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2. A **bibliography,** alphabetical and double-spaced, or references made in text only. Refer to bibliographies in this copy of *The Journal* and follow style exactly.
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Preparation of manuscript: Manuscripts must be typewritten, double-spaced with wide margins. Write out figures under 100 except percentages, degrees, or figures 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 less than two years' follow-up be accepted.

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1972-1973

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ORTHOPAEDIC EDUCATIONAL ENDOWMENT FUND

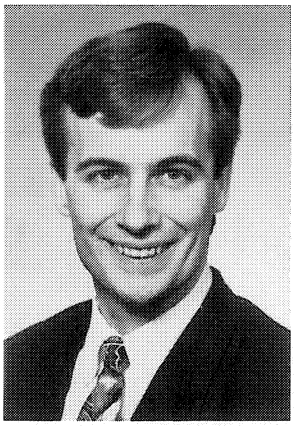
In honor of Dr. Michael Bonfiglio's distinguished career in teaching, patient care and research, University of Iowa students, orthopaedic residents, colleagues and friends initiated a campaign for the Bonfiglio Orthopaedic Education Endowment in 1994. This endowment will serve as permanent recognition of Dr. Bonfiglio's commitment to the department as well as provide a variety of educational materials and activities for the fellows, residents, and students. Specifically the resources from the endowment will be used for individualized and small-group student and resident educational programs, sponsorship of the Bonfiglio Visiting Professorship, and the continual upgrading of educational resources. The Education Center in the new department 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 only the earnings from the Bonfiglio endowment will support the center's educational activities. In this way, the center will enhance training opportunities for medical students, orthopaedic residents and fellows, clinicians and allied health care personnel at the University of Iowa for years to come. As of April 5, 1995, $192,728 had been raised toward the goal of $250,000.

The Education Center will be formally dedicated to Dr. Bonfiglio September 21-23 at the University of Iowa Orthopaedic Alumni Meeting. Please make plans to donate to the fund and attend the meeting this fall.

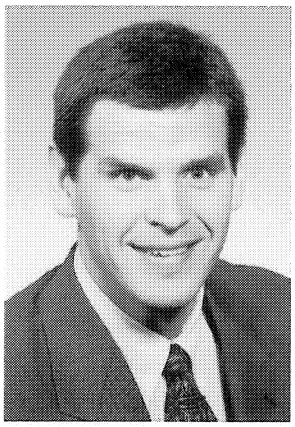
Gifts and pledges to the Endowment should be directed to the University of Iowa Foundation and qualify as charitable contributions.

1995 GRADUATING SENIOR RESIDENTS



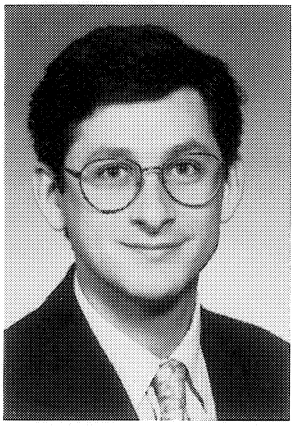
W. Timothy Ballard, M.D.
Tim was born in Dayton, Ohio, on April 1, 1965. There he attended Wright State University where he received a B.S. in Biology. Subsequently he received his M.D. from the University of Cincinnati College of Medicine in 1990, soon after marrying his wife Lorrie. During residency, they were blessed with two children, their son Brandon, born February 10, 1991, and daughter Jaime, born September 5, 1993. Next year, Tim will be an Adult Reconstructive Fellow at Rush-Presbyterian Hospital in Chicago under the direction of Dr. Jorge Galante.

Ralph P. Katz, M.D.
Ralph was born and raised in New Orleans, LA. He graduated from Tulane University in 1983 with a B.S. in Biology and then obtained a M.S. in Anatomy in 1987. He attended Tulane University School of Medicine and received his M.D. in 1990. The following year, Ralph did a surgical internship at CHNO. His plans for next year include a general fellowship at the University of Iowa with emphasis on Trauma and Spine. He plans to return New Orleans to practice general Orthopaedics.



George J. Emodi, M.D.
M.D.
George was raised in the midwest and considers Omaha his home. He graduated from the University of Nebraska in 1986 with a B.S. in Chemistry. He received his M.D. from the University of Nebraska College of Medicine in 1990. Next year George, his wife Maureen and children Matthew and Margaret plan to return to Omaha where George will start a general Orthopaedic practice.

Randy G. Delcore, M.D.
Randy was born and raised in Plattsburgh, New York. He graduated from the State University of New York at Albany in 1986 with a B.S. degree in Biology. He then attended Jefferson Medical College in Philadelphia, PA and received his M.D. in 1990. Upon completing his Orthopaedic residency training, Randy will pursue a general Orthopaedic practice in Cedar City, Utah.



James C. Krieg, M.D.
Jim was born and raised in Morristown, New Jersey. After receiving a B.A. from Northwestern University he returned to New Jersey to attend the New Jersey Medical School. Next year he will be moving to Seattle, Washington to complete a fellowship in Orthopaedic Traumatology at Harborview Medical Center.

DEPARTMENT OF ORTHOPAEDIC SURGERY
LECTURESHIPS AND CONFERENCES

TITLE and GUEST SPEAKERS

The Iowa Orthopaedic
Alumni Association
October 21-23, 1993

Dempsey S. Springfield, M.D.
Massachusetts General Hospital
Boston, MA

James Herndon, M.D.
University of Pittsburgh
Pittsburgh, PA

Richard Hawkins, M.D.
University of Colorado
Vail, CO

Hand Surgery Lectures
November 11-12, 1993

Adrian E. Flatt, M.D.
University of Texas
Dallas, Texas

Sports Medicine Symposium
November 18-20, 1993

Ronald Losee, M.D.
Ennis, MT

William Post, M.D.
West Virginia University Hospitals
Morgan town, WV

Camp Lectureship in Spinal Disorders
December 10, 1993

Steven Garfin, M.D.
University of California
San Diego, CA

Carroll B. Larson Shrine Memorial Lecture
April 8-9, 1994

J. Anthony Herring, M.D.
University of Texas
Dallas, Texas

Senior Residents' and Fellows' Days
June 10-11, 1994

Robert D. D'Ambrosia, M.D.
Louisiana State University
New Orleans, LA

Herbert Kaufer, M.D.
University of Kentucky
Lexington, KY

TITLE and GUEST SPEAKERS

Johnston Lectureship in Hip Reconstruction
October 7-8, 1994

Jorge O. Galante, M.D.
Rush-Presbyterian-St. Luke's Medical Center
Chicago, IL

William N. Capello, M.D.
University of Indiana
Indianapolis, IN

Camp Lectureship in Spinal Disorders
November 8, 1994

Henry Bohlman, M.D.
University Hospitals
Cleveland, OH

Carroll B. Larson Shrine Memorial Lecture
February 3-4, 1995

William Cole, MBBS, MSC, Ph.D., FRCAS, FRCSC
University of Toronto
Toronto, Canada

Senior Residents' and Fellows' Days
May 26-27, 1995

Richard D. Coutts, M.D.
University of California
San Diego, CA

Lawrence D. Dorr, M.D.
University of Southern California School of Medicine
Los Angeles, CA

Michael Bonfiglio Iowa Orthopaedic Alumni Meeting
September 21-23, 1995

Robert H. Cofield, M.D.
Mayo Clinic
Rochester, MN

Edward McCarthy, M.D.
Johns Hopkins Hospital
Baltimore, MD

Russell Warren, M.D.
Hospital for Special Surgery
New York, NY

James Urbaniak, M.D.
Duke University
Durham, NC

EDITORS' NOTE

Welcome to the fifteenth edition of the *Iowa Orthopaedic Journal*! The primary purpose of this publication is education, and we hope that all who read this edition will benefit in some way from the listed articles. The 1995 *Journal* contains the largest collection of articles in the history of the publication. 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.

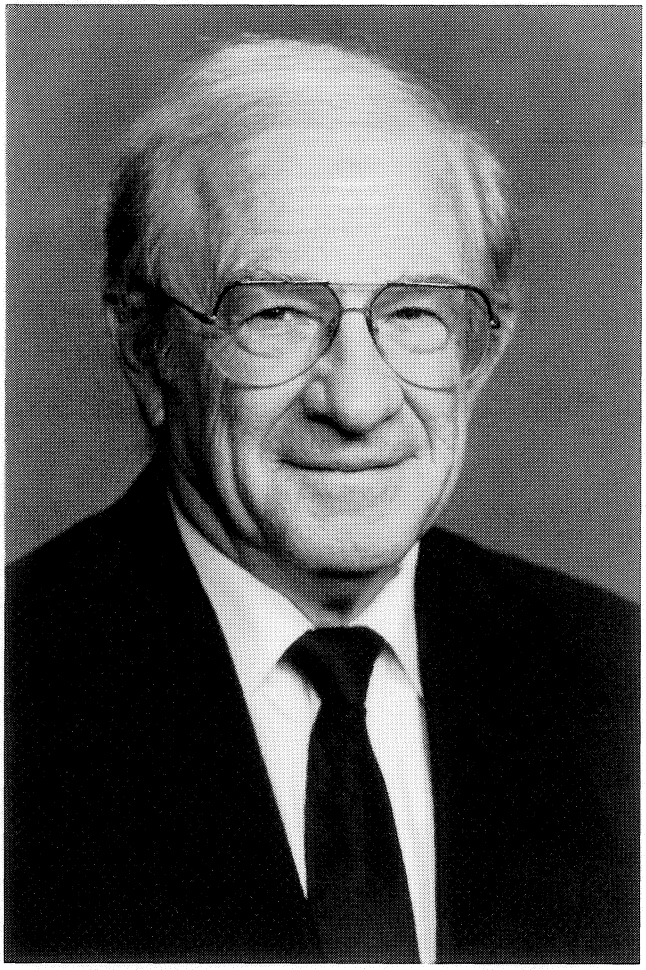
The fifteenth edition also marks the first time the *Journal* will be referenced in the *Index Medicus*. This publication has a longstanding reputation for high quality and is now being recognized internationally as such.

Our goal this year was to compile a variety of articles covering a wide spectrum of orthopaedic issues. We feel this was a success as you will find topics in the subspecialties of joint reconstruction, sports medicine, trauma, musculoskeletal oncology, hand, foot, spine and pediatric orthopaedics. There is also a large section devoted to cell biology and biomechanics. For a special touch, there are articles recalling memories of the earlier days in the Iowa Department of Orthopaedics. We have included current research projects as well as review articles and case reports.

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 and privilege of the residents. However, we could not have completed this project without the assistance of others involved in the production of the *Journal*. We'd like to thank our faculty advisors, Drs. Buckwalter, Cooper and Clark for their guidance. We also appreciate the assistance of Mr. Paul Etre and Ms. Laura Cole. We hope that you will benefit from our efforts, and we welcome your comments and criticism.

Steven Madey
Kristy Weber

JOURNAL DEDICATION



The 1995 *Iowa Orthopaedic Journal* is dedicated to an individual who has made major contributions to the University of Iowa Orthopaedic Program and to the specialty as a whole, Dr. Donald B. Kettelkamp. Don was born in Anamosa, Iowa in 1930. He attended Cornell College and then completed his M.D. at the University of Iowa. After his internship Don worked for the U.S. Public Health Service in Anchorage, Alaska where he also completed a general surgery residency. He came home to Iowa for his orthopaedic residency training, and then returned to Alaska to work in private practice for several years.

