Nature does not apply mathematics to Her domain. Nature is ignorant of mathematics.

Let me also cite at some length, Julius Weinberg, from his essay "Causation:" "The development of natural science since the seventeenth century has tended to emphasize functional determination, for example, as expressed in the generalizations of physics and chemistry, rather than regularities of succession[5]..." (Weinberg, 1973) He correctly notes, "The conviction that some kind of uniformity governs the play of events in the natural world has been one of the most influential beliefs of man since the beginning of human reflection. Attempts of various kinds, as we have seen, were made to base this conviction on the deliverances of reason. In particular, the belief that the causal maxims could be established by the purely logical (i.e., mathematics), dominated almost the entire history of the subject." Weinberg concludes, "The criticisms of this rationalistic view of causal connection gradually undermined these convictions so that today it is not too much to say that they have been abandoned by a considerable number of philosophers and are in no way operative in the practice of scientists." Weinberg's assertion of abandonment of mathematical causality, in contrast to Whitehead's belief they were persistent, is unfortunately overly optimistic. Many scientists, particularly in mathematically based fields still cling to ancient ideas. Ironically, Newton well understood mathematics did not imply causality: "Hypotheses non fingo, " he remarked, in the *Principia Mathematica*: "I propose no explanation."

The point made by Oreskes, Whitehead, Weinberg, and many others is mathematics plays no role in causality. Mathematics has documented its powerful ability to describe and even predict regularities in Nature; it cannot, however, establish causality. This distinction must be made, since mathematical models can never explain Nature's mechanisms. In the interest of causality, we must distinguish description or prediction from explanation.

It would be easy to appear overly critical of both engineers and orthopaedic surgeons in their failure to recognize the lack of link between mathematics and causality. As I earlier mentioned, both arose from empiricism, where prediction is critical, but explanation is not. Traditionally, engineers and orthopaedic surgeons have rarely been interested in how some physical phenomenon works, but they have been critically interested in *whether* it works. Only recently has the question of "*how*?" become common with biomechanicians and surgeons for at least two reasons: First, as a practical matter, if some intervention works well, *how* it works is less critical, and second, only recently have the problems of surgery been amenable to intervention at mechanistic levels. Today, an increasing number of medical interventions depend upon intimate knowledge of causality: the capacity to interfere with the cause of some ordinarily complex chain of events. Mathematical models will not help us here, except in a descriptive (i.e., statistical) or predictive sense. Associations suffice for prediction, but not causal explanation. A mathematical model of bone adaptation which accurately predicts bone behavior in select situations should not be thought to explain behavior. That does not mean mathematical models are of no utility, quite the contrary: we cross oceans on planes developed through numerical theory; predictive numerical models are likely to afford the potential to ascertain optimal surgical reconstructions in the foreseeable future. Rather, we must recognize they are inherently limited for causal explanation. This limitation has few practical effects when we have no means of beneficially intervening in causal connections; it has major effects when, as is now the case, we do.

Beyond recognition of such inherent limitations in science, fields of knowledge, just as humans and societies, go through developmental stages on the journey toward maturity. The eminent and late philosopher of science, Thomas Kuhn, remarked, ". . . once current views of nature were, as a whole, neither less scientific nor more the product of human idiosyncrasy than those current today." (Kuhn, 1970) Consider alchemy which developed in the dark and middle ages to a high state, then faded in the Renaissance being replaced by chemistry and physics and even pharmacology. Empirical arts progress through periods of observations, then predictions, and finally explanations using ever more efficient and sophisticated paradigms. Surgical sciences are now experiencing this sort of scientific maturity.

"When I use a word," Humpty Dumpty said in a rather scornful tone, "it means just what I choose it to mean - neither more nor less."

Through the Looking Glass
Lewis Carroll

If I may paraphrase Humpty Dumpty, "When I use the term scientific maturity, I mean just what I choose it to mean - neither more nor less." (Carroll, 1998) What do I mean by scientific maturity? Certainly moving from observation to explanation. Yet, I imply ever more efficient conduct and effective reporting of science through hypothetical thinking.

And what do I mean by "hypothetical thinking" or "hypothesis"? An hypothesis is simply an explanation of a group of relevant yet selected biological or clinical observations, or a prediction or deduction which necessarily and logically arises from some explanation. I might equally employ the terms "theory," "view," "model," or any number of related words and without hierarchical implications, but, taking license from Humpty Dumpty, I choose "hypothesis" or "explanation." As will become apparent, any testable hypothesis has an unambiguous answer. I would argue one of the principal signs of scientific maturation includes reporting of hypothetical thinking.

I recently ascertained whether past abstracts of the Orthopaedic Research Society posed and meaningfully addressed hypotheses: that is, focused statements explaining observations so formulated as to have unambiguous answers. I considered the titles and first paragraph or two, as well as the final paragraph of the first 25 abstracts in each year of the ORS Transactions. Realizing legitimate hypothesis- and design-driven studies (i.e., those developing technological approaches) might be differently reported, I then characterized the work, liberally interpreting design-driven not only for devices, but also experimental or technical design. For these, I included clear objectives or goals.

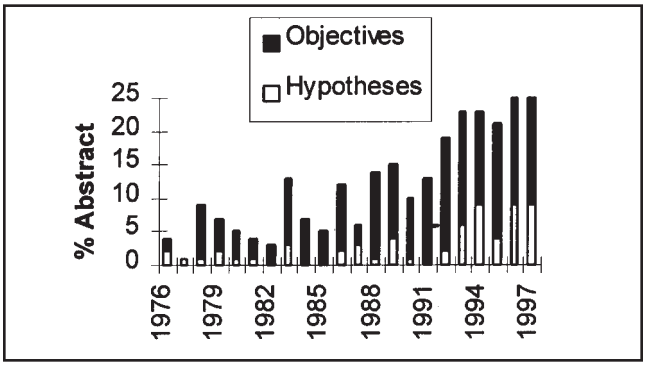


Figure 1. Percent of ORS abstracts having clear objectives (solid bars) or hypotheses (open bars) from 1976 until 1997. Note an increasing percent, particularly after 1993. Note, however, only 25% of all abstracts in 1997 had clear objectives or hypotheses.

In the early years I encountered few statements I deemed effective hypotheses or objectives (Figure 1). When the abstracts did explicitly mention purposes, they were most often descriptive: "We characterized, or investigated, or determined, or quantified...x, y, or *z*": observations, if you will, not explanations. In many cases, abstracts provided little or no rationale for their observations. I do not imply investigators did not think of some hypothesis - only they reported none.

In more recent years, I encountered increasing numbers of reasonable hypotheses or objectives. In 1993, ORS abstract instructions to authors requested explicit objectives, questions, or hypotheses. Thus, in part, their presence in the abstracts relates to explicit instructions, although I would argue this, too, implies maturation.

Now, I make no claim for scientific validity of my little study. Rather, I argue we are more effectively reporting our investigations. Effectively conveying findings is as critical as efficiently conducting studies, since the most brilliant theory or experiment remains incomplete until effectively communicated. These data also suggest we are moving from an era of observation to an era of explanation. Might I add, we have a way to go in pursuing explanations: seventy-five percent of the 1997 ORS abstracts remained more or less isolated observations.

"The least questioned assumptions are often the most questionable."

Paul Broca

Meaningful collaboration is surely another critical sign of maturity, for it suggests diverse sophistication of observation. More importantly, true collaboration implies a willingness to consider the often disparate ideas of others, an implied willingness to question assumptions: assumptions of the sort the eminent 19th Century French neuropsychologist, Paul Broca, considered most questionable. A molecular biologist may challenge an assumption long accepted by an engineer, or vice versa. Knowledge seldom advances without abandoning cherished assumptions. Collaboration blurs man-made inter-disciplinary boundaries: boundaries of which Nature is unaware. How many scientific articles in our literature now include the authorship of engineers, molecular biologists, geneticists, even immunologists, psychologists, and (of all people) surgeons? How many included such diverse authorship even twenty years ago?

The Weber brothers, in 1836, published one of the very first collaborative scientific endeavors, which was not coincidentally, the first scientific work on locomotion. (Weber and Weber, 1836) Neither Wilhelm, a mathematician, nor Eduard, an anatomist, had any background in locomotion. Neither had a particular interest in locomotion. Scientific interest played no role in their motivation. Rather, they commented in their foreword, "And though we are convinced the choice of our objective requires no justification, we do not wish to hide our true motivation . . . It was the joy we found in a unified endeavor; an endeavor to which each of us brought unusual strength and abilities and which became all the more valued and treasured because of the very lack of resources. Man is never more capable or persistent in scientific study than when there is mutual participation and excitement, not only at the completion of the work, but during its entire course." Imagine our endeavors if we simply sought and found those with whom we enjoyed working.

Such meaningful collaboration implies trust and respect. We collaborate precisely because others know what we do not know, and others can do what we cannot. We cannot truly know another's limits, and while trust and respect derive partly from experience, without trust and respect true collaboration is impossible. Surely the ability to trust implies maturity.

In presuming maturation of a field, what changes can we anticipate? While I suggest more efficient conduct of science as well as more effective reporting, I will address primarily the former and note but six means to conduct more efficient explorations.

First, we must formulate the most effective hypotheses. The pre-eminent philosopher of science, Sir Karl Popper recognized, "We do not know: we can only guess . . ." (Popper, 1968) Accordingly, he introduced the concept of "high" and "low informative content hypotheses": High informative content hypotheses were those for which the answers were most uncertain: guesses if you will. They must be unique. From these we are most likely to gain critical information. Low informative content hypotheses, on the other hand, were those for which the answers were almost certain. From formulations such as, "We hypothesize we can develop a model to do whatever" we gain little new insight or information. We can always fit some model to select data, but that process, in and of itself, does not guarantee a meaningful general model, so the hypothesis as such is trivial. Poorly formulated hypotheses or questions fail to efficiently and effectively answer questions. Well-formulated questions, on the other hand require time and effort and, I hasten to add, creativity. Focus on explanation rather than technical development, and emphasis on high informative content hypotheses confers efficiency. I am not suggesting we must not advance technology, only that focus on explanation is most efficient.

Second, Popper additionally and compellingly argued we can never prove any explanation, we can only disprove them. Henrí Poincaré, the French mathematician and philosopher recognized this point when he said, "If a phenomenon admits of a complete mechanical explanation it will admit of an infinity of others which will account equally well for all the peculiarities disclosed by the experiment." As Poincaré, Popper, Oreskes, and many others (including Phaedrus, the protagonist of *Zen and the Art of Motorcycle Maintenance* (Persig, 1974)) recognized, all sets of observations may be equally well explained by an infinite number of choices limited only by our creativity. Thus, even with what we consider experimental or theoretical support and appropriate confirmation, we can never insure our own explanations are the correct ones. In fact, Popper went so far as to suggest we should design experiments to *disprove* our hypotheses, since we could never entirely "prove" them. This does not mean our explanations cannot be of practical effect: quite obviously our explanations suffice to clone species and create gene therapy. However, attempting to disprove explanations raises different approaches than attempting to prove explanations.

Third, formulating explanations based upon the largest practical number of observations lends efficiency. One needn't review many manuscripts to realize even technically well-formulated hypotheses are typically based upon few observations. Since added observations may effectively falsify explanations, considering more at the outset is both efficient and effective. While more sophisticated observations obviously advance a field, more effective hypothetical thinking never depends entirely on technical sophistication.

Fourth, efficient hypothetical thinking demands succinct, unambiguous questions or hypotheses that minimize the possibility experiments will fail to clearly address critical issues. Imagine we formulate only questions that can be answered "yes" or "no" by our theoretical or experimental design; imagine we always formulate hypotheses which can be plainly supported or refuted. Seemingly small differences in wording of explicit questions or hypotheses can make large differences in experimental design or choice of variables. Furthermore, no hypothesis can be tested which is not posed in terms of independent and valid dependent variables. Other hypotheses may have heuristic value, but cannot be tested. We should practice proposing questions and hypotheses in measurable terms. Good questions inevitably imply scientific design, and vice versa.

Fifth, once we have posed a high informative content question or hypothesis, we should conduct thought experiments. Imagine every conceivable outcome. Plot out potential results. Imagine the implications of each. This procedure will often result in reformulating the question owing to its heuristic insights.

Sixth, in advance of initiating our experiments, as we formulate and reformulate our hypotheses, we should imagine the most simple approaches which will address the real questions. We might even alter approach to take advantage of some more simple, yet powerful technique.

Imagine we formulated only high informative content hypotheses. Imagine in these formulations we identified and considered ten relevant observations, not merely one or two or three. How many explanations could we quickly eliminate from among the immense pool? Imagine our questions had unambiguous answers. Imagine we used only the minimum essential approach. How many unnecessary experiments could we avoid? How many resources would we save? And how much better the answers.

Decades ago, when technical sophistication was not what it is today, Sir Bertrand Russell commented: "One of the troubles of our age is that habits of thought cannot change as quickly as techniques with the result that as skill increases, wisdom fails." Technology seductively and perniciously focuses attention on observation, not explanation. In a culture that worships technology, we should pay heed to Russell's observation. Wisdom dictates we spend greater time formulating hypotheses as technical sophistication increases. Imagine we spent even a fifth of the time formulating hypotheses or questions as we did solving technical problems. What scientist spends one full day in the workweek merely reflecting? Yet, is not the mind our most powerful tool?

These six suggestions enhance efficiency. Yet effective science requires more than efficiency, more than wisdom: it demands creativity. The creative scientist must prepare for resistance to novel ideas, and unfortunately at times even personal attacks. Thomas Lounsbury astutely commented, "We must view with profound respect the infinite capacity of the human mind to resist the introduction of useful knowledge." We humans have infinite capacity to resist accepting new and useful knowledge, particularly when the ideas arise from a "competitor." As Persig's Phaedrus realized, ". . . no one is willing to give up the truth as he sees it . . ." (Persig, 1974) Most of our scientific views are not arbitrary, but based upon considerable past, if not current reflection. Thus, it is not surprising we do not easily discard what we have learned with such effort to believe. But to repeat Bernard's admonition: "It is what we think we know that keeps us from learning." Any framework we maintain rests on limited or even filtered information, not any complete or even coherent framework, and this fact alone should make us be more willing to abandon tenaciously-held views. The requirement

for creativity is both bane and joy of the scientist. Bane because we stubbornly cling to old, comfortable, and uncreative habits of thought; bane because creativity is the most difficult task we confront as scientists; bane because we encounter such resistance to novelty. Joy because creativity affords unexcelled, if often only internal rewards for the scientist. Joy because in the long run, little in science matches creativity for efficiency and effectiveness.

Scientific maturity, however, implies more than even efficiently, wisely, and creatively conducted explorations. Maturity implies certain attitudes and conduct in science, ethics if you will. As Kuhn emphasized, the history of science teaches us sooner or later our explanations will be replaced as new concepts, connections, observations, or paradigms appear. Without negating their heuristic value, we must consider all explanations tentative.

The ephemeral nature of our explanations and our inherent inability to prove them should imbue a spirit of tolerance and humility: a humility driven by historical, philosophical, and ethical imperatives. Humility, I hasten to add, is unfortunately far from universal among scientists.

Bronowski further argued the value of science to society resided principally in its search for truth. (Bronowski, 1965) "Truth," he recognized, "is the drive at the center of science; it must have the habit of truth, not as dogma but as a process . . ."—truth as a *process* to be transmitted to and incorporated within society. Truthfulness accompanies maturation of a field: truthfulness not only in the design, conduct, and reporting of our work, but in interactions with colleagues—an implicit acknowledgment our approaches, observations, explanations may someday be deemed inadequate or even seriously flawed. The concept of truthfulness applies to oneself: the scientist who deeply admits his or her own ideas will be replaced will less likely resist the new ideas of another, and less likely deceive him—or herself.

Openness accompanies truthfulness. "Scientific knowledge, like language, is intrinsically the common property of a group or else nothing at all," Kuhn suggested. (Kuhn, 1970) Common property, as described by Kuhn, is nowhere more obvious than in the Human Genome Project where newly-discovered gene sequences belong to the community, not the individual. One needn't reflect long to recognize the critical value of common property and the candor it implies.

What have trust, respect, humility, truthfulness, and openness to do with scientific maturity? Each of these qualities intrinsically follows maturation. And, do they not contribute to the wisdom suggested by Russell? Our challenge is to conduct ever more mature investigations: restricted resources and boundless technology demand ever more efficient conduct and effective communication in a spirit of humility, tolerance, truthfulness.

But even creatively, wisely, efficiently conducted investigations do not suffice. One must responsibly and effectively convey those explanations to the broader community. The implications must be clear for the widest audience, for we may never predict which explanations, which observations, will affect someone in a diverse field. (I equate parochial reporting—not to be confused with detailed, focused investigations—with irresponsibility.) Contemporary searching capabilities insure our ideas potentially reach a large audience, but they will never reach the appropriate persons unless we write in broad and inclusive terms.

I make no pretense I fully understand how to teach what I intellectually and even to some degree emotionally understand. Einstein commented, "The real difficulty, the difficulty that has baffled the sages of all times, is rather this: how do we make our teaching so potent in the emotional life of men that its influence should withstand the pressures of the elemental psychic forces in the individual?" Our psyches contain immense forces opposing trust, opposing respect, opposing complete truthfulness, opposing openness—forces resisting the finest conduct of science. And those forces act towards ourselves as well as towards others. Yet, we must recognize and resist those forces to practice the most wise, efficient, effective, and mature science.

Once we as teachers employ efficient and ethical science and effective reporting, we must actively teach the processes of science to students as best we can. Example of the mentor provides a critical key for any student. However, we cannot presume students innately grasp those processes, or that mentors somehow magically transfer them merely by example. We cannot presume maturity occurs in a vacuum. Just as fields mature owing to newly-identified thought which changes processes, we must teach these processes. We must encourage and support the creativity of our students, as well as our own. We must teach students fair, respectful, thorough, constructive peer review. As experienced by the Weber brothers, we must communicate to the young the "Joy of Science": pleasure in the process, not merely in techniques or outcomes. The ethics and responsibilities we identify and teach to students must withstand the elemental psychic forces within all of us, for only with such an approach is our field maturing.

REFERENCES

1. **Brownowski, J.:** *Science and Human Values.* Harper and Row, New York, 1965.
2. **Carroll, L.:** *The Annotated Alice : Alice's Adventures in Wonderland and Through the Looking Glass.* Wings Press, New York, 1998.
3. **Elsasser, W.E.** *Reflections on a Theory of Organisms.* Osiris, Quebec, 1991.
4. **Kuhn, T.S.:** *The Structure of Scientific Revolution,* 2nd Ed. University of Chicago Press, Chicago, 1970.
5. **Oreskes, N.; Shrader-Frechette, K.;** and **Belitz, K.:** Verification, validation, and confirmation of numerical models in the earth sciences. *Science* 263:641-646, 1994.
6. **Persig, R.M.:** *Zen and the Art of Motorcycle Maintenance.* William Morrow, New York, 1974.
7. **Popper, K.R.:** *The Logic of Scientific Discovery.* Harper and Row, New York, 1968.
8. **Richards, R.J.:** *The Meaning of Evolution : The Morphological Construction and Ideological Reconstruction of Darwin's Theory (Science and Its Conceptual Foundations)*. University of Chicago Press, Chicago, 1992.
9. **Roux, W.:** *Der Züchtende Kampf der Theile oder die "Theilauslese" im Organismus." Zugleich eine Theorie der "Functionelle Anpassung."* 1881. Verlag von Wilhelm Engelmann, Leipzig.
10. **Weber, W.,** and **Weber, E.:** *Mechanik der menschilichen Gewerkzeuge.* Dieterischen Buchhandlung, Göttingen, 1836.
11. **Weinberg, J.:** *Causation*, in Weiner, P.P., Ed.: *Dictionary of the History of Ideas.* Charles Scribner's Sons, New York, 1973.
12. **Whitehead, A.N.:** *Science and the Modern World.* The Macmillan Company, New York, 1925.
13. **Wolff, J.:** *Das Gesetz der Transformation der Knochen.* 1892. Verlag von August Hirschel, Berlin.

ENDNOTES

1 Throughout this essay, I will quote a variety of individuals. I unfortunately collected many quotes over time without availability to the source. For most I have been unable to trace the source, and therefore cannot verify their authenticity. However, whether the individual cited is in fact responsible, the points remain valid. I provide the source when known.

2 Wolff's illustrations contained many figures "disproving" his hypothesis: more trabeculae crossed at acute than at right angles! It is easy in retrospect to be too critical of the thought Wolff stimulated, for he nearly single-handedly focused attention on the effects of the mechanical environment on tissue adaptation, despite the fact that some before and many after him did the same with much less effect. However, as I will later note, one need take into account as many observations as possible when initially formulating a hypothesis: some observations may disprove the notion.

3 In expressing the relationship between mathematics and biology, Wolff used the terms, "unter" and "nach," meaning literally, "under" and "after." In context, it seems clear he believed mathematics "governed" bone adaptation. However, toward the end of his monograph, he quotes Heizen, ". . . zunächst an das mechanische Wirken denken, oder wenigstens für alle wirkenden Urshachen eine Analogie suchen in dem Mechanismus . . ." "For the time being when one thinks of mechanistic causes, or at least for all causal mechanisms, one will seek a mechanical analogy." Thus, while he acknowledges mathematics may reflect only analogy, he writes as if they were effective causes: ". . . die Natur, so zu sagen, ein mathematisches Problem gelöst . . . hat . . ." "We may say, Nature has solved a mathematical problem."

4 Scientists typically imply connections between mathematics and causality, rather than stating them. Thus, one must understand belief or assumption within context. The responsible scientist, however, leaves no major known assumptions open to question.

5 That is, chain of events.

THE ROLE OF ULTRASONOGRAPHY IN THROMBOEMBOLIC DISEASE MANAGEMENT IN THE ORTHOPAEDIC PATIENT

William J. Ciccone II, MD
J. Spence Reid, MD
Vincent D. Pellegrini, Jr., MD

ABSTRACT

Deep venous thrombosis (DVT) is a well-recognized contributor to increased morbidity and mortality following trauma and elective musculoskeletal procedures. Ultrasound has become a popular noninvasive modality for use in the detection of *symptomatic* DVT. However, its use as a screening tool in asymptomatic or postoperative patients has been questioned. The reliability of ultrasound rests mainly in the ability of the technicians performing the exam. Ultrasound has been shown to be less reliable in identifying asymptomatic calf thrombi; in institutions where ultrasound DVT surveillance is not performed routinely, the technique suffers from inadequate sensitivity to be utilized for routine screening purposes. Recognition of patients at high risk for DVT, along with an understanding of the limitations of ultrasound, will allow for appropriate clinical application of this modality.

Deep venous thrombosis (DVT) is a well-recognized complication following major orthopaedic procedures, both emergent and elective. Due to the inaccuracy of the bedside clinical diagnosis of DVT[4,13] various invasive and noninvasive surveillance modalities have been developed. Ultrasound has recently gained popularity for use in the diagnosis of *symptomatic* DVT due to its low morbidity and noninvasive nature. However, various studies have questioned its use as a screening tool to identify the presence and location of DVT in *asymptomatic* high-risk patients[6,11,15,23,45]. An understanding of the benefits as well as the limitations of ultrasound will allow for a more appropriate application in the clinical arena.

While ascending venography remains the gold standard for the diagnosis of DVT, various noninvasive surveillance modalities have been introduced. These include [^{125} I] labeled fibrinogen, impedance plethysmography, magnetic resonance venography, and ultrasonography. Due to the fear of transmission of infectious agents by transfusion of blood products [^{125} I] labeled fibrinogen has been removed from the market and, therefore, is no longer an option for use[44].

Impedance plethysmography is based upon the electrical impedance measured between two electrodes placed on the calf. In patients with DVT proximal to the electrodes there is decreased electrical impedance as the leg becomes swollen with venous blood, thereby increasing its electrical conductivity. When using a tourniquet technique, an expected increase in electrical impedance with the release of the cuff occurs due to the decompression of the venous system. Failure of the impedance to change an appreciable amount after tourniquet release implies the presence of DVT[22,46]. While plethysmography appears to be best suited to diagnose occlusive proximal thrombosis in symptomatic individuals, a lack of sensitivity exists in its ability to identify sizable thrombi if they remain nonocclusive[34].

Magnetic resonance venography (MRV), although still investigational, appears to be an effective modality in the detection of DVT. Recent studies have shown that when compared to ascending venography, MRV displays a sensitivity between 97 percent to 100 percent for proximal vein thrombosis[10,39]. Further, MRV can identify thrombi located in the deep pelvic veins,[31] an area difficult to visualize even with venography. Magnetic resonance venography is noninvasive, requires no potentially hazardous contrast media, and images the proximal deep venous system of both extremities simultaneously. With further study and greater affordability MRV may become a promising choice for surveillance of proximal thrombotic disease in the lower extremity and pelvis.

From:
The Department of Orthopaedics and Rehabilitation
The Pennsylvania State University
Milton S. Hershey Medical Center
Hershey, Pennsylvania

Correspondence to:
Vincent D. Pellegrini, Jr., M.D.
The Pennsylvania State University, College of Medicine
Milton S. Hershey Medical Center
Department of Orthopaedics and Rehabilitation
P.O. Box 850
Hershey, PA 17033
Tel: (717) 531-4803
Fax: (717) 531-7583

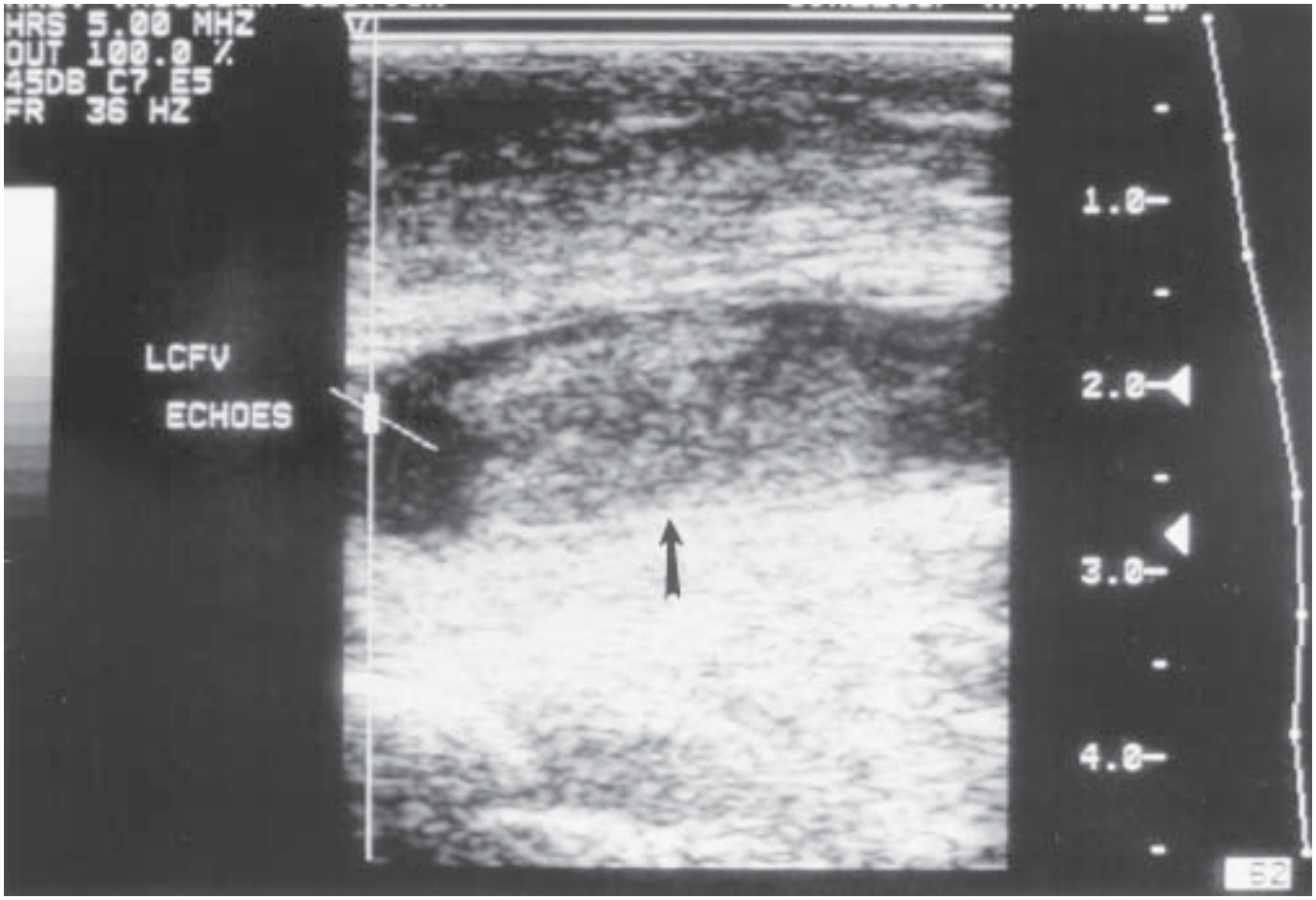


Figure 1. Intraluminal thrombus visualized with ultrasound (with permission).

BASICS OF ULTRASONOGRAPHY

Ultrasound utilizes the reflections of sound waves to evaluate soft tissue structures[40]. Real time imaging has improved the use of ultrasound with dynamic images that are viewed instantaneously. Two modes of ultrasound are used in the evaluation of DVT: B-mode and duplex ultrasound. B-mode (brightness modulation) imaging utilizes real time imaging combined with a linear array of transmission beams to produce a two dimensional image. This enables the visualization of venous anatomy without the use of contrast media.

More recently, duplex scanning has been introduced as another modality for DVT diagnosis. Duplex ultrasound combines B-mode imaging with pulsed-wave Doppler technology[42]. Doppler ultrasonography is based on the physical principles of Christian Doppler (1803 to 1853),[8] who described changes in sound wave frequency when reflected from a moving object. When sound waves are reflected by a stationary object, they return at the same frequency at which they were transmitted. However, objects moving toward the transducer reflect waves of higher frequency, and objects moving away reflect waves at a lower frequency. This phenomenon is called the Doppler shift. Pulsed-wave Doppler can be utilized to evaluate the direction and pulsatile nature of blood flow within vessels. With the addition of color flow, Doppler ultrasound allows simplified evaluation of flow directionality with blue arbitrarily indicating flow toward the transducer and red indicating flow away from it. The advantages of color flow imaging are the improved identification of vessels by visualizing blood flow and the ability to establish the direction of flow to differentiate arteries from veins. However, its utility to enhance the identification of DVT in the clinical setting is still debated[24,27].

Venous augmentation is a term used to describe transducer and patient manipulations utilized to improve the sensitivity of surveillance for DVT. Criteria considered to show the presence of DVT include the direct visualization of thrombus, the absence of spontaneous flow by Doppler, absence of phasicity of flow with respiration, and the incompressibility of deep veins with probe pressure (Figure 1). In a study performed by Lensing et al.,[28] 220 consecutive outpatients with *clini-*

cally suspected DVT underwent B-mode ultrasound evaluation using the single criterion of vein compressibility for diagnosis. All results were verified with concomitant venography. They concluded that ultrasound evaluation of vein compressibility is a highly accurate, simple and objective method for detecting symptomatic *proximal* DVT. These findings were confirmed by other studies[3,14]. A more thorough overview of the sensitivities of commonly used augmentation techniques was described by Killewich et al[25]. In their prospective double blind study, 47 patients, both symptomatic and asymptomatic, underwent both duplex and ascending venographic exams to assess ultrasound augmentation maneuvers that improve DVT detection. When analyzed individually, visualization of intramural thrombus and the absence of spontaneous flow both had low sensitivities (50 percent and 76 percent) but high specificity, respectively (92 percent and 100 percent). The compressibility of veins, in contrast with previously discussed studies, showed low values for both sensitivity (79 percent) and specificity (67 percent). Absence of flow phasicity with respiration was the single best diagnostic finding with a sensitivity and specificity of 92 percent. The most sensitive combination was that of visualization of thrombus and the evaluation of flow phasicity (sensitivity 95 percent). They concluded that isolated diagnostic criteria should not be used to diagnose DVT, but rather a combination of augmentation maneuvers be employed to optimize the reliability of ultrasonography. They further suggested that in equivocal cases of proximal DVT a contrast venogram should be performed to confirm the diagnosis.

PREVALENCE OF DVT

Following Trauma

It is widely believed that DVT and pulmonary embolism are major contributors to the morbidity and mortality following major trauma. The literature examining the prevalence and risk factors associated with DVT in this population is sparse. However, in a landmark study by Geerts et al., these questions were more thoroughly examined[18]. In a prospective trial of 349 patients involved in major trauma (injury severity score of at least nine), ascending venography was performed to determine the prevalence of DVT and to better define the characteristics of trauma that predisposes to thrombus formation. All patients in this study underwent bilateral ascending contrast venography 14 to 21 days following the traumatic event. These patients received no antithrombotic prophylaxis. Deep venous thrombi were discovered in the lower extremities of 201 of the 349 patients studied (58 percent). Proximal thrombosis was found in 18 percent, while calf DVT was diagnosed in 40 percent of patients. Further, in patients with lower extremity orthopaedic injuries, up to 80 percent developed DVT. Specifically, the incidence of DVT was 77 percent following tibia fractures, 80 percent after femur fractures, 61 percent after pelvic fractures, and 62 percent after spinal column injury. Of the 201 patients with DVT, *only three* had clinical signs or symptoms suggestive of the condition, suggesting the need for adequate screening techniques. It was concluded that safe antithrombotic prophylaxis is needed, as DVT is a common complication in patients with major multisystem trauma.

Following Joint Replacement

Deep venous thrombosis is the most common complication threatening the life of a patient following total joint arthroplasty (Figure 2). The prevalence of DVT in patients undergoing joint replacement without prophylaxis is between 45 percent to 70 percent for total hips and 50 percent to 84 percent for total knees[16,41,21]. With modern prophylactic techniques the DVT prevalence is reduced to 10 percent to 20 percent after hip and 22 percent to 50 percent following knee replacement. Pulmonary embolism (PE) from DVT is responsible for historical mortality rates ranging from 1.7 percent to 3.4 percent in unprotected patients[21,32,37,41].

It has been shown that the risk of PE is higher from proximal DVT than thrombi confined to the calf[32]. The clinical importance of calf thrombi is increasingly recognized; 17 percent to 23 percent of calf clots have been demonstrated to propagate to proximal deep veins and, subsequently, assume the same risk for embolism. Furthermore, calf thrombi historically account for 40 percent to 60 percent of all thrombi following hip replacement and as high as 95 percent following knee replacement[21,30,36]. A more recent study has shown that with contemporary DVT prophylaxis up to 90 percent of thrombi after hip replacement were confined to the calf[11]. Sensitive screening techniques are mandated as nearly all patients are asymptomatic for venous thromboembolic disease during the initial postoperative period encompassing the acute hospitalization.

ULTRASONOGRAPHY IN DVT DIAGNOSIS

Proximal DVT

The use of ultrasound as a surveillance modality to detect proximal thrombosis in asymptomatic patients has been previously examined[17,20,48]. Woolson et al.[48] commented on the ability of ultrasound to detect proximal DVT following total hip replacement. In their study 150 ultrasound exams were compared with venographic

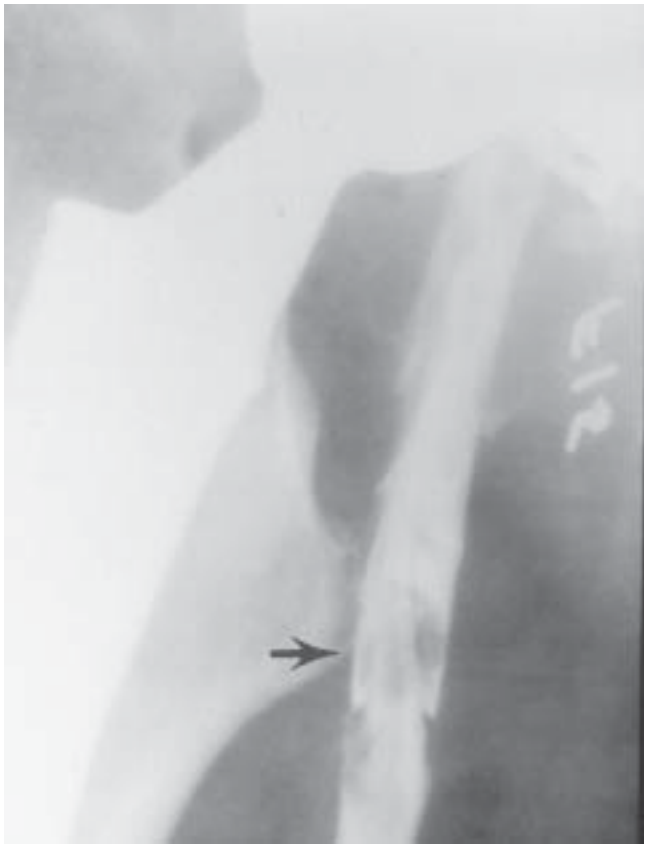


Figure 2. Venographic identification of a large femoral vein thrombus following total hip arthroplasty.

results. Nineteen proximal thrombi were diagnosed with venography and 17 of these 19 were also identified by ultrasound (sensitivity 89 percent). Grady-Benson et al[20] studied ultrasound surveillance following total knee arthroplasty and detected seven of seven proximal thrombi (sensitivity 100 percent). Various reports have noted improvements in the ability of ultrasound to diagnose DVT as technicians become accustomed to study protocols[17,49]. A recent study by Garino et al. compared ultrasonography with ascending venography following total joint surgery in an effort to determine factors that influence the accuracy of ultrasonography[17]. The study was performed on asymptomatic patients in two phases, and the results were compared to determine the effect of experience on the technician's ability to detect DVT with ultrasound. In the first phase, 121 patients who underwent total joint replacement were included and compared with 84 patients in a second phase. In phase one seven thrombi were diagnosed by venography in the proximal veins. Four of these thrombi were large measuring two to 15 centimeters; the remaining three were small, nonocclusive, and less than 1 centimeter in length. Ultrasound was unable to detect any of these thrombi (sensitivity 0 percent). By contrast, in phase two, after becoming accustomed to study protocols, seven proximal thrombi were diagnosed by ultrasound and five were confirmed by venography (two false positives; sensitivity 100 percent; positive predictive value 71 percent). When combined, these three widely cited papers only account for a total of 36 *proximal* thrombi with an overall ultrasound sensitivity of 81 percent (29 of 36). Yet, despite these limited data, ultrasound has prematurely become accepted as a viable surveillance option following total joint replacement. Initial use of concomitant venography should be practiced to provide an effective means of individual institutional evaluation of ultrasound screening accuracy in this challenging patient population.

The ability of ultrasound to detect proximal venous thrombi is dependent upon the clinical milieu in which it is applied. The sensitivity of ultrasound to detect proximal vein thrombosis in *symptomatic* patients has been shown to be 94 percent to 97 percent[2,3,25,28,47]. In a meta-analysis performed by Wells et al., the accuracy of ultrasound to diagnose DVT in *asymptomatic* patients was assessed[45]. Eleven studies with venogram controls were identified from the literature which met an established criteria for a low level of bias. In these studies the sensitivity of ultrasound to detect proximal thrombi ranged from 38 percent to 100 percent[15,44]. More recently, two studies have evaluated the usefulness of the addition of color Doppler ultrasound in the identification of asymptomatic proximal thrombi[24,27]. Both studies were performed as surveillance exams following total hip or knee replacement. Duplex ultrasound displayed sensitivities of 56 percent and 60 percent respectively when attempting to identify proximal thrombi. With the addition of color Doppler imaging one institution improved its sensitivity to 93 percent[24], while the second study showed no improvement[27]. It has been suggested that these lower sensitivities are due to the presence of smaller and less occlusive thrombi than those present in symptomatic patients[23,29]. In fact, one study found that ultrasound missed 60 percent of nonocclusive thrombi, less than five centimeters in length, in the thigh[23]. Therefore, the reliability of ultrasound as a surveillance modality should be questioned even for proximal DVT when used in asymptomatic high-risk patients.

Distal DVT

The utility of ultrasound in the diagnosis of calf DVT has been shown to be poor[1,38] (Figure 3). A meta-analysis performed by Wells et al.[44] identified only two studies which evaluated the accuracy of ultrasonography with a defined low level of bias. B-mode ultrasonography was used in one study, and color flow Doppler was used in the other; both results were confirmed with

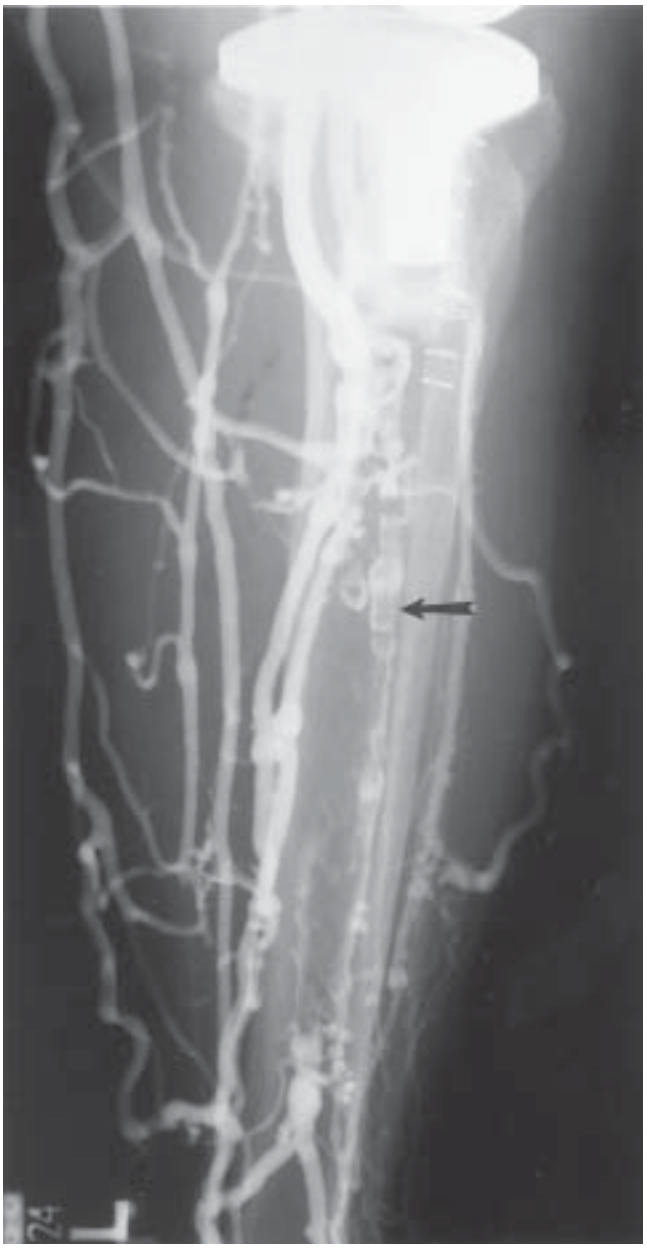


Figure 3. Venographic visualization of calf vein thrombosis.

venographic controls. Overall, 14 of 29 distal DVT were identified (sensitivity 48 percent). These results were confirmed by institutions that routinely utilize ultrasound for postoperative DVT surveillance. Grady-Benson et al.[20] were able to identify seven of eight distal thrombi, with two false positive and one false negative result (sensitivity 88 percent; specificity 98 percent; accuracy 98 percent; positive predictive value 78 percent; negative predictive value 50 percent). Further, in a study performed at our own institution data were combined from the University of Rochester and The Pennsylvania State University to determine ultrasound sensitivity[11]. One hundred thirty-two postoperative total joint patients were managed at the University of Rochester. Sixteen distal thrombi were diagnosed by venography of which none were identified with ultrasound (sensitivity zero percent). At Penn State 36 distal DVT were identified by venography in 210 postoperative patients. Ultrasound identified only five distal DVT with one false positive (sensitivity 14 percent; specificity 99.4 percent; accuracy 85 percent; positive predictive value 83 percent; negative predictive value 85 percent). With the combined data of these two studies, only 12 of 60 distal thrombi were identified by ultrasound (sensitivity 20 percent). As these institutions routinely utilize ultrasound for DVT diagnosis we would expect the quality of the ultrasound exam to be better than the average. However, the sensitivities still do not meet the criteria for acceptance of a study employed for routine surveillance. There is a wide variation of color flow and duplex ultrasound sensitivities even among the more experienced institutions.

COMPLICATIONS OF PROPHYLAXIS

Sensitive surveillance modalities are desirable to limit extended anticoagulant prophylaxis to only those at risk for pulmonary embolism because bleeding risks associated with the use of anticoagulants have been well-documented. Coventry et al.[12] initially reported bleeding complications in 4.1 percent of patients following total hip replacement surgery when treated with full intensity warfarin. Following trauma, complications have been reported in up to 36 percent of patients[7]. More recently, based on a review of 25 studies, Landefeld et al.[26] noted a 3 percent annual frequency of major bleeding complications and further found the risk to be elevated ten-fold during the first month of anticoagulant therapy. In trauma the risk of DVT has been shown to increase with age[9,18]. Further, anticoagulant related bleeding events have been noted to increase in the elderly due to the increased prevalence of comorbidities and polypharmacy, as well as vascular endothelial fragility[5]. These data underscore the need for the accurate surveillance of thrombosis as an integral component of a strategy to limit exposure of extended prophylaxis to only those who are at the greatest embolic risk.

CONCLUSIONS

Management Strategy

In the postoperative setting, ultrasound is an unreliable modality when used for surveillance of asymptomatic DVT. It is therefore difficult to justify full intensity anticoagulant therapy for presumed DVT with its inher-

ent risks based on the results of this test alone. The complications of intravenous heparin therapy following total joint arthroplasty have been studied by Patterson et al. who found an overall 30 percent incidence of bleeding complications which increased to 45 percent in patients within the first six days postoperatively[35]. With the current trend of decreasing postoperative hospitalization following total joint procedures, most contemporary DVT surveillance occurs within the first seven days after surgery. The results of ultrasound screening in this setting are unreliable and should be confirmed prior to the commencement of anticoagulant treatment.

The treatment of calf vein thrombosis remains controversial. Lotke noted a 72 percent incidence of DVT following total knee arthroplasty, with most thrombi located in the calf[30]. The 1.1 percent incidence of clinically important embolic events in this group of patients led to the recommendation that prophylaxis be deferred. However, recent data following joint replacement confirms propagation rates from the calf to the thigh in 17 percent to 23 percent of patients[21,33,37]. In a study performed by Pellegrini et al., it was estimated that one in five fatal pulmonary emboli may arise from isolated calf vein thrombosis[36]. Further, contemporary prophylaxis techniques, while limiting the number of proximal thrombi, have a limited effect on calf vein thrombosis. In trauma patients, Geerts et al noted a 40 percent prevalence of calf vein thrombosis in unprophylaxed patients[18]. However, when low-molecular-weight heparin was added as prophylaxis the prevalence only dropped to 32 percent[19]. The high prevalence of calf thrombi combined with the associated risks of propagation puts a large number of patients at risk for delayed pulmonary embolism and accentuates the need of a safe and effective strategy for surveillance and/or extended prophylaxis.

The high prevalence of deep venous thrombosis following orthopaedic procedures and musculoskeletal trauma necessitates an appropriate management strategy. Ultrasound, when used as a surveillance modality, displays a poor sensitivity in detecting *asymptomatic* calf and thigh thrombosis. Alternatively, an approach of extended prophylaxis for all, without surveillance, is an acceptable method to prevent pulmonary embolism. While this approach avoids the issue of surveillance reliability, it exposes the majority of patients who are not at risk for venous thromboembolic disease to the unnecessary risks of anticoagulant therapy. We prefer a surveillance modality be utilized to identify patients at risk for embolic events, as well as identify these patients not at risk, so prophylaxis may be limited to those at greatest risk for a thromboembolic event. At our institution we continue to rely on venography to screen for DVT in postoperative total joint patients; outpatient post-discharge anticoagulation is used only for patients with identified DVT on contrast venography.

The multiply injured patient presents unique challenges to the detection of DVT. Lower extremity edema makes intravenous access to the foot difficult. The presence of casts, external fixation devices, and implanted fixation hardware further hinders radiographic venous evaluation. Patients must also be hemodynamically stable when transported to the radiology department for venography. Thus, in the trauma patient, the inherent difficulties in obtaining venographic studies preclude its routine use. We have adopted a protocol in which all at risk trauma patients receive DVT prophylaxis preferably with low molecular weight heparin as soon as clinically safe. Each patient undergoes weekly duplex ultrasound with color flow to screen the proximal venous system. In those physiologically stable patients with equivocal ultrasound results, we have a low threshold to obtain a venogram to confirm the diagnosis. Since these high-risk patients are already receiving prophylaxis, these studies are used to detect *failure* of prophylaxis and the need for more aggressive treatment.

The limitations of ultrasound must be realized when this method is selected for DVT screening in the high-risk postoperative or post-injury orthopaedic patient. The ultrasound exam is highly dependent upon technician experience; its reliability should be determined in each institution by comparison with contrast venography before it is adopted as the sole surveillance method for thromboembolic disease.

REFERENCES

1. **Agnelli, G.; Volpato, R.; Radicchia, S.; Veschi, F.; DiFilippo, P.; Lupatelli, L.;** and **Nenci, G.G.:** Detection of asymptomatic deep vein thrombosis by real-time B-mode ultrasonography in hip surgery patients. *Thrombosis and Haemostasis,* 68:257-260, 1992.
2. **Aitken, A.G.F.;** and **Godden, D.J.:** Real-time ultrasound diagnosis of deep vein thrombosis: a comparison with venography. *Clin. Radiol.,* 38: 309-313, 1987.
3. **Appleman, P.T.; DeJong, T.E.;** and **Lampman, L.E.:** Deep venous thrombosis of the leg: ultrasound findings. *Radiology,* 163:743-746, 1987.
4. **Barnes, R.W.; Wu, K.K.;** and **Hoak, J.C.:** Fallibility of the clinical diagnosis of venous thrombosis. *JAMA,* 234:605-607, 1975.
5. **Beyth, R.J.;** and **Landefeld, C.S.:** Anticoagulants in older patients: A safety perspective. *Drugs & Aging,* 6:45-54, 1995.
6. **Borris, L.C.; Christiansen, H.M.; Lassen, M.R.; Olson, A.D.;** and **Schott, P.:** Comparison of real-time B-mode ultrasonography and bilateral ascend-

ing phlebography for detection of postoperative deep vein thrombosis following elective total hip surgery. *Lancet,* 343:1142-1144, 1994.

7. **Braithwaite, C.E.M.; Mure, A.J.; O'Malley, K.F.; Spence, R.K.;** and **Ross, S.E.:** Complications of anticoagulation for pulmonary embolism in low risk trauma patients. *Chest,* 104: 718-720, 1993.
8. **Burn, P.N.:** The physical properties of Doppler and spectral analysis. *J. Clin. Ultrasound,* 15:567-590, 1987.
9. **Burns, G.A.; Cohn, S.M.; Frumento, R.J.; Degutis, L.C.;** and **Hammer, L.:** Prospective ultrasound evaluation of venous thrombosis in high risk trauma patients. *J. Trauma,* 35:405-408, 1993.
10. **Carpenter, J.P.; Holland, G.A.; Baum, R.A.; Owen,R.S.; Carpenter, J.T.;** and **Cope, C.:** Magnetic resonance venography for the detection of deep venous thrombosis: comparison with contrast venography and duplex Doppler ultrasonography. *J. Vasc. Surg.,* 18:734-741, 1993.
11. **Ciccone II, W.J.; Fox, P.S.; Neumyer, M.; Rubens, D.; Parrish, W.M.;** and **Pellegrini, V.D.:** Ultrasound surveillance for asymptomatic deep venous thrombosis after total joint replacement. *J. Bone and Joint Surg.,* 80(A):1167-1174, 1998.
12. **Coventry, M.B.; Nolan, D.R.;** and **Beckenbaugh, R.D.:** Delayed prophylactic anticoagulation: A study of results and complications in 2,012 total hip patients. *J. Bone and Joint Surg.,* 550(A):1487-1492, 1973.
13. **Cranley, J.J.; Ganos, A.J.;** and **Sull, W.J.:** The diagnosis of deep venous thrombosis: Fallibility of clinical symptoms and signs. *Arch. Surg.,* 111:34-36, 1995.
14. **Cronan, J.J.; Dorfman, G.S.; Scola, F.H.; Schepps, B.;** and **Alexander, J.:** Deep venous thrombosis: Ultrasound assessment using vein compression. *Radiology,* 162:191-194, 1987.
15. **Davidson, B.L.; Elliott, G.C.;** and **Lensing, A.W.A.:** Low accuracy of color Doppler ultrasound in the detection of proximal leg vein thrombosis in asymptomatic patients. *Ann. Int. Med.,* 117:735-738, 1992.
16. **Francis, C.W.; Pellegrini, V.D.; Stulberg, B.N.; Miller, M.L.; Totterman, S.;** and **Marder, V.J.:** Prevention of venous thrombosis after total knee arthroplasty: Comparison of antithrombin III with low dose heparin and dextran. *J. Bone and Joint Surg.,* 72(A):976-982, 1990.
17. **Garino, J.P.; Lotke, P.A.; Kitziger, K.J.;** and **Steinberg, M.E.:** Deep venous thrombosis after total joint arthroplasty the role of compression ultrasonography and the importance of the experience if the technician. *J. Bone and Joint Surg.,* 78(A):1359-1365, 1996.
18. **Geerts, W.H.; Code, K.I.; Jay, R.M.; Chen, E.;** and **Szalai, J.P.:** A prospective study of venous thromboembolism after major trauma. *N. Engl. J. Med.,* 331:1601-1606, 1994.
19. **Geerts, W.H.; Jay, R.M.; Code, K.I.;** and **Chen, E.:** A comparison of low-dose heparin with low molecular weight heparin as prophylaxis against venous thromboembolism after major trauma. *N. Engl. J. Med.,* 335:701-707, 1996.
20. **Grady-Benson, J.; Oishi, C.S.; Hanson, P.B.; Colwell, C.W.; Otis, S.M.;** and **Walker, R.H.:** Postoperative surveillance for deep venous thrombosis with duplex ultrasonography after total knee arthroplasty. *J. Bone and Joint Surg.,* 76(A): 1649-1657, 1994.
21. **Hodge, W.A.:** Prevention of deep vein thrombosis after total knee arthroplasty: Coumadin versus pneumatic calf compression. *Clin. Orthop.,* 271:101-105, 1991.
22. **Hull, R.; van Aken, W.G.; Hirsh, J.; Gallus, A.S.; Hoicka, G.; Turpie, A.G.G.; Walker, I.;** and **Gent, M.:** Impedance plethysmography using the occlusive cuff technique in the diagnosis of venous thrombosis. *Circulation,* 53:696-700, 1976.
23. **Jongbloets, L.M.; Lensing, A.W.; Koopman, M.M.; Buller, H.R.;** and **ten Cate, J.W.:** Limitations of compression ultrasound for the detection of symptomless postoperative deep vein thrombosis. *Lancet* (England), 343(8906): 1142-1144, 1994.
24. **Kawdiki, E.; Nicolaides, A.N.; al-Kutoubi, A.; Cunningham, D.A.;** and **Crofton, M.:** Duplex scanning on the postoperative surveillance of patients undergoing total hip arthroplasty. *J. Arthroplasty,* 12(3):310-316, 1997.
25. **Killewich, L.A.; Bedford, G.R.; Beach, K.W.;** and **Strandness, D.E.:** Diagnosis of deep venous thrombosis: A prospective study comparing duplex scanning to contrast venography. *Circulation,* 79:810-814, 1989.
26. **Landefeld, C.S.;** and **Beyth, R.J.:** Anticoagulant-related bleeding: Clinical epidemiology, prediction, and prevention. *American J. Med.,* 95:315-328, 1993.
27. **Lensing, A.W.; Doris, C.L.; McGrath, F.P.; Cogo, A.; Sabine, M.J.; Ginsberg, J.; Pradoni, P.; Turpie, A.G.;** and **Hirsh, J.:** A comparison of compression ultrasound with color Doppler for the diagnosis of symptomless postoperative deep vein thrombosis. *Arch. Int. Med.,* 157(7):765-768, 1997.
28. **Lensing, A.W.; Prandoni, P.; Brandjes, D.; Huisman, P.M.; Vigo, M.;** and **Tomasella, A.:** Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N. Engl. J. Med.,* 320:342-345, 1980.

29. **Leutz, D.W.;** and **Stauffer, E.S.:** Color duplex Doppler ultrasound scanning for detection of deep venous thrombosis in total knee and hip arthroplasty patients: Incidence, location, and diagnostic accuracy compared with ascending venography. *J. Arthroplasty,* 9(5):543-548, 1994.
30. **Lotke, P.A.; Ecker, M.L.; Alavi, A.;** and **Berkowitz, H.:** Indications for the treatment of deep venous thrombosis following total knee replacement. *J. Bone and Joint Surg.,* 66(A):202-208, 1984.
31. **Montgomery, K.D.; Potter, H.G.;** and **Helfet, D.L.:** Magnetic resonance venography to evaluate the deep venous system of the pelvis in patients who have an acetabular fracture. *J. Bone and Joint Surg.,* 77:1639-1649, 1995.
32. **Moser, K.M.;** and **LeMoine, J.R.:** Is embolic risk conditioned by location of deep venous thrombosis. *Ann. Int. Med.,* 94:439-444, 1981.
33. **Oishi, C.S.; Grady-Benson, J.C.; Otis, S.M.; Colwell, C.W.;** and **Walker, R.H.:** The clinical course of distal deep venous thrombosis after total hip and total knee arthroplasty as determined by duplex ultrasonography. *J. Bone and Joint Surg.,* 76(A):1658-1663, 1994.
34. **Paiemont, G.; Wessinger, S.J.; Waltman, A.C.;** and **Harris, W.H.:** Surveillance of deep vein thrombosis in asymptomatic total hip replacement patients: Impedance phlebography and fibrinogen scanning versus roentgenographic phlebography. *Am. J. Surg.,* 155:400-404, 1988.
35. **Patterson, B.M.; Marchand, R.;** and **Ranawat, C.:** Complications of heparin therapy following total joint replacement. *J. Bone and Joint Surg.,* 71(A):1130-1134, 1989.
36. **Pellegrini, V.D.; Langhans, M.J.; Totterman, S.; Marder, V.J.;** and **Francis, C.W.:** Embolic complications of calf thrombosis following total knee arthroplasty. *J. Arthroplasty,* 8:449-457, 1993.
37. **Philbrick, J.T.;** and **Becker, J.M.:** Calf deep venous thrombosis: A wolf in sheep's clothing? *Arch. Int. Med.,* 148:2131-2138, 1988.
38. **Rose, S.C.; Zweibel, W.J.; Murdock, L.E.; Hofman, A.A.; Priest, D.L.; Knighton, R.A.; Swindel, T.M.; Lawrence, P.F.;** and **Miller, F.J.:** Insensitivity of color Doppler flow imaging for detection of acute calf venous thrombosis in asymptomatic postoperative patients. *J. Vasc. Interv. Rad.,* 4(1):111-117, 1993.
39. **Spritzer, C.E.; Norconk, J.J.; Sostman, H.D.;** and **Coleman, R.E.:** Detection of deep venous thrombosis by magnetic resonance imaging. *Chest,* 104:54-60, 1993.
40. **Stewart, J.H.;** and **Grubb, M.:** Understanding vascular ultrasonography. *Mayo Clin. Proc.,* 67:1186-1196, 1992.
41. **Stulberg, B.N.; Insall, J.N.; William, G.W.;** and **Ghelman, B.:** Deep-vein thrombosis following total knee replacement. *J. Bone and Joint Surg.,* 66(A):194-201, 1984.
42. **Sumner, D.S.:** Noninvasive tests in the diagnosis and management of thromboembolic disease. *Surg. Annu.,* 18:1-28, 1986.
43. **Weinmann, E.E.;** and **Salzman, E.W.:** Deep vein thrombosis. *N. Engl. J. Med.,* 331:1630-1642, 1994.
44. **Wells, P.S.; Lensing, A.W.; Anderson, D.R.;** and **Hirsh, J.:** The distribution of deep vein thrombosis in asymptomatic post-operative patients and the implications for screening. *Blood,* 80:316a, 1992.
45. **Wells, P.S.; Lensing, A.W.A.; Davidson, B.L.; Prins, M.H.;** and **Hirsch, J.:** Accuracy of ultrasound for the diagnosis of deep venous thrombosis in asymptomatic patients after orthopedic surgery: A meta-analysis. *Ann. Int. Med.,* 122:47-53, 1995.
46. **Wheeler, H.B.; Pearson, D.; O'Connell, D.;** and **Mullick, S.C.:** Impedance phlebography. *Arch. Surg.,* 104:164-170, 1972.
47. **White, R.H.; McGahan, J.P.; Daschbach, M.M.;** and **Hartling, R.P.:** Diagnosis of deep vein thrombosis using duplex ultrasound. *Ann. Int. Med.,* 111:297-304, 1989.
48. **Woolson, S.T.; McGrory, D.W.; Walter, J.F.; Maloney, W.J.; Watt, J.M.;** and **Cahill, P.D.:** B-mode ultrasound scanning in the detection of proximal venous thrombosis after total hip replacement. *J. Bone and Joint Surg.,* 72(A):983-987, 1990.
49. **Woolson, S.T.;** and **Pottorff, G.:** Venous ultrasonography in the detection of proximal vein thrombosis after total knee arthroplasty. *Clin. Orthop.,* 273: 131-135, 1991.

DOES PULSED LOW INTENSITY ULTRASOUND ALLOW EARLY RETURN TO NORMAL ACTIVITIES WHEN TREATING STRESS FRACTURES?
A review of one tarsal navicular and eight tibial stress fractures

Jeff C. Brand, Jr., M.D.*
Tim Brindle, MS, PT, ATC**
John Nyland, EdD, PT SCS, ATC, CSCS***
David N.M. Caborn, M.D.‡
Darren L. Johnson, M.D.‡‡

ABSTRACT

We sought to evaluate the efficacy of daily pulsed low intensity ultrasound (LIUS) with early return to activities for the treatment of lower extremity stress fractures.

Eight patients (2 males, 6 females) with radiographic and bone scan confirmed tibial stress fractures participated in this study. Additionally, a case report of a tarsal navicular stress fracture is described. All patients except one were involved in athletics. Prior to the study, subjects completed a 5 question, 10 cm visual analog scale (VAS) regarding pain level (10 = extreme pain, 1 = no pain) and were assessed for functional performance. Subjects received 20-minute LIUS treatments 5 times a week for 4 weeks. Subjects maintained all functional activities during the treatment period. Seven patients with posterior-medial stress fractures participated without a brace. Subjects were re-tested after 4 weeks of treatment. Mann-Whitney U tests (VAS data) and paired t-tests (functional tests) assessed statistical significance ($p<0.05$).

Although the intensity of practice was diminished in some instances, no time off from competitive sports was prescribed for the patients with the tibial stress fractures. The patient with the anterior tibial stress fracture underwent tibial intramedullary nailing at the conclusion of a season of play.

In this uncontrolled experience, treatment of tibial stress fractures with daily pulsed LIUS was effective in pain relief and early return to vigorous activity without bracing for the patients with posterior-medial stress fractures.

*Alexandria Orthopaedics and Sports Medicine, P.A.
1500 Irving
Alexandria, MN 56308
Phone 320-762-1144
Fax 320-762-1935
e-mail jbrand@inet-serve.com

**3643 White Pine Dr.
Lexington, KY 40514

***University of South Florida
School of Physical Therapy
12901 Bruce B. Downs Blvd. MDC 77
Tampa, FL 33612-4766
Phone 813-974-1666
Fax 813-974-8915

‡Associate Professor of Orthopaedic Surgery

‡‡Associate Professor of Orthopaedic Surgery
Chief of Section of Sports Medicine

University of Kentucky School of Medicine
Kentucky Clinic
K-439
740 Limestone
Lexington, KY 40536
Phone 606-323-5533 Ext. 250
Fax 606-323-2412

INTRODUCTION

It has been estimated that up to 5% to 10% of all sports-related injuries involve stress fractures[6,7,9,10]. The tibia has surpassed the metatarsals to become the most common location for the development of stress fracture[6,8,5]. Traditional treatment has included rest, relative rest, casting and ambulatory braces and results in substantial loss of time from activities. Recently, the AIRCAST™ pneumatic tibial brace with an anterior pad hastened return to recreational activities[11]. Use of this brace shortened the time out of strenuous activities from 77 +/- 7 days to 21 +/- 2 days in a prospective randomized trial comparing traditional methods of stress fracture treatment 11.

Non-invasive daily pulsed LIUS (Exogen, Piscatway, New Jersey) therapy hastened tibial fracture[2] and distal radius fracture healing[4]. Consolidation time of spine fusion improved with daily pulsed LIUS[13]. No research has reported success with the use of low-intensity pulsed ultrasound in the acceleration of stress fracture healing. We sought to evaluate the efficacy of daily pulsed LIUS for the treatment of tibial stress fractures

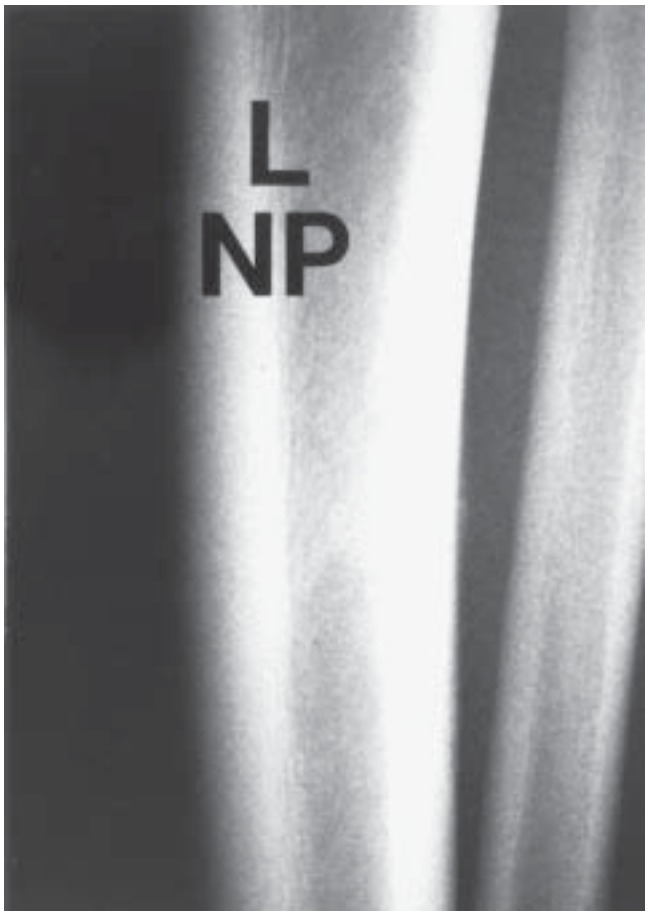


Figure 1A

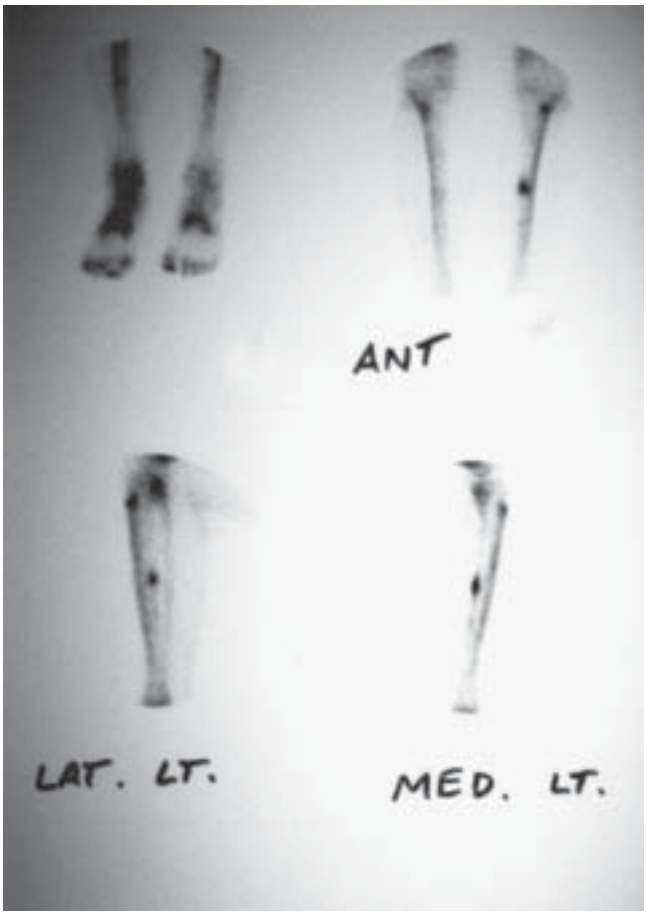


Figure 1B

Figure 1. N.P. is a 19 year old white male college level soccer play who complained of posterior-medial pain along the mid portion of the tibia. (A) Plain radiographs of the tibia and fibula showing a small "cloud" of periosteal reaction consistent with a tibial stress fracture at the posterior-medial border of the left tibia. The accompanying bone scan confirmed the diagnosis. (B) The bone scan is of both tibias. Increased uptake is noted along the posterior-medial border of the left tibia in the diaphysis.

with early return to activities. Our goals were to avoid losing time out of an athleteís short competitive season, and avoid brace treatment for sporting activities, as sports such as soccer make it difficult to wear a brace in competition.

MATERIALS AND METHODS

Eight patients with a positive bone scan (Figure 1) and one case of MRI documented stress fracture were treated with daily pulsed LIUS and immediate return to usual activities. There were 3 males and 6 females, 8 of the 9 patients were high school or college level athletes. Seven patients had posterior-medial tibial stress fractures and one patient, a female college level basketball player, suffered from an anterior tibial stress fracture diagnosed in the pre-season conditioning period. One patient had a tarsal navicular stress fracture diagnosed with MRI. The athletic patients participated in soccer and basketball.

Patients were identified at the sports medicine clinic, where a history, physical exam, plain radiographs and nuclear medicine technetium bone scan were performed for the patients with tibial stress fractures. The patient with a tarsal navicular stress fracture had his diagnosis made by MRI. A pre-test and post-test of functional activities were administered in Physical Therapy. Prior to the study, subjects completed a 5 question, 10 cm visual analog scale (VAS) regarding pain level (10 = extreme pain, 1 = no pain) and were assessed for functional performance. Subjects received 20 minutes daily pulsed LIUS treatments of operating frequency = 1.5 MHz, radiating area = 3.88 cm^2, pulse width = 200 microseconds and temporal average power=117 mW that were administered 5 treatments/week for 4 weeks. Patients with tibial stress fractures maintained all functional activities during the treatment period. Eight patients participated without bracing, one patient with an anterior tibial stress fracture participated with the

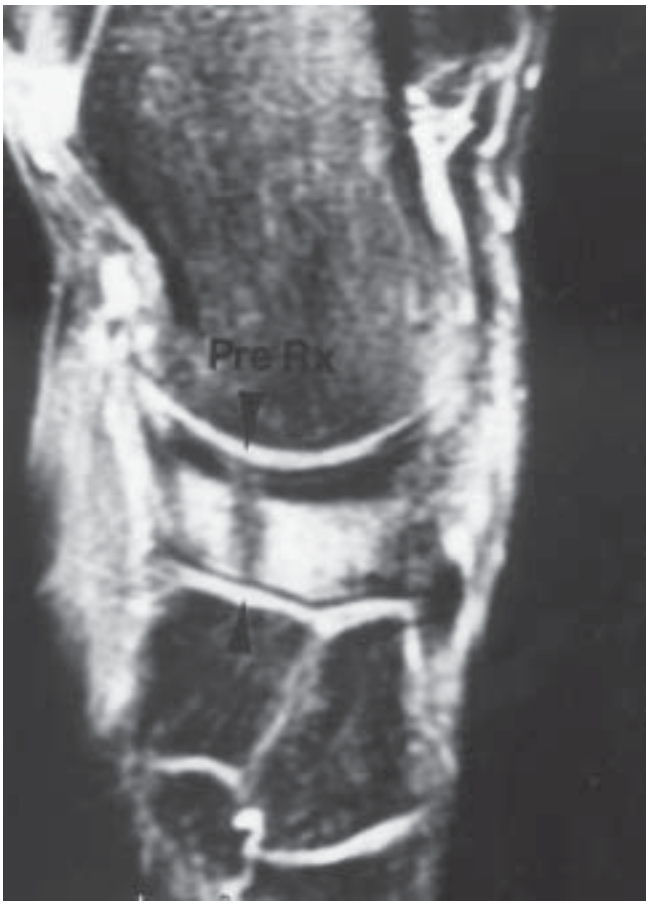


Figure 2. W.B. is a 20 year old African American male, college level basketball player with an MRI documented tarsal navicular fracture. This image is from 12/16/97, before treatment was initiated. The stress fracture is visualized across the entire width of the tarsal navicular on the coronal view. The fracture line can be seen extending into subchondral bone.

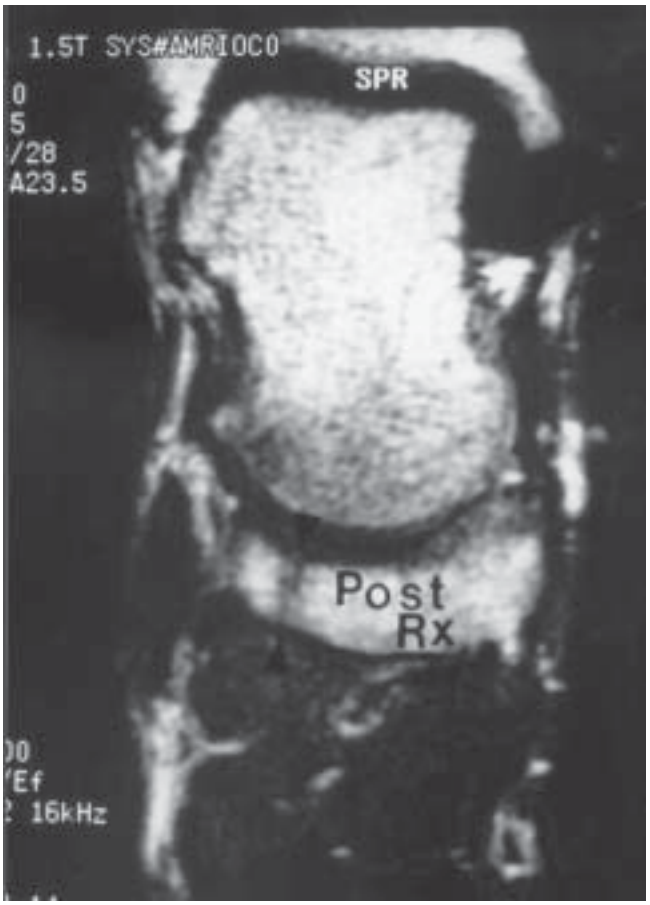


Figure 3. This is the post treatment MRI from 1/27/98, which was obtained before he was allowed to return to competitive basketball. The fracture line appears less distinct, not as long and the articular margins appear to show consolidation of the fracture line. This is the coronal view, which is similar to the view from Figure 2.