Dr. Kettelkamp has held numerous academic positions at the Albany Medical College in New York, the University of Arkansas, Indiana University, and Texas Tech University. From 1968-1971 he was a member of the faculty at the University of Iowa Department of Orthopaedics. He has recently retired as the Executive Director of the American Board of Orthopaedic Surgery.

He has been a member and leader in many professional societies including the American Board of Orthopaedic Surgery, American Orthopaedic Association, Orthopaedic Research Society, and Association of Orthopaedic Chairmen. Don is a member of Phi Beta Kappa and Alpha Omega Alpha honoraries. He is an honorary member of the South African Orthopaedic Association. He has devoted his time to serving as the President of the American Orthopaedic Association, President of the Association of Orthopaedic Chairmen, and Chairman of the Residency Review Committee. He currently serves on the Board of Trustees of the *Journal of Bone and Joint Surgery.*

Don has committed a lifetime to patient care, research and education. He has published hundreds of articles, but is probably best known for his work on high tibial osteotomy, knee biomechanics, and meniscectomy as related to degenerative joint disease of the knee. He has taught generations of orthopaedic residents and inspired them with his committment to the highest standard of orthopaedic practice.

Don has not limited his great energy and talent to orthopaedics. His list of orthopaedic publications is only matched by his muzzle loading resume! Dr. Kettelkamp is an avid hunter and has many stories to tell about charging leopards and stampeding wildebeest. One of his article titles is "Adventures with Texas Turkeys".

So, in tribute to Don Kettelkamp's long and distinguished career and committment to the University of Iowa and the field of orthopaedic surgery, we are honored to dedicate this edition of the *Iowa Orthopaedic Journal* to him.

REFLECTIONS

Donald B. Kettelkamp, M.D.

One of the prerogatives of becoming a senior citizen is feeling comfortable speaking of things beyond the realm of immediate application. Perhaps it is the absence of the immediate applicability that engenders a lack of enthusiasm for introspective assessment on the part of the young. Be that as it may, I will take this opportunity to set down some thoughts related to the University of Iowa Orthopaedic Surgery Program and to orthopaedic surgery in general.

The three legged stool of academia - teaching, research and patient care - really relates to practice and academics. It is how well one does these things that determines the reputation of both the practitioner and the program. Too often, I think, the people who elect to practice outside of a teaching institution forget that they also contribute each day to the reputation of their training program and their colleagues. This daily excellence is the most important contribution any of us make.

A group of people, or perhaps more correctly a sequence of groups, who do well, create a tradition that benefits everyone by making each person work harder to contribute to the reputation of all. The excellent reputation of the University of Iowa Orthopaedic Surgery Residency Program is thus the product of each of our colleagues who has passed before and the current residents and staff. The future of the program rests with each of them and with those to come. This is tradition, defined by the Random House College Dictionary as "that which is so handed down". Building a tradition is a long and difficult process. Maintaining and enhancing that tradition is even more difficult. Maintenance and enhancement of the tradition for excellence by the University of Iowa Orthopaedic Surgery Program makes it one of the very few in this country to do so over more than 50 years. Since tradition can be handed down by word of mouth and by legend, I would ask you to forgive any errors in memory which the following paragraphs may reveal. It is the principles rather than the facts which I want to emphasize.

Tradition began in the Iowa Orthopaedic Surgery Program with Dr. Arthur Steindler. Certainly his scholarship, particularly in published writings, received recognition. While Dr. Steindler published many articles and books, his publications and particularly his book on kinesiology contributed lasting benefit to orthopaedic surgery. Dr. Steindler was also a renowned educator who accepted residents, and what we would now call "fellows," from all over the world.

During my years as a medical student at the University of Iowa, the commitments made by Dr. Steindler were being honored by Dr. Carroll B. Larson. The department was sometimes referred to as the "foreign legion" by the students. Unquestionably we students were short sighted, for Dr. Steindler made a major contribution to my generation and the patients of Iowa when he accepted a young man from Spain as a resident, Dr. Ignacio Ponseti. A tradition for excellence in teaching, investigation and patient care was beginning. In addition, Dr. Arthur Steindler contributed to organized orthopaedic surgery by serving as President of the American Orthopaedic Association in 1933. During that time, the AOA formed two committees, one of which resulted in the foundation of the American Academy of Orthopaedic Surgeons and the other in the American Board of Orthopaedic Surgery.

My first recollection of Dr. Steindler was a lecture he gave to the residents on stabilization of the foot when I was on my senior student rotation in orthopaedic surgery. The last year of his life was the first year of my residency. During that year Dr. Steindler presented a series of lectures on the history of orthopaedic surgery. These lectures were particularly interesting because he added first hand knowledge about many of the personages of orthopaedic surgery. It made each of us realize that we were inheriting the contributions of many of our predecessors.

Early in my senior year of medical school I made an appointment with Dr. Larson to discuss becoming an orthopaedic surgery resident after I completed an internship and two years in the service. I remember saying I was interested in trauma. At that point Dr. Larson suggested that if trauma was my interest, perhaps I should consider general surgery. At that time orthopaedic surgery had just taken over one-half of the fracture admissions. I quickly denied my interest in trauma and have never regretted it.

Initially my service in the U.S. Public Health Service, Division of Indian Health, was at Cass Lake Indian Hospital, Cass Lake, Minnesota on the Leech Lake Indian Reservation. Dr. Larson had a summer home on the reservation and invited my wife, Micki, and me to visit. This further confirmed my desire to enter orthopaedic surgery at the University of Iowa. It wasn't until I finally arrived at Iowa where, in addition to Dr. Larson, Dr. Ponseti, Dr. Michael Bonfiglio and Dr. Adrian E. Flatt were on the faculty that I began to understand the Iowa tradition for excellence in teaching, patient care and research. More importantly, there was a gradual realization that the philosophies of the faculty toward patient care and orthopaedic surgery were developing a tradition which would influence orthopaedic surgery for the next 20 years

or more. This tradition for humanistic and excellent patient care, while continuing teaching and research, was taken by the graduates of the Iowa program to many practices and training programs. Thus an Iowa tradition became a positive influence on programs in Arkansas, Illinois, Indiana, Maryland, Massachusetts, Minnesota, New York, Texas, Vermont and Wisconsin to name a few.

I have been speaking of the "Iowa tradition" but perhaps it is time to relate how this became formalized. During the 1950's and into the 1960's there was a Steindler Alumni group but no organization of Iowa Orthopaedic Alumni. At one of the Academy meetings in the late 1960's, a meeting was held by all who had trained at the University of Iowa. Dr. Joseph E. Milgram of the Steindler era and Dr. William Baird, who over-lapped both the Steindler and the Larson eras, stated that there should be an Iowa Orthopaedic Surgery Alumni group to include both those who trained under Dr. Steindler and those who trained under Dr. Larson. All agreed and so became the Iowa Orthopaedic Surgery Alumni, the group which carries on the Iowa tradition of which I write.

In the 1950's and 1960's two modes of teaching were particularly important in shaping the orthopaedic surgery residents. These were the daily Indications Conference and the informal sessions held around the coffee pot in the dressing area near the operating room.

The Indications Conferences required the residents to think and plan a course of treatment when they saw the patients in the clinic. These conferences were conducted by the faculty and taught the residents to think "on their feet" when they were called upon for an opinion about the treatment plans for the patient presented to conference. The residents learned to never, ever plan a course of treatment for a patient that had anything other than the patient's well being as the top priority. This policy of always thinking of the patient first became the keystone of patient care in the Iowa program.

In some respects the informal sessions in the coffee room at the end of the day were the most important. Dr. Larson usually found his way to the coffee room about 4:30 PM or so. Gradually other faculty and residents joined in as they completed their duties for the day. The discussions seldom concerned a specific orthopaedic problem and most often concerned subjects only indirectly related to medicine. This was the time when the residents gradually learned the philosophies of the faculty. I am not certain how the time for these sessions was found, but I give all of the credit to Dr. Larson. In subsequent years, even recognizing their value, I never found the time to continue the informal sessions, either when I was on the faculty at Iowa or elsewhere. Had we continued these sessions or instituted them in other programs, perhaps some of the criticisms the public has of orthopaedic surgeons could have been avoided.

I believe a significant contribution to the Iowa tradition for excellence in individual patient care came from this period of time. The Iowa tradition contains several other facets. These are scholarly activities and contributions to orthopaedic surgery in other areas.

One of the goals of the residency in the 1950's and 1960's was the development of academic orthopaedic surgeons. This was the time of federally funded training grants. All residents had to produce at least one paper during the residency with direction from one of the faculty. Frequently a project started at Indications Conference when one of the faculty would comment that someone should look up and study a specific clinical problem that had just been seen. This was the origin of a paper I wrote on the Steindler Flexorplasty. The referral and record system in the Department, which included gait films and old x-rays, made Iowa an ideal place for long term clinical studies. Fortunately this is a situation that still exists.

A Masters degree program was established in orthopaedic surgery, and most residents during the late 1950's and early 1960's obtained that degree. In addition some residents obtained Masters degrees in other fields before starting residency. This inquisitive, scholarly approach to patients' problems on the part of the faculty led to the establishment of research laboratories in biochemistry, biomechanics, and electron microscopy.

The tradition for excellence in scholarly pursuits which began with Dr. Steindler developed and flourished under the direction of Dr. Larson, Dr. Ponseti, Dr. Bonfiglio and Dr. Flatt. This growth in productivity and excellence has expanded even further under the direction of Dr. Reginald Cooper and the current faculty. Perhaps of equal importance is that the foundation for productive scholarly activities which was formed during residency at Iowa has been carried by former residents to many other institutions and practices.

Current Iowa faculty and former Iowa residents and faculty have contributed to orthopaedic organizations and their activities over the years. As I noted earlier, Dr. Steindler was President of the American Orthopaedic Association in 1933, a time when committees of the AOA founded the American Academy of Orthopaedic Surgeons and the American Board of Orthopaedic Surgery. Dr. Larson was President of the American Academy of Orthopaedic Surgeons and served on the American Board of Orthopaedic Surgery as did Dr. Michael Bonfiglio. Dr. Ponseti was President of the Orthopaedic Research Society and Dr. Flatt presided over the American Society for Surgery of the Hand. There are many others and, lest I forget someone, I will just mention a few. Of all those with an Iowa heritage, there have been at least two Presidents

of the American Orthopaedic Association, three Presidents of the American Academy of Orthopaedic Surgeons, one President and six other members of the American Board of Orthopaedic Surgery, four Presidents of the Orthopaedic Research Society, one President of the Association of Orthopaedic Chairmen (now the Academic Orthopaedic Society), two Presidents of the Hip Society, one President of the American Society for Surgery of the Hand, one President of the Knee Society, one President of the American Orthopaedic Society for Sports Medicine, two Chairmen of the Residency Review Committee for Orthopaedic Surgery, one Chairman of the Board of Regents of the American College of Surgeons and officers in numerous other societies and committees. In addition, there are or have been seven Chairmen of Departments or Divisions of Orthopaedic Surgery in medical schools. Many scientific papers, instructional courses, seminars and other educational offerings have been given by those with an Iowa heritage.

Excellence in patient care, furthering orthopaedic knowledge, and service to the orthopaedic and medical community are the traditions and legacies of the University of Iowa Orthopaedic Residency program. May each of us strive to leave these characteristics to those who follow, that this tradition may continue to grow and flourish.

COMPUTER-AIDED PREOPERATIVE PLANNING IN KNEE OSTEOTOMY

Edmund Y.S. Chao, Ph.D.*
Franklin H. Sim, M.D.#

"This paper is dedicated to two of our orthopaedic mentors: Donald B. Kettelkamp and Mark B. Coventry, from whom we have benefited so tremendously in our careers. They taught us the sciences and clinical knowledge related to Knee Osteotomy. We wish to honor these two giants in our field and we shall forever remember them and their profound philosophy, strict discipline and the utmost ethical standards endowed upon us!"

ABSTRACT

It has been demonstrated that osteoarthritis (OA) is activity related and may worsen when joint contact stress becomes excessive due to overloading. Hence, joint **alignment** and **loading** are considered to be the key biomechanical determinants for OA. The initiation of pathologic changes in the knee has been described by the mechanism termed, **"vicious cycle"** in which joint axial malalignment creates excessive stresses to the localized joint cartilage/subchondral bone regions and the surrounding soft tissue which in turn produces more laxity and joint deformity and thus repeats the cyclic degradation mechanism. If this degenerative cycle can be broken with joint alignment surgery such as **osteotomy,** a procedure to realign the knee joint and thus redistribute joint forces applied to each compartment, performed properly and at the appropriate time, the osteoarthritic disease process can be decelerated and even reversed. The main goals of this paper are to emphasize the importance of accurate preoperative planning for osteotomy in order to properly correct joint alignment, and to justify the application of an existing computer program, **OASIS** (Osteotomy Analysis and Simulation Software) using plain radiographs to perform appropriate surgical planning. Normal subjects and knee osteotomy patients were studied to establish a database for the purpose of establishing the utility and efficacy of the presently proposed concept. We wish to rationalize knee osteotomy as a preferred and cost-effective treatment for patients with early symptoms of OA in the knee. This paper presents a new concept of preoperative planning for knee ostetomy based on the underlying etiology of the disease and biomechanical viewpoint with strong emphasis on surgical treatment rationales. The established principles in this paper can be applied to other joints of the body and will help implement preventive measures and other non-surgical means to manage patients with axial malalignment or early degenerative changes.

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INTRODUCTION

An estimated 16 million Americans suffer from osteoarthritis (OA), the most common form of joint degeneration and one of the least understood diseases involving musculoskeletal systems. Altman et al.[1] described OA as "a heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone and at the joint margins." OA starts with local cartilage damage and becomes more severe and widespread at later stages[41]. The most common radiographic findings are osteophytes and subchondral stiffening or sclerosis[49, 20, 58, 51, 52, 19]. The knee is the most affected peripheral joint in patients with symptomatic OA. Lesions are ten times more prevalent in the knee than in the ankle and almost absent in the wrist[18, 34, 46].

Although OA is proposed to have its etiological causes related to genetic, metabolic and environmental factors, mechanical loading (stresses) and joint angular deformity remain the most intriguing and convincing determinants in certain occupations and physical activities[52, 4, 39, 3]. Other OA pathogenesis indicators such as age, obesity, joint trauma, repetitive loading, etc. are all mechanical-related. The close correlation between OA and biomechanical factors can be easily established at the knee since it is the most heavily loaded joint with a large range of motion but the least stable structure due to its predominant dependence on soft tissue constraints and muscle contraction. Slight axial malalignments can initiate the **"vicious cycle"** as proposed by Coventry[13,14] (Figure 1). This progressive disease process can be described as when a "load increase in one compartment of the knee due to slight axial malalignment causes cartilage degeneration, subchondral bone sclerosis, cyst formation and joint laxity which in turn produces an increased load on the affected side thus causing a cyclic reaction." The introduction of knee joint alignment procedures was intended to interrupt such a degenerative cycle[12, 6, 32, 59, 33, 42, 8, 17].

Unfortunately, knee osteotomy has fallen into disfavor for two main reasons. First, several investigators discov-

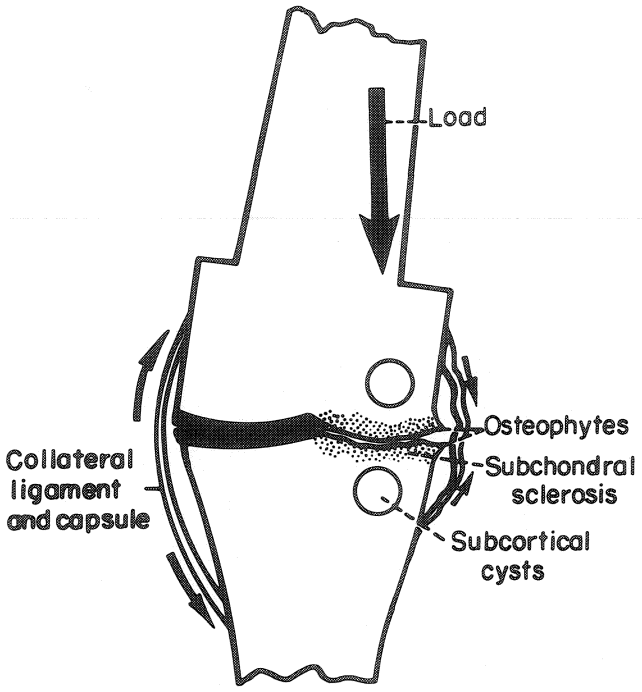


Figure 1 The "vicious cycle" hypothesis relating joint axial alignment and abnormal loading to osteoarthritis in the knee.

ered that knee osteotomy could not maintain long lasting good results and thus is regarded as only a temporary procedure yielding five to seven years of pain-free activity before deformity recurrence[45, 50, 17, 22, 24, 32]. Second, in the recent two decades, prosthetic replacement of the knee by either unicompartmental or total joint arthroplasty has pushed osteotomy aside in favor of the more popular and perhaps easier surgical procedure. The reasons for not obtaining long-term excellent results after knee osteotomy could be due to prognostic factors[48, 50, 60], the uncertainty of which osteotomy procedure to indicate based on specific pathological involvement[54, 61, 47, 27, 35, 43] or the inability to produce adequate overcorrection[16]. While total knee replacement for unicompartmental disease may be over-indicated, unicompartmental knee joint replacement has produced controversial and highly variable results[5, 44, 40, 57, 31, 7]. In addition, prosthetic replacement is certainly more costly and does not leave many options for revision if the surgery is not successful. With today's health care management reform and DRG regulations, more conservative procedures should be considered.

In knee osteotomy, regardless of the type, the issue of overcorrection has created controversial debate[38, 14, 53]. Preoperative planning using biomechanical analysis has a long history of development[10, 37, 28], but these early analytical approaches were tedious and impractical. In addition, no capability was available to visualize the analysis results in the proper selection of the type, location and wedge magnitude of osteotomy correction. Since the osteotomy procedure is designed to correct alignment and to re-distribute joint pressure, careful preoperative planning should be done based on proven biomechanical principles. The publication by Coventry et al.[16] clearly indicated that when osteotomy was performed correctly (proper overcorrection) on carefully selected patients (<30% over the normal weight), excellent results lasted for more than ten years following the initial procedure.

Motivated by the potential value of computer-aided preoperative planning for knee osteotomy, a special analysis algorithm and computer program were developed by the principal investigator and his associates[25, 29]. This analysis has been applied to a large normal population of different age ranges and genders which demonstrated that osteoarthritis of the knee did not seem to associate with age and gender[28]. However, the age range in this study did not include those in their seventh decade. The same population group will need to be followed longitudinally to rule out age as the key determining factor for OA. This program (Osteotomy Analysis and Simulation Software - "OASIS") was applied to a large patient population with surprisingly good results[55, 56, 21]. Following the optimal correction guidelines, not all varus deformities resulted in upper tibial osteotomy. On the contrary, there were significant numbers of cases that required double osteotomy (upper tibial combined with supracondylar) based on axial alignment, contact pressure distribution and joint line obliquity. Although follow-up is still limited in these cases, the patients and attending surgeons have been extremely satisfied with the outcome following the recommended osteotomy.

The current preoperative analysis is limited to two-dimensional calculation constraints and only based upon the standing radiograph in the AP projection. These limitations pose significant concerns as to the validity of the current analysis scheme and the optimal selection criteria for the final osteotomy procedure. Hence, verification experiments using knee specimens on a simulator should be incorporated. It is also important to assess the biological and biomechanical changes affected by the osteotomy. While these concerns are being investigated in various basic science studies, one must assume that proper unloading of the affected joint can not only bring symptom relief but can also allow the degenerative process caused by biomechanical factors to cease and reverse. In addition, one must also assume that alignment correction performed when the knee is in the neutral extended position will have the same therapeutic effect in all joint flexion positions during activity.

It is clear that joint alignment and pressure (loading) distribution are important determinants affecting osteoarthritis. Knee osteotomy, if performed correctly, can stop

and even reverse the "vicious cycle." Proper timing must be taken into consideration in order for surgery to be effective before the joint is irreversibly damaged. These important principles can only be substantiated by following patients with early symptoms of OA that are not severe enough for surgical correction. How to determine the threshold for surgery to maximize the therapeutic effect of osteotomy and whether to use braces or other non-surgical management to correct high joint compartment load caused by side-thrust during gait[50] are questions that remain unanswered. Hence, this paper offers several significant contributions to the basic understanding of unicompartmental OA in the knee, to the justification of the more conservative and cost-effective procedures on these patients, and finally to the achievement of quality assurance for long-lasting good results to a large patient population.

DEVELOPMENT OF KNEE OSTEOTOMY ANALYSIS PROGRAM —OASIS

In orthopaedic surgical procedures where joint/limb alignment, joint coverage and surface contact pressure distribution are of great importance, accurate modeling and analysis of the involved system based on the patient's 2D (radiographic) imaging data can offer significant information for operative planning to optimize treatment results. Sim et al.[55] and Hanssen and Chao[21] have reported using full-length standing plain radiographs of the lower extremity for the measurement of mechanical axial alignment for preoperative planning of knee osteotomies. Use of the mechanical axis description of alignment is reported to be more reliable than the anatomic description for defining knee joint deformity, especially when other skeletal deformities are present away from the knee joint. These axes provide a more precise description of load transmission through the joint. Hanssen reports using the mechanical axis description of alignment and overlaying a templated wedge using trigonometric principles for angular correction.