AIRCAST™ pneumatic tibial brace with an anterior pad because of the risk for fracture during activities. The remaining patients wore an AIRCAST™ pneumatic tibial brace with an anterior pad when not participating in activities or sports. Subjects were then re-tested after 4 weeks of treatment. Mann-Whitney U tests (VAS data) and paired t-tests (functional tests) assessed statistical significance to the $p<0.05$ level.

Case Report

W.B. was a 20 year old African American male, Division II college level basketball player, who in early December of 1997 landed awkwardly on his foot. The foot was painful over the dorsal posterior mid-foot, in the area of the anterior tibialis tendon. He attempted to play, which he was able to do with an antalgic limp. The range of motion (ROM) was symmetric to the opposite foot. Tenderness was palpable diffusely across the dorsal mid-foot and did not localize to a discreet area. Single leg hop was similar to the opposite foot but painful. Taping, NSAIDS, ultrasound, electrical stimulation, ice and shoe modification failed to improve his pain or allow athletic participation. Pain improved immediately with an injection of local anesthetic and a cortisone compound in the area of the anterior tibialis attachment onto the tarsal navicular, but relief failed to be sustained for a significant time frame.

Plain radiographs of the foot did not reveal an explanation for his pain. An MRI, 12/16/97, of the foot was obtained, to evaluate soft tissues. A tarsal navicular stress fracture was evident (Figure 2).

Six weeks of NWB casting, while the standard treatment for this injury[12,3], would have likely ended his competitive season. Because, we had used the daily pulsed LIUS effectively in tibial stress fractures, we proceeded to treat his injury with equally hopeful results. Fortunately, his injury coincided with almost two weeks of rest from competitive basketball because of his school's holiday break. His treatment included the Sonic Accelerated Fracture Healing System (SAFHS) (Exogen,

Piscatway, New Jersey) device and three and a half weeks of non-weight bearing crutch walking in a brace, which was removed for physical therapy. On a graded basis, activities were added, and ultimately returned to competition at 5 weeks after his injury.

A repeat MRI,1/27/98, demonstrated early consolidation of the stress fracture (Figure 3).

RESULTS

All subjects resumed or maintained sporting activities at the same level as at the time of diagnosis. No adverse sequelae or recurrence of symptoms occurred in the seven patients with the posterior-medial stress fractures or in the patient with the tarsal navicular stress fracture. The patient with the anterior tibial stress fracture underwent tibial intramedullary nailing after a successful season of competition.

The results of functional testing both before and after treatment are in Table I.

DISCUSSION

No tibial stress fracture patients were removed from athletic activities because of their injuries. The patient with the tarsal navicular fracture missed five weeks of season, but this included two weeks Christmas vacation when his team had time off from practice and competition. This mode of treatment is remarkably different from the traditional treatment of tarsal navicular stress fractures, which is six weeks of non-weight bearing (NWB) casting[3,12]. Our patient was treated with a removable brace and three and one-half weeks of NWB.

Objective improvement in the tibial stress fractures was documented using reported scales[1]. Our mode of treatment was successful in compression, posterior-medial, stress fractures. The one patient with an anterior or tension side fracture didnít respond to low intensity pulsed ultrasound treatment and required intramedullary nailing of her stress fracture at the end of the competitive season. So, this method of treatment may not be useful in this type of tibial stress fracture.

This is the first reported use of this technique to accelerate healing for lower extremity stress fractures. Daily pulsed Low-Intensity Pulsed Ultrasound significantly minimized time off from normal activities. This is a comparatively expensive form of treatment and medical reimbursement may be an issue. Thus, further review would be advised. A prospective, controlled randomized trial is the obvious next step, if not here perhaps another center. This treatment method may be useful in the select instance of a high demand athlete who cannot afford time away from competition to rehabilitate this injury. Until efficacy is documented with a randomized prospective trial, reimbursement by insurance carriers may not be forthcoming.

ACKNOWLEGMENTS

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TABLE I

Summary of the results of the functional testing of patients before and after treatment

	Stepdowns / 1 min	**Pain with Palpation**
Pre-Treatment	28 ± 7 repetitions	7.5 ± 2
Post-Treatment	36 ± 5 repetitions	3.3 ± 3
Mean Difference	8 ± 6 more repetitions	4.3 + 3 reduced pain
P	0.02	0.02

REFERENCES

1. **Flandry, F.; Hunt, J.P.; Terry, G.C.;** and **Hughston, J.C.:** Analysis of subjective knee complaints using visual analog scales. *Am. J. Sports Med.,* 19:112-118, 1991.
2. **Heckman, J.D.; Ryaby, J.P.; McCabe, J.; Frey, J.J.;** and **Kilcoyne, R.F.:** Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. *J. Bone and Joint Surg.,* 76-A:26-34,Jan. 1994.
3. **Khan, K.M.; Fuller, P.J.; Brukner, P.D.; Kearney, C.;** and **Burry, H.C.:** Outcome of conservative and surgical management of navicular stress fracture in athletes. Eight-six cases proven with computerized tomography. *Am. J. of Sports Med.,* 20:657-666, 1992.
4. **Kristiansen, T.K.; Ryaby, J.P.; McCabe, J.; Frey, J.J.;** and **Roe, L.R.:** Accelerated healing of distal radius fractures with the use of specific, low-intensity ultrasound. A multicenter, prospective, randomized, double-blind, placebo-controlled study. *J. Bone and Joint Surg.,* 79-A:961-973, July,1997.
5. **Maitra, R.S.;** and **Johnson, D.L.:** Stress fractures: Clinical History and Physical Examination. *Clin. Sports Medicine,* 16:259-274, April 1997
6. **Meyer, S.:** Stress fractures of the foot and leg. *Clin. Sports Med.,* 12:395,1993.
7. **Monteleone, G.:** Stress fractures in the athlete. *Orthop. Clin. North Am.,* 26:423, 1995.
8. **Renstrom, P.:** Mechanism, diagnosis, and treatment of running injuries. *Instr. Course Lect.,* 42:225-234, 1993.
9. **Smrcina, C.:** Stress fractures in athletes. *Nurs. Clin. North Am.,* 26:159, 1991.
10. **Sterling, J.; et al:** Stress fractures in the athlete: Diagnosis and management. *Sports Med.,* 14:336, 1992.
11. **Swenson, E.J.; DeHaven, K.E.; Sebastianelli, W.J.; Hanks, G.; Kakenak, A.;** and **Lynch, J.M.:** The effect of a pneumatic leg brace on return to play in athletes with tibial stress fractures. *Am. J. of Sports Med.,* 25:322-328, May-June, 1997.
12. **Torg, J.S.; Pavlov, H.;** and **Cooley, L.H.:** Stress fracture of the tarsal navicular. *J. Bone and Joint Surg.,* 64A:700-712, June,1982.
13. **Whitecloud, T.S.:** Spine fusions heal more quickly with ultrasound in animal model. *Orthopedics Today,* 17:1 & 36, Dec. 1997.

LONG-TERM FOLLOW-UP OF PERSISTENT HUMERAL SHAFT NON-UNIONS TREATED WITH TRICORTICAL BONE GRAFTING AND COMPRESSION PLATING

Annette Billings, M.D.
Sherman S. Coleman, M.D.

ABSTRACT

Three percent of all fractures occur in the humeral shaft. A very high union rate is achieved with nonoperative treatment. When non-unions occur, however, they are often very difficult to treat, and often require multiple procedures to achieve union. Even with multiple procedures, true pseudoarthroses have only a 59% union rate[10]. We conducted a retrospective study of ten patients having persistent non-union of the humeral shaft, three of whom had a true pseudoarthrosis. All patients were treated with a compression plate and a tricortical iliac crest bone graft anchored rigidly across the fracture site with two screws applied at 90 degrees to the plate. A solid union was achieved in all ten (100%) patients.

INTRODUCTION

Humeral shaft fractures have a high rate of union whether they are treated with open reduction and internal fixation, closed IM nailing or treated nonoperatively with a hanging arm cast or a functional brace. 90-95% of these fractures unite with good return of function[4,7,9,18,19,20]. However, up to a 13% non-union rate has been reported following open reduction and internal fixation or closed IM nailing and up to an 8% nonunion rate has been reported for fractures treated nonoperatively[9]. When a nonunion occurs a major therapeutic challenge is incurred, often resulting in multiple procedures. Non-union is defined here as a fracture that shows no substantial evidence of healing and exhibits pathological radiographic changes showing cessation of attempts at repair. It is a radiological as well as a clinical diagnosis.

MATERIALS AND METHODS

A retrospective study of ten patients with humeral shaft non-unions treated with tricortical bone grafting and compression plating was conducted. A chart review was performed and eight of the ten patients were re-examined clinically and radiographically. Two patients were unable to return for re-examination, so their charts were used for their most recent follow-up. All procedures were performed by the same surgeon between 1974 and 1993.

The average age of the patients was 49 (range 22-72). The average time from fracture to treatment of the nonunion was 29.3 months (range 4 to 124 months). The average time to follow-up was 12.4 years (range 3-22 years). One fracture was a pathologic fracture through a bone cyst, two fractures were open including one gunshot wound, and one fracture was a segmental fracture. The types of nonunions were atrophic in four patients, hypertrophic in three patients and a synovial pseudoarthrosis was present in three patients. One patient had Paget's disease and rheumatoid arthritis and had been treated with methotrexate along with other anti-arthritic medications and as a result had extremely poor bone quality. Three patients had radial nerve dysfunction preoperatively, which completely resolved after treatment. In addition one patient also had ulnar nerve dysfunction preoperatively which likewise resolved after treatment.

A total of seventeen previous procedures were performed with an average of 1.7 procedures per patient. Prior treatments included hanging arm casts, functional braces, slings, electrical stimulation, open reduction and internal fixation, cerclage wires, compression plates with and without bone graft, and intramedullary nails with and without bone graft.

Operative Technique

An anterolateral or lateral approach to the humerus was used, according to the site of the non-union. Dissection was carried out down to the non-union site, taking care to identify and protect the radial nerve. In one patient the radial nerve was encased in scar tissue. This was very carefully dissected free. Both the proximal and distal fragment ends were then debrided of all soft tissue and resected back to bleeding bone. A dynamic compression plate was applied with at least six points of cortical fixation on both sides of the non-union. It is critically important that the compression plate be inserted prior to applying the iliac crest graft. A one to

Corresponding Author: Sherman S. Coleman, M.D., Department of Orthopedics, 50 North Medical Dr., Salt Lake City, UT 84132, (801) 581-7601, Fax: (801) 581-6178

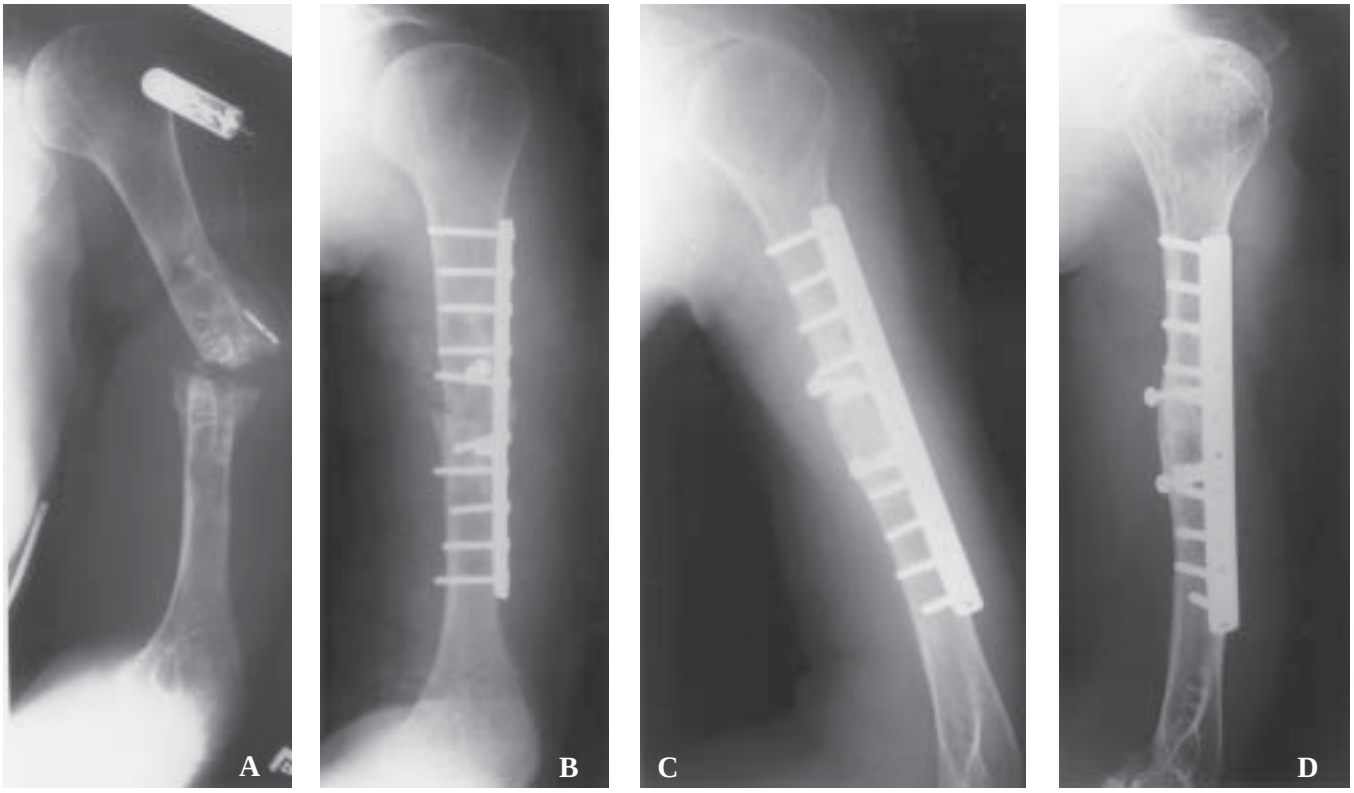

Figure 1. (A) Preoperative roentgenogram (7/27/83). Primary treatment was hanging arm cast for one year. Secondary treatment was ORIF and tertiary treatment was electrical stimulation. (B) Immediate post-operative roentgenogram (7/28/83). Iliac crest bone graft is applied 90 degrees from the compression plate. (C) Six month post-operative roentgenogram (12/23/83). Healed nonunion after treatment with dynamic compression plating and rigidly fixed tricortical bone grafting. (D) Most recent roentgenogram (6/19/96). Humerus remains solid clinically and radiographically.

two by five cm cortical cancellous graft was then obtained from the anterior iliac crest, along with several strips of cancellous bone. The onlay bone graft was placed over the non-union area on the anterior or anteromedial aspect of the humerus (90 degrees to the plate) with two small fragment screws, one above and one below the non-union site. This firmly secured the graft to the humerus. The firm fixation of the graft is an important aspect of the treatment, because the graft not only adds some stability, but we believe more rapid osteogenesis results. The remainder of the cancellous bone was placed in the medial aspect of the humerus. After copious irrigation the wound was closed in a routine fashion.

RESULTS

All ten patients achieved a solid union of their non-union within four months of this program of treatment (see Figure 1). There were no failures, and no repeat procedures were required. One patient had decreased range of motion at the elbow (with a range of 70 to 110 degrees) twenty-three years after the procedure, probably the result of periarticular or periosseous scarring due to his long-standing non-union (three years). In the patient with Paget's Disease and rheumatoid arthritis, after solid union was achieved the patient refractured the same humerus. The procedure was not repeated even though the patient developed a non-union.

DISCUSSION

The reasons for non-union are multifactorial and include older age, poor nutritional status, obesity, diabetes mellitus, alcoholism, use of corticosteroids, anticoagulation, previous radiation, fractures underlying burns, and poor patient compliance. Other factors contributing to delayed or non-union are open fractures, fractures with a transverse fracture pattern, infections, primary open reduction, soft tissue interposition, inadequate immobilization, limitation of shoulder motion and distraction of the fracture site (most often the result of a transverse or short oblique fracture treated with a hanging arm cast)[8,9,20].

Humeral shaft fractures resulting in a non-union pose major therapeutic challenges, and many patients with this fracture are exposed to multiple operative procedures in efforts to achieve union. Compression plating

with screws and intramedullary nail fixation with interlocking screws are currently the most common methods of treating non-unions, although good results have also been achieved with less conventional methods[1,2,3,13,16,18]. Four authors who treated four to six nonunions each reported a 100% union rate using an interlocking IM nail[6,11,14,17]. Trotter et al also reported a 100% union rate in five patients with very osteoporotic bone using compression plating with methylmethacrylate for screw fixation[15]. And Jupiter et al achieved a 100% union rate in four patients using a vascularized fibular graft[12]. In complicated non-unions, however, a much lower rate of union has been achieved. In nonunions with true pseudoarthroses a mere 59% union rate has been reported[10].

In a study done by Collie and co-workers at the Mayo Clinic, nine patients with persistent non-unions and having had multiple previous procedures were treated with a long compression plate and a tibial onlay bone graft with screw fixation applied at 90 degrees to the plate. Additional cancellous bone was also used. In this study all nine fractures achieved union[5].

A similar procedure was employed in our retrospective study of ten patients with persistent humeral shaft non-unions with a comparable success rate. The reasons for success, we believe, consist in debriding the tissue in the area of the non-union, rigid internal fixation utilizing a compression plate, and firm fixation of a tricortical iliac graft to bridge the non-union site.

CONCLUSION

Although humeral shaft non-unions are not frequent, when they do occur they can be very difficult to treat. This paper presents a treatment option that has been very successful in achieving union even in patients who have a true pseudoarthrosis and in patients who have failed multiple prior procedures (six in one patient). This technique offers an alternative to the use of the much more extensive and complicated vascularized bone grafting, and may be applied to other sites of non-union. We have employed this technique in treating clavicular nonunions, also with a 100% success rate.

REFERENCES

1. **Burdeaux, B. D., Jr.,** and **York, B. P., Jr.:** Treatment of difficult fractures and nonunions of the humerus and elbow with a modified Kuntscher Nail. *Iowa Orthop. J.,* 13: 196-203, 1993.
2. **Catagni, M. A.; Guerreschi, F.;** and **Probe, R. A.:** Treatment of humeral nonunions with the Ilizarov technique. *Bull. Hosp. Jt. Dis. Orthop. Inst.,* 51(1): 74-83, 1991.
3. **Catteneo, R.; Catagni, M. A.;** and **Guerreschi, F.** Applications of the Ilizarov method in the humerus: lengthenings and nonunions. *Hand Clin.,* 9(4): 729-739, November 1993.
4. **Christensen S.:** Humeral shaft fractures: operative and conservative treatment. *Acta Chir. Scand.,* 133: 455-460, 1967.
5. **Collie, L. P.; Cooney, W. P.;** and **Kelly, P. J.:** Nonunions of the humeral shaft. *Orthop. Trans.,* 7: 517, 1983.
6. **Corradi, M.; Petriccioli, D.; Panno, B.;** and **Merenghi, P.:** Seidel locked nailing for the treatment of unstable fractures and nonunion of the humerus. *Chir. Organi. Mov.,* 81(2): 189-195, 1996.
7. **Foster, R. J.; Dixon, G. L.; Bach, A. W.; Appleyard, R. W.;** and **Green, T. M.:** Internal fixation of fractures and non-unions of the humeral shaft: indicators and results in a multi-center study. *J. Bone and Joint Surg.,* 67-A: 857-864, July 1985.
8. **Foulk, D. A.,** and **Szabo, R. M.:** Diaphyseal humerus fractures: natural history and occurrence of nonunion. *Orthopedics,* 18(4): 333-335, April 1995.
9. **Healy, W. L.; White, G. M.; Mick, C. A.; Brooker, A. F.;** and **Weiland, A. J.:** Nonunion of the humeral shaft. *Clin. Orthop.,* 219: 206-213, 1987.
10. **Heppenstall, R. B.; Brighton, C. T.; Esterhai, J. L., Jr.; Katz, M.;** and **Schumacher, R.:** Synovial pseudoarthrosis: a clinical, roentgenographic, scintigraphic, and pathologic study. *J. Trauma,* 27(5): 463-470, May 1987.
11. **Ingman, A. M.,** and **Waters, D. A.:** Locked intramedullary nailing of humeral shaft fractures: implant design, surgical technique, and clinical results. *J. Bone and Joint Surg.,* 76-B(1): 23-29, 1994.
12. **Jupiter, J. B.:** Complex non-union of the humeral diaphysis: treatment with a medial approach, an anterior plate and a vascularized fibular graft. *J. Bone and Joint Surg.,* 72-A: 701-707, June 1990.
13. **McKee, M. D.; Miranda, M. A.;** and **Riemer, B. L.:** Management of humeral nonunion after the failure of locking intramedullary nails. *J. Orthop. Trauma,* 10(7): 492-499, 1996.

14. **Pietu, G.; Raymond, G.;** and **Letenneur, J.:** Treatment of delayed and nonunions of the humeral shaft using the Seidel locking nail: a preliminary report of five cases. *J. Orthop. Trauma,* 8(3): 240-244,1994.
15. **Trotter, D. H.,** and **Dobozi, W.:** Nonunion of the humerus: rigid fixation, bone grafting, and adjunctive bone cement. *Clin. Orthop.,* 204: 162-168, March 1986.
16. **Wright, T. W.:** Treatment of humeral diaphyseal nonunions in patients with severely compromised bone. *J. South. Orthop. Assoc.,* 6(1): 1-7, 1997.
17. **Wu, C. C.:** Humeral shaft nonunion treated by a Seidel interlocking nail with a supplementary staple. *Clin. Orthop.,* 326: 203-208, May 1996.
18. **Wu, C. C.,** and **Shih, C. H.:** Treatment for nonunion of the shaft of the humerus: comparison of plates and Seidel interlocking nails. *Can. J. Surg.,* 35(6): 661-665, December 1992.
19. **Zagorski, J. B.; Latta, L. L.; Zych, G. A.;** and **Finnieston, A. R.:** Diaphyseal fractures of the humerus: treatment with prefabricated braces. *J. Bone and Joint Surg.,* 70-A: 607-610, April 1988.
20. **Zuckerman, J. D.,** and **Koval, K. J.:** Fractures of the shaft of the humerus. In *Rockwood and Green's Fractures in Adults,* edited by Rockwood, C. A.: Green, D. P.; Bucholz, R. W.; and Heckman, J. D. Fourth Ed., Vol. 1, pp. 1025-1053. Philadelphia, Lippincott, 1996.

EXTERNAL FIXATION OF OPEN HUMERUS FRACTURES

J.L. Marsh, M.D.*
Craig R. Mahoney, M.D.**
Dave Steinbronn, M.D.‡

ABSTRACT

Fifteen patients with open shaft of humerus fractures were treated with a monolateral external fixator. Nine patients presented with nerve palsies. Two radial nerves were disrupted and required grafting. Of the seven others, six spontaneously recovered and one brachial plexus partially improved. All fractures healed. The average duration of external fixation was 21 weeks. Four patients required additional procedures prior to healing (external fixator reapplication - 2, plating and bone grafting - 2). Two of these four experienced breakage of 4.5 mm external fixation pins. Eight patients developed pin tract infections, which all resolved with local care and antibiotics.

Thirteen patients were contacted at an average of 63 months after injury. Eleven reported they were satisfied with their result, nine had no functional limits, and eight reported no pain.

The results of treatment of closed humeral shaft fractures are excellent using a variety of techniques including bracing[1,19,20,23], hanging casts[6,8,17], plate fixation[2,7,8,17,22], and intramedullary nailing[4,12,21]. There is less data available on the best technique of skeletal stabilization and outcome of patients with open humeral shaft fractures. Although open fractures are included in large series of humeral shaft fractures, analysis of this subgroup is often not reported separately[2,4,7,12,19,20,22,23]. The high energy forces which create humeral shaft fractures with associated open wounds may predispose to complications and poor outcomes.

External fixation has been used extensively for severe open fractures of the tibia[15], but there are few reports on the results of treatment of humerus fractures by external fixation, and even less on its use in open humeral fractures[3,5,9,13,14,18]. The purpose of this study was to determine the outcome of open humeral shaft fractures treated by a uniform technique of monolateral external fixation.

MATERIALS AND METHODS

Fifteen patients with open humeral shaft fractures were treated with external fixation between January 1986 and May of 1994, at the University of Iowa Hospitals and Clinics. During this time period, sixteen additional patients were treated for open humeral fractures with other methods (plate - three, intramedullary rod - two, splint/brace - eleven) and were excluded from the study group. External fixators were chosen for the higher energy fractures and those with more severe soft tissue wounds. Humeral fractures caused by low velocity hand gun wounds were excluded.

Eleven males and four females sustained seven fractures of the right arm and eight fractures of the left arm. The average patient age was 27 years (range seven to 42 years). The mechanisms of injuries were MVA (six), shot gun wound (four), clothes extractor (one), power takeoff (one), snowmobile (one), MVA-pedestrian (one) and fall (one). Four patients had other major fractures of the ipsilateral arm (open acromioclavicular fracture dislocation-one, both bone forearm fracture-two, ulna-one). Ten sustained multiple systems injuries. Nine had one or more nerve palsies associated with the open humerus fracture (radial nerve - seven, median nerve - two, ulnar nerve - one, brachial plexus - one).

The fractures were classified by the method of Muller et al. as seven A fractures (A1-0, A2-1, A3-6), one B fracture (B1 - 1, B2 - 0, B3 - 0), and seven C fractures (C1-0, C2-1, C3-6)[16]. The associated soft tissue wounds were classified by the method of Gustilo et al. as type I (one), type II (two), type IIIA (five), type IIIB (five) and type IIIC (two)[11]. All wounds were treated with emergent irrigation and debridement. Intravenous antibiotics were started at the time of admission and continued until twenty four hours after wound closure. The two bra-

*Professor
University of Iowa Hospitals and Clinics
Department of Orthopaedics
Iowa City, IA 52242

**Omaha, NE

‡Akron General Medical Center
Akron, Ohio

Corresponding Address
J.L. Marsh, M.D., Professor
University of Iowa Hospitals and Clinics
Department of Orthopaedics 01071 JPP
200 Hawkins Drive
Iowa City, IA 52242
Phone: 319 356-0430
Fax: 319 353-6754

chial artery injuries were repaired emergently with saphenous vein grafts. With the exception of the brachial plexus injury, all patients with evidence of neurologic injury had exploration of the nerves during wound management. In two arms, there was segmental loss of the radial nerve, which was treated during subsequent procedures with nerve grafting. All other nerves were found to be in continuity.

Five wounds were closed by primary suture. Ten patients were returned to the operating room for at least one repeat debridement prior to wound closure by delayed primary suture (four), split thickness skin graft (three), local muscle transfer and split thickness skin graft (one), and humeral shortening to allow closure by a combination of muscle transfer and split thickness skin graft (one). One open wound was allowed to heal by secondary intention. Three fractures were bone grafted at the time of wound closure. One had delayed bone grafting. The fixator was applied to the humerus at the time of initial irrigation and debridement at an average of seven hours after injury (range three - eleven) in twelve patients. One fixator was applied during the second irrigation and debridement, two days after the injury. Two patients had delayed fixator application (nine and eleven days after injury) after receiving initial treatment at another institution.

OPERATIVE TECHNIQUE

A monolateral fixator (Orthofix Inc., Dallas, Texas) was applied to tapered pins. The fixator bodies and pins (six millimeter tapered) are the same size as those used for lower extremity applications. Fixators are applied with the patient supine and the arm on a radiolucent table extension. Fluoroscopic control is required for fracture reduction and pin insertion.

The distal pins are inserted through a small incision over the lateral supracondylar ridge. Direct visualization of the supracondylar ridge facilitates predrilling and subsequent pin insertion in the narrow distal humerus. After predrilling, the most distal pin is applied one cm above the olecranon fossa perpendicular to the axis of the humerus. A template is then applied to this pin which determines the location of the other pins. The second distal pin is applied in the three or four position in the distal template clamp. Use of this location assures that the distal pins will be distal to the radial nerve (Figure 1). The proximal two pins are applied through the proximal template clamp percutaneously through the posterior third of the deltoid. Drilling and screw insertion is done through sleeves after carefully spreading the deltoid muscle fibers. All pins are placed through two cortices.

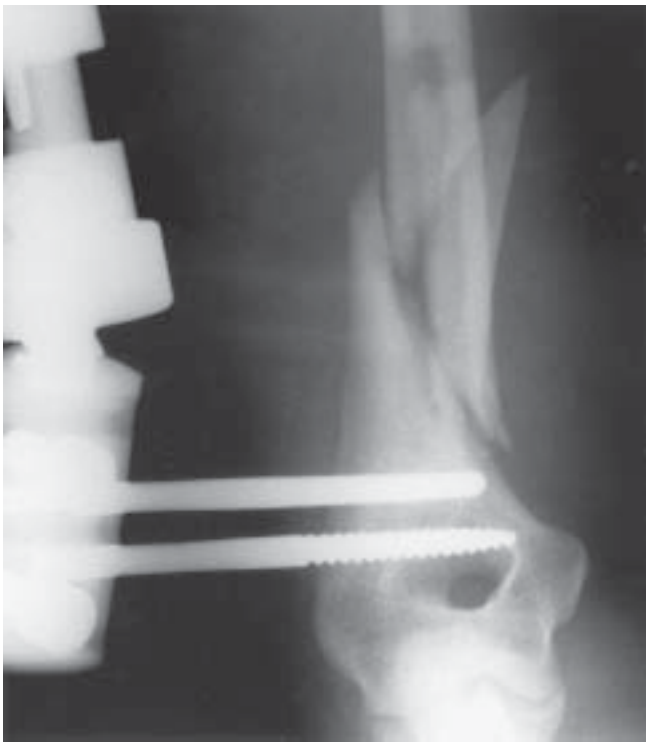

Figure 1. The optimal position for distal pin insertion is in the lateral supracondylar ridge just above the olecranon fossa. The distal pin cluster will then be below the radial nerve.

The template is then removed and the fixator is applied to the pins. The humerus is then aligned by gentle axial traction and the reduction is confirmed fluoroscopically. Reduction is often assisted by direct visualization and occasionally manipulation of the fracture through the open wound. The ball joints are then locked with the torque wrench (22 nm). Examination of rotation of the shoulder is required to assure accurate rotational alignment of the arm. If the fracture pattern permits, a compression distraction apparatus is used to compress the fracture. Tight wraps are placed on the pins and the arm is supported in a sling.

Postoperatively elbow and shoulder range of motions are encouraged. Free use of the arm when necessary and weight bearing with crutches are permitted.

The charts and radiographs of all patients were retrospectively reviewed. Data collected included the number of days in the hospital, time to upper extremity weight bearing in patients requiring crutch use, time to clinical union, duration of external fixation, number of fractures requiring post fixation bracing, the range of motion of the elbow and shoulder, and the occurrence of any complications related to the fracture or fixator. Anteroposterior and lateral radiographs from the time of injury, post fixator application, at the time of fixator removal and at latest follow up were reviewed by all

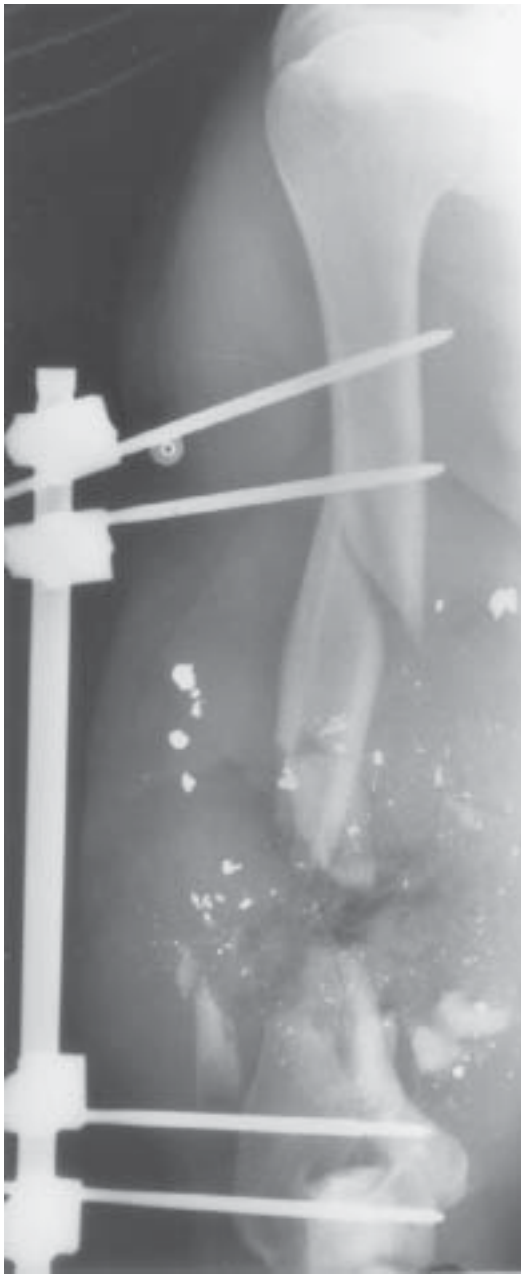

Figure 2A. An AP radiograph of the right humerus at presentation.

Figure 2B. An AP radiograph three weeks after placement of a lateral monolateral non-ball joint fixator. Distal fixation was enhanced by including a transcapitellar/trochlear pin. Soft tissue coverage was obtained by some skeletal shortening, local muscle rotation and split thickness skin grafts.

Figures 2A-E. A thirty-one year-old male received a shotgun blast to his right humerus. The patient was debrided and placed in an external fixator and transferred to us four days after injury.

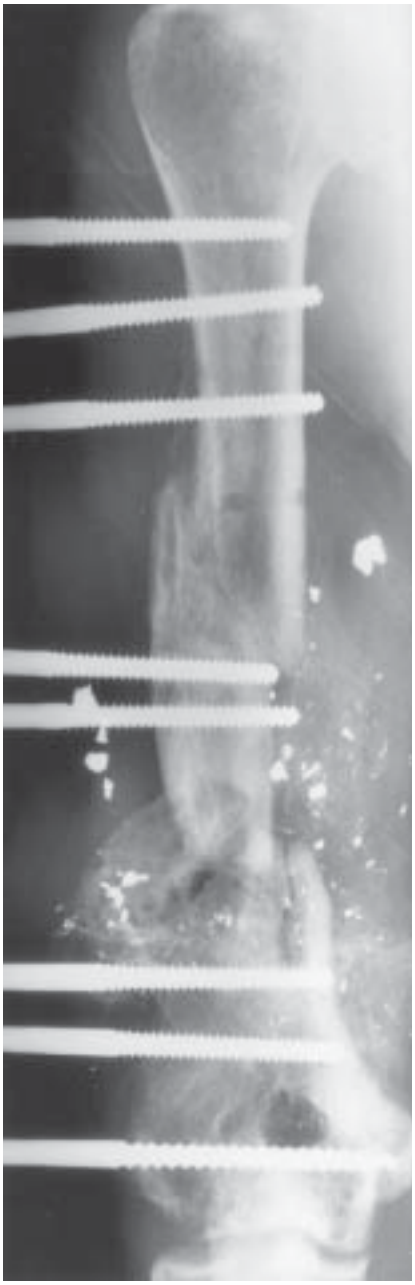

Figure 2C. An AP radiograph taken six months after injury demonstrating repair at both levels. No bone grafts were used.

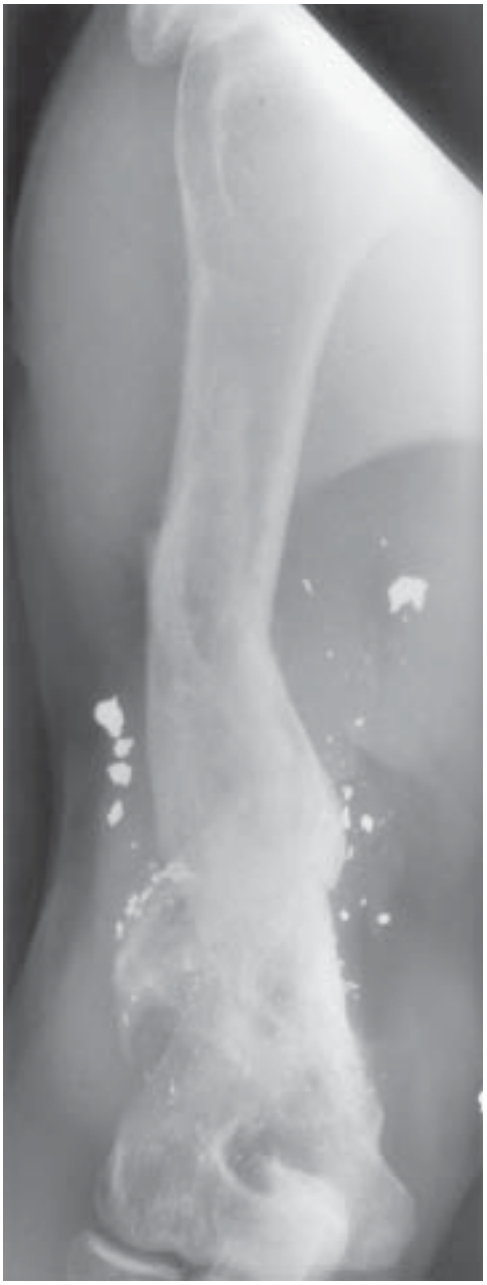

Figure 2D.

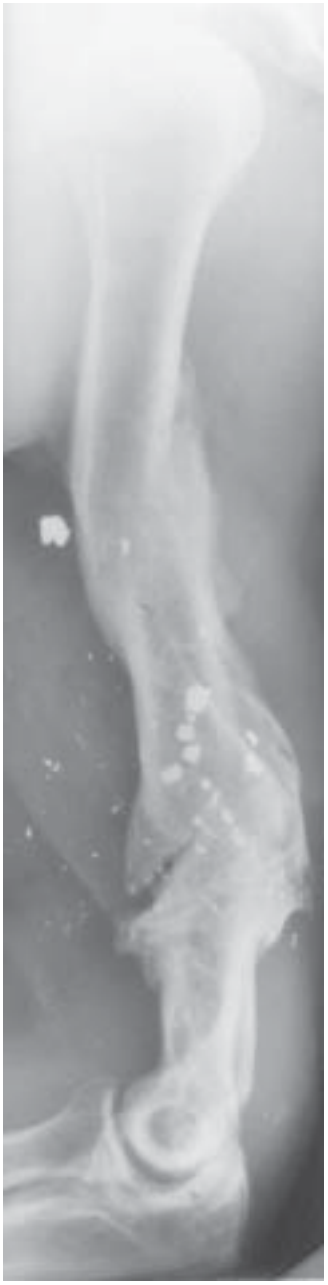

Figure 2E.

Figures 2D and 2E. An AP (D) and lateral (E) radiograph 27 months after injury show union. The patient had no complaints and full function of the shoulder and elbow.

three investigators. Healing was defined as bridging callus on biplane radiographs. Angulation was measured both in the fixator and at removal and was defined as greater than ten degrees of shaft angulation in any plane.

A questionnaire was used to assess the level of pain (mild, moderate or severe), functional limitations (mild, moderate or severe), work status and whether the patients were pleased or displeased with the outcome.

RESULTS

The number of hospital days averaged eighteen (range seven to 53 days). Upper extremity weight-bearing was required for crutch use in six patients with lower extremity injuries and was achieved at an average of sixteen days post injury (range 11 - 37 days). The average duration of external fixation was 20 weeks (range 6-32 weeks). Nine limbs were protected after fixator removal with a Sarmiento brace.

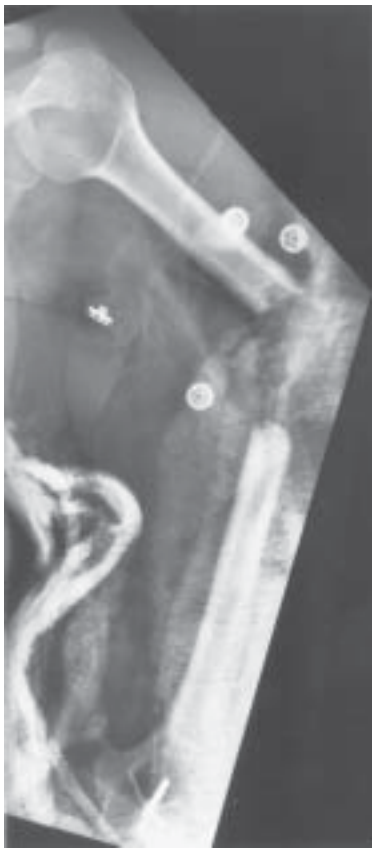

Figure 3A. The initial AP radiograph.

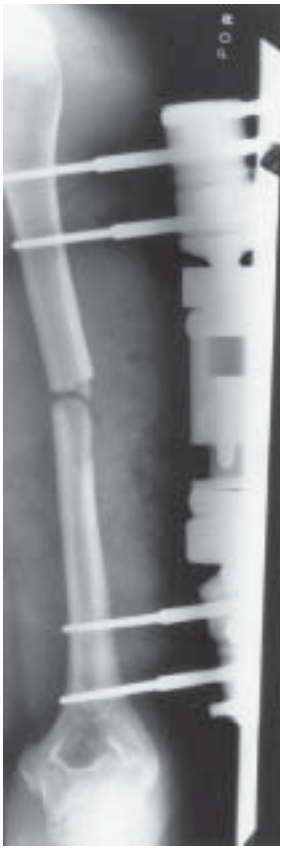

Figure 3B. An AP radiograph taken after wound debridement, vascular repair, slight skeletal shortening, and external fixator application. 4.5 mm fixator pins were used.

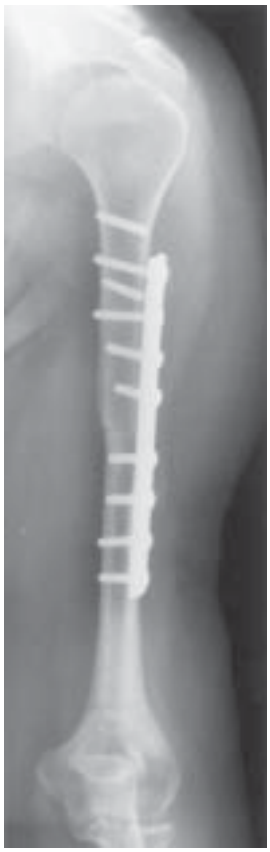

Figure 3C. An AP radiograph demonstrates proximal pin breakage 6 weeks after injury.

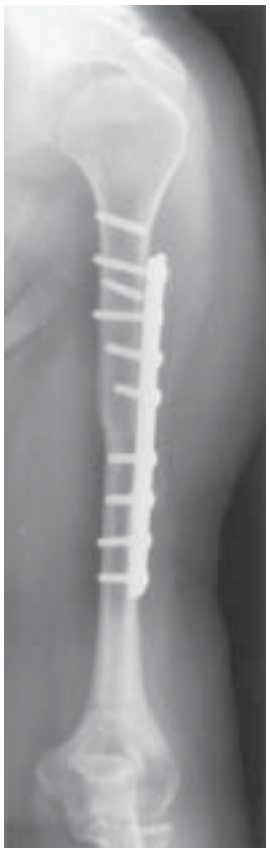

Figure 3D. AP radiograph taken 9 months after plating and grafting shows union.

Figures 3A-D. A thirty-two year-old female was in an MVA. The patient had the left arm out of window of the car and struck a bridge. She had a severe open wound and brachial artery disruption.

The soft tissue wounds all healed. There were no infections. All fifteen fractures healed. Eleven healed without further intervention other than replacement of a cracked fixator body in one patient. The average time to radiographic healing for these patients was 21 weeks (range 8-30 weeks) (Figures 2a-e).

Four patients required additional procedures prior to healing. Two patients experienced proximal pin breakage, one at 47 days and one at 44 days after placement of the fixator (Figures 3a-d). In both of these cases 4.5 millimeter and not six mm pins had been utilized. These are the only patients where the smaller pins had been used. Both were successfully treated, one with re-application of the fixator and bone grafting and one with open reduction and plate fixation and bone grafting. Two patients were judged to be healed but developed recurrent motion after fixator removal at 60 and 80 days respectively. One was treated with fixator re-application and one was plated and bone grafted. Both healed after these procedures.

All nerve palsies were caused by the original injury. None occurred from fixator application. Two radial nerve palsies were treated with grafting and had partial return of function. The brachial plexus palsy had not improved at the latest follow-up. Three radial, one medial, one combined radial and ulnar, and one combined radial and median palsy resolved without intervention.

The range of motion of the elbow was recorded both while in the fixator and after removal. While in the fixator, the average range of motion was from 20° of flexion to 104° flexion (Figure 4). After the fixator was removed the average range of motion was from 8° flexion to 127° flexion. The only patient who did not achieve a functional arc of elbow motion (95° flexion) had distal intraarticular extension of his humeral fracture.

Figure 4. A clinical photograph demonstrates the ranges of elbow flexion in the external fixator.

Shoulder range of motion was at or near the contralateral shoulder range of motion in fourteen cases. One patient required shoulder manipulation under anesthesia to achieve full motion. The patient with a brachial plexus palsy had a flail shoulder and restricted motion.

Twelve patients healed without angulatory deformity. Three patients had healed humeri with angulation measured greater than 10° (all apex anterior - 25°, 20° and 25°). All of these deformities were accepted at the time of fixator application, and none occurred during treatment.

Eight patients experienced pin tract infections. Three were treated with IV antibiotics during their initial hospitalization. The other five were treated as outpatients with oral antibiotics. All of these healed with local care and there were no cases of osteomyelitis secondary to pin infections.

Thirteen patients were contacted, and completed the questionnaire at an average of 63 months after injury (range 11- 89 months). Eight patients reported no pain in the arm, elbow, or shoulder. Three patients reported having mild pain in their arm associated with increased activity. One patient reported moderate pain in the shoulder, which had required manipulation to increase range of motion. Another patient described moderate pain in the elbow, which occurred with weather changes.

The patients were asked whether they had functional limitations secondary to their arm injury. The patient with the brachial plexus palsy reported that he had functional limitation secondary to weakness. One patient described mild triceps and deltoid fatigue with overhead activity but denied specific limitations. One patient reported limitation in function and decreased elbow range of motion (5-95°). The patient requiring shoulder ma-

nipulation had mild functional limits with overhead activity and heavy lifting (eleven month follow-up) but reported continued improvement. Nine patients reported no functional limitations.

One patient reported displeasure with the outcome secondary to elbow range of motion, and one because of a brachial plexus palsy (see above). The eleven other patients were pleased with their outcomes.

Nine patients returned to their former job at an average of nine months after injury (range five - fourteen months). Three patients were unable to return to their jobs. All were manual laborers. One reported continued progress toward employment at eleven months post injury and two were on disability. Two study subjects were in school at the time of injury. One was still in school at follow up and one was employed as a cosmetologist.

The two patients who could not be located were seen at 25 and 28 months after their injuries during their regular clinic appointments. One had returned to full employment and had no complaints. The second, incarcerated at the time of the last visit, had full range of motion and voiced no complaints.

DISCUSSION

Humeral shaft fractures associated with severe open wounds present complex management problems. As with other open fractures, the management of the soft tissue injury is of primary importance. This should include emergent surgery for irrigation and expert debridement. We feel that delayed closure is safest, although the five cases closed primarily did not develop infectious complications. Free tissue transfer was not required for soft tissue coverage, which was always obtained with the use of local tissues. The humerus has circumferential muscle cover and slight shortening to assist in closure was tolerated without obvious adverse functional outcome.

Nerve palsy frequently complicates open humeral shaft fractures. Nine of the fifteen arms (60%) had neurologic deficits. Two of the seven radial nerve injuries had complete anatomic disruption. Although this is lower than the 64%, anatomic radial disruption associated with open humeral fractures reported by Foster et al.[10], we agree with their recommendations that radial nerve injuries associated with open humeral fractures should be explored. These patients require surgery for irrigation and debridement. The additional time and effort for nerve exploration during wound debridement is warranted based on the significant chance of anatomic disruption.

At an average follow-up of 63 months, these patients reported only relatively mild residual problems with their arm. Although the amount of soft tissue damage was extensive, only three reported functional deficits and only four had pain in either the elbow, arm or shoulder. Most were able to return to work.

The optimal choice for skeletal stabilization for open humeral shaft fractures is not well defined in the literature. Union rates are high with functional bracing[19,20,23], but severe open fractures are less suited to this method. Zagorski et al.[23], reported on a subgroup of open fractures treated with bracing, but noted that severe soft tissue injury or bone loss were contraindications.

A plate can often be applied to an open humeral fracture through the wound with little additional stripping. Vander Griend et al.[22], reported on thirteen open fractures treated with plating, all of which united within one year. However, the severity of the grade of the open wounds was not described or classified. Two of those patients had superficial wound infections. Bell et al.[2], included 14 open fractures among a larger group treated with plating, but most were low grade wounds and the results in this group were not specified.

Brumback et al.[4] and Hall et al.[12] reported on eleven and twenty-eight open fractures treated with IM rodding, but most were low grade wounds secondary to hand guns, and the results in these subgroups were not specified. Stern et al.[21] reported that delayed and nonunion occurred in 33% of the open fractures in their humeral rodding study.

There is little data available on open fractures of the humerus treated by external fixation and the results have varied. Browner et al.[3], reported good results with the use of Hoffman external fixation in 20 complex humerus fractures. Included in this group were 13 Grade III open fractures and three closed fractures with vascular injuries. In this severe group of open fractures, seventeen united.

Smith and Cooney[18], reported that six of nine high energy humerus fractures treated with external fixation achieved a good to excellent result. However, they had significant complications which included delayed union in five, pin loosening in two and chronic osteomyelitis in one.

Humeral external fixation was well tolerated in our patients. When required upper extremity weightbearing was achieved with the fixator in place. Fixators were not removed early for pin tract problems or pain. Pin tracts caused no long-term complications. Shoulders and elbows were actively moved in the post operative period. We observed only modest reduction in range of motion while the fixator was in place, and little evidence of long term joint impairment.

All of our patients healed, but significant complications occurred in four of fifteen prior to healing. Al-

though this is a high incidence; this method was selected for only the most severe fractures, making it hard to make valid comparisons with other methods of skeletal stabilization. External fixator pins broke proximally, causing two of these complications. In both cases, the pins were small diameter (4.5 mm/3.5 mm tapered) usually recommended for forearm applications. We have not seen pins similar in size to those utilized in the lower extremity (6 mm/5 mm tapered) break, and recommend that this size pin be used for all adult humeral applications. This technical error compromised the overall results in this series.

In summary, monolateral external fixation is easily applied remote from the fracture site. It provides rigid fixation, for early joint mobilization and weight bearing, and there is good access to the wound. There were no wound infections. Patients tolerated the humeral fixator remarkably well. For these reasons we have continued to use external fixation for the most severe open fractures of the humerus.

REFERENCES

1. **Balfour, G.W.; Mooney, V.;** and **Ashby, M.E.:** Diaphyseal fractures of the humerus treated with a ready-made fracture brace. *J. Bone and Joint Surg.,* 64A:11-13, 1982.
2. **Bell, M.; Beauchamp, C.G.;** and **Kellam, J.K.:** The results of plating humeral shaft fractures in patients with multiple injuries. The Sunnybrook experience. *J. Bone and Joint Surg.,* 67B:293-296, 1985.
3. **Browner, B.D.; Edwards, C.C.;** and **Hritz, M.:** Hoffman external fixation treatment of complex fractures. *Orthop. Trans.,* 6:357-358, 1982.
4. **Brumback, R.J.; Bosse, M.J.;** and **Poka. A.:** Intramedullary stabilization of humeral shaft fractures in patients with multiple trauma. *J. Bone and Joint Surg.,* 68A:960-970, 1986.
5. **Choong, P.F.;** and **Griffiths, J.D.:** External fixation of complex open humeral fractures. A*ustralian and New Zealand Journal of Surgery,* 58:137-142, 1988.
6. **Ciernik, I.F.; Meier, L.;** and **Hollinger, A.:** Humeral mobility after treatment with hanging cast. *J. Trauma,* 31:230-233, 1991.
7. **Dabezies, E.J.; Banta, C.J.;** and **Murphy, C.P.:** Plate fixation of the humeral shaft for acute fractures, with and without radial nerve injuries. *J. Orthop. Trauma,* 6:10-13, 1992.
8. **Dameron, T.B. Jr.;** and **Grubb, S.A:** Humeral shaft fractures in adults. *Southern Medical Journal,* 74:1461-1467, 1981.
9. **DeBastiani, G.; Aldegheri, R.;** and **Renzi Brivio, L.:** The treatment of fractures with a dynamic axial fixator. *J. Bone and Joint Surg.,* 66B:538-545, 1984.
10. **Foste, R.J.; Swiontkowski, M.F.;** and **Back, A.W.:** Radial nerve palsy caused by open humeral shaft fractures. *J. Hand Surg.,* 18A, 1993.
11. **Gustilo, R.B.;** and **Anderson, J.T.:** Prevention of infection in the treatment of one-thousand and twenty-five open fractures of long bones. Retrospective and prospective analysis. *J. Bone and Joint Surg.,* 58A:453-458, 1976.
12. **Hall, R.F. Jr.;** and **Pankovich, A.M.:** Ender nailing of acute fractures of the humerus. A study of closed fixation by intramedullary nails without reaming. *J. Bone and Joint Surg.,* 69A:558-567, 1987.
13. **Hinsenkamp, M.; Burny, F.;** and **Andrianne, Y.:** External fixation of the fracture of the humerus: A review of 164 cases. *Orthopaedics,* 7:1309-1314, 1984.
14. **Kamhin, M.; Michaelson, M.;** and **Waisbrod, H.:** The use of external skeletal fixation in the treatment of fractures of the humeral shaft. *Injury,* 9:245-248, 1978.
15. **Marsh, J.L.; Nepola, J.V.;** and **Wuest, T.K.:** Unilateral external fixation until healing with the dynamic axial fixator for severe open tibial fractures. *Journal of Orthop. Trauma,* 5:341-348, 1991.
16. **Müller, M.E.; Nazarian, S.;** and **Koch, P.:** The Comprehensive Classification of Fractures of Long Bones. Springer-Verlag, Berlin Heidelberg, 1990.
17. **Rüedi, T.; Moshfegh, A.;** and **Pfeiffer, K.M.:** Fresh fractures of the shaft of the humerus —conservative or operative treatment. R*econstructive Surg. & Traumatology,* 14:65-74, 1974.
18. **Smith, D.K.;** and **Cooney, W.P.:** External fixation of high-energy upper extremity injuries. *J. Orthop. Trauma,* 4:7-18, 1990.
19. **Sarmiento, A.; Kinman, P.B.;** and **Galvin, E.G.:** Functional bracing of fractures of the shaft of the humerus. *J. Bone and Joint Surg.,* 59A:596-601, 1977.
20. **Sarmiento, A.; Horowitch, A.;** and **Aboulafia, A.:** Functional bracing for comminuted extra-articular fractures of the distal third of the humerus. *J. Bone and Joint Surg.,* 72B:283-287, 1990.
21. **Stern, P.J.; Mattingly, D.A.;** and **Pomeroy, D.L.:** Intramedullary fixation of humeral shaft fractures. *J. Bone and Joint Surg.,* 66A:639-646, 1984.
22. **Vander Griend, R.; Tomasin, J.;** and **Ward, E.F.:** Open reduction and internal fixation of humeral shaft fractures. Results using AO plating techniques. *J. Bone and Joint Surg.,* 68A:430-433, 1986.
23. **Zagorski, J.B.; Latta, L.L.;** and **Zych, G.A.:** Diaphyseal fractures of the humerus. Treatment with prefabricated braces. *J. Bone and Joint Surg.,* 70A:607-610, 1988.

OSTEOPOROSIS: THE INCREASING ROLE OF THE ORTHOPAEDIST

Matthew B. Dobbs, M.D.*
Joseph Buckwalter, M.D.*
Charles Saltzman, M.D.*

INTRODUCTION

Osteoporosis contributes to many of the fractures of the spine, proximal femur, distal radius as well as some diaphyseal fractures seen by orthopaedic surgeons. The number of patients with fractures associated with osteoporosis will increase dramatically in the next decade. Patients with decreased bone density with one fracture are at increased risk for another fracture and thus it is critical that these patients be identified and treated for their decreased bone density. For these reasons, orthopaedic surgeons will have an increasing role in the diagnosis of osteoporosis, prevention of fractures in patients with osteoporosis and in at least some instances treatment of osteoporosis. This article will address the current therapeutic options available to the orthopaedist for the prevention and treatment of osteoporosis. The field is progressing so rapidly that the physician now has a vast array of efficacious therapies.

Osteoporosis, a disorder characterized by low bone mass, and associated with pathologic fractures is the most common metabolic bone diseases in the developed countries. It effects more than 25 million Americans and leads to more than 1.5 million fractures each year[6]. Osteoporotic fractures may affect any part of the skeleton except the skull. Most commonly fractures occur in the distal forearm, thoracic and lumbar vertebrae, and proximal femur. The incidence of osteoporotic fractures increases with age, is higher in whites than in blacks, and higher in women than in men[18]. It has been estimated that after menopause a woman's lifetime risk of sustaining an osteoporotic fracture is one in two[18]. One in every three men over the age of 75 will be affected by the disease. A single hip fracture is estimated to cost $30,000, and the overall cost of acute and long-term care associated with osteoporosis exceeds 10 billion dollars annually. Because of the increased life expectancy of the aging population, the economic burden of osteoporosis is projected to reach $240 billion by the year 2040[6].

CLASSIFICATION

Two categories of osteoporosis have been identified: primary and secondary. Primary osteoporosis is the most common form of the disease and includes postmenopausal osteoporosis (type I), and senile osteoporosis (type II). Secondary osteoporosis is characterized as having a clearly definable etiologic mechanism. Type I is associated with a loss of estrogen and androgen resulting in increased bone turnover, with bone resorption exceeding bone formation, and a predominant loss of trabecular bone compared with cortical bone. Type II, which represents the gradual age-related bone loss found in both sexes caused by systemic senescence, is induced by the loss of stem-cell precursors, with a predominant loss of cortical bone[28].

After attaining peak bone mass at age 30, men and women lose bone at a rate of approximately 0.3% and 0.5% per year, respectively. Bone loss in women is accelerated further by a deficiency in estrogen at a rate of 2% year during menopause and continues for 6 years thereafter. Because age-related bone loss is a universal phenomenon in humans, any circumstance that limits an individual's ability to maximize peak adult bone mass increases the likelihood of developing osteoporosis later in life. In addition, since there are no safe and effective ways to rebuild the osteoporotic skeleton, prevention emerges as the crucial strategy[29]. Consequently, a knowledge of preventive approaches is essential, including the efficacy and safety of estrogen and progestin therapy, intake of calcium and vitamin D, exercise, bisphosphonates. Prevention also requires an understanding of the indications for estimating bone density and the methods of obtaining this data.

Some of the most important risk factors for osteoporosis are advanced age, white or Asian race, low body mass index, and family incidence of the disease. Other risks include low calcium intake, premature ovarian failure, smoking, alcohol use, and low level of physical activity (see Table 1).

*Address reprints: Department of Orthopaedic Surgery, The University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, Iowa 52242

Table 1
Osteoporosis risk factors

Age-Related	
	Each decade beyond the fourth decade is 1.5-fold risk
	Reduction in absorption of calcium
	Rise in parathyroid hormone levels
	Decline in calcitonin
Genetic	
	White, Asian, Latino, and black (in order of risk potential)
	Women more than men
	Familial prevalence
	High concordance in monozygotic twins
Nutritional	
	Low calcium intake
	High alcohol
	High caffeine
	High sodium
	High animal protein
Lifestyle	
	Cigarette use
	Low physical activity
Endocrine	
	Menopausal age
	Obesity
	Exercise-induced amenorrhea

Table 2
Drugs associated with osteoporotic syndromes

Thyroid replacement therapy
Glucocorticoid drugs
Anticoagulants
Chronic lithium therapy
Chemotherapy (breast cancer or lymphoma)
Gonadotropin-releasing hormone
Anticonvulsants
Chronic phosphate binding antacid use
Extended tetracycline use
Diuretics producing calciuria
Phenothiazine derivatives
Cyclosporin A

Table 3
Laboratory Tests

Routine	
	Complete blood cell count
	Sedimentation rate
	Electrolytes
	Creatinine
	Blood urea nitrogen
	Calcium
	Phosphorus
	Protein
	Albumin
	Alkaline phosphatase
	Liver enzymes
	24-hour urine calcium
	Serum protein electrophoresis

DIAGNOSIS

The insidious removal of mineral from bone is asymptomatic until the bone fails under physiologic stress. Any patient over the age of 50 who presents to an orthopaedist with a hip, distal radius, or vertebral compression fracture should be evaluated for the presence of osteoporosis. The same diagnostic approach should be taken to patients suspected of having osteoporosis whether or not they have sustained a fracture. A thorough medical evaluation should seek potential causes of secondary osteoporosis, such as hyperthyroidism, Cushing's disease, or the use of drugs known to be associated with osteoporosis (Table 2). Although postmenopausal and senile osteoporosis are the most prevalent forms of the disease, it must be remembered that as many as 20% of women who otherwise appear to have postmenopausal osteoporosis can be shown to have additional etiologic factors above and beyond their age, gender, and ethnic background.

Therefore, it is appropriate to perform simple screening studies looking for secondary causes in each patient (Table 3). A simple biochemical profile will provide information about renal and hepatic function, primary hyperparathyroidism, and possible malnutrition. Hematologic profile might also provide clues for the presence of myeloma or malnutrition. Thyroid function should also be assessed. Serum protein electrophoresis should be performed on all potentially osteoporotic patients at initial evaluation. A normal pattern excludes the presence of multiple myeloma in 90% of patients.

Metabolic bone markers, such as urinary hydroxyproline, pyridinoline, deoxypyridinoline, and N-telopeptides (Table 4), are useful for determining which patients have high bone resorption. They also provide a convenient index of whether a chosen therapy is successfully curtailing bone loss; however, they are not sensitive for diagnosing osteoporosis or identifying associated fracture risk[6]. In addition, there are markers of new bone formation, such as osteocalcin and bone-specific alkaline phosphatase, that may be increased in patients with high bone turnover but are unreliable for

Table 4
Biochemical Markers of Bone Formation and Resorption

Bone Formation
Osteocalcin
Bone-specific alkaline phosphatase
Procollagen extension peptides
Bone Resorption
Tartrate-resistant acid phosphatase
Urinary calcium
Urinary hydroxyproline
Urinary hdroxyproline/creatinine ratio
Urinary pyridinoline/deoxypyridinoline
Urinary N-telopeptide

detecting osteoporosis. Large studies in older postmenopausal women show an association between elevated levels of free urinary deoxy-pyridinoline, low bone mass, and increased fracture risk, independent of low bone mineral density (BMD)[37,10]. One study showed that the combination of these markers and measurement of BMD could identify women who had a four-times-higher risk for hip fracture than women who had only a single risk factor[10].

RADIOGRAPHY

The most characteristic feature of osteoporosis is decreased radiodensity. However, conventional radiographs are neither sensitive nor accurate for the diagnosis of early bone loss. It has been reported, for example, that a reduction in bone-calcium content must exceed 30 percent to be observed with certainty on conventional radiographs. In addition, factors such as differences in film development, patient weight, and the amount of x-ray exposure can lead to variability in radiodensity and affect the accuracy of conventional radiographs.

BONE DENSITOMETRY

The most effective way of screening for osteoporosis and then following the results of treatment is by the measurement of bone density. Current methods include radiographic absorptiometry, single-energy x-ray absorptiometry, dual-energy x-ray absorptiometry, quantitive computed tomography, and quantitive ultrasound. Of these, dual-energy x-ray absorptiometry, is the most widely used modality for the clinical measurement of bone-mineral content. This technique is rapid, taking only 3 to 7 minutes, and delivers a radiation dose that is so low as to be equivalent to approximately 5% of the radiation dose of one chest radiograph. DEXA scanners simultaneously use a high- and a low-energy x-ray beam to measure BMD. The difference in soft-tissue and bone penetration of these two beams is used to calculate BMD. The relationship of decreased BMD seen on DEXA and increased fracture risk is exponential-for each standard deviation decrease of BMD, fracture risk increases twofold[32].

The World Health Organization defines osteoporosis as BMD or bone mineral content of more than 2.5 standard deviations (SD) below the young adult mean normal value[1]. Patients with a BMD of 1 to 2.5 SD below the young adult mean value are defined as osteopenic. BMD is important to measure because it correlates so strongly with the risk of osteoporotic fractures. For every SD of decrease in BMD, the relative risk of osteoporotic fracture in the elderly population increases by a factor of 1.5 to 1.8[32]. Therefore, a relatively small increase in BMD can significantly reduce fracture risk.

There are numerous potential indications for bone densitometry. However, there are insufficient data to justify routine screening with use of this technique. Recently, the Health Care Financing Administration defined five diagnostic categories that it considers to be indications for the use of bone densitometry.[12] These categories are listed in Table 5.

Perhaps the major value of bone densitometry in current orthopaedic practice is the identification of patients with osteoporosis who are at increased risk for fracture. Fracture of the proximal aspect of the femur is the most serious consequence of osteoporosis. Approximately 250,000 such fractures occur in the United States each year, resulting in annual expenditure exceeding 8 billion dollars. It has been estimated that after menopause a woman's lifetime risk of sustaining an osteoporotic fracture is one in three. There is an associated 20% mortality following an osteoporotic hip fracture. Perhaps more importantly, following such fractures less than one-third of the patients are restored to their prefracture functional state within 12 months of the fracture. Most patients require some form of ambulatory support and many require institutional care.

PREVENTION

Prevention of osteoporosis is of primary importance, since there are no safe and effective methods for restoring healthy bone tissue and normal bone architecture once they have been lost. Bone loss is an asymptomatic process and in some ways can be considered clinically to be equivalent to hypertension. In each case patients present to the health care system when a complication arises, either fracture, in the case of osteoporosis, or stroke in hypertension. The key in each case is

Table 5
Current recommended indications for DEXA

Group	*Comments*
Women who are estrogen-deficient as a result of premature ovarian failure or menopause	Many of these women are reluctant to take ERT because of a slightly increased risk of breast cancer. They will be more likely to take estrogen if there is objective evidence of pending or existing bone loss. DEXA scanning will also identify the significant subset of women who are not at risk for osteoporosis and do not require ERT for this indication.
Patients with established osteopenia or compression fractures	Patients with compression fractures are at extremely high risk for future osteoporotic fractures; most require urgent therapy. DEXA will establish a baseline for BMD that can be used to measure the effectiveness of future therapy. Patients with established osteopenia require follow-up DEXA within 6-12 months, depending on their risk factors for fracture.
Patients taking long-term corticosteroid therapy	Most of these patients are at risk for rapid and significant bone loss. Patients need to be studied at initiation of therapy, with follow-up in 6-12 months.
Patients with asymptomatic primary hyperparathyroidism or hyperthyroidism	Unlike type II osteoporosis, primary hyperparathyroidism usually leads to thinning of cortical bone.
Patients on drug therapy for treatment of osteoporosis	This allows monitoring of the effectiveness of various treatment modalities.

early identification of the patients at greatest risk, targeting those for intervention; the orthopaedist should be a key player in this process. For osteoporosis, these clues are divided into risk factors and estimates of skeletal status (Table 1).

In general, for each patient, the more risk factors present, and the longer the duration of their presence, the greater the risk of future problems[29]. Physicians can use the presence of these factors in two ways. First, they can be used to sensitize the patient, and physician, to the likelihood of osteoporosis. Second, those risk factors that are amenable to elimination or alteration should be discussed with the patient. Practically, menopause is the usual time when evaluation of the patient for osteoporosis begins, although nutritional and lifestyle habits should be changed as early in life as possible. Because most orthopaedists are exposed to a cross section of patients with respect to age, playing a proactive role in osteoporosis prevention is possible.

ADOLESCENCE AND YOUNG ADULTHOOD

Adequate calcium nutrition during growth and maturation are key determinants of adult bone mass. In addition, weight-bearing exercise, such as walking or jogging for 3 to 4 hours per week is beneficial. Exercise is highly effective in favorably affecting the skeleton and preventing falls[36,23]. The mechanism by which exercise signals the cell is still to be determined. Low levels of exercise are critical for maintenance of bone mass. Higher levels will lead to modeling of the bone to adapt to its new environment, and even higher levels will lead to failure.

The optimal type and duration of exercise have not been established, although several investigators have demonstrated that minimal amount of exercise of appropriate type may be sufficient to stimulate the osteoblasts for 24 to 48 hours. Bone mass is very closely correlated with the muscle mass acting on that bone. Thus, programs that are aimed at developing increased muscle strength will be translated into increased bone mass in the affected limb. The strength of a bone has been demonstrated to be related to the mass of the bone and the distribution of the mass. The latter is affected by exercise.

It is recommended that individuals adopt all three components of an ideal exercise program-impact exercises, strengthening exercises, and balance training. The impact exercises are utilized to directly stimulate

osteoblast formation and to ward off resorption. Exercises that meet these criteria include jogging, brisk walking, and stair climbing. Strengthening exercises will affect the bones underlying the exercised muscle. It is recommended that patients utilize light weights in a comprehensive program that strengthens the major axial and appendicular muscle groups. All exercises should be developed in terms of the potential of the individual and should progress from minimal loads to greater loads, giving sufficient time for the patient to accommodate to the program. Exercise to the point of caloric drain or development of amenorrhea is associated with stress fractures and osteoporosis.

It is also important to recognize risks in the young patient such as anorexia, bulimia, excessive athleticism, and prolactinoma which all can be associated with estrogen deficiency and resultant loss in skeletal mass. Certain medications can also impair skeletal metabolism such as glucocorticoids and antiepileptic drugs.

PERIMENOPAUSE AND POSTMENOPAUSE

At the time of menopause, each patient should be evaluated for the presence of risk factors, ascertained as part of a complete medical history. It is then important to assist in the modification of the patient's behavior to reduce the impact of the factors that are amenable to intervention. A strong family history of osteoporosis or a medical and social history that suggests an increased risk of osteoporosis should lead to the performance of a bone-density examination. If low bone mass is detected, a high calcium intake alone will not significantly mitigate the accelerated spinal loss of the postmenopausal period. Estrogen is the therapy of choice and will be discussed under the treatment section.

Changing the pattern of physical activity may be difficult, especially for patients who are less positively motivated. This is especially true when discussing prevention with patients, who are, by definition, asymptomatic. A number of studies have evaluated exercise in the prevention of bone loss after menopause[2]. A moderate level of exercise by an individual who receives an appropriate diet, with adequate calcium and vitamin D, can diminish the rate of bone loss. Load-bearing exercise is most effective in preserving or increasing skeletal mass. To be effective in altering bone density, the exercise must directly strain the skeletal sites. In the absence of proven benefit for any exercise for prevention of osteoporosis, any weight-bearing activity suffices[7].

TREATMENT

The treatment of patients who have sustained osteoporotic fractures includes maintaining their quality of life, encouraging mobilization, controlling pain, and promoting social interaction. Prolonged bed rest, poor nutrition, and social isolation are avoidable pitfalls.

For all patients with low bone mass or an osteoporotic fracture, a complete history and physical examination are necessary, and a thorough laboratory workup should be ordered to exclude common medical disorders known to cause bone loss. Treatment mainstays include adequate calcium intake, weight-bearing exercise, and the use of appropriate medications, which will be discussed below (Table 6).

CALCIUM

Adequate calcium is required during growth because the body does not make calcium. It continues to be an essential nutrient throughout life because the body loses calcium every day through shedding of skin and nails, as well as in sweat, urine, and feces. There is evidence of an increasing prevalence of calcium and/or vitamin D deficiency in the general population[13,31]. Sixty-five percent of women past the age of menopause have varying degrees of lactose intolerance and by preference avoid lactose-containing dairy products. Consequently, whether by choice, habit, or design most Americans have calcium intakes below the recommenced level, particularly in elder years. Therefore, addition of calcium-containing supplements is required if age-corrected physiologic calcium intake is to be achieved. The effect of calcium supplementation on bone mass and vertebral fracture rate in established osteoporotic syndromes is not well studied. Studies that are available suggest that calcium supplementation in perimenopausal females does decrease the rate of bone loss when administered in doses of 1,000-1,500 mg per day, especially in individuals with histories of marginally low calcium intakes[9]. A combination of calcium supplements and exercise has also proven effective in stabilizing skeletal bone loss rates in postmenopausal female populations. The current recommended dietary allowance in the United States is 1,200 mg/day in adolescence through age 24 and 800 mg/day for older adults. It is recommended that men and postmenopausal women ingest 1,000 mg/day and that postmenopausal women not receiving estrogen ingest 1,500 mg/day. When individuals taking calcium are compared with a placebo historical group who are not taking calcium, there is clear evidence that calcium supplementation is associated with a lower rate of bone loss[25]. However, high calcium intake alone will not significantly mitigate the accelerated spinal loss of the postmenopausal period.

Table 6
Options for prevention and treatment of osteoporosis

Therapy	*Appropriate population*	*Comments*
Exercise	All persons	Increases bone density; improves strength and coordination; reduces risk of falls
Calcium, 1,000-1,500 mg/day	Persons older than 4 years of age	In childhood, increases peak bone mass; in adulthood, prevents bone loss
Vitamin D, 400-800 IU/day	Persons older than 65 years of age	Dose of 800 IU/day may be preferred
Oral conjugated estrogen, 0.625 mg/day, or transdermal estradiol, 0.05 mg/day	All estrogen-deficient women, except those at high risk for an estrogen-sensitive tumor	Only agents for osteoporosis shown to reduce mortality; given with progesterone in women with an intact uterus
Alendronate sodium (Fosamax)	Postmenopausal women not taking estrogen whose bone-mineral density is 2.5 SD below mean peak levels POTENTIAL POPULATIONS Postmenopausal women not taking estrogen who: —Are less than 60 years of age and have a bone-mineral density of 1 to 2.5 SD below mean peak levels —Have had an osteoporotic fracture	Studies of use in potential populations have not been reported
Calcitonin, nasal, 200 IU/day	Same as for alendronate	Shown to have analgesic qualities; studies of use in potential populations have not been reported
Slow-release sodium fluoride, 25 mg bid for 12 mo, in 14-mo cycles	Postmenopausal women with an osteoporotic vertebral fracture	Not yet approved by FDA; only agent that stimulates bone formation; has neutral effect on appendicular bone mass and nonvertebral fractures

Calcium carbonate contains 40% elemental calcium and requires acidity to be solubilized. Therefore, it should be taken with foods. Achlorhydric individuals will not absorb calcium carbonate. The side effects of calcium carbonate intake include a sensation of gas and constipation.