In order to accurately determine knee joint pressures and mechanical deformities of candidates for knee osteotomies, a computer software program, OASIS (Osteotomy Analysis and Simulation Software), was developed by the principal investigator when at the Mayo Clinic. The OASIS software is based on the Rigid Body Spring Model (RBSM) technique described by Kawai and Toi[36], An et al.,[2] and Ide et al.[30] When this modeling technique is applied to the human knee, the femur and tibia are represented by rigid

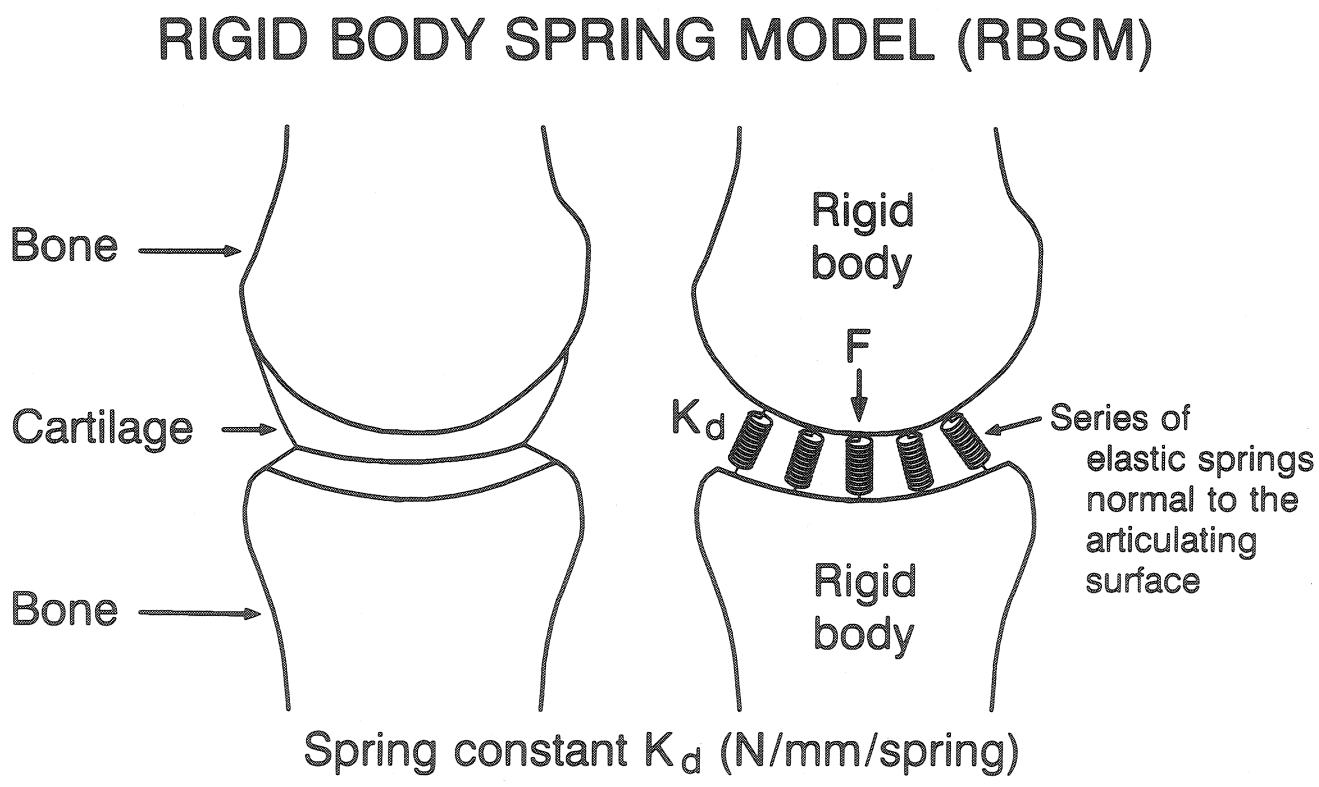


Figure 2 The Rigid Body Spring Model (RBSM) used to obtain contact stress distribution in articulating joints. K_d = cartilage spring stiffness value. The stiffness value for each spring will be designated as K_i.

bodies while articular cartilage and ligaments are modeled as systems of springs between the bodies.

To determine the contact force acting on the femoral condyle, a set of evenly spaced data points are calculated on the tibial contact surface using a cubic polynomial. Cartilage is modeled on the tibial surface as linear compressive springs positioned in the normal direction on the tibial surface (Figure 2). The compressive stresses are obtained by considering the constitutive relationships of the cartilage and assigning a stiffness value for the spring element (k_i) that approximates the properties of the cartilage in that region. The stiffness of the cartilage springs is determined as:

$$k_i = \begin{cases} \dfrac{E(1-\nu)}{(1+\nu)(1-2\nu)}\dfrac{ds_i}{h}, & \Delta u_n > 0 \\ 0, & \Delta u_n \le 0 \end{cases};$$

where E is Young's modulus, v is Poisson's ratio, and h is the thickness of the cartilage. The compressive force applied by each spring is:

$$\vec{f}_i = -k_i \Delta u_n \mathbf{n}_i = -k_i(\Delta z_i \bullet \mathbf{n}_i)\mathbf{n}_i = -k_i(\Delta z_i \bullet (\mathbf{R} \bullet \mathbf{n}_i'))\mathbf{n}_i.$$

The total compressive force on the femur is:

$$\vec{F}_c = \sum_{i=1}^{m} \vec{f}_i = \sum_{i=1}^{m} -k\Delta u_n \mathbf{n}_i = \sum_{i=1}^{m} -k_i(\Delta z_i \bullet (\mathbf{R} \bullet \mathbf{n}_i'))\mathbf{n}_i.$$

The free body diagram used in the RBSM analysis of the lower extremity can be seen in Figure 3. The muscle force directions are determined from the input data. Muscle force components are recalculated at each iteration of the model. The ligament action is specified by their original points on the tibia and insertion points on the femur.

The final equilibrium equations, a system of six equations with six unknowns, are:

$$\begin{cases} \vec{F}_c + \vec{F}_l + \vec{F}_w = 0; \\ \vec{M}_c + \vec{M}_l + \vec{M}_w = 0. \end{cases}$$

The equilibrium equations satisfy the condition that the sum of all forces and moments due to cartilage compression (Fc), ligament tension (Fl) and body weight (Fw) equal zero. The relative equilibrium positions of the tibia and femur are calculated for given external loads and kinematic constraints. Displacement of the knee center is denoted by U, where:

$$\mathbf{U} = (U_x, U_y, \Theta_z)$$

The three displacement unknowns in translation (Ux, Uy) and rotation (θz) can be determined from the three equilibrium equations. An iterative process is used to solve the equilibrium equations. If a cartilage spring is found to be in tension or a ligament spring in compression, its stiffness is subtracted from the equilibrium equation and the process begins again. When there are no inadmissible spring forces, an osteotomy simulation will be com-

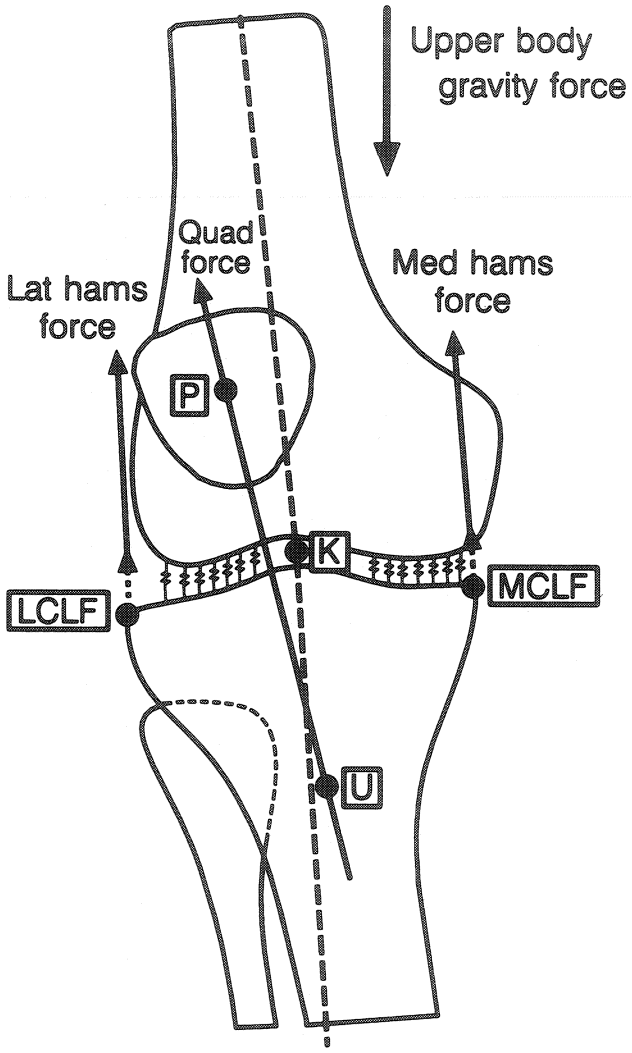


Figure 3 The 2D RBSM model of the knee used in osteotomy preoperative planning. U = patella tendon insertion; K = knee joint center; P = patella center, LCLF = lateral collateral ligament force.

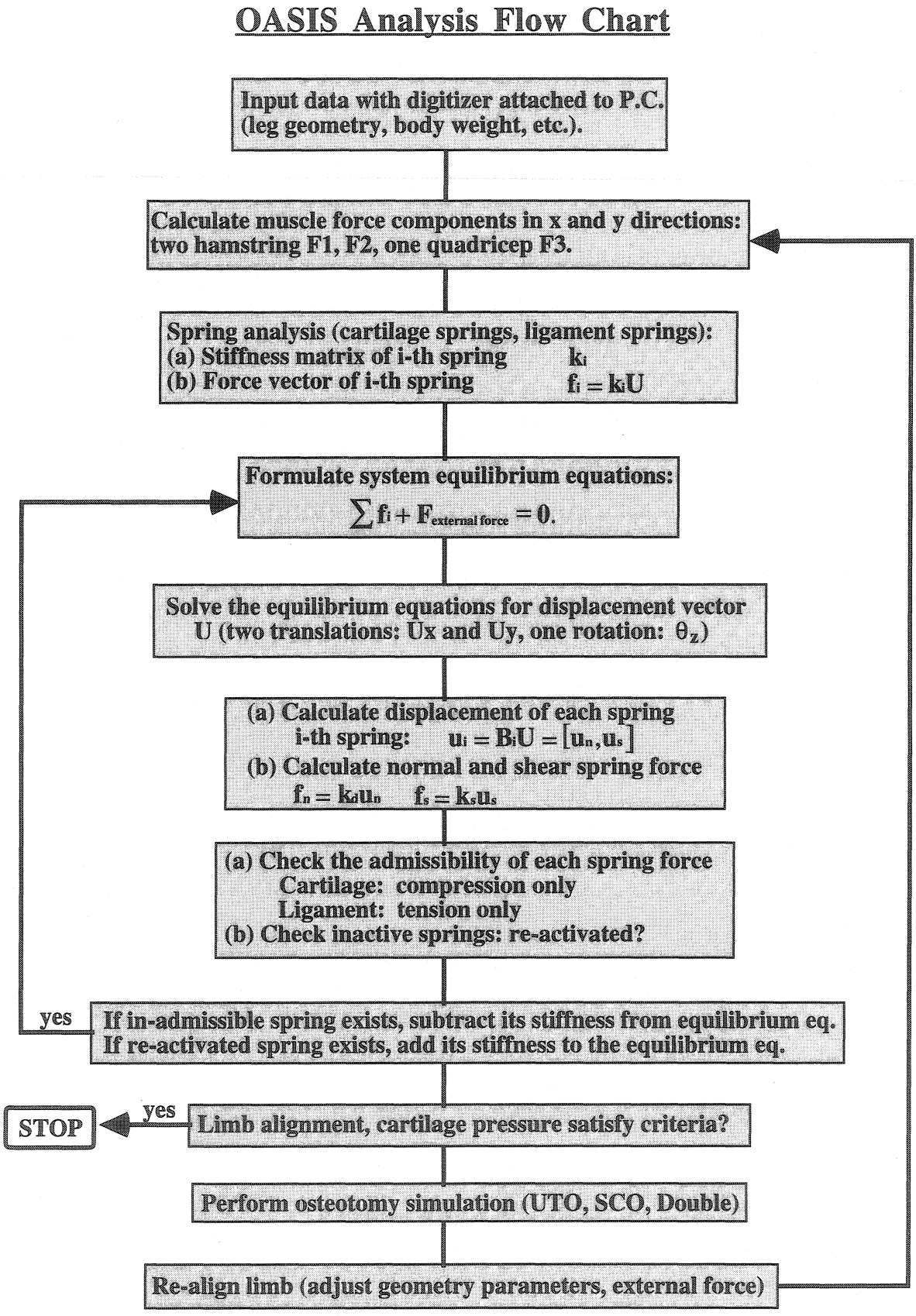


Figure 4 The iterative computational algorithm of the computer program "OASIS."

pleted as illustrated in the flow chart outlining the computational algorithm of the OASIS program (Figure 4).