Calcium citrate is 21% elemental calcium and will dissolve even in the absence of acidity. It does not form gas and tends to ameliorate constipation. Calcium citrate is chosen for those individuals who are achlorhydric, and it decreases the risk of kidney stones[15].

VITAMIN D

Vitamin D, a secosteroid that increases the functional absorption of calcium, usually is given in conjunction with calcium therapy. Most multivitamin supplements contain 400 IU of vitamin D. More than 800 IU of vitamin D per day is not recommended because of its potential toxic side effects. While vitamin D supplementation might offer some benefit, particularly among those with marginal or deficient intake or production of vitamin D, it is generally believed that it does not offset the rapid bone loss associated with estrogen deficiency due to menopause[35]. In those patients with subclinical vitamin-D deficiency, low doses of vitamin D (800IU

daily) are effective in maintaining bone mass and reducing the rate of fractures by 30%[3]. Consequently, it was the recommendation of the National Institutes of Health consensus conference (NIH) that individuals should take between 400 and 800 units of vitamin D daily, particularly if they have poor dietary intake or increased risk factors for osteoporosis. At this dosage there is no essentially no major risk. However, individuals who take 50,000 units of vitamin D per week have an increase risk of the development of kidney stones, nausea, and other manifestations of hypercalcemia.

ESTROGENS AND HORMONE REPLACEMENT

The most potent intervention for preventing osteoporosis in women with low levels of estrogen or men with low levels of androgen is sex hormone replacement therapy. Loss of estrogen at any age results in increased bone remodeling, which is associated with loss of bone mass. Estrogen replacement therapy returns bone remodeling to the level seen in premenopausal women and therefore reduces fracture risk. Estrogen is an "antiresorptive" agent in that it inhibits bone resorption by decreasing the frequency of activation of the bone remodeling cycle. Estrogen would be expected to be most efficient if bone remodeling or bone turnover was increased. This is why it is so effective in the early stages of menopause. If initiated at the time of menopause, estrogen replacement may prevent many cases of osteoporosis and reduce the incidence of fractures of the hip by 50%. Estrogen also acts to reduce the risk of coronary artery disease; maintain sexual characteristics; and minimize hot flushes, dysuria, and dyspareunia. Some studies have shown that estrogen may protect against osteoarthritis of the hip and Alzheimer's disease[20,34].

A definitive role for estrogen in established osteoporosis is much less well established. There is little evidence that estrogen reduces the rate of occurrence of new vertebral fractures in patients with established osteoporosis. Short-term complications of estrogen therapy in women with established osteoporosis include breast tenderness and vaginal bleeding[24]. If estrogens are given without progesterone there is increased risk of endometrial cancer. The relationship between estrogen therapy and breast cancer is not well established, but most studies suggest that there is little increased risk of breast cancer during the first 10-15 years of therapy[33]. Estrogen replacement therapy, if recommended by an orthopaedist, should be used in conjunction with the consultation of an obstetrician-gynecologist or endocrinologist.

BISPHOSPHONATES

Etidronate disodium (Didronel) and alendronated sodium (Fosamax) are analogues of pyrophosphate that are absorbed onto the hydroxyapatite of bone, thereby inhibiting bone resorption. Bisphosphonates have a long duration of skeletal retention, which raises concern about potential long-term side effects. In phase three clinical trials, alendronate was given daily for up to three years with no toxicity; it produced continued increases in bone density and resulted in a significant reduction in the rate of fractures[16]. Continuous dosing eventually results in impaired bone mineralization. Intermittent use of bisphosphonates prevents bone resorption and permits synthesis of new bone.

Cyclical treatment with etidronate has been shown to significantly increase spinal bone-mineral density and decrease the rate of vertebral fractures over the short term in severely osteoporotic older women. At high doses, however, impaired mineralization of bone occurs, potentially leading to osteomalacia. Thus, etidronate is used only in intermittent regimens for women with severe osteoporosis who are unable or unwilling to take estrogen. The use of this agent has been largely replaced by alendronate.

Alendronate is a selective inhibitor of bone resorption that is 400 times more potent than etidronate, without being detrimental to bone mineralization. There have been two fairly recent prospective, randomized, double-blind, placebo-controlled trials or oral alendronate in post-menopausal women with established osteoporosis[5,16]. Chestnut found that 5 to 10 mg daily of oral alendronate increased bone-mineral density in the spine and hip by 4% to 7% after 2 years. Liberman confirmed these results in a similar study, which also showed significant reduction in vertebral fractures. The 10 mg daily dose was considered optimal and was well tolerated; abdominal symptoms were the primary adverse effect.

An important aspect of the Liberman study is that the subjects were asymptomatic postmenopausal women with osteoporosis. Most previous trials have been limited to patients with symptomatic preexisting vertebral fractures. Therefore, this represents an advance in primary prevention of osteoporotic fractures.

Alendronate has been approved by the FDA for treatment of osteoporosis in postmenopausal women who are not receiving estrogen replacement therapy. Of postmenopausal women who do not take estrogen, three patient populations are reasonable candidates for therapy with alendronate:

— Women with osteoporosis (bone-mineral density of at least 2.5 SD below mean peak levels, as measured in young, healthy women)

— Women less than 60 years of age who have osteopenia (bone-mineral density of 1 to 2.5 SD below mean peak levels).
— Women who have already sustained an osteoporotic fracture.

It is uncertain how long alendronate should be continued. There is now evidence that bone mass continues to improve for at least 4 years. Cessation of alendronate does not lead to the rapid bone loss that occurs after cessation of estrogen. Besides the complications of dyspepsia and esophagitis, alendronate has been associated with occasional episodes of diarrhea and bone pain, the latter particularly in those individuals who did not receive calcium supplementation before treatment. Therefore, it is recommended that calcium be given in addition to alendronate.

Alendronate does not provide the analgesic benefit of calcitonin and does not offer the nonskeletal benefits that are associated with estrogen. There is some suggestion, currently being tested in clinical trials, that alendronate and estrogen may be synergistic, as they have different sites of action[11]. If a patient has not responded to one of the agents, the addition of the other may result in a positive bone-accretion stage.

CALCITONIN

Calcitonin is a non-sex, non-steroid hormone that specifically binds to osteoclasts and decreases their activity. Since the introduction of nasal formulations of calcitonin, interest in this agent has been renewed. Early studies of parenteral calcitonin therapy showed bone effects similar to those with estrogen replacement therapy; however, there have been many reported complications with use of parenteral forms[17].

There is one prospective study showing that nasal calcitonin, 50 IU daily for 5 consecutive days a week, significantly prevented postmenopausal bone loss over 5 years. In addition, small increases in bone-mineral density also were noted with the 200 IU dose[26]. Two other prospective studies showed that in women with established osteoporosis nasal calcitonin reduced the incidence of recurrent vertebral fracture by 60% compared with calcium alone[27,22].

The FDA has approved nasal calcitonin for treatment of osteoporosis in postmenopausal women not receiving estrogen replacement therapy. The recommended dose is 200 IU sprayed into alternating nostrils once a day. The most common side effects include facial flushing, gastrointestinal upset, and rash. Unlike the other osteoporotic agents, calcitonin appears to have an analgesic effect. Because of this analgesic effect, calcitonin is frequently used in patients with symptomatic acute vertebral fractures.

SODIUM FLUORIDE

The only therapeutic agent for osteoporosis that stimulates osteoblastic activity and bone formation is sodium fluoride. An early study involving a high-dose, immediate-release formulation[30] showed a marked increase in vertebral bone-mineral density but no decrease in spinal fracture rate. The rate of nonvertebral fractures actually increased, presumably owing to abnormal bone formation caused by excessive exposure to fluoride.

Slow-release formulations are now available and are able to maintain serum fluoride concentrations within the narrow therapeutic window. Pak recently published a prospective, randomized, controlled trial of cyclic slow-release sodium fluoride in post-menopausal women with vertebral fractures. Spinal bone-mineral density increased 4% to 5% a year, and the rate of new vertebral fractures in previously unaffected vertebrae was markedly decreased, particularly in patients with mild to moderate disease. The new fracture rate in patients with severe disease was not significantly reduced, and the rate of fractures in previously fractured vertebrae was unaffected by therapy. Therefore, the least benefit was seen in patients with the most severe disease (the opposite of that seen with bisphosphonates). Appendicular bone-mineral density and non-vertebral fracture rates were not significantly affected. Thus, slow-release sodium fluoride seems best used in patients with mild to moderate disease that have sustained a vertebral fracture.

In addition, the long-term safety of fluoride therapy remains to be established, but few side effects have been published (mainly gastrointestinal upset). This drug is currently awaiting approval by the FDA and thus is not available

SUMMARY

Osteoporosis is an ever-increasing problem as our population ages. However, it is also to a large extent a preventable problem. The orthopaedist now has the ability to determine bone mass, the rate of turnover, and the fracture risk. Skeletal bone mass can be evaluated with DXA; the rate of bone resorption can be determined by assessment of collagen-degradation urinary products; and the weight status, fracture history, and history of smoking can be used to predict the fracture risk in individual patients. The orthopaedic physician also needs to take an active role in advising their younger patients about achieving peak bone mass. All individuals should follow a program that includes adequate calcium replacement, 400 to 800 units of vitamin D, appropriate exercise, avoidance of significant weight loss, and cessation of smoking.

At menopause, women should evaluate their risk factors and consider the use of estrogen not only for its skeletal benefits but also for its nonosseous effects. In patients with contraindications or an aversion to hormone therapy, bone densitometry should be performed to determine risks before expensive nonhormonal treatment is initiated. Additional studies such as measurement of collagen degradation products will help establish whether the patient's resorptive rate is high or stable. If the bone mass is 2.5 SDs below normal peak or if there is an increase in resorption, use of either estrogen, bisphosphontes, or calcitonin may be appropriate. If there is evidence of low-turnover osteoporosis with decreased osteoblast formation, sodium fluoride should be considered.

Two thirds of the cost of osteoporosis in the United States is due to hip fractures. The orthopaedist is the primary physician who comes in contact with these fracture patients. It is therefore his or her responsibility to become knowledgeable about the treatment and prevention of osteoporosis. The bisphosphonates, hormones, and calcitonin provide predictable restoration of bone mass and significantly decrease the rate of osteoporotic fractures.

BIBLIOGRAPHY

1. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis-report of a WHO study group. *World Health Organ Tech Rep Ser.,* 843:1-129, 1994.
2. **Ayalon, J.; Simkin, A.; Leichter, I.;** and **Raifmann, S.:** Dynamic bone loading exercises for postmenopausal women: Effect on the density of the distal radius. *Arch. Phys. Med. Rehabil.,* 68:280-283, 1987.
3. **Chapuy, M.C.;** and **Arlot, M.E.:** Vitamin D and calcium to prevent hip fractures in elderly women. *N. Engl. J. Med.,* 327:1637-1642, 1992.
4. **Chestnut, C.H.:** Noninvasive methods for bone mass measurement. In: *Alvioli, L.V.,* ed. The Osteoporotic Syndrome: Detection, Prevention, and Treatment. 3rd ed. New York: Wiley-Liss Inc; 1993: 77-87.
5. **Chestnut, C.H.; McClung, M.R.;** and **Ensrud, K.E.:** Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am. J. Med.,* 99:144-152, 1995.
6. **Cummings, S.R.;** and **Rubin, S.M.:** The future of hip fractures in the United States: Numbers, costs, and effects of postmenopausal estrogen. *Clin. Orthop.,* 252:163-166, 1990.
7. **Dalsky, G.P.; Stocke, K.S.;** and **Ehsani, A.A.:** Weight-bearing exercise training and lumbar bone mineral content in postmenopausal women. *Ann. Intern. Med.,* 108:824-828, 1988.
8. **Dawson-Hughes, B.:** Calcium supplementation and bone loss: A review of controlled clinical trials.
9. **Dawson-Hughes, B.; Dallal, G.E.; Krall, E.A.; Sadowski, L.; Sahyoun, N.;** and **Tannenbau, S.:** Controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N. Engl J. Med.,* 323:878-883, 1990.
10. **Garnero, P.; Hausherr, E.;** and **Chapuy, M.C.:** Markers of bone resorption predict hip fracture in elderly women: the EPIDOS Prospective Study. *J. Bone and Min. Res.,* 11:1531-1538, 1996.
11. **Greenspan, S.; Bankhurst, A.;** and **Bell, N.:** Effects of alendronate and estrogen, alone or in combination, on bone mass and turnover in postmenopausal osteoporosis. *Bone,* 23:S174, 1998.
12. Health Care Financing Administration: Medicare Program: Medicare coverage of and payment for bone mass measurements (42 CFR Part 410). *Fed. Reg.,* 63:34320-34328, 1998.
13. **Lane, J.M.; Riley, E.H.;** and **Wirganowicz, P.Z.:** Osteoporosis: Diagnosis and treatment. *J. Bone and Joint Surg.,* 78-A:618-632, 1996.
14. **Lane, J.M.:** Osteoporosis: Medical prevention and treatment. *Spine,* 22:32S-37S, 1997.
15. **Lane, J.M.;** and **Nydick, M.:** Osteoporosis: Current Modes of Prevention and Treatment. *J. Am. Acad. Orthop. Surg.,* 7:19-31, 1999.
16. **Liberman, U.A.;** and **Weiss, S.R.:** Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N. Engl. J. Med.,* 533:1437-1443, 1995.
17. **MacIntyre, I.; Stevenson, J.C.;** and **Whitehead, M.I.:** Calcitonin for prevention of postmenopausal bone loss. *Lancet,* 1:900-902, 1988.
18. **Melton, L.J. III; Chrischilles, E.A.;** and **Cooper, C.:** Perspective: how many women have osteoporosis? *J. Bone and Min. Res.,* 7:1005-1010, 1992.
19. **Mirsky, E.C.;** and **Einhorn, T.A.:** Bone Densitometry in Orthopaedic Practice. *J. Bone and Joint Surg.,* 80-A:1687-1698, 1999.
20. **Nevitt, M.C.;** and **Cummings, S.R.:** Association of estrogen replacement therapy with the risk of osteoarthritis of the hip in elderly white women. *Arch. Intern. Med.,* 156:2073-2080, 1966.
21. NIH Consensus Development Panel on Optimal Calcium Intake: Optimal calcium intake. *JAMA,* 272:1942-1948, 1944.

22. **Overgaard, K.; Hansen, M.A.;** and **Jensen, S.B.:** Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose-response study. *BMJ,* 305:556-561, 1992.
23. **Paganini-Hill, A.; Chao, A.; Ross, R.K.;** and **Henderson, B.E.:** Exercise and other factors in the prevention of hip fracture: The Leisure World study. *Epidemiology,* 2:16-25, 1991.
24. **Prince, R.L.; Smith, M.; Dick, I.M.; Price, R.I.; Webb, P.G.; Henderson, N.K.;** and **Harris, M.M.:** Prevention of postmenopausal osteoporosis. Comparative study of exercise, calcium supplementation, and hormone replacement therapy. *N. Engl. H. Med.,* 325:1189-1195, 1991.
25. **Recker, R.R.; Hinders, S.;** and **Davies, K.M.:** Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J. Bone and Min. Res.,* 11:1961-1966, 1966.
26. **Reginster, J.Y.; Deroisy, R.;** and **Lecart, M.P.:** A double-blind, placebo-controlled, dose-finding trial of intermittent nasal salmon calcitonin for prevention of post-menopausal lumbar spine bone loss. *Am. J. Med.,* 98:452-458, 1995.
27. **Rico, H.; Revilla, M.;** and **Hernandez, E.R.:** Total and regional bone mineral content and fracture rate in postmenopausal osteoporosis treated with salmon calcitonin: a prospective study. *Calcif. Tissue Int.,* 56:181-185, 1995.
28. **Riggs, B.L.;** and **Melton, L.J. III.:** Evidence for two distinct syndromes of involutional osteoporosis. *Am. J. Med.,* 75:899-901, 1983.
29. **Riggs, B.L.;** and **Melton L.J. III.:** The prevention and treatment of osteoporosis. *N. Engl. J. Med.,* 327:620-627, 1992.
30. **Riggs, B.L.;** and **Hodgson, S.F.:** Effect of fluoride treatment on fracture rate in psotmenopausal women with osteoporosis. *N. Engl. J. Med.,* 322:802-809, 1990.
31. **Rosen, C.J.; Hunter, S.J.;** and **Vereault, D.:** A randomized placebo-controlled trial of calcium carbonate vs dairy supplementation in elderly New England women. *J. Bone and Min. Res.,* 11:S133, 1996.
32. **Ross, P.D.; Davis, J.W.; Vogel, J.M.;** and **Wasnich, R.D.:** A critical review of bone mass and the risk for fractures in osteoporosis. *Calcif. Tissue Int.,* 46:149-161, 1990.
33. **Steinberg, K.K.; Thacker, S.B.;** and **Smith, S.J.:** A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. *JAMA,* 265:1985-1990, 1991.
34. **Tang, M.X.;** and **Jacobs, D.:** Effects of estrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet,* 348:429-432, 1996.
35. **Tilyard, M.W.; Spears, G.F.S.;** and **Thompson, J.:** Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N. Engl. J. Med.,* 326:357-362, 1992.
36. **Tinetti, M.E.; Baker, D.I.; Garrett. P.A.; Gottschalk, M.; Koch, M.L.;** and **Horwitz, R.I.:** Risk factor abatement strategy for fall prevention. *J. Am. Geriatric Soc.,* 41:315-320, 1993.
37. **Uebelhart, D.; Schlemmer, A.;** and **Johansen, J.:** Effect of menopause and hormone replacement therapy on the urinary excretion of pyridinium crosslinks. *J. Clin. Endocrinol. Metab.,* 72:367-373, 1991.

PSEUDOACHONDROPLASTIC DYSPLASIA: AN IOWA REVIEW FROM HUMAN TO MOUSE*

Jeff W. Stevens

ABSTRACT

Lamellar inclusions of the rough endoplasmic reticulum in growth plate chondrocytes, first identified (1972) in the Department of Orthopaedic Surgery, University of Iowa, has become the cytochemical hallmark for the pseudoachondroplastic dysplasia (PSACH) phenotype, linking an endoplasmic reticulum storage disorder with the osteochondrodysplasia. Since this original observation, great advances have been made, leading to the molecular understanding of this altered longitudinal bone growth anomaly. A PSACH canine model suggested that abatement of cumulative vertical growth of growth plate chondrocytes seen in PSACH results from (1) altered extracellular matrix constraints for horizontal growth and (2) uncoupling of endochondral and perichondral growth that causes metaphyseal flaring. PSACH, an autosomal dominant disease, is linked to mutation of the cartilage oligomeric matrix protein (COMP) gene. Amino acid substitutions, deletions, or additions is proposed to alter COMP structure that cause its retention in the rough endoplasmic reticulum of growth plate chondrocytes, leading to (1) compositional and structural change of the extracellular matrix, and (2) altered cellular proliferation and volume expansion. Normal growth and development occurs in COMP gene knockout mice that do not synthesis COMP, demonstrating that a mutant COMP, not absence of COMP, is required for the PSACH phenotype. The mechanism by which mutant COMP induces a PSACH phenotype remains to be elucidated.

At the University of Iowa a cell culture system has been developed whereby mutant COMP transgenes are introduced into chondrocytes and the expressed product COMP is retained in the endoplasmic reticulum. This readily manipulated system makes it possible to decipher systematically the system's cellular secretory processing pathway, in order to clarify the mechanism(s) by which the mutant COMP is retained within the endoplasmic reticulum. Concurrent with this is the development of transgenic mice expressing the mutant COMP used in the cell culture system. This will make it possible to establish that expression of a human PSACH-linked mutant COMP will produce a PSACH phenotype. A PSACH animal model will provide a means to characterize the mechanism of altered longitudinal bone growth and to test gene therapy approaches for correcting the anomaly.

INTRODUCTION

Maroteaux and Lamey in 1959 were the first to separate pseudoachondroplastic dysplasia (PSACH) from the complex group of spondylo-epiphyseal dysplasias as the pseudoachondroplastic type[44]. PSACH presents some features the similar to those of achondroplasia and Morquio's disease but does not match the phenotype of either disease[44]. A decreased longitudinal bone growth is seen in both PSACH and achondroplasia. Cranial and facial normal features are seen in PSACH, however, in contrast to achondroplasia. An onset of approximately 2 years is required to usually identify skeletal dysplasia with PSACH, while altered bone growth is seen at birth in achondroplasia. Abnormalities of the vertebrae and pelvis are present in PSACH as in Morquio's disease. Lack of (1) corneal opacities and (2) keratan sulfate in the urine distinguish PSACH phenotype from Morquio's disease[40].

Mutant gene linkage studies support the clinical findings that PSACH is a separate type of osteochondrodysplasia. Autosomal dominant linkage of the extracellular matrix protein, cartilage oligomeric matrix protein (COMP), located at chromosome 19p13.1[8,24] is linked with PSACH[9,25]. Achondroplasia is linked with

Department of Orthopaedic Surgery, The University of Iowa, Iowa City, Iowa

Correspondence should be directed to Jeff W. Stevens at the Ignacio V. Ponseti Laboratory of Biochemistry and Cell Biology, 1182 Medical Laboratories, Department of Orthopaedic Surgery, The University of Iowa, Iowa City, Iowa 52242-1181, Phone: 319/335-7550, Fax: 319/335-7968, E-mail: jeff-stevens@uiowa.edu

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mutation of fibroblast growth factor receptor-3 gene located at chromosome 4p16.3[57] and Morquio's disease (mucopolysaccharidosis type IVA) is linked with mutation of galactosamine-6-sulfatase gene (chromosome 16q24.3)[2].

CLINICAL EVALUATION

Hall and Dorst[22] classified PSACH into four types, a dominant mild and severe type (formally designated types I and III) and a recessive mild and severe type (formally designated types II and IV). However, recent genetic and natural history studies have refined the demarcation between type classification. Germline/somatic mosaicism identified in apparently unaffected parents of two or more siblings with PSACH previously diagnosed with autosomal recessive inheritance[21,23], demonstrates that PSACH is, in fact, an autosomal dominant disease. Mild versus severe PSACH phenotype is poorly delineated clinically, and natural history is more informative in describing the degree of musculoskeletal involvement in PSACH. Limb dwarfism is identifiable at childhood being reflected at onset of altered longitudinal bone growth. The head and facial features are normal. Lumbar lordosis, kyphosis, scoliosis, and atlantoaxial dislocation are features that can be found in the spine. Neurological chronic cervical cord compression myelopathy occurs resulting from atlantoaxial dislocation. Brachydactyly, without trident hand, telescoping fingers, and ulnar deviation of wrist are seen in the limbs. Limited elbow and hip extension and ligamentous laxity are seen in the joints accompanied with genu valgum and bowleg. Radiographic evaluation shows platyspondyly, tongue-shaped anterior vertebrae, short pedicles, short tubular bones, widened metaphyses, and fragmented irregular epiphyses. No extraskeletal medical problems are associated with PSACH[46,66].

The natural history of PSACH is associated with early onset of arthritis. Weight bearing joints of the knee, hip, and foot at ~20 years of age are first in showing signs of arthritic pain[46]. The elbow, shoulder, and neck can be affected later in life. Windswept deformity, knock knees, bowed legs, scoliosis, and cervical spine instability are frequently present and commonly require corrective surgery intervention at adolescence. Total hip replacement is often required at an earlier age than in normal individuals. Whether the abnormal composition (extracellular matrix formation) of the femoral head / acetabulum and joint laxity or in some instances formation of shallow acetabuli or protrusio acetabuli during growth is responsible for onset of the arthritis has yet to be delineated.

HISTOMORPHOMETRIC EVALUATION

Altered longitudinal bone growth is the most apparent phenotype seen in PSACH individuals. Long bone growth entails the conversion of an expanding cartilage template into trabecular bone through the process of endochondral ossification. Growth plate chondrocytes subsequently undergo a program of matrix expansion during hypertrophy, calcification, and cell death. The calcified, hypertrophic cartilage provides a scaffold for the formation of trabecular bone. Continuous proliferation of the chondrocytes with cell and matrix expansion dictates the length of the limb through adolescence. In PSACH individuals, dramatically reduced limb lengthening appears to result from altered expansion of the extracellular matrix and longitudinal growth of the chondrocytes prior to ossification.

Light microscopy analyses of epiphyses and metaphyses identified an array of abnormal chondrocytes in PSACH, suggesting altered maturation and potential proliferation of chondrocytes affects longitudinal growth. In the advent of electron microscopic examination of the chondrocytes, Lindseth et al.[40] observed "occasional inclusion bodies of unidentified nature within the chondrocytes" and "endoplasmic reticulum was not prominent" within the chondrocytes. Maynard et al.[45] identified accumulation of alternately electron-lucent and electron-dense layers of material in the rough endoplasmic reticulum, forming extensive lamallae (Figure 1), in affected chondrocytes of the growth plate and proposed that PSACH is a rough-surfaced endoplasmic reticulum storage disorder[11,45]. The extracellular matrix molecules 1) aggrecan[59-61], 2) COMP[16,26,42], and 3) type IX collagen[26,42] have since been identified in the lamellar structures, suggesting that defects in post-translational processing of the core proteins lead to their retention in the cell. It is important to note, however, that this is not a general defect in protein processing. Type II collagen secretion, for example, is unaffected[60]. Rather, the data imply that the defect affects a subset of extracellular matrix molecules that includes aggrecan, COMP, and type IX collagen.

PSACH ANIMAL MODEL

A human PSACH phenotype has been identified in a Scottish deerhound dog pedigree[5,6]. As seen in humans, no skeletal abnormalities were observed at birth and first evidence of chondrodysplasia was detected at four to five weeks of age. Kyphosis and limb deformities gradually developed with radiographic shorter long bones and vertebrae, irregular and delayed ossification, and metaphyseal flaring. Joint laxity was additionally noted with increase of age, suggesting ligament involvement. With closure of the proximal distal and radial

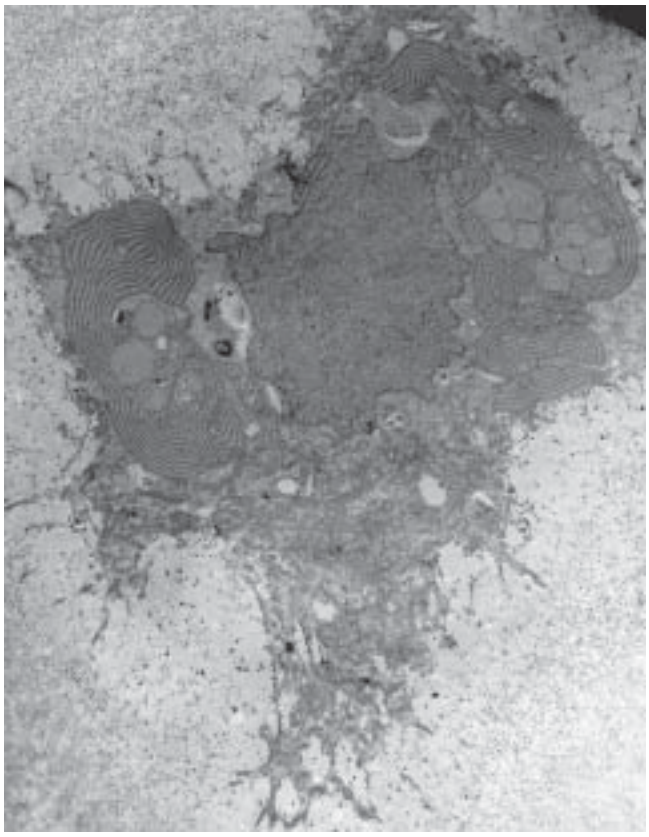

Figure 1. Transmission electron micrograph of a pseudoachondroplastic dysplasia growth plate chondrocyte identifying alternately electron-lucent and electron-dense layers of material in the rough endoplasmic reticulum, the cytochemical hallmark pattern associated with pseudoachondroplastic dysplasia. Magnification = 3,900x.

growth plates, the radii were 65% shorter in length than age matched normal animals. One litter, with three animals being dwarf and two animals being phenotypically normal, was sacrificed at 17 weeks of age for histocytochemical and stereological analyses[6]. Chondrocytes of the proximal and distal growth plates of the radius and costochondral junctions of the sixth rib contained alternately electron-lucent and electron-dense layers of material in the rough endoplasmic reticulum within chondrocytes as seen in the human PSACH. Weight-bearing load to the growth plates was not found to be a factor in inducing the lamellar inclusions of the chondrocytes since the inclusions were also present in the non-weight-bearing growth plates of the ribs. In the articular cartilage of the distal radius, lamellar inclusions were limited to chondrocytes of the deep zone, but were not present in chondrocytes of the superfical zone, indicating specificity in altered chondrocyte phenotype of growth plates.

Distal radial growth plates of dwarf Scottish deerhounds showed no difference in thickness to age matched normal littermates. However, abnormalities that included disruption of the normal columnar arrangement, apparent hypocellularity, and irregularity of the hypertrophic chondrocyte-ossification junction were seen in the metaphysis. The bone septa were thicker in the dwarf dogs, suggesting altered endochondral ossification. The identified 65% decrease in growth of longitudinal long bone was attributed, in part, to altered shape and volume of the growth plate chondrocytes. Cell shape of the growth plate chondrocytes of PSACH-like canines was statistically different from age-matched control animals. The dwarf Scottish deerhound had 50% less horizontal and 63% higher vertical diameters of proliferating chondrocyes and 65% less horizontal and 82% less vertical diameter in the hypertrophic zone. Decreased cumulative vertical growth of chondrocytes as a result of altered cellular volume, in effect, could contribute to the limb shortness. Metaphyseal flaring is reflected by uncoupling of endochondral and perichondrial growth, where a change in matrix composition alters restrained lateral expansion of the growth plate. Loss of the dwarf Scottish Deerhound dog pedigree (Dr. Gert J. Breur, Perdue University, West Lafayette, IN, personal communication) precludes thymidine labeling studies, that would measure growth plate chondrocyte proliferation relative to longitudinal growth.

GENETIC ANALYSES

The understanding of the molecular basis of PSACH was dramatically advanced with autosomal dominant gene linkage studies mapping PSACH[7,8,24] and the much milder osteochondrodysplasia, multiple epiphyseal dysplasia (MED)[52], to chromosome 19p13.1. Mutation of the COMP gene located at chromosome 19p13.1 is linked to PSACH and MED[3,9,10,15,16,21,25,26,27,41,42,63,64]. While only one chromosomal locus is linked to PSACH, at least two additional loci are identified for MED[8,14] of which one is COL9A2 that encodes the (2(IX) chain of type IX collagen[50]. Sixty-six COMP gene mutations that have been identified in either PSACH or MED are listed in Table I. Mutations predict in-frame deletions and insertions as well as single nucleotide substitutions but do not introduce a premature stop codon. Forty-one (62%) of 66 COMP gene mutations are identified for the codons of aspartic acid (Table II). Of the two possible codons, GAC and GAT, 39 (95%) mutations involve the GAC codon for aspartic acid, suggesting a preference for mutation of the GAC. A mutational hot spot is identified at the five GAC repeat sequence located at nt1405-1419. At this site the 20 identified mutations (30% of 66 total mutations) consist of 18 trinucleotide deletions and 2 insertions. A recently identified family of diseases,

TABLE I. COMP GENE MUTATIONS

Exon	Sequence change[a]		Domain	Phenotype	Frequency	Reference
	Nucleotide	Amino acid				
9(14)	868G→A	290Asp→Asn	Hybrid	PSACH	1	Ikegawa (1998)
9(14)	895G→A	299Gly→Arg	CR1	PSACH	1	Ikegawa (1998)
9(14)	919G→A	309Gly→Arg	CR1	PSACH	2	Délot (1998)
10(15)	982T→C	328Cys→Arg	CR1	PSACH	1	Briggs (1995)
10(15)	1024G→T	342Asp→Tyr	CR2	MED (Fairbank)	1	Briggs (1995)
10(15)	1046A→G	349Asp→Gly	CR2	PSACH	1	Ikegawa (1998)
10(15)	1081G→T	361Asp→Tyr	CR3	MED (typical)	1	Loughlin (1998)
10(15)	1082A→T	361Asp→Val	CR3	MED (Fairbank)	1	Ikegawa (1998)
10(15)	1109delCGGGGC	367delArgGly	CR3	MED (typical)	1	Loughlin (1998)
10(15)	1111T→C	371Cys→Ser	CR3	MED (Fairbank)	1	Susic (1997)
10(15)	1111delGAC	372delAsp	CR3	PSACH	1	Briggs (1995)
				PSACH	1	Briggs (1998)
11(16)	1159T→G	387Cys→Gly	CR3	PSACH	1	Ikegawa (1998)
11(16)	1109delACCC-AACTCAGA	389delArgValProAsn	CR3	PSACH	1	Loughlin (1998)
	1109insTGT	389insCys				
11(16)	1222G→T	408Asp→Tyr	CR4	MED (typical)	1	Loughlin (1998)
12(17A)	1280G→A	427Gly→Glu	CR5	PSACH	1	Deere (1998)
				PSACH	1	Délot (1998)
13(17B)	1318G→A	440Gly→Arg	CR5	PSACH	1	Loughlin (1998)
				PSACH	1	Briggs (1998)
13(17B)	1320G→A	440Gly→Glu	CR5	PSACH	2	Briggs (1998)
13(17B)	1336G→A	446Asp→Gln	CR5	PSACH	1	Madox (1997)
			CR5	PSACH	1	Délot (1998)
13(17B)	1345C→A	449Pro→Thr	CR5	PSACH	1	Deere (1998)
13(17B)	1358G→A	453Asn→Ser	CR6	MED (Fairbank)	1	Briggs (1998)
13(17B)	1367delAGG	457delGlu	CR6	PSACH	1	Ferguson (1997)
13(17B)	1375delTCA	459delSer	CR6	PSACH	1	Hecht (1995)
13(17B)	1403G→A	468Cys→Tyr	CR6	PSACH	1	Hecht (1995)
13(17B)	1405delGAC	469delAsp	CR6	PSACH	5	Hecht (1995)
				PSACH	1	Hecht (1998)
				PSACH	2	Deere (1998)
				PSACH	7	Briggs (1998)
				PSACH	3	Ikegawa (1998)
13(17B)	1405insGAC	469insAsp	CR6	MED (unclassified)	1	Délot (1998)
13(17B)	1405insGACGAC	469insAspAsp	CR6	PSACH	1	Délot (1998)
13(17B)	1414G→T	472Asp→Tyr	CR6	PSACH	1	Hecht (1995)
13(17B)	1417G→A	473Asp→Asn	CR6	PSACH	1	Deere (1998)
13(17B)	1418A→G	473Asp→Gly	CR6	PSACH	1	Ikegawa (1998)
13(17B)	1423G→A	475Asp→Asn	CR6	PSACH	1	Deere (1998)
13(17B)	1445A→G	482Asp→Gly	CR6	PSACH	1	Susic (1998)
14(18A)	1520A→G	507Asp→Gly		PSACH	1	Deere (1998)
14(18A)	1526A→C	509Asp→Ala	CR7	PSACH	1	Deere (1998)
14(18A)	1526A→G	509Asp→Gly	CR7	PSACH	1	Deere (1998)
14(18A)	1531G→C	511Asp→His	CR7	PSACH	1	Deere (1998)
14(18A)	1537delGTGGT-AGACAAG	513delValValAspLys	CR7	PSACH	1	Susic (1997)
14(18A)	1552G→A	518Asp→Asn	CR7	PSACH	1	Deere (1998)
			CR7	PSACH	1	Ikegawa (1998)
14(18A)	1569C→G	523Asn→Lys	CR7	MED (Ribbing)	1	Ballo (1997)
14(18A)	1579A→G	527Thr→Ala	COOH	PSACH	1	Hecht (1998)
16(19)	1754C→T	585Thr→Met	COOH	PSACH	1	Briggs (1998)
16(19)	1754C→G	585Thr→Arg	COOH	MED	1	Briggs (1998)
16(19)	1760A→G	587His→Arg	COOH	PSACH	1	Deere (1998)

[a]nucleotides and amino acids are numbered from the start site of translation; thrombospondin[1] corresponding exons are indicated in parentheses; PSACH, pseudoachondroplastic dysplasia: MED; multiple epiphyseal dysplasia; del, deletion; ins, insertion; →, substitution; Hybrid, Type-3 repeat hybrid; CR, calmodulin-like repeat; COOH, globular carboxyl domain; amino acids presented in three letter code; nucleotides presented in one letter code.

TABLE II. LOCATION OF ASPARTIC ACID MUTATIONS IN COMP

Domain		Number of Mutations	Aspartic Acid	Codon GAC
Type-3 repeats				
-Hybrid		1	1	1
-Calmodulin-like				
	CR 1	4	0	
	CR 2	2	2	2
	CR 3	7	4	4
	CR 4	1	1	1
	CR 5	9	2	2
	CR 6	29	25	25
	CR 7	9	6	4
COOH		4	0	
Total		66	41(62%)[a]	39 (95%)[b]

[a]percentage of total mutations; [b]GAC percentage of total possible (GAC, GAT) codons for aspartic acid; GAC, codon for Asp; COOH, globular carboxyl domain. See Figure 1 identifying location of aspartic acid mutations in the Type-3 repeats.

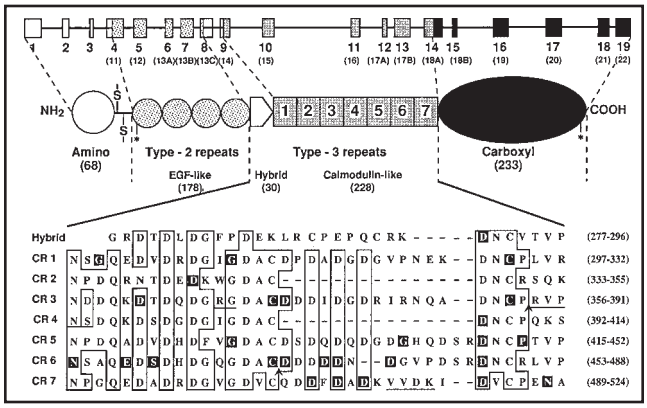

Figure 2. Diagrammatic representation of the COMP gene, protein domains, and mutation sites within the Type-3 repeats. The COMP gene consists of 19 exons, to which corresponding protein domains are indicated [(1) circle, globular Amino; (2) stippled circles, Type-2 repeats, EGF-like; (3) Type-3 repeats: (i) pentamer box, Hybrid; (ii) square boxes, Calmodulin-like; (4) oval, globular Carboxyl]. Corresponding thrombospondin[1] exons are indicated in parentheses. Asterisks identify *N*-linked high oligosaccharides at N^{121} and N^{741}. Two cysteines (C^{69}, C^{72}) identified in the Amino domain are involved in interchain pentamer oligomerization. CR, calmodulin-like repeats; Amino acids are shown in one letter code and numbered (parentheses) from the start site in translation. Amino acids homology: boxed area, identical sequence; underlined, deletion; dark background, substitution; ↑, insertion. Sequence alignment (277-524), with gaps (- - -) to optimize sequence homologies.

triplet repeat expansion diseases, is associated with expansion of trinucleotide sequences during replication of duplex DNA[47]. Formation of stable hairpin loops resulting from trinucleotide repeats folding over onto themselves promotes expansion of the triplets during DNA replications. Ability of GAC repeats to form stable hairpin loops[67] has prompted Délot et al.[17] to explain observed GAC insertions of the nt1405-1419 $(GAC)_5$ site identified in PSACH $[(GAC)_1]$ and MED $[(GAC)_2]$ to have resulted from trinucleotide expansion mutations[47]. With 18 sporadic GAC trinucleotide deletion mutations seen at this same site (nt1405-1419), the $(GAC)_5$ repeat sequence is potentially a hot spot for replication error.

MOLECULAR STRUCTURE OF COMP

The human COMP gene consists of 19 exons[9] with a coding sequence that predicts a 757 amino acid core protein[51]. Amino acid sequence homology with thrombospondins puts COMP in the thrombospondin family. In Table III structural and functional similarities identify COMP with the four member human thrombospodin family. Gene map, model of COMP, and amino acid mutation sites in the predicted calcium-binding Type-3 repeats are identified in Figure 2. From cDNA sequencing, the predicted 757 amino acid minus

TABLE III. HUMAN THROMBOSPONDIN FAMILY

	TSP1	TSP2	TSP3	TSP4	COMP
STRUCTURE					
Chromosomal location	15q15[29]	6q27[33]	1q21-q24[65]		19p13.1[51]
Number of exons	21		23		19
Transcript size	6[26]	6.5[26]	3.4[26]	2.8[26]	2.6[26]
Protein	1170[a]	1173	956	961	757
Domains					
-Signal peptide	18[b] (1-18) (>10%)	18 (1-18)	21 (1-21)	21 (1-21)	20 (1-20)
-Globular amino	299 (19-317) (>10%)	301 (19-319) (>10%)	255 (22-276) (>10%)	264 (22-285) (>10%)	68 (21-88)
-Procollagen	57 (318-374) ---	57 (320-376) ---	---	---	---
-Type 1 repeats (properdin-like)	167, 3 (380-546) ---	167, 3 (382-548) ---	---	---	---
-Type 2 repeats (EGF-like)	124, 3 (546-689) (23%)	143, 3 (549-691) (33%)	179, 4 (277-455) (51%)	176, 4 (286-461) (55%)	178, 4 (89-266)
-Type 3 repeats					
Hybrid	33 (690-722) (57%)	33 (692-724) (53%)	32 (456-487) (47%)	29 (462-491) (57%)	30 (267-296)
Calmodulin-like	228, 7 (723-950) (60%)	228, 7 (725-952) (64%)	232, 7 (488-719) (67%)	232, 7 (492-723) (74%)	228, 7 (297-524)
-Globular carboxyl	220 (951-1170) (55%)	221 (953-1173) (58%)	237 (720-956) (84%)	239 (724-961) (87%)	233 (525-757)
Molecular mass (SDS-PAGE)					
reduced	180 kDa[36]	185 kDa(mouse)[12]	145 kDa(mouse)[12]	135 kDa[26]	110 kDa[26]
nonreduced	420 kDa[36]	480 kDa(mouse)[12]	590 kDa(mouse)[12]	675 kDa[26]	550 kDa[26]
FUNCTIONAL DOMAINS					
Interchain oligomerization	trimer[56]	trimer[56]	pentamer[43]	pentamer[43]	pentamer[43]
-α-helical bundle	37 (266-302)	37 (262-298)	46 (225-270)	46 (217-262)	46 (28-73)
-disulfhydral	Cys270, Cys274	Cys266, Cys270	Cys266, Cys269	Cys258, Cys261	Cys69, Cys72
Calcium-binding motif (DxDxDxxxDxxD)	228, 13 (723-950)	228, 13 (725-952)	232, 13 (488-719)	232, 13 (492-723)	228,13 (297-524)
Cell adhesion sites					
-Heparin-binding (heparan sulfated proteoglycans)	binds	binds	binds	binds	no binding site
-RGD/integrin	T3/CR7 (926-928) functional[38]	T3/CR7 (928-930) functional[34]	No site	T3/CR3 (562-564) not functional[51]	T3/CR3 (367-369) not functional[51]

[a]number of amino acids from GenBank Accession numbers: TSP1, X14787; TSP2, L12350; TSP3, L38969; TSP4, Z19585; COMP, L32137;

[b]quantity of amino acids within domain, amino acid location identified in parentheses (number from start site translation). Transcript size expressed in kilobase pairs. RGD, arginine-glycine-aspartic acid tripeptide – cell surface recognition sequence. T3, Type 3 repeats; CR7, calmodulin-like 7 repeat. Repeats: number of repeats or calcium binding sites are indicated following identification of amino acid number within the domain.

the predicted 20 amino acid leader sequence (i.e., 737 amino acids) mass of human COMP is 83,547 Da, prior to post-translational modifications[51]. The human COMP deduced amino acid sequence predicts: 1) 20 amino acid signal peptide (residues 1-20); 2) 68 amino acid globular amino domain (residues 21-88); 3) 178 amino acid Type-2 repeats with 4 epidermal growth factor (EGF)-like motifs (residues 89-266); 4) 258 amino acid Type-3 repeats that consist of a 30 amino acid sequence hybrid calmodulin-like (residues 267-296) followed by a 228 amino acid sequence of 7 calmodulin-like motifs (residues 297-524); and 5) 233 amino acid globular carboxyl domain (residues 525-757)[37,51,53]. As a glycoprotein, no *O*-linked oligosaccharides are attached to COMP[68]. Three NXT/S *N*-linked oligosaccharide recognition sites are identified from the deduced human COMP sequence (GenBank accession number L32137) with N^{121} and N^{741} being glycosylated and the third *N*-linkage site (N^{144}) being unoccupied[68]. In the adult, carbohydrate compositional and estimated mass of the *N*-oligosaccharide at N^{121} is consistent with expected mass of a high mannose oligosacharride with the structure of $(HexNAc)_2$-$(Man)_8$-$(Fuc)_1$. From fetal tissue, however, four composition carbohydrate ratios are linked to N^{121}, suggesting presence of different carbohydrate moities at this site. The oligosaccharide structure attached to N^{741}, being the same for both fetal and adult, with a calculated mass of 1723.8 +/- 225 Da, could not accurately be determined resulting from the large error value associated with its analyses[68].

Sequence homology with the family of four thrombospondins has placed COMP as the fifth member (TSP5) of the family. All with unique chromosomal locations, the COMP gene produces the smallest (2.6 kb) transcript[26] with an open reading frame of 2274 nt. The globular Amino domain of COMP has the least sequence homology with thrombospondins, with 200 amino acids fewer than thrombospondins. COMP's inability to bind to heparin[18] is attributed to the lack of these amino acids. However, in COMP as in thrombospondins, an identical disulfhydral site is involved in interchain interactions that result in formation of multimeric structures. As with TSP3 and TSP4, COMP is a pentamer resulting from interchain disulfyhdral cross-linking and formation of a 5 α-helical bundle from a 46 amino acid sequence within the globular Amino domain of COMP[19,43,49]. PSACH growth plate chondrocytes express COMP retained in the rough endoplasmic reticulum as a pentamer[16,26,42] suggesting PSACH-linked COMP mutations do not alter interchain formation. In the Type-2 repeats four EGF-like sequences (44-55 amino acid units), based on positions of the six cysteine residues[4], are identified in COMP with 51% and 55% identical sequence homology with human TSP3 and TSP4, respectively. Proteins containing EGF-like motifs have been documented in forming ligand-receptor interactions at cell surfaces, initiating signal transduction cascades that alter metabolic parameters of the cell such as growth regulation. Functional significance of the EGF-like repeats in COMP remains to be identified.

Of the 66 mutations, 62 (94%) are located in the 228 amino acid continuous sequence that make up the Type-3 repeats to which calcium binding sites have been ascribed. Utilizing amino acid sequence homologies of COMP with thrombospondins, a seven repeat consensus sequence of 23-38 amino acids is identified with the alignment of two cysteines and eleven aspartic acids. An eighth hybrid sequence with one cysteine and four aspartic acids is additionally identified within the domain. Figure 2 combines alignment of the 8 homologous peptide sequence motifs and identifies of COMP and MED associated mutations within these sequences. Further amino acid alignments in the Type-3 repeats with a consensus sequence of DxDxDxxxDxxD (D, aspartic acid; x, any amino acid) identifies 13 sequences, also seen in TSP1[48], with similar EF-hand calcium coordinates that have been established in calmodulin-like proteins[32]. Proteins with EF-hands bind calcium within a helix-loop-helix structure having 6 amino acids whose vertices approximate an octahedron with the positions designated X,Y,Z,-X,-Y,-Z. Oxygen containing side chains of the amino acids at these coordinates, such as that seen in COMP with aspartic acid are involved in calcium coordination. Figure 3 identifies EF-hand consensus sequences in the Type-3 repeats of COMP. Removal of calcium from TSP1 results in (1) accessibility to otherwise unavailable proteolytic cleavage sites within the

```
X Y Z-Y-X -Z  (EF-hand calcium coordinates)
DTDLDGFPDEKL RCPEPQCRKDNCVTVPNSGQE     (279-301)
DVDRDGIGDACD ---------------P          (302-314)
DADGDGVPNEKD ----------NCPLVRNPDQR     (315-337)
NTDEDKWGDACD ----------NCRSQKNDDQK     (338-360)
DTDQDGRGDACD ------------------D       (361-373)
DIDGDRIRNQAD ----------NCPRVPNSDQK     (374-396)
DSDGDGIGDACD ----------NCPQKSNPDQA     (397-419)
DVDHDFVGDACD ----------------SDQ       (420-434)
DQDGDGHQDSRD ----------NCPTVPNSAQE     (435-457)
DSDHDGQGDACD ------------------D       (458-470)
DDDNDGVPDSRD ----------NCRLVPNPGQE     (471-493)
DADRDGVGDVCQ ------------------D       (494-506)
DFDADKVVDKID ----------VCPE--NA        (507-524)
DxDxDxxxDxxD  (COMP consensus)
```

Figure 3. Calcium-binding sequence homologies in the Type-3 repeats of human COMP. Thirteen amino acid sequences are numbered (parentheses) from the start site in translation. Sequence alignment (residues 279-524), with gaps (- - -) to optimize sequence homologies. Amino acid, one letter code; underline, mutation site.

Type-3 repeats[35] and (2) decrease in size of the Type-3 repeats containing globular structures[36,55], establishing calcium's ability to effect structural conformation of TSP1 potentially through the EF-hand calcium binding coordinates. Mutations within the EF-hand consensus sequences [53 (85%) of Type-3 repeats domain 62] potentially could alter normal conformational structure of COMP by changing the ability of calcium to interact with COMP, which as a result could cause formation of the lamallar structures in the rough endoplasmic reticulum growth plate chondrocytes[25]. Other mutations located within the Type-3 repeats, not in the EF-hand calcium coordinates, potentially change the structure of COMP, indirectly altering ability of the calcium-binding pocket to interact with calcium. For example, in the COMP mutation of Ser^{371} is substitution for Cys^{371} it is expected that loss of the disulfhydral linkage occurs that would cause alteration in the tertiary structure of COMP, indirectly, changing a calcium binding site. Mutation in the COMP gene predicts 97% of COMP molecules, as a pentamer, would have at least one monomeric unit containing a mutation.

FUNCTION OF COMP MOLECULE

COMP is normally localized in the extracellular matrix of connective tissues with an unknown function. Thrombospondins, glycoprotein homologs of COMP, as extracellular matrix molecules, are identified with growth, cellular/tissue differentiation, cell motility, and cell adhesions through either cell surface interactions or interactions with extracellular matrix molecules. Cell surface heparin-binding and Arg-Gly-Asp (RGD) sites have been mapped to sequences within the thrombospondins. COMP, however, does not have the heparin-binding site sequence (minus 200 amino acid within the globular Amino domain), nor does it have a functional RGD site[51], therefore, this eliminates these sequences as potential functional sites within COMP.

Difference in COMP extracellular matrix location and carbohydrate composition identified between fetal and adult suggests altered function of COMP in cartilage. Prior to longitudinal bone growth, COMP, synthesized by the chondrocytes, is found localized in the interterritoral compartment of the extracellular matrix[20,58]. During longitudinal bone growth COMP becomes localized to the pericellular and territorial compartments of the extracellular matrix[18,58] with the highest level of mRNA detected in chondrocytes in the proliferative zone[58]. COMP, within the growth plate, may be involved in regulating cell growth and proliferation[58]. Differences in N-linked glycosylation structure patterns of COMP isolated from fetal and adult cartilage[68] may contribute to differences in molecular interactions within the matrix.

COMP is selectively expressed in cells of cartilage, tendon, ligament, and synovium. In the growth plate of PSACH individuals, COMP is localized to the electron-lucent lamellae of the rough endoplasmic reticulum, but the rough endoplasmic reticulums of tendon and ligament tissues are unaltered[45]. Radiolabel metabolic studies demonstrate COMP is retained as a pentamer intracellularly and not processed for secretion in chondrocytes isolated from PSACH individuals. COMP secretion from cultured cells isolated from tendon, ligament[16,26,42], and chondrocytes differentiated to a fibroblastic phenotype[26] demonstrate that COMP retention in PSACH individuals is specific to chondrocytes. Normal development of a COMP gene knockout mouse (personal communication Dr. JT Hecht, Department of Pediatrics, University of Texas-Houston Medical Center, Houston, TX) demonstrates that it is the mutation, not the absence of COMP, that affects cartilage extracellular matrix deposition. Eliminating expression of COMP is not sufficient to alter cartilage extracellular matrix, a mutant COMP molecule must be expressed.

FUTURE DIRECTION OF RESEARCH ON PSACH

The mechanism(s) linking COMP gene mutations with the PSACH phenotype has yet to be elucidated. Several questions are proposed in order to characterize mutant COMP's role in generation of a PSACH phenotype. With the presence of a COMP gene mutation it is predicted that 97% of expressed pentameric COMP will contain at least one monomeric unit. The actual amount of mutated monomeric units within the pentameric species is not known. It would be anticipated that with an increase in percentage of mutated monomeric units that a greater altered structure of the pentameric species would occur, that could influence severity of the phenotype. Identifying a correlation between quantity of mutant COMP monomeric units and a PSACH phenotype would be beneficial in attempts to correct the anomaly through a gene therapy approach.

A PSACH phenotype is not clinically identified at birth, even though COMP is being synthesized. Potentially a required amount of mutated monomeric units are needed for the PSACH phenotype to be evident. Alternatively, during growth, mutant COMP alters COMP normal interaction with molecules that are expressed during growth that are not present during development. Potentially, this altered molecular interaction leads to generation of PSACH phenotype.

Altered function of tissues normally expressing COMP is observed in PSACH, suggesting expression of the mutant COMP is occurring universally. However, tendon and ligament cells do not present with extended rough endoplasmic reticulum as seen in growth plate

chondrocytes, suggesting difference in molecular interactions of mutant COMP in these tissues. Hecht et al.[26], identified co-precipitation of COMP and TSP4 with antibodies either specific for COMP or TSP4 from PSACH tendon cells, but not with chondrocytes, suggesting difference in interactions with COMP. One explanation for observed molecular co-precipitation is that COMP and TSP4 are found as heteropentamers, similarly seen with TSP1 and TSP2[54]. As well as differences in synthesis observed between tendon and ligaments compared to chondrocytes, molecular interactions of mutant COMP with TSP4 could attribute to a difference in cellular phenotype.

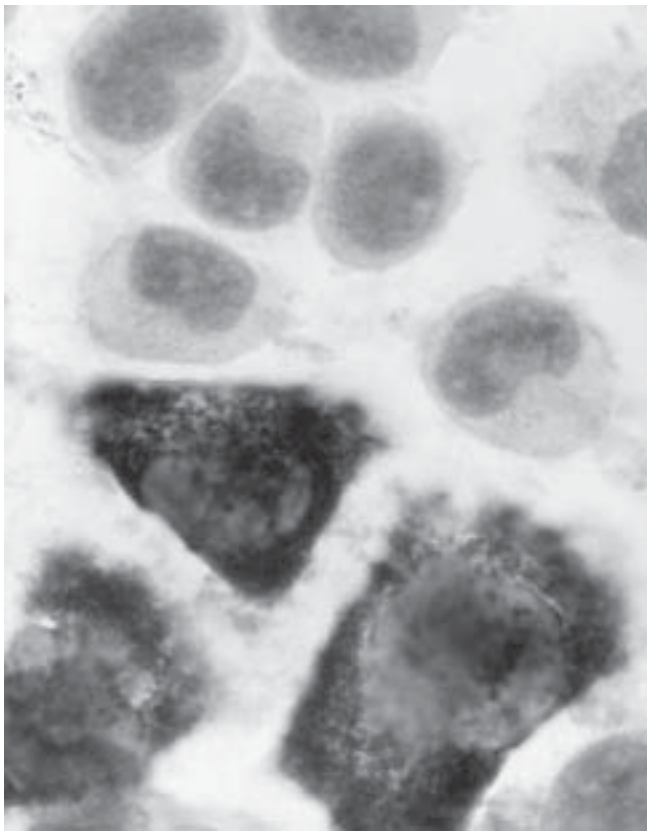

Figure 4. Immunohistochemical identification of human PSACH-linked mutant COMP tagged with a selective immunoreactive sequence distinct from rat COMP in Swarm rat chondrosarcoma cells cultured for 4 days. Brown staining identifies retention of expressed mutant COMP within the cells. Magnification = 1,500x.

Figures 5A-B (next column). Histochemical staining of sulfated proteoglycans with safranin O of the Swarm rat chondrosarcoma tumor expressing a human PSACH-linked mutant COMP (panel A), grown subcutaneously in rat for 59 days. Less proteoglycans are incorporated into the extracellular matrix of the chondrosarcoma containing the mutant COMP transgene, suggesting expression of the mutant COMP is altering deposition of aggrecan in the extracellular matrix as similarly seen in PSACH. Control tumor is presented in panel B. Magnification = 95x.

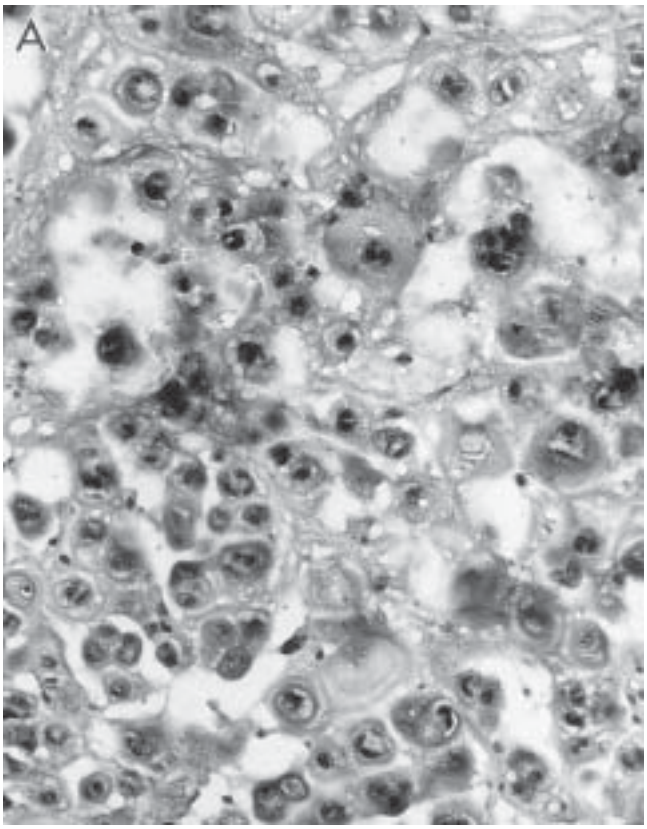

Figure 5A.

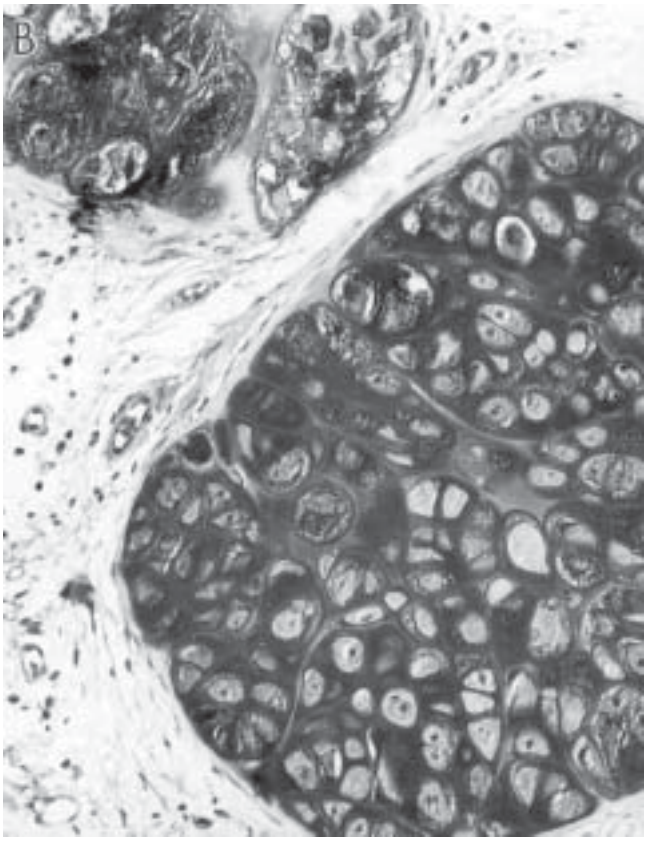

Figure 5B.

A cell culture system has been developed at the University of Iowa, whereby a PSACH-linked mutant COMP transgene is expressed in a cell line having a chondrocyte phenotype[13,30,62]. Coupling an amino acid codon sequence to COMP cDNA, for immunological monitoring of the expressed human COMP transgenes, retention of expressed transgene was observed in the rough endoplasmic reticulum (Figure 4). Proteoglycan metabolism was altered in the cell culture system when mutant COMP was expressed by the chondrocyte-like cells (Figure 5). Establishing a PSACH-like cell culture system, with unlimited amounts of cells, permits us to perform manipulative experiments, which are impossible using human tissue or isolated cells. Concurrent studies have been initiated at the University of Iowa in developing mouse transgenics, expressing the same human mutant COMP transgene developed in our cell culture system. Development of a PSACH animal model will permit studies to be performed that are not ethically feasible in humans and impossible in the cell culture system.

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REFERENCES

1. **Adolph, K.W.; Long, G.L.; Winfield. S.; Ginns, E.I.;** and **Bornstein. P.:** Structure and organization of the human thrombospondin 3 gene (THBS3). *Genomics,* 27:329-36, 1995.
2. **Baker, E.; Guo, X-H.; Orsborn, A.M.; Sutherland, G.R.; Callen, D.F.; Hopewood, J.J.;** and **Morris, C.P.:** The Morquio A syndrome (mucopolysaccharidosis IVA) gene maps to 16q24.3. *Am. J. Hum. Gene.,* 52:96-98, 1993.
3. **Ballo, R.; Briggs, M.D.; Cohn, D.H.; Knowlton, R.G.; Beighton, P.H.;** and **Ramesar, R.S.:** Multiple epiphyseal dysplasia, Ribbing type: A novel point mutation in the COMP gene in a South African family. *Amer. J. Med. Genet.,* 68:396-400, 1997.
4. **Bender, W.:** Homeotic gene products as growth factors. *Cell,* 43:559-560, 1985.
5. **Breur, G.J.; Zebre, C.A.; Slocombe, R.F.; Padgett, G.A.;** and **Braden, T.D.:** Clinical, radiographic, pathologic, and genetic features of osteochondrodysplasia in Scottish deerhounds. *J. Am. Veter. Med. Assn.,* 195:606-612, 1989.
6. **Breur, G.J.; Farnum, C.E.; Padgett, G.A.;** and **Wilsman, N.J.:** Cellular basis of decreased rate of longitudinal growth of bone in pseudoachondroplastic dogs. *J. Bone and Joint Surg.,* 74-A:516-528, 1992.
7. **Briggs, M.D.; Rasmussen, I.M.; Weber, J.L.; Yuen, J.; Reinker, K.; Garber, A.P.; Rimoin, D.L.;** and **Cohn, D.H.**: Genetic linkage of mild pseudoachondroplasia (PSACH) to markers in the pericentromeric region of chromosome 19. *Genomics,* 18:656-660, 1993.
8. **Briggs, M.D.; Choi, H.; Warman, M.L.; Loughlin, J.A.; Wordsworth, P.; Sykes, B.C.; Irven, C.M.; Smith, M.; Wynne-Davies, R.; Lipson, M.H.; Biesecher, L.C.; Garber, A.P.; Lachman, R.; Olsen, B.R.; Rimoin, D.L.;** and **Cohn, D.H.:** Genetic mapping of a locus for multiple epiphyseal dysplasia (EDM2) to a region of chromosome 1 containing a type IX collagen gene. *Am. J. Hum. Genet.,* 55:678-684, 1994.
9. **Briggs, M.D.; Hoffman, S.M.G.; King, L.M.; Olsen, A.S.; Mohrenweiser, H.; Leroy, J.G.; Mortier, G.R.; Rimoin, D.L.; Lachman, R.S.; Gaines, E.S.; Cekleniak, J.A.; Knowlton, R.G.;** and **Cohn, D.H.:** Pseudoachondroplasia and multiple epiphyseal dysplasia due to mutations in the cartilage oligomeric matrix protein gene. *Nature Genet.,* 10:330-336, 1995.
10. **Briggs, M.D.; Mortier, G.R.; Cole, W.G.; King, L.M.; Golik, S.S.; Bonaventure, J.; Nuytinck, L.; De Paepe, A.; Leroy, J.G.; Biesecker, L.; Lipson, M.; Wilcox, W.R.; Lachman, R.S.;**

Rimoin, D.L.; Knowlton, R.G.; and **Cohn, D.H.:** Diverse mutations in the gene for cartilage oligomeric matrix protein in the pseudoachondroplasia-multiple epiphyseal dysplasia disease spectrum. *Am. J. Hum. Genet.,* 62:311-319, 1998.

11. **Cooper, R.R.; Ponseti, I.V.;** and **Maynard, J.A.:** Pseudoachondroplastic dwarfism. A rough-surfaced endoplasmic reticulum storage disorder. *J. Bone and Joint Surg.,* 55-A:475-484, 1973.
12. **Chen, H.; Aeschlimann, D.; Nowlen, J.;** and **Mosher. D.F.:** Expression and initial characterization of recombinant mouse thrombospondin 1 and thrombospondin 3. *FEBS Lett.,* 387:36-41, 1996.
13. **Chen, L.L.; Stevens, J.W.; Martin, J.A.; Hecht, J.T.;** and **Vertel, B.M.:** A cell model for pseudoachondroplasia and COMP. *Mol. Biol. Cell.,* 1998.
14. **Deere, M.; Blantin, S.H.; Scott, C.I.; Langer, L.O.; Pauli, R.M.;** and **Hecht, J.T.:** Genetic heterogeneity in multiple epiphyseal dysplasia. *Am. J. Hum. Genet.,* 56:698-704, 1995.
15. **Deere, M.; Sanford, T.; Ferguson, H.L.; Daniels, K.;** and **Hecht, J.T.:** Identification of twelve mutations in cartilage oligomeric matrix protein (COMP) in patients with pseudoachondroplasia. *Am. J. Med. Genet.,* 80:510-513, 1998.
16 **Délot, E.; Brodie, S.G.; King, L.M.; Wilcox, W.R.;** and **Cohn, D.H.:** Physiological and pathological secretion of cartilage oligomeric matrix protein by cells in culture. *J. Biol. Chem.,* 273:26692-26697, 1998.
17. **Délot, E.; King, L.M.; Briggs, M.D.; Wilcox, W.R.;** and **Cohn, D.H.:** Trinucleotide expansion mutations in the cartilage oligomeric matrix protein (COMP) gene. *Hum. Mol. Genet.,* 8:123-128, 1999.
18. **Di Cesare, P.E.; Möglin, M.; Carlson, C.S.; Pasumarti, S.;** and **Paulsson, M.:** Cartilage oligomeric matrix protein: Isolation and characterization from human articular cartilage. *J. Orthop. Res.,* 13:422-428, 1995.
19. **Efimov, V.P.; Lustig A.;** and **Engel, J.:** The thrombospondin-like chains of cartilage oligomeric matrix protein are assembled by a five-strand (-helical bundle between residues 20 and 83. *FEBS Letters,* 341:54-58, 1994.
20. **Ekman, S.; Reinholt, F.P.; Hultenby, K.;** and **Heinegård, D.:** Ultrastructural immunolocalization of cartilage oligomeric matrix protein (COMP) in porcine growth cartilage. *Calci. Tissue Int.,* 60:547-553, 1997.
21. **Ferguson, H.L.; Deere, M.; Evans, R.; Rotta, J.; Hal, J.G.;** and **Hecht, J.T.:** Mosaicism in pseudoachondroplasia. *Am. J. Med. Genet.,* 70:287-291, 1997.
22. **Hall, J.G.,** and **Dorst, J.P.:** Pseudoachondroplastic SED, recessive Maroteaux-Lamy type. *Birth Defects Orig. Art. Ser.,* V(4):254-259, 1969.
23. **Hall, J.G.; Dorst, J.P.; Rotta, J.;** and **McKusick, V.A.:** Gonadal mosaicism in pseudoachondroplasia. *Am. J. Med. Genet.,* 28:143-151, 1987.
24. **Hecht, J.T.; Francomano, C.A.; Briggs, M.D.; Deere, M.; Conner, B.; Horton, W.A.; Warman, M.; Cohn, D.H.;** and **Blanton, S.H.:** Linkage of typical pseudoachondroplasia to chromosome 19. *Genomics,* 18:661-666, 1993.
25. **Hech, J.T.; Nelson, L.D.; Crowder, E.; Wang, Y.; Elder, F.F.B.; Harrison, W.R.; Francomano, C.A.; Prange, C.K.; Lennon, G.G.; Deere, M.;** and **Lawler, J.:** Mutations in exon 17B of cartilage oligomeric matrix protein (COMP) cause pseudoachondroplasia. *Nature Genet.,* 10:325-329, 1995.
26. **Hecht, J.T.; Deere, M.; Putnam, E.; Cole, W.; Vertel, B.; Chen, H.;** and **Lawler, J.:** Characterization of cartilage oligomeric matrix protein (COMP) in human normal and pseudoachondroplasia musculoskeletal tissues. *Matrix Biol.,* 17:269-278, 1998.
27. **Ikegawa, S.; Ohashi, H.; Nishmura, G.; Kim, K.C.; Sannohe, A.; Kimizuka, M.; Fukushima, Y.; Nagai, T.;** and **Nakamura, Y.:** Novel and recurrent COMP (cartilage oligomeric matrix protein) mutations in pseudoachondroplasia and multiple epiphyseal dysplasia. *Hum. Genet.,* 103:633-638, 1998.
28. **Incardona, F.; Lawler, J.; Cataldo, D.; Panet, A.; Legrand, Y.; Foidart, J.M.;** and **Legrand, C.:** Heparin-binding domain, type 1 and type 2 repeats of thrombospondin mediate its interaction with human breast cancer cells. *J. Cell Biochem.,* 15:431-442, 1996.
29. **Jaffe, E.; Bornstein, P.;** and **Disteche, C.M.:** Mapping the thrombospondin gene to human chromosome 15 and mouse chromosome 2 by in situ hybridization. *Genomics,* 7:123-126, 1990.
30. **Kim, H.W.; Martin, J.A.; Schroeder, A.C.; Kurriger, G.L.; Maynard, J.A.;** and **Stevens, J.W.:** PSACH-linked COMP mutation alters chondrosarcoma ECM formation. *Trans. Orthop. Res. Soc.,* 24:430, 1999.
31. **Knowlton, R.G.; Cekleniak, J.A.; Cohn, D.H.; Briggs, M.D.; Hoffman, S.M.; Brandriff, B.F.;** and **Olsen, A.S.:** High-resolution genetic and physical mapping of multiple epiphyseal dysplasia and pseudoachondroplasia mutations at chromosome 19p13.1-p12. *Genomics,* 28:513-519, 1995.

32. **Kretsinger, R.H.:** Crystallographic studies of calmodulin and homologs. *Ann. N.Y. Acad. Sci.,* 356:1-19, 1980.
33. **LaBell, T.L.; McGookey-Milewicz, D.J.; Disteche, C.M.;** and **Byers, P.H.:** Thrombospondin II: Partial cDNA sequence, chromosome location, and expression of a second member of the thrombospodin gene family in humans. *Genomics,* 12:421-429, 1992.
34. **Laherty, C.D.; O'Rourke, K.;** and **Wolf, F.W.:** Thrombospondin 1 and thrombospondin 2 are expressed as both homo- and heterotrimers. *J. Biol. Chem.,* 267:24921-24924, 1992.
35. **Lawler, J.,** and **Simons, E.R.:** Cooperative binding of calcium to thrombospondin. The effect of calcium on the circular dichroism and limited tryptic digestion of thrombospondin. *J. Biol. Chem.,* 258:12098-12101, 1983.
36. **Lawler, J.; Derick, L.H.; Connolly, J.E.; Chen, J.H.;** and **Chao, F.C.:** The structure of human platelet thrombospondin. *J. Biol. Chem.,* 260:3762-3772, 1985.
37. **Lawler, J.,** and **Hynes, R.O.:** The structure of human thrombospondin, an adhesion glycoprotein with multiple calcium-binding sites and homologies with several proteins. *J. Cell Biol.,* 103:1635-1648, 1986.
38. **Lawler, J.; Weinstein, R.;** and **Hynes, R.O.:** Cell attachment to thrombospondin: the role of ARG-GLY-ASP, calcium, and integrin receptors. *J. Cell Biol.,* 107:2351-2361, 1988.
39. **Lawler, J.; McHenry, K.; Duquette, M.;** and **Derick, L.:** Characterization of human thrombospondin-4. *J. Biol. Chem.,* 270:2809-2814, 1995.
40. **Lindseth, R.E.; Danigelis, J.A.; Murray, D.G.;** and **Wray, J.B.:** Spondylo-epiphyseal dysplasia (Pseudoachondroplastic type). *Amer. J. Dis. Child.,* 13:721-726, 1967.
41. **Loughlin, J.; Irven, C.; Mustafa, Z.; Briggs, M.D.; Carr, A.; Lynch, A-A.; Knowlton, R.G.; Cohn, D.H.;** and **Sykes, B.:** Identification of five novel mutations in cartilage oligomeric matrix protein gene in pseudoachondroplasia and multiple epiphyseal dysplasia. *Human Mutat. Suppl.,* 1:S10-S17, 1998.
42. **Maddox, B.K.; Keene, D.R.; Sakai, L.Y.; Charbonneau, N.L.; Morris, N.P.; Ridgway, C.C.; Boswell, B.A.; Sussman, M.D.; Horton, W.A.; Bachinger, H.P.;** and **Hecht, J.T.:** The fate of cartilage oligomeric matrix protein is determined by the cell type in the case of a novel mutation in pseudoachondroplasia. *J. Biol. Chem.,* 272:30993-30997, 1997.
43. **Malashkevich, V.N.; Kammerer, R.A.; Efmov, V.P.; Schulthess, T.;** and **Engel, J.:** The crystal structure of a five-stranded coiled coil in COMP: A proteotype in channel. *Science,* 274:761-765, 1996.
44. **Maroteaux, P.,** and **Lamy, M.:** Les formes pseudo-achondroplastiques des dysplasies spondylo-epiphysaires. *Presse. Med.,* 67:383-386, 1959.
45. **Maynard, J.A.; Cooper, R.R.;** and **Ponseti, I.V.:** A unique rough surface endoplasmic reticulum inclusion in pseudoachondroplasia. *Lab. Invest.,* 26:40-44, 1972.
46. **McKeand, J.; Rotta, J.;** and **Hecht, J.T.:** Natural history study of pseudoachondroplasia. *Am. J. Med. Genet.,* 63:406-410, 1996.
47. **Mitas, M.:** Trinucleotide repeats associated with human diseases. *Nucleic Acids Res.,* 12:2245-2253, 1997.
48. **Misenheimer, T.M.,** and **Mosher, D.F.:** Calcium ion binding to thrombospondin 1. *J. Biol. Chem.,* 270:1729-1733, 1995.
49. **Mörgelin, M.; Heinegård, D.; Enge, J.;** and **Paulsson, M.:** Electron microscopy of native cartilage oligomeric matrix protein purified from the Swarm rat chondrosarcoma reveals a five-arm structure. *J. Biol. Chem.,* 267:6137-6141, 1992.
50. **Muragaki, Y.; Mariman, E.C.M.; van Berrsum, S.E.C.; Perala, M.; van Mourik, J.B.A.; Warman, M.L.; Olsen, B.R.;** and **Hamel, B.C.J.:** A mutation in the gene encoding the alpha-2 chain of the fibril-associated collagen IX, COL9A2, causes multiple epiphyseal dysplasia (EDM2). *Nat. Genet.,* 12:103-105, 1996.
51. **Newton, G.; Weremowicz, S.; Morton, C.C.; Copeland, N.G.; Gilbert, D.J.; Jenkins, N.A.;** and **Lawler, J.:** Characterization of human and mouse cartilage oligomeric matrix protein. *Genomics,* 24:435-439, 1994.
52. **Oehlmann, R.; Summerville, G.P.; Yeh, G.; Weaver, E.J.; Jimenez, S.A.;** and **Knowlton, R.G.:** Genetic linkage mapping of multiple epiphyseal dysplasia to the pericentromeric region of chromosome 19. *Am. J. Hum. Genet.,* 54:3-10, 1994.
53. **Oldberg, Å.; Antonsson, P.; Lindbloom, K.;** and **Heinegård, D.:** COMP (cartilage oligomeric matrix protein) is structurally related to the thrombospondins. *J. Biol. Chem.,* 267:22346-22350, 1992.
54. **O'Rourke, K.M.; Laherty, C.D.;** and **Dixit, V.M.:** Thrombospondin 1 and thrombospondin 2 are expressed as both homo- and heterotrimers. *J. Biol. Chem.,* 267:24921-24924, 1992.
55. **Qabar, A.; Derick, L.; Lawler, J.;** and **Dixit, V.:** Thrombospondin 3 is a pentameric molecule held together by interchain disulfide linkage involving two cysteine residues. *J. Biol. Chem.,* 270:12725-12729, 1995.

56. **Sottile, J.; Seleue, J.;** and **Mosher, D.F.:** Synthesis of truncated amino-terminal trimers of thrombospondin. *Biochemistry,* 30:6556-6562, 1991.
57. **Shiang, R.; Thompson, L.M.; Zhu, Y-Z.; Church, D.M.; Fielder, T.J.; Bocian, M.; Winokur, S.T.;** and **Wasmuth, J.J.:** Mutations in the transmebrane domain of FGFR3 cause the most common genetic from of dwarfism, achondroplasia. *Cell,* 78:335-342, 1994.
58. **Shen, Z.; Heinegård, D.;** and **Sommarin, Y.:** Distribution and expression of cartilage oligomeric matrix protein and bone sialoprotein show marked changes during rat femoral head development. *Matrix Biology,* 14:773-781, 1995.
59. **Stanescu, V.; Maroteaux, P.;** and **Stanescu, R.:** The biochemical defect of pseudoachondroplasia. *Europ. J. Pediat.,* 138:221-225, 1982.
60. **Stanescu, V.; Stanescu, R.;** and **Marteaux, P.:** Pathogenic mechanisms in osteochondro-dysplasias. *J. Bone and Joint Surg.,* 66-A:817-836, 1984.
61. **Stanescu, R.; Stanescu, V.; Muriel, M-P.;** and **Maroteaux, P.:** Multiple epiphyseal dysplasia, Fairbank type: Morphologic and biochemical study of cartilage. *Am. J. Med. Genet.,* 45:501-507, 1993.
62. **Stevens, J.W.; Rapp, T.B.; Martin, J.A.; Maynard, J.A.; Vertel, B.A.;** and **Hecht, J.T.:** Stable transfection of chondrocytes with mutant human COMP. *Trans. Orthop. Res. Soc.,* 23:103, 1998.
63. **Susic, S.; McGrory, J.; Ahier, J.;** and **Cole, W.G.:** Multiple epiphyseal dysplasia and pseudoachondroplasia due to novel mutation in the calmodulin-like repeats of cartilage oligomeric matrix protein, *Clin. Genet.,* 51:219-224, 1997.
64. **Susic, S.; Ahier, J.;** and **Cole, W.G.:** Pseudoachondroplasia due to the substitution of the highly conserved Asp482 by Gly in the seventh calmodulin-like repeat of cartilage oligomeric matrix protein. *Hum. Mutat. Suppl.,* 1:S125-S127, 1998.
65. **Vos, H.L.; Devarayalu, S.; de Vries, Y.;** and **Bornstein, P.:** Thrombospondin 3 (Thbs3), a new member of the thrombospondin gene family. *J. Biol. Chem.,* 267:12192-12196, 1992.
66. **Wynne-Davies, R.; Hall, C.M.;** and **Young, I.D.:** Pseudoachondroplasia: Clinical diagnosis at different ages and comparison of autosomal dominant and recessive types. A review of 32 patients (26 kindred). *J. Med. Genet.,* 23:425-434, 1986.
67. **Yu, A.; Dill, J.;** and **Mitas, M.:** The purine-rich trinucleotide repeat sequences d(CAG)15 and d(GAC)15 form hairpins. *Nucleic Acids Res.,* 23:4055-4057, 1995.
68. **Zaia, J.; Boynton, R.E.; McIntosh, A.; Marshak, D.R.; Olsson, H.; Heinegård, D.;** and **Barry, F.P.:** Post-translational modifications in cartilage oligomeric matrix protein. Characterization of the N-linked oligosaccharides by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. *J. Biol. Chem.,* 272:14120-14126, 1997.

COLLAGEN FIBRIL DIAMETER DISTRIBUTIONS IN RABBIT ANTERIOR CRUCIATE AND MEDIAL COLLATERAL LIGAMENTS: CHANGES WITH MATURATION

Robert A. Hart*
Wayne H. Akeson**
Kevin Spratt***
David Amiel**

ABSTRACT

This study presents morphometric analyses of the collagen fibril diameters of rabbit anterior cruciate and medial collateral knee ligaments of New Zealand White rabbits (young, age two months and adult, age thirty-six to forty months). Measurements were made from transmission electron micrographs of transverse ligament sections of approximately 50,000x magnification. Statistically significant differences in the mean fibril diameters were found between the anterior cruciate and medial collateral ligaments of the thirty-six to forty month old animals (.069 ± .005, .092 ± .016 mm, p < .1); however, no statistical significance was found for differences between these ligaments in two month old animals (.077 ± .006, .082 ± .009, p > .1). These data support the idea that known differences in fibril distributions of adult rabbit anterior cruciate and medial collateral ligaments develop with maturation, and may reflect both the cellular environment in which the fibrocytes of these ligaments are subject to, as well as the developmental genetic program of these cell populations.

*Department of Orthopaedics and Rehabilitation, Oregon Health Sciences University, Portland Oregon.

**Department of Orthopaedics, University of California San Diego and Veterans Administration Medical Center, La Jolla, California.

***Department. of Orthopaedics, University of Iowa Hospitals and Clinics, Iowa City, Iowa

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Address correspondence to
David Amiel, Ph.D.
Professor of Orthopaedics
Department of Orthopaedics
University of California, San Diego
La Jolla CA 92093-0630.
PH: 619 534 2676
FAX 619 534 5304
fshepherd@ucsd.edu

INTRODUCTION

Substantial work has been performed in recent years describing differences between dense collagenous tissues with similar gross appearances. It is well recognized that extra-articular ligaments such as the medial collateral ligament can heal effectively when injured, while intra-articular ligaments such as the anterior cruciate ligament fail to mount an effective healing response. Careful examination of these and other connective tissues has led to the realization that variation in structure and function exists between these ligaments as well as within individual ligaments themselves[1-6,11].

Differences between the anterior cruciate and medial collateral ligaments have been identified at the histological, biochemical, ultrastructural, and biomechanical levels. Differences in fibroblast populations exist within the rabbit anterior cruciate and medial collateral ligaments, and anterior cruciate ligament fibroblasts having an ovoid, more chondrocytic appearance than those of the medial collateral ligament, with less rapid proliferation noted on cell cultures[5-6]. A greater amount of ground substance surrounding anterior cruciate ligament fibroblasts was also observed. Significant differences in the mechanical properties have also been described, the anterior cruciate ligament being found to have a substantially lower linear modulus and tensile strength than the medial collateral ligament. Biochemical testing has shown a higher glycosaminoglycan (GAG) level in the cruciates compared to the medial collateral ligament, as well as a difference in the pattern of reducible cross-links[1,2]. Morphometric studies comparing the fibril diameter distributions of anterior cruciate and medial collateral ligaments have demonstrated a significantly greater mean fibril diameter in the medial collateral ligaments of adult rabbits[4].

Substantial work has demonstrated changes in many of these same properties with maturation and aging in many types of collagenous tissues. Woo et al. (1990) demonstrated an increase in both the mechanical stiffness and linear modulus of the medial collateral ligament with maturation to adulthood in rabbits with a gradual decline with aging from twelve to thirty-six months in male and twelve to forty-eight months in fe-

male rabbits[12]. Similar mechanical changes with aging have been shown in the anterior cruciate ligament of dogs as well as humans and rhesus monkeys[7,10].

The biochemistry and ultrastructure of these ligaments has also been shown to alter with maturation and aging. Amiel et al. (1991) showed that reducible crosslinks decreased substantially from age two months to twelve months, with further smaller decreases to age thirty-six months in rabbit anterior cruciate and medial collateral ligaments, while nonreducible pyridinoline crosslinks were shown to increase in density during the same intervals. Changes in cell morphology and collagen fibril fragmentation of rabbit anterior cruciate and medial collateral ligaments were also noted, as well as a decrease dry weight collagen densities with aging from twelve to thirty-six months[2].

Vasseur et al. (1985) described changes including decreased fibroblast densities and failure to maintain collagen fibers and bundles with aging in the anterior cruciate ligament of dogs[10]. Parry et al. (1978a, 1978b) measured changes in the fibril diameter distributions in the suspensory ligament and superficial flexor tendon of the horse, demonstrating a decrease in the number of larger diameter fibrils with age[8,9].

In this study, the fibril diameter distributions of rabbit anterior cruciate and medial collateral ligaments are measured for rabbits sacrificed at ages of two months and thirty-six to forty months, respectively. Comparisons of these data are made between the anterior cruciate and medial collateral ligaments at these two age groups. The goal of this study is to determine whether previously observed differences between the fibril distributions of anterior cruciate and medial collateral ligaments of mature rabbits[4] are present in immature animals and whether these differences are maintained with aging beyond skeletal maturity.

MATERIALS AND METHODS

The anterior cruciate and medial collateral ligaments from the hind limbs of three female New Zealand White rabbits from each of two groups aged two months and thirty-six to forty months were dissected and prepared for transmission electron microscopy as previously described[4]. All animals were treated in compliance with the National Research Counsel's criteria for humane care according to a protocol reviewed and approved by the Animal Use and Care Committee of the University of California San Diego.

Micrographs were taken from a single thin section using a Zeiss EM10 transmission electron microscope. A series of three micrographs was taken at high magnification (20,000x) of collagen fibrils within the subfascicular substance of two sampling blocks from each ligament, giving a total of six micrographs. Locations of all micrographs were randomly chosen except for the exclusion of artifacts in both series and the avoidance of cellular and external boundaries. Micrographs were printed at final magnifications of approximately 50,000x and calibrated using equal magnification micrographs of a 2160 line/mm grating replica.

Individual collagen fibril diameters were digitized from the micrographs, as previously described[4]. Based on the previous study, the sampling methods in the current study were modified. As it was previously shown that most of the variation in the data was due to variability within the fibril populations themselves and only minimally due to variation between ligament locations and animals, the current study reduced the number of animals and locations from each ligament sampled and increased the number of fibrils measured at each location.

Diameters of all fibrils falling within a 3.0 μm2 area were digitized from each micrograph. A random subsample of 175 fibrils were then chosen from each micrograph to standardize the number of fibrils in each sample. Thus, 525 fibrils were used from each longitudinal section, and a total of 1050 fibrils were used for comparison from each ligament. Average fibril diameters from each animal were computed and compared between the anterior cruciate and medial collateral ligaments for two month and thirty-six to forty month old animals using a one-way ANOVA. The level of statistical significance chosen for these comparisons was 0.1.

Due to the non-normality of the distributions, additional statistical tests were also performed. A square root transformation was first applied to the raw data to produce more normal distributions. Following this, transformed data within each high power micrograph were ranked and then separated into three sub-populations based on their rank, consisting of all fibrils falling within a 10 percentile range of the 25th, 50th, and 75th percentiles, respectively. Thus sub-populations of small, middle, and large diameter fibrils were generated from the fibril population of each micrograph. ANOVAs were then performed on these fibril sub-populations for each of six micrograph/block (three micrographs each from two sampling blocks) pairs in order to remove the potential for population variance due to the sampling variance. The comparisons of the large diameter sub-populations are reported as these are the regions of greatest difference in the curves.

RESULTS

Low power (2,500x) micrographs showed significant differences between the appearance of two month and thirty-six to forty month old animals for both the anterior cruciate and medial collateral ligaments. Ligaments from younger animals showed evidence of cellular ac-

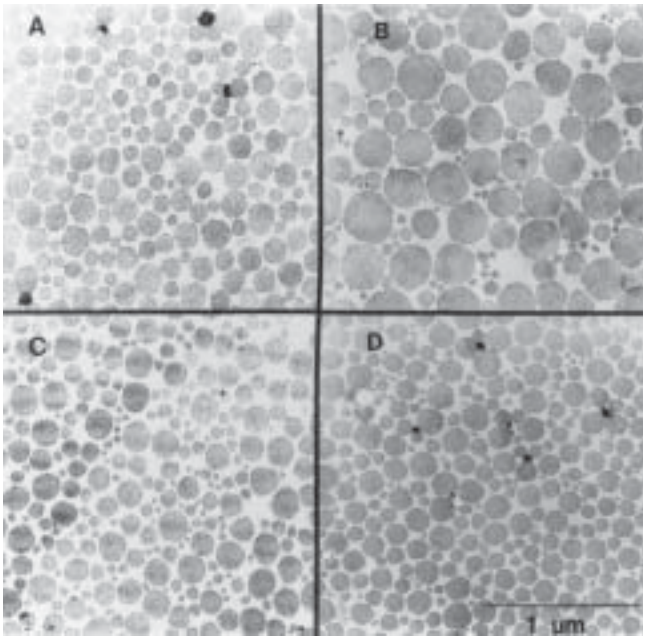

Figure 1. High power (20000x) magnification transmission electron micrographs of medial collateral ligament from two (A) and thirty-six to forty month old (B) animals. Note the clear increase in the number of larger diameter fibrils in the older specimen. (C) and (D) show corresponding photomicrographs of the anterior cruciate ligament. There is much less apparent change in the fibril content between the younger and older animals than for the medial collateral ligament.

tivity, with large, plump fibroblasts and significant amounts of rough endoplasmic reticulum. Micrographs of older animals appeared similar to those previously described for twelve month old animals, with a significantly greater amount of pericellular ground substance in the anterior cruciate ligament in comparison to the MCL, which largely consisted of uniform, densely packed collagen fibrils[4].

Micrographs of approximately 20,000x magnification are shown in Figures 1a-d. A substantial increase in the fibril diameters of the medial collateral ligament between animals of ages two and 36 months can be appreciated by comparison of Figures 1a and 1b. In contrast, it is difficult to discern substantial differences between micrographs between the anterior cruciate ligament at two months and thirty-six to forty months of age (Figures 1c and 1d).

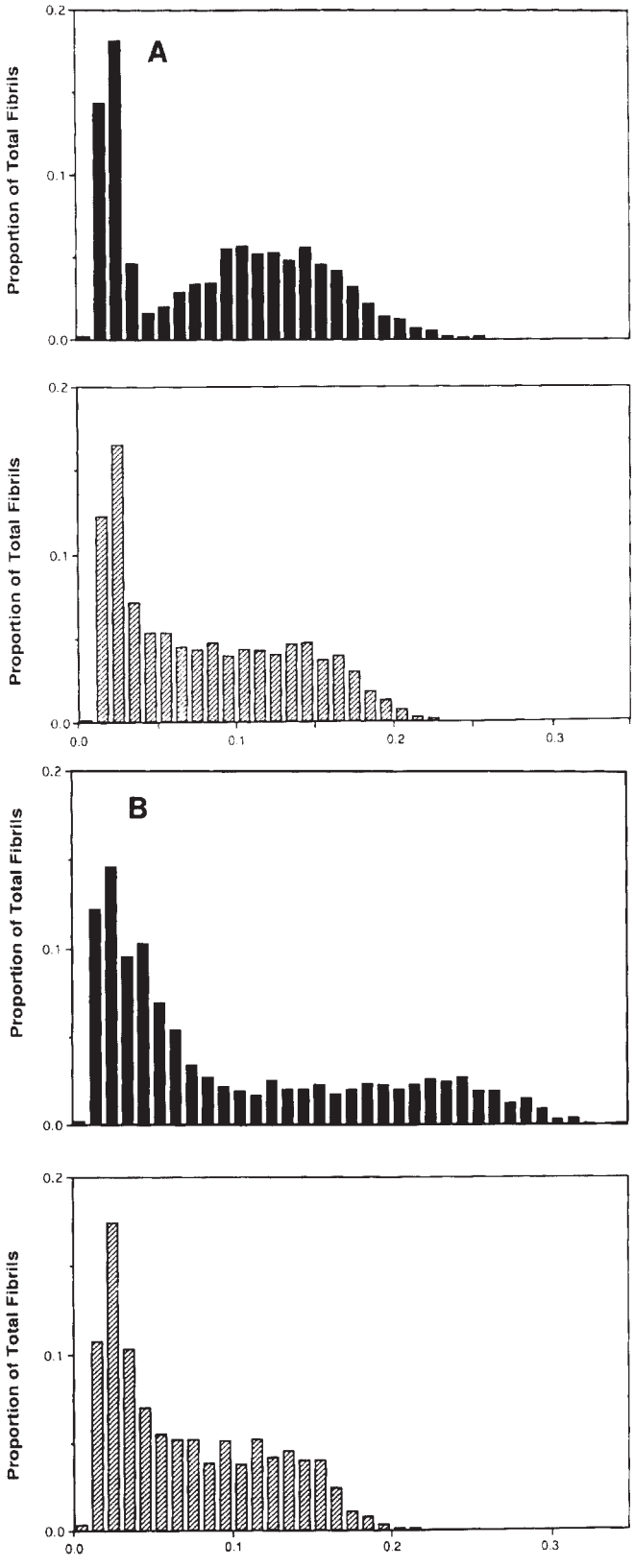

Figure 2. (A) Fibril diameter distributions for anterior cruciate and medial collateral ligaments from two month old animals. Note that the overall spread and mean of the distributions is similar. (B) Fibril diameter distributions for anterior cruciate and medial collateral ligaments from thirty-six to forty month old animals. The distributions have developed and maintained their characteristic adult profiles, with the medial collateral ligament distribution showing a larger spread and mean fibril diameter than the anterior cruciate ligament.

Figures 2A and 2B

The fibril diameter distributions for the anterior cruciate and medial collateral ligaments of two month and thirty-six to forty month old animals are shown in Figures 2a-b. It can be seen that a significantly bimodal appearance is already present in the distributions of both the anterior cruciate and medial collateral ligaments by two months of age. It can be appreciated that the distribution spreads and maximum fibril diameters are quite similar are quite similar for the ligaments at this age. By comparison, the fibril diameter distributions of older animals show more substantial differences, with the distribution of the medial collateral ligament developing and maintaining a much greater spread and maximum fibril diameter than that of the anterior cruciate ligament.

The mean fibril diameters (± one standard deviation) for anterior cruciate and medial collateral ligaments in two month old animals was .077 ± .006 and .082 ± .009 mm, respectively. In thirty-six to forty month old animals, the corresponding values were .069 ± .005 and .092 ± .016 for the anterior cruciate and medial collateral ligaments, respectively. While no detectable difference was found between these values for immature animals ($p>.1$), a statistically significant difference between the mean fibril diameters of thirty-six to forty month old animals did emerge ($p<.1$).

For all six micrograph pairs there was a statistically significant relationship between age and ligament type (anterior cruciate ligament vs. medial collateral ligament) for the large diameter fibril sub-populations ($p< .0001$). In all instances, the diameters of the fibrils from medial collateral ligament of the thirty-six to forty month old animals were significantly larger than those of the anterior cruciate ligament. These differences had increased for the thirty-six to forty month old animals over the two month old animals in all of the six comparisons.

DISCUSSION

These data can be compared with the data for mature rabbit anterior cruciate and medial collateral ligaments previously described[4]. It can be noted that the previously described differences between the anterior cruciate and medial collateral ligament fibril distributions do not appear to be present in immature animals. In addition, the distributions of the thirty-six to forty month old rabbits in the current study are very similar to those described for the twelve to eighteen month old rabbits for both the anterior cruciate and medial collateral ligaments. It thus appears that these differences develop with maturity and are largely maintained through adulthood.

The distribution of fibril diameters in collagenous tissues have been previously documented to change with maturation and aging of the animal[3,8,10]. Frank et al. found slight increases in the mean fibril diameter of the medial collateral ligament from two to ten months of age 3. While their reported mean values do not show as great an increase as those reported here, their published micrographs do appear similar to those shown here. These differences may be due to their use of automated fibril diameter measurement, while the current study used hand digitization.

These data concur with previously described biochemical, histological, and biomechanical data which show that while striking changes occur with maturation of these tissues, changes with aging appear to be somewhat less prominent[2,11]. While our results do not allow conclusions regarding cause and effect, it can be concluded that the previously reported differences between anterior cruciate and medial collateral ligament collagen fibril populations are much less striking at birth, and that following their appearance by the time of maturation they appear to be essentially maintained into senescence.

REFERENCES

1. **Amiel, D.; Frank, C.; Harwood, F.; Fronek, J.;** and **Akeson, W.:** Tendons and ligaments: A morphological and biochemical comparison. *J. Ortho. Res.,* 1:257-265, 1984.
2. **Amiel, D.; Kuiper, S.; Wallace, C.; Harwood, F.;** and **VandeBerg J.:** Age-related properties of medial collateral ligament and anterior cruciate ligament: A morphologic and collagen maturation study in the rabbit. *J Gerontology:Biological Sciences,* 46:B159-165, 1991.
3. **Frank, C.; Bray, D.; Rademaker, A.; Chrusch, C.; Sabiston, P.; Bodie, D.;** and **Rangayyan, R.:** Electron microscopic quantification of collagen fibril diameters in the rabbit medial collateral ligament: a baseline for comparison. *Connect. Tiss. Res.,* 19:11-25, 1989.
4. **Hart, R.A.; Woo, SL-Y.;** and **Newton P.:** Ultrastructural morphometry of anterior cruciate and medial collateral ligaments: an experimental study in rabbits. *J. Orthop. Res.,* 10:96-103, 1992.
5. **Lyon, R.; Akeson, W.; Amiel, D.; Kitabayashi, L.;** and **Woo, SL-Y.:** Ultrastructural differences between the cells of the medial collateral and the anterior cruciate ligaments. *Clin Orthop.,* 272:279-286, 1991.

6. **Nagineni, C.; Amiel, D.; Green, M.; Berchuck, M.;** and **Akeson, W.H.:** Characterization of the intrinsic properties of the anterior cruciate and medial collateral ligament cells: An in vitro cell culture study. *J. Orthop. Res.,* 10:465-475, 1992.
7. **Noyes, F.;** and **Grood, E.:** The strength of the anterior cruciate ligament in humans and rhesus monkeys: Age-related and species-related changes. *J. Bone Joint Surg.,* 58A:1074-1082, 1976.
8. **Parry, D.; Barnes, G.;** and **Craig, A.:** A comparison of the size distribution of collagen fibrils in connective tissues as a function of age and a possible relation between fibril size distribution and mechanical properties. *Proc. R. Soc. Lond.,* B203:305-321, 1978a.
9. **Parry, D.; Craig, A.;** and **Barnes G.:** Tendon and ligament from the horse: An ultrastructural study of collagen fibrils and elastic fibers as a function of age. *Proc. R. Soc. Lond.,* B203:293-303, 1978b.
10. **Vasseur, P.; Pool, R.; Arnoczky, S.;** and **Lau, R.:** Correlative biomechanical and histologic study of the cranial cruciate ligament in dogs. *Am. J. Vet. Res.,* 46:1842-1854, 1985.
11. **Woo, SL-Y.; Newton, P.; MacKenna, D.;** and **Lyon, R.:** A comparative evaluation of the mechanical properties of the rabbit medial collateral and anterior cruciate ligaments. *J. Biomech.,* 25:377-386, 1992.
12. **Woo, SL-Y.; Ohland, K.;** and **Weiss, J.:** Aging and sex-related changes in the biomechanical properties of the rabbit medial collateral ligament. *Mech. Aging Devel.,* 56:129-142, 1990.

EFFECT OF INTERMITTENT ADMINISTRATION OF PARATHYROID HORMONE ON FRACTURE HEALING IN OVARIECTOMIZED RATS

Hyun Woo Kim, MD and Jun Seop Jahng, MD

ABSTRACT

To evaluate the potential use as a therapeutic agent for osteoporotic fractures, we examined the effects of intermittent administration of parathyroid hormone on fracture healing in ovariectomized rats. At three months post-ovariectomy, bilateral tibial shaft fractures were induced and stabilized by intramedullary nailing with Kirschner-wires. Saline, 17-estradiol, or recombinant human PTH(1-84) was given once a day for 30 consecutive days during fracture healing. Fracture healing was assessed by morphometric and mechanical analysis of fracture callus. Intermittent parathyroid hormone administration increased the morphometric and mechanical parameters in a dose-dependent manner. 17-estradiol, a bone-resorption inhibiting agent, did not offer advantage in terms of fracture healing in ovariectomized rats. Our findings suggest that intermittent parathyroid hormone administration may benefit osteoporosis and fracture.

Osteoporosis is a major health care problem in the older population and frequently leads to orthopedic treatment for fracture repair. Drugs to treat osteoporosis can be classified according to the response of the bone. They either stimulate bone formation or inhibit bone resorption. Among the bone-forming agents, intermittent parathyroid hormone (PTH) administration has anabolic effects on bone of animals[5-7,14,15,18,19,33,34] and humans[1,21-24,32]. PTH can increase bone mass at all four envelopes: cancellous, endocortical, intracortical, and periosteal. This anabolic action of PTH does not require previous stimulation of bone resorption induced by ovariectomy[12,26,27].

From the Department of Orthopaedic Surgery
Yonsei University College of Medicine,
Severance Hospital, Seoul, Korea

Corresponding author:
Hyun Woo Kim, MD
Shriners Hospital for Children
12502 N. Pine Dr.
Tampa, FL 33612
Tel; 813-972-2250 Ext.7724
Fax; 813-978-9442
E-mail; hkim@shctampa.usf.edu

Fracture healing involves a complex pattern of interactions between local and systemic regulatory factors. The processes of normal and abnormal fracture healing, and the various factors affecting them have been widely studied. Hormones may play a substantial role in bone repair but there is lack of uniformity in the presentation of data. Many authors presume aging decreases the quality of fracture repair, and an age-related decline in the capacity for fracture repair has been noted[2,4,8,25,29]. However, the question of impaired fracture healing in osteoporotic patients, and the role of estrogen deficiency in its etiology still remains unclear.

Traditionally, PTH is well known for its catabolic action on the skeleton. To date, we are not aware of any study investigating the influences of exogenous PTH administration on fracture healing which is essentially an anabolic process. The ovariectomized (OVX) rat model causes changes in bone that resemble most of the characteristics of human postmenopausal bone loss[9,13,16,17]. It is now generally accepted that OVX rats should be used as the animal model for screening new agents for osteoporosis therapy. The present study was designed to compare fracture healing in normal and OVX rats, and to examine the effect of intermittent administration of PTH on fracture healing to evaluate its potential use as a therapeutic agent for osteoporotic fractures.

MATERIALS AND METHODS

Experimental protocols

All animal studies were carried out with the approval of the institutional review board. A total of 75, four month-old mature female Sprague-Dawley rats were used. The mean and standard deviation of weight was 256 7 grams. The animals were randomly divided into 5 groups and weight matched. They were then treated according to the protocol shown in Figure 1. Fifteen animals underwent a sham operation and served as intact controls (Group I). Bilateral ovariectomies were performed from a dorsal approach in the remaining 60 animals in the other 4 groups (Groups II, III, IV, and V). Groups of four animals were housed in a cage kept at a constant temperature and humidity. They had free access to a standard diet of rat chow and water.

Group I	Sham	Fx———— [Saline] ————
Group II	OVX	Fx———— [Saline] ————
Group III	OVS	Fx———— [Ex] ————
Group IV	OVX	Fx———— [L-PTH] ————
Group V	OVX	Fx———— [H-PTH] ————

Figure 1. Experimental protocol. Sham = sham operation, OVX = ovariectomy, Fx=fracture, E2 = 17 beta-estradiol, L-PTH = low doses of PTH, H-PTH = high doses of PTH

At three months post-surgery, all animals in the five groups underwent bilateral controlled tibial shaft fractures under intraperitoneal anesthesia with ketamine hydrochloride and xylazine at doses of 50 mg/Kg and 25 mg/Kg body weight, respectively. The desired fracture patterns were created using a modified technique of Bak and Andreassen[2,3]. Both lower extremities were shaved and prepped with povidone-iodine solution. A hole was made 4 mm proximal and 2 mm medial to the tibial tuberosity percutaneously using a 20-gauge needle. The needle was driven into the medullary canal. By rotating the needle, the canal was reamed to just proximal to the ankle joint allowing for the wire to seat and prevent it from perforating the cortex. A fracture was then created 5 mm above the tibiofibular junction by three-point bending using specially designed forceps with blunt jaws. The fractures were immediately stabilized by closed intramedullary nailing using a 0.73 mm Kirschner wire (Zimmer Co., Warsaw, Indiana, USA) through the prepared hole. Rotation was checked by comparing the alignment of the foot and the thigh. Radiographs were taken after surgery to document the fracture configuration and wire placement. A satisfactory fracture pattern was defined as transverse mid-shaft fracture without obvious angulation, comminution, or displacement, and with intramedullary fixation bridging the fracture. After recovering from the procedure, the animals were allowed to resume free activities and weight bearing in the cage.

Every day from the day of fracture surgery on, saline, estrogen, or PTH was administered to rats once a day by subcutaneous injection for 30 consecutive days: saline solution (a volume equal to the volume of the drugs given) in Group I and Group II, 17 b-estradiol (30 μg/Kg) in Group III, low doses of recombinant human PTH(1-84) (15 μg/Kg) in Group IV, and high doses of recombinant human PTH(1-84) (150 μg/Kg) in Group V. Recombinant human PTH(1-84) was commercially available from Korean Green-Cross Pharm. Corp. (Seoul, Korea) and 17-estradiol from Sigma Chemical Corp. (St. Louis, MO, USA). Animals were killed by CO_2 inhalation at 30th day post-fracture surgery, and the success of the ovariectomy was confirmed by absence of any residual ovarian tissue at sacrifice. Healing left and right tibiae were harvested after the hindlimbs were disarticulated at the knee joints. The soft tissues and fibulae were carefully cleared, preserving the integrity of callus. The intramedullary Kirschner wires were taken out through the original entrance. All tibiae of the left side were examined by morphometric analysis of periosteal callus (quantitative analysis of fracture healing), and all right tibiae were tested mechanically (qualitative analysis of fracture healing), respectively.

Morphometric measurement of fracture callus

For the decalcified section, all left tibiae were fixed in 5% formalin, decalcified, and embedded in paraffin. Serial 3-m thick sections were cut through the longitudinal axis of the tibia and stained with Hematoxylin and Eosin. Three central slices of each series showing the maximal width of the medullary cavity were selected for morphometric analysis. The evaluation was aided by a fully automated computerized image analysis system (Media Cybernetics Corp., Silverspring, Maryland, USA) attached to the light microscope. The callus area was defined as the area between the original cortex and the thin outer bridging bone shell. The length of the callus was determined by the distance from distinct lifting of periosteal tissue to a distinct "normalization", and the width of the callus was measured in its widest part. Trabecular bone per tissue area inside the callus, and the quantitated surface area of the trabecular bone in the callus were also assessed. Both sides of the callus were assessed per section, and the obtained values were averaged and plotted.

Mechanical measurement of fracture callus

For mechanical testing, all right tibiae were stored in gauze soaked in normal saline solution at -20° C until needed. All mechanical testing was done within forty-eight hours of death. All bones were similarly oriented in a material testing machine (Instron LTD WYCOMBE, Buckinghamshire, UK) and the area to be tested defined as the medial aspect of the fracture callus. A custom jig ensured consistent alignment of the bone axis with the axis of the testing machine. The bones were placed on two rounded bars separated a distance of 15 mm, and deflected by lowering a third centered bar on the healed fracture site at a constant rate of 1 mm/min until failure. The load-deflection curves were digitized and immediately analyzed. The following parameters were calculated: ultimate load, deflection until ultimate load, absorbed energy until ultimate load, and ultimate

stiffness. To normalize the raw data to compensate for differences in bone mass and cross-sectional area, the fracture surface induced by mechanical testing was further studied by scanning electron microscopy (SEM). Internal and external diameters in the load direction and perpendicular to it were obtained using a computer image analysis system. Cross-section was approximated to a thick-walled elliptical tube, and the ultimate stress was then calculated from the bending moment and the second moment of area[2,3,17].

Measurements of all parameters are expressed as group means ± SD. Significant differences between group means ($p < 0.05$) were determined from analysis of variance (ANOVA) followed by *post hoc* multiple comparisons using Tukey's Studentized Range test for inter-group differences.

RESULTS

Of 75 rats used for this study, 12 were eliminated; five rats died during surgery, and technical failure of the fracture procedure or intramedullary nailing resulted in another seven animals being eliminated from the experiment. There were no postoperative infections. In the remaining 63 rats, the intramedullary fixation maintained axial alignment of the fracture without interfering with the formation of external fracture callus.

Morphometric measurements of fracture callus (Table I)

Morphometric evaluation of the callus in the group of animals that underwent the sham operation revealed a relatively smaller callus that mainly consisted of a trabecular, woven bone network. On the other hand, the rats post-OVX with or without 17-estradiol treatment (Groups II and III) exhibited a much looser cancellous network in the callus which was more abundant in the fibrous marrow and cartilage than in the sham-operated or PTH-treated OVX group.

There were pronounced differences between saline or estrogen-treated OVX rats (Groups II and III) and PTH-treated OVX rats (Groups IV and V) in the size and structure of the external calluses. The PTH-treated animals showed a more pronounced callus formation affecting a larger area beyond the original cortex. The callus was not as loosely woven as trabecular bone of Group II or III. Specifically, the high dose PTH group was comparable to the sham group in terms of percent trabecular bone volume within the callus, and the total trabecular bone volume area of callus.

TABLE I

MORPHOMETRIC MEASUREMENTS OF TIBIAL FRACTURES IN THE RAT. (MEAN ± SD)

	Group I (n=13)	Group II (n=14)	Group III (n=12)	Group IV (n=13)	Group V (n=11)
Callus length (mm)	8.92 ± 2.38	10.08 ± 2.34	10.20 ± 2.02	10.45 ± 2.04	11.27 ± 2.07
Callus diameter (mm)	0.91 ± 0.21	1.11 ± 0.17	1.08 ± 0.19	1.41 ± 0.27 [a,b,c]	1.45 ± 0.34 [a,b,c]
% Trabecular bone in callus (%)	92.04 ± 2.80	58.44 ± 5.24 [a]	61.16 ± 4.77 [a]	76.83 ± 0.84 [a,b,c]	86.60 ± 6.53 [a,b,c,d]
Trabecular bone area of callus (mm^2)	7.34 ± 1.54	7.14 ± 1.18	7.19 ± 0.96	8.40 ± 1.85 [b]	9.22 ± 2.07 [b,c]

[a] $p < 0.05$, versus Group I

[b] $p < 0.05$, versus Group II

[c] $p < 0.05$, versus Group III

[d] $p < 0.05$, versus Group IV

TABLE II

MECHANICAL MEASUREMENTS OF FRACTURE CALLUS

	Group I (n=13)	Group II (n=14)	Group III (n=12)	Group IV (n=13)	Group V (n=11)
Ultimate load (N)	79.73 ± 6.06	34.93 ± 9.57[a]	36.24 ± 12.39 [a]	55.08 ± 7.27 [a, b,c]	70.55 ± 8.02 [b,c,d]
Deflection (mm)	0.21 ± 0.08	0.35 ± 0.15 [a]	0.31 ± 0.17	0.25 ± 0.09	0.27 ± 0.14
Absorbed energy (N • mm)	10.60 ± 3.47	4.41 ± 1.46 [a]	4.59 ± 2.34 [a]	4.72 ± 2.00 [a]	8.32 ± 1.20 [b,c,d]
Ultimate stiffness (N / mm)	51.15 ± 12.49	23.45 ± 6.84 [a]	27.69 ± 9.43 [a]	34.17 ± 12.90 [a]	42.67 ± 19.52 [b]
Ultimate stress (N / mm^2)	37.94 ± 5.32	16.10 ± 2.90 [a]	15.70 ± 2.34 [a]	19.32 ± 4.02 [a]	31.18 ± 2.52 [b,c]

[a] $p < 0.05$, versus Group I

[b] $p < 0.05$, versus Group II

[c] $p < 0.05$, versus Group III

[d] $p < 0.05$, versus Group IV

Mechanical measurements of fracture callus (Table II)

The specimens tested mechanically all failed at the original fracture site. Mechanical testing indicated that PTH administration resulted in an increase in ultimate load in OVX rats, whereas no significant differences were seen between the groups injected with saline or 17- estradiol (Group I>V>IV>III=II, $p<0.05$). Other significant differences were in the increase in the absorbed energy and the ultimate stress of the group of saline-treated normal rats and high doses of PTH-treated OVX rats (Group I=V>IV=II=III, $p<0.05$). Scanning electron microscopy showed a tendency for PTH-treated rats to have more trabecular bone in their callus resulting in the increase of callus diameter and cross sectional area of the fracture than that of sham, OVX only, or OVX plus estrogen-treated groups. However, they were also more porotic than the sham operated group (Fig. 2).

DISCUSSION

This study confirmed earlier observations that fracture healing is impaired in the ovariectomized rat[11,28,31]. An inhibition of mineralized bone formation and reduction of trabecular bone formation in later stages of fracture healing have been noted in this model. Although, in our study, there were no significant differences in external callus diameter between the sham (Group I) and the OVX-only group (Group II), Group II rats tended to have larger diameters of callus which also showed poorer bone formation in the callus than in the sham group. Many studies showed that ovariectomy in mature female rats results in an increase in transient periosteal and endosteal bone formation, which then exhibits a time-related decline[5,15]. As we only observed the end of the callus phase, it is uncertain that our findings are a consequence of an increase in periosteal bone formation and possibly a small increase in endosteal bone formation at early times postovariectomy, or are a characteristic pattern of fracture repair found in OVX rats.

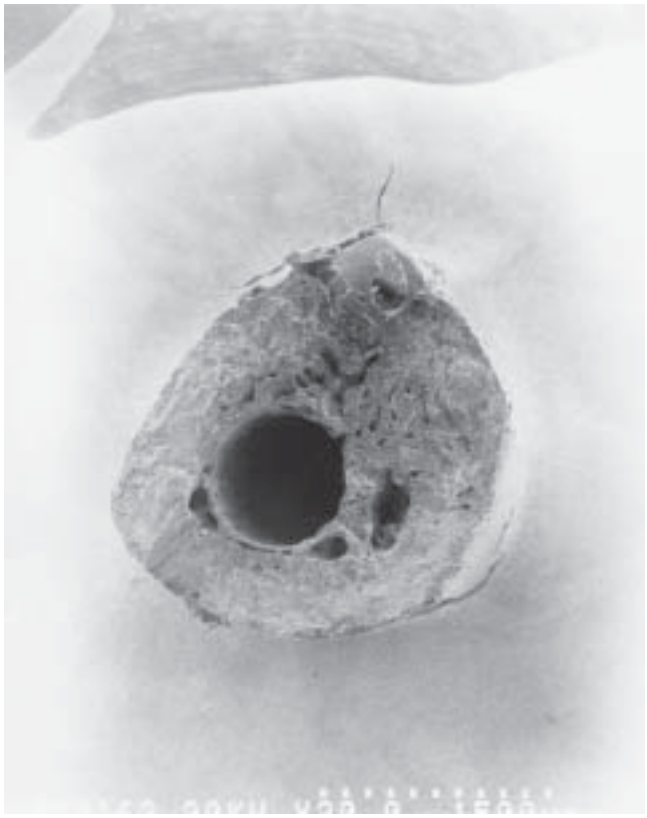

Figure 2A.

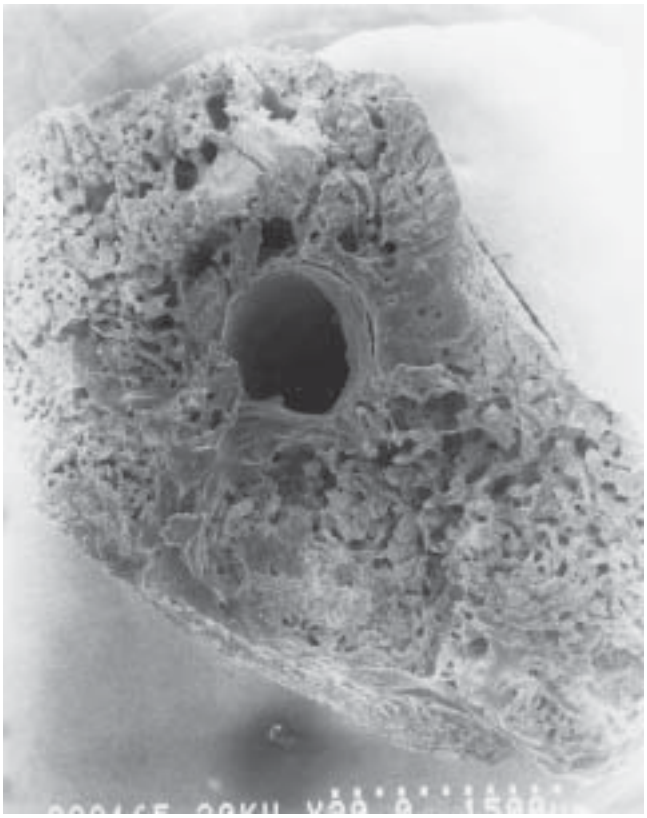

Figure 2B.

Figures 2A-B. SEM findings of fracture callus cross-section in sham-operated (a) and PTH-treated OVX rats (b). PTH-treated OVX rats have more trabecular bone in their callus than that of sham-operated group and they were more porotic than sham-operated rats.

The primary question addressed in this study is whether PTH improves fracture repair in OVX rat model. Our results demonstrated that intermittent PTH administration increased the morphometric and mechanical parameters of fracture callus. PTH is commonly believed to trigger the catabolism of bone by stimulating osteoclastic resorption. On the other hand, intermittent administration of PTH has been found to stimulate bone formation in many human and animal studies. In human studies, reported side effects have been confined to transient reddening around the injection site and transient elevation of plasma calcium above the upper limit of normal at about 6 hours after injection. The mechanism behind the anabolic effect of intermittent PTH treatment is not fully understood, but most studies in rodents using PTH analogues suggest that c-AMP dependent pathways play the predominant role in mediating the osteoinductive actions of PTH[6]. PTH acts directly on the osteoblast by binding to membrane receptors. The resulting increased presence of secondary messengers as c-AMP, phosphoinositol metabolites and cytosolic Ca^{2+} may lead to cellular proliferation and differentiation. Recently, it has been suggested that the anabolic action of PTH is substituted or partly mediated via an increased synthesis of local growth factors in the bone tissues[10,20]. Pfeilschifter et al[20] revealed that the anabolic effect of PTH on bone mass is accompanied by progressive increases in bone matrix-associated insulin-like growth factor-I (IGF-I) and transforming growth factor-β (TGF-β), and PTH has no effect on circulating IGF-I. It may suggest that the increase of bone matrix IGF-I is due to the local effect of PTH on bone tissue directly rather than to an increase of circulating IGF-I. Recent studies also demonstrated regulatory roles for those local growth factors in the initiation and the development of the fracture callus. On the basis of those findings, we questioned whether PTH also enhance fracture healing.

We found that the major effect of PTH on fracture healing was an increase in the bony tissue of the fracture callus, as reflected by morphometric parameters. But as we did not make serial observations of the entire fracture healing process, we are not certain that the increase in bony callus is due to an increase in car-

tilaginous cell number, or due to an increase in intracellular or extracellular matrix. Although we can not clarify whether our findings resulted from increases in one of two distinct mechanisms (intramembranous bone formation and endochondral replacement), seemingly increased cross-sectional area associated with relative narrowing of the central marrow cavity of the fracture surface noted in scanning electron microscopic study in PTH-treated rats suggests both possibilities. Histologic findings and SEM also indicated that PTH-treated rats have more trabecular bone in their callus resulting in an increase of callus diameter, but remained more porotic than the sham-operated group. This fact explains the lack of significant differences in ultimate load and ultimate stress value between sham-operated and PTH-treated groups despite differences in their external callus diameter or cross-sectional area. It means a qualitative difference rather than a quantitative difference in callus tissue between groups, and that PTH treatment of the OVX rats induces increased amounts of bone tissue in their callus, but which also has the altered mechanical properties induced by ovariectomy.

From studies concerning the effects of estrogen in OVX rats, signs both of enhanced and delayed bone repair in the rats have been reported. Danielsen et al[1] noted estrogen treatment of both intact and ovariectomized rats tended to reduce the rate of periosteal bone formation. Turner et al[30] found transient increases in the rate of bone formation, an early effect of ovariectomy, were reversed by the administration of 17-β estradiol. Our results showed administration of 17-β estradiol, an inhibitor of bone resorption, does not significantly influence any of the parameters in question, which means estrogen offers no advantage in terms of fracture healing in OVX rats.

The development of systemic methods for the enhancement of fracture healing is attractive, but the introduction of a systemic agent that targets the fracture healing process requires a high degree of specificity and more extensive investigation. To date, no exogenously administered systemic factors or treatments have been shown to accelerate fracture healing in a reproducible manner. Based on our preclinical study, it is suggested that intermittent PTH therapy in the estrogen-deficient osteopenic state benefits fracture healing, and PTH is likely to receive increasing study on fracture repair as well as osteoporosis. Further study is needed in large animal models, and attention should be focused on the effects of different doses or duration of the drugs used, and the relationship with local growth factors.

REFERENCES

1. **Audran, M.; Basle, M.;** and **Defontaine, A.:** Transient hyperparathyroidism induced by synthetic hPTH(1-34) treatment. *J. Clin. Endocrinol. Metab.,* 64:937-943, 1987.
2. **Bak, B.,** and **Andreassen, T.T.:** The effect of aging on fracture healing in the rat. *Calcif. Tissue Int.,* 45:292-297, 1989.
3. **Bak, B.; Jorgensen, P.H.;** and **Andreassen, T.T.:** The stimulating effect of growth hormone on fracture healing is dependent on onset and duration of administration. *Clin. Orthop.,* 264:295-301, 1991.
4. Bick, E,M.: The physiology of the aging process in the musculoskeletal apparatus. Clin. Orthop., 316:5-9, 1995.
5. **Danielsen, C.C.; Mosekilde, L.;** and **Svenstrup, B.:** Cortical bone mass, composition, and mechanical properties in female rats in relation to age, long-term ovariectomy, and estrogen substitution. *Calcif. Tissue Int.,* 52:26-33, 1993.
6. **Dempster, D.W.; Cosman, F.; Parisien, M.; Shen, V.;** and **Lindsay, R:** Anabolic actions of parathyroid hormone on bone. *Endocr. Rev.,* 14:690-709, 1993.
7. **Ejersted, C.; Andreassen, T.T.;** and **Oxlund, H.:** Human parathyroid hormone (1-34) and (1-84) increase the mechanical strength and thickness of cortical bone in rats. *J. Bone Miner Res.,* 8: 1097-1101, 1993.
8. **Ekeland, A.; Engesaeter, L.B.;** and **Langeland, N.B.:** Influence of age on mechanical properties of healing fractures and intact bones in rats. *Acta Orthop. Scand.,* 53:527-534, 1982.
9. **Frost, H.M.,** and **Jee, W.S.S.:** On the rat model of human osteoporosis. *Bone Miner,* 18:227-236, 1992.
10. **Gunness, M.,** and **Hock, J.M.:** Anabolic effect of parathyroid hormone is not modified by supplementation with insulin like growth factor (IGF-I) or growth hormone in aged female rats fed on energy-restricted or ad libitum diet. *Bone,* 16:199-207, 1995.
11. **Hill, E.L.; Kraus, K.;** and **Lapierre, K.P.:** Ovariectomy impairs fracture healing after 21 days in rats. *Trans. Orthop. Res. Soc.,* 20:230, 1995.
12. **Hock, J.M.; Gera, I.; Fonseca, J.;** and **Raisz, L.G.:** Human parathyroid hormone (1-34) increases bone mass in ovariectomized and orchidectomized rats. *Endocrinology,* 122:2899-2904, 1988.
13. **Kalu, D.N.:** The ovariectomized rat model of postmenopausal bone loss. *Bone Miner,* 1991; 15:175-192, 1991.
14. **Liu, C.C.,** and **Kalu, D.N.:** Human parathyroid hormone prevents bone loss and augments bone formation in sexually mature ovariectomized rats. *J. Bone Miner Res.,* 9:973-982, 1990.

15. **Liu, C.C.; Kalu, D.N.; Salerno, E.; Echon, R.; Hollis, B.W.;** and **Ray, M.:** Preexisting bone loss associated with ovariectomy in rats is reversed by parathyroid hormone. *J. Bone Miner Res.,* 6:1071-1080, 1991.
16. **Miller, S.C.; Bowman, B.M.; Miller, M.A.;** and **Bagi, C.M.:** Calcium absorption and osseous organ-, tissue-, and envelope-specific changes following ovariectomy in rats. *Bone,* 12:439-446, 1991.
17. **Mosekilde, L.:** Assessing bone quality - animal models in preclinical osteoporosis research. *Bone.* 1995; 17:343s-352s, 1995.
18. **Mosekilde, L.; Danielsen, C.C.; Sogaard, C.H.; McOsker, J.E.;** and **Wronski, T.J.:** The anabolic effects of parathyroid hormone and cortical bone mass, dimensions and srength-assessed in a sexually mature, ovariectomized rat model. *Bone,* 16:223-230, 1995.
19. **Oxlund, H.; Ejersted, C.; Andreassen, T.T.; Torring, O.;** and **Nilsson, M.H.L.:** Parathyroid hormone (1-34) and (1-84) stimulate cortical bone formation both from periosteum and endosteum. *Calcif. Tissue Int.,* 53:394-399, 1993.
20. **Pfeilschifter, J.; Laukhuf, F.; Muller-Beckmann, B.; Blum, W.F.; Pfister, T.;** and **Ziegler, R.:** Parathyroid hormone increases the concentration of insulin-like growth factor-I and transforming growth factor beta 1 in rat bone. *J. Clin. Invest.,* 96:767-774, 1995.
21. **Reeve, J.:** PTH: A future role in the management of osteoporosis ? *J. Bone Miner Res.,* 11:440-445, 1996.
22. **Reeve, J.; Davies, U.M.; Hesp, R.; McNally, E.;** and **Katz, D.:** Treatment of osteoporosis with human parathyroid peptide and observations on effect of sodium fluoride. *Br. Med. J.,* 301:314-318, 1990.
23. **Reeve, J.; Meunier, P.J.;** and **Parsons, J.A.:** Anabolic effect of human parathyroid hormone on trabecular bone in involutional osteoporosis: a multicenter trial. *Br. Med. J.,* 280:1340-1344, 1980.
24. **Reeve, J.; Williams, D.; Hesp, R.; Hulme, P.;** and **Klenerman, L.:** Anabolic effects of low doses of a fragment of human parathyroid hormone on the skeleton in postmenopausal osteoporosis. *Lancet.,* 1:1035-1038, 1976.
25. **Siver, J.J.,** and **Einhorn, T.A.:** Osteoporosis and aging. *Clin. Orthop.,* 316:10-20, 1995.
26. **Tada, K.; Yamamuro, T.; Okamura, H.; Kasai, R.;** and **Takahashi, H.E.:** Restoration of axial and appendicular bone volumes by hPTH in parathyroidectomized and osteopenic rats. *Bone,* 11:163-169, 1990.
27. **Tam, C.S.; Heersche, J.N.M.; Murray, T.M.;** and **Parsons, J.A.:** Parathyroid hormone stimulates the bone apposition rate independently of its resorptive action. *Endocrinology,* 110:506-512, 1982
28. **Tsahakis, P.J.; Martin, D.F.; Harrow, M.E.; Kiebzak, G.M.;** and **Meyer, Jr., R.A.:** Ovariectomy impairs femoral fracture healing in adult female rats. *Trans. Orthop. Res. Soc.,* 21:624, 1996.
29. **Tonna, E.A.,** and **Cronkite, E.P.:** Changes in skeletal proliferative response to trauma concomitant with aging. *J. Bone and Joint Surg.,* 44-B: 1557-1568, 1962.
30. **Turner, R.T.; Vandersteenhoven, J.J.;** and **Bell, N.H.:** The effects of ovariectomy and 17- estradiol on cortical bone histomorphometry in growing rats. *J. Bone Miner Res.,* 2:115-122, 1987.
31. **Walsh, W.R.; Sherman, P.; Howlett, C,R.; Sonnabend, D.H.;** and **Ehrlich, M.G.:** Fracture healing in a rat osteopenia model. *Clin. Orthop.,* 342:218-27, 1997.
32. **Whitfield, J.F.,** and **Morley, P.:** Small bone-building fragments of parathyroid hormone: New therapeutic agents for osteoporosis. *Trends Pharmacol. Sci.,* 16:382-386, 1995.
33. **Whitfield, J.F.; Morley, P.; Ross, V.;Isaacs, R.J.;** and **Rixon, R.H.:** Restoration of severely depleted femoral trabecular bone in ovariectomized rats by parathyroid hormone (1-34). *Calcif. Tissue Int.,* 56:227-231, 1995.
34. **Wronski. T.J.,** and **Yen, C.F.:** Anabolic effects of parathyroid hormone on cortical bone in ovariectomized rats. *Bone,* 15:51-58, 1994.

HIP OSTEOTOMY ARTHROPLASTY: TEN-YEAR FOLLOW-UP

Thomas A. DeCoster, MD*
Steven J. Incavo, MD**
Darren Swenson, MD***
John W. Frymoyer, MD****

ABSTRACT

We previously reported the initial success of combined osteotomy and arthroplasty of the hip for arthritis with femoral deformity. This technique has gained acceptance. We now report, for the first time, the ten year clinical and radiographic results with histology of 2 specimen.

The osteotomies healed and the proximal femoral segment remained viable. One of three patients is symptom free without subsequent operative treatment. One of three patients had revision for acetabular loosening at eight years and biopsy of the proximal femur showed the proximal femoral segment to be viable. One of three patients had loosening of a macrofit bipolar prosthesis which required revision to total hip replacement at five years. Histology revealed viability of the proximal femur. All three patients are doing well at ten year follow-up.

Based on the results of this study and current knowledge, the technique of osteotomy and arthroplasty for hip arthritis associated with femoral deformity is effective when combined with current techniques of ingrowth femoral component of total hip arthroplasty.

INTRODUCTION

Femoral osteotomy is indicated for a variety of pathologic conditions of the hip. The Southwick subtrochanteric antero-lateral closing wedge femoral osteotomy for slipped capital femoral epiphysis restores the normal relationship of the femoral head to shaft by creating a subtrochanteric deformity to compensate for the chronic deformity of the head-neck junction from SCFE. If hip degenerative arthritis occurs years later, standard total hip arthroplasty is not possible due to the subtrochanteric iatrogenic deformity. We previously described the technique of postero-medial closing wedge subtrochanteric osteotomy combined with arthroplasty for the treatment of patients with severe hip arthritis and proximal femoral deformity. Our initial report indicated that the technique was technically feasible, the osteotomies healed and results in 3 patients at 2 years was comparable to standard hip arthroplasty. We now report the results at minimum ten year follow-up of this small series of patients.

MATERIALS AND METHODS

Three patients previously reported with combined femoral osteotomy and hip arthroplasty were reviewed at a minimum of ten years with clinical and radiographic examinations and a hip score. Particular review of the appearance of the osteotomized proximal femoral segment was performed. Biopsy of the proximal femur was performed on two patients.

RESULTS

In all patients the osteotomy healed, the proximal femoral segment appeared viable and subsequent treatment was facilitated by the restoration of normal alignment of the femur. Three different techniques of arthroplasty and three different types of fixation to the femur was utilized in this series and results varied deIn one patient with a long stem cemented prosthesis had no subsequent surgery and a good clinical result at ten years. Her Harris hip score is 89. Radiographic appearance at ten years (Figure 1) is good and demonstrates good alignment of the prosthesis. There is mild non-progressive radiolucency of the acetabulum in Zone 3 and mild non-progressive radiolucency of the femoral component in Zone 7. The osteotomy is healed and remodeled and there is normal alignment of the proximal femur. There is Grade 2 Brooker heterotopic ossification.

One patient with an uncemented femoral prosthesis and a total hip (Figure 2) suffered polyethylene wear and acetabular loosening at eight years which required revision of the acetabulum only. The femoral component was well fixed in good alignment with healing of

*Professor, Department of Orthopaedics, University of New Mexico, Albuquerque, NM 87131-5296

**Associate Professor, Department of Orthopedics, University of Vermont, Burlington, VT 05401

***Research Assistant, University of New Mexico, Albuquerque, NM

****Professor and Dean, School of Medicine, University of Vermont, Burlington, VT 05401

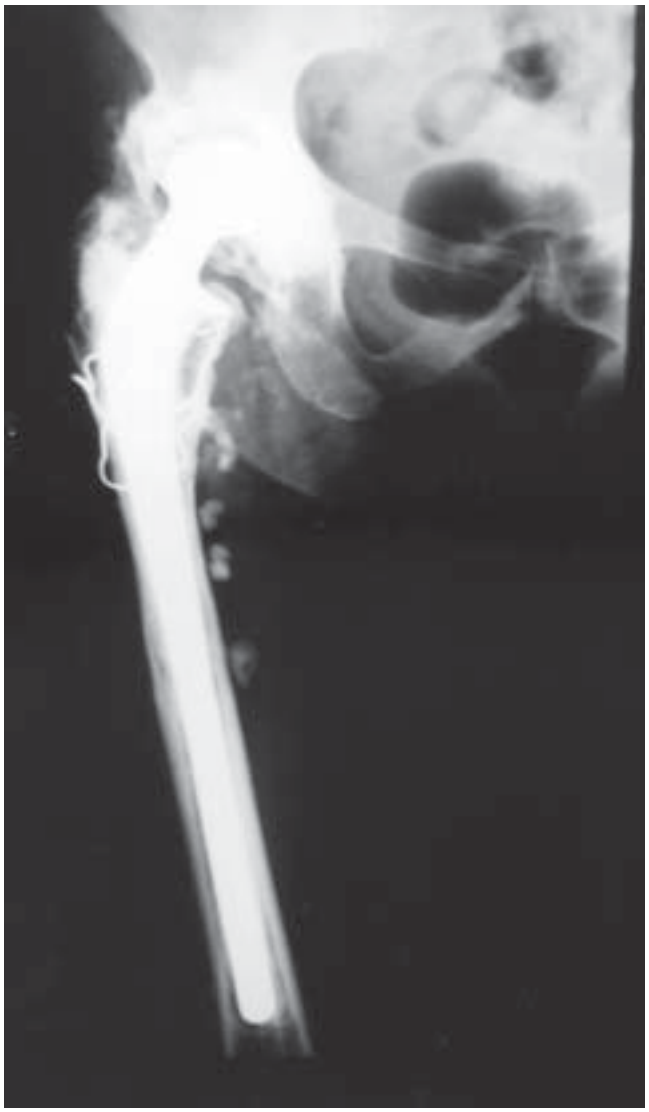

Figure 1. Ten year follow-up radiograph of case #2 with retention of the original prostheses, normal alignment and radiographic viability of the proximal femur.

Figures 2A-AC. Case #1

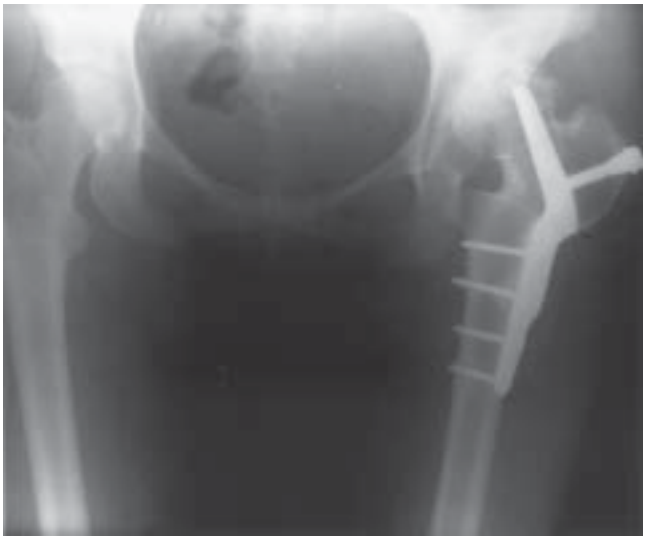

Figure 2A. Radiograph demonstrating healed proximal femoral osteotomy with Osbourne-Ball plate fixation and hip arthritis.

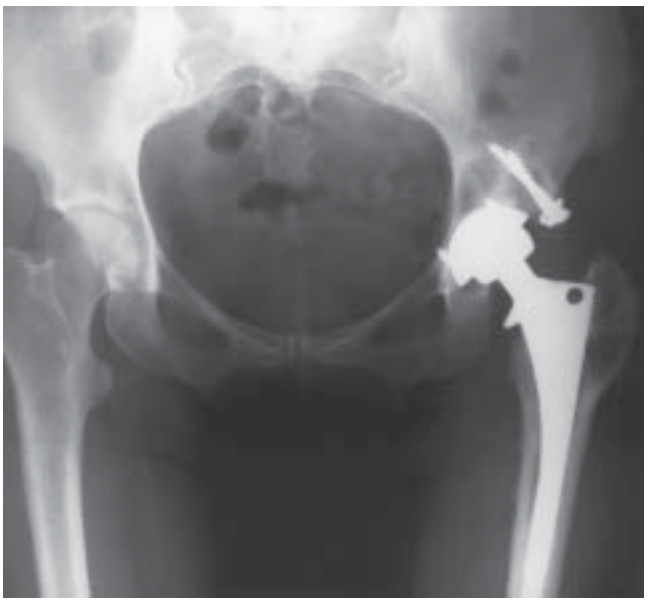

Figure 2B. AP radiograph seven years after osteotomy and hip arthroplasty with a well aligned femur and well fixed femoralcomponent but polyethylene wear and acetabular lucency.

the osteotomy by radiographic and direct operative observation. Proximal femoral biopsy was performed during acetabular revision and is shown in figure 2D. This demonstrates viability of the proximal femoral segment with a small dysvascular area undergoing creeping substitution. There did appear to be some stress shielding osteopenia of the proximal femur attributable to the cemented femoral prosthesis. Ten years after initial arthroplasty she is doing well with a Harris hip score of 84.

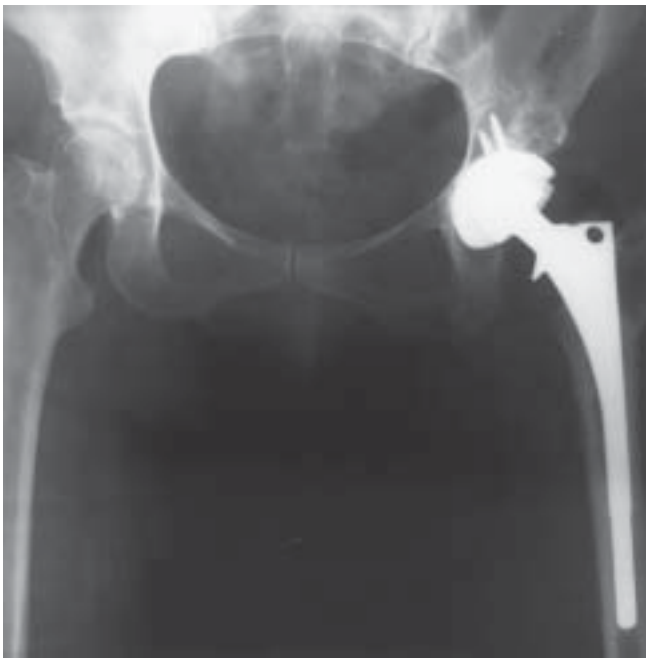

Figure 2C. Radiograph three years following revision of the acetabular component and 11 years after initial arthroplasty demonstrating continued good function of the femoral implant.

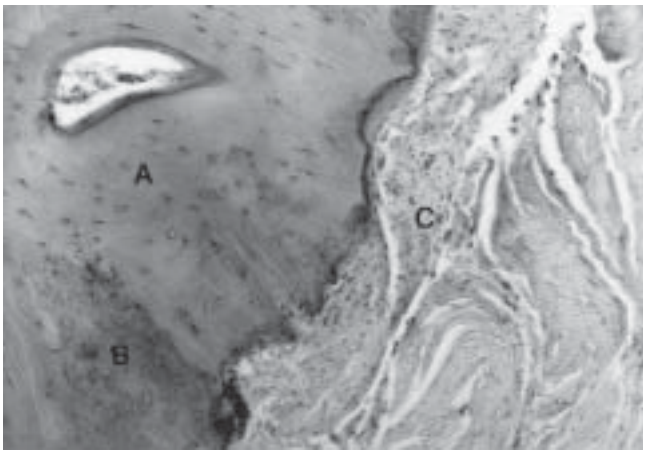

Figure 2D. Bone biopsy taken at the time of acetabular revision viewed at magnification times 100. There is extensive normal viable bone (A), a small zone of creeping substitution (B) and fibrous tissue (C).

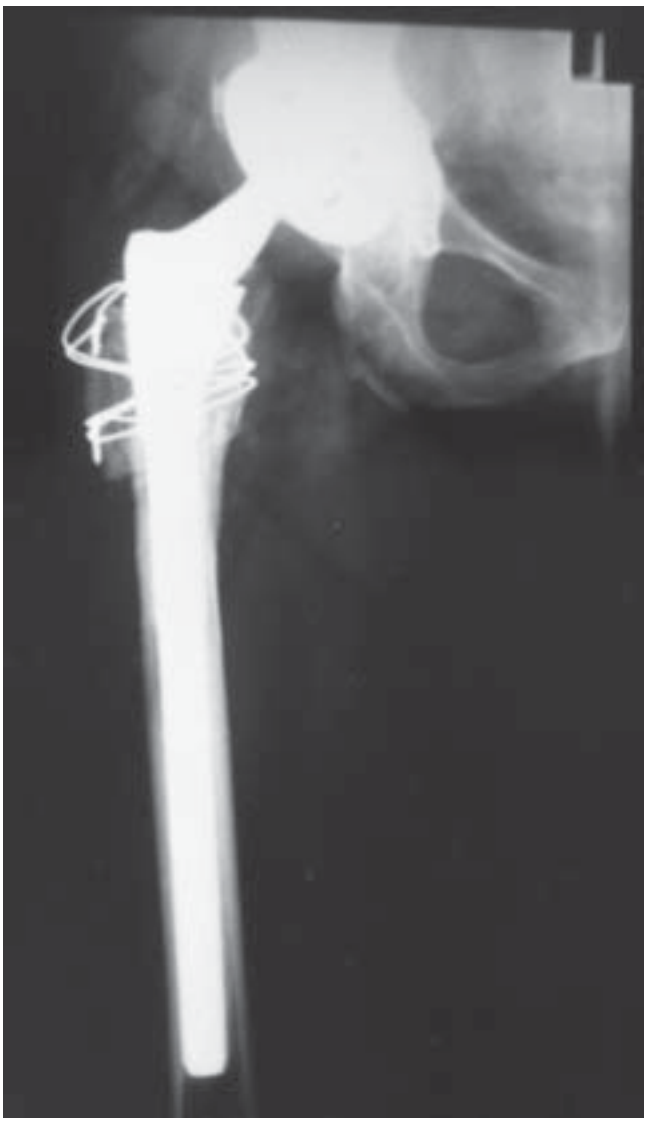

Figure 3. Ten year follow-up radiograph of Case #3 with revised components and greater trochanter fragmentation but normal femoral alignment and viability of the proximal femur.

The third patient underwent osteotomy arthroplasty with a macrofit bipolar prosthesis. This implant has subsequently been shown to suffer from a high rate of loosening failure in most applications. In this patient, femoral alignment was restored, the osteotomy healed, and results were good at two years. She subsequently developed loosening of the femoral component and wear of the acetabular cartilage requiring revision total hip arthroplasty with a long stem ingrowth femoral prosthesis at five years. The proximal femur was observed to be viable by inspection and histology although there was extensive endosteal resorption attributed to gross loosening around the macrofit prosthesis. There was some fragmentation of the greater trochanter. At ten years she is doing well with minimal abductor weakness, a Harris hip score of 78 and a radiograph in figure 3 which demonstrates a revision prosthesis in good position with a healed subtrochanteric osteotomy.

DISCUSSION

Distorted proximal femoral anatomy from previous osteotomy, fracture, or excessive anteversion makes insertion of a femoral component technically difficult or impossible. Femoral osteotomy combined with arthroplasty has been advocated for this problem and we previously reported the good short term results with this technique. No information is available regarding the long term results and viability of the proximal femur following this combination of a procedures.

The vascular supply of the proximal femur has been well described. The arteries supplying the trochanteric area are the medial and lateral femoral circumflex and perforating branches from the deep femoral artery. The lateral femoral circumflex, after passing over the iliopsoas and pectineus provides branches to the adductor muscles, gracilis, and obturator internus, then branches to supply the lesser trochanter, femoral head and neck.

With subcapital and subtrochanteric osteotomy, medullary reaming, and placement of a femoral prosthesis, the blood supply to the proximal femur is significantly altered. The results of this series demonstrates the long term viability of the proximal femur in the face of significant vascular disruption associated with combined osteotomy and arthroplasty. Difficulty with the greater trochanter in Case #3 was attributed to the bone resorption from gross loosening of the macrofit femoral stem, a problem known now to occur with this prosthesis even in primary hip replacement without osteotomy. We do not recommend macro-fit femoral component for arthroplasty combined with osteotomy.

The presence of subclinical osteonecrosis does, however, raise concern regarding the reliability of fixation of the femoral prosthesis to the osteotomized proximal femur. The best results appeared when the femoral component was a porous ingrowth in the distal part of the stem in contrast to proximal (trochanteric) ingrowth or macro fit.

Medullary fixation provided by the prosthesis was sufficient to achieve bony union. In the cases of ingrowth and cemented femoral prostheses, the original femoral component continues to function well at ten years. None of the patients had particular problem with shortness, a theoretical concern with closing wedge osteotomy. This was attributable to the increased length achieved by straightening deformity and the use of longer necked prosthesis.

SUMMARY

To our knowledge this is the first report of long term follow-up of patients after combined femoral osteotomy and hip arthroplasty. The proximal femoral bone remains viable, and normal alignment is effectively restored. The revision rate in this small series was higher than hip replacement in older patients without deformity or prior surgery as expected. However, problems appeared to be related to the type of femoral component chosen. Revision arthroplasty using standard current implants was facilitated by the restored femoral alignment.

Based on the results of this study and current knowledge we recommend closing wedge subtrochanteric osteotomy and total hip arthroplasty for patients with hip arthrosis and proximal femoral deformity. We recommend utilizing a distal ingrowth femoral stem and standard acetabular ingrowth components.

BIBLIOGRAPHY

1. **DeCoster, T.A.; Incavo, S.J.; Frymoyer, J.W.;** and **Howe, J:** Hip arthroplasty after biplanar femoral osteotomy. *J. Arthroplasty,* 4(1):79-86, 1989.
2. **Engh, C.A. Jr.; Culpepper, W.J. II;** and **Engh, C.A.:** Long-term results of the use of the anatomic medullary locking prosthesis in total hip arthroplasty. *J. Bone Joint Surg.,* 79A:177-184, 1997.
3. **Ferguson, G.M.; Cabanela, M.D.;** and **Ilstrup, D.M.:** Total hip arthroplasty after failed intertrochanteric osteotomy. *J. Bone Joint Surg.,* 76B:252-257, 1994.
4. **Howe, J.; William, W.; Lacey, T. II.;** and **Schwartz, R.P.:** A study of the gross anatomy of the arteries supplying the proximal portion of the femur and acetabulum. *J. Bone Joint Surg.,* 32A:856-866, 1950.
5. **Trueta, J.,** and **Harrison, M.H.M:** The normal vascular anatomy of the femoral head in adult man. *J. Bone Joint Surg.,* 35B:422-461, 1953.

POSTERIOR CRUCIATE LIGAMENT FUNCTION FOLLOWING TOTAL KNEE ARTHROPLASTY: THE EFFECT OF JOINT LINE ELEVATION

George J. Emodi, M.D.
John J. Callaghan, M.D.
Douglas R. Pedersen, Ph.D.
Thomas D. Brown, Ph.D.

ABSTRACT

One of the most commonly cited reasons for retaining the posterior cruciate ligament (PCL) during total knee arthroplasty is to preserve femoral rollback and theoretically improve extensor mechanism efficiency (lengthening the moment arm). This study was undertaken to assess PCL function in this regard and to delineate the effects of joint line elevation that can be manipulated intraoperatively by the surgeon. The anterior movement of tibiofemoral contact following PCL resection at flexion angles 60 degrees demonstrated the beneficial effect of the PCL on extensor function. This anterior translation and the concomitant increases in quadriceps tendon load and patellofemoral contact pressures were consistently observed. This study demonstrated that small changes of the joint line position significantly influenced PCL strain and knee kinematics. In order to preserve the desired functions that would be lost with an overly lax PCL and to avoid the potential adverse effects of an overly tight PCL (posterior edge loading and increased tibiofemoral contact), the surgeon should make every effort to restore the preoperative joint line. If this is not possible, consideration should be given to posterior cruciate recession or use of a posterior cruciate substituting design.