KNEE JOINT AXIAL ALIGNMENT AND PRESSURE DISTRIBUTION

One hundred and twenty normal subjects of different gender and age ranges were studied for their knee joint alignment and 2D contact pressure distribution using the analysis program OASIS[28]. The tibiofemoral angle was consistent within the entire normal population studied (1.2° ± 2.2° varus). There was no significant difference between male and female subjects or different age groups ($p > 0.05$). In measuring the femoral anatomic valgus, the selection of the anatomic axis of the femur was important since the proximal femoral, distal femoral, and the overall femoral anatomic axes were different. Based on the distal anatomic axis, the femoral anatomic valgus for the entire population studies was 4.2° ± 1.7°. When the proximal femoral anatomic axis was used, the femoral anatomic valgus became 5.8° ± 1.9°, as opposed to 4.9° ± 0.7° when the overall femoral anatomic axis was used. Gender and age did not cause any significant differences.

The patellofemoral Q angle was 5.8° ± 6.7° for the entire group, and there was no gender-related difference. However, the patellotibial Q angle was significantly larger in the female subjects (9.9° ± 4.9°) than in the male subjects (6.8° ± 5.9°; $p<0.05$), while age did not produce any significant variation. The anatomic Q angle (Q_A) was also significantly greater ($p<0.05$) in the female subjects (18.8° ± 4.6°) compared to the male subjects (15.6° ± 3.5°). The knee joint obliquity angle (e) was 1.0° ± 1.5° varus (tilting medially) for the male subjects, which was significantly different from the female subjects (0.1° ± 1.7° valgus, $p<0.05$). Again, age did not produce any significant difference in this parameter.

The normal contact force distribution on the medial plateau was 75% ± 12% of the total knee joint force under simulated one-legged standing. There was no statistical difference between gender and age groups tested. The resultant force passing through the knee articular surface was mainly perpendicular to the joint line (94.3% body weight) with only a minor shear component (0.9% body weight) pointing medially. Only the lateral collateral ligament carried minute tension in all the normal subjects studied.

The plateau pressure was normalized against the subject's body weight and expressed as a percentage of body weight per millimeter. The maximum pressure on the plateau was higher in female subjects (4.0 ± 1.3% body weight/mm) than in the male subjects (3.5 ± 1.0% body weight/mm), and this difference was statistically significant ($p < 0.05$). However age did not change plateau pressure distribution. A parametric analysis was performed to correlate plateau force distribution with tibiofemoral angle,

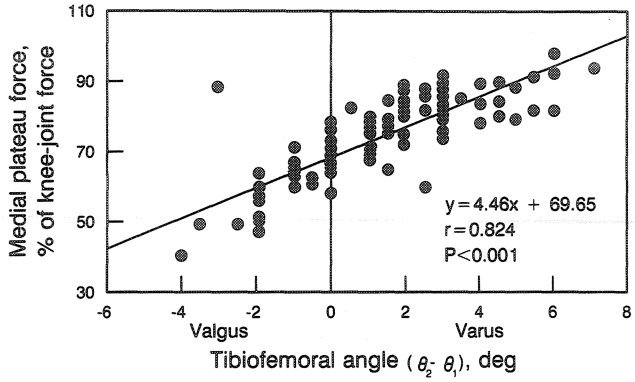


Figure 5 Correlation of medial plateau force and tibiofemoral angle in the normal population studied.

G location, joint cartilage thickness and knee joint muscle contraction. Changing the tibiofemoral angle and its effect on plateau force distribution can be used to study the pathomechanics of genu varum or valgum associated with joint malalignment. In order to establish such a relationship, the tibiofemoral angles of all the normal subjects studied were correlated with their medial plateau contact forces expressed as a percentage of the total knee joint force. The medial plateau force distribution had a negative linear relationship with the tibiofemoral angle ($R = 0.824$; $p <0.001$; Figure 5). A positive tibiofemoral angle represents a varus axial alignment while a negative value stands for a valgus alignment. This diagram also illustrates the scattering of the tibiofemoral angle and medial plateau contact force among the normal population studied.

Variation of G location was achieved by changing IR from -1 (through the opposite hip joint center) to 2 (laterally to distance of "C" from H; Figure 6). Different values of IR can be used to simulate a varus or valgus moment applied to the knee in the frontal plane during gait. When G is lateral to K ($IR > 0.8$), there will be a valgus moment (abduction moment) applied through the knee joint. On the other hand, when G is medial to K ($IR < 0.8$), there will be a varus moment (abduction moment or lateral thrust) applied to the knee joint. Such variation significantly affects the plateau force distribution (Figure 7). The selection of $IR = 0.8$ (approximating the one legged standing posture) as the demarcation point between valgus and varus moments was based on the values obtained from the normal population groups. When IR approaches 2, medial contact force approaches 0 with the medial collateral ligament in tension in order to maintain knee joint equilibrium. When IR becomes less than 0.3, all knee joint force will be borne by the medial plateau with the lateral ligament in strong tension.

The effect of cartilage thickness on plateau force distribution and joint peak pressure magnitude was insignificant based on the present model and its analytical assumption. Increasing quadriceps and hamstring contractions caused

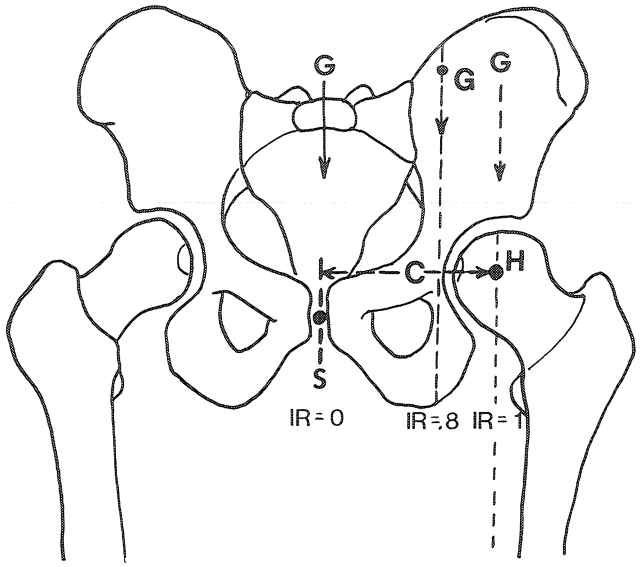


Figure 6 Effect of upper body gravity (G) during gait on knee joint contact force distribution. IR = interval ratio. IR = 1, gravity passing through the hip center, H; IR = 0, gravity passing through the pubic symphysis, S.

joint peak pressure to increase proportionally, but the relative plateau contact force distribution was not affected. Hence, the association of age with knee alignment deformity and early OA was not established. However, this study covered wider age ranges and no longitudinal follow-up was performed.

COMPUTER-AIDED PREOPERATIVE PLANNING

Traditionally, the axial alignment of the limb has been determined by measuring the femoral-tibial (anatomic) angle from standing radiographs and then judging the amount of correction required to normalize, or to over-correct. The normal anatomic axis measured five degrees of valgus[38]. The mechanical axis normally averages 1.2 degrees varus and is more reliable than the anatomic axis when defining lower limb alignment[28]. This is particularly true when there are femoral or tibial deformities away from the knee joint that contribute to the limb malalignment. The same standing radiograph has been used to estimate osteotomy wedge length based on the assumption that the arc of the wedge is approximately 1 mm per degree of the angular correction. The use of such a simplified and erroneous method to estimate osteotomy wedge size is totally unacceptable. This is one of the faulty procedural steps in previous knee osteotomy preoperative planning which was responsible for the unsuccessful outcomes.

In addition to the mechanical alignment, the effects of soft tissue tension, obliquity of the joint line, and gravity shift of the upper body all affect the tibiofemoral plateau pressure distribution and ultimately the correct location and magnitude of an intended osteotomy. These factors are difficult to assess with visual inspection and manual planning. For these reasons, the software program OASIS was developed to provide a comprehensive preoperative assessment of the factors that guide the surgeon's final determination of the location, magnitude, and type of knee osteotomy most appropriate for the individual patient[28, 56]. On the full length anteroposterior weight bearing radiograph, the joint centers, mechanical and anatomic tibiofemoral axes, patella center, joint contour outline, muscle and ligament insertion points, and joint articular surface contact areas are identified and manually digitized on a translucent, background-lighted electrostatic digitizer. With this analytical model, the muscles, ligaments, and cartilage are represented by a series of linear springs while the bony structures are assumed to be rigid bodies (Figure 7).

Simulation analysis input data include body weight, muscle contraction, ligament and cartilage stiffness properties, and the upper body gravity location. Osteotomy simulation parameters for the magnitude and location of the osteotomy wedge can then be performed interactively with immediate tabulation and graphical display of the simulation session. A printout of the upper tibial closing wedge valgus osteotomy at its usual location is provided to the surgeon (Figure 8). Alternative options of an opening wedge, barrel-vault (also known as the dome) osteotomy at any level of the femur or tibia can also be simulated and made available for the surgeon. The output of the software "OASIS" includes the tibiofemoral angle based on the mechanical and anatomic axes, percent of force passing through the medial plateau, peak plateau pressure, joint shear force, collateral ligament tension, joint line obliquity in degrees from a horizontal line, joint loading axis (a line connecting the hip and ankle joint centers), location in reference to tibial plateau width, and the lower extremity length change. The size of the osteotomy angle, as measured along the bone surface, is also provided to the

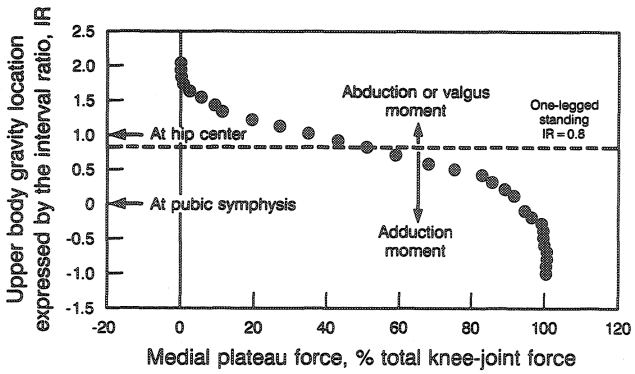
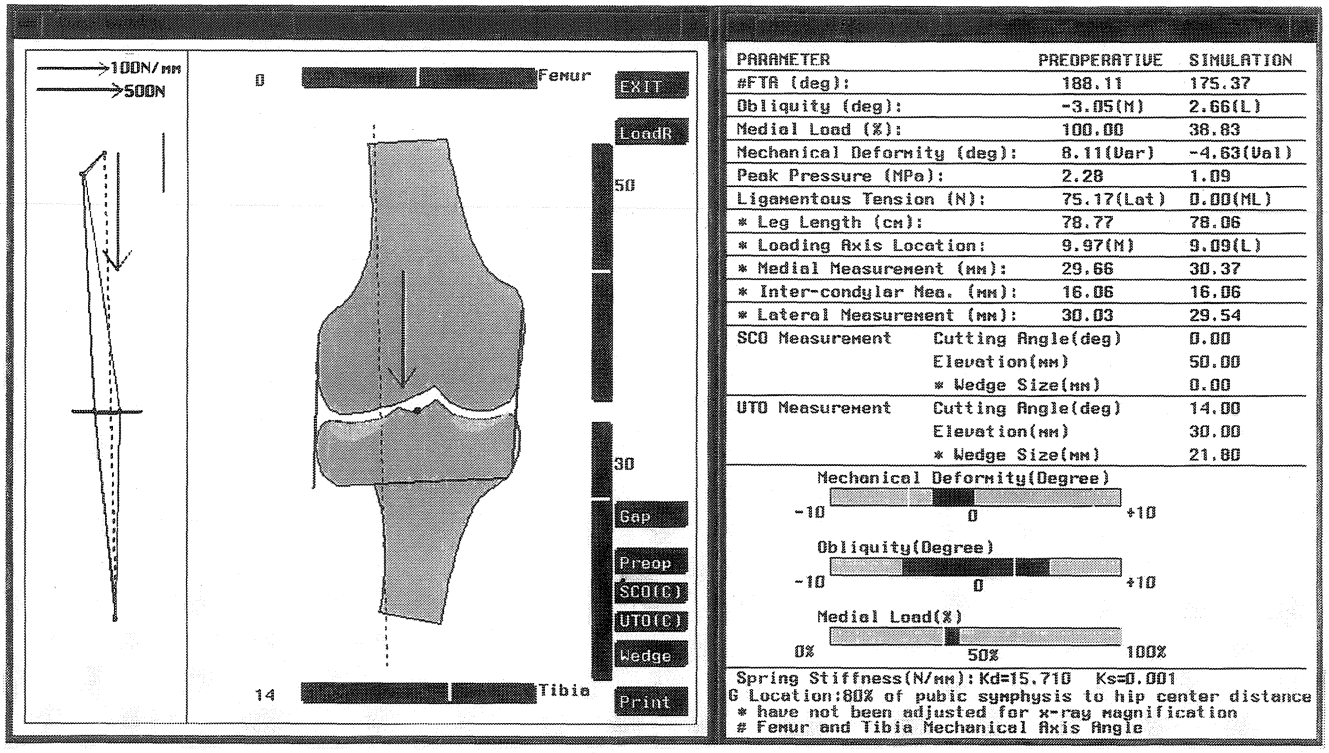


Figure 7 Effect of upper body loading location on the medial plateau force distribution as a means of stimulating walking effects on knee joint loading in the AP plane.



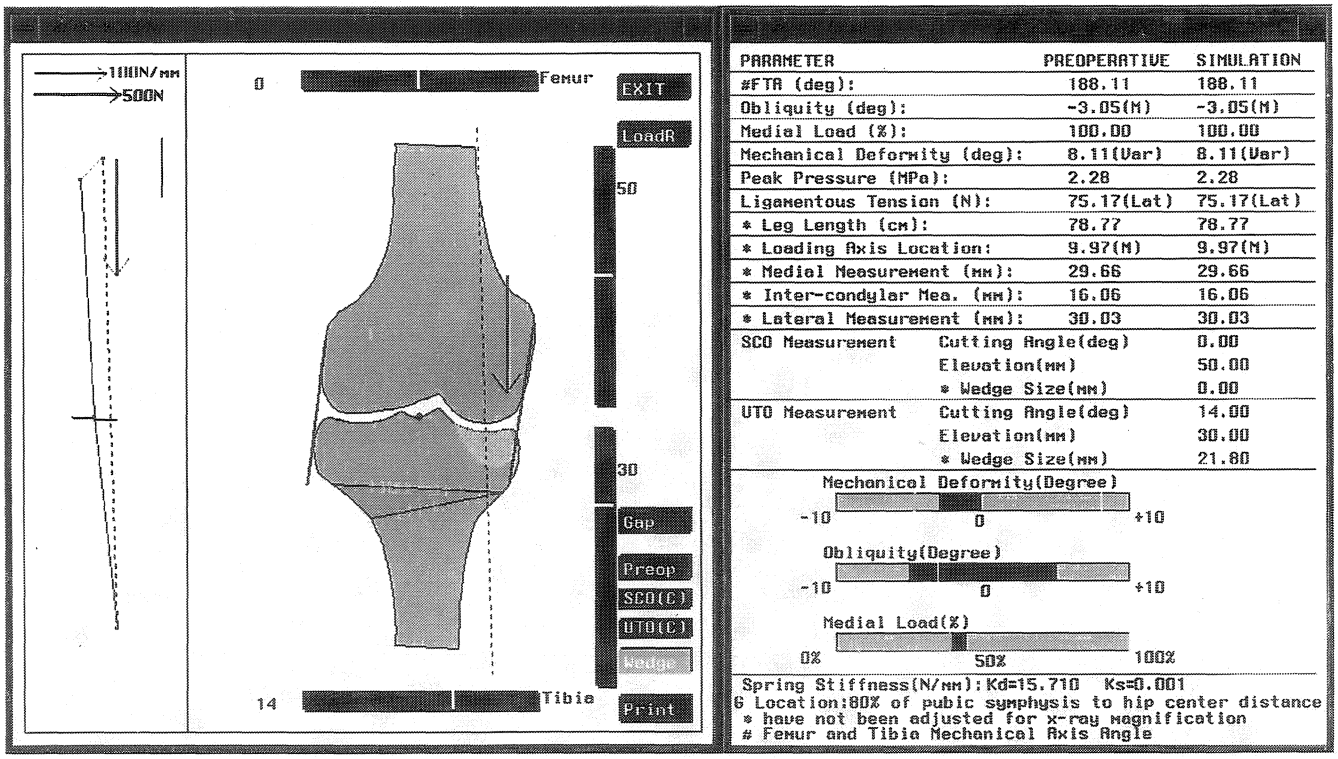
PARAMETER		PREOPERATIVE	SIMULATION
#FTA (deg):		188.11	175.37
Obliquity (deg):		-3.05(M)	2.66(L)
Medial Load (%):		100.00	38.83
Mechanical Deformity (deg):		8.11(Var)	-4.63(Val)
Peak Pressure (MPa):		2.28	1.09
Ligamentous Tension (N):		75.17(Lat)	0.00(ML)
* Leg Length (cm):		78.77	78.06
* Loading Axis Location:		9.97(M)	9.09(L)
* Medial Measurement (mm):		29.66	30.37
* Inter-condylar Mea. (mm):		16.06	16.06
* Lateral Measurement (mm):		30.03	29.54
SCO Measurement	Cutting Angle(deg)		0.00
	Elevation(mm)		50.00
	* Wedge Size(mm)		0.00
UTO Measurement	Cutting Angle(deg)		14.00
	Elevation(mm)		30.00
	* Wedge Size(mm)		21.80

Mechanical Deformity(Degree)
-10 0 +10
Obliquity(Degree)
-10 0 +10
Medial Load(%)
0% 50% 100%

Spring Stiffness(N/mm): Kd=15.710 Ks=0.001
G Location:80% of pubic symphysis to hip center distance
* have not been adjusted for x-ray magnification
# Femur and Tibia Mechanical Axis Angle

Figure 8 An example case of a man with 8.11° varus deformity in his right knee. All critical information on the preoperative planning analysis is included.

A. Preoperative conditions

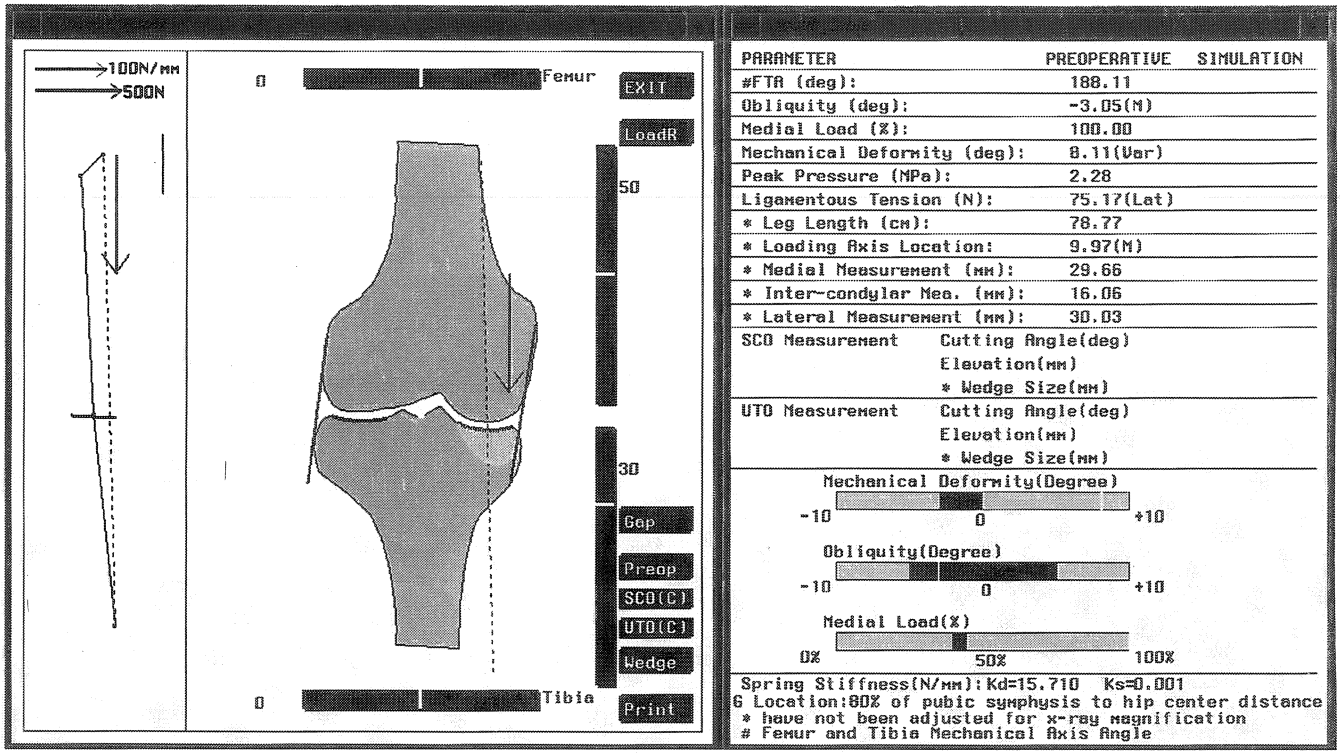


PARAMETER		PREOPERATIVE	SIMULATION
#FTA (deg):		188.11	188.11
Obliquity (deg):		-3.05(M)	-3.05(M)
Medial Load (%):		100.00	100.00
Mechanical Deformity (deg):		8.11(Var)	8.11(Var)
Peak Pressure (MPa):		2.28	2.28
Ligamentous Tension (N):		75.17(Lat)	75.17(Lat)
* Leg Length (cm):		78.77	78.77
* Loading Axis Location:		9.97(M)	9.97(M)
* Medial Measurement (mm):		29.66	29.66
* Inter-condylar Mea. (mm):		16.06	16.06
* Lateral Measurement (mm):		30.03	30.03
SCO Measurement	Cutting Angle(deg)		0.00
	Elevation(mm)		50.00
	* Wedge Size(mm)		0.00
UTO Measurement	Cutting Angle(deg)		14.00
	Elevation(mm)		30.00
	* Wedge Size(mm)		21.80

Mechanical Deformity(Degree)
-10 0 +10
Obliquity(Degree)
-10 0 +10
Medial Load(%)
0% 50% 100%

Spring Stiffness(N/mm): Kd=15.710 Ks=0.001
G Location:80% of pubic symphysis to hip center distance
* have not been adjusted for x-ray magnification
# Femur and Tibia Mechanical Axis Angle

B. Simulated postoperative results with a 14° wedge at the upper tibial region



C. Wedge size and location simulation

surgeon. In addition, a joint gap in either compartment of the knee can be closed to compensate for weight-bearing effects causing the joint to open in severely deformed knees. It should be realized that this method is a static, two-dimensional analysis that assumes that an improved redistribution of joint forces in the standing position will be beneficial to the patient during dynamic knee performance. Experimental and analytical studies have been performed to validate this model[29]. Large numbers of normal and clinical case studies have been investigated to evaluate the efficacy of this program[28]. The value of this method of preoperative planning on the final clinical outcome of patients undergoing osteotomy is being prospectively studied.