Corresponding Author:
Douglas R. Pedersen, Ph.D.
Orthopaedic Biomechanics Lab
2181 Westlawn
Iowa City, IA 52242-1100
Phone: (319) 335-7533

INTRODUCTION

The decision to retain or sacrifice the posterior cruciate ligament (PCL) during total knee arthroplasty (TKA) remains a controversial issue. Rational arguments have been proposed to support the use of both PCL-retaining and PCL-sacrificing implants.[2,4,5,18,20,25-27,31,35,55] Despite the theoretical advantages of each design type, there have been no substantial differences in clinical performance and both have enjoyed greater than 90% good or excellent outcomes at 1- to 10-year follow-up in most series.[1,8,11,15,20,23,29,33,44,45,48-52] Yet, for a variety of reasons there is a widespread preference for retention of the PCL.[18]

The many arguments for retaining the PCL during TKA include improved stability, reduced shear stresses at the fixation interface, improved proprioception, and more efficient gait patterns during level walking and stair climbing.[2,11,12,18,25-27,49,55] However, one of the most commonly cited reasons for retaining the PCL is to preserve femoral rollback, which improves extensor efficiency by lengthening the moment arm and improves the range of flexion by minimizing the potential for impingement of the femur on the tibial component.[2,6,12,13,18,26,49,54]

Physiologic rollback in the normal knee is a complex combination of rolling, gliding and rotation of the femoral condyles relative to the tibial plateau that results in a net posterior movement of tibiofemoral contact in flexion.[2,6,13,21,28,39] Normal rollback is dependent on the integrity of the cruciate ligaments, which form a four-bar planar linkage between the femur and tibia that constrains the relative movements of the articular surfaces.[28,39,40] During TKA, the ACL is resected and the complex complementary geometry of the articular surfaces is altered. Therefore, the normal interaction of the four-bar linkage mechanism and the articular surface is lost and rollback cannot occur. However, under these circumstances, *if appropriately tensioned,* the retained PCL can exert a beneficial checkrein effect to counteract the naturally occurring shear forces which would otherwise result in anterior translation of the femur on the tibia in flexion.[56]

Insall has stressed the importance of appropriately tensioning the PCL during a cruciate-retaining TKA by restoring the joint line to the pre-arthritic position, restoring the shape and size of the femoral condyles and using nonconforming relatively flat tibial inserts. If too lax postoperatively, the PCL will lose its beneficial effects and, if too tight, it could limit flexion, elevate tibiofemoral contact pressures, cause edge-loading and possibly posterior knee pain.[26,38] Recent biomechanical studies have questioned whether the PCL can reliably be tensioned using contemporary techniques and instrumentation.[22,37,38]

Advocates of cruciate-sacrificing have argued that the PCL cannot be appropriately tensioned during TKA in the presence of deformities and contractures associated with advanced osteoarthritis.[15,33,37] This viewpoint has seemingly been supported by recent studies of PCL strain following TKA. Lotke et al.,[37] observed marked variability in the strain of the anteromedial portion of the PCL *in vivo* in ten knees following cruciate-retaining TKA. In six of the knees the maximum postoperative strain was less than the preoperative values, and in three knees the PCL strain was elevated in early flexion. Only one of the ten knees demonstrated a postoperative pattern similar to the preoperative pattern. However, the strain was measured with unfixed trial components during passive flexion of unloaded knees, and no attempt was made to identify the zero point of strain or balance the ligament prior to testing.

Mahoney et al.,[38] have also recently studied PCL strain following TKA in non-arthritic cadaver specimens and observed normal patterns in only three of eight specimens. The knees were tested in stair ascending and descending configurations and average maximum strains of 4.5 0.5% and 4.1 0.4% at 110 to 120 degrees of flexion were observed for the ascending and descending configurations respectively compared to corresponding values of 2.4 0.1% and 2.5 0.1% preoperatively. No mention was made of how the PCLs were tensioned in their study, but all knees were deemed clinically acceptable in terms of range of motion and stability, and the joint line was accurately restored.

The position of the reconstructed joint line is one of several factors that influence the tension of the retained PCL.[26] In advanced arthrosis associated with coronal and sagittal plane deformities, restoration of the joint line can be quite difficult.[33] For this reason, many surgeons either resect the PCL and utilize cruciate-sacrificing designs which are less sensitive to changes in the joint line position, or recess the ligament in order to achieve appropriate tension in flexion.[47] Yoshii et al., have demonstrated that the joint line can accurately be restored in non-arthritic cadaver knees during TKA using standard instrumentation and techniques.[58] However, in the presence of a fixed flexion contracture there is often a need to resect more distal femur in order to gain full extension. This results in joint line elevation.

The effect of joint line elevation, which results from resection of too much distal femur, has been studied for cruciate-sacrificing designs.[17,33] However, there is little in the literature that documents the effects of joint line elevation using cruciate-retaining designs.[9] The purpose of this investigation was to answer the following questions: To what extent does elevation of the reconstructed joint line affect PCL function? Can the retained PCL be appropriately tensioned to cause rollback and improve extensor efficiency using standard instrumentation and techniques?

Materials and Methods

Normal adult fresh-frozen cadaver knees, instrumented with an electrogoniometer, a quadriceps tendon load cell and a PCL force probe and strain gauge, were tested in a materials testing machine (MTS Corp., Eden Prairie, Minnesota). Data was collected during loading at 15, 30, 60, 90 and 105 degrees preoperatively, postoperatively at 0, 2, 4 and 6 mm of joint line elevation, and following resection of the PCL. Joint line elevation was achieved by removing shims from between the distal femoral cut and femoral component and inserting a thicker polyethylene spacer. Pressure sensitive film was utilized to ascertain patellofemoral contact pressures in each knee postoperatively.

One left and three right adult fresh-frozen cadaver limbs (two male, two female, average age 60, range 40-79 years) were thawed overnight in a sealed polyethylene bag prior to testing. Specimens with knee joint contractures, advanced arthrosis and evidence of previous trauma or surgery were excluded from the study. Antero-posterior, lateral and hip-to-ankle alignment radiographs were obtained for templating and preoperative planning. After sectioning the femur at mid shaft, the skin, fat and muscle were resected leaving the knee capsule and periarticular ligaments intact. The rectus femoris and vastus intermedius tendons were sectioned at the level of the myotendinous junction of the rectus, and prepared for application of a serpentine clamp by stripping the attached muscle fibers. Following mid-calf sectioning, the fibula was secured by a threaded Steinman pin to the approximately 24 cm long tibia, which then was potted in a copper tube with polymethylmethacrylate. A 15-mm stainless steel intramedullary rod was inserted into the reamed proximal shaft of the femur resulting in an approximate femoral length of 32 cm.

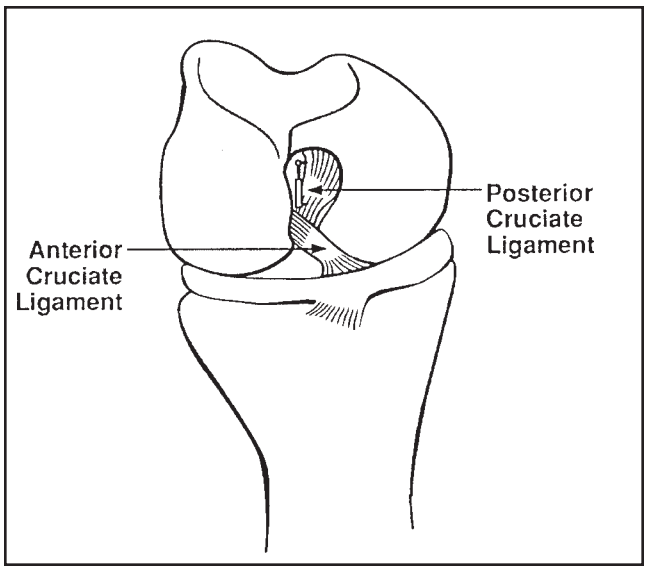

Figure 1. The DVRTs were implanted on the anterior portion of the anterolateral bundle of the PCL.

Differential variable reluctance transducers (DVRT) (Microstrain, Burlington, Vermont) were calibrated at 50 m increments through their linear and non-linear ranges using a micrometer. Occasionally, DVRT output fell outside the linear range, which necessitated interpolation of results from the calibration curves. To minimize the size of the bundle of fibers being tested, DVRT anchoring barbs were trimmed to one half of their original lengths and secured with 5-0 prolene sutures. The PCL was exposed through small medial parapatellar and posterior arthrotomies. The overlying synovium and a portion of the ligament of Humphrey were resected to facilitate application of the strain gauge and force probe to the anterior portion of the anterolateral bundle of the PCL19,57 through the medial parapatellar arthrotomy (Figure 1). Once preoperative testing was completed, the attachment sites were marked with ink and the DVRT was removed and subsequently reinserted following TKA.

An arthroscopic force probe (Microstrain, Burlington, Vermont) was inserted parallel to the posterior fibers of the anterolateral component of the PCL through the posterior arthrotomy. The point of zero strain was identified by an abrupt change in the output of the probe as the loaded knee was taken through a range of motion. Strain (E) was calculated as:

$$E = \frac{dL - dL\ (reference)}{L\ (closed) + dL\ (reference)} \qquad \text{Equation 1}$$

where; dL is the measured displacement, dL (reference) is the point of zero strain, and L (closed) is the closed length of the DVRT.

A 250-pound load cell (Sensotec, Columbus, Ohio) was placed in series with the quadriceps tendon via an attachment to the serpentine tendon clamp and eyebolt in order to measure quadriceps force. The loading fixture used was adapted from the design utilized by Huberti and Hayes.[24] During loading, the Q-angle was kept physiologic by aligning the quadriceps tendon with the shaft of the femur. Knee joint motions were generated by the application of collinear compressive forces to spherical bearings representing the hip and ankle joints. A three-second-ramp signal was used to apply the desired loads. The tension on the quadriceps tendon was adjusted using an eyebolt so that the desired load was applied at the appropriate flexion angle (Figure 2).

The target moments for stair descent were estimated to be 35, 105, 115, 80 and 60 N-m for flexion angles of 15, 30, 60, 90 and 105 degrees, respectively, from Andriacchi's study of lower-limb mechanics during stair climbing[3]. Subsequent to several early specimen failures at these loads, the applied moments were reduced by 75%. The applied axial force necessary to achieve a target moment was calculated as:

$$Fa = \frac{\text{desired moment}}{\cos \times \text{length of tibia}} \qquad \text{Equation 2}$$

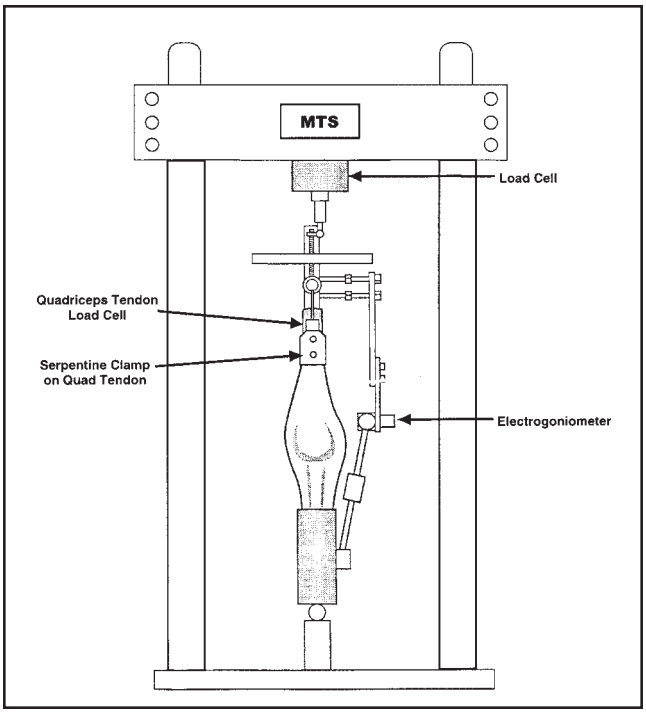

Figure 2. Diagram of the loading fixture. The desired moments were achieved by applying compressive forces to ball joints representing the hip and ankle. The tension in the quadriceps tendon was adjusted using an eye-bolt so that the load was applied at the appropriate flexion angle.

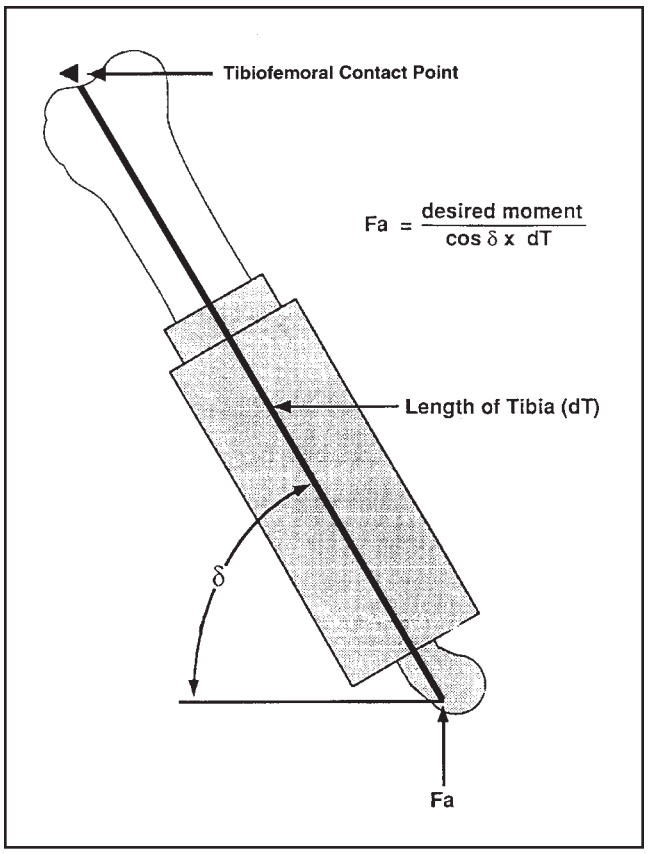

Figure 3. The applied load necessary to achieve the desired moment for a given flexion angle was calculated using the above equation. The angle was measured using an angle finder and the length of the potted tibia from the ball joint to the estimated point of tibiofemoral contact was measured with a ruler.

This equation assumes sagittal plane geometry and neglects the weight of the tibia and the effect of the PCL (Figure 3). The angle was measured using an angle finder (Dasco Pro Inc., Rockford, Illinois).

Primary cruciate-retaining TKAs were performed using J&J P.F.C. prostheses (Johnson and Johnson Professional, Inc., Raynham, MA) and posterior curved tibial inserts. Preoperative templating with standardized antero-posterior and lateral radiographs determined anatomic axes for use of the intramedullary distal femoral cutting guide. After resection of the fat pad, the anterior cruciate ligament (ACL) and the menisci, the tibia was cut perpendicular to its longitudinal axis using an extramedullary alignment guide, paying special attention to reproduce the normal posterior slope. Approximately 8 mm of bone and cartilage were resected from the medial side leaving the posterior tibial spine and the PCL intact. Next, an 8-mm distal femoral cut was made using the appropriate bushing and an intramedullary femoral guide. A trial reduction was performed, and the tibial cut was revised with the 0 degree cutting block until the 8 mm trial tibial insert did not lift off the tibial tray (book open) at 120 degrees of flexion. The posterior tibial spine was then carefully resected leaving the PCL fibers intact. A modular tibial tray was positioned as posteriorly as possible and cemented in the appropriate amount of rotation. Ten mm of patellar bone and cartilage were resected to accommodate the maximal thickness of the oval three-post patellar component per J&J protocols.

Once all of the standard cuts were made, an additional 6 mm of distal femur was resected leaving the PCL femoral attachment intact. Aluminum shims placed between the surface of the distal cut and the femoral component restored femoral length. The joint line was elevated by removing shims, revising the chamfer cuts and inserting the next thicker tibial insert. The femoral component was cemented at each joint line position to prevent rocking. The thickness of the shims corresponded to the minimum polyethylene thickness of the posterior curved tibial inserts (Table 1). After each successive joint line elevation, the knee was taken through a range of motion and assessed clinically for tightness in flexion by noting whether or not the tibial trial insert lifted off anteriorly.

Each specimen was tested preoperatively, postoperatively at 0, 2, 4 and 6 mm of joint line elevation, and following PCL resection at 0 mm of joint line elevation. A test sequence included three trials each at flexion angles of 15, 30, 60, 90 and 105 degrees. The simultaneous voltage outputs for the MTS load cell, the quadriceps load cell, the PCL DVRT, the force probe and the electrogoniometer were sampled by MTS Test Ware

Table 1

	Minimum Polyethylene Thickness (mm)		
Insert Thickness	Size 3	Size 4	Size 5
8. 0 mm	6. 0	6. 1	6. 1
10. 9 mm	8. 1	8. 0	8. 1
12. 5 mm	10. 1	10. 1	10. 2
15. 0 mm	12. 4	12. 3	12. 3

The minimum thickness of the articular surface of each polyethylene tibial spacer was measured using a micrometer. The thickness of the shims used between the femoral component and the distal femoral cut to vary the position of the joint line corresponded to the differences in the minimum polyethylene thickness between spacers. For example, to elevate the joint line from 0 mm to 2 mm for the size 3 tibial tray, a 2. 1mm shim was removed from between the femoral component and the distal femoral cut and the tibial insert was changed from the 8. 0 mm size to the 10. 0 mm size.

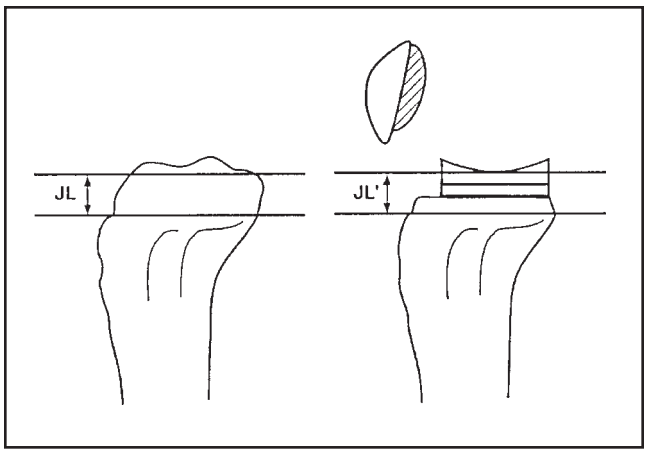

Figure 4. The joint line was measured using the method of Figgie et al.[15]

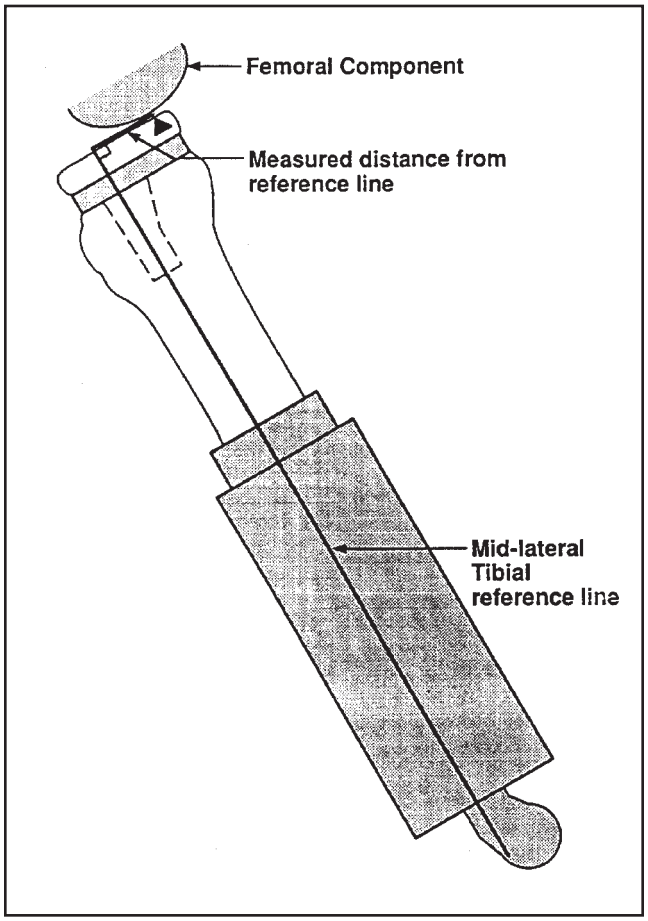

Figure 5. The location of the estimated center of tibiofemoral contact was quantified from standardized lateral radiographs relative to the mid-lateral tibial line.

SX software every tenth of a second for a ten second interval that included the three second ramp load.

Standardized lateral radiographs centered at the joint line were obtained for each loaded specimen, pre- and postoperatively, at each flexion angle and successive joint line position, and after PCL resection. The anatomic axis, joint line position and posterior slope from the pre- and postoperative AP and lateral radiographs were measured using the method of Figgie et al.[16] (Figure 4) Femoral rollback was estimated using a technique similar to that described by Stiehl et al.56 The estimated center of tibiofemoral contact was identified and its perpendicular distance from the mid-lateral tibial line was measured (Figure 5). Each radiographic measurement was repeated three times on separate occasions.

Patellofemoral contact pressures were ascertained with medium range Pressensor pressure sensitive film (Inteque Resources Corp., Fort Lee, New Jersey). Two-inch square pieces of monolayer film were packaged between two sealed layers of Saran Wrap (Dow Brands L.P., Indianapolis, Indiana). The film was placed between the femoral component and the patellar component prior to loading. Reference marks were made on the film using two Kirschner wires passed through two small drill holes in the superior rim of the patellar component. Three trials were performed and the most representative stain with the least artifact was optically scanned at a resolution of 210 pixels/inch. The digital 256-gray-level images were processed to calculate the contact pressure.[53] Total contact pressures were not calculated because this would have required integrating patterns from low, medium and high films. Rather, the films demonstrated differences in patellofemoral pressures at given flexion angles for the various knee testing protocols.

Normalized loads were calculated by dividing the measured forces by the applied moment. The data analysis was a repeated measures analysis of variance. The mean results for normalized quadriceps load, normalized patellofemoral contact pressure, PCL strain, and rollback between the six trials (preoperative, 4 postoperative, and cruciate resected) were compared at each angle using Bonferroni's t-test at the 0.05 significance level.

RESULTS

The joint line was restored within 2 mm, axial alignment within 2 degrees, and posterior slope within 3 degrees for all specimens. All knees demonstrated marked tightness in flexion at elevations of 4 and 6 mm and all but one "booked open" before 120 degrees of flexion at 2 mm of joint line elevation. The average strain recorded in the anterolateral band of the PCL is re-

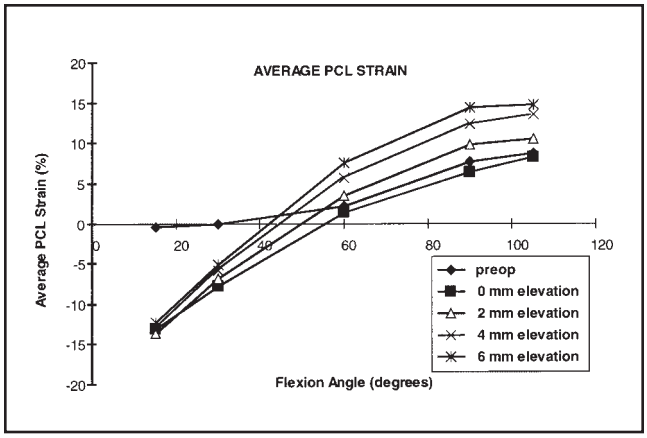

Figure 6. Average strain of the anterolateral band of the PCL as a function of flexion angle.

ported as a function of flexion angle for the preoperative condition and the four PCL-intact TKAs (Figure 6). Average femoral rollback is plotted as posterior displacement from the reference point through the range of flexion angles tested (Figure 7). The average normalized quadriceps tendon load and selected normalized patellofemoral contact pressures are also displayed as functions of the knee flexion angle (Figures 8 and 9, respectively). Representative digitized patellofemoral contact pressure recordings at 15, 30, 60, 90 and 105 degrees demonstrate the change of loading patterns during flexion (Figure 10).

DISCUSSION

Monotonic increases in strain in the anterior portion of the anterolateral component of the PCL were observed in all specimens preoperatively and postoperatively as they were flexed from 15 to 105 degrees (Figure 6). Maximum strain occurred at 105 degrees in all

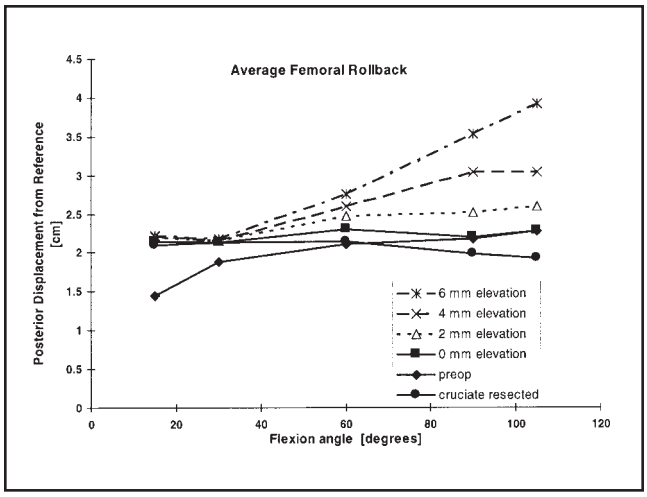

Figure 7. Average femoral rollback as a function of flexion angle.

specimens, averaging 8.7 1.7% preoperatively and 8.3 1.5% postoperatively. The average difference between the observed strains preoperatively versus postoperatively was 26 10% at 90 degrees (range 18 - 40%) and 14 5% at 105 degrees (range 7 - 20 %). The point of zero strain occurred at an average flexion angle of 36 10 degrees preoperatively and 56 6 degrees in the postoperative specimens. As the joint line was elevated, PCL strain increased at all measured flexion angles above 30 degrees. These increases were statistically significant at 4 mm for flexion angles of 90 and 105 degrees (p=.007, p=.04) and at 6 mm for angles 60, 90 and 105 degrees (p=.007, p=.0004, p=.0007). At 2 mm of joint line elevation, the average increases in strain of 2.1, 3.4 and 2.1% at flexion angles of 60, 90 and 105 degrees, respectively, were not statistically significant. The average maximum strain of 14.7 2.2% at 6 mm of elevation and 105 degrees of flexion represents a 77% increase in PCL strain over the initial average postoperative strain. All specimens eventually failed during testing at this level of strain. (three PCLs avulsed from their tibial insertions and the fourth knee dislocated posteriorly).

In this investigation the tibial cut was revised until the 8-mm trial tibial insert did not book open at 120 degrees. This resulted in joint lines that were 0.5 to 2.0 mm below the preoperative joint line level. The observed postoperative strain patterns were similar to the preoperative patterns in that the ligament was lax in extension and became taut in flexion. However, there were consistently observed differences. Preoperatively the point of zero strain occurred at an average flexion angle of 36 10 degrees and strain increased thereafter to an average maximum of 8.7 1.7 % at 105 degrees of flexion. These values fall well within the range of previous reports.[7,10,32,38] Postoperatively the point of zero strain occurred at an average flexion angle of 56 6 degrees reflecting relative laxity of the ligament in extension. This is presumably the result of resecting the ACL and the posterior tibial spine. From the point of zero strain, steady increases in PCL strain were observed as the knee was flexed to 105 degrees. The maximum average postoperative strain of 8.3 1.5% was similar to the corresponding preoperative value. This maximum average was associated with percent differences ranging from 18-40% at 90 degrees of flexion and 7-20% at 105 degrees. These differences are smaller than the previously reported values.[37,38]

Despite the similarities of the pre- and postoperative strain patterns, normal rollback was not observed. Rather, the average estimated tibiofemoral contact postoperatively occurred well posterior to the corresponding location preoperatively at 15 degrees and remained relatively stationary as the knee was flexed to 105 de-

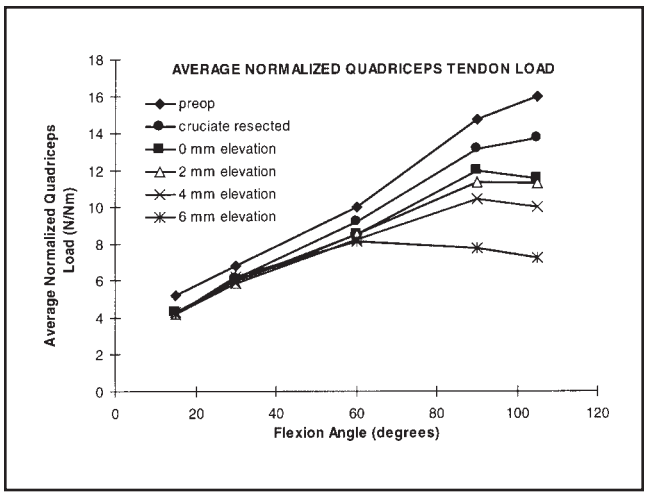

Figure 8. Average normalized quadriceps tendon load as a function of flexion angle.

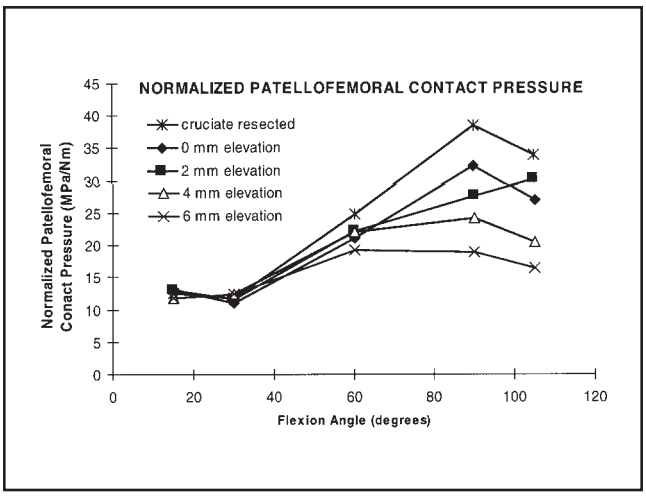

Figure 9. Average normalized patellofemoral contact pressure as a function of flexion angle.

grees. This observation corresponds well with previous reports.[14,31,38,56] Following PCL resection the tibiofemoral contact did not change at lower flexion angles, but moved anteriorly an average of 1.7 0.7, 2.2 0.7 and 3.4 0.4 mm at flexion angles of 60, 90 and 105 degrees respectively compared to the corresponding values in the knees tested with the PCL intact. These differences were not statistically significant but a similar trend was observed in all specimens. These results differ from those reported by Horwood who observed no difference in the extensor mechanism moment arms in postoperative cadaver knees tested before and after PCL resection.[22]

The average value of 8.3 2.5 mm of preoperative femoral rollback observed in this experiment during flexion from 15 to 105 degrees is similar to reported average values of 13.5 1.5 mm from 0 to 90 degrees of flexion by Draganich[12] and 8 mm from 0 to 115 degrees reported by Stiehl.[56] Smooth continuous patterns were observed for all specimens (Figure 7). Postoperatively, the center of tibiofemoral contact at 15 degrees occurred an average of 6.9 3.5 mm posterior to the corresponding position preoperatively. From this relatively posterior starting point, the center of tibiofemoral contact movement was erratic and averaged a net 1.4 0.8 mm posterior as the knee was flexed to 105 degrees. The average position of the tibiofemoral center of contact at 105 degrees postoperatively was equal to the preoperative value. As the joint line was elevated the center of tibiofemoral contact did not change at the flexion angles of 15 and 30 degrees. However, at 60, 90 and 105 degrees the tibiofemoral contact center moved posteriorly with each successive elevation of the joint line. The changes in the position of the contact center were statistically significant for 60, 90 and 105 degrees at 6 mm of elevation (p=.02, p=<.0001, p=<.0001), and for 90 and 105 degrees at 4 mm of elevation (p=.0007, p=.008). This resulted in the tibiofemoral contact occurring on the posterior lip of the tibial tray in 50% of specimens at 4 mm of elevation and in all of the specimens at 6 mm of elevation and 105 degrees of flexion. The changes were not statistically different at 2 mm of elevation for any of the angles. Following resection of the PCL there was no significant statistical difference in the tibiofemoral contact center position for any angle. However, the average center moved anteriorly 1.7 0.7, 2.2 0.7 and 3.5 0.4 mm at flexion angles of 60, 90 and 105 degrees and did not change at lower flexion angles. The net average movement of the tibiofemoral center of contact following resection of the PCL from 15 to 105 degrees was 1.7 1.0 mm anterior to the starting point.

Following TKA the normalized quadriceps load decreased in all specimens at all flexion angles (Figure 8). This was most notable at flexion angles of 60, 90 and 105 degrees where average decreases of 13.2 8, 17.6 7 and 27.7 7% were observed. These decreases were not statistically significant except at the flexion angle of 105 degrees (p=.0028). Following resection of the PCL the average normalized quadriceps load increased at higher flexion angles but did not change at 15 and 30 degrees. The normalized quadriceps load increased an average of 7.4 4.1, 10.1 2.5 and 22.2 17.1% at 60, 90 and 105 degrees of flexion. These differences were not statistically significant (p>.75). Elevation of the joint line 2 mm resulted in an average decrease in quadriceps load of 5.0 and 2.5 % at 90 and 105 degrees respectively (statistically insignificant). However, elevations of 4 and 6 mm decreased the normalized quadriceps load by an

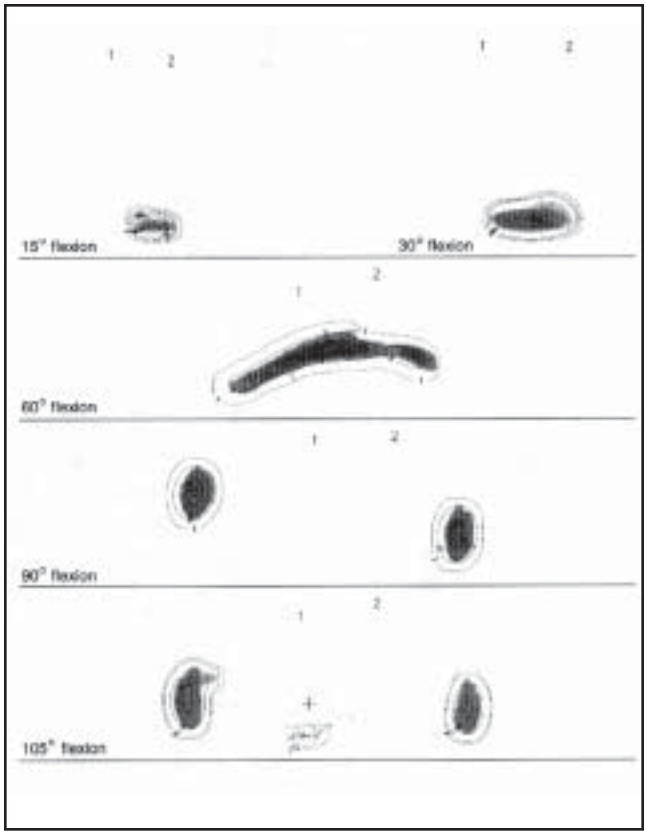

Figure 10. Representative digitized patellofemoral contact pressure patterns at 15, 30, 60, 90 and 105 degrees. 1 and 2 represent the location of the reference marks which were made by indenting the film with small Kirschner wires passed through drill holes at the superior edge of the patellar button. "+" represents the center of patellofemoral contact.

average of 35 20 and 40 20% at flexion angles of 90 and 105 degrees (p=.0038, p=.0038) with no change at flexion angles of 15, 30 and 60 degrees. . Rueben et al., have also reported no statistical difference in quadriceps load postoperatively vs. preoperatively using the optimal patellar cut in ten cadaver knees from flexion of 0 to 90 degrees.[46]

Similar trends were observed for the average normalized patellofemoral contact pressures (Figure 9). Following resection of the PCL, the average patellofemoral contact pressure did not change at flexion angles of 15 and 30 degrees but increased by an average of 10 12, 17 8 and 26 10% for angles 60, 90 and 105 degrees. Again, these differences did not reach statistical significance but a similar trend was observed in each specimen. Elevation of the joint line decreased patellofemoral contact at flexion angles of 60, 90 and 105 degrees but these changes were not statistically significant except at 105 degrees and 6 mm of elevation (p=.06). Mahoney observed a similar decrease in extensor efficiency in cruciate-sacrificing designs in which there was no built-in mechanism for cruciate substitution. However, the patellofemoral joint was not replaced in their specimens.[38]

The patellofemoral contact patterns for each specimen were similar. Contact occurred on the central portion of the component at 15 and 30 degrees (Figure 10). The contact at 90 and 105 degrees was bifocal and occurred more toward the periphery of the patellar button. The pattern observed at 60 degrees represented a transition between the patterns observed at lower and higher flexion angles.

One of the functions of the retained, appropriately tensioned PCL is to counteract the natural anteriorly directed shear forces which occur in flexion and result in movement of the tibiofemoral contact center anteriorly. Based on the findings of this investigation, this effect occurs only at flexion angles greater than 60 degrees due to the laxity in the PCL at lesser flexion angles. Interestingly, this angle is similar to the angle of 69.2 2.4 degrees at which the cam mechanism for a cruciate-substituting device has been observed to engage.[38] Thus, the advantages of retaining the PCL from the improved extensor efficiency standpoint must be weighed against the associated increases in tibiofemoral contact pressures described by Soudry.[55] The magnitude of these increased pressures was not addressed in this study. However, they may play a significant role in the posterior tibial wear recently reported by Feng[16] and Lewis[36], especially if the postoperative PCL strains are excessively high.

The effect of joint line elevation on knee range of motion following cruciate-retaining TKA has been studied by Carpenter et al.[9] Significant decreases in flexion were observed with as little as 2 mm of elevation. Flexion was limited further as the joint line was elevated 4 and 6 mm, and was partially restored following cruciate excision. Similar trends were observed in this investigation. Elevating the joint line 2 mm resulted in statistically insignificant increases in the measured PCL strain averaging 2.1, 3.4 and 2.1% at flexion angles of 60, 90 and 105 degrees. Statistically significant differences were observed at these angles for joint lines 4 and 6 mm higher than the initial level. The maximum average strain observed was 14.7 2.2% at 6 mm of elevation and 105 degrees of flexion. This value is lower than reported maximum strains for intrasubstance failure;[22,42,43] however, three PCLs failed by avulsion of the tibial insertion, which represents the weak link following the proximal tibial cut.[41]

The tibiofemoral contact center was noted to move posteriorly at flexion angles of 60, 90 and 105 degrees as the joint line was elevated. The differences were small at 2 mm of elevation but were very significant at

elevations of 4 and 6 mm where tibiofemoral contact occurred on the posterior curve and posterior lip of the tibial insert at 90 and 105 degrees.

The effect of joint line elevation on normalized quadriceps load and patellofemoral contact pressures was observed only at higher flexion angles. Statistically significant decreases were observed at 4 and 6 mm of elevation with average reductions of 35-45%. These marked decreases are not due entirely to the improved extensor mechanism moment arm. Rather they reflect a combination of the increased resistance to flexion by the excessively tight PCL, changes in the patellar ligament angle and differences in the quadriceps-to-patellar ligament force transfer ratio that accompany the abnormal knee kinematics at these joint line positions.

The results of this study must be considered in light of several limitations in addition to the small sample size. For one, no attempt was made to account for the function of the hamstrings, which have been demonstrated to influence PCL strain.[7] Secondly, the model does not account for soft tissue remodeling that may occur postoperatively. Finally, the specimens used in this study had no significant underlying arthrosis and the TKAs were performed under optimal conditions. Therefore, the results observed must be interpreted as the "best case scenario" and may not be routinely achievable intraoperatively in the face of severe arthrosis.

SUMMARY

In this investigation, the maximum postoperative strain in the anterolateral portion of the PCL was similar to preoperative values in all specimens. However, the ligament consistently remained lax at flexion angles smaller than 60 degrees. Despite these similar strains at higher flexion angles, normal rollback was not observed. The anterior movement of tibiofemoral contact following PCL resection at flexion angles 60 degrees demonstrated the beneficial effect of the PCL on extensor function. This anterior translation and the concomitant increases in quadriceps tendon load and patellofemoral contact pressures were consistently observed. This study demonstrated that small changes of the joint line position significantly influenced PCL strain and knee kinematics. In order to preserve the desired functions that would be lost with an overly lax PCL and to avoid the potential adverse effects of an overly tight PCL (posterior edge loading and increased tibiofemoral contact), the surgeon should make every effort to restore the preoperative joint line. If this is not possible, consideration should be given to posterior cruciate recession or use of a posterior cruciate substituting design.

ACKNOWLEDGMENT

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REFERENCES

1. **Aglietti, P.; Rinonapoli, E.:** Total condylar knee arthroplasty: a five year follow-up study of 33 knees. *Clin. Orthop.* 186:104, 1984.
2. **Andriacchi, T.P.:** Biomechanics and gait analysis in total knee replacement. *Orthopaedic Review* 17(5):470-473, 1988.
3. **Andriacchi, T.P.; Andersson, G.B.J.; Fermier, R.W.; Stern, D.; Galante, J.O.:** A study of lower-limb mechanics during stair climbing. *J. Bone and Joint Surg.* 62-A(5):749-757, 1980.
4. **Andriacci, T.P.; Galante, J.O.:** Retention of the posterior cruciate in total knee arthroplasty. *J. Arthroplasty* 35:13-19, 1988.
5. **Andriacci, T.P.; Galante, J.O.; Fermier, R.W.:** The influence of total knee-replacement design on walking and stair climbing. *J. Bone and Joint Surg.* 64-A(9):1328-1335, 1982.
6. **Andriacci, T.P.; Tarnowski, L.E.; Berger, R.A., Galante, J.O.:** New insights into femoral rollback during stairclimbing and posterior cruciate ligament function. p. 20. In *Proceedings of the 45th Annual Meeting of the Orthopaedic Research Society,* 1999.
7. **Arms, S.W.; Johnson, R.J.; Pope, M.H.:** Strain measurement of the human posterior cruciate ligament. p. 335. In *Proceedings of the 30th Annual Meeting of the Orthopaedic Research Society,* 1984.
8. **Becker, M.W.; Insall, J.N.; Faris, P.M.:** Bilateral total knee arthroplasty. one cruciate retaining and one cruciate substituting. *Clin. Orthop.* 271:122-125, 1991.
9. **Carpenter, C.W.; Cummings, J.F.; Grood, E.S.; Leach, D.U.; Paganelli, J.V.; Manley, M.T.:** The influence of joint line elevation in total knee arthroplasty. *Am J Knee Surg.,* 7(4):164-176, 1994.
10. **Covey, D.C.; Sopega, A.A.; Sherman, G.M.; Torg, J.S.:** Testing for "isometry" during posterior cruciate ligament reconstruction. p. 665. In *Proceedings of the 38th Annual Meeting of the Orthopaedic Research Society,* 1992.
11. **Dorr, L.D.; Ochsner, J.L.; Gronley, J.; Perry, J.:** Functional comparison of posterior cruciate-retained versus cruciate-sacrificed total knee arthroplasty. *Clin. Orthop.* 236:36-43, 1988.
12. **Draganich, L.F.; Andriacci, T.P.; Andersson, G.B.T.:** Interaction between intrinsic knee mechanics and the knee extensor mechanism. *J. Orthopaedic Research* 5:539-547, 1987

13. **Dyrby, C.O.; Andriacci, T.P.:** Three-dimensional measurement of the dynamic envelope of knee motion. p. 934. In *Proceedings of the 45th Annual Meeting of the Orthopaedic Research Society,* 1999.
14. **El Nahass,G.G.; Walker, P.S.:** Does the knee joint rotate normally after total knee replacement? p. 372. In *Proceedings of 35th Annual Meeting of the Orthopaedic Research Society,* 1989.
15. **Faris, P.M.; Herbst, S.A.; Ritter, M.A.; Keating, E.M.:** The effect of preoperative knee deformity on the initial results of cruciate-retaining total knee arthroplasty. *J. Arthroplasty* 7(4):527-530, 1992.
16. **Feng, E.L.; Stulberg, S.D.; Wixson RL.:** Progressive subluxation and polyethylene wear in total knee replacements with flat articular surfaces. *Clin. Orthop.* 299:60-71, 1994.
17. **Figgie III, H.E.; Goldberg, V.M.; Heiple, K.G.; Moller, H.S.; Gordon, N.H.:** The influence of tibial patellofemoral location on function of the knee in patients with the posterior stabilized condylar knee prosthesis. *J. Bone and Joint Surg.,* 68A(7)1035-40, 1986.
18. **Freeman, M.A.R.; Railton, G.T.:** Should the posterior cruciate ligament be retained in condylar nonmeniscal knee arthroplasty?: The case for resection. *J. Arthroplasty* 35:3-12, 1988.
19. **Harner, C.D.:** The posterior cruciate ligament relevant anatomy and biomechanics. Instructional Course 104 The PCL Injured Knee: Current Concepts. Presented at the 62nd Annual Meeting of the American Academy of Orthopaedic Surgeons, February, 1995.
20. *Hirsch, H.S.; Lotke, P.A.; Morrison, L.D.:* The posterior cruciate ligament total knee surgery: save, sacrifice or substitute?: *Clin. Orthop.* 309:64-88, 1994.
21. **Hollister, A.M.; Jatana,S.; Singh, A.K.; Sullivan, W.W.; Lupichuk, A.G:** The axes of rotation of the knee. *Clin. Orthop.* 290:259-68, 1993.
22. **Horwood, R.L.; Beden, E.N.; Focht, L.M.; Colwell, C.W.:** The role of the posterior cruciate ligament in the kinematics of total knee arthroplasty. p. 360. In *Proceedings of the 34th Annual Meeting of the Orthopaedic Research Society,* 1988.
23. **Horwood, R.L.; Beden, E.N.; Wyatt, M.P.; Colwell, C.W.**: Gait analysis of total condylar knee arthroplasty during stair ascent. p. 543. In *Proceedings of the 34th Annual Meeting of the Orthopaedic Research Society,* 1988.
24. **Huberti, H.H.; Hayes, W.C.:** Patellofemoral contact pressures: the influence of q-angle and tendofemoral contact. *J. Bone and Joint Surg.* 66-A(5):715-724, 1984.
25. **Insall, J.N.:** Presidential address to the Knee Society: Choices and compromises in total knee arthroplasty, *Clin. Orthop.* 226:43-48, 1988.
26. **Insall, J.N.:** Surgical techniques and instrumentation in total knee arthroplasty. pp. 750-753. *Surgery of the Knee,* 2nd edition, Churchill Livingstone, 1993.
27. **Johansson, H.; Sjolander, P.; Sojka P.:** A sensory role for the cruciate ligaments. *Clin. Orthop.* 268:161-178, 1991.
28. **Kapandji, I.A.:** *The Physiology of the Joints. Vol II.* Churchill Livingstone, 1970.
29. **Kelman, G.J.; Biden, E.N.; Wyatt, Ritter, M .A..; Colwell, C.W.:** Gait laboratory analysis of a posterior cruciate-sparing total knee arthroplasty in stair ascent and descent. *Clin. Orthop.* 248:21-26, 1989.
30. **Kennedy, J.C.; Hawkins, R.J.; Willis, R.B.; Danylchuk, K.D.:** Tension studies of human knee ligament: yield point, ultimate failure, and disruption of the cruciate and tibial collateral ligaments. *J. Bone and Joint Surgery* 58-A(3):350-355, 1976.
31. **Kurosawa, H.; Walker, P.S.; Abe, S.; et al.:** Geometry and motion of the knee for implant and orthotic design. *J. Biomech.* 18:487, 1985.
32. **Kurosawa, H.; Yamakoshi, K.I.; Yasuda, K.; Saski, T.:** Simultaneous measurement of changes in length of the cruciate ligaments during knee motion. *Clin. Orthop.* 265:233-240, 1991.
33. **Laskin, R.S:** RMC total knee replacement. *J. Arthroplasty* 1:11, 1986.
34. **Lee, J.G.; Keating, E.M.; Ritter, M.A.; Garis, P.M.:** Review of all polyethylene component in total knee arthroplasty. *Clin. Orthop.* 260:87-92, 1990.
35. **Lew, W.D.; Lewis, J.L.:** The effect of knee-prosthesis geometry of cruciate ligament mechanics during flexion. *J. Bone and Joint Surg.* 64-A(5):734-739, 1982.
36. **Lewis, P.; Rorabech, C.H.; Bourne, R.B.; Devane, P.:** Posteromedial tibial polyethylene failure in total knee replacements. *Clin. Orthop*. 299:11-17, 1994.
37. **Lotke, P.A.; Corces, A..; Williams, J.L.; Hirsh, H.S.:** Strain characteristics of the posterior cruciate ligament after total knee arthroplasty. *Am. J. Knee Surg.* 6(3):104-107, 1993.
38. **Mahoney, O.; Noble, P.C.; Rhoads, D.D.; Alexander, J.W.; Tullos, H.S.:** Posterior cruciate function following total knee arthroplasty: a biomechanical study. *J. Arthroplasty* 9(6):569-578, 1994.
39. **Mow, V.C.; Ratcliffe, A.; Woo, SL-Y:** *Biomechanics of Diarthrodial Joints, Volume II,* Chapter 25, pp. 197-199, Spinger-Verlag New York, Inc. ,1990.
40. **Müller, W.:** Kinematics of the cruciate ligaments. pp. 217-220. *The Cruciate Ligaments*, Ed. Feagin JA.; Churchill Livingstone, 1988.

41. **Oschner, L.A.; McFarland, G.; Boffes, G.C.; Cook, S.D.:** Posterior cruciate ligament avulsion in total knee arthroplasty. *Orthopaedic Review,* October 1993.
42. **Prietto, M.P.; Bain, J.R.; Stonebrook, S.N.; Settlage, R.A.:** Tensile strength of the human posterior cruciate ligament (PCL). p. 195. In P*roceedings of the 34th Annual Meeting of the Orthopaedic Research Society,* 1988.
43. **Race, A.; Amis, A.A.:** The mechanical properties of the two bundles of the human posterior cruciate ligament. *J. Biomechanics* 27(1):13-24, 1994.
44. **Ranawat, C.S.; Boachie-Adjei, O.:** Survivorship analysis and results of total condylar knee arthroplasty. *Clin. Orthop.* 226:6-13, 1988.
45. **Ranawat, C.S.; Hansraj, K.K.:** Effect of posterior cruciate sacrifice on durability of the cement-bone interface: a nine-year survivorship study of 100 total condylar knee arthroplasties. *Orthop. Clin. North Am.* 20:63-69, 1989.
46. **Reuben, J.D.; McDonald, C.L.; Woodard, P.C.; Hennington, L.S.:** Factors affecting patella strain before and after total knee replacement. p. 281. In *Proceedings of the 36th Annual Meeting of the Orthopaedic Research Society,* 1990.
47. **Ritter, M.A.; Faris, P.M.; Keating, M.:** Posterior cruciate ligament balancing during total knee arthroplasty. *J. Arthroplasty* 3(4):323-326, 1988.
48. **Ritter, M.A.; Silisk, J.; Werland, R.; Faris, P.M.; Keating, E.M.; Meding, J.B.; Helphenstine, JV.:** Flat on flat, non constrained, compression molded polyethylene total knee replacement: a ten year survival analysis. p. 19. *Proceedings of the 1995 Knee/ AAHKS Combined Specialty Day Meeting*, 1995.
49. **Scott, R.D.; Volatile, T.B.:** Twelve years' experience with posterior cruciate-retaining total knee arthroplasty. *Clin. Orthop.* 205:100-107, 1986.
50. **Scott, W.N.; Rubinstien, M.; Suuderi, G.:** Results after knee replacement with a posterior cruciate-substituting prosthesis. *J. Bone and Joint Surg.* 70A:1163, 1988.
51. **Scuderi, G.R.; Insall, J.N.; Windsor, R.E.; Moran, M.C.:** Survivorship of cemented knee replacements. *J. Bone and Joint Surg.* 71B:798-803, 1989.
52. **Shoji, H.; Wolf, A.; Packard, S.; Yoshino, S.:** Cruciate retained and excised total knee arthroplasty: a comparative study in patients with bilateral total knee arthroplasty. *Clin. Orthop.* 305:218-222, 1994.
53. **Singerman, R.J.; Pedersen, D.R.; Brown, T.D.:** Quantitation of pressure-sensitive film using digital image scanning. *Exp. Mech.* 27:99, 1987.
54. **Skyhar, M.J.; Warren, R.F.; Oritz, G.T.; Schwartz, E.; Otis TC.:** The effects of sectioning of the posterior cruciate ligament and the posterolateral complex on the articular contact pressures within the knee. *J. Bone and Joint Surg.* 75-A(5):694-699, 1993.
55. **Soudry, M.; Walker, P.S.; Reilly, D.T.; Kurosawa, H.; Sledge, C.B.:** Effects of total knee replacement designs on femoral-tibial contact conditions. *J. Arthroplasty* 1(1):35-43, 1986.
56. **Stiehl, J.B.; Komistek, R.D.; Dennis,D.A.; Paxson, R.D.:** Kinematic analysis of the knee following posterior cruciate retaining total knee arthroplasty using fluoroscopy. Presented at the *62nd Annual Meeting of the American Academy of Orthopaedic Surgeons,* February, 1995.
57. **VonDommelin, B.A.; Fowler, P.J.:** Anatomy of the posterior cruciate ligament: a review. *Am. J. Sports Med.* 17(1):24-29, 1989.
58. **Yoshii, I.; Whiteside, L.A.; White, S.E.; Milliano, M.T.:** Influence of prosthetic joint line position on knee kinematics and patellar position. *J. Arthroplasty* 6(2):169-179, 1991.

ARTHROSCOPIC MUMFORD PROCEDURE VARIATION OF TECHNIQUE

Paul D. Lesko, M.D.

ABSTRACT

Fifty-seven patients had arthroscopic Mumford procedures for acromioclavicular pain non-responsive to conservative treatment. Thirty-nine of these patients had concomitant rotator cuff repairs. All had significant improvement of their distal clavicular pain. Neither the amount nor the completeness of distal clavicle resection affected the results. Arthroscopic distal clavicle resection is a safe and effective method of alleviating acromioclavicular pain.

INTRODUCTION

Acromioclavicular joint symptomatology is a common finding in shoulder pathology, both as a result of direct injury to the acromioclavicular joint and rotator cuff/impingement phenomenon with acromioclavicular arthrosis. Non-operative treatments including physical therapy, anti-inflammatories, and corticosteroid injections can help resolve the symptoms. Certain cases, however are not amenable to conservative care and require operative intervention. Resection of the distal clavicle, as described by Mumford[7], is a reliable method of treatment in post-traumatic degenerative disease of the AC joint, distal clavicle fractures, and shoulder impingement syndrome.

Traditionally, distal clavicle resection has been performed using an open incision over the acromioclavicular joint with detachment of the deltoid and trapezius muscle and their adjacent fascia. Symptom improvement has been satisfactory in most reported series[6,7,8,9,10]. However, significant morbidity can occur with these open procedures. Some of the complications with distal clavicle resections have included: residual acromioclavicular joint instability, postoperative shoulder weakness, and cosmetic complaints[5]. Arthroscopic subacromial decompression and resection of the distal clavicle can avoid the problems associated with traditional open procedures. Additionally, arthroscopic surgery allows adequate visualization and identification of glenohumeral joint pathology (labral tears, loose bodies, chondral injuries)[11] as well as rotator cuff pathology[3].

Several surgical arthroscopic approaches to the acromioclavicular joint have been proposed. One is the superior approach in which the arthroscope and instruments are inserted through the acromioclavicular joint from a superior portal[8]. The second approach is the subacromial technique, in which the arthroscope and burr are inserted via posterior or lateral subacromial portals[7].

A variation of the subacromial technique for arthroscopic resection of the distal clavicle has been used in a number of patients, with a clinical presentation of rotator cuff/impingement pathology. In all cases a diagnostic arthroscopy was performed followed by a bursoscopy and acromioplasty and distal clavicle resection. In a number of patients, mini open procedures for rotator cuff repairs were also performed.

MATERIALS AND METHODS

From 1994-95, fifty-seven arthroscopic procedures were performed. For all patients, the indications for surgery were: impingement phenomena with pain at the acromioclavicular joint, a positive adduction sign, and tenderness of the distal clavicle to palpation[9]. All patients had been non-responsive to conservative care: oral anti-inflammatories, physical therapy, and injections of corticosteroid into the subacromial spaces. In all cases preoperative and postoperative x-rays were obtained to assess the amount of distal clavicle excised as well as any retained distal clavicular fragments within the superior capsule of the acromioclavicular joint.

OPERATIVE PLANNING AND TECHNIQUE

Surgical Technique

The patients were placed in a lateral decubitus position. Bucks traction was used to secure the forearm for traction. The arm was placed in approximately 30 degrees abduction, and 10-15 degrees of forward flexion. The upper extremity was then prepped with Duraprep and the forearm draped sterilely with Ioband drape. Four ccs of 1:1000 dilution of epinephrine were placed

University of Kansas School of Medicine - Wichita
Department of Surgery, Section of Orthopaedics

Correspondence to:
Paul D. Lesko, M.D., Orthopaedic and Athletic Medicine, P.A., P.O. Box, Vidalia, GA 30745,
Telephone: 319/538-9999, Fax: 912/538-7701

in each 3L bag of arthroscopic fluid. The Dyonics pump was used to distend the shoulder joint and subacromial space.

Glenohumeral Evaluation

The glenohumeral joint was slightly evaluated using standard anterior and posterior portals. The biceps tendon and the underside of the rotator cuff were evaluated. Any fraying or edema of the critical zone was noted. Both anterior and posterior labra were visualized as well as the articular surface of the glenoid and the humerus. Any anterior pathology was surgically addressed at this time.

Subacromial Evaluation

The arthroscope was then removed from the glenohumeral joint and placed in the subacromial bursa through the posterior portal. A third portal was made approximately 2 cc lateral to the lateral border of the acromion. Any shaving and decompressive work was done through the lateral portal. After an adequate bursectomy was done, the rotator cuff was evaluated. The humerus was maximally rotated both internally and externally while probing the rotator cuff at the critical zone. Any penetration through the rotator cuff and critical zone into the glenohumeral joint was considered to be an essential tear of the rotator cuff. If hooking or spurring of the anterior acromion was present or thickening of the bursa was noted on the undersurface of the acromion, an acromioplasty was performed using the Dyonics stone cutting burr. The anterior 7-10 mm of anterior acromion was resected, encompassing the anterior one-half to two-thirds of the acromion. Care was taken to leave a smooth underside and not to violate the anterior deltoid fascia. If the coracoacromial ligament was noted to be thickened, it was then resected using electrocautery.

The arthroscope was then placed in the lateral portal. This allowed an excellent view of the angle of resection of the acromion. This further allowed a second view of the rotator cuff from above, and any additional probing of the cuff was done at this time.

Distal Clavicle Resection

The arthroscope remained in the lateral portal for this aspect of the procedure. Through the posterior portal the underside of the acromioclavicular joint capsule was then excised using the Dyonics and synovial resector. If thickened, the inferior capsule of the acromioclavicular joint was first elevated using the electrocautery. The underside of the distal clavicle was exposed for a distance of approximately two centimeters, taking care to stay lateral to the coracoclavicular ligaments. The Dyonics stone cutter burr was then used to resect the distal clavicle, working from inferiorly to superiorly. Care was taken not to violate the superior capsule of the acromioclavicular joint.

A useful technique was to remove the clavicle from lateral to medial. This prevented floating lateral fragments of clavicle remaining within the superior acromioclavicular capsule[7]. Digital pressure on the distal clavicle by an assistant allowed a better view of the superior capsule of the AC joint and any retained capsular fragments. If needed, the Dyonics resector was placed in the anterior portal, which allowed better access to the posterior aspect of the AC joint.

Postoperatively, all patients were placed in an abduction pillow for 7-10 days. If a rotator cuff repair was performed, the abduction pillow was used for 4-5 weeks. Immediately postoperatively, passive motion was initiated by a physical therapist and continued on an outpatient basis. At two weeks, hydrotherapy was initiated.

RESULTS

Fifty-seven patients underwent arthroscopic distal clavicle resection arthroscopically performed. All fifty-seven had acromioplasties performed as well. Thirty-nine of these patients also underwent a rotator cuff repair. Improvement or elimination of the distal clavicle pain was reported in all subjects.

Radiographic Results

Of the 57 clavicle resections, 20 had retained clavicle fragments. Six were large fragments. Fourteen had small pieces, most visible only under hot light. All were asymptomatic. Eight patients showed radiographic evidence of a superior spike distal clavicle within the superior capsule of the AC joint (type II). Persistent symptoms of crepitus and pain occurred in one patient. These symptoms improved when the superior spike was subsequently resected.

DISCUSSION

Distal clavicle resections have been shown to be a useful adjunct in treating patients with AC pan and associated impingement who were otherwise not responsive to conservative care[6,8,9,10]. Cook and Tibone[5] have shown the symptomatic and subject improvement of distal clavicle resections in a group of athletes. However, a loss of bench press strength was a complaint of four athletes who did not return to their previous performance level. Diligent attention to reconstruction of the deltoid and trapezius fascia was emphasized. The arthroscopic technique allows the procedure to be performed without the morbidity of detaching and reattach-

ing the deltoids or the trapezius from the distal clavicle and the anterior acromion[5,6,9]. Postoperative weakness is avoided and a more rapid return to activity is expressed[8].

The use of the arthroscope in the distal clavicle resection allows the thorough evaluation of both the glenohumeral joint as well as the subacromial space including partial full thickness rotator cuff tears[3] and instability[11]. Some authors have suggested that less than optimum results can occur when shoulder laxity or other intra-articular causes of distal clavicle pain or impingement are not addressed[11]. Correction of the underlying instability is imperative to correct the impingement phenomena. Whether this be repair of a labral tear or capsulorrhaphy depends on the presentation. The thoroughness of this evaluation in an experienced arthroscopist and shoulder surgeon should not be underscored.

Several different techniques have been suggested for arthroscopic Mumford procedures. Synder[8] recommends that all soft tissue be removed from the inferior AC joint. A pilot hole is then drilled in the center of the clavicle to a depth of 1.5 cm. With external pressure on the clavicle, the pilot hole is then enlarged in a circular fashion until only a shell of the cortical bone of the lateral clavicle remains. The remainder of the shell is then removed with the acromionizer. However, these pieces of clavicle, especially those still attached to the superior capsule, can be difficult to remove.

Flatow and Bigliani et al.[8] reported on arthroscopic resections of the lateral clavicle using the superior approach. The area of arthroscopy is small and the 2.7 mm wrist arthroscope is used for this technique. With this technique they do not routinely arthroscopically examine the subacromial bursa nor the glenohumeral joint.

Our technique is a variation of the technique used by Synder[7]. With the Dyonics stone cutter burr and arthroscopic pump, this procedure can be quickly and safely performed. The distal clavicle does not need to be continually manually depressed, which can be technically difficult. Using the shaver from both the posterior and anterior portals, while visualizing laterally, allows the distal clavicle to be well resected and the superior capsule of the AC joint to be well visualized[8].

A surprising finding was that retained clavicular fragments were not associated with residual clavicular pain. The presence of a prominent lateral spike was found to give symptoms in one patient and improved with further resection.

SUMMARY

The arthroscopic Mumford procedure is a safe, reliable method of resecting the distal clavicle. Using the lateral portal for visualization and the posterior and anterior portals for resection allows the surgeon to visualize the distal clavicle resection and is an effective method for clavicle resection.

The indication for distal clavicle resection was pain at exam either to palpation of the acromioclavicular joint or pain demonstrated at the AC joint with activity[9].

Table I

	# Subjects
Type 0	29
Type Ia (small fragment)	14
Type IIb (large fragment)	6
Type II (lat spike)	8

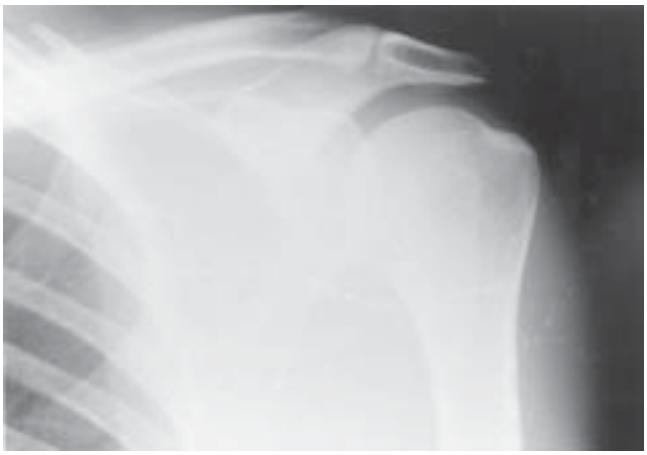

Figure 1. Preoperative x-ray: Note the spur on the inferior aspect of the clavicle as well as the hazy spur on the underside of the acromion.

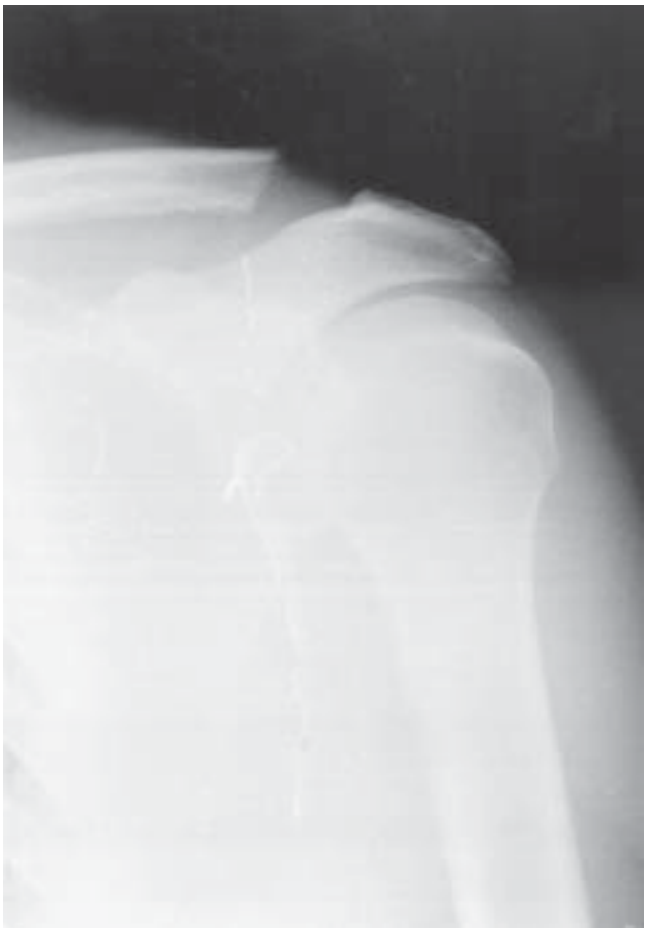

Figure 2. Postoperative x-ray. Note the extent of the distal clavicle resection. The underside of the acromion has also been thinned as compared to Figure 1.

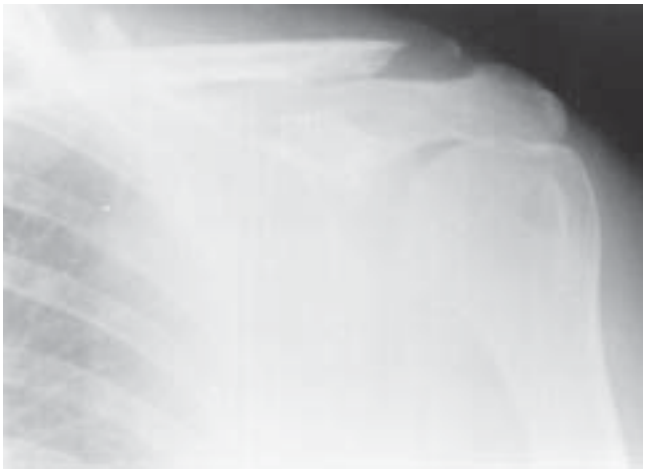

Figure 3. Distal clavicle resection with retained clavicular fragment within the superior capsule, Type Ia.

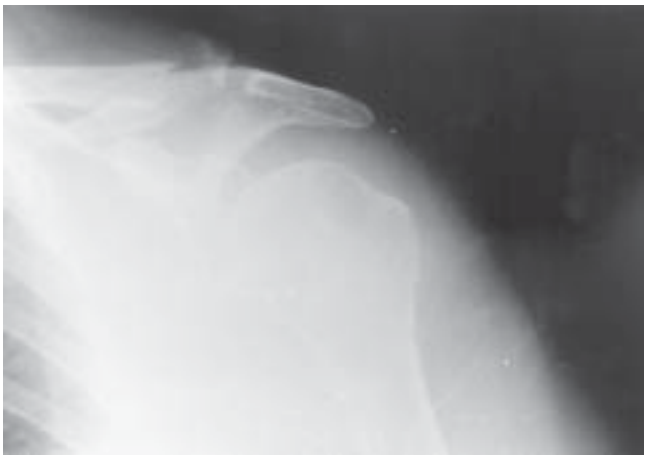

Figure 4. Large retained clavicular fragment within the AC space. This is a Type Ib. The patient was asymptomatic.

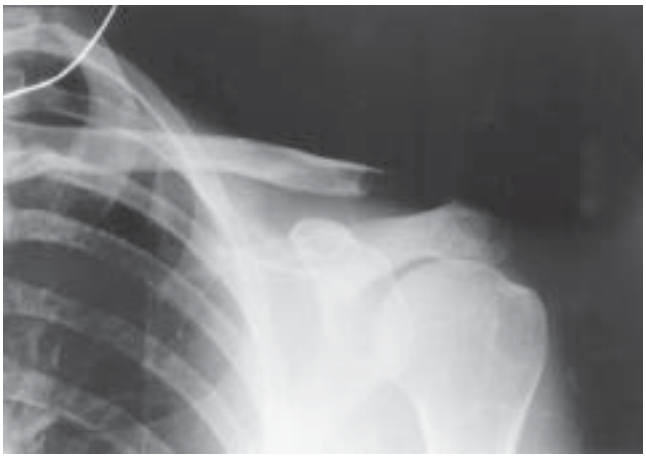

Figure 5. Superior spike of the distal clavicle, Type II. The patient complained of persistent lateral clavicular pain.

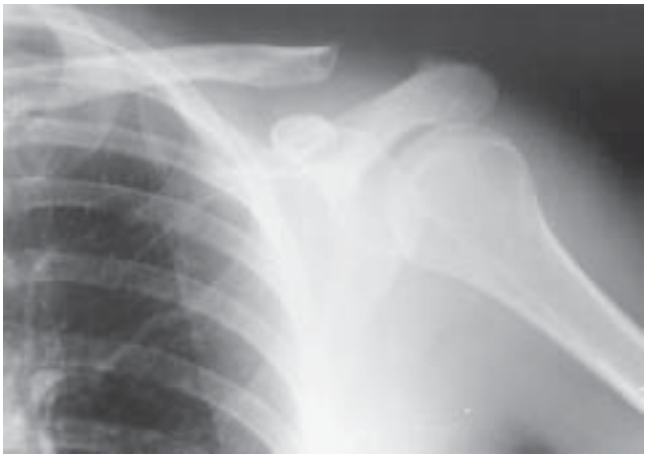

Figure 6. Status post resection of the spike of the lateral clavicle. Patient reported improved symptoms but still had residual distal clavicle pain.

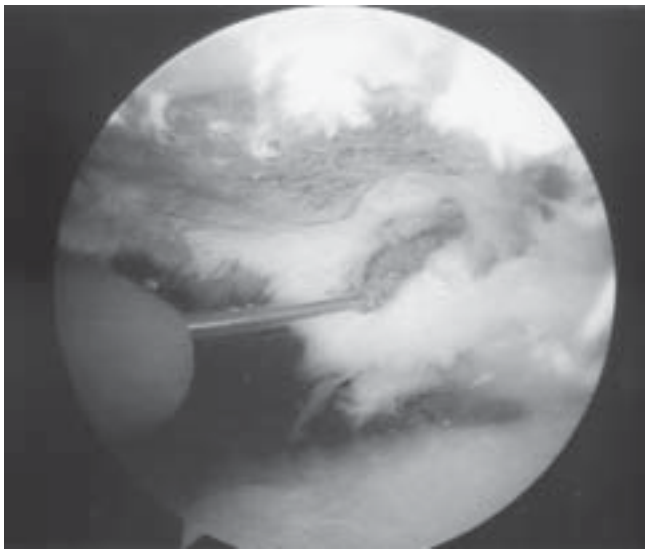

Figure 7. Lateral view of the subacromial space. Electrocautery incising the inferior capsule of the AC joint.

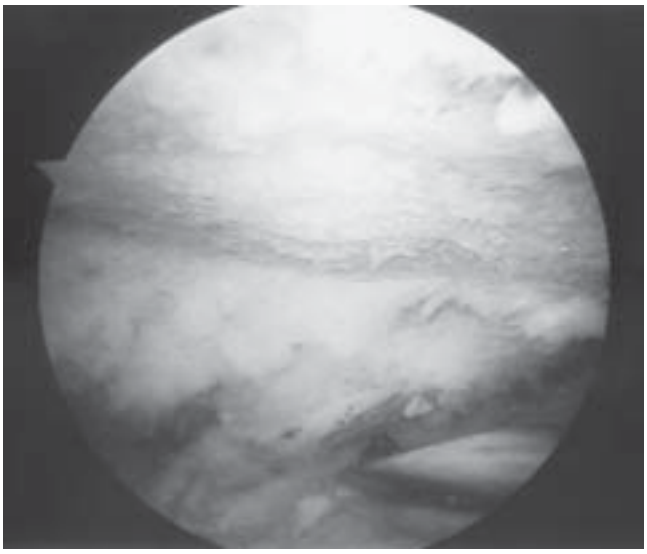

Figure 9. Lateral view of acromion status-post acromioplasty. Exposed underside of the distal clavicle.

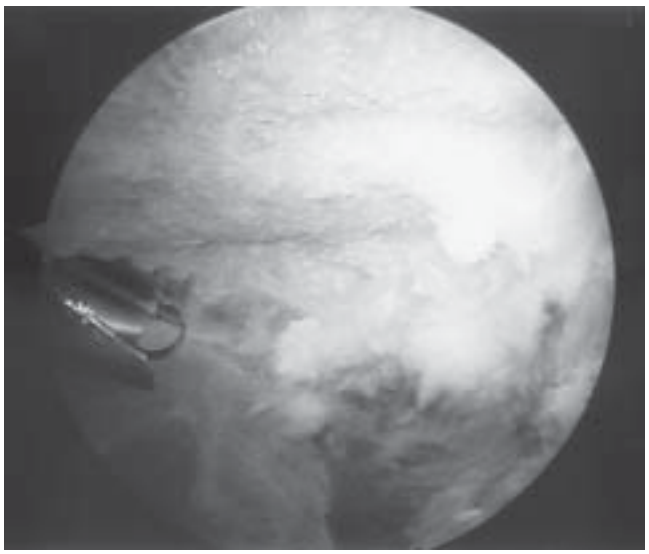

Figure 8. Lateral view of the acromion, status-post acromioplasty. Anterior is at 3 0'clock.