APPLICATION OF OASIS TO KNEE OSTEOTOMY PATIENTS

The 2D models for the knee were constructed using normal subjects' and patient' plain radiographs in standing posture. Static force analyses were performed based on estimated muscle/tendon contractions and measured external loading. The RBSM was used to predict joint pressure distribution by assuming that bones are rigid bodies and that joint cartilage constitutes a series of elastic springs.

Using a normal database, the analysis software ("OASIS" Osteotomy Analysis and Simulation Software) was expanded for osteotomy preoperative planning. An osteotomy affects the leg alignment, muscle force direction, muscle length and weight bearing areas of joints. These are all biomechanical factors which play an important role in preoperative planning to improve long term osteotomy results[11]. However, it is impossible to quantify the effects of osteotomy on all of these biomechanical factors using conventional methods, such as cutting and pasting sections traced from radiographs by hand. This practical and easy to use computer program is capable of analyzing each patient's preoperative condition and interactively generating the optimal surgical procedure[21].

This software has been used to provide clinical service in over 375 cases analyzed by the principal investigator. It is important to note that intrinsic pathomechanical changes in articular cartilage depend upon local stress levels rather than global joint loading. The stress within the joint cartilage is not only determined by the magnitude and direction of the contact force but also by the size and shape of the articular surface. Therefore, it is essential to estimate the pressure distribution on the joint and the peak values before and after the osteotomy simulation; this is accomplished using the RBSM technique. With this software, bone geometry and loading conditions can be changed according to the osteotomy procedure. The calculated pressure distribution is then displayed in three

dimensions super-imposed on the geometry of the articular surface. In many cases, such analysis has proved to be helpful. Example cases are used to demonstrate the potential utility of such software (Figure 9). The computer-aided osteotomy type and wedge angle location are also available in the general output of the program.

In an unpublished study to determine the significant factors which indicate whether an osteotomy candidate should receive an upper tibial osteotomy (UTO) or a supracondylar osteotomy (SCO), 266 knees with unicompartmental osteoarthritis and varus deformity were analyzed using OASIS. The optimal criteria used to select osteotomy type and wedge angle were: 1) medial plateau force, 40 ± 2% of the total knee joint force, 2) joint obliquity ≤ ± 3°, and 3) minimal collateral ligament tension. The type of osteotomy selected based on the optimal criteria was correlated with key parameters (FTA - femorotibial angle based on mechanical axis, joint peak pressure, plateau line obliquity, ligament tension and joint loading axis location) using unpaired t-tests and ANOVA. There was a significant correlation between the pre-operative joint obliquity and the type of osteotomy (UTO/SCO) that provided acceptable results[11]. UTO was most suitable for mean pre-operative joint obliquity of 1.9° (medial tilt) and a mean FTA of 5.9° varus. SCO was necessary for mean pre-operative joint obliquity of 2.7° (lateral tilt) and a mean FTA of 7.5° varus. Cases requiring a double osteotomy were those having an average preoperative FTA of 11.3° varus. In this study, it was concluded that use of the FTA (mechanical or anatomical axis) and lower extremity loading axis alone cannot satisfactorily predict optimal results since they do not correlate with joint obliquity, the key determining factor based on the current analysis.

DISCUSSION

One goal of reconstructive surgery in orthopaedics is to realign the appendicular skeleton so that the related joints can transmit physiologic pressures without causing high contact stress induced osteoarthritis. In the hip, femoral head coverage has a significant effect on cartilage degeneration and joint dislocation, especially among patients with developmental dysplasia of the hips. Proximal femoral and/or pelvic osteotomies have demonstrated excellent clinical results, alleviating pain and mobility limitations in affected patients. Unicompartmental joint disease of the knee is a common condition among middle aged men and women. It also affects a large population in Asia due to their style of activities of daily living. Joint deformity and pain often prevent these otherwise healthy individuals from enjoying life and being productive. Performing limb/joint alignment surgery redistributes knee joint stress between the diseased and the unaffected compartment to allow normal functional use of the knee. Knowing how to perform such procedures and determining the appropriate angular corrections are key factors for successful treatment outcome. Longevity of excellent clinical results also correlates closely with the site and amount of surgical correction. Hence, a careful preoperative planning guide for this type of procedure saves surgeons' time by providing various surgical options and potentially improving postoperative results.

The biomechanical justification of knee osteotomy is that it will realign the lower extremity weight bearing axis and unload the affected tibial plateau thus relieving the compartment pressure. Pain may be relieved thereby allowing functional recovery in patients with unicompartmental arthritic involvement. However, in the preoperative preparation of the procedure, the magnitude, type and location of the osteotomy to be performed are often difficult to determine as each patient may have a different deformity with widely varying pathologic involvement. It has been well demonstrated that even a small amount of angular change in knee alignment can drastically alter joint pressure distribution, which may negate the therapeutic effect of such a reconstruction procedure. In addition, the effects of soft tissue tension, joint line obliquity and upper body gravity shift on knee plateau pressure distribution may also influence the long term result of osteotomy. Thus, manual planning and visual inspection on preoperative radiographs can be inadequate. In addition, key information such as joint load distribution, joint pressure, joint line obliquity, etc., will not be available. For these reasons, an Osteotomy Analysis Simulation Software (OASIS) program was developed to provide comprehensive presurgical planning of knee osteotomy, so as to provide all rational options for surgeons.

An analytical model is derived based on the AP standing radiograph of the patient's lower extremities, covering the hip and ankle joints. The joint centers, mechanical and anatomical axes of the femur and tibia, patella center, joint contour outline, muscle and ligament insertion points, and joint articular surface contact area are manually digitized on a translucent, background-lighted electrostatic digitizer. In this model, muscle, ligaments, and joint cartilage are represented by a series of linear springs, while the bone segments are assumed to be rigid bodies. Body weight, muscle contraction, ligament and cartilage stiffness properties, and the upper body gravity location are the input data for the simulation analysis. The entire digitizing procedure and model analysis takes approximately 40-60 minutes.

The computer program is interactive with graphic display and tabulation of analysis results for any simulated osteotomy. Input parameters and osteotomy wedge angle and location are introduced using a mouse or a keyboard guided by clear menu instructions on the monitor screen.

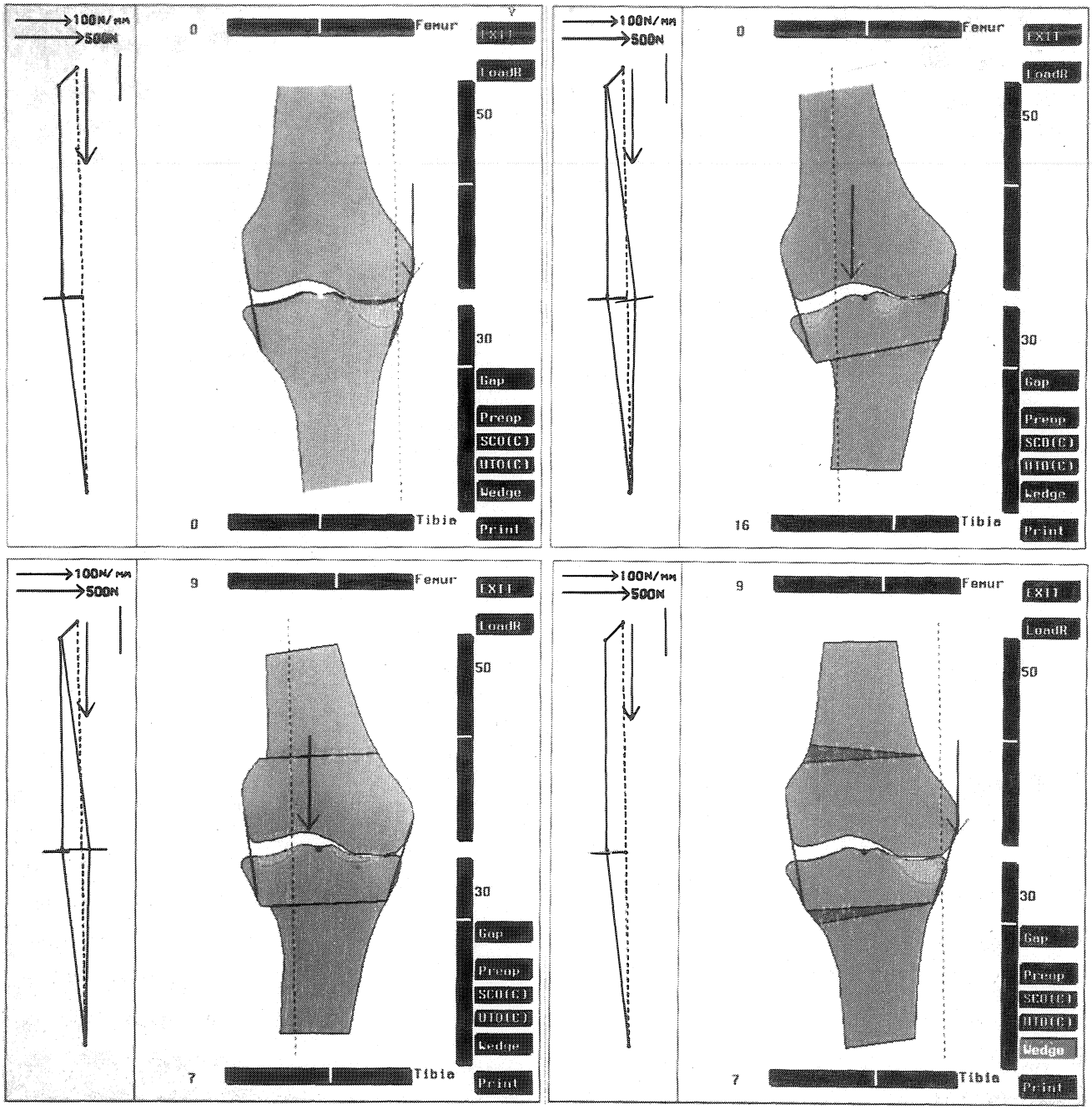


Figure 9 A difficult bilateral double osteotomy case of a man with large varus deformity in both knees.