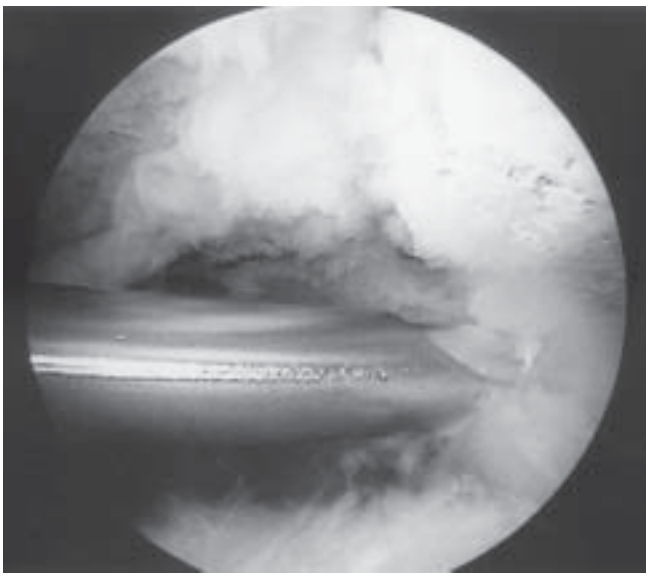

Figure 10. Dyonics bur in place to begin distal clavicle resection.

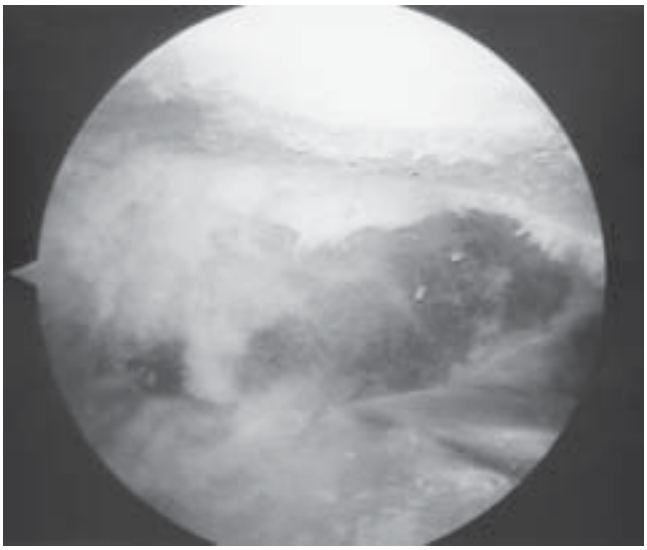

Figure 11. Distal clavicle resection completed. Rotator cuff is well visualized from this portal.

BIBLIOGRAPHY

1. **Warner, J.; Kann, D.;** and **Maddox, L.:** The arthroscopic impingement test. *J. Arthroscopic and Related Surg;* 10(2):224-230, 1994.
2. **Caspari, R.;** and **Thal, R.:** A technique for arthroscopic subacromial decompression. *J. Arthroscopic and Related Surg.,* 8(1):23-30, 1992.
3. **Paulos, L.;** and **Franklin, J.:** Arthroscopic shoulder decompression development and application-a five year experience. *Am. J. Sports Med.,* 18(4):235-244, 1990.
4. **Gartsman, G.:** Arthroscopic acromioplasty for lesions of the rotator cuff. *J. Bone and Joint Surg.,* 72(2):169-180, 1990.
5. **Cook, F.F.;** and **Tibone, J.E.:** The Mumford procedure in athletes, an objective analysis of function. *Am. J. Sports Med.,* 16(2):97-100, 1988.
6. **Daluga, D.J.** and **Dobozi, W.:** The influence of distal clavicle resection and rotator cuff repair on the effectiveness of anterior acromioplasty. *Clin. Orth. Rel. Res.,* 247:117-123, 1989.
7. **Snyder, J.J.; Banas, M.P.;** and **Karzel, R.P.:** The arthroscopic Mumford procedure: an analysis of results. *J. Arthroscopic Rel. Surg.,* 11(2):157-164, 1995.
8. **Flatow, E.L.; Duralde, X.A.; Nicholson, G.P.; Pollock, R.G.;** and **Bigliani, L.U.:** Arthroscopic resection of the distal clavicle with a superior approach. *J. Shoulder-Elbow Surg.,* 4(1):41-50, 1998.
9. **Novak, P.J.; Bach, B.R. Jr.; Romeo, A.A.;** and **Hager, C.A.:** Surgical resection of the distal clavicle. *J. Shoulder-Elbow Surg.,* 4(1):35-40, 1998.
10. **Petchell, J.F.: Sonnabend, D.H.;** and **Hughes, J.S.:** Distal clavicular excision: a detailed functional assessment. *Australia-New Zealand J. Surg.,* 65:262-266, 1995.
11. **Jobe, F.W.:** Shoulder instability in the overhand or throwing athlete. *Clin. J. Sports Med.,* 14(4):917-935, 1995.

THE VARIABLE PRESENTATION AND NATURAL HISTORY OF LANGERHANS CELL HISTIOCYTOSIS

Joseph A. Buckwalter, M.D.*
Eric Brandser, M.D.**
Robert A. Robinson, M.D.***

ABSTRACT

Langerhans cell histiocytosis is not a well defined or predictable disease. Instead, it is a spectrum of disorders of unknown etiology that vary widely in presentation and natural history, but have in common the proliferation of histiocytic cells and infiltration of these cells into normal tissues. Although the lesions of Langerhans cell histiocytosis consist primarily of histiocytes, eosinophils are a prominent feature in some lesions. Lesions may develop in any tissue, but bone, skin and lymph nodes are the most commonly affected, and more than 75% of patients have skeletal lesions. Bone lesions caused by Langerhans cell histiocytosis vary from focal sharply defined areas of bone lysis to diffuse osteopenia and can resemble lesions caused by a wide variety of metabolic, infectious and neoplastic diseases. The natural history varies from a benign disorder that resolves spontaneously to a progressive fatal disease. In general, the younger the individual at the time of onset of the disease, the poorer the prognosis and the more extensive the disease. Treatment may include surgery, chemotherapy and radiation therapy, depending on the extent and severity of the disease

No disease of the skeleton varies more in presentation and natural history than Langerhans cell histiocytosis. (Langerhans cell histiocytosis was formerly referred to as histiocytosis X). The only feature that all forms of this disease have in common is the proliferation of histiocytic cells and infiltration of these cells into normal tissues[11,16,17]. These cells can affect any bone and cause changes that mimic a wide variety of metabolic, infectious and neoplastic diseases; and, the course of untreated Langerhans cell histiocytosis varies from a systemic progressive fatal illness to a localized self-limited bone lesion[15-17]. The most commonly affected tissues are bone, skin and lymph nodes. Langerhans cells may also invade and proliferate in the liver, lung, spleen and bone marrow as well as other organs. Although Langerhans cell histiocytosis involves bone more frequently than other tissues, it is a relatively rare skeletal disorder, representing less than 2% of all biopsied bone lesions.

In general, the younger the patient at the time of onset of the disease, the poorer the prognosis and the more severe and extensive the disease[10,15]. In its mildest form, Langerhans cell histiocytosis is an isolated lesion in bone (Figures 1 and 2). In its most severe form it extends through the skeleton and mulitple viscera. Classically, the various forms of Langerhans cell histiocytosis have been grouped into three categories based on the severity of the disease although there are many patients with intermediate forms of the disease and one form may change into another form.

The most severe form of Langerhans cell histiocytosis, Letterer-Siwe Disease, is most commonly seen in infants and in children less than three years of age. This form of the disease has an extremely poor prognosis. Although Letterer Siwe disease may occur in older children, most patients who develop this form of disorder do so within the first year of life. It usually involves the skeleton diffusely, and patients with this disorder commonly have fever, otitis media, papular rash, exophthalmos, hepatosplenomegaly, adenopathy, and cachexia. They are extremely vulnerable to infection. The rapid progression of the skeletal disease may cause generalized osteopenia or multiple small bone defects.

A less severe form of Langerhans cell histiocytosis, Hand-Schuller Christian Disease, occurs most commonly in children older than one year and less than 15 years of age. It typically causes multiple skeletal lesions including lesions of the skull as well as diabetes insipidus and exophthalmos. Any bone may be involved, but the vast majority of these patients, probably over 90%, have skull lesions. The bone lesions may range in size from as little as 1 cm to involvement of an entire long bone. Otitis media is the most frequent complaint and

University of Iowa College of Medicine
*Department of Orthopaedic Surgery
**Department of Radiology
***Department of Pathology

Please address correspondence to Joseph A. Buckwalter, 01013 Pappajohn Pavilion, Department of Orthopaedics, University of Iowa College of Medicine, Iowa City, IA 52242, Phone (319) 356-2595, FAX (319) 356-8999, email: joseph-buckwalter@uiowa.edu

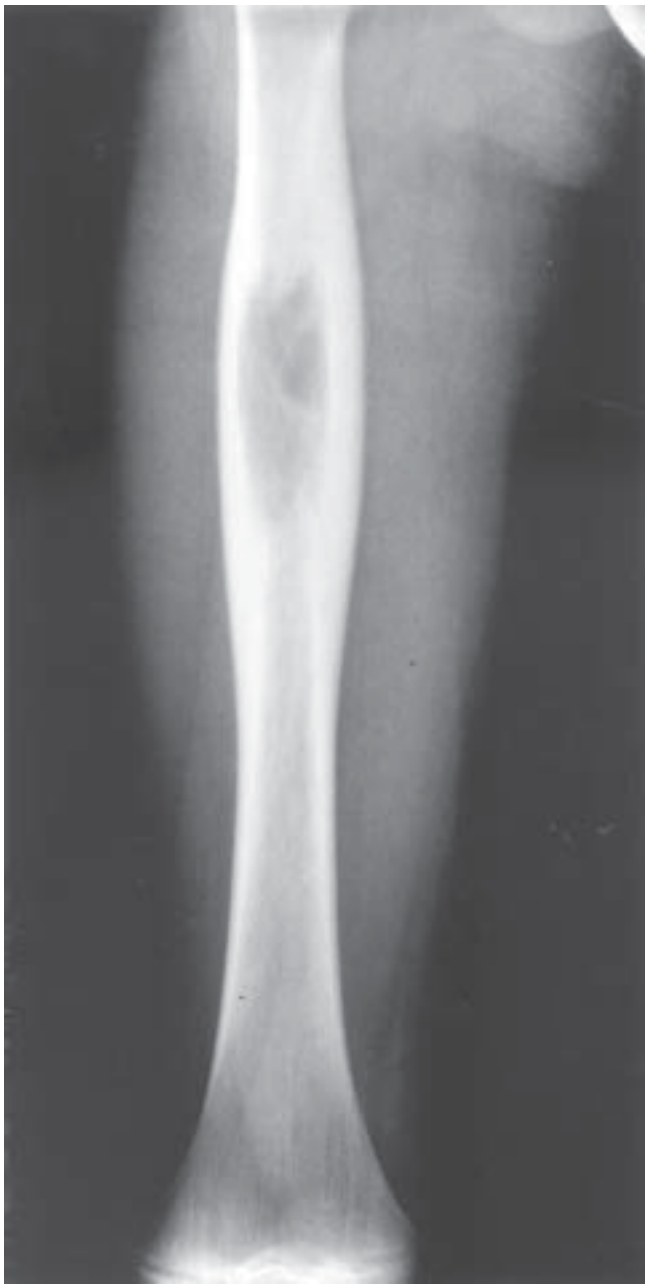

Figure 1A. Anterior-posterior radiograph of the femur showing a central lytic lesion and expansion of the cortex.

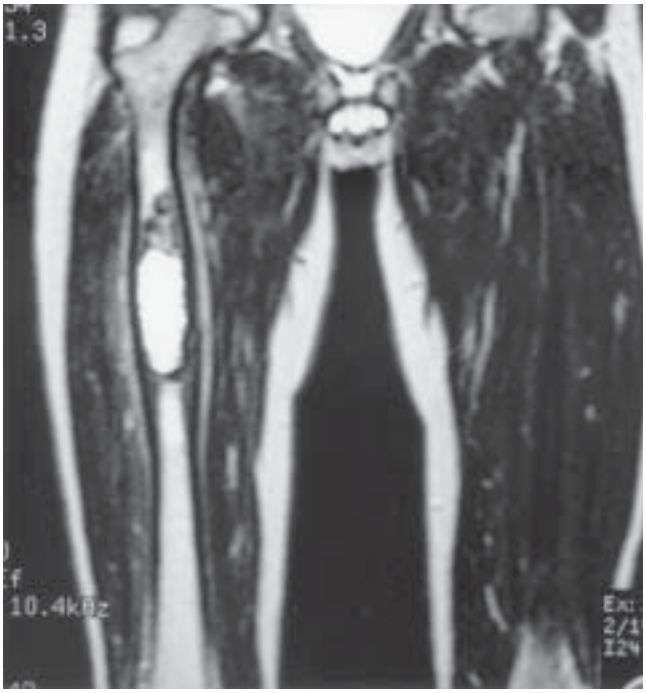

Figure 1B. Cornal MRI image of the femur showing the diaphyseal lesion.

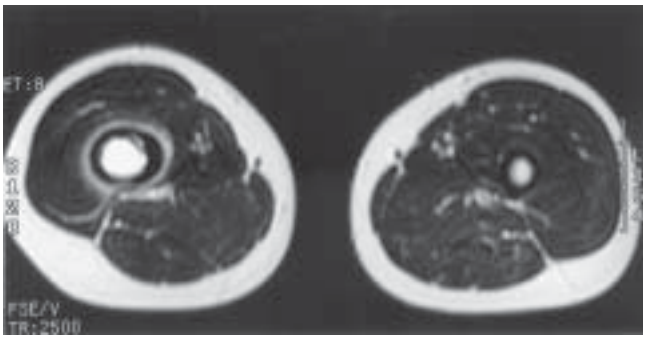

Figure 1C. Transverse MRI image of the femur showing the central lesion and a ring of periosteal reaction.

Figures 1A-1D. Langerhans cell histiocytosis of the femoral diaphysis in a 12 year old boy. The patient presented with a history of six months of increasing thigh pain. He had no systemic symptoms. A bone survey and bone scintigraphy did not show any other lesions.

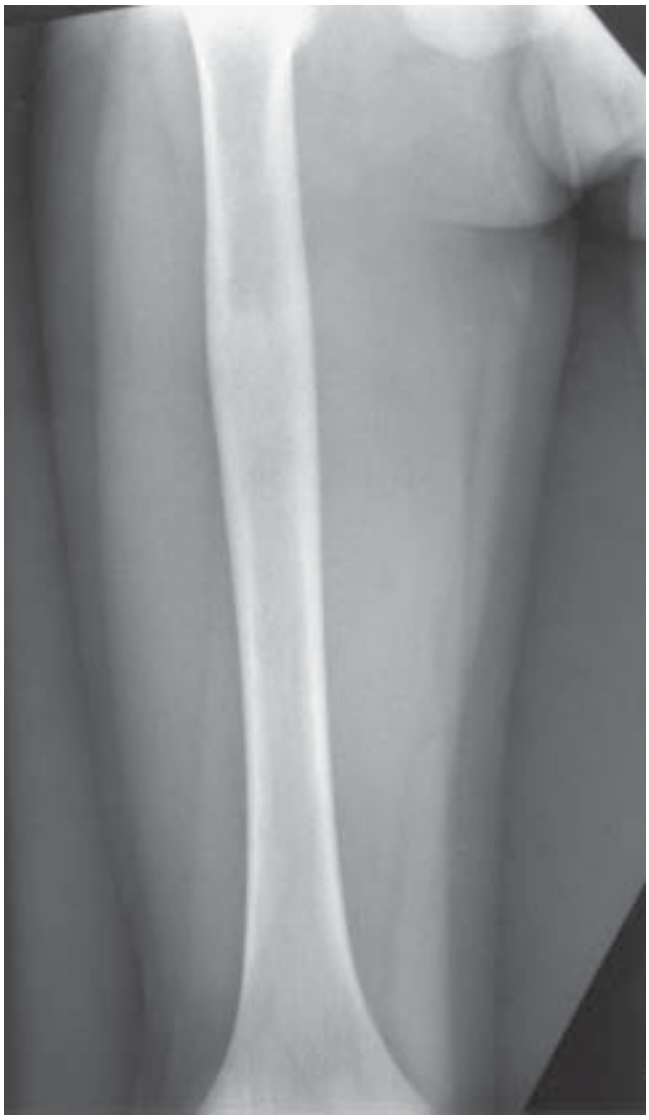

Figure 1D. Anterior-posterior radiograph of the femur six months after treatment of the lesion by curretage and grafting with demineralized bone matrix.

a large portion of the patients at some point develop diabetes insipidus and may develop exophthalmos. Lymphadenopathy, hepatosplenomegaly and anemia are also commonly seen in patients with Hand-Schuller Christian disease.

The mildest form of Langerhans cell histiocytosis, frequently referred to as eosinophilic granuloma of bone, generally occurs in individuals between the ages of 5 and 15 years, but it has been reported in middle aged and elderly adults. Most of the skeletal lesions involve flat bones including the skull, jaw, spine and pelvis. However, approximately one-third of the lesions occur in long bones (Figure 1). The common presenting complaint is bone pain. With spinal involvement collapse of the vertebral body may develop leading to neurologic symptoms (Figure 3). Lesions may also cause pathologic fractures of long bones.

The cell responsible for Langerhans cell histiocytosis is the Langerhans cell, a cell of the dendritic cell system[4,5,11]. Langerhans cells are roughly 12 microns in diameter and typically have nuclei that are folded, indented or lobulated (Figure 4). They are believed to have a role in the T-cell mediated immune system that involves transfer of antigens. The cytoplasm of the Langerhans cells in the lesions of Langerhans cell histiocytosis contain specific inclusion bodies identical to the Birbeck granules in normal Langerhans cells. Demonstration of Birbeck granules by electron microscopy or staining for ??CD1a and S-100 antigens by immunohistochemistry can help establish the diagnosis. Although the factors that cause these cells to proliferate and invade normal tissues are unknown, there is some evidence that the disorder results from a disturbance in immune regulation[6,14].

Eosinophils are a prominent feature in some lesions, but may be difficult to find in others. They may be seen singly, in sheets, or in focal clusters, and the proportions of eosinophils and histiocytes may vary greatly from field to field or from one lesion to another in the same individual. In some instances, eosinophils may be the predominant cell type and in others histiocytes predominate.

Bone lesions appear in more than 75% of patients and vary from small focal collections of Langerhans cells and eosinophils in cancellous bone that can be difficult to detect to masses of cells that destroy cancellous and cortical bone (Figures 1, 2 and 3)[8,11,12]. Imaging studies demonstrate the bone lesions of Langerhans cell histiocytosis, but imaging studies alone are rarely sufficient to establish the diagnosis. The radiographic appearance of Langerhans cell histiocytosis in bone varies among patients and locations and may resemble a variety of other bone lesions. In some patients it causes

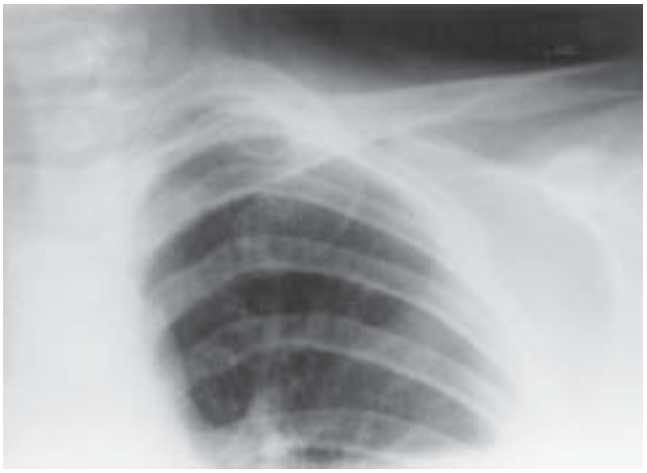

Figure 2A. Anterior-posterior radiograph of shows a lucency of the superior medial left clavicle.

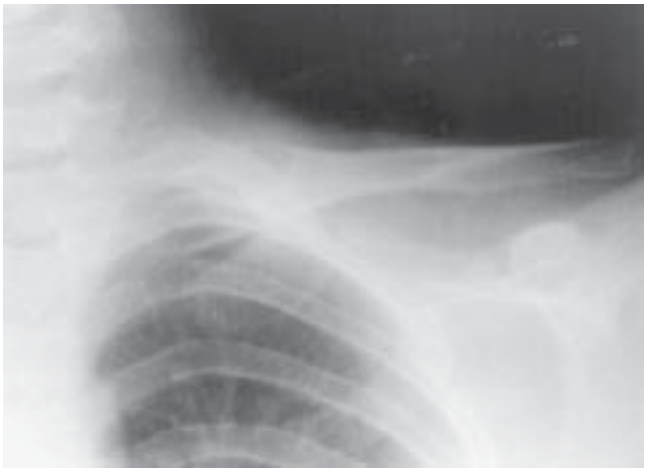

Figure 2B. A ten degree cephalic angled radiograph shows the lucent lesion more clearly.

Figures 2A-B. Langerhans cell histiocytosis of the clavicle in a nine year old boy.

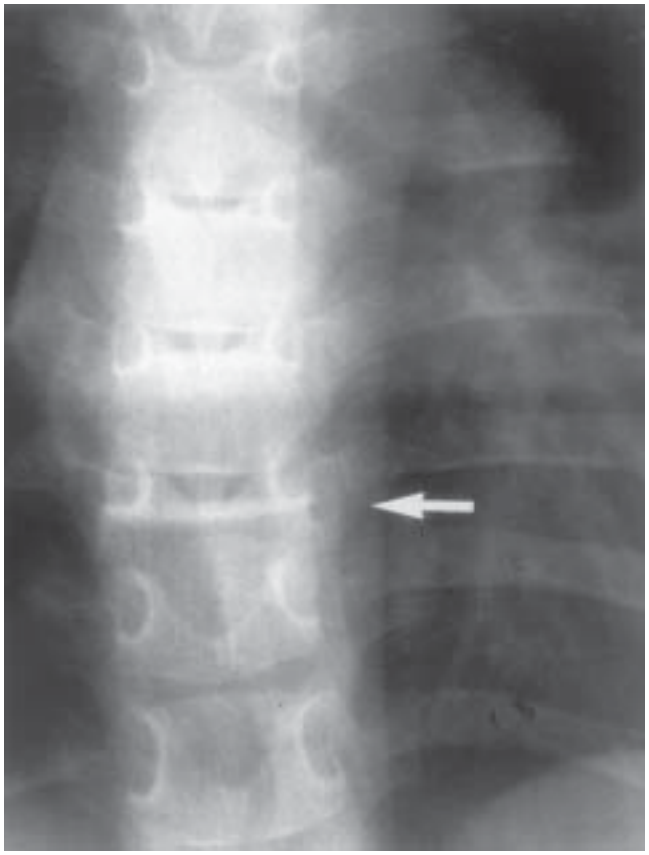

Figure 3A

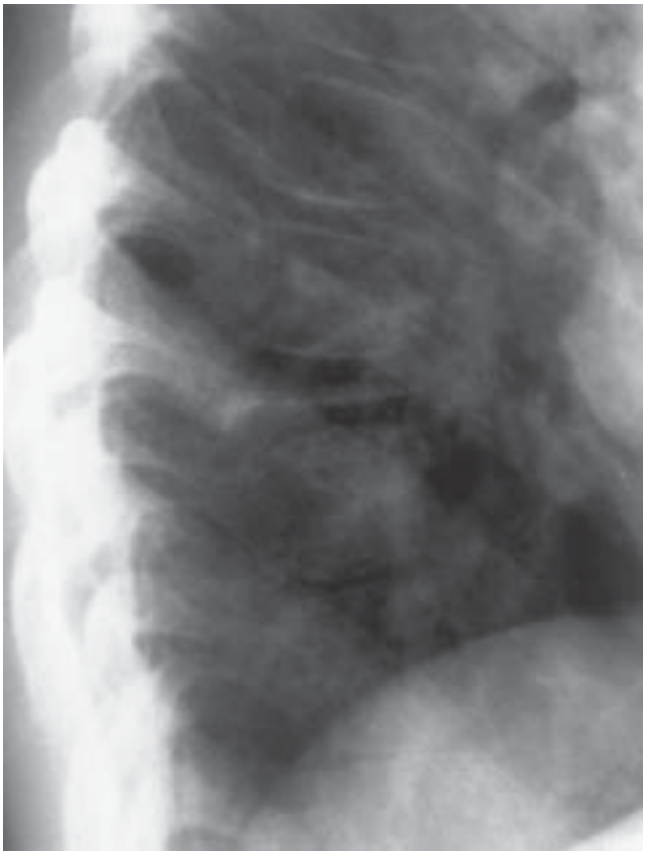

Figure 3B

Figures 3A-E. Langerhans cell histiocytosis of the spine causing vertebral plana in a 12 year old boy.
An anterior-posterior radiograph (3A) and a lateral radiograph (3B) of the thoracic spine show collapse of the T3 vertebral body.
T1-weighted (3C) and T2 weighted (3D) sagittal MRI studies show collapse of the vertebral body and displacement of the spinal cord.
An axial T2-weighted MRI study (3E) shows circumferential extension of the soft tissue mass from the vertebral body.

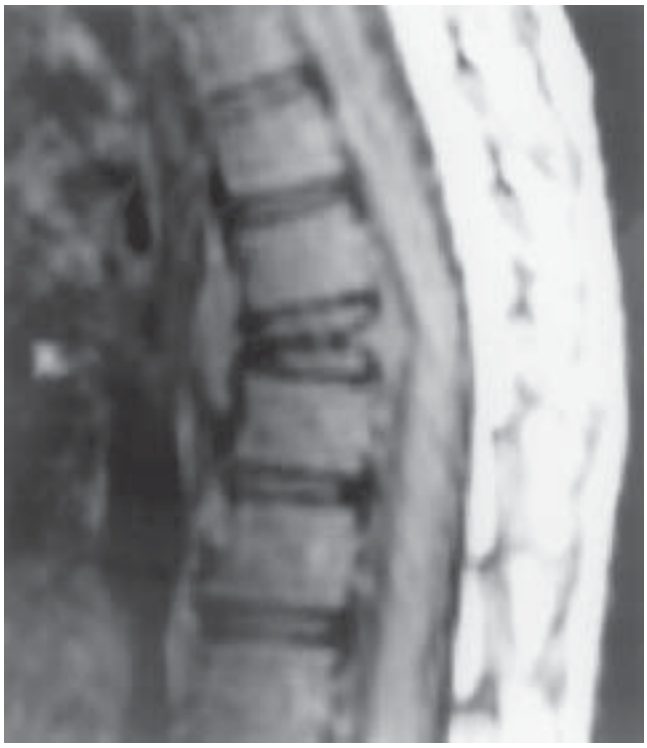

Figure 3C

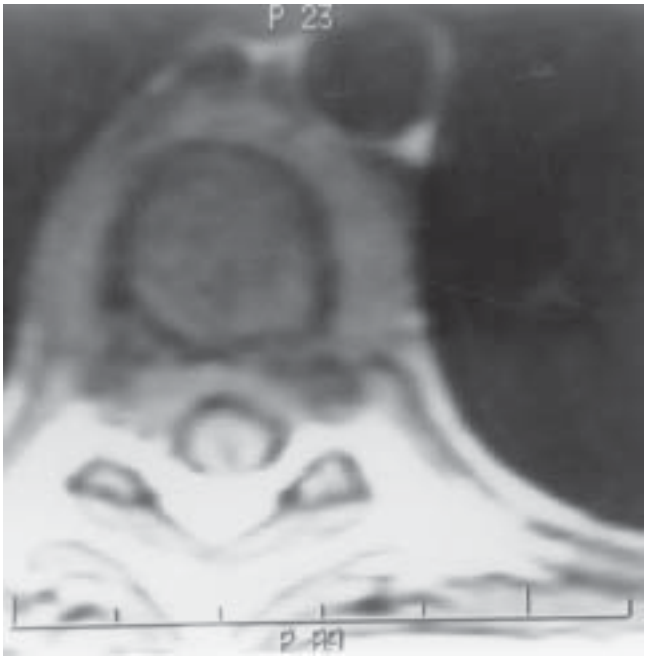

Figure 3E

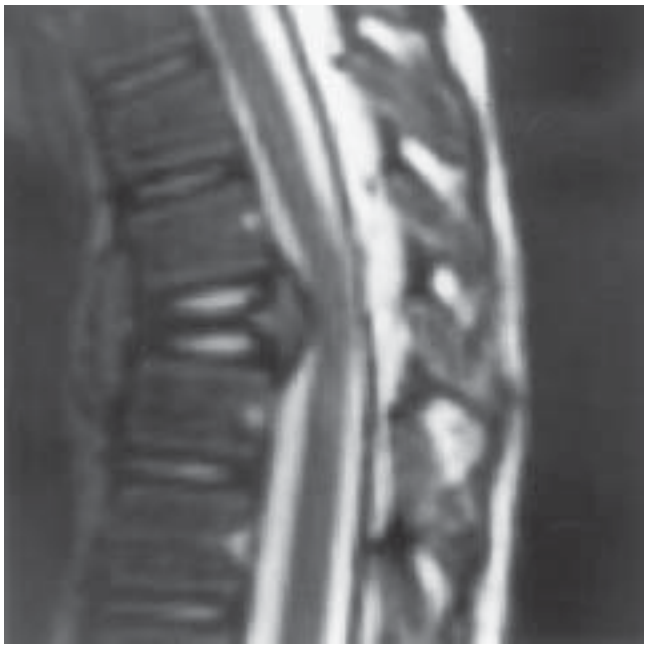

Figure 3D

diffuse osteopenia, but in others it appears as focal sharply-defined lesions or irregular destructive defects with significant reactive bone formation. Lesions of the flat bones and ribs frequently have a punched out appearance with minimal endosteal or periosteal reaction. Many of the lesions of the long bones are circumscribed by sharply defined endosteal cortical scalloping and moderate periosteal reaction (Figure 1), although infiltration of bone by Langerhans cells can cause a wide variety of radiographic abnormalities[8]. Lesions of the vertebral body, present as collapse of the vertebral body, a condition referred to as vertebral plana (Figure 4). Like plane radiographic studies, Bone scans, CT scans and MRI scans are not diagnostic for Langerhans cell histiocytosis. However, computerized tomography and magnetic resonance (Figures 1 and 3) may be helpful in the assessment of the extent of a lesion especially in sites that are difficult to evaluate with plain radiographs. Bone scans provide a method of indentifying lesions throughout the skeleton, but in some instances, they may be negative even when lesions can be demonstrated by radiography[9,16].

The varied clinical presentation of Langerhans cell histiocytosis can make diagnosis difficult. The clinical and radiographic findings frequently are not specific enough to determine the diagnosis. Some patients may have an elevated erythrocyte sedimentation rate and patients with disseminated disease frequently have ane-

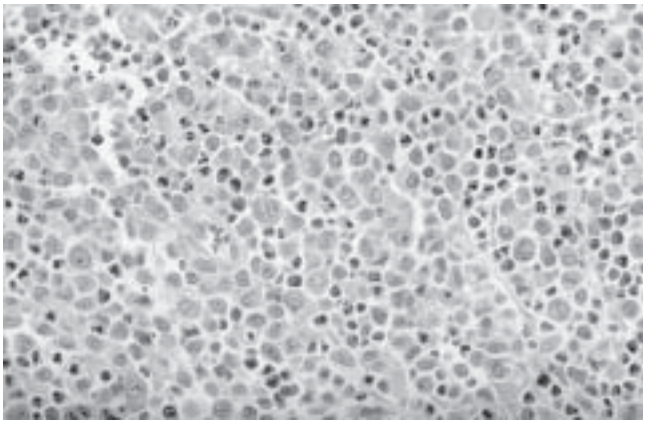

Figure 4A. A low magnification micrograph showing a mixture of large pale cells with light pink cytoplasm and large single nuclei (histiocytes) and scattered eosinophils. The eosinophils have intensely bright eosinophilic granules in their cytoplasm and bilobed nuclei. A few polymorphonuclear leukocytes are also present.

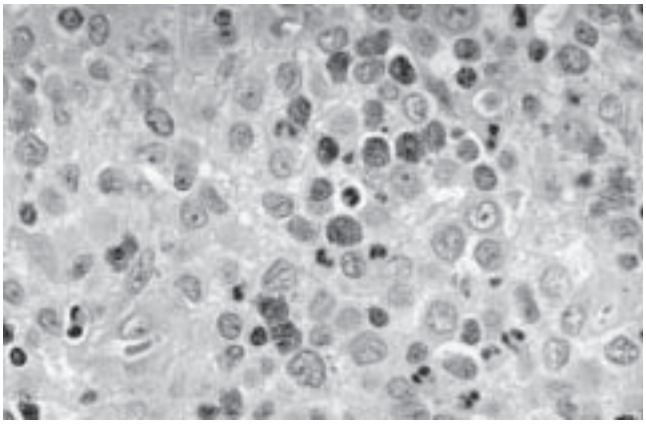

Figure 4B. A higher magnification micrograph showing the mixture of histiocytes and eosinophils. The granules in the eosinophils are visible and some of the Langerhans cell histiocytes have nuclear grooves and folds.

Figures 4A-B. Micrographs showing Langerhans cell histiocytosis.

mia[16]. There are no diagnostic laboratory studies, and in many instances biopsy is necessary to establish the diagnosis. However, in patients with vertebra plana, the clinical presentation and radiographic appearance of the vertebra (Figure 3) may be sufficient to establish a presumptive diagnosis[16]. In these patients biopsy is often not necessary, and it may cause a growth disturbance. Patients with diagnosis of Langerhans cell histiocytosis should be evaluated for possible systemic disease and those with an apparently isolated skeletal lesion should be evaluated for other possible lesions. In most patients this evaluation should include a bone scan and a skeletal survey using radiographs[9,13].

The great variability in the severity and prognosis of Langerhans cell histiocytosis makes it difficult to develop uniform treatment plans. However, increasing clinical experience has helped define a general approach to the management of patients with this disorder. Individuals with isolated bone lesions can be effectively treated by biopsy and curettage of the lesion (Figure 1). In most instances this leads to healing. In individuals with large, painful bony lesions, and lesions that may lead to pathologic fracture, internal fixation and bone grafting is appropriate. Steroid injection may also be effective treatment for selected bone lesions 1-3. Individuals with wide spread skeletal disease may benefit from low dose radiotherapy. Patients with systemic symptoms and dysfunction of organs such as the liver, lungs, spleen or bone marrow should be considered for chemotherapy. Currently accepted drug treatments include corticosteroids and etoposide, vinblastine, methotrexate and interferon[7,16]. Even patients with isolated Langerhans cell skeletal histiocytosis should be followed for at least five years as other lesions may appear and recurrences have been reported in approximately 10% of patients[7,16,17]. Nonetheless, individuals with isolated skeletal Langerhans cell skeletal histiocytosis have an excellent prognosis.

REFERENCES

1. **Bernstrand, C.; Bjork, O.; Ahstrom, L.;** and **Henter, J.I.:** Intralesional steroids in Langerhans cell histiocytosis of bone. *Acta Pediatrica,* 85(4):502-504, 1996.
2. **Capanna, R.;Springfield, D.S.; Ruggieri, P.; Biagini, R.; Picci, P.; Bacci, G.; Giunti, A.; Lorenzi, E.G.;** and **Campanacci, M.:** Direct cortisone injection in eosinophilic granuloma of bone: a preliminary report on 11 patients. *J. Pediat. Orthop.,* 5:339-342, 1985.
3. **Cohen, M.; Zornoza, J.; Cangir, A.; Murray, J.A.;** and **Wallace, S.:** Direct injection of methylprednisolone sodium succinate in the treatment of solitary eosinophilic granuloma of bone: a report of 9 cases. *Radiology,* 136:289-293, 1980.
4. **de-Graaf, J.H.,** and **Egeler, R.M.:** New insights into the pathogenesis of Langerhans cell histiocytosis. *Curr. Opinion Pediatrics,* 9(1):46-50, 1997.
5. **Egeler, R.M.,** and **D'Angio, G.J.:** Langerhans cell histiocytosis. *J. Ped.,* 127(1):1-11, 1995.
6. **Favara, B.E.:** Langerhans' cell histiocytosis pathobiology and pathogenesis. *Sem. Oncol.,* 18:3-7, 1991.
7. **Giona, F.; Caruso, R.; Testi, A.M.; Moleti, M.L.; Malagnino, F.; Martelli, M.; Ruco, L.; Giannetti, G.P.; Annibali, S.;** and **Mandelli, F.:** Langerhans' cell histiocytosis in adults: a clinical and theraputic analysis of 11 patients from a single institution. *Cancer,* 80(9):1786-1791, 1997.
8. **Hindman, R.W.; Thomas, R.D.; Young, L.W.;** and **Yu, L.:** Langerhans cell histiocytosis: unusual skeletal manifestations observed in thirty-four cases. *Skel. Radiol.,* 27:177-181, 1998.
9. **Howarth, D.M.; Mullan, B.P.; Wiseman, G.A.; Wenger, D.E.; Forstrom, L.A.;** and **Dunn, W.L.:** Bone scintigraphy evaluated in diagnosing and staging Langerhans' cell histiocytosis and related disorders. *J. Nuc. Med.,* 37(9):1456-1460, 1996.
10. **Kilpatrick, S.E.; Wenger, D.E.; Gilchrist, G.S.; Shives, T.C.; Wollan, P.C.;** and **Unni, K.K.:** Langerhans' cell histiocytosis (histiocytosis X) of bone. A clinicopathologic analysis of 263 pediatric and adult cases. *Cancer,* 76(12):2471-2484, 1995.
11. **Lieberman, P.H.; Jones, C.R.; Steinman, R.M.; Erlandson, R.A.; Smith, J.; Gee, T.; Huvos, A.; Garin-Chesa, P.; Filippa, D.A.; Urmacher, C.; Gangi, M.D.**; and **Sperber, M.:** Langerhans cell (eosinophilic) ganulomatosis. A clinicopathologic study encompassing 50 years. *Am. J. Surg. Path.,* 20(5):519-552, 1996.
12. **Meyer, J.S.; Harty, M.P.; Mahboubi, S.; Heyman, S.; Zimmerman, R.A.; Womer, R.B.; Dormans, J.P.;** and D'Angio, G.J.: Langerhans cell histiocytosis: presentation and evolution of radiologic findings with clinical correlation. *Radiographics,* 15(5):1135-1146, 1995.
13. **Nieuwenhuyse, J.P.; Clapuyt, P.; Malghem, J.; Everarts, P.; Melin, J.; Pauwels, S.; Brichard, B.; Ninane, J.; Vermylen, C.;** and **Cornu, G.:** Radiographic skeletal survey and radionuclide bone scan in Langerhans cell histiocytosis of bone. *Ped. Radiol.,* 26(10):734-738, 1996.
14. **Osband, M.E.; Lipton, J.M.; Lavin, P.; Levey, R.; Vawter, R.; Greenberger, J.S.; McCaffrey, R.P.;** and **Parkman, R.:** Histiocytosis-X: demonstration of abnormal immunity, T-cell histamine receptor deficiency and successful treatment with thymic extract. *New Eng. J. Med.,* 304:146-153, 1981.
15. **Rivera-Luna, R.; Alter-Molchadsky, N.;** and **Cardenas-Cardos, R.:** Langerhans cell histiocytosis in children under 2 years of age. *Med. Ped. Oncology,* 26(5):334-343, 1996.
16. **Salvatore, S.; Sommelet, D.; Lascombes, P.;** and **Prevot, J.:** Treatment of Langerhans-Cell Histiocytosis in children. *J. Bone and Joint Surg.,* 76A:1513-1525, 1994.
17. **Willis, B.; Ablin, A.; Weinberg, V.; Zoger, S,; Wara, W.M.;** and **Matthay, K.K.:** Disease course and late sequelae of Langerhans' cell histiocytosis: 25-year experience at the University of California San Francisco. *J. Clin. Oncology,* 14(7):2073-2083, 1996.

A BRIEF HISTORY OF WORKERS' COMPENSATION

Gregory P. Guyton

The modern system of workers' compensation is so complex and arcane it produces considerable grief to those who must deal with it on a daily basis. Yet these often cumbersome regulations are so ultimately vital to society they appear, in one form or another, in all industrialized nations. A look at workers' law over the years demonstrates the failure of the historical alternatives to formal workers' compensation systems to meet either the goals of social justice or economic efficiency. While the orthopaedic surgeon may often lament the difficult compensation case appearing in clinic, it may add some perspective to review how and why this system became entrenched in the workplace.

WORKERS' COMPENSATION IN ANTIQUITY

The history of compensation for bodily injury begins shortly after the advent of written history itself[1]. The Nippur Tablet No. 3191 from ancient Sumeria in the fertile crescent outlines the law of Ur-Nammu, king of the city-state of Ur. It dates to approximately 2050 B.C.[2]. The law of Ur provided monetary compensation for specific injury to workers' body parts, including fractures. The code of Hammurabi from 1750 B.C. provided a similar set of rewards for specific injuries and their implied permanent impairments. Ancient Greek, Roman, Arab, and Chinese law provided sets of compensation schedules, with precise payments for the loss of a body part. For example, under ancient Arab law, loss of a joint of the thumb was worth one-half the value of a finger. The loss of a penis was compensated by the amount of length lost, and the value an ear was based on its surface area[3]. All the early compensation schemes consisted of "schedules" such as this; specific injuries determined specific rewards. The concept of an "impairment" (the loss of function of a body part) separate from a "disability" (the loss of the ability to perform specific tasks or jobs) had not yet arisen.

Yet the compensation schedules of antiquity were gradually replaced as feudalism of the Middle Ages gradually became the primary structure of government. The often arbitrary benevolence of the feudal lord determined what, if any, injuries garnered recompense. The concept of compensation for the worker was bound up in the doctrine of noblesse oblige; an honorable lord would care for his injured serf.

COMMON LAW AND THE EARLY INDUSTRIAL REVOLUTION

The development of English common law in the late Middle Ages and Renaissance provided a legal framework that persisted into the early Industrial Revolution across Europe and America. Three critical principles gradually developed which determined what injuries were compensable. They were generally so restrictive they became known as the "unholy trinity of defenses[4].

1. Contributory negligence. If the worker was in any way responsible for his injury, the doctrine of contributory negligence held the employer was not at fault. Regardless of how hazardous the exposed machinery of the day was, any worker who slipped and lost an arm or leg was not entitled to any compensation. This was established in the United States through the case of Martin v. the Wabash Railroad, in which a freight conductor fell off his train. Although inspectors subsequently blamed a loose handrail, his injuries did not receive compensation because inspecting the train for faulty equipment was one of his job duties.

2. The "fellow servant" rule. Under the "fellow servant" rule, employers were not held liable if the worker's injuries resulted in any part from the action or negligence of a fellow employee. This was established in Britain through the case of Priestly v. Fowler in 1837, a case of an injured butcher boy. In America, precedent was provided five years later by Farnwell v. The Boston and Worcester Railroad Company.

3. The "assumption of risk." The doctrine of "assumption of risk" was exceptionally far-reaching. It held simply that employees know of the hazards of any particular job when they sign their contracts. Therefore, by agreeing to work in a position they assume any inherent risk it carries. Employers were required to provide such safety measures as were considered appropriate in the industry as a whole. In the nineteenth century, this often left a great deal to be desired. Assumption of risk was often formalized at the beginning of an employee's tenure; many industries required contracts in which workers abdicated their right to sue for injury. These became known as the "worker's right to die," or "death contracts."

Department of Orthopaedics
University of North Carolina
Chapel Hill, NC

While these common law principles were quite restrictive, it was their method of enforcement that proved most cumbersome. An injured worker's only recourse was through the use of torts. In the nineteenth century as in our own, these were exceptionally expensive legal affairs. Most countries required considerable fees simply to file a personal injury lawsuit. These more often than not were beyond the limited means of the injured worker. It was so uncommon for a working man to win compensation for injury that private organizations such as the English "Friendly Societies" and German "Krankenkassen" were formed that offered more affluent laborers the option of buying various kinds of disability insurance[5]. Nevertheless, the worker did occasionally prevail through tort legislation. As the century wore on, this began to happen frequently enough that employers too became uncomfortable with the capricious nature and high cost of battling civil suits.

A PRAGMATIC CHAMPION

The watershed events in the development of modern workers' compensation law occurred in the improbable setting of Prussia under the even more improbable leadership of its stern Chancellor, Otto von Bismarck[4,5,6]. The Chancellor was certainly no great humanitarian, but he was the force behind Realpolitik, the school of political pragmatism. Germany at the time had a very active Marxist and socialist movement, and social protection for workers was at the top of their agenda. The active left was a considerable thorn in Bismarck's side, particularly given his need for a stable home front while pursuing foreign empire-building. He resorted to straightforward political oppression, and in 1875, he outlawed the Social Democratic Party.

But Bismarck was shrewd. While suppressing the institutions of his socialist opponents, he maintained the loyalty of the common Prussian by co-opting key features of their agenda. The most important of these was a system of social insurance. His first foray into the field was through the Employers' Liability Law of 1871, providing limited social protection to workers in certain factories, quarries, railroads, and mines. Later, and far more importantly, Bismarck pushed through Workers' Accident Insurance in 1884 creating the first modern system of workers' compensation. This was followed over the next few years by Public Pension Insurance providing a stipend for workers incapacitated due to non-job related illnesses and Public Aid providing a safety net for those who were never able to work due to disability. The system as a whole valued the active worker; the greatest benefits were granted to job-related injuries and medical care and rehabilitation were covered. The state-administered Prussian system also established an important precedent: it was regarded as an "exclusive remedy" to the problem of workers' compensation, employers under the system could not be sued through the civil courts by employees.

The Prussian system has served as a basic model for the social insurance programs of a variety of countries including the United States. It is worth noting that the complex nature of modern workers' compensation law has been present almost from the start. Indeed, the dark writings of Franz Kafka were partly inspired by his job as a minor functionary in the arcane machinery of the workers' compensation board in (then Prussian) Prague just after the turn of the century[10].

WORKERS INSURANCE SPREADS

Other western nations gradually began to accept the notion that modern industrial society required some form of mandated workers' insurance. As early as 1880, the British Prime Minister William Gladstone pushed through the Employer's Liability Act[5]. This abolished the old common-law defenses in theory, but it did not establish a "no-fault" system. A proof of negligence on the part of the employer was necessary for the employee to collect. Most importantly, "right to die" contracts in which workers renounce their right to sue for injury were still legal and widely used by English industry. Thus, the 1880 law had little effect.

The Workers' Compensation Act was proposed in Parliament in 1893 and was largely equivalent to the 1884 Prussian law in establishing a "no-fault" doctrine of compensation. Unlike the German model, it did not fully rely on state administration. Instead the "Friendly Societies" which had organized various forms of private disability insurance for workers for many years were relied upon to provide the insurance itself. Nevertheless, the Act encountered staunch opposition from manufacturing interests in Parliament, and the House of Lords delayed its passage by attempts to add language which would have made "right to die" contracts a permissible means of circumventing the entire system. Finally, the Act was passed in 1897 after a four-year legislative struggle[5].

WORKERS' COMPENSATION IN THE UNITED STATES

The winds of change were slower across the Atlantic. Populist sentiment for organized workers movements began to grow in the first decade of the twentieth century. Social change was heralded by the literary

"muck-rakers" movement, a group of authors who, while often uninspired in their literary craftsmanship, passionately wrote about the plight of the common man in modern industrial society. Most famous among these was Upton Sinclair, socialist author of *The Jungle*, a novel detailing the horrors experienced by a Lithuanian immigrant working in the Chicago slaughterhouses. Critical acclaim was lacking. A *Time Magazine* critic once said of him, "Of the many millions of words Sinclair wrote, few are the right ones in the right order." Despite his limited skills, *The Jungle* proved immensely popular, full of compelling and graphic passages such as:

"(The fertilizer workers') particular trouble was that they fell into the vats; and when they were fished out, there was never enough of them to be worth exhibiting, - sometimes they would be overlooked for days, till all but the bones of them had gone out to the world as Durham's Pure Leaf Lard!"

Mr. Sinclair's immediate goals were not realized. In the short term, the swell of public opinion in the book's wake led not to legislation aimed at improving workers' conditions, but to the Food and Drug Act of 1906 and the Meat Inspection Act of 1906, both primary milestones in the evolution of the Civil War-era Bureau of Chemistry into the modern Food and Drug Administration.

Nevertheless, a reform-minded public did gradually come to demand changes in workers' benefits. As early as 1893, the Department of Labor prepared a report by J. G. Brooks on the topic *Compulsory Insurance in Germany*[7]. Congress passed the Employers' Liability Acts of 1906 and 1908, softening the common-law doctrine of contributory negligence. Failed or limited efforts to pass comprehensive workers' compensation acts were attempted in New York (1898), Maryland (1902), Massachusetts (1908), and Montana (1909). At the federal level, sentiment for modern workers' compensation ranged a few years ahead of the state legislatures, but the matter was generally considered best left to the states. The federal government did regulate interstate commerce, however, and what is arguably the first compensation system in America was proposed by President Taft and put into law in 1908 to cover those workers involved in interstate trade[4].

Unlike Europe, the decentralized nature of labor regulation in the United States provided a key additional obstacle delaying implementation of the laws. As in England, many manufacturers were ready for change provided it included tort relief, but they strongly objected to state-by-state regulation. It would, they appropriately argued, create an uneven playing field for unregulated competitors in neighboring jurisdictions. In the most telling example, phosphorus match manufacturers brazenly testified before Congress that, despite the widespread problem of "phossy jaw" poisoning in their workers, they were unwilling to invest in alternative compounds unless the law in all states mandated it. In 1910, this problem led to a special conference in Chicago attended by representatives of the industrial states to outline a uniform set of guidelines for compensation law[4].

The first comprehensive workers' compensation law was finally passed shortly thereafter in Wisconsin in 1911. Nine other states passed regulations that year, followed by thirty-six others before the decade was out. The final state to pass workers' compensation legislation was Mississippi in 1948.

The response of the medical community was lukewarm at best, particularly from the young but subspecialty of orthopaedics. The noted shoulder specialist Codman decried workers' compensation statutes with their regulated physicians' fees as part of "the great effort which the majority is making to socialize the medical profession." To put his views in some perspective, he also objected to public parks, mass transit, municipal piers, regulation of interstate commerce, and even public hospitals[4].

The attitudes of medical professionals changed dramatically in the 1930's, however, when Social Security Disability Insurance was created to insure those who could not work due to infirmities that were not work-related. This vast expansion of the need for physician involvement and evaluation proved very lucrative. The American Medical Association quickly published the popular *Guides to the Evaluation of Permanent Impairment*, which has been through multiple editions since. As managed care has come to play a greater role in the health care system, many physicians have come to realize that compensation evaluations represent a stable and high-paying source of income.

THE STRUCTURE OF AMERICAN WORKERS' COMPENSATION SYSTEMS

The various workers' compensation statutes in America are all modeled loosely after the original Prussian system[6,8]. The central tenet is that of "no-fault" insurance; industrial accidents are accepted as a fact of life and the system exists to deal with their financial consequences in as expeditious a manner as possible. Employers participating in the system have the notable benefit of tort exemption for injuries covered by workers' compensation. Employees can sue third parties who may be responsible for their on-the-job injuries, but any

proceeds from such suits must first go to reimburse their employer's compensation insurance carrier.

All American workers' compensation schemes are fully employer-funded either by the purchase of commercial insurance or setting up a self-insurance account. In their original form, however, most state compensation acts made employer participation "optional." Because they also often precluded the use of the common-law defenses if participation was declined, the vast majority of employers have historically participated, and approximately eighty percent of the work force is currently covered under compensation schemes. Most states have exclusion criteria for small firms and, most significantly, for domestic and agricultural workers.

As a general rule, claims are handled by legislatively created state compensation boards, although decisions can be appealed to the state court system. In five exceptions, Wyoming, Tennessee, New Mexico, Alabama, and Louisiana, claims are taken directly to the courts, but special state agencies exist to assist the processing of claims. The definition of compensable injury has gradually evolved over the years. Although it was once interpreted to mean a sudden industrial accident, in recent years most states have added language to include occupational exposures and overuse syndromes. The Kentucky law currently defines "injury" as "any work-related harmful change in the human condition.

A distinction is made between "impairment," a medical definition of the degree of loss of anatomy or function of a body part or system, and "disability," a legal definition of the degree to which an employee's impairment limits his ability to perform work. Some states due continue to have "schedules" for certain injuries, however, which directly correlate the loss of certain anatomical parts to amounts of compensation. For instance, the loss of a thumb in South Dakota entitles the worker to fifty weeks of compensation regardless of his disability[6].

In general, compensation is paid both in the form of wage-replacement (usually at about two-thirds salary) for the period of total disability and in the form of lump-sum payments for any residual permanent partial disability. Employers also must pay for the workers' medical and rehabilitation costs. Many employers quite aggressively pursue rehabilitation and pay for services such as work-hardening programs that are not required by the letter of the law. They have found these to be highly cost-effective given that the outcome if the worker fails to return to work could be permanent total disability payments for life.

One special case that most states have now come to recognize is that of the "second injury." In Oklahoma in the 1920's, a one-eyed worker lost his remaining eye in an industrial accident. His employer was forced by the compensation board to pay not for the loss of a single eye, but for total permanent disability given the patient's blindness. Immediately, virtually all the one-eyed, one-armed, and one-legged workers in the state were deemed by their employers to represent unnecessary risks and were fired. To solve this dilemma, most states have now created "second injury funds" run by the government which all the private insurers pay into. These are used to make up the difference when a second injury proves incapacitating only because of a prior injury to another body part. Although their cost is relatively minimal and they initially appear to be a minor detail, second injury funds are absolutely critical in maintaining the employability of amputees.

THE CHANGING FACE OF AMERICAN WORKERS' COMPENSATION

The basic structure of the American workers' compensation system has remained unchanged throughout the century and is, overall, a success in the eyes of employers and employees alike. Only in the last five years have major changes in the landscape of workers' compensation law begun to appear.

The primary instrument of change has been the Americans With Disabilities Act of 1990, one of the central pieces of legislation to emerge from the Bush Administration[8]. The ADA actually represents a dramatic expansion of a much earlier law, Section 504 of the Rehabilitation Act of 1973. Section 504 required government programs, contractors, and any entity receiving federal funding to make their facilities accessible to the handicapped. Its language was relatively restrictive, and the law applied only when persons were excluded from a program or employment "solely" because of their disability.

The ADA was the result of a massive campaign to improve the employability of the disabled in America. It met with resounding legislative success; there were only 6 no votes in the Senate and 28 in the House. Unlike Section 504, the ADA encompasses all of the American workplace, not just that fraction associated with the federal government. It also contains language that allows much broader judicial freedom in interpretation.

The ADA requires that employers make "reasonable accommodation" for workers with disabilities, but no legal standards for the definition of "reasonable" are provided. A precedent does exist for accommodating workers' with special needs: a series of rulings has mandated that employers need accommodate employees religious wishes (Sabbath day off, wearing of religious clothing, etc.) only if the cost is minimal and the accommodation would not significantly disrupt the central business enterprise. Some state disability laws

placed specific monetary caps on the amount employers could be required to spend to accommodate individual workers. By avoiding this kind of more specific language, many employers fear the ADA has created an environment in which the costs of employing disabled workers are highly unpredictable[8].

The new law is fuzzy, too, in its definition of disability. Traditional government policy toward the disabled focused on three groups: the legally blind (numbering 400,000), the deaf (numbering 1.7 million), and the absolute wheelchair-bound (numbering 720,000). From these relatively small numbers, to reach the commonly cited figure that one-in-six Americans (approximately 43 million) are disabled requires the inclusion of a large number of less immobilizing physical impairments and mental disabilities. Indeed, mental illness alone creates significant confusion. The DSM as first published contained just over 100 disorders; it now contains three times that number.

For the employer, simply knowing whether or not a potential employee has a disability is often difficult. The ADA severely restricts employers' access to prior medical records before an offer of employment is made. Incidentally, these provisions have been successfully used by physicians to prevent state medical boards and hospitals from obtaining records indicating prior drug or alcohol addiction.

These gray areas of the ADA have been used by entrepreneurial lawyers to apply the law to areas removed from its original intended scope. Relatively few suits under the ADA have related to hiring discrimination. A substantial number allege discrimination against those who are already employed, and many allege disabilities acquired on the job. Thus, by a subtle shift in wording and emphasis, the ADA is seen by some lawyers as an opportunity to circumvent or augment the settlements their clients would reach through traditional workers' compensation. The most commonly cited disability in employment-related suits filed under the ADA is back pain (19% of the total), followed by compressive neuropathy and similar neurologic disorders (12%), and mental illness (12%). Only 8% of complaints have come from the wheelchair-bound and 3% from the deaf or blind[8].

In one celebrated Texas case, a worker for the Santa Fe Railroad was awarded a $305,000 workers' compensation settlement for permanent total disability based on physicians' testimony that he would never be able to work again after his work-related back injury. Eight days after his settlement, he filed suit under the ADA claiming he was wrongfully terminated due to a disability and should be rehired with accommodation. Although the case was thrown out, this apparent legal double jeopardy highlights the legitimate fear of employers that the tort relief that is such a central feature of workers' compensation law is in danger of slowly being eroded.

CONCLUSION

Although excessively intricate and burdened by separate implementation schemes for each of the fifty states, workers' compensation law remains one of the relative success stories of American legislation. Its three critical benefits remain. First, the employer gets tort relief. Second the employee gets a relatively quick, equitable, and predictable no-fault compensation scheme. Finally, the system carries an intrinsic incentive toward rehabilitation of the injured worker. The subjective nature of defining impairment and disability themselves will almost certainly allow creative personal injury lawyers to find new ways to collect for their clients and themselves whether through the ADA or other legislation. The survival of a viable workers' compensation system will require continued vigilance by both federal and state governments.

REFERENCES

1. **Louis, D.S.:** Evolving concerns relating to occupational disorders of the upper extremity. *Clin. Orthop. Rel. Res.,* 254:140-143, 1990.
2. **Kramer, S.N.:** *History Begins at Sumer.* p. 93. London, Thames and Hudson, 1958.
3. **Geerts, A.; Kornblith, B.;** and **Urmson, J.:** *Compensation for Bodily Harm.* pp. 7-211. Brussels, Fernand Nathan, 1977.
4. **Haller, J.S.:** Industrial accidents-worker compensation laws and the medical response. *Western J. of Med.,* 148:341-348, 1988.
5. **Hadler, N.M.:** The disabling backache, an international perspective. *Spine,* 20:640-649, 1995.
6. **Gerdes, D.A.:** Workers' compensation, an overview for physicians. *South Dakota Med. J.,* p. 17-23, July 1990.
7. **Brooks, J.G.:** *Compulsory Insurance in Germany.* Washington, United States Department of Labor, 1893.
8. **Olson, W.:** *The Excuse Factory.* pp. 85-118. New York, Free Press, 1997.
9. **Steinberg, F.:** The law of workers' compensation as it applies to hand injuries. *Occupational Med.,* 4:559-569, 1989.
10. **Schäff, S.;** and **Whelan, S.:** "Constructing Franz Kafka."

CONTESTED CLAIMS IN CARPAL TUNNEL SURGERY: OUTCOME STUDY OF WORKER'S COMPENSATION FACTORS

James R. Olney, M.D.
Delwin E. Quenzer, M.D.
Michael Makowsky, M.D.

ABSTRACT

We retrospectively analyzed the importance of factors relating to worker's compensation for 273 wrists in 211 consecutive patients who underwent primary carpal tunnel release. Patients were divided into three groups: non-work related, worker's compensation—uncontested, and worker's compensation—contested. *Contested* claims were those in which the worker's compensation carrier denied authorization for surgery, and in which such authorization was given following intervention by a plaintiff's attorney. Results: there were no statistically significant differences in postoperative return of grip strength and in postoperative return to work intervals in comparing groups I and II. However, the *contested* worker's compensation patients were much less likely (and much slower) to return to light duty and to return to full duty work. Return of grip strength was slower and less complete in this group as well. Within worker's compensation, a contested claim portends a poorer prognosis. Uncontested worker's compensation claimants have nearly as good a prognosis as non-compensation patients.

INTRODUCTION

For a variety of conditions including carpal tunnel syndrome, worker's compensation "claimants" have generally been reported to have a poorer prognosis than non-compensation patients[24,7,14,10,11,15]. Ergonomic factors of force, repetitive pinching and grasping, awkward postures, frequent or prolonged pressure over the volar wrist, and vibration have been implicated in the pathogenesis of carpal tunnel syndrome, whether related to work or to avocational activities[20,22,3]. Other personal conditions including obesity, advancing age, physical inactivity, and individual wrist dimensions have more recently been implicated[17,27,21], although not without controversy[18,6]. Cigarette smoking has also been associated with carpal tunnel syndrome[26].

In several recent reports, investigators have attempted to differentiate whether this poorer prognosis affects all worker's compensation claimants or merely a subgroup. Bonzani et al. cited administrative and psychosocial issues[1], and others have suggested that involvement of a plaintiff's attorney complicates matters[4,5,23,25]. Some investigators have concluded that a normal or nearly normal nerve conduction test predicts a poor prognosis for worker's compensation patients[11], but others have concluded that nerve tests have little predictive value[8,2,12]. We hypothesized that a subgroup of worker's compensation has a poorer prognosis than the overall worker's compensation population regarding carpal tunnel surgery, and we retrospectively attempted to identify one or more factors that may portend a poorer prognosis.

In a related previous unpublished study of 285 patients who underwent 347 open carpal tunnel releases, we did not prove any significant differences between the compensated versus non-compensated patients regarding subjective outcomes. Therefore, for the present study, we elected to study objectively measurable outcomes: complications, further surgery, postoperative recovery of grip strength, and return to light duty and full duty work.

MATERIALS AND METHODS

An independent reviewer retrospectively evaluated all patients in the practice of a single surgeon (DEQ) who underwent primary carpal tunnel release between January 1, 1990 and January 31, 1994. Patients were excluded from the study if they had diabetes mellitus, renal failure, a collagen vascular disease, carpal instability, or if they were pregnant when first seen or had delivered a baby within six months of the primary carpal tunnel release. Patients were also excluded if they

Departments of Orthopaedic Surgery and Occupational Medicine, Iowa Methodist Medical Center, Des Moines, Iowa

Correspondence and Reprints:
Delwin E. Quenzer, M.D.
Attending Hand Surgeon and Director, Hand Surgery Education, Iowa Methodist Med. Ctr.
Des Moines Orthopaedic Surgeons, P.C.
6001 Westown Parkway
West Des Moines, IA 50266
(515) 224-5210 voice, 224-5102 fax
e-mail: dque@home.com

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Iowa Methodist Medical Center, Des Moines, Iowa 50309

TABLE 1. MATERIALS

	Group I Non-WC	Group II WC Not Contested	Group III WC Contested
Number of patients	73	110	28
Female	78%	78%	79%
Mean Age, yrs	54.2	40.3	37.7
Right-handed	88%	94%	93%
Bilateral CTS	34%	54%	75%*
Total # wrist with CTS	98	169	49
Total CTS wrists undergoing surgery(%)	89%	83%	94%
Total CTS wrist undergoing Bilateral Surgery	14%	22%	39%**

Note: CTS= carpal tunnel syndrome
* p<.001, chi-sq. analysis
** p<.01, chi-sq. analysis

had a history of a significant injury, e.g. Colles' fracture or crush injury, to the affected hand or wrist within 24 months of the primary carpal tunnel release. Patients were included who had other surgical procedures on an upper extremity at the time of primary carpal tunnel release, as long as the other procedures did not include surgery within the wrist joint or shoulder area. Patients were followed for six months postoperatively, at which time they were dismissed if they had reached maximum medical improvement and no further active medical or surgical treatment was planned. This review yielded 211 eligible patients who had undergone 273 primary carpal tunnel releases, all of whom were included in this study.

Preoperative evaluations always included serial thorough histories and physical examinations, and almost always included electrodiagnostic testing. The diagnosis of carpal tunnel syndrome required classic median dysesthesias of greater than three months' duration, made worse by activities and/or wrist position, and was confirmed by provocative (percussion, position, and direct pressure) and nonprovocative (sensation and strength) physical examinations.

Conservative nonsurgical treatment was exhausted in all cases prior to surgical intervention, except in cases of electrically confirmed severe neuropathies, in which dense numbness and/or thenar atrophy was present, or in which no response was demonstrated to sensory latency testing. Clinical indications for surgery included persistent pain or numbness, inability to perform activities of daily living, and obvious weakness. Candidates for surgery either had a positive electrodiagnostic test or showed temporary improvement of wrist pain and median dysesthesias following a steroid injection into the affected carpal tunnel in almost all cases.

Surgical methods included either an open carpal tunnel release through a short palmar incision[19] (earlier part of study) or a two-portal endoscopic carpal tunnel release by the extrasynovial modification of the method of Chow[16] (later part of study). Patients were instructed to remove their bandages at any time after the second postoperative day and were allowed then to shower and wash their wounds, wearing a wrist splint as needed for comfort. In 32 cases when a flexor tenosynovectomy was indicated or a severe neuropathy existed, a longer open incision was employed and the surgical bandage was left in place for ten to fourteen days. The postoperative protocol varied somewhat when concurrent surgical procedures were performed.

Most of the worker's compensation patients in this series were referred by an occupational physician through a managed care network. The occupational physician rechecked the patients three to five days postoperatively, at which time patients were sent back to work if the clinical condition permitted and if suitable light duty was available.

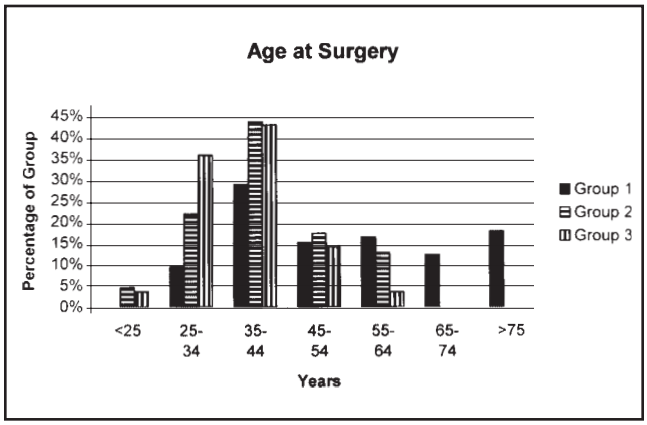

Figure 1. Age of patients at time of first carpal tunnel release. Surgery was performed upon patients of varying ages. The youngest patients were worker's compensation patients, and the oldest patients were not employed.

Patients were followed postoperatively as necessary by the hand surgeon, and objective data were collected per protocol at two weeks, six weeks, and six months postoperatively. At each visit, grip strength was measured using the average of three tests of each hand with a Jaymar dynamometer, and work status was recorded.

Evaluation showed that the population could be divided into three samples based upon their Worker's Compensation status. The three groups were designated:

Group I—Non-Worker's Compensation cases
Group II—Worker's Compensation cases, Not Contested
Group III—Worker's Compensation cases, Contested

Contested claims *were those in which the worker's compensation insurance carrier denied authorization for surgery, and in which such authorization was given after the patient retained an attorney.*

Comprehensive statistical analysis of data was performed. The specific tests used are noted appropriately in the following section.

RESULTS

Demographics, diagnoses, preoperative clinical data, and surgical procedures

Group I (Non-Worker's Compensation) had 73 patients, including 98 affected wrists, with 87 wrists undergoing primary carpal tunnel release. Group II (Worker's Compensation, Non-Contested) comprised 110 patients, including 169 affected wrists, with 141 wrists undergoing primary carpal tunnel release. Group III (Worker's Compensation, Contested) had 28 patients, including 49 affected wrists, with 46 wrists undergoing primary carpal tunnel release. Table 1 presents demographic data regarding sex, age, hand dominance, and affected hand. Group I (Non-Worker's Compensation)

TABLE 2. EMPLOYMENT

	Group I Non-WC	Group II WC Not Contested	Group III WC Contested
Work Type:			
Heavy (%)	16	21	18
Factory (%)	6	21	11
Meat Packing (%)	1	7	21*
Clerical (%)	29	49	50
Light Or Unemp.(%)	48**	2	0
Preoperative Work Status:			
Full duty (%)	39	48	39
Light duty (%)	10	39	29
Not Working (%)	51	13	32

* p=.002, chi-sq.
** p<.001, chi-sq

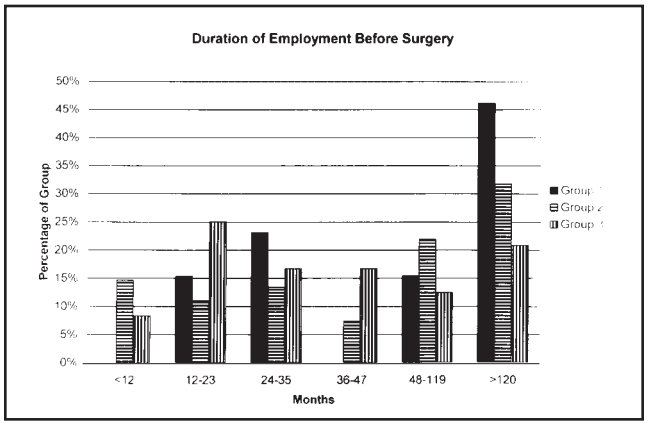

Figure 2: Duration of Employment Before Surgery. We were unable to statistically correlate the onset of carpal tunnel syndrome with duration of employment. Some worker's compensation patients developed significant symptoms after less than one year on the job; many non-compensation patients had endured symptoms for over ten years.

included older patients (Table 1, Figure 1). The patients in Group I were significantly older than patients in either of the other groups, even when those patients over age 65 were excluded ($p<.002$ in each case, t-test). The two worker's compensation groups did not differ significantly in age, although Group III (Worker's Compensation, Contested) patients were younger. There were no significant differences regarding sex, hand dominance, and affected hand (chi-square analysis). Group III (Worker's Compensation, Contested) had a significantly higher incidence of bilateral carpal tunnel syndrome and underwent a significantly higher percentage of bilateral carpal tunnel releases than either of the other groups (chi-square analysis, see Table 1).

Data regarding employment are presented in Table 2 and Figure 2. The only significant differences between groups were that fewer Group I (Non-Worker's Compensation) patients were employed, and that more patients in Group III (Worker's Compensation, Contested) worked in a meat packing plant. We were unable to correlate the onset of carpal tunnel syndrome with duration of employment.

Diagnostic data regarding carpal tunnel syndrome are listed in Table 3. Patients in Group III (Worker's Compensation, Contested) more commonly had pain as the major clinical finding, and less commonly had a positive confirmatory electrodiagnostic test. These values were not statistically significant.

Concurrent diagnoses are listed in Table 4. Obesity, defined as body weight at least 30% above recommended normal weight, was common at 25-30% in each group. For each patient, a thorough and detailed examination often disclosed one or more additional diagnoses in addition to carpal tunnel syndrome. The most common associated diagnosis was cubital tunnel syndrome. Group I (Non-Worker's Compensation) more commonly had trapeziometacarpal arthritis. Patients in Group III (Worker's Compensation, Contested) tended to have a higher number of entrapment neuropathies and to more commonly have diffuse myofascial pain, whether limited to the upper extremity and shoulder or not. Group III patients also tended to have more diagnoses than

TABLE 3.
DIAGNOSIS OF CARPAL TUNNEL SYNDROME (PERCENTAGE OF SYMPTOMATIC WRISTS)

	Group I Non-WC	Group II WC Not Contested	Group III WC Contested
Nocturnal Dysesthesias, Pain	69	61	82
Positive Tinel Sign	65	47	60
Positive Phalen Test	80	58	89
Positive Direct Pressure Sign	63	55	51
Decreased Sweating	9	12	2
Abnormal Static 2 Point Discrim.	36	21	27
Electrodiagnostic Testing			
Affected wrists tested (%)	95	93	98
Confirmed clinical diagnosis (%)	95	90	69

TABLE 4.
CONCURRENT DIAGNOSES (PERCENTAGE OF SYMPTOMATIC WRISTS)

	Group I Non-WC	Group II WC Not Contested	Group III WC Contested
Obesity	30	28	25
Cubital Tunnel Syndrome	15	18	35
Myofascial Pain Syndrome	6	8	20*
(Neck, Shoulder, Upper Arm)	4	5	18
(Low Back Pain Or Headaches)	0	1	4
Median Nerve Entrapment At Elbow	5	5	12
Medial Or Lateral Epicondylitis	2	6	8
Thoracic Outlet Syndrome	2	1	4
Dequervain's (Extensor Tendon)	5	3	4
Arthritis Trapeziometacarpal Jt.	13**	4	4
Ulnar Nerve Compression At Wrist	0	2	4
Radial Nerve Entrapment At Elbow	2	4	2
Stenosing Flexor Tenosynovitis	4	4	2
Dupuytren's Or Palmar Fibromas	0	1	2
Shoulder Impingement Syndrome	6	3	0
Other Diagnoses per extremity with CTS:			
One other diagnosis	44	37	45
Two other diagnoses	7	11	16
Three other diagnoses	4	0	8

* p=.04, chi-sq.

** p<.05, chi-sq.

the other two groups, indicating a propensity to have both more generalized pathology and more focal pathologies than the other groups.

Details of nonsurgical treatment are listed in Table 5. As previously noted, nonsurgical care was exhausted preoperatively for all patients, unless a very severe neuropathy was noted, in which case surgery was done immediately.

Data regarding the index primary carpal tunnel release operation are presented in Table 6. There were no significant differences between the groups regarding the method used for the carpal tunnel release operation (chi-square analysis). Bilateral carpal tunnel releases were more commonly performed for Group III (Worker's Compensation, Contested) patients. Data regarding concurrent surgical procedures are shown in Table 7. Each of the worker's compensation groups underwent more surgical procedures than the non-compensation group (p=.0013, chi-square analysis).

Complications of surgery

The only surgical complications were a total of four infections in this series of 277 wrists (1.4%). All resolved with wound care and oral antibiotics. However, excessive postoperative pain and dysfunction were noted in 11% (10 of 87) of the Group I (Non-Worker's Compensation) patients and in 31% of each of the two worker's compensation groups (46 of 141 and 15 of 46 patients respectively) (p<.001 in each case, chi-sq.). This problem was treated with a specific program of hand therapy

TABLE 5.
NONSURGICAL TREATMENT, PREOPERATIVE, PERCENTAGE OF PATIENTS

	Group I Non-WC	Group II WC Not Contested	Group III WC Contested
Wrist Splint (%)	66	84	82
Steroid Injection IM (%)	5	14	25
Oral Medications (%)	51	80	100
Physical Therapy (%)	1	6	18
Ergonomic Modifications—Job (%)	11	36	39
Steroid Inject.Carpal Tunnel (%)	11	36	46
Work Restrictions (%)	0	19	4
Time Completely Off Work (%)	0	3	11
None—Severe Neuropathy (%)	14	3	0

TABLE 6.
SURGICAL PROCEDURES (INDEX OPERATION), NUMBER OF WRISTS

	Group I Non-WC	Group II WC Not Contested	Group III WC Contested
Short incision open CTR	51	79	23
Two-portal Endoscopic CTR	29	45	15
Standard CTR	7	17	8
Bilateral CTR (staged)	14	31	18*

* $p<.05$, chi-sq.

TABLE 7.
CONCURRENT SURGICAL PROCEDURES (AT INDEX OPERATION), PERCENTAGE OF PATIENTS UNDERGOING

	Group I Non-WC	Group II WC Not Contested	Group III WC Contested
Ulnar neuroplasty at elbow	14	25	29
Median neuroplasty at elbow	6	5	14
Extens. Tendon sheath incision wrist	5	2	2
Flexor or extensor tenosynovectomy	2	4	2
Injection joint hand or wrist	2	3	0
Fasciectomy epicondyle at elbow	1	2	2
Injection shoulder	1	1	0
Opponensplasty	1	0	0
Ulnar neuroplasty at wrist	1	5	8
Excision palmar fascia	0	0	2
Incision flexor tendon sheath	0	1	0
Radial neuroplasty at elbow	0	2	0
Totals:			
One concurrent procedure w/ CTR	30	45	33
Two or more concurrent procedures	2	8	14

and/or an intramuscular injection of a long-acting corticosteroid. There were no cases of documented reflex sympathetic dystrophy.

Further surgery

Two of 73 patients in Group I (Non-Worker's Compensation) underwent a later surgical procedure. Only one of these procedures, a median neurolysis at the elbow, was on a previously operated extremity.

Eight of 110 patients in Group II (Worker's Compensation, Non-Contested) underwent a later surgical procedure. These patients underwent a total of three ulnar neuroplasties at the elbow, three median neuroplasties at the elbow, two flexor tendon sheath incisions, and two wrist flexor or extensor tenosynovectomies. Each of these procedures was done within twelve months of the index primary carpal tunnel release, and each was performed on the ipsilateral upper extremity.

One of 28 patients in Group III (Worker's Compensation, Contested) underwent a later surgical procedure, which was an ulnar neuroplasty at the elbow.

Postoperative recovery of grip strength

We excluded patients over 65 years of age in order to better study the importance of compensation. Using linear regression analysis for each operated wrist, we plotted the slope of the best fit line for data points (days since surgery, grip strength). Patients in Group III (Worker's Compensation, Contested) recovered grip strength more slowly than patients in Group I (Non-Worker's Compensation) (p=.036, Mann-Whitney rank sum test). Similarly, patients in Group III (Worker's Compensation, Contested) recovered grip strength more slowly than patients in Group II (Worker's Compensation, Non-Contested) (p=.005, Mann-Whitney rank sum test). There was no difference in recovery of grip strength in comparing Group I (Non-Worker's Compensation) and Group II (Worker's Compensation, Non-Contested) (p=.769, Mann-Whitney rank sum test). (Data regarding postoperative return of grip strength had large variances, and this data cannot be fairly or accurately extrapolated to a population. Therefore, we used the rank sum statistical test.)

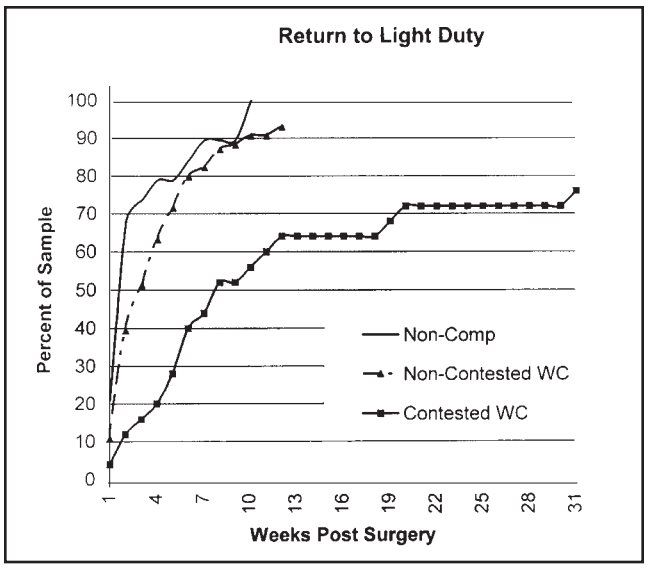

Figure 3. Postoperative return to light duty work. Patients with contested worker's compensation claims returned to *restricted work* significantly less rapidly and less often than patients in the other two groups. The remainder of the worker's compensation patients returned to work nearly as quickly as non-compensated patients.

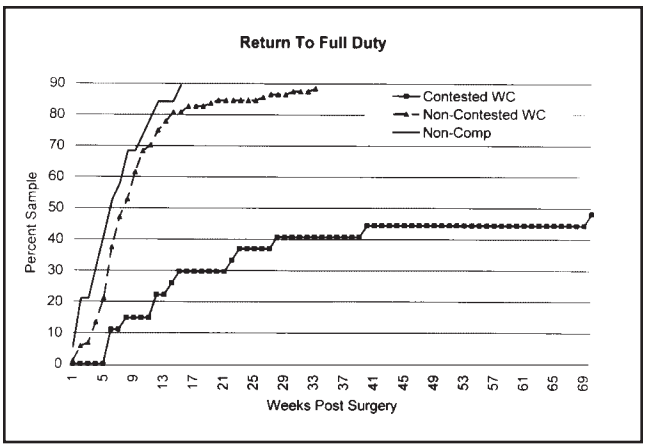

Figure 4. Postoperative return to full duty work. Patients with contested worker's compensation claims returned to unrestricted work significantly less rapidly and less often than patients in the other two groups. The remainder of the worker's compensation patients returned to work nearly as quickly as non-compensated patients.

Postoperative return to light duty work

Effect of compensation status: Data are presented in Figure 3. Average time completely off work was 3.26 weeks for Group I (range 0.5- 10.0 weeks), 3.89 weeks for Group II (0.5- 12.0 weeks), and 8.74 weeks for Group III (1.0- 31.0 weeks). Data were evaluated using a standard t-test and the Mann-Whitney rank sum test. Patients in Group III (Worker's Compensation, Contested) returned to light duty work less rapidly and less often than patients in Group I (Non-Worker's Compensation) ($p=.005$, t-test). Similarly, patients in Group III (Worker's Compensation, Contested) returned to light duty work less rapidly and less often than patients in Group II (Worker's Compensation, Non-Contested) ($p<.001$, t-test). There was no significant difference in time to return to light duty work in comparing Groups I and II using the t-test ($p=.365$). However, Mann-Whitney test results showed a significant difference between all three groups ($p<.001$ in each case). The return to work time for the non-worker's compensation cases is lower than that of either compensated group, but a more obvious difference is noted between Group III and Groups I and II (Figure 3).

Postoperative return to light duty work

Effect of multiple procedures: In the entire study population as a whole, patients who underwent one surgical procedure (primary carpal tunnel release) were off work an average of 3.2 weeks (range 1-10 wks). Patients who underwent two surgical procedures (primary CTR plus one other procedure) were off work an average of 4.1 weeks (range 1-10 weeks). Patients who underwent three surgical procedures (primary CTR plus two other procedures) were off work an average of 8.0 weeks (range 2-31 weeks).

Postoperative return to full duty work

We evaluated this data using a standard t-test and the Mann-Whitney rank sum evaluation. Data are presented in Figure 4. Average time to return to full time unrestricted work was 6.4 weeks for Group I (range 1.0-15 weeks), 8.7 weeks for Group II (1.0- 33 weeks), and 20.15 weeks for Group III (6.0- 70 weeks).

Patients in Group III (Worker's Compensation, Contested) returned to full duty work less rapidly and less often than patients in Group I (Non-Worker's Compensation) ($p<.005$, t-test, $p<.001$, Mann-Whitney test). Similarly, patients in Group III (Worker's Compensation, Contested) returned to full duty work less rapidly and less often than patients in Group II (Worker's Compensation, Non-Contested) ($p<.001$, t-test, $p<.001$, Mann-Whitney test). There was no significant difference in return to full duty work in comparing Groups I and II using the t-test ($p=.10$). However, Mann-Whitney test results showed a significant difference between all three groups ($p<.001$ in each case). The time to return to full duty for the non-worker's compensation cases is lower than that of either compensated group, but a more obvious difference is again noted between Group III and Groups I and II (Figure 4).

About 90% of in Group II (Worker's Compensation, Non-Contested) patients did return to full time, full duty work at the original employer without restrictions. In Group III (Worker's Compensation, Contested), 70% did return to the work force, but only 46% returned to full time unrestricted work at the original employer.

Surgical method

We found no significant differences between populations in the rates of return of grip strength in comparing the two methods of carpal tunnel release, i.e. short open palmar incision vs. two-portal endoscopic method, although a small number of patients undergoing the endoscopic release had a remarkably rapid recovery. In this retrospective review, we did not demonstrate a more rapid return to work following endoscopic carpal tunnel release when compared with open carpal tunnel release through a short palmar incision.

DISCUSSION

Many factors influence the outcome of carpal tunnel surgery. Worker's compensation patients have been reproved because they are claimants in a legal process[9]. For various physical conditions, many reports associate worker's compensation with a higher chance of a poor outcome[24,7,14]. However, other reports identify the involvement of a plaintiff's attorney and pending litigation as the more significant factor within the population of worker's compensation claimants, and these reports associate this litigation with a prolonged recovery and less desirable outcome[4,5,23,25]. The present study confirms that minimally invasive surgery is generally associated with a relatively rapid return to work[19,16], and also demonstrates that additional surgical procedures will predictably delay the return to work. According to our results, the vast majority of patients who undergo primary carpal tunnel release can expect to return to work regardless of their compensation status. However, there is a subgroup of worker's compensation hand surgery patients for whom the prognosis must be much less optimistic.

We retrospectively evaluated comparable populations of compensation and non-compensation patients undergoing primary carpal tunnel surgery. Within the compensation group, a subgroup existed which had the following characteristics: patients were younger, more often had bilateral carpal tunnel syndrome, more commonly complained of pain, and more commonly had negative electrodiagnostic tests. However, in the face of classic repeated history and physical examination findings, the clinicians involved concluded that the patient met the criteria for carpal tunnel syndrome. These patients more commonly had myofascial pain syndromes and also more commonly had clinical and electrodiagnostic evidence of multiple entrapment neuropathies. Like others with carpal tunnel syndrome, they were often overweight[21,18]. When nonsurgical treatment failed, these patients underwent carpal tunnel release in an attempt to relieve the portion of their symptoms that was due to median nerve entrapment at the wrist.

Within this subgroup, in all cases, the employer or worker's compensation insurance carrier initially denied a request for authorization to perform surgery. Following intervention by a plaintiff's attorney, this authorization was later received. *These patients have a conflict with the employer or with the worker's compensation insurance carrier.* (We did not attempt to identify a similar subgroup of patients who were lost to follow-up after the surgeon requested authorization for surgery and received a letter of denial.)

The occupational physician and hand surgeon are often unaware of the dynamics relating to the decision to deny authorization for surgery. The duration of employment, the employee's work record, and the employee's personal relations with co-workers, management, company health workers, insurance adjusters, and other physicians may be important. Other medical conditions affecting the employee, previous injuries, and prior worker's compensation claims can make a difference. Ergonomic considerations regarding the current or responsible employment must be considered in light of other past or current employment. Outside activities which demand repetitive pinching or grasping are relevant. We carefully evaluate these factors in all cases. If, in this setting, the surgeon recommends surgery yet the insurance carrier rejects the claim, declining to authorize surgery, the patient is likely to be dissatisfied, and may seek legal advice. In our state, once the patient retains an attorney, all communication from the insurance carrier must then be through the patient's attorney. The delays of the legal process further compound the emotional, social, and financial factors relating to the disability.

Sometimes, a part of the problem is that the diagnosis and causation are less than clear. Many patients in the practices of occupational medicine and hand surgery have the primary problem of pain. While these patients may have compressive neuropathies, they may also have other soft tissue problems which are variously labeled tendonitis, myofascial pain, repetitive strain injury, cumulative trauma, occupational cervicobrachial disorder, or one of many other names. These conditions, whether work related or not, may compromise surgical and nonsurgical outcomes[9,13]. Each of the worker's compensation groups in this study did have a more significant problem of disabling postoperative pain for which therapy and/or corticosteroids were necessary.

However, we have shown very satisfactory outcomes from carpal tunnel surgery in our worker's compensation patients in whom the diagnosis was not contested. Indeed, the results are very comparable to those of non-compensation patients. Objective measurements of postoperative return of grip strength, postoperative return to light duty work, and postoperative return to full duty work correlated very well with each other. After surgery, the *contested* worker's compensation claimants were slower and less likely to regain preoperative grip strength, and the results regarding return to work paralleled this finding.

Before performing surgery, we discuss the anticipated postoperative rehabilitation with each patient. Our experience is that patients will do much better if they are promptly returned to light duty after surgery. This requires cooperation from the patient and the employer. Through our managed care network, we have educated employers and representatives of insurance carriers regarding the need to create suitable light duty work in order to return the employee to work as soon as possible. We instruct patients to elevate their hands for three days. After that time, patients rarely need narcotic pain medication and are usually able to drive an automobile with care. Therefore, we expect that our patients will be able to return to light duty work three to seven days following carpal tunnel surgery via either of the methods discussed in this article, although this decision may be influenced by a variety of other factors.

This study is limited in that we were unable to exactly determine the earliest date of return to work in many cases. Rather, work status was noted in the chart at each follow-up visit, and was retrospectively assessed. We expect to be able to document, in a new prospective study, the more rapid return to work (usually three days postoperatively) that we generally prescribe. We continue to believe that elucidation of factors which influence outcomes can help to clarify the prognosis in worker's compensation cases.

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REFERENCES

1. **Bonzani, P.J.; Millender, L.; Keelan, B.;** and **Mangieri, M.G.:** Factors prolonging disability in work-related cumulative trauma disorders. *J. Hand Surg.,* 22-A:30-34, 1997.
2. **Braun, R.M.;** and **Jackson, W.J.:** Electrical studies as a prognostic factor in the surgical treatment of carpal tunnel syndrome. *J. Hand Surg.,* 19-A:893-900, 1994.
3. **Centers for Disease Control, committee:** Occupational disease surveillance: carpal tunnel syndrome. *Morbidity Mortality Weekly Report,* 38(28):485-489, July 21, 1989.
4. **Dichraff, R.M.:** When the injured worker retains an attorney. *AAOHN J.,* 41(10):491-8, 1993.
5. **Dworkin, R.H.; Handlin, D.S.; Richlin, D.M.; Brand, L.;** and **Vannucci, C.:** Unraveling the effects of compensation, litigation, and employment on treatment response in chronic pain. *Pain,* 23(1):49-59, 1985.
6. **Gerr, F.;** and **Letz, R.:** Letter re: Nathan et al.: Obesity as a risk factor. *J. Occup. Med.,* 34:1117-1118, 1992.
7. **Greenough, C.G.; Taylor, L.J.;** and Fraser, R.D.: Anterior lumbar fusion. A comparison of noncompensation patients with compensation patients. *Clin. Orthop.,* 300:30-37, 1994.
8. **Grundberg,A.B.:** Carpal tunnel decompression in spite of normal electromyography. *J. Hand Surg.,* 8-A:348-349, 1983.
9. **Hadler, N.M.;** Repetitive upper-extremity motions in the workplace are not hazardous. *J. Hand Surg.,* 22-A:19-29, 1997.
10. **Higgs, P.E.; Edwards, D.F.; Martin, D.S.;** and **Weeks, P.M.:** Carpal tunnel surgery outcomes in workers: effect of worker's compensation status. *J. Hand Surg.,* 20-A:354-359, 1995.
11. **Higgs P.E.; Edwards D.F.; Martin D.S.;** and **Weeks P.M.** Relation of preoperative nerve-conduction values to outcome in workers with surgically treated carpal tunnel syndrome. *J. Hand Surg.,* 22-A:216-221, 1997.
12. **Louis, D.S.;** and **Hankin, F.M.:** Symptomatic relief following carpal tunnel decompression with normal electroneuromyographic studies. *Orthopaedics,* 10:434-436, 1987. [Retracted by **Hankin, F.M.;** and **Louis, D.S.** in *Orthopaedics,* 11:532, 1988 and 11:1244, 1988.]
13. **McKinnon, S.E.;** and **Novak, C.B.:** Repetitive strain in the workplace. *J. Hand Surg.,* 22-A:2-18, 1997.
14. **Misamore, G.W.; Ziegler, D.W.;** and **Rushton, J.L., II:** Repair of the rotator cuff. A comparison of results in two populations of patients. *J. Bone Jt. Surg.,* 77-A:1335-1339, 1995.

15. **Mont, M.A.; Mayerson, J.A.; Krackow, K.A.;** and **Hungerford, D.S.:** Total knee arthroplasty in patients receiving worker's compensation. *J. Bone Jt. Surg.,* 80-A:1285-1290, 1998.
16. **Nagle, D.J.:** Endoscopic carpal tunnel release: Chow dual-portal technique. *AAOS Instr. Course Lect.,* 44:155-160, 1995.
17. **Nathan, P.A.;** and **Keniston, R.C.:** Carpal tunnel syndrome and its relation to general physical condition. *Hand Clinics,* 9:253-261, 1993.
18. **Nathan, P.A.; Keniston, R.C.; Myers, L.D.;** and **Meadows, K.D.:** Obesity as a risk factor for slowing of sensory conduction of the median nerve in industry. *J. Occup. Med.,* 34:379-383, 1992.
19. **Nathan, P.A.; Meadows, K.D.;** and **Keniston, R.C.:** Rehabilitation of carpal tunnel surgery patients using a short surgical incision and an early program of physical therapy. *J. Hand Surg.,* 18-A:1044-1050, 1993.
20. **Silverstein, B.A.; Fine, L.J.;** and **Armstrong, T.J.:** Occupational factors and carpal tunnel syndrome. *Am. J. Industrial Med.,* 11:343-58, 1987.
21. **Stallings, S.P.; Kasdan, M.L.; Soergel, T.M.;** and **Corwin, H.M.:** A case-control study of obesity as a risk factor for carpal tunnel syndrome in a population of 600 patients presenting for independent medical examination. *J. Hand Surg.,* 22-A:211-215, 1997.
22. **Stock, S.R.:** Workplace ergonomic factors and the development of musculoskeletal disorders of the neck and upper limbs: a meta-analysis. *Am. J. Industrial Med.,* 19:87-107, 1991.
23. **Talo. S.; Hendler, N.;** and **Brodie, J.:** Effects of active and completed litigation on treatment result. *J. Occup. Med.,* 31(3):265-269, 1989.
24. **Tollison, C.D.:** Compensation status as a predictor of outcome in nonsurgically treated low back injury. *Southern Med. J.,* 86(11):1206-1209, 1993.
25. **Trief, P.;** and **Stein, N.:** Pending litigation and rehabilitation outcome of chronic back pain. *Arch. Phys. Med. Rehabil.,* 66:95-99, 1985.
26. **Vessey, M.P.; Villard-Mackintosh, L.;** and **Yeates, D.:** Epidemiology of carpal tunnel syndrome in women of childbearing age. *Int. J. Epidemiol.,* 19(3):655-9, 1990.
27. **Werner, R.A.; Albers, J.W.; Franzblau, A.;** and **Armstrong, T.J.:** The relationship between body mass index and the diagnosis of carpal tunnel syndrome. *Muscle Nerve,* 17:632-636, 1994.

THE DIAGNOSIS OF THE OS TRIGONUM SYNDROME WITH A FLUOROSCOPICALLY CONTROLLED INJECTION OF LOCAL ANESTHETIC

Darron M. Jones, M.D.*
Charles L. Saltzman, M.D.**
George El-Khoury, M.D.#

ABSTRACT

Purpose

To report the results of excision of the os trigonum using a fluoroscopically controlled injection of local anesthetic to diagnose the os trigonum syndrome.

Design and patients

Os trigonum syndrome is a recognized cause of pain in the posterior aspect of the foot and ankle. The symptoms and physical findings, however, are often nonspecific and difficult to differentiate from other causes of posterior ankle pain. We report four patients with persistent posterolateral ankle pain despite prolonged nonoperative treatment. An os trigonal syndrome was diagnosed by a positive response to a fluoroscopically guided local anesthetic injection in the region of synchondrosis between the os trigonum and the posterior talus.

Results

All four patients underwent excision of the os trigonum with complete resolution of symptoms and return to full activity.

Conclusions

Fluoroscopically controlled injection can help confirm the suspected diagnosis of an os trigonum syndrome and may have positive predictive value regarding the outcome of excisional surgery.

INTRODUCTION

The os trigonum is a small bone on the posterolateral aspect of the talus formed from a separate ossification center which fails to unite with the talus itself[1,2]. The incidence of the os trigonum has been reported to be 3-15%[2,3,4] and it is more often bilateral than unilateral[3]. The os trigonum syndrome is characterized by pain, and sometimes swelling, in the posterolateral aspect of the ankle. The two mechanisms of injury originally described by McDougal involve either micro trauma from repetitive hyperplantar flexion or an episode of acute forced hyperplantarflexion[5]. These mechanisms make it easy to understand why this syndrome has been most frequently described in ballet dancers[1,6,7,8,9] and soccer players[5]. Much less frequently, forced dorsiflexion causing avulsion of the os trigonum by the posterior talofibular ligament or direct trauma to the posterior aspect of the ankle may cause a painful os trigonum[4].

The diagnosis can be difficult to make as symptoms and physical exam findings mimic those that occur with problems related to an accessory soleus muscle, flexor hallucis longus, posterior tibialis, or peroneal tendons; or arthritis involving the posterior tibiotalar or subtalar joints. Radiographs typically reveal an os trigonum less than one centimeter in size and, in chronic cases, the margins may appear irregular with cystic and sclerotic changes along either the talus or the ossicle. Tomograms, CT scans, and MRI have all been described with subtle, nonspecific findings[10]. Bone scintigraphy which shows increased uptake in the posterior aspect of the talus has been recommended by several authors to aid in the diagnosis[2,10,11,12]. We have utilized fluoroscopically controlled anesthetic injections to help diagnose painful os trigonum. In this report, we present our early experience with this simple, inexpensive, and promising diagnostic technique.

*University of Iowa Departments of Orthopaedic Surgery,
**Biomedical Engineering, and Radiology#

Corresponding Author:
Darron M. Jones, M.D., University of Iowa Hospitals and Clinics, Department of Orthopaedic Surgery, 200 Hawkins Drive, Iowa City, Iowa, 52242

Phone: (319) 356-0430
Fax: (319) 353-6754
E-mail: Darron-Jones@uiowa.edu

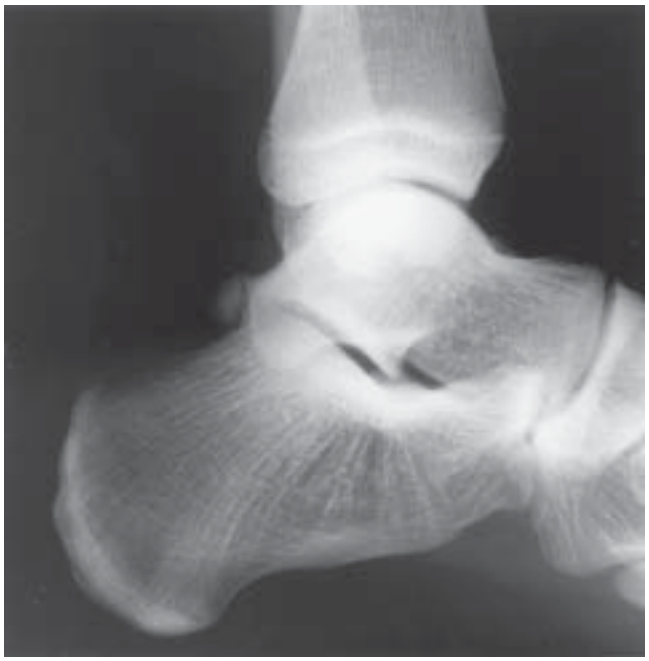


Figure 1. A lateral radiograph showing an os trigonum. Note irregular margination between the talus and the ossicle.

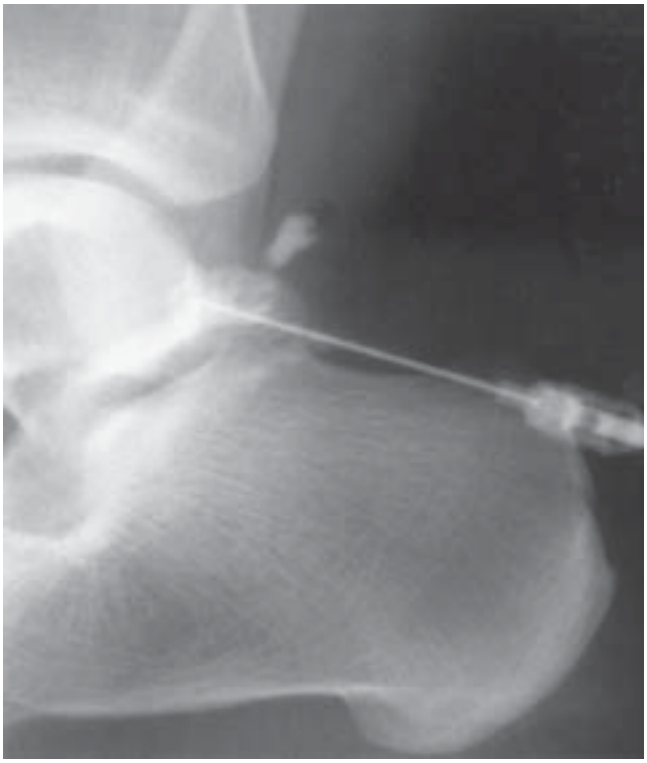


Figure 2. A lateral fluoroscopic image documenting the position of the needle using a small amount of radiographic contrast prior to injection.

MATERIALS AND METHODS

Four patients who presented with pain located in the posterior aspect of the ankle form the basis of this study. All patients had a history of a minor acute plantarflexion injury or repetitive hyper-plantarflexion associated with the onset of symptoms. Symptoms included pain in the posterior aspect of the ankle, usually just posterior to the lateral malleolus, and mild swelling. These symptoms were exacerbated with activities and had persisted for a minimum of six months despite conservative treatment using removable walking boots and/or casting, anti-inflammatories, and activity modifications. The physical examination universally revealed mild posterior ankle swelling and tenderness to palpation. Pain with plantarflexion was also noted for each patient.

Plain radiographs on each patient revealed the presence of an os trigonum with no other abnormalities (Figure 1). No patient underwent CT or MRI or technetium bone scan. Based on the history, physical exam findings, and the presence of an os trigonum the patients underwent a fluoroscopically controlled diagnostic injection of local anesthesia between the os trigonum and the talus. Initially, 0.5 cc of radiographic contrast medium was injected to confirm the proper needle tip position (Figure 2). A maximum of 0.5 milliliter of 1% lidocaine was then injected into the area. Each patient was then asked to walk up and down a flight of stairs and then self reported the amount of pain relief. In this series, all four patients reported nearly complete, or complete relief and were indicated for os trigonal excision.

SURGICAL TECHNIQUE

Patients were positioned prone and a well padded tourniquet placed at the mid-calf level. A 2-3cm longitudinal incision was made lateral to the Achilles tendon. The branches to the sural nerve were protected during the dissection to the os trigonum. A Freer elevator was used to circumferentially free the ossicle of soft tissue attachments and it was removed in its entirety. After irrigating the wound, the skin was closed with a subcuticular stitch. The total time of the procedure was less than 30 minutes. A Robert Jones dressing was applied and the patients were instructed to remain touch weight bearing with crutches until their first post-operative visit at two weeks. A hard sole shoe or removable walking boot were used for another two weeks. At one month, the patients were allowed to resume activities as tolerated including return to sports.

Table 1

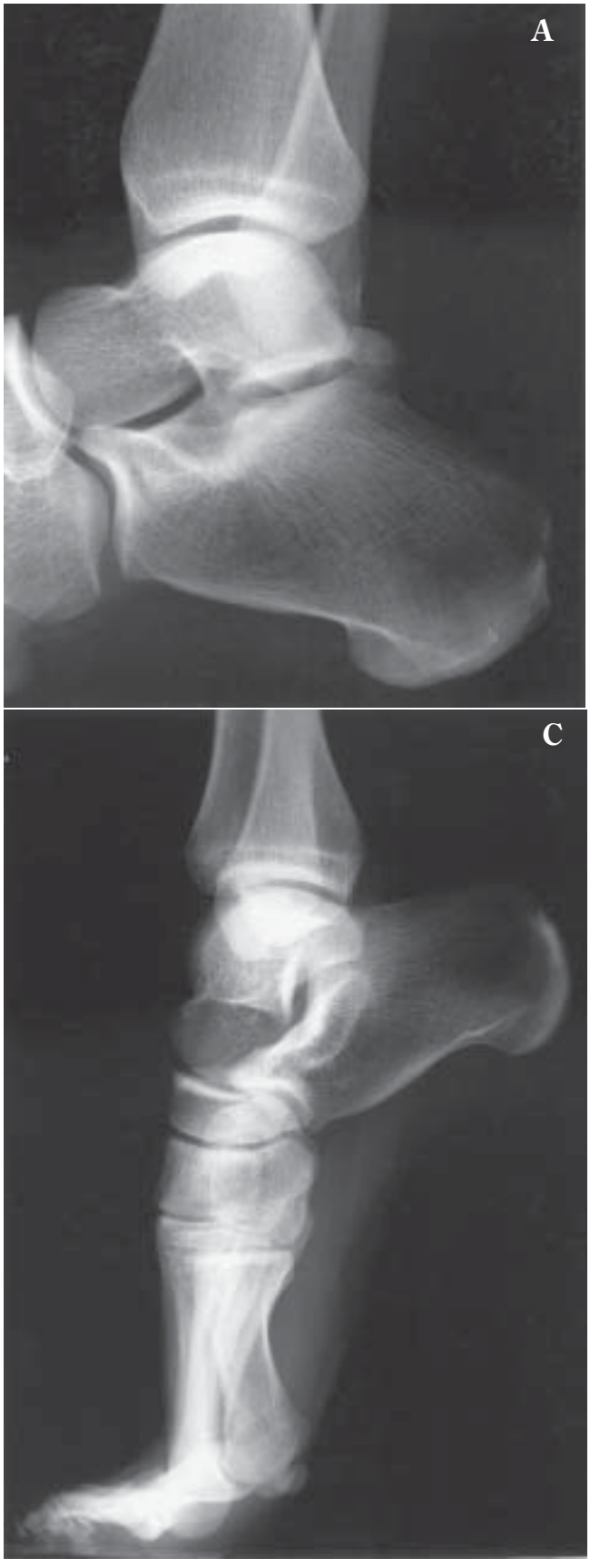
Patient	Age	Sex	Presentation	Anesthetic Injection Result	Surgical Result	Comment
1	20	F	2 year posterolateral ankle pain after twisting injury while playing volleyball	100% pain relief	Success	Complete pain relief Return to intercollegiate level track and field.
2	14	M	6 months posterior ankle pain after kicking a ball during a soccer game	80% pain relief	Success	Pain free at 1 month and returned to soccer.
3	22	F	Dance instructor with 2 years of posterior ankle pain in the en or demi pointe positions	100% pain relief	Success	Complete pain relief with return to dancing.
4	40	F	1 year lateral ankle pain after fall on ice with twist to ankle	100% pain relief	Success	Complete pain relief

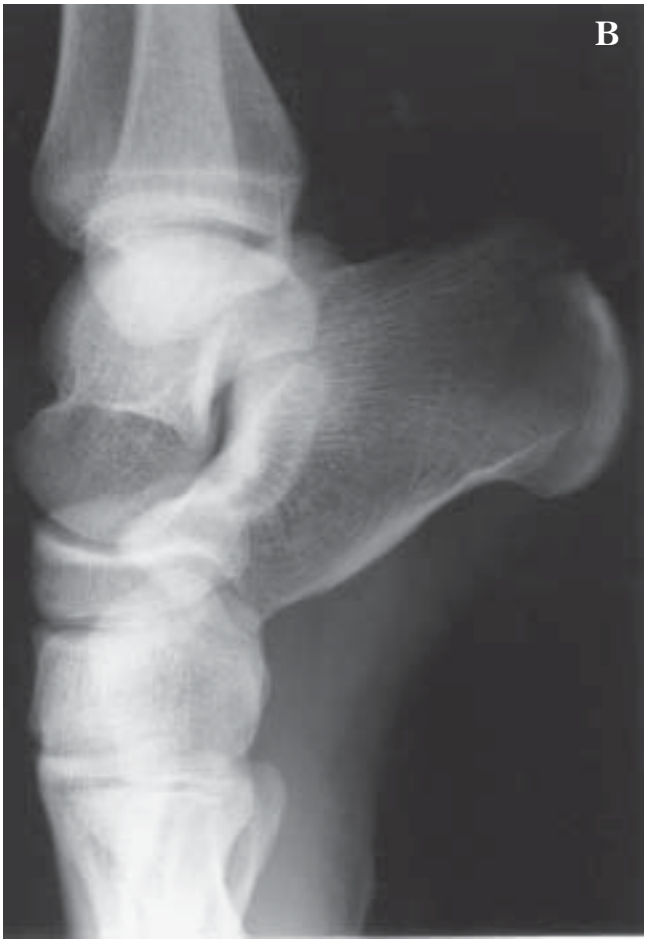
RESULTS

The four patients included 3 women and one man with a mean age of 24 years and a range from 14 to 40 years. The minimum duration of symptoms prior to confirmation of the diagnosis was 6 months (average 16 months, range 6-22 months). Excision of the os trigonum was performed in each after a favorable response to the injection of local anesthesia. All four patients reported relief of pre-operative symptoms at one year following the operation (Table 1). All had returned to full activities between one and three months postoperatively. Patient two had returned to intercollegiate track and field and patient three to high school soccer without return of symptoms. Patient four, a ballet dance instructor had complete resolution of her symptoms with dancing including the en pointe position (Figure 3).

DISCUSSION

The differential diagnosis of posterior ankle pain includes Achilles tendon problems, flexor hallucis longus tenosynovitis, inflammation of the retrocalcaneal bursa, subluxation of the peroneal tendons, painful accessory soleus muscle, tarsal tunnel syndrome, fracture of the dome or posterior process of the talus, focal posterior tibiotalar or subtalar arthritis or osteonecrosis of the talus[2,7]. Most of these conditions can be diagnosed with a careful physical and radiographic examination. The diagnosis of the os trigonum syndrome is usually a diagnosis of exclusion based solely upon the presence of posterior ankle pain and an os trigonum. The mean duration of symptoms prior to diagnosis in our series was over one year and most patients had seen an average of three physicians prior to referral to the senior author. The problem with making the diagnosis is well





Figures 3A-C. Radiographs of a 22 year old dance instructor.

Figure 3A. A lateral radiograph demonstrating the presence of an os trigonum. Note smooth surfaces at the synchondrosis.

Figure 3B. Preoperative radiograph taken in the en pointe position showing obvious impingement of the posterior tibia on the os trigonum.

Figure 3C. Postoperative radiograph taken in the en pointe position with absence of the os trigonum, improved plantarflexion and no evidence for impingement. The patient had complete resolution of her symptoms after injection with dancing after surgery.

described in the literature[2,4,5] and a higher degree of suspicion in dancers and soccer players may lead to a quicker diagnosis9. It is particularly important to rule out associated tenosynovitis of the flexor hallucis longus by assuring pain free active and passive flexion of the FHL tendon and absence of medial sided tenderness[9].

Plain radiographs typically reveal the presence of an os trigonum (Figure 1) but the high normal presence of this finding (3-15%) makes it nonspecific. Irregular margination that develops with repetitive microtrauma at either side of the synchondrosis suggests a potential source of symptoms. Tomograms or CT scans may better image those irregularities but offer no specific information on the cause of the posterior ankle pain[10]. With os trigonum syndrome, technetium bone scanning may demonstrate increased uptake in the posterior aspect of the talus[2,10,11,12]. However, positive scans are sometimes bilateral and have unclear predictive value. MRI may show only fluid between the synchondrosis and can be helpful with excluding other causes of posterior ankle pain[10]. Injection of local anesthesia under fluoroscopic guidance into the area of the trigonal synchondrosis has been suggested as a method of confirming the diagnosis in isolated cases[4,7,10,12].

Wenig reported a case of a symptomatic os trigonum presenting with posterolateral ankle pain of 1 1/2 years duration. In this case, an injection of lidocaine was performed to confirm the diagnosis after tomograms revealed an irregular margin of the os trigonum and bone scan showed increased uptake posterior to the talus. Os trigonal excision resulted in complete symptom resolution.

This is the first report using patient satisfaction results following a fluoroscopically controlled anesthetic injection to diagnose os trigonum syndrome. Under radiographic visualization, less than 0.5cc of 1% lidocaine was infused at the junction of the os trigonum and the posterior aspect of the talus. All four patients in this study had complete symptom resolution after anesthetic injection. The post-excisional clinical results paralleled the results following injection. Based on this preliminary experience, the authors believe this is a promising and straightforward strategy to diagnose a painful os trigonum with predictive value regarding the outcome of excisional surgery.

REFERENCES

1. **Hamilton, W.G.; Geppert, M.J.;** and **Thompson FM:** Pain in the posterior aspect of the ankle in dancers. *J. Bone Joint Surg.,* 78A:1491-1500, 1996.
2. **Johnson, R.P.; Collier, B.D.;** and **Carrera, G.F.:** The os trigonum syndrome: Use of bone scan in the diagnosis. *J. Trauma,* 24:761-764, 1984.
3. **Grogan, D.P.; Walling, A.K.;** and **Odgen, J.A.:** Anatomy of the os trigonum. *J. Pediatr. Orthop.,* 10:618-622, 1990.
4. **Wenig, J.A.:** Os trigonum syndrome. *J. Amer. Podiatric Med. Assoc.,* 80:278-282, 1990.
5. **McDougall, A.:** The os trigonum. *J. Bone Joint Surg.,* 37B: 257-265, 1955.
6. **Brodsky, A.E.;** and **Khalil, M.A.:** Talar compression syndrome. *Amer. J. Sports Med.,* 6:472-476, 1986.
7. **Marotta, J.J.;** and **Micheli, L.J.:** Os trigonum impingement in dancers. *Amer. J. Sports Med.,* 20:533-536, 1992.
8. **Quirk, R.:** Talar compression syndrome in dancers. *Foot and Ankle,* 3:65-68, 1982.
9. **Wredmark, T.; Carlstedt, D,A.; Bauer, H.,** and **Saartok T:** Os trigonum syndrome: A clinical entity in ballet dancers. *Foot and Ankle,* 11: 404-406, 1991.
10. **Karasick, D.;** and **Schweitzer, M.E:** The Os trigonum syndrome: Imaging features. *Amer. J. Rad.,* 166:125-129, 1996.
11. **Hedrick, M.R.;** and **McBryde, A.M.:** Posterior ankle impingement. *Foot and Ankle,* 15:2-8, 1994.
12. **Veazey, B.L.; Heckman, J.D.; Galindo, M.J.;** and **McGanity, P.L.J.:** Excision of ununited fractures of the posterior process of the talus: A treatment for chronic posterior ankle pain. *Foot and Ankle,* 13:453-457, 1992.

ENTRAPMENT OF THE INDEX FLEXOR DIGITORUM PROFUNDUS TENDON AFTER FRACTURE OF BOTH FOREARM BONES IN A CHILD

Paul A. Watson, M.D.,C.M., Orthopaedic Resident
William Blair, M.D., Professor of Orthopaedics

ABSTRACT

Entrapment of the index FDP tendon in a radius fracture callus occurred after fracture of both forearm bones in a 4-year-old boy. Surgical release of the FDP tendon, three months after fracture, resulted in normal index finger motion. This clinical problem can be avoided by a detailed physical examination of children with forearm fractures, verifying full passive range-of-motion of the hand after cast immobilization. Prompt supervised active range-of-motion should be done to prevent adhesions at the fracture site.

INTRODUCTION

Entrapment of the flexor digitorum profundus tendon can occur following forearm fractures in children.[1-3] In the four cases reported to date, a midshaft ulna fracture entrapped the ring finger flexor digitorum profundus (FDP) tendon near its origin. Diagnosis was often delayed until after bony union. Surgery was necessary to release adhesions and extricate the muscle bellies from the fracture site.[1-3] There have been no reports of other FDP tendons being entrapped, nor have FDP tendons been entrapped in the radius after a both bone forearm fracture. We report an index finger FDP entrapment in the radius of a child.

CASE REPORT

A 4-year-old, right handed boy sustained a closed both bone forearm fracture at the distal diaphyseal/metaphyseal level. Acceptable alignment was obtained with manipulation under Bier block anesthesia and a long arm cast was applied. Lack of full index extension was noted five days post reduction. Following cast treatment, the fractures healed clinically and radiographically.

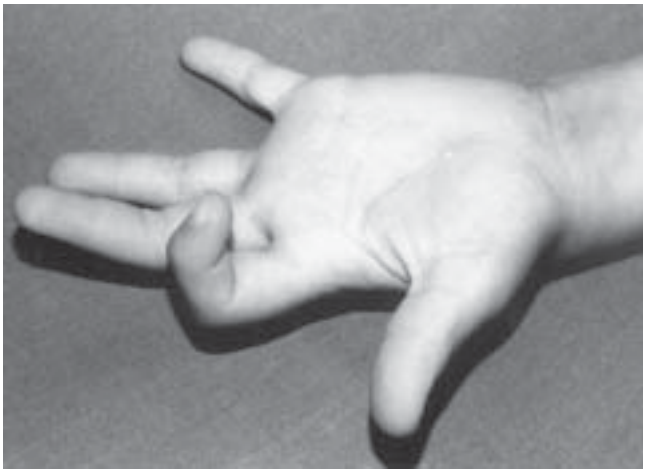


Figure 1. With the wrist and metacarpophalangeal joints held in a neutral position, the patient was unable to actively or passively extend the proximal or distal interphalangeal joints.

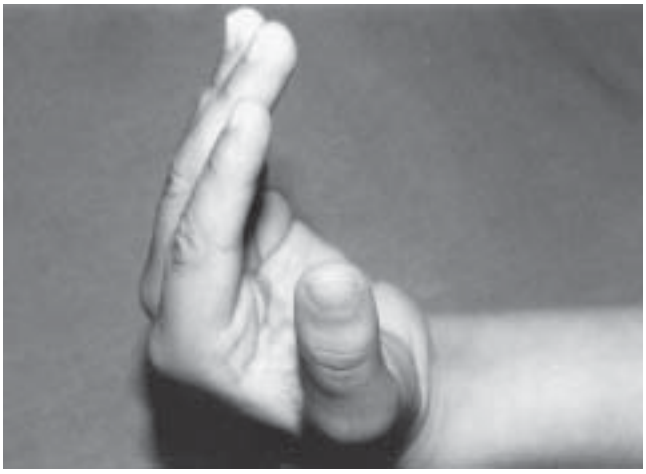


Figure 2. With the wrist and metacarpophalangeal joints held in flexion, the patient had full active and passive extension of the proximal and distal interphalangeal joints.

The patient was referred three months after the injury for evaluation of contracture of the index flexor tendons. On examination, he had full index motion with the wrist flexed, but was unable to extend the index finger with the wrist in neutral or extension. (Figs. 1 and 2) Adhesion of the index FDP at the fracture site was diagnosed.

University of Iowa, Iowa City, Iowa

Correspondence to :
Paul A. Watson, M.D., Resident, Department of Orthopaedic Surgery, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, Iowa 52242, (319) 356-3470

At surgery, a volar longitudinal approach to the radius was made. Adhesions between the index FDP and the radial fracture callus were identified at the fracture site. (Figure 3) The FDP tendon was identified proximal and distal to the fracture callus. Using sharp dissection, the tendon was freed from the callus, resulting in immediate full passive index finger extension with the wrist in both flexion and extension. Post-operatively the patient was immediately started on active and passive range of motion exercises to prevent adhesion formation. Three months post-operatively the patient had full active range-of-motion of the index finger in all wrist positions.

DISCUSSION

This report describes entrapment of the index FDP tendon in the radius after fracture of both forearm bones in a 4-year-old boy. Rayan and Hayes[2] described one patient with entrapment of the ring finger FDP tendon in the ulna after a both bone forearm fracture. Surgical release revealed muscle belly entrapment in a cortical defect at the healed fracture site. They concluded that this complication could be avoided with anatomic reduction, careful examination and encouragement of early active and passive range-of-motion exercises after both bone forearm fractures. Jeffery[1] described two cases of ring finger FDP entrapment in the ulnar fracture site, suggesting that muscle belly entrapment and adhesions to the fracture site caused the tenodesis effect observed in these two cases.

A tenodesis effect, that is a lack of extension of the involved digit with a neutral or extended wrist and full range-of-motion with the wrist flexed, confirms the diagnosis. In this case, the index FDP tendon was adherent to the abundant fracture callus. Whether pain caused the child to stop moving his finger, leading to adhesions, or adhesions forming secondary to consolidation of the fracture hematoma and callus is unclear. At surgery, differentiating between callus and tendon at the site of adhesion can be difficult. Therefore, identification of the FDP tendon both proximal and distal to the adhesion site was essential to avoid injuring the tendon.

This clinical problem can be identified early by performing a detailed physical examination of children with forearm fractures after reduction. Full passive range of motion of the hand should be verified after cast immobilization. Prompt supervised active range-of-motion may also help prevent FDP adhesions at the fracture site after reduction and cast application or in the rare case where surgical release of a flexor tendon is required. Careful examinations and appropriate hand therapy should help to prevent this clinical problem in the future.

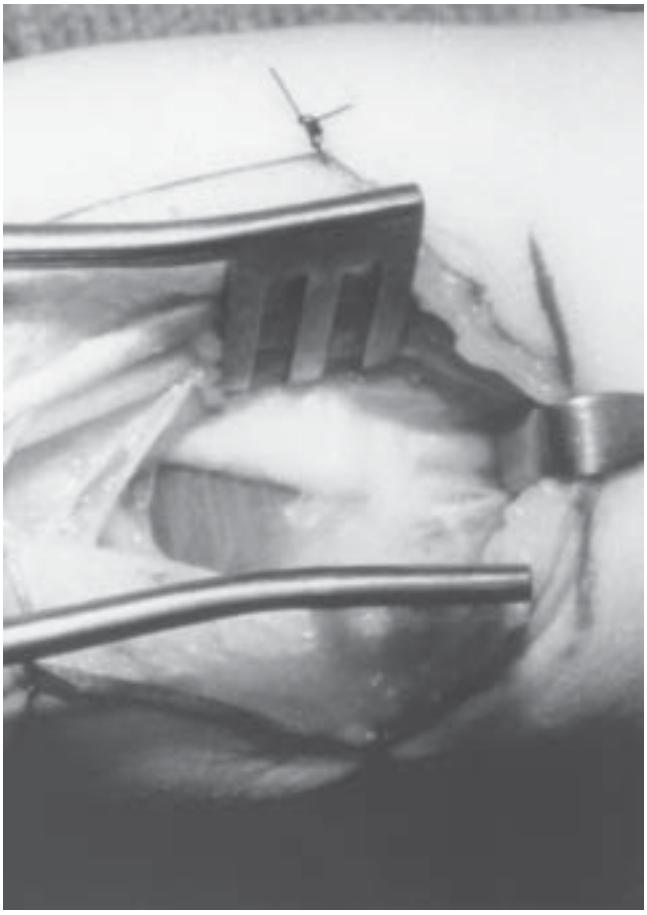


Figure 3. Adhesions between the flexor digitorum profundus to the index and the fracture callus.

REFERENCES

1. **Jeffery, C.C.:** Contracture of fingers due to fixation of the flexor profundus digitorum to the ulna. *Hand,* 8(1):32-35,1976.
2. **Rayan, G.M.; Hayes, M.:** Entrapment of the flexor digitorum profundus in the ulna with fracture of both bones of the forearm. *J. Bone Joint Surg.,* 68A(7):1102-1103, 1986.
3. **Hendel, D.; Aner, A.:** Entrapment of the flexor digitorum profundus of the ring finger at the site of an ulnar fracture., *Ital. J. Ortho. Traum.,* 18(3):417-419, 1992

SUBCHONDRAL METASTASIS: REPORT OF FIVE CASES

Jeffrey J. Peterson
Thomas A. Manning, MD
John J. Callaghan, MD
George Y. El-Khoury, MD

ABSTRACT

Subchondral metastasis is a rare occurrence and poses a diagnostic dilemma as initial films may show a lytic lesion in the subchondral region often misinterpreted as being benign.. We present five cases of subchondral metastasis as well as a review of the literature. In our cases, we present subchondral metastasis in the elbow, shoulder, and hip joints. All patients had pain over the affected joint and most presented with a lytic lesion in the subchondral bone. Three patients have died since presentation and two are doing well at last follow up visit. Subchondral metastasis is a rare entity, but it should be included in the differential of a lytic lesion in the subchondral bone.

INTRODUCTION

The entity of subchondral metastasis is a subset of yellow marrow metastasis. In some joints, there is an area of yellow marrow immediately adjacent to the cartilagenous articular surface. T2-weighted MRI images of a normal shoulder joint show this region as an area of increased signal from its increased adipose content (Figure 1). Involvement of this area by contiguous spread of bone tumors as well as spread of leukemia and lymphoma has been reported[1,2], but reports of direct involvement specifically of the subchondral marrow with tumor metastasis are exceedingly rare. The predominance of reports in this area deal with disease involving the synovium, patella or adjacent red marrow tumors. These lesions pose a diagnostic dilemma as patients may have no other symptoms of malignancy and initial films may be negative. Furthermore, these lesions may show as a well-circumscribed lytic area and may be misinterpreted as being benign. We present five cases of subchondral metastasis.

MATERIALS AND METHODS

Review of our records yielded five cases of subchondral metastasis. The patient's ages ranged from 50 to 85 with four men and one woman. The primaries were non-small-cell lung carcinoma, papillary thyroid carcinoma, squamous skin carcinoma and renal cell carcinoma. Plain films, CT and MRI scans as well as the medical records were reviewed.

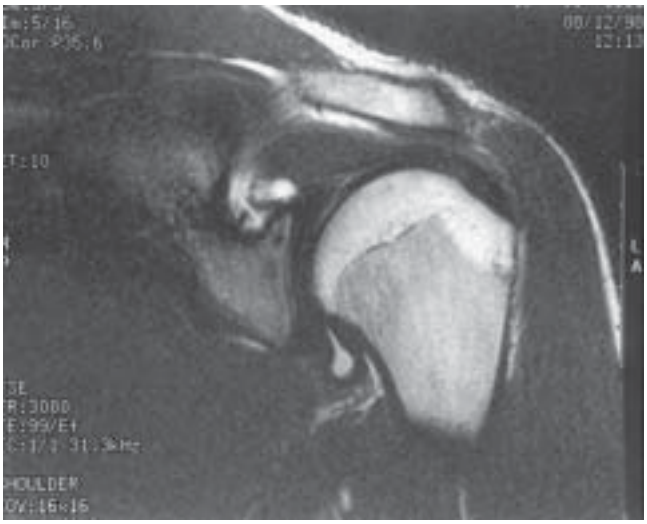


Figure 1. T2-weighted image of a normal 19-year old shoulder illustrating increased signal in the subchondral region.

From the Departments of Radiology (J.J.P., G.Y. E-K) and Orthopaedic Surgery (J.J.C.), The University of Iowa College of Medicine, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242, and Radiology Department (T.M.) Marian Health Center, Sioux City, IA

Address reprint requests to J.J.P., Department of Radiology, University of Iowa Hospitals and Clinics, 200 Hawkins Dr., Iowa City, IA 52242.

Corresponding author:
Jeffrey J. Peterson, Department of Radiology, The University of Iowa Hospitals and Clinics. 200 Hawkins Drive, Iowa City, IA 52242
Telephone: 319-338-7324

Case Number	Age	Primary	Presentation
1	66	Lung	Right shoulder pain and swelling
2	79	Squamous skin	Right elbow pain and swelling
3	50	Papillary thyroid	Right hip pain
4	85	Renal cell	Right arm and hip pain
5	55	Lung	Right arm and shoulder pain

Case 1 - F.B.

A 66-year-old man with a long history of smoking and alcoholism presented to an outside clinic with a seven month history of right shoulder pain and swelling. The pain had progressed to a constant dull ache, radiating to the neck and down the right arm. The patient had a long history of COPD, as well as a lung mass on chest film a year earlier. This mass was biopsied and histologic exam revealed granulomatous disease. Plain films of the shoulder demonstrated a 2.5 cm lytic area in the humeral head. A technetium-99m methylene diphosphonate (Tc-99m-MDP) bone scan demonstrated high uptake in the proximal right humerus without other areas of abnormal uptake. Flexible sigmoidoscopy, prostate specific antigen, barium enema, and upper gastrointestinal series films were within normal limits.

The patient was referred to our institution a month later with persistent shoulder pain and worsening swelling. Plain films demonstrated a large lytic lesion in the humeral head with associated collapse (Figure 2). Chest films and chest CT showed a spiculated soft tissue density in the right upper lobe as well as a smaller nodule in the left lower lobe. MR images of the right shoulder demonstrated a 4.5cm mass in the proximal humerus with isointense signal on T1 weighted images and hyperintense signal on T2 weighted images. The mass had a scalloped appearance and was associated with a moderate joint effusion. An open biopsy of the mass demonstrated atypical glandular structures consistent with poorly differentiated adenocarcinoma. The patient was treated with radiation therapy to the right shoulder, but he died 6 months later from widespread metastasis.

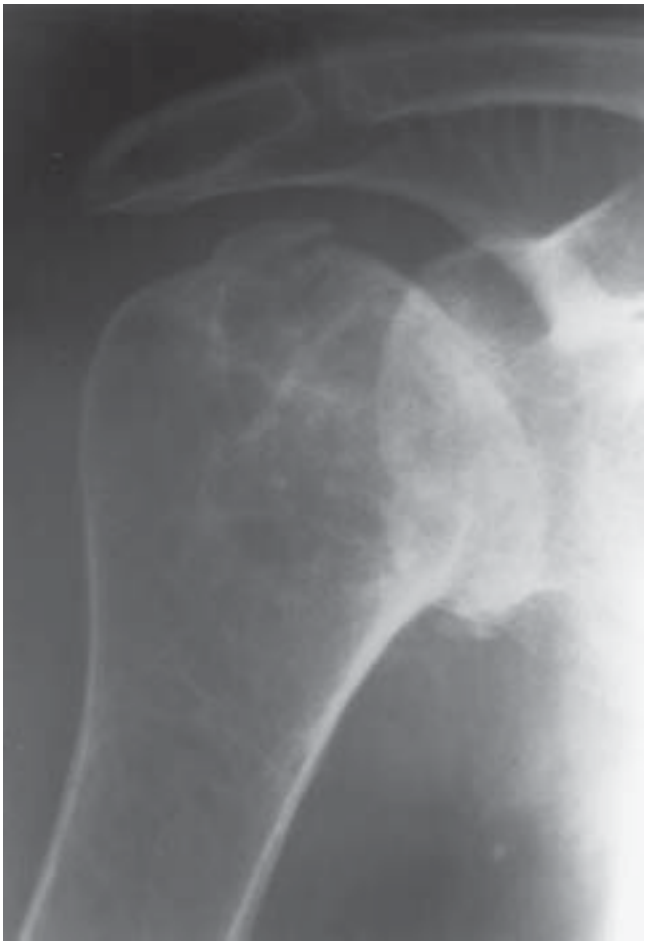


Figure 2. Case 1 - A 66-year-old man presents with a seven-month history of right shoulder pain and swelling. A plain film of the shoulder demonstrates a subchondral lytic lesion in the humeral head with pathologic fracture.

Case 2 - D.C.

A 79-year-old man presented to the oncology service with right elbow pain and swelling for six weeks. His history is significant for recurrent squamous as well as basal cell cancers on the face and trunk, as well as transitional cell carcinoma of the bladder. He had undergone many resections for the skin tumors, as well as a cystoprostatectomy for his transitional cell carcinoma. Metastatic workups were negative after each resection. The patient developed a subcutaneous nodule on the abdomen which was biopsy proven as metastatic squamous carcinoma.

At initial presentation at the Oncology service, the patient was treated with Indocin for presumed osteoarthritis or pseudogout. Subsequent plain films of the elbow demonstrated a lytic subchondral lesion in the distal right humerus, involving the trochlea and capitulum (Figure 3). A Tc-99m-MDP bone scan showed increased uptake in the right elbow as well as the left sixth rib. The masses were presumed to be metastatic nodules. The patient received 3000cGy of radiation therapy to the right distal humerus, with a modest decrease in size of the lytic area. The area continued to be painful and the swelling increased in the next two months. The patient elected to pursue medical management rather

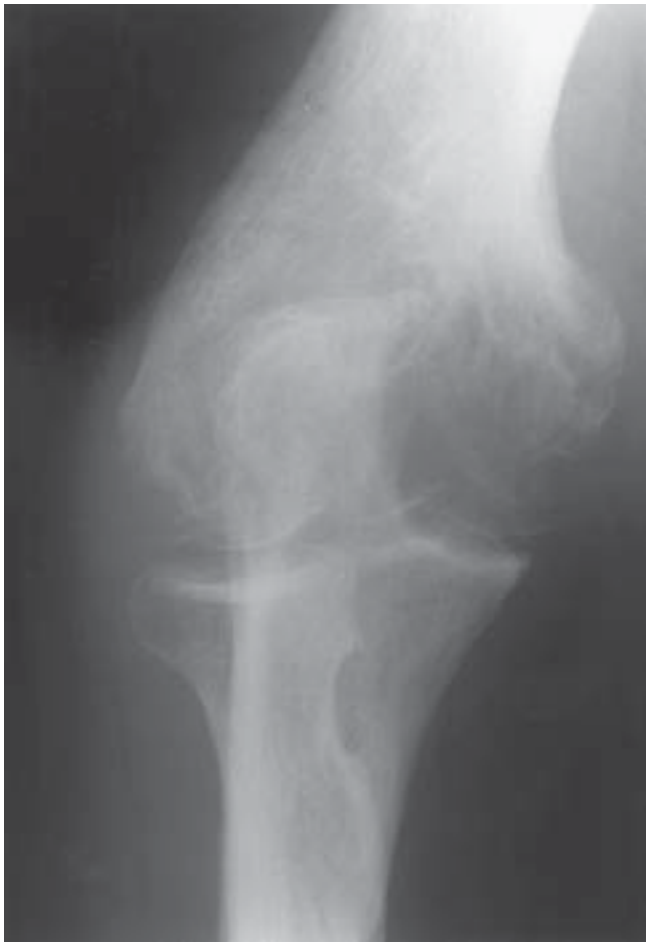
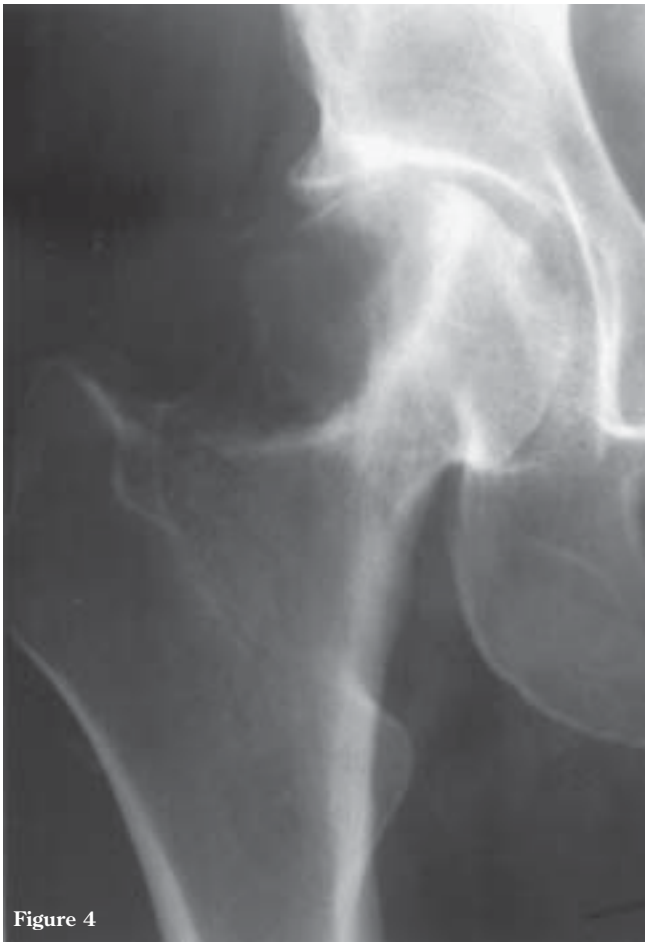


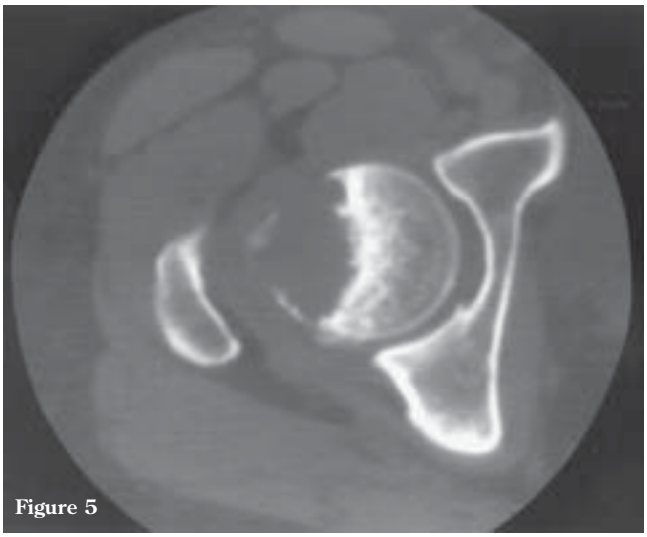
Figure 3. Case 2 - A 79-year-old man presented with a three-month history of pain and swelling in the right elbow. Plain films demonstrate a subchondral lucency involving the medial and lateral epicondyles.

that surgical resection, and has been managed with pain medications and nine courses of infusional pamidronate. The patient was doing well 15 months after the initial discovery of metastasis to the right elbow.

Case 3 - R.V.

A 50-year-old woman with no previous history of malignancy presented with a 2-year history of right hip pain that had worsened over the last 3 months. Plain films and a CT scan of the right hip demonstrated a geographic lucency in the right femoral head (Figures 4 and 5). Because of the subchondral location of the lesion, a giant-cell tumor was considered the most likely diagnosis, and a femoral head and neck resection followed by total hip arthroplasty was performed. Histologic examination of the specimen revealed a metastatic papillary thyroid carcinoma. The patient was treated with total thyroidectomy and 150mCi of iodine-131. A





Figures 4 & 5. Case 3 - A 50-year-old woman with no previous history of malignancy presented with a 2-year history of right hip pain. Plain films demonstrate a geographic, well-marginated lesion involving the subchondral region of the femoral head and lateral portion of the femoral neck. A CT scan of the right hip demonstrates cortical destruction laterally and sclerosis medially. A giant-cell tumor was considered the most likely diagnosis.

subsequent I-131 imaging study showed increased uptake in the proximal right femur without other evidence of metastasis. The proximal right femur then treated with 5000 cGy of external beam radiation over 5 weeks. After a five year asymptomatic period, the patient presented with new left hip pain. An I-131 scan showed diffuse uptake in the right and left femurs as well as focal intensities in the proximal and distal right femur and right lung base. The patient was treated with 329 mCi of I-131 at that time. Another I-131 scan taken a year later showed persistent uptake in the proximal right femur and the patient was treated with an additional 300 mCi of I-131. The patient was managed with pain medications until her eventual death from disseminated metastasis two years later, a total of seven years after initial presentation of her subchondral hip metastasis.

Case 4 - G.D.

A 65-year-old man presented to the urologic oncology service with a three month history of right arm and hip pain. His history is significant for stage III renal cell cancer with a radical nephrectomy five years earlier. One year later, the patient developed pulmonary metastasis and was treated with chemotherapy. He subsequently developed neck pain which radiated down both arms. Plain films showed a lucent area in the body of C6, and the patient underwent 3600 cGy of local radiation therapy followed by corpectomy, tumor debulking, and spinal canal stabilization. The patient presented with the right hip and arm pain 18 months later.

Plain films taken at the presentation to the oncology service of the demonstrated a pathologic fracture in the midshaft of the right humerus as well as a lytic area in the anterolateral aspect of the femoral head and neck (Figure 6). MR images of the pelvis demonstrated an area of low T1 signal and high T2 signal in the proximal right femur consistent with subchondral metastasis. The patient underwent embolization of the femoral mass followed by hemiarthroplasty of the right hip. Histologic analysis revealed a metastatic clear cell adenocarcinoma. The patient has since undergone a tumor resection of the right humeral mass and was doing well at last follow-up, seven years after initial presentation.

Case 5- J.L.

A 55-year-old man with a 60-pack-year smoking history, but no diagnosis of malignancy, presented with a 2-month history of right arm, shoulder and hip pain, and hemoptysis. A chest radiograph revealed an extensive right superior sulcus tumor with rib destruction. A

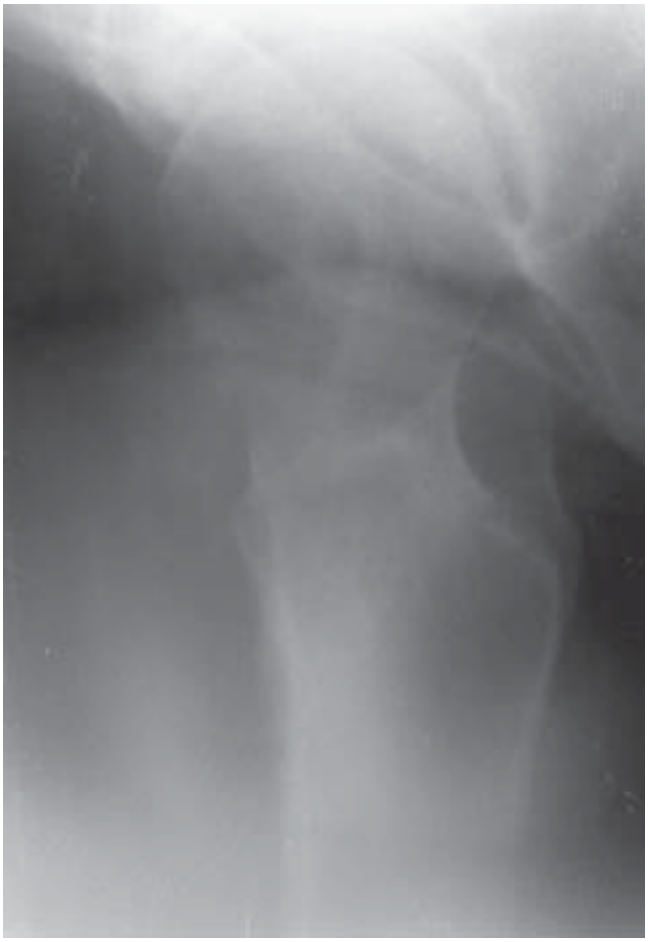


Figure 6. Case 4 - A 65-year-old man presented with a three month history right hip pain. Plain films of the right hip demonstrate a lytic area in the anterolateral distal femoral head and the proximal femoral neck.

CT scan of the chest showed invasion of the right axilla, but no evidence of mediastinal or hilar disease. Fine needle aspirate of the chest lesion showed a poorly differentiated non-small-cell carcinoma. A metastatic work-up included a Tc-99m-MDP bone scan negative for metastasis. Plain films and CT scans of the right hip showed no abnormalities.

The lung tumor was staged as T3N0M0, and the patient began radiation therapy in preparation for surgical resection. Over a period of four weeks, however, the pain in the right hip increased. On physical examination, there was pain, weakness and limited range of motion in the right hip. Other joints were unremarkable. A repeat plain film of the right revealed a lytic lesion in the right femoral head. A scalp lesion was biopsied, demonstrating a non-small-cell metastasis.

Radiation therapy was continued to the lung mass as well as to the right hip. Approximately three weeks later, the patient was discovered to have diffuse abdominal

metastases. Plain films of the right femur now demonstrated a pathologic fracture. In spite of a short course of chemotherapy, the patient's clinical condition deteriorated, and he died three weeks later.

DISCUSSION

Metastasis is a common occurrence in many cancer patients. There are two general theories of the mechanisms of metastasis. One deals with mechanical factors[3] and the other is termed the "seed and soil" theory[4]. The mechanical theory suggests the vascular architecture of certain organs is conducive to implantation and growth of metastatic cells from hematogenous spread. Organs with transitions from large to small vessels or a prominent small vessel bed are areas where metastatic cells would become trapped by mechanical factors. Even so, studies suggest a discrepancy between the vascular patterns and frequency of metastasis of certain organs[5]. As cancer cells circulate, they encounter numerous antigens in the endothelium of different organs. The seed and soil theory implies that certain cancers preferentially interact with some of these antigens, thus increasing the probability of metastasis to a particular site. Once attached, cancer cells must extravasate and proceed to grow in the target organ. It is the interaction of these two theories which explains the discrepancy between vascular anatomy and preferential metastatic sites

Bone metastasis is a common event in many tumors such as breast, prostate, lung, thyroid, and kidney[5]. Metastasis to bone preferentially involves the red marrow and bones rich in red marrow[5,6], and consequently, metastases generally arise proximal to the elbows and the knees. Red marrow possesses a prominent vascularity with many sudden transitions from large to small vessels, a large sinusoidal vessel bed and a porous endothelium made for the entrance of hematopoietic cells into the blood stream[5,7,8]. Red marrow also is postulated to have a different antigen composition of its endothelium from that of other locations of bone, although this is currently under evaluation. Cancer cells show a preferential adherence to certain red marrow endothelial antigens[8]. This increases the probability that circulating cancer cells will become entrapped in this area and establish a metastatic focus. Yellow marrow, on the other hand, is predominantly fatty tissue with sparse vascularity. The prominent sinusoidal vessels of red marrow are replaced by capillaries and venules with a continuous endothelial lining[6]. The paucity of blood vessels suggests that growth of tumor would be difficult in this area. Also, it has been suggested that the endothelial antigen composition of yellow marrow differs from that of red marrow. Metastasis may occur in mixed red and yellow marrow, but the involvement of purely yellow marrow is distinctly rare[8]. Numerous animal models have been created to evaluate the pathogenesis of metastatic tumors to bone[9].

The patients involved in this study possessed identifiable primary tumors. Three of the patients had no previous history of malignancy, while the other two patients had a history of previous cancer resection. Three patients had biopsy proven metastasis, while one patient elected conservative care due to his advanced age and another died shortly after presentation. All patients presented with pain in the area of metastasis, that being the hip, shoulder or elbow. All patients eventually showed a lytic lesion on plain film at the site of metastasis, with a well-circumscribed border also being a common presentation. Bone scan was done on two patients, with one showing increased radionucleotide uptake and the other showing no identifiable uptake in the area of metastasis. CT examination showed a lucent area in the areas of metastasis, and MR images demonstrated an area of low signal intensity on T1 imaging and high signal on T2 imaging. Three patients died from disseminated metastasis, one at seven years, another at six months and the other at three weeks since presentation. Two patients have remained stable following radiation therapy and pain management.

In a review of the literature, 10 cases of involvement of subchondral bone of metastatic tumor were found. The ages ranged from 29 to 77 with an average age of 58. The cases include: melanoma metastatic to the distal femur[10,11], rhabdomyosarcoma metastatic to distal femur[12], renal cell metastatic to proximal humerus[13], bronchogenic carcinoma metastatic to distal femur[14,15,16] bronchogenic carcinoma metastatic to the proximal humerus[14], breast carcinoma metastatic to distal femur[17] and unknown primary metastatic to proximal femoral head[2]. As in our study, all cases presented with persistent pain and/or swelling in the joint of metastatic disease. Seven of the ten cases had a previous diagnosis of cancer and three patients presented with monoarticular arthropathy as the first manifestation of malignancy[2,13,14]. In comparison, our study included three initial presentations of cancer. Nine of ten cases showed a lytic lesion of plain films of the area involved[10,12-18]. Five of ten cases showed abnormal areas of uptake on bone scan in the metastatic areas[2,11,15,16,17], four cases did not have bone scanning, and one case had a negative bone scan at the time of presentation[12]. Our cases demonstrated one positive and one negative bone scan in the area of metastasis. The presence of subchondral metastasis was indicative of a poor prognosis with an average survival of 3.5 months after diagnosis. Two patients were successfully managed with radiation therapy to the area of metastasis[11,13]. This is

in contrast to our study where two patients were well at last follow-up and three patients died of metastatic disease at seven years, six months and three weeks after presentation.

The presentation of subchondral metastasis is similar to metastasis to other tissue compartments of the joint space. These areas which can cloud the diagnosis of subchondral metastasis include: patellar metastasis[18,19,20,21,22,23], synovium[17,24,25,26,27,28,29,30,31], acetabulum[32], glenoid and scapula[33,34], sternoclavicular joint[1], and calcaneus[35]. The most common tumor associated with joint space metastasis is bronchogenic carcinoma, followed by breast and gastrointestinal tract malignancies[30]. The joint most commonly involved is the knee, with case reports of involvement in the hip, shoulder, and elbow[30].

Since the most common presentation of subchondral metastasis is a well-circumscribed subchondral lytic lesion on plain film, metastasis can be confused with many benign entities. Osseous involvement may mimic subchondral cysts, periarticular osteopenia or subchondral sclerosis in common arthropathies[1]. Involvement may also simulate crystal-induced arthritis[21], ischemic necrosis[19], infection[36], giant-cell tumors and myeloma. Similarly, the synovial thickening often seen with metastasis to subchondral bone may simulate rheumatoid arthritis, villonodular synovitis, calcium pyrophosphate deposition or gout. Subchondral metastasis should be considered whenever a lytic lesion at the end plate of bone fails to respond to standard arthritic therapy.

BIBLIOGRAPHY

1. **Murray, G.C.,** and **Persellin, R.H.:** Metastatic carcinoma presenting as monoarticular arthritis: a case report and review of the literature. *Arthritis and Rheumatism,* 23:95-100, 1980.
2. **Meals, R.A.; Hungerford, D.S.;** and **Stevens, M.B.:** Malignant disease mimicking arthritis of the hip. *JAMA,* 239:1070-1072, 1978.
3. **Ewing, J.:** Metastasis. In *Neoplastic Diseases,* A textbook on Tumors. Ed. 3, pp. 77-89. Philadelphia, W.B. Saunders, 1928.
4. **Paget, S.:** The Distribution of Secondary Growths in Cancer of the Breast. *Lancet,* 1:571-573, 1889.
5. **Berrettoni, B.A.,** and **Carter, J.R.:** Mechanisms of cancer metastasis to bone. *J. Bone and Joint Surg.,* 68-A:308-312, 1986.
6. **Jacobsson, H.,** and **Goransson, H.:** Radiological detection of bone and bone marrow metastases. *Med. Oncol. & Tumor Pharmacotherapy,* 8:253-260, 1991.
7. **Vogler, J.B.,** and **Murphy, W.A.:** Bone marrow imaging. *Radiology,* 168:679-693, 1988.
8. **Kricun, M.E.:** Red-yellow conversion: its effect on the location of some solitary bone lesions. *Skeletal Radiology,* 14:10-19, 1985.
9. **Scher, H.I.,** and **Chung, L.W.K.:** Bone metastases: improving the therapeutic index. *Seminars in Oncology,* 21:5 630-656, 1994.
10. **Shenberger, K.N.,** and **Morgan, G.J.:** Recurrent malignant melanoma presenting as monoarthritis. *J. Rheumatology,* 9:328-330, 1982.
11. **Speerstra, F.; Boerbooms, A.M.; Van De Putte, L.B.A.; Kruls, H.J.A.; Van Haelst, U.J.G.M,.;** and **Vooijs, G.P.:** Arthritis caused by metastatic melanoma. *Arthritis and Rheumatism,* 25:223-226, 1982.
12. **Weinblatt, M.E.,** and **Karp, G.I.:** Monarticular arthritis: early manifestation of a rhabdomyosarcoma. *J. Rheumatol.,* 8:685-688, 1981.
13. **Kagan, A.R.,** and **Steckel, R.J.:** Metastatic carcinoma presenting as shoulder arthritis. *AJR,* 129:137-139, 1977.
14. **Fam, A.G.; Kolin, A.;** and **Lewis, J.L.:** Metastatic carcinomatous arthritis and carcinoma of the lung. *J. Rheumatol.,* 7:1 98-104, 1980.
15. **Khan, F.A.; Garterhouse, W.;** and **Khan, A.:** Metastatic bronchogenic carcinoma: an unusual cause of localized arthritis. *Chest,* 67:738-739, 1975.
16. **Gerster, J.C.; Jaquier, E.;** and **Ribaux, C.:** Nonspecific inflammatory monoarthritis in the vicinity of bony metastases. *J. Rheumatology,* 14:844-847, 1987.
17. **Moutsopoulos, H.M.; Fye, K.H.; Pugay, P.I.;** and **Shearn, M.A:** Morarthric arthritis caused by metastatic breast carcinoma. *JAMA,* 234:75-76, 1975.

18. **Ashby, M.E.,** and **Dappen, N.:** Esophageal carcinoma metastatic to the patella. *JAMA,* 235:2519-2520, 1976.
19. **Patel, M.R.,** and **Shekhar, S.D.:** Patellar metastases: a case report and review of the literature. *Orthopaedic Review,* 17:687-690, 1988.
20. **Rothermel, F.J.; Miller, F.J.; Hottenstein, D.W.;** and **Dunn, E.J.:** Metastases to the patella with bone scan, tomography, magnification film correlation. *Pennsylvania Medicine,* July, 50-51, 1977.
21. **Sur, R.K.; Singh, D.P.; Dhillon, M.S.; Gupta, B.D.; Murali, B.;** and **Sidhu, R.:** Patellar metastasis: a rare presentation. *B. J. of Radiology,* 65:722-724, 1992.
22. **Gall, E.P.; Didizian, N.A.;** and **Park, Y.:** Acute monoarticular arthritis following patellar metastasis. *JAMA,* 229:188-189, 1974.
23. **Stoler, B.,** and **Staple, T.W.:** Metastases to the patella. *Radiology,* 93:853-856, 1969.
24. **Lario, B.A.; Lopez, J.A.; Santos, J.T.;** and **Lizarraga, S.R.:** Chronic metastatic arthritis as the first symptom of lung adenocarcinoma. *Scand. J. Rheumatology,* 18:169-170, 1989.
25. **Byrne, P.A.C..; Rees, J.I.S.;** and **Williams, B.D.:** Iliopsoas bursitis-an unusual presentation of metastatic bone disease. *British Journal of Rheumatology,* 35:285-288, 1996.
26. **Newton, P.; Freemont, A.T.; Noble, J.; Scott, N.; Grennan, D.M.;** and **Hilton, R.C.:** Secondary malignant synovitis: report of three cases and review of the literature. *Quarterly Journal of Medicine,* 209:135-143, 1984.
27. **Goldenberg, D.L.; Kelley, W.;** and **Gibbons, R.B.:** Metastatic adenocarcinoma of synovium presenting as an acute arthritis. *Arthritis and Rheumatism,* 18:107-110, 1975.
28. **Karten, I.,** and **Bartfeld, H.:** Bronchogenic carcinoma simulating early rheumatoid arthritis. *JAMA,* 162-163, 1962.
29. **Lagier, R.:** Synovial reaction caused by adjacent malignant tumors: anatomicopathological study of three cases. *J. Rheumatol.,* 4:65-72, 1977.
30. **Benhamou, C.L.; Tourliere, D.; Brigant, S.; Maitre, F.;** and **Cauderlier, P.:** Synovial metastasis of an adenocarcinoma presenting as a shoulder monoarthritis. *J. Rheumatol.,* 15:1031-1033, 1988.
31. **Hatem et al.:** Metastatic carcinomatous arthritis from mucinous adenocarcinoma of the colon. *AJR,*169:291-292, 1977.
32. **Graham, D.F.:** Hip pain as a presenting symptom of acetabular metastasis. *Br. J. Surg.,* 63:147-148, 1986.
33. **Daluga, D.J.; Quast, M.; Bach, B.R.;** and **Gitelis, S.:** Shoulder neoplasms mimicking rotator cuff tears. *Orthopedics,* 13:765-767, 1990.
34. **Ritch, P.S.; Hansen, R.M.;** and **Collier, B.D.:** Metastatic renal cell carcinoma presenting as shoulder arthritis. *Cancer,* 51:968-972, 1983.
35. **Bevan, D.A.; Ehrlich, G.E.;** and **Gupta, V.P.:** Metastatic carcinoma simulating gout. *JAMA,* 237:2746-2747, 1977.
36. **Chakravarty, K.K.,** and **Webley, M.:** Monarthritis: an unusual presentation of renal cell carcinoma. *Ann. Rheum. Dis.,* 51:681-682, 1992.

GLOMUS TUMOR OF THE FINGER TIP AND MRI APPEARANCE

David H. Kim, MD

INTRODUCTION

The glomus tumor is a rare benign neoplasm that arises from the neuroarterial structure called a glomus body[1], which accounts for 1 % to 4.5 % of tumors in the hand. The normal glomus body is located in the stratum reticulare throughout the body, but is more concentrated in the digits[6]. They are believed to function in thermal regulation. The average age at presentation is from 30 to 50 years of age, although can occur at any age[1]. Typical time from onset of symptoms to the correct diagnosis is seven years.

The patient with glomus tumor seeks medical attention early, but the mass is frequently too small to be identified on physical examination[5]. Although the classic triad of moderate pain, temperature sensitivity, and point tenderness has been described, these are nonspecific and not all may be present[6]. Furthermore, because the mass is usually less than 7 mm in diameter, it is very difficult to palpate. Upon biopsy, the histopathology typically reveals organoid appearance of polyhedral cells. It also can display darkly staining nuclei with fibrous stroma, and few blood cells[1].

The plain radiographs are typically normal, although in longer standing lesions bony erosions can be seen. Although ultrasound has been advocated to aid in the diagnosis of glomus tumor, it is operator and techniques dependent[2]. Magnetic Resonance has become the imaging modality of choice when evaluating soft tissue masses. However, MRI descriptions of glomus tumors are rare in the English literature[4,5].

ILLUSTRATIVE CASE REPORT

A 43 year old Korean female presented to the orthopaedic clinic with a six year history of pain at the tip of her left non-dominant thumb. She had numerous visits to different health care providers in the past, with various diagnosis documented in her medical records to include neuroma, radiculitis, Raynaud's phenomenon, and conversion reaction. There were no systemic complaints.

The patient complained of sharp pain whenever pressure was applied to the volar tip of her thumb during the activities of daily living. Although the patient denied night pain or cold sensitivity, she stated that she could feel a "grainy" mass at the tip of the digit.

The physical examination revealed no discoloration of the digit and the nail appeared normal. Although a distinct mass could not be appreciated by the examiner, the reproduction of pain was achieved by palpating the central area of the pulp. The radiographs and routine laboratory results were within normal limits.

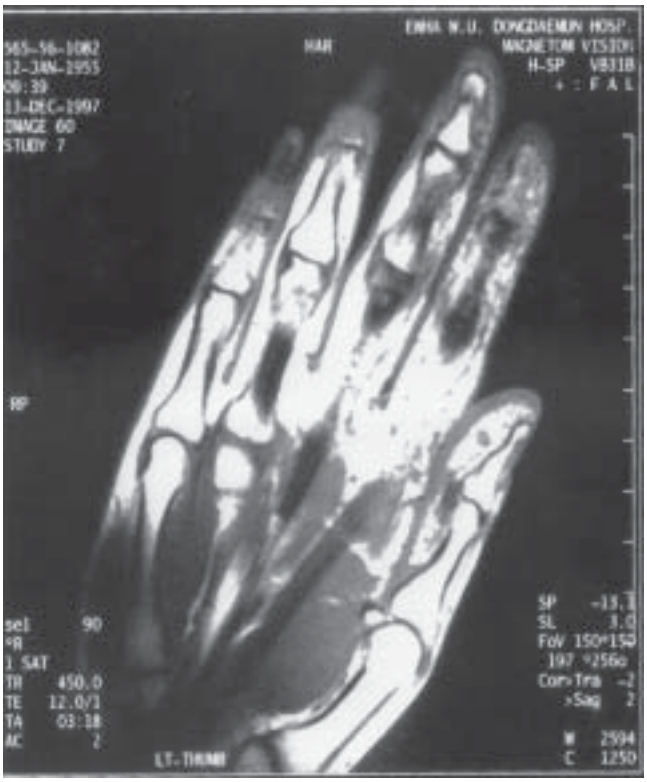


Figure 1. T1 weighted image of the mass, pre-gadolinium

Uniformed Services University, Department of Surgery and Orthopaedic Surgery Service, Tripler Army Medical Center

Correspondence to:
David H. Kim, MD
Uniformed Services University
Department of Surgery and Orthopaedic Surgery Service
Tripler Army Medical Center
MCHK-DSO
1 Jarrett White Road
Honolulu, HI 96859
808) 433-6727
FAX (808) 433-1554

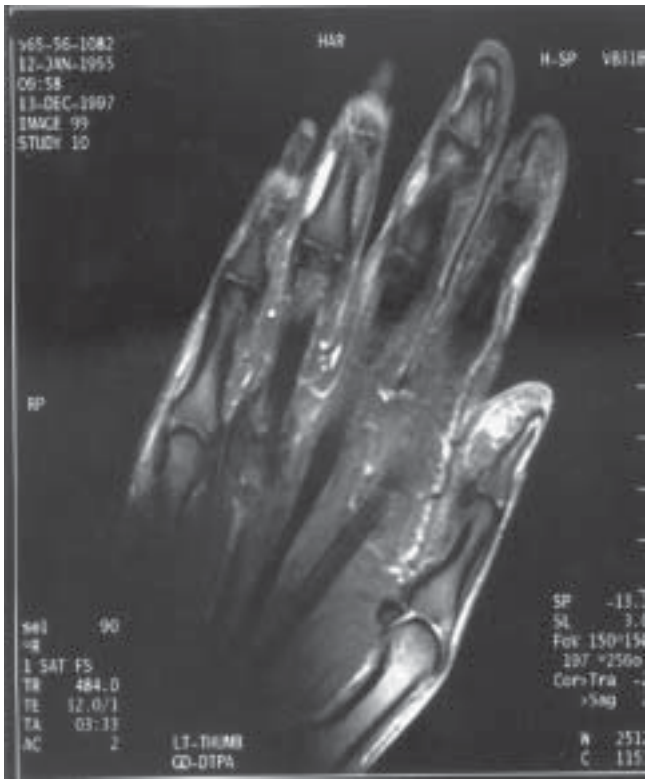


Figure 2.

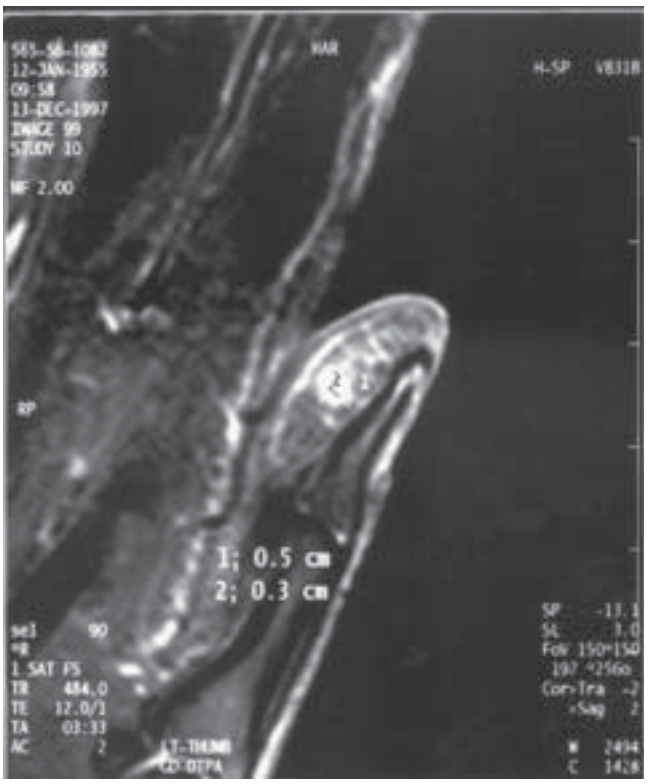


Figure 3.

Figures 2, 3. T1 weighted, post-gadolinium, fat saturation images demonstrating the 3 mm x 5 mm mass.

The MRI obtained revealed a spherical mass at the tip of distal phalanx. The lesion appears as a dark, well-defined mass on T1 weighted images and as a bright contrast enhancing mass on T1 post-gadolinium fat saturation images (Figures 2, 3). The small size (3 mm x 5 mm) and the spherical nature of the lesion was easily demonstrated.

A volar approach to the thumb was made, and excision performed. A spherical-brownish mass measuring 5 mm was identified, without gross surrounding tissue abnormality. The resulting histopathology was consistent with the pre-operative diagnosis of glomus tumor.

At follow up, the patient reported complete relief of her pre-operative symptoms.

DISCUSSION

Glomus tumor is a benign condition in which a complete excision usually leads to cure, with low incidence of recurrence. However, this benign condition has an unusually high morbidity to the patient before the correct diagnosis is made. This attests to the difficulty in correctly diagnosing this lesion initially. Although history and carefully performed physical examination significantly narrow the differential diagnosis, the plain radiographs are minimally helpful until the bony erosion occurrs at the later stages of the disease.

Glomus tumor is a vascular entity, reflecting its typically dark on T1 and bright MRI appearance on T2 weighted images. Post-gadolinium and fat saturation images further delineate the mass. Although this signal pattern can be seen with any vascular tumor, the location at the digits and its small size should lead one to suspect glomus tumor in most cases.

With increased index of suspicion, carefully performed history and physical examination, along with the findings on the MRI, the treating orthopaedist can significantly decrease the pre-operative morbidity to the patient with glomus tumor.

BIBLIOGRAPHY

1. **Carroll, R.E.;** and **Berman, A.T.:** Glomus tumors of the hand. *J. Bone Joint Surg.,* 54A(4):691-703,1972.
2. **Fornage, B.D.:** Glomus tumors in the fingers: Diagnosis with US. Radiology, 167(1): 183-185, 1988.
3. **Heys, S.D.; Brittenden, J.; Atkinson, P.;** and **Eremin, O.:** Glomus tumor: An analysis of 43 patients and the review of the literature. *Br. J. Surg.,* 79:345-347, 1992.
4. **Matloub, H.S.; Muoneke, V.N.; Prevel, C.D.; Sanger, J.R.;** and **Yousif, N.J.:** Glomus tumor imaging: use of MRI for localization of occult lesions. *J. Hand Surg.,* 17A: 472-275, 1992.
5. **Mohler, D.G.; Lim, C.K.;** and **Martin, B.:** Glomus tumor of the plantar arch: A case report with magnetic resonance image findings. *Foot & Ankle Int.,* 18(10): 672-74, 1997.
6. **Rettig, A.C.;** and **Strickland, J.W.:** Glomus tumor of the digits. *J. Hand Surg.,* 2A (4):261-265, 1977.

CASE REPORT: PARAARTICULAR SOFT-TISSUE OSTEOMA OF THE HIP

John Holmen, M.D., M.S.E.E.*
Max A. Stevens, M.D.
George Y. El-Khoury, M.D.

ABSTRACT

A case of paraarticular soft-tissue osteoma of the hip is presented. The patient is a 30-year-old white male with a two year history of progressive left hip pain. Plain film and cross-sectional imaging in conjunction with pathologic correlation are used to make the diagnosis. The lesion lacks the typical zoning pattern of myositis ossificans, shows no direct communication with native bone, and is extraarticular in location as opposed to synovial osteochondromatosis. Soft tissue osteomas most commonly occur around the knee, the foot, and the ankle. Soft tissue osteomas are rare tumors and this case is unusual in that it occurs around the hip.

INTRODUCTION

Soft tissue osteomas are rare tumors containing both cartilaginous and osseous components. Reith et al recently reviewed 21 cases described as paraarticular osteochondroma which occurred around the knee (76%), the foot (19%), and the ankle (5%)[1]. Schweitzer et al reported two cases of soft tissue osteomas of the thigh[2]. Although the exact etiology of these lesions is unknown, it has been proposed that soft-tissue chondroma, myositis ossificans, soft-tissue osteochondroma, and soft-tissue osteoma lie on a spectrum related to soft tissue injury[2]. The radiologic and histologic appearances of these lesions differ based upon the relative amount and appearance of the osseous and cartilaginous components.

CASE REPORT

A 30-year-old white male with a two year history of progressive left hip pain, particularly with flexion and rotation, presented for evaluation. Plain radiographs showed a sclerotic lesion projecting over the femoral neck. MR imaging was interpreted as normal. Non-steroidal anti-inflammatory medications did not provide significant relief. His pain continued which began limiting his daily activities. One year after his initial evaluation a bone scan was performed because of persistent pain. This showed focal increased uptake adjacent to the left femoral neck. Plain films taken at this time showed findings consistent with myositis ossificans.

Approximately one year later he was evaluated at a different institution. Physical examination revealed no soft tissue or bony mass although an antalgic gait was present. Range of motion was limited. AP and lateral plain radiographs showed an ossified mass posterior to the left femoral neck which had enlarged in size from 2 years prior (Figure 1A). Subsequent CT examination demonstrated a densely ossified mass measuring 1.5cm by 1.5cm, directly adjacent to the posterior aspect of the femoral neck (Figure 1B). Because of interval growth, persistent pain, and limitation of motion, surgical excision was performed. Pathologic analysis showed a solitary mass composed of a mixture of regionally arranged woven and lamellar bone with peripheral cartilaginous components (Figure 1C). Radiographs at 6 and 12 months showed no recurrence.

DISCUSSION

Extraskeletal osseous and cartilaginous tumors of the extremities are rare. Benign osseous lesions include myositis ossificans, fibro-osseous pseudotumor, fibrodysplasia ossificans progressiva, and soft-tissue osteoma. Malignant osseous lesions include extraskeletal osteosarcoma. Benign cartilaginous lesions include soft-tissue chondroma, and the tumor-like process of osteochondromatosis. Malignant cartilaginous lesions include extraskeletal chondrosarcoma. The differential diagnosis for these extraskeletal cartilaginous and osseous lesions include soft-tissue sarcoma, benign mesenchymoma, malignant mesenchymoma, calcified gouty tophi, melorheostosis, pilomatrixoma (calcifying epithelioma of Malherbe), and tumoral calcinosis[3].

Department of Radiology, Musculoskeletal Division
University of Iowa Hospitals and Clinics
200 Hawkins Drive
Iowa City, IA 52242
phone (319) 356-1616
fax (319) 356-2220
email: holmen@avalon.net
*corresponding author

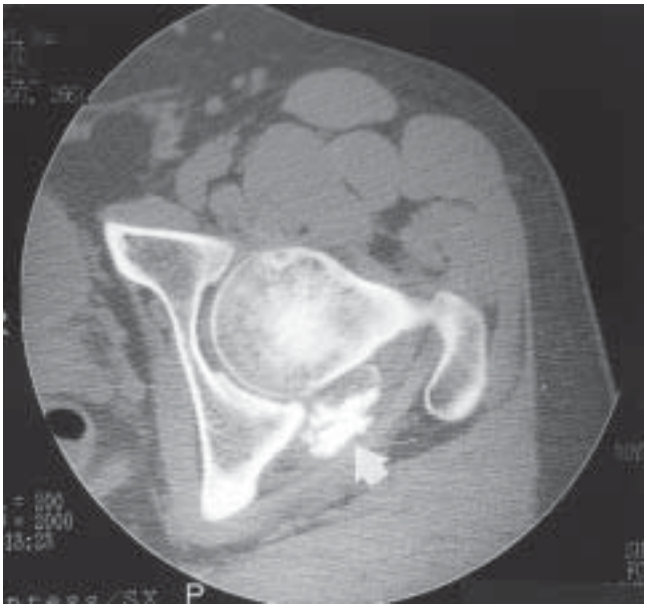


Figure 1A. AP radiograph shows an ossified mass adjacent to the posterior aspect of the femoral neck.

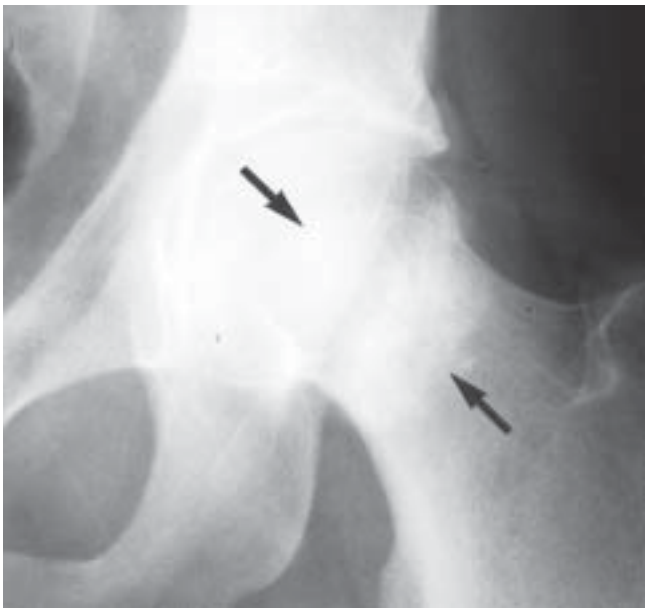


Figure 1B. CT scan done two days after A shows this ossified mass in greater detail. Note it is separate from the femur.

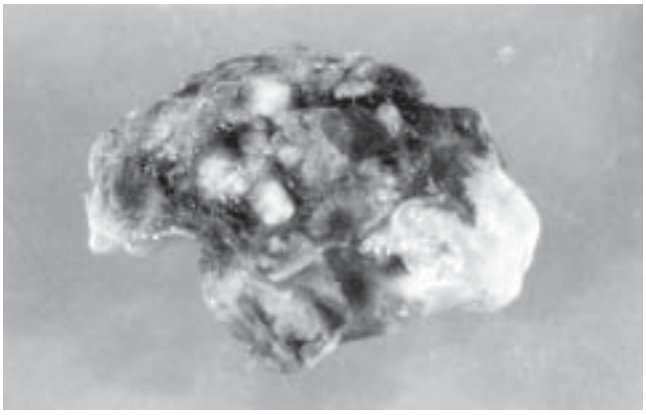


Figure 1C. Gross specimen taken ten days after B shows a solitary mass composed of a mixture of regionally arranged woven and lamellar bone with peripheral cartilaginous components.

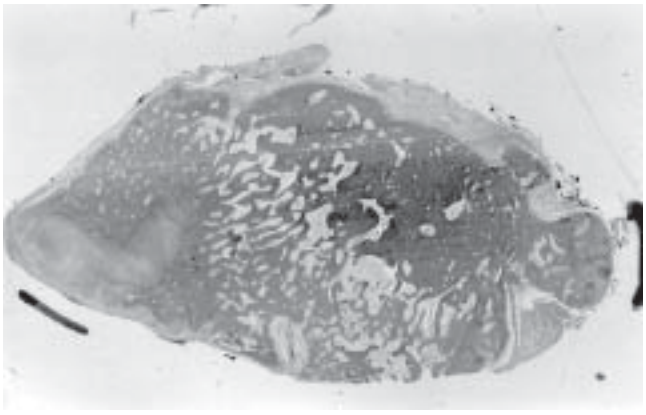


Figure 1D. Photomicrograph of C shows sheet-like areas and broad trabeculae of woven and lamellar bone. On higher magnification some chondrocyte atypia but no abnormal mitotic activity was seen.

Figures 1A-1D. 30-year-old man with hip pain and progressive limitation of motion over two years.

The terminology used to describe osteocartilaginous lesions is inconsistent and confusing. Soft tissue osteomas, osteochondromas, chondromas, and myositis ossificans form a spectrum of post traumatic ossifying soft tissue lesions[2]. Soft tissue osteoma, chondroma, and osteochondroma are characterized histologically by adult hyaline-type cartilage[4]. They differ from each other in the relative amounts and location of the cartilaginous tissue and in the maturity of the osseous tissues. Several cases of soft tissue osteoma have previously been described in the literature, most near the mouth. Two recently reported cases occurred in the soft tissues of the thigh[2]. Histologically soft tissue osteomas consist of mature lamellar bone with a predominantly cartilaginous capsule blending into benign hyaline cartilage[3]. Soft-tissue chondromas usually appear in the hands and feet and display at least focal areas of hyaline cartilage formation[3].

Paraarticular osteochondromas are seen in the soft tissues adjacent to a joint. The knee is the most common location, followed by the foot and ankle[1]. There are several shared histologic features of paraarticular

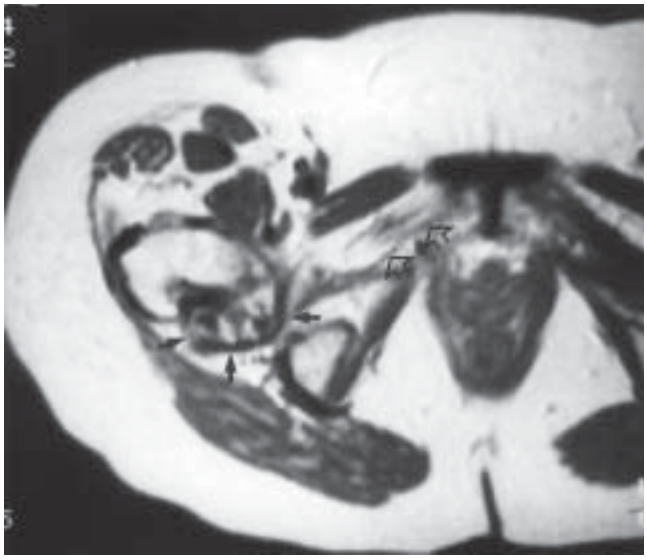


Figure 2. 56-year-old woman with chronic right hip pain. T1-weighted axial MR image of the pelvis shows atrophy of the obturator externus muscle (open arrows) due to compression by a soft tissue osteoma (arrows).

osteochondromas including peripheral cartilaginous areas surrounding central areas of lamellar or trabecular bone.

Differentiation of these different tumor types is possible when utilizing both radiographic and pathologic information. For example, on plain film myositis ossificans has a characteristic zoning pattern of ossification with areas of radiolucency within the central portion of the lesion and a denser rim at the periphery[3]. Cross sectional imaging will help to show the extraarticular location of a paraarticular osteochondroma as opposed to the intraarticular location of synovial osteochondromatosis. It also reveals that there is no direct continuity with native bone. In contrast to benign chondroid tumors, a soft tissue chondrosarcoma usually contains little or no recognizable hyaline cartilage[5,6]. Pain, limitation of motion, and atrophy are potential complications related to these soft tissue tumors (Figure 2).

Soft tissue osteoma of the hip is rare. Characteristic radiographic appearances should allow differentiation from other similar lesions but pathologic correlation may be required to make a confident and accurate diagnosis.

REFERENCES

1. **Reith, J.D.; Bauer, T.W.;** and **Joyce, M.J.:** Paraarticular osteochondroma of the knee. *Clin. Orthop.,* 334:225-232, 1997.
2. **Schweitzer, M.E.; Greenway, G.; Resnick, D.;** and **Haghighi, P.:** Osteoma of soft parts. *Skel. Rad.,* 21:177-180, 1992.
3. **Kransdorf, M.J.,** and **Meis J.M.:** Extraskeletal osseous and cartilaginous tumors of the extremities. *Radiographics,* 13:853-884 1993.
4. **Li, C.; Arger, P.H.;** and **Dalinka, M,K.:** Soft tissue osteochondroma. *Skel. Rad.,* 18:435-437, 1989.
5. **Reiman, H.M.,** and **Dahlin, D.C.:** Cartilage and bone forming tumors of the soft tissues. *Semin. Diagn. Pathol.,* 3:388-305, 1986.
6. **Hagan, P.F.,** and **Schoenecker, P.L.:** Paraarticular osteochondroma. *Am. J. Orthop.,* 1995; 1:65-67.

ALUMNI AND FACULTY LIST

The following list was generated from responses to a recent mailing, the Iowa Foundation database, and a review of our current Alumni list. In an effort to keep this list up to date and complete, we would appreciate notification of needed changes and additions.

Dr. John F. Abele (Retired)
1614 Northeast Hogan Drive
Gresham, OR 97030-4140

Dr. R. Marshall Ackerman
9715 Medical Center Drive #415
Rockville, MD 20850
Resident 1966 - 1969

Dr. Brian D. Adams
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Resident 1984 - 1987
Staff 1993 - Present

Dr. Cemil M. Adli
9400 Churchill Downs Dr.
Las Vegas NV 89117-7220

Dr. Seymour M. Albert
5401 Old York Road #200
Philadelphia, PA 19141
Resident 1940 - 1943

Dr. John P. Albright
Univ of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Staff 1971 - Present

Dr. Fernando P. Aleu
70 East 55 Street
New York, NY 10022
Fellow 1954 - 1955

Dr. James D. Alway
Address Unknown
Resident 1954-1957

Dr. Dennis J. Andersen
St. Mary's Medical Center
3807 Spring Street
Racine, WI 53405-9982
Fellow 1994-1995

Dr. Leon J. Armalavage (Retired)
509 Neopolitan Way
Naples, FL 33940
Fellow 1945 - 1946

Dr. J. Garcia Arosemena
Clinica San Fernando,
P.O. Box 461
Panama, 9A
Panama, CENTRAL AMERICA
Resident 1953 - 1955

Dr. Dennis R. Assenmacher
1050 Isaac St. Dr. #122
Oregon, OH 43616-3207
Resident 1970 - 1974

Dr. William A. Baird (Retired)
3911 Stone Brooke Circle
Ames, IA 50010
Resident 1948 - 1951

Dr. W. Timothy Ballard
Chattanooga Orthopaedic Group
2415 McCallie Ave.
Chattanooga, TN 37404
Resident 1990 - 1995

Dr. James M. Banovetz
2501 Main St.
Stevens Point, WI 54401
Fellow 1995-1996

Dr. M. Bruce Bardenstein (Retired)
6420 Hills Drive
Bloomfield Hills, MI 48301
Resident 1954 - 1957

Dr. Samuel Barley
Taylor Medical Arts Bldg. Box 601
Dubois, PA 15801

Dr. Robert M. Barnett
305 E. Nicollet Blvd., #282
Burnsville, MN 55337
Resident 1953 - 1956

Dr. Jorge M. Basora
Address Unknown

Dr. Robert L. Bass
Univ. of Texas SW Med Schl
5323 Harry Hines Blvd
Dallas, TX 75248
Resident 1988 - 1993

Dr. George S. Bassett
Mid-County Orthopaedics &
Sports Med.
621 S. New Ballas Road
St. Louis, MO 63141
Resident 1976 - 1981

Dr. Jerry R. Becker
1489 State Street
Salem, OR 97301
Resident 1962 - 1966

Dr. Lawrence Bell
173 Evergreen Tr.
Beaver Falls, PA 15010-1174
Fellow 1983 - 1984

Dr. Richard A. Berger
Mayo Clinic, Orthopaedic Surgery
200 First Street SW
Rochester, MN 55905
Resident 1984 - 1989

Dr. J. Sybil Biermann
Comprehensive Cancer Center
University of Michigan
2912 Taubman Center
1500 East Medical Center Drive
Ann Arbor, MI 48109-0328
Resident 1987 - 1992

Dr. John E. Bishop
1075 N Curtis Rd., #300
Boise, ID 83706-1309
Resident 1969 - 1972

Dr. Arcelino C.M. Bitar
R. Eduardo Guinle 23, Apt. 204
Rio de Janeiro
RJ 22260-090, BRAZIL
Fellow 1944 - 1945

Dr. Donald W. Blair
3600 30th St., VMAC
Des Moines, IA 50310
Resident 1948 - 1951

Dr. William F. Blair
Steindler Orthopaedic Clinic
2403 Towncrest Drive
Iowa City, IA 52240
Staff 1980 - 1997

Dr. Jamie Isidoro Blumenfeld
BERUTI 3340 P.16, "H"
Buenos Aires
ARGENTINA 1425

Dr. William G. Boettcher
1221 Madison #1012
Seattle, WA 98104
Resident 1966 - 1969

Dr. Susan K. Bonar
Rock Hill Medical Plaza North
6675 Holmes Rd. Suite 360, Floor 3
Kansas City, MO 64131
Resident 1989 - 1994

Dr. Daniel F. Borgen
103 Oakdale Bldg.
Robbinsdale, MN 55422
Resident 1970 - 1974

Dr. Wouter J. Bosch
2525 S. Union Avenue, Suite 300
Tacoma, WA 98405
Resident 1964 - 1969

Dr. Thomas R. Boyce
1530 N. 115th Street
Seattle, WA 98133
Resident 1972 - 1975

Dr. David W. Boyer
2805 5th Street #120
Black Hills Orthopaedic Clinic
Rapid City, SD 57701
Resident 1970 - 1975

Dr. Richard A. Brand
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Staff 1974 - Present

Dr. Celio D. Brandao
Universidade Federal Do Rio De Janeiro
Rio de Janeiro
RJ Cep 20531-070, BRAZIL
Resident 1954 - 1957

Dr. Mark P. Brodersen
4500 San Pablo Rd.
Jacksonville, FL 32224

Dr. John D. Broms
Ventura Orthopaedic & Sports Medical Group, Inc.
3525 Loma Vista Road
Ventura, CA 93003
Resident 1962 - 1965

Dr. Andew W. Brown
704 Vendom Lane
Ballwin, MO 63011
Fellow 1996 - 1998

Dr. George A. Brown
The University of New Mexico Health Sciences Center
Dept. of Orthopaedics & Rehabilitation
Albuquerque, NM 87131-5296
Fellow 1972 - 1976

Dr. S. Pearce Browning III
5 Case Street
Norwich, CT 06360
Fellow 1961

Dr. Joseph A. Buckwalter
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Fellow 1975 - 1978
Staff 1979 - Present

Dr. Suhall D. Bulos
American University Medical Ctr.
P.O. Box 113-6044
590 Rue Hamra
Beirut, LEBANON

Dr. Ronald K. Bunten
VA Medical Center
30th & Euclid
Des Moines, IA 50310
Resident 1965 - 1968

Dr. Thomas E. Cain
Address Unknown
Fellow 1960 - 1961

Dr. John J. Callaghan
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Resident 1978 - 1983
Staff 1990 - Present

Dr. Barbara J. Campbell
RD 4, P.O. Box 283
Somerset, PA 15501
Fellow 1984 - 1985

Dr. William N. Capello
541 Clinical Drive, Room 600
Indianapolis, IN 46202
Resident 1970 - 1973

Dr. Major Brian Carney
Shriners Hosp. for Crippled Children
1900 Richmond Rd.
Lexington, Kentucky 40502
Fellow 1986 - 1987

Dr. Ronald D. Carter
400 Kenne St.
Columbia, MO 65201
Resident 1970 - 1974

Dr. Charles Cassel
1414 W. Lombard St.
Davenport, IA 52804
Resident 1980 - 1985

Dr. William Catalona
1608 Cedar St.
Muscatine, IA 52761
Fellow 1954 - 1955

Dr. George H. Chambers (Retired)
HC 62, Box 559
Calico Rock, AR 72519
Fellow 1951 - 1952

Dr. Joseph B. Chandler
5671 Peachtree Dunwoody Rd., Suite 900
Atlanta, GA 30342

Dr. Laurette Chang
P.O. Box 1228
Honolulu, HI 96807

Dr. Christopher S. Chenault
1015 East 32nd Street, Suite 101
Austin, TX 78705
Resident 1968 - 1971

Dr. Marvin L. Chernow
1600 Esplanade, #G
Chico, CA 95926
Fellow 1954 - 1955

Dr. Charles R. Clark
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Staff 1979 - Present

Dr. Winfred H. Clarke (Retired)
1701 SE Oak Shore Lane
Portland, OR 97267-3628
Resident 1945 - 1947

Dr. Elliott A. Cobb
202 Lee Blvd.
Savannah, GA 31405
Fellow 1944 - 1944

Dr. Nathan Cohen
Address Unknown

Dr. Herbert G. Cohen
1 Linden Crest Dr.
Danbury, CT 06810
Fellow 1946 - 1947

Dr. Don A. Coleman
University of Utah Med. Center
50 No. Medical Dr.
Salt Lake City, UT 84132
Resident 1980 - 1984

Dr. Patrick M. Collalto
1100 Wescott Drive, Suite G-6
Flemington, NJ 08822
Fellow 1985 - 1986

Dr. Dennis K. Collis
1200 Hilyard, Suite 600
Eugene, OR 97401
Resident 1967 - 1970

Dr. Ben Colloff
1333 Jones St., #1510
San Francisco, CA 94109
Fellow 1946

Dr. Ralph H. Congdon
1414 W. Lombard St.
Davenport, IA 52804
Resident 1969 - 1972

Dr. Rololfo Consentino
Diagional 173 #2575
La Plata
ARGENTINA

Dr. Neil A. Conti
Transitional Program
Greenville Memorial Hospital
701 Grove Road
Greenville, SC 29605

Dr. William F. Conway
Medical Univ. of South Carolina
Dept. of Radiology
171 Ashley Ave.
Charleston, SC 29425
Resident 1981 - 1983

Dr. Douglas Cooper
312 E. Main St.
Marshalltown, IA 50158
Resident 1988 - 1993

Dr. Reginald R. Cooper
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Staff 1962 - Present

Dr. Ralph L. Cotton
Department of Orthopaedic Surgery
130 Vine St.
Denver, CO 80206-4627

Dr. Lewis N. Cozen
P.O. Box 350567
Los Angeles, CA 90035
Fellow 1935 - 1936

Dr. Mark G. Creighton
Southampton Ortho. Group 315
Meeting House Lane
Southampton, NY 11968
Resident 1991 - 1996

Dr. William F. DeCesare
431 E. Clairemont Ave
Eau Claire, WI 54701
Resident 1973 - 1977

Dr. Thomas DeCoster
Department of Orthopaedics
Univ. of New Mexico Medical Ctr.
Albuquerque, NM 87131-5296
Fellow 1985 - 1986

Dr. Donald W. Delahanty (Retired)
77 Nelson Street
Auburn, NY 13021
Resident 1952 - 1956

Dr. Randy G. Delcore
1335 N 380 W #200
Cedar City, UT 84720
Resident 1990 - 1995

Dr. Frederick R. Dietz
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Resident 1977 - 1984
Staff 1984 - Present

Dr. Julie Dodds
Michigan State University
Dept. of Surgery
2900 Hannah Blvd., Suite 104
East Lansing, MI 48824-1315
Fellow 1990 - 1991

Dr. Richard B. Donaldson
Suite E 580
Memorial Medical Bldg.
725 Glenwood Drive
Chattanooga, TN 37404

Dr. Wallace T. Dooley
Meharry Medical College
1005 18th Avenue North
Nashville, TN 37208
Fellow 1953 - 1955

Dr. William J. Dougherty
520 Valley View Drive
Moline, IL 61265
Resident 1964 - 1968

Dr. Daniel M. Downs
1010 Carondelet Drive, #426
Kansas City, MO 64114
Fellow 1981 - 1982

Dr. Randall F. Dryer
6818 Austin Center Blvd, #200
Austin, TX 78731-3165
Resident 1977 - 1982

Dr. Marvin H. Dubansky (Retired)
Iowa Orthopaedic Center, P.C.
411 Laurel Street, Suite 3300
Des Moines, IA 50314
Resident 1951 - 1954

Dr. John W. Durham
Northern Arizona
Orthopaedics, Inc.
77 West Forest Avenue, Suite 302
Flaggstaff, AZ 86001-1489
Fellow 1990 - 1991

Dr. Raymond L. Emerson
250 S. Cresecent Drive
Mason City Clinic
Mason City, IA 50401
Resident 1976 - 1979

Dr. George J. Emodi
1550 So. 126th Street
Omaha, NE 68144
Resident 1990 - 1995

Dr. William D. Engber
Univ. of Wisconsin Med Ctr.
600 Highland Avenue
Madison, WI 53792
Fellow 1976

Dr. Bobbi Farber
St. Francis Park Bldg. H, Suite 104
Columbia, GA 31904
Resident 1983 - 1988

Dr. C. Baring Farmer
Orthopaedic Medical Clinic
620 California Boulevard, Suite R
San Luis Obispo, CA 93401
Fellow 1965

Dr. Margaret J. Fehrle
312 E. Main St.
Marshalltown, IA 50158
Resident 1991 - 1996

Dr. Joseph Feinberg
Kessler Institute for Rehabilitation
Pleasant Valley Way
W. Orange, NJ 07052
Fellow 1986 - 1987

Dr. Ray H. Fenner
1103 38th East
Seattle, WA 98122
Resident 1964 - 1967

Dr. Richard Fitzsimmons
16661 Loie St.
Yorba Linda, CA 92886

Dr. Adrian E. Flatt
Baylor Univ. Medical Center
3500 Gaston
Dallas, TX 75246
Staff 1956 - 1979

Dr. Ernest M. Found
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Staff 1987 - Present

Dr. Thomas J. Fox
12738 Spruce Pond Rd.
Town & Country, MO 63131
Resident 1979 - 1984

Dr. Kermit W. Fox (Retired)
2809 Townes Lane
Austin, TX 78703
Postgraduate 1945 - 1946

Dr. Albert L. Freedman
10044 S. Ocean Dr., #1102
Jensen Beach, FL 34957-2450
Resident 1941 - 1944

Dr. Morris S. Friedman 1522
Meadow Trl.
South Bend, IN 46614
Fellow 1940 - 1041

Dr. Barry A. Friedman (Retired)
12396 Grande Ct.
San Diego, CA 92128
Resident 1947 - 1950

Dr. Edgar Frigerio
Arroyo 863
Buenos Aires
ARGENTINA
Fellow 1957 - 1958

Dr. Michael N. Fulton
Address Unknown
Resident 1974 - 1978

Dr. Thomas M. Fyda
845 Aitken St.
Reno, NV 89502
Resident 1991-1996

Dr. Kyle Galles
411 Laurel St., Suite 3300
Des Moines, IA 50314
Resident 1987 - 1991

Dr. Webster B. Gelman
2403 Towncrest Drive
Iowa City, IA 52240
Fellow 1946 - 1947

Dr. Timothy A. Gibbons
Mason City Clinic
250 S. Cresent
Mason City, IA 50401
Fellow 1994 - 1995

Dr. Robert Gitchell
1215 Duff Ave.
Ames, IA 50010
Resident 1968 - 1972

Dr. John A. Glaser
Medical Univ. of South Carolina
708 CBS 171 Ashley Ave.
Charleston, SC 29425
Fellow 1988 - 1989

Dr. James L. Gluck
Kansas Ortho Center
1507 West 21st Street
Wichita, Kansas 67203
Fellow 1990 - 1991

Dr. Devon Goetz
Des Moines Orthopaedic Surgeons
6001 Westown Parkway
W. Des Moines, IA 50266
Resident 1987 - 1992

Dr. Walter E. Gower
1000 E. 1st Street, #404
Duluth, MN 55805
Resident 1968 - 1971

Dr. Abron A. Grandia
2710 College Avenue
Alton, IL 62002
Resident 1958 - 1961

Dr. Avrum V. Gratch
1459 Greenwood
Berkeley, CA 94708-1935

Dr. Leon J. Grobler
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Staff 1996 - Present

Dr. Arnis B. Grundberg
6001 Westown Pky
West Des Moines, IA 50216
Resident 1966 - 1969

Dr. Gregory P. Guyton
1509 137th Avenue
San Leandro, CA 94578
Resident 1993 - 1998

Dr. James L. Guyton
1400 S. Germantown Rd.
Memphis, TN 38138
Resident 1985 - 1990

Dr. James G. Hackett
N84 W16889 Menomonie Ave.
Menomonie Falls, WI 53051
Resident 1974 - 1978

Dr. Bernard M. Halbstein
Address Unknown

Dr. Robert F. Hall
790 Wellington, #204A
Grand Junction, CO 81501

Dr. William Hamsa
609 Doctors Bldg.
Omaha, NE 68131
Fellow 1930 - 1931

Dr. Eugene J. Hanavan
77 Broadway St., #100
Buffalo, NY 14203-1642

Dr. Harris D. Hanson
1 Medical Park Drive
Helena, MT 59601
Fellow 1993

Dr. T. C. Harper
541 West Second Street
Reno, NV 89503
Fellow 1947

Dr. Irwin E. Harris
Section of Orthopaedic Surgery
Arizona Health Sciences Ctr.
Tucson, AZ 85724
Resident 1978 - 1982

Dr. William B. Harris
7445 Soland St.
Carlsbad, CA 92009
Resident 1956 - 1958

Dr. Robert A. Hart
Oregon Health Sciences
University Section of Spine Surgery
3183 S.W. Sam Jackson Park
Rd., L-477
Portland, OR 97201
Resident 1992 - 1997

Dr. Mark R. Harwood (Retired)
407 University Ave.
Syracuse, NY 13210
Fellow 1947 - 1948

Dr. James W. Hayes
316 North Graham-Hopedale Road
Burlington, NC 27215
Resident 1959 - 1962

Dr. Richard C. Henderson
CB # 7055 University of
North Carolina
Division of Orthopaedic Surgery
Chapel Hill, NC 27599
Resident 1980 - 1985

Dr. Ronald L. Henderson
Medford Orthopaedic Group
840 Royal Ave., Suite #1
Medford, OR 97504
Resident 1989 - 1990

Dr. Edgar O. Hicks
Ihle Orthopaedic Clinic, Ltd.
836 Richard Drive
Eau Claire, WI 54701
Resident 1974 - 1978

Dr. Daniel T. Hinkin
Address Unknown
Fellow 1988 - 1989

Dr. Howard P. Hogshead
1325 San Marco Blvd
Jacksonville, FL 32207
Resident 1960 - 1963

Dr. Jon D. Hop
Flat 4, Girdlestone Close
Headington, Oxford
England OX37NS
Resident 1992 - 1997

Dr. Gerald W. Howe (Retired)
2403 Towncrest Drive
Iowa City, IA 52240
Resident 1954 - 1959

Dr. John W. Hugus
3000 Westhill Dr., #300
Wausau, WI 54401
Resident 1982 - 1987

Dr. David D. Hunt
14911 National Avenue, Apt. 2
Los Gatos, CA 95032-2632

Dr. Shiro Inoue
Dept. of Orthopaedic Surgery
Kyoto Prefectural Univ. of Me.
Hirokog Kawaramachi
JAPAN

Dr. Richard L. Jacobs
Albany Medical College
47 New Scotland Avenue
Albany, NY 12208
Resident 1959 - 1965

Dr. Paul A. Jacobson
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195-5242
Fellow 1993-1994

Dr. Sylwester Jacubowski
Piekarska 5-9
00-264 Warsaw, POLAND

Dr. Stanley L. James
1200 Hilyard St., #5-600
Eugene, OR 97401
Resident 1964 - 1967

Dr. Jay C. Jansen
American Sport Medicine Institute
1313 13th St. South
PO Box 550039
Birmingham, Alabama 35255
Resident 1992 - 1997

Dr. Peter Jebson
Univ. of Michigan Med Center
Box 0328
Second Level Taubman Center
Ann Arbor, MI 48109-0328
Fellow 1995 - 1996

Dr. Jerry L. Jochims
600 N. Main
Burlington, IA 52601
Resident 1971 - 1975

Dr. Robert J. Johnson III
University of Vermont
Stafford Hall, Rm 426A
Burlington, VT 05405-0084
Resident 1965 - 1969

Dr. Richard C. Johnston
University of Iowa
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Resident 1964 - 1967

Dr. Michael L. Jones
414 San Antonio Medical Center
414 Navarro, Suite #809
San Antonio, TX 78205
Fellow 1989 - 1990

Dr. Mark Kabins
600 So Racho Drive, Suite 107
Las Vegas, NV 89106
Resident 1986 - 1991

Dr. R. Kumar Kadiyala
University of Iowa
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Staff 1998 - Present

Dr. David B. Kalayjian
51 S. Main Ct.
Middletown, CT 06457
Resident 1968 - 1972

Dr. Nathan Kaplan
945 Corsica Drive
Pacific Palisades, CA 90272-4011

Dr. Ralph P. Katz
Westside Orthopaedic Clinic
4500 10th St.
Marreo, LA 70072
Resident 1990 - 1995

Dr. Daniel O. Kayfetz (Retired)
P. O. Box 1453
San Ramon, CA 94583
Fellow 1945 - 1946

Dr. George Kemble, Jr.
P.O. Box 470305
Fort Worth, TX 76147-0305

Dr. Donald B. Kettelkamp (Retired)
Amer. Bldg. of Ortho. Surg., Inc.
400 Silver Cedar Ct.
Chapel Hill, NC 27514-1512
Resident 1958 - 1961

Dr. John J. Killeffer
4610 Chestnut St.
Signal Mountain, TN 37377

Dr. John P. Kim
1771 Rose Street
Regina, Saskatchewan
CANADA S4P 1Z4
Resident 1955 - 1958

Dr. Sydney Klein
3715 Warrensville Center Road
Cleveland, OH 44122

Dr. Thomas K. Kobayashi
7342 Northwest 38th Place
Coral Springs, FL 33065-2107

Dr. Robert J. Kolasky
4760 Belgar St., NW
Box 36959
Canton, OH 44735
Resident 1975 - 1979

Dr. Leo J. Koven (Retired)
340 Henry St.
Brooklyn, NY 11201
Fellow 1949 - 1950

Dr. James C. Krieg
Portland Orthopaedic Group
PO Box 23200
Portland, OR 97281
Resident 1990 - 1995

Dr. Frank E. Kugler
2934 Timbercrest Drive
Cincinnati, OH 45238
Fellow 1939 - 1941

Dr. Salvatore J. La Pilusa
858 Avenue "C"
Bayonne, NJ 07002
Fellow 1950 - 1951

Dr. Sterling J. Laaveg
250 S. Crescent Drive
Mason City, IA 50401
Resident 1974 - 1978

Dr. Michael D. Lahey
Parkside Professional Village
700 West Kent
Missoula, MT 59801
Fellow 1985 - 1986

Dr. Edward R. Lambert
1931 Tiari Drive
Ojai, CA 93023

Dr. Thomas A. Lange
Regents Hospital
640 Jackson Street
St. Paul, MN 55101-2595
Fellow 1992 - 1993

Dr. Keith J. Lassen
2010 59th West #4400
Bradenton, FL 33529
Resident 1970 - 1973

Dr. Edward G. Law
2403 Towncrest Drive
Iowa City, IA 52240
Resident 1979 - 1984

Dr. John W. Leabhart
2500 North Van Dorn Street
Alexandria, VA 22302
Resident 1955 - 1960

Dr. Thomas R. Lehmann
Louisville Orthopaedic Clinic
4130 Dutchman's Lane
Louisville, KY 40207

Dr. Paul D. Lesko
110 N. Thompson Church Rd.
Vidalia, GA 30474

Dr. Robert L. Lillo (Retired)
275 Darrell Road
Hillsborough, CA 94010
Resident 1956 - 1959

Dr. Thomas N. Lindenfeld
12115 Sheraton Lane
Springdale, OH 45246
Resident 1980 - 1984

Dr. John R. Lindstrom
820 E. Grant St.
Appleton, WI 54911
Resident 1972 - 1977

Dr. Paul R. Linquist
1720 El Camino Real, Suite 116
Burlingame, CA 94010
Resident 1966 - 1970

Dr. M. F. Longnecker
P.O. Box 4720
Biloxi, MS 39535
Fellow 1967 - 1968

Dr. Juan C. Lorenzo
37 Copernino
Barcelona, SPAIN

Dr. Chester S. Lowendorf
284 Granada Avenue
Youngston, OH 44504-1820

Dr. Don A. Lowry
2 Celeste Dr.
Johnstown, PA 15905
Resident 1979 - 1984

Dr. James R. MacKenzie
Address Unknown

Dr. Steven M. Madey
Portland Orthopaedic Group
PO Box 23200
Portland, OR 97281
Resident 1991 - 1996
Fellow 1996 - 1997

Dr. Thomas P. Malvitz
750 E Beltline N.E., #301
Grand Rapids, MI 49506
Resident 1982 - 1987

Dr. J. L. Marsh
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Staff 1987 - Present

Dr. E. Byron Marsolais
2074 Abington Road
Cleveland, OH 44106
Resident 1961 - 1970

Dr. Joseph G. Martin
Orthopaedic Surgery Assoc., PC
1414 W. Lombard
Davenport, IA 52804
Resident 1988 - 1993

Dr. James S. Martin
American Sports Medicine Institute
1313 13th Street South
Birmingham, AL 35205
Resident 1993 - 1998

Dr. Mark McAndrew
Vanderbilit University
T-4311 Medical Center N.
Nashville, TN 37232-2550
Resident 1978 - 1983

Dr. Andrew A. McBeath
G5/361, 600 Highland Avenue
Madison, WI 53792-3228
Resident 1963 - 1966

Dr. Donovan L. McCain
655 Sibley Memorial Hwy.
St. Paul, MN 55118
Fellow 1940 - 1941

Dr. Edward F. McCarthy
The Johns Hopkins Hospital
Dept. of Pathology
600 North Wolfe Ave.
Baltimore, MD 21287

Dr. Thomas D. McClain
Orthopaedic Associates Inc.
2115 South Freemont, Suite 1000
Springfield, MO 65804
Resident 1985 - 1990

Dr. Robert S. McClintock
Orthopaedic Surgeon Med. Consultant
2110 E. Flamingo Road, #105
Las Vegas, NV 89119
Resident 1952 - 1955

Dr. Stuart B. McConkie
215 Ridge Once Cir.
Hot Springs, AR 71901
Resident 1955 - 1958

Dr. Robert E. McCoy (Retired)
Mason City Clinic
250 S. Crescant Dr.
Mason City, IA 50401
Resident 1956 - 1960

Dr. Fred J. McGlynn
1800 Glenside Drive, Suite 101
Richmond, VA 23226
Resident 1976 - 1981

Dr. Robert F. McLain
Cleveland Clinic Foundation
9500 Euclid Ave Desk A41
Cleveland, OH 44195
Resident 1984 - 1990

Dr. Orin P. McMillan
9859 W IH 10, Ste 600
San Antonio, TX 78230-2295

Dr. Paul D. McNally
Red Cedar Clinic
211 Stout Road
Menomonie, WI 45751
Fellow 1997 - 1998

Dr. Fred G. McQueary
Orthopaedic Associates, Inc.
2115 South Freemont, Suite 1000
Springfield, MO 65804
Resident 1980 - 1985

Dr. Gerald L. Meester
444 N. Grandview Ave.
Dubuque, IA 52001
Resident 1971 - 1975

Dr. Steven D. Meletiou
May Clinic
Department of
Orthopaedic Surgery
Rochester, MN 55901
Resident 1993 - 1998

Dr. Paul M. Melvin
2800 11th Ave. South
Great Falls, MT 59405
Resident 1968 - 1971

Dr. Matthew Mendelsohn
c/o Scott Mendelsohn
580 Solano Avenue
Sonoma, CA 95476-6135

Dr. Alan C. Merchant
2500 Hospital Drive Bldg. #7
Mountain View, CA 94040
Resident 1959 - 1962

Dr. Thomas C. Merchant
151 N. Sunrise Ave., #1005
Roseville, CA 95661-2930
Resident 1983 - 1988

Dr. Albert J. Meyer
1245 Wilshire Blvd., Ste. 804
Los Angeles, CA 90052
Resident 1955 - 1959

Dr. Michael R. Mickelson
560 Memorial Drive
Pocatello, ID 83201
Resident 1973 - 1977

Dr. William R. Miely
3600 Olentangy River Road
14 Bldg B
Columbus, OH 43214
Fellow 1987 - 1988

Dr. Nancy Hadley-Miller
Johns Hopkins Medical Center
Department of Orthopaedics
601 N. Caroline St.
Baltimore, MD 21287-0882
Fellow 1987 - 1989

Dr. Thomas R. Miller
1250 Lakewood Drive
Lexington, KY 40502-2528

Dr. Ray F. Miller
P. O. Box 3026
Cedar Rapids, IA 52406
Resident 1969 - 1972

Dr. Leo J. Miltner (Retired)
1104 Kimberly Road
Bettendorf, IA 52722
Fellow 1926 - 1930

Dr. Leslie Mintz
701 South Tico Road
Ojai, CA 93023
Fellow 1990 - 1991

Dr. Sinesio Misol
411 Laurel St., #3300
Des Moines, IA 50314
Resident 1966 - 1971

Dr. Craig Mohler
Orthopedic & Fracture Clinic
1200 Hilyard
Eugene, OR 97401-8820
Resident 1986 - 1991

Dr. William J. Montgomery
21 SW 23RD TER
Gainesville, FL 32607-3156

Dr. John T. Moor
943 South Beneva Road, Suite 313
Sarasota, FL 34232-2473

Dr. Gordon M. Morrison
Box 1026
Pinecrest, CA 95364

Dr. Seymour Morse
4225 Point La Vista Rd W.
Jacksonville, FL 32207-6247

Dr. J. Michael Moses
2 Celeste Drive
Johnstown, PA 15905
Resident 1971 - 1975

Dr. Joseph C. Mulier (Retired)
Schapenstraat 101
B 3000 Leuven
BELGIUM
Resident 1950 - 1954

Dr. Joseph S. Mulle
86-50 164th St.
Jamacia, NY 11432
Fellow 1940 - 1941

Dr. Brian Mulliken
8322 Bellona Ave
Towson, MD 21204
Resident 1988 - 1993

Dr. Joseph E. Mumford
909 Mulvane Avenue
Topeka, KS 66606-168
Resident 1986 - 1991

Dr. David G. Murray
550 Harrison Center #100
Syracuse, NY 13202
Resident 1959 - 1962

Dr. Peter M. Murray
Univ. of South Carolina
School of Med.
Dept. of Orthopaedics
2 Richland Medical Park, #404
Columbia, SC 29203

Resident 1985 - 1990

Dr. Mark Mysnyk
Steindler Orthopedic Clinic
2403 Towncrest Drive
Iowa City, IA 52240

Resident 1983 - 1988

Dr. Charles I. Nadel
9 Colt Rd.
Summit, NJ 07901

Fellow 1947 - 1948

Dr. David Naden
600 Edwards Ave.
Frankfort, MI 49635

Resident 1968 - 1971

Dr. David A. Neal (Retired)
2172 Blackmore Ct.
San Diego, CA 92109

Fellow 1973 - 1974

Dr. Duane K. Nelson
Nelson Orthopaedics PC
2918 Hamilton Blvd., Lower D
Sioux City, IA 51104

Resident 1978 - 1981

Dr. Benjamin Nelson
101 Marilyn Avenue
Goshen, IN 46526

Resident 1981 - 1986

Dr. James V. Nepola
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242

Staff 1984 - Present

Dr. Kenneth E. Newhouse
560 Memorial Drive
Pocatello, Idaho 83201

Resident 1987 - 1992

Dr. Mary Lynn Newport
22 Avon Rdg.
Avon, CT 06001-4039

Fellow 1988 - 1989

Dr. Jeroen G. Neyt
Chase Farm Hospital
The Ridgeway, Enfield
Middlesex EN2 KJL
United Kingdom

Fellow 1997 - 1998

Dr. P. James Nichols
106 North Country Club Drive
Phoenix, AZ 85014-5443

Dr. Nina Njus
4248 Granger RD.
Akron, OH 44313

Resident 1980 - 1986

Dr. Kenneth J. Noonan
Indiana University Med Cntr
Dept. of Orthopaedic Surgery
702 Barnhill Drive
Indianapolis IN 46202-5215

Resident 1989 - 1994
Fellow 1994 - 1995

Dr. Benjamin E. Obletz (Retired)
800 W. Ferry St.
Buffalo, NY 14222

Resident 1935 - 1937

Dr. Larry D. Olson
940 N. Marr Rd.
Columbus, IN 47201

Resident 1975 - 1980

Dr. William R. Osebold
Sacred Heart Doctors Bldg., #6060
W. 105 8th Avenue
Spokane, WA 99204

Resident 1975 - 1979

Dr. David M. Oster
Denver Orthopaedic Clinic, P.C.
1601 E. 19th Avenue, Suite 500
Denver, CO 80218

Resident 1984 - 1989

Dr. Lewis Oster
Hand Surgery Associates, P.C.
2535 S. Downing, Suite 500
Denver, CO 80210

Fellow 1987 - 1988

Dr. Bernard D. Packer (Retired)
11823 Coal Bridge Ln.
Richmond, VA 23233-3438

Fellow 1939 - 1940

Dr. Gregory R. Palutsis
1144 Wilmette Avenue
Wilmette, IL 60091

Fellow 1986 - 1987

Dr. Kent M. Patrick
2715 K St., #A
Sacramento, CA 95816-5113

Resident 1973 - 1977

Dr. Luis Piedrahita
P.O. Box 2821
Orthopedia-Traumatologia
Quito, ECUADOR

Dr. Raymond O. Pierce, Jr.
960 Locke Street
Indianapolis, IN 46202

Fellow 1961 - 1962

Dr. Patrick A. Plunkett
1231 Blair Avenue
South Pasadena, CA 91030-3505

Dr. Fred A. Polesky
414 N. Camden Dr., # 1000
Beverly Hills, CA 90210

Resident 1937 - 1939

Dr. Ignacio Ponseti
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242

Staff 1946 - Present

Dr. David Pope
308 Park Place Dr.
Alexandria, LA 71301

Dr. Howard W. Popp
343 Walmar Drive
Bay Village, OH 44140

Fellow 1991 - 1992

Dr. Robert E. Porter
Hilltop Old Coach Rd
Norwich, UT 05055
Resident 1963 - 1967

Dr. Laura J. Prokuski
University of Wisconsin
Division of Orthopaedic Surgery
600 Highland Ave.
Madison, WI 53792
Resident 1992 - 1997

Dr. Michael T. Pyevich
Nemours Children's Clinic
Arnold Palmar Hospital
83 West Columbia
Orlando, FL 32856
Resident 1993 - 1998

Dr. Robert M. Rankin (Retired)
4441 SW Greenlead Dr.
Portland, OR 97221
Resident 1950 -1954

Dr. Douglas S. Reagan
Des Moines Orthopaedic Surgeons
6001 Westown Pkwy.
W. Des Moines, IA 50266
Resident 1973 - 1978

Dr. Williams J. Robb III
1000 Central St., #880
Evanston, IL 60201-1702
Resident 1972 - 1975

Dr. Edwin G. Robinson
3777 Parkwood Way
West Linn, OR 97068

Dr. Andrew P. Robinson
4601 Henry Hudson Pkwy, #A-15
Riverdale, NY 10471
Fellow 1992 - 1993

Dr. Bertil Romanus
Orthopaedic Department
Ostra sjukhuset S-416 85
Goteborg SWEDEN
Visiting Prof. 1981 - 1982

Dr. Irwin E. Rosen
38690 Stivers St., #A
Fremont, CA 94539
Fellow 1954 - 1955

Dr. Myron G. Rosenbaum
200 Oak Street N.E.
Albuquerque, NM 87106
Fellow 1937 - 1938

Dr. Robert T. Rosenfeld
455 N. Roxbury Drive
Beverly Hills, CA 90210

Dr. Randy N. Rosier
Dept. of Ortho., Univ. of Rochester
601 Elmwood Avenue
Rochester, NY 14642
Resident 1978 - 1984

Dr. Francis B. Roth
1165 Park Ave.
New York, NY 10128

Dr. Richard A. Ruffin
Orthopaedic Associates, Inc.
3301 Northwest 50th Street
Oklahoma City, OK 73112-5691
Resident 1985 - 1990

Dr. Richard E. Saar
8875 La Mesa Blvd., #A
La Mesa, CA 92041
Resident 1956 - 1959

Dr. Charles L. Saltzman
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Staff 1991 - Present

Dr. Jan C. Sarnecki
1416 S. Commercial St.
Neenah, WI 54956
Resident 1970 - 1973

Dr. Andrea Saterbak
St. Croix Orthopaedics
1701 Curve Cross Blvd.
Stillwater, MN 55082
Resident 1992 - 1997

Dr. John J. Schaffer
4024 N. Witchduck Dr.
Virginia Beach, VA 23455-5615
Fellow 1987 - 1988

Dr. David D. Scherr
725 Kaylyn Drive
Jefferson City, MO 65101
Resident 1960 - 1967

Dr. Maurice D. Schnell
1351 W. Central Park, #420
Davenport, IA 52804
Resident 1961 - 1964

Dr. Kary R. Schulte
14052 Lakeshore Dr.
Clive, IA 50325
Resident 1989 - 1994

Dr. Kim R. Sellergren
Tuckahoe Orthopaedic
Associates, Ltd.
8919 Three Chopt Road
Richmond, VA 23229
Resident 1976 - 1981

Dr. William O. Shaffer
St. Louis University
3635 Vista at Grand Blvd.
St. Louis, MO 63110-0250
Fellow 1986 - 1987

Dr. Nathan Shechter
5701 W. 119th St., Ste. 308
Overland Park, MO 66209

Dr. Russell N. Shroyer
Veterans Administration Hospital
2615 E Clinton
Fresno, CA 93703
Resident 1950 - 1953

Dr. John J. Silensky
P.O. Box 1110
Johnstown, PA 15907-1110

Dr. Herbert M. Simonson
10 Tower Drive
Maplewood, NJ 07040-1008

Dr. John E. Sinning, Jr.
1414 W. Lombard St.
Davenport, IA 52804
Resident 1961 - 1964

Dr. Edward J. Sitz (Retired)
394 Carolina Meadows Villa
Chapel Hill, NC 27514-7522
Resident 1953 - 1959

Dr. Bruce D. Smith
3107 Frederick Ave
St. Joseph, MO 64506
Fellow 1987 - 1988

Dr. Koert R. Smith
600 N. Main
Burlington, IA 52601
Resident 1972 - 1976

Dr. Eugene N. Smoley
P.O. Box 2794
Rancho Santa Fe, CA 92067
Resident 1958 - 1961

Dr. Robert P. Soiseth (Retired)
West Star Route, Box 104C
Two Harbors, MN 55616
Resident 1962 - 1965

Dr. Earnest E. Somers
355 Roland Avenue
Chambersburg, PA 17201-1447

Dr. Edward C. Spencer
201 E 5900 S, #206
Salt Lake City, UT 84107-7379

Resident 1971 - 1975

Dr. Adrienne A. Spirit
Dept. of Orthopaedic Surgery
The Mayo Clinic 200 1st St, SW
Rochester, MN 55905
Fellow 1993 - 1995

Dr. Bruce L. Sprague
148 East Ave.
Norwald, CT 06851
Fellow 1958 - 1968

Dr. Curtis M. Steyers
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Staff 1985 - Present

Dr. S. Jack Sugar
Address Unknown

Dr. Patrick Sullivan
Des Moines Orthopaedic Surgeons
6001 Westown Pkwy.
W. Des Moines, IA 50266
Resident 1981 - 1986

Dr. Stanley S. Tanz
Address Unknown

Dr. Jorge Tapia (Retired)
Eurogar B 20 Las Rozas
Madrid, SPAIN

Dr. David S. Tearse
Univ. of Iowa Hopsitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Staff 1989 - Present

Dr. Kathi F. Teixeira
Auburn Memorial Med. Bldg.
77 Nelson St.
P.O. Box 157
Auburn, NY 13201
Fellow 1993 - 1994

Dr. L. Eugene Thornburg
20 McDowell Street
Asheville, NC 28801
Resident 1989 - 1994

Dr. Jeffrey Tiedeman
GIKK
7710 Mercy Rd, #500
Omaha, NE 68124
Fellow 1992 - 1993

Dr. James E. Tozzi
106 Irving St., N.W., #318
Washington, D.C. 20010
Fellow 1984 - 1985

Dr. Laura Trombino
3722 Greysolon Rd.
Duluth, MN 55804
Resident 1984 - 1990

Dr. Steven L. Tuck
9715 Medical Center Dr. #415
Rockville, MD 20850
Resident 1975 - 1980

Dr. James W. Turner
Iowa Medical Clinic
600 7th ST SE
Cedar Rapids, IA 52401-2112
Resident 1967 - 1970

Dr. James Van Olst
3855 NW Lincoln Avenue
Corvallis, OR 97330
Resident 1959 - 1963

Dr. John A. Vann
1050 Grove Rd.
Greenvill, SC 29615
Fellow 1946

Dr. Mark D. Visk
323 N. Pine Street
Spartanburg, SC 29302
Resident 1981 - 1986

Dr. Edward M. Voke
3340 Providence Drive, #564
Anchorage, AK 99508
Resident 1963 - 1966

Dr. Donald J. Walla
Lincoln Orthopedic & Sports Med. Clinic
6920 Van Dorn
Lincoln, NE 68506
Fellow 1982 - 1983

Dr. Robert J. Walsh
1120 N. Arlington Heights Road
Arlington Heights, IL 60004
Fellow 1966

Dr. Thomas R. Walsh
St. Francis Medical Park Building H, Suite 104
Columbus, GA 31904-7991
Resident 1983 - 1988

Dr. Harry D. Wassel
6352 33rd Avenue Court N.
St. Petersburg, FL 33710-2410

Dr. Kristy L. Weber
Univ. of Texas
MD Anderson Cancer Center
Dept. of Surg. Oncology Box 106
1515 Holcombe
Houston, TX 77030
Resident 1991 - 1996

Dr. Marwan A. Wehbe
988 Garrett Mill Rd.
Newtown Square, PA 19073

Dr. James N. Weinstein
Dartmouth Medical School
7251 Strasenburgh Hall, Rm. 309
Hanover, NH 03755-3863
Staff 1983 - Present

Dr. Stuart L. Weinstein
Univ. of Iowa Hospitals & Clinics
Dept. of Orthopaedic Surgery
Iowa City, IA 52242
Resident 1973 - 1976
Staff 1976 - Present

Dr. Andrew B. Weiss
100 Bergen Street
Newark, NJ 07103
Resident 1968 - 1970

Dr. Dennis R. Wenger
3030 Childrens Way, #410
San Diego, CA 92123
Resident 1971 - 1975

Dr. Mark E. Wheeler
2616 Pierce St.
Sioux City, IA 51104
Resident 1975 - 1980

Dr. William R. Whitmore
1414 W. Lombard St.
Davenport, IA 52804
Resident 1960 - 1963

Dr. Leo V. Willett
140 Green Road
Meriden, CT 06450
Fellow 1963 - 1964

Dr. Eugene S. Willett Jr.
38 Peach Knob Drive
Asheville, NC 28804
Resident 1970 - 1974

Dr. Todd M. Williams
Rice Clinic
Stevens Point WI 54481
Resident 1993 - 1998

Dr. Lenita Williamson
Address Unknown
Fellow 1993 - 1994

Dr. Cathy Jo Wilson
Department of Anesthesiology
Bristol Royal Infirmary
Bristol BS28HW
ENGLAND

Dr. Randall R. Wroble
Sports Medicine Grand
323 East Town St.
Columbus, OH 43215-4676
Resident 1982 - 1987

Dr. Thomas K. Wuest
Ortho & Fracture Clinic
of Eugene, P.C.
1200 Hilyard Street, Suite 600
Eugene, OR 97401
Resident 1987 - 1992

Dr. Stephen A. Yoder
1100 Surrey Circle
Ashland, OH 44805
Resident 1977 - 1982

Dr. William Zaayer (Retired)
11851 Saint Bernard Dr.
Truckee, CA 96161
Fellow 1962- 1966

Dr. Debra Zillmer
Gundersen Clinic
1836 South Avenue
LaCrosse, WI 54601
Fellow 1989 - 1990

Department of Orthopaedics
1998-99

(Starting front, left to right) Stuart L. Weinstein, Matthew B. Dobbs, Erin E. Forest, Reginald R. Cooper, Rola H. Rashid, John P. Albright, Haemish A. Crawford, Joffrey T. Thompson, Dennis P. Weigel, Darron M. Jones, Richard A. Brand, Charles L. Saltzman, Curtis M. Steyers, David S. Tearse, Alfonso Osuna, Brian D. Adams, Michael R. O'Rourke, Sean B. Kaminsky, Lisa M. Coester, R. Dow Hoffman, Peter D. Pardubsky, Jose A. Morcuende, Mark J. Spoonamore, Stephen L. Knecht, John J. Callaghan, Steven A. Herbst, Frederick R. Dietz, Gregory N. Lervick, Daniel C. Fitzpatrick, Joseph G. Khoury, Leon J. Grobler, Kumar Kadiyala, David K. Sneller, Brian R. Wolf, Scott R. Stevens, Paul A. Watson, Ernest M. Found