Figure 9A. Computer-aided preoperative planning on his right knee showing single upper tibial osteotomy will be inadequate to correct the alignment and joint pressure distribution when compared to the double osteotomy;

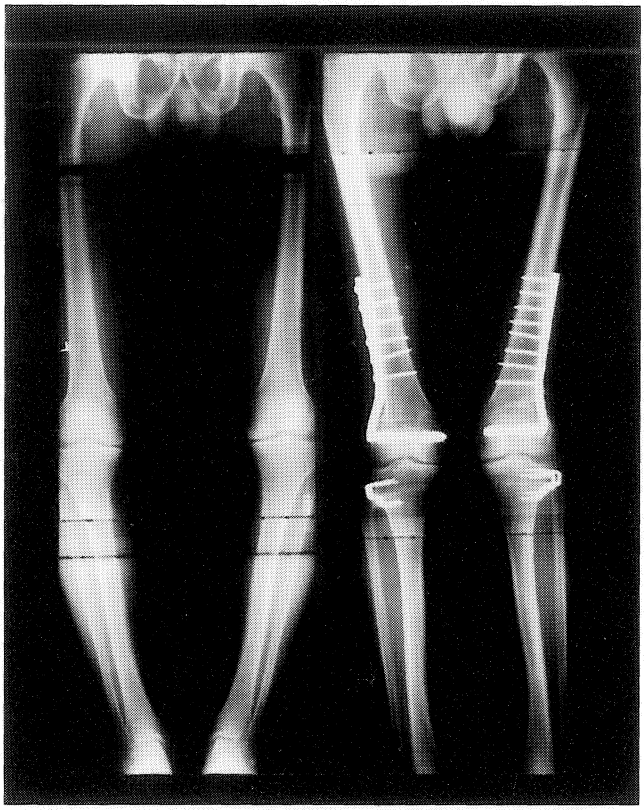


Figure 9B. The pre and postoperative radiographs of this patient.

Upper tibial and supracondylar osteotomies at the usual level of proximal tibia and distal femur are routinely provided, while additional options of closed-wedge, open-wedge or dome/barrier type of osteotomy at any level of the long bones can be easily performed. The output of the program includes tibiofemoral angle based on both mechanical and anatomic axes of the femur and tibia, percent of joint force passing through the medial plateau, peak joint pressure, joint shear force, collateral ligament tension, joint line obliquity analysis, joint loading axis (the line joining the hip and ankle center), location in reference to tibial plateau width, and the lower extremity length change. The osteotomy size measured along the bone surface is also provided based on the estimated x-ray magnification using proper markers on the radiograph. These truly provide unprecedented information required to achieve reliable and relevant preoperative planning in knee osteotomy as the surgeon is not limited to the specific type of osteotomy.

Large normal data base and clinical case follow-up analyses are being conducted to study the efficacy of this program. Experimental and analytical studies should also be performed in order to validate the model. The true value of this simulation program must await the clinical and functional results of prospective studies conducted in different institutions involving large patient populations. Thus far, the program has saved an enormous amount of time in providing preoperative planning while the information provided to the surgeons has been utilized with great enthusiasm. It is important to realize that the current analysis is static, two-dimensional, and based on the fundamental assumption that improved joint force redistribution under standing posture will carry its therapeutic effect to the dynamic performance of the knee. Without this assumption, the current analysis is invalid. From a practical point of view, such an assumption is essential as with all reconstructive procedures in orthopaedics. Finally, various indicators have been suggested to predict the outcome of knee osteotomy[50]. Unfortunately, these indicators cannot be used to obtain the optimal osteotomy wedge. Therefore, the true utility of such indicators is questionable. However, they may provide unique value in assessing the functional outcome of these patients before and after the reconstructive surgery.

SUMMARY

We believe the osteotomy should play a major role in the knee surgeon's armamentarium. Long term satisfactory results can be obtained in well-selected patients with unicompartmental degenerative arthritis of the knee associated with malalignment. The success of this procedure is highly dependent on selection of the patient with appropriate surgical indications. Surgical technique must be precise and based on accurate preoperative planning. Knee osteotomy, regardless of its type and location, performed with modern technological tools, should provide satisfactory long term clinical results in the majority of patients. If the osteotomy is properly performed with careful planning, the patient can expect a relatively uncomplicated conversion to a prosthetic replacement when increasing knee symptoms require further surgical intervention. Based on the unique pathomechanics involving osteoarthritis and the success demonstrated in recent studies, knee osteotomy has met original expectations and continues to be a viable option. In severely deformed knees, a single osteotomy at high tibial or femoral supracondylar regions may not be able to correct the alignment and maintain proper joint line obliquity. A complex dual osteotomy may be necessary to achieve proper knee alignment and provide the essential requirements for appropriate pressure redistribution in the knee joint. A computer-aided preoperative planning software package like "OASIS" can help to produce surprisingly positive clinical results for these different reconstructive procedures. Long term prospective follow-up studies of patients are required to validate the effectiveness of this preoperative planning scheme and are now in progress. When such methods are properly established, the surgeon should be even more confident in performing osteotomies about the knee for the treatment of unicompartmental

knee degenerative disease. This allowed definitive treatment for patients with early osteoarthritis in the knee. Such procedures should be considered first before other more aggressive joint replacement procedures are performed.

ACKNOWLEDGMENT

The computer program, "OASIS" used in the knee osteotomy preoperative planning and the normal database on knee axial alignment and pressure distribution was developed under the partial support of ZONA Medical Technology Inc., Tokyo, Japan. The technical staff and research fellows of the Biomechanical Laboratories at the Mayo Clinic and Johns Hopkins University contributed enormously in the computer software development and the establishment of the patient database.

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REHABILITATION FOLLOWING ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION: WHAT DO WE REALLY KNOW?

Robert J. Johnson, M.D.
Bruce D. Beynnon, Ph.D.

"It was a great pleasure for me to provide this article to the issue of the Iowa Orthopaedic Journal which has been dedicated to Don Kettlekamp. During my last two years of residency when Don was with us at the University of Iowa, his input into the development of my career was certainly of immeasurable value to myself. I wish to express my deepest thanks to Don for his assistance in the development of my career."

Robert J. Johnson, M.D.

Post-operative rehabilitation is a major factor in the success of anterior cruciate ligament (ACL) reconstructions. Over the last 15 years, there have been dramatic changes in the aggressiveness and timing of ACL rehabilitation protocols[8,29,30,32,34]. From information we have gained from our colleagues and those at sports medicine and Academy courses, it appears that fast-track, aggressive rehabilitation programs allowing athletes to return to full activities four to six months following ACL surgery are widely accepted and utilized. The reasons cited for more aggressive rehabilitation include the use of stronger ACL grafts, better fixation techniques, and better understanding of the positioning of the grafts within the tibia and femur. Additional reasons include the assumption that patients who don't follow a more conservative program have done well and the supposition that animal models concerning ACL healing cannot be applied to humans. A recent trend toward rapid rehabilitation with return to sports in four to six months following ACL reconstruction appears to be successful[32]. Yet Frank Noyes[26] recently informed the attendees of the American Academy of Orthopaedic Surgeons Sports Medicine Course in January 1995 that he was aware of no studies proving that rapid rehabilitation is safe and efficacious. In spite of the reports of successful rapid and aggressive rehabilitation, we have never felt comfortable with the evidence presently available in the literature.

There is little doubt that the prolonged immobilization utilized 10 to 20 years ago following the trauma of ACL surgery had many disadvantages. The significant atrophy of thigh musculature, damage to the articular cartilage, and development of arthrofibrosis were frequently seen as a result of the most conservative rehabilitation programs. However, in those days, it was felt that protection of repaired or reconstructed ligamentous structures was required to avoid stretching or failing the tissues as they healed. Experimental studies demonstrate that the quadriceps acts antagonistically with the ACL when the knee is brought from 50° flexion to full extension with a concentric contraction[7]. These factors led to the avoidance of early weight-bearing, joint motion, vigorous muscle activity, and early return to sport. As the more aggressive and rapid rehabilitation programs become accepted, the goals of immediate full range of motion, allowing weight-bearing as tolerated, beginning muscle activities that could potentially strain but hopefully not overload the ACL graft during healing, and returning to unrestricted activity four to six months following an ACL reconstruction occur if muscle strength and range of motion are completely restored. The more rapid rehabilitation programs currently suggested are advocated because patients who did not follow a more conservative approach suggested by the surgeon did not appear to have inferior results, but actually had better results[11,32]. Our experience with patients not complying with their post-operative rehabilitation protocols is not as universally satisfactory as suggested by Clancy and Shelbourne. We see many failed ACL grafts and other complications due to patients more aggressively rehabilitating themselves against the surgeon's advice. Likewise, it is frequently reported in the literature that undesirable joint kinematics recur in the form of abnormal anterior translation of the tibia relative to the femur following ACL reconstruction. In a 7.9 year follow-up, we demonstrated that 29% of the patients had greater than a four mm increase in anterior laxity on the side reconstructed compared to their normal knee[18]. In a two year follow-up study, Shelbourne demonstrated that 25% of his patients had greater than a three mm increase in anterior laxity for the reconstructed knees compared to the opposite side[33]. In a two year follow-up, O'Brien et al. demonstrated that 24% of their patients had greater than a three mm increase in anterior laxity for the reconstructed knees compared to normal knees[27]. Although some authors suggest that side-to-side differences of up to five mm are considered satisfactory, even a three mm side-to-side difference should be of concern to those who are seeking excellent results. In a current study at the University of Vermont we demonstrated that immediately following ACL reconstruction, laxities at time zero are

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essentially the same as those of the opposite normal knee, but we noted increased anterior laxity when followed up to one year. How these changes are affected by rehabilitation is not known, but biomechanical factors such as overloading the graft fixation or overloading the healing graft tissue may be important. We know that healing tissue must not be overloaded, and it is stated by other investigators that these tissues must be stressed an appropriate amount during rehabilitation[34]. However, no one knows what is the proper amount of loading. With these issues in mind, Minkoff and Sherman stated "the physician is adrift in an ocean of isolated scientific findings that are not readily coordinated"[24]. There is little information available to the clinician to allow identification of those rehabilitation activities which are safe and/or when they are safe to institute.

The current literature concerning the effects of rehabilitation programs on the eventual outcome of ACL reconstructions, especially involving biological and biomechanical factors, is only sketchy at this time. We can divide the literature concerning rehabilitation factors into clinical, animal, and biomechanical investigations of the normal ACL *in vivo*.

Clinical Investigations

Glasgow and Torg found no difference in KT-1000 measurements of anterior-posterior (A-P) knee laxity 45 months following ACL reconstruction between groups allowed to return to vigorous activities at five months versus nine months[14]. The use of a CPM during the first 30 days after ACL reconstruction in comparison to early active motion produced similar KT-1000 measurements of A-P knee laxity and range of joint motion according to Rosen et al[31]. Initiating early CPM did not produce a significant change in KT-1000 measurements of A-P knee laxity in comparison to seven days of immobilization[25]. Immediate knee motion and early weight-bearing did not increase the incidence of abnormal A-P displacement of the tibia relative to the femur in a study by Barber et al[2].

What is lacking in these clinical investigations is a prospective randomized clinical trial comparing ACL rehabilitation programs that are aggressive and rapid to those which are more conservative and protracted.

Animal Investigations

The advocates of rapid rehabilitation have correctly discerned that the results of animal reconstructions and their post-operative care cannot be readily transferred to humans. There is little doubt that the cooperation necessary to complete a post-operative rehabilitation program is not manifest in any animal model. However, since it is impossible for us to perform destructive studies that determine the biomechanical and histological end results of ACL reconstructions in a human model, we cannot totally ignore the investigations that have evaluated these factors following the reconstruction of animal ACLs. The ultimate failure loads of patellar tendon autografts in animals models are all well below the control ACL values at the time of sacrifice varying from three to 24 months following ACL reconstruction. Expressed as a percentage of the contralateral normal, return of ultimate strength of the graft has ranged as high as 55% in primates, 40% in goats, 30% in canines, and only 12% in rabbits[1,6,9,10,12,22,23,35,38]. The stiffness values of patellar tendon autografts in animal models are found to be far below normal between three and 24 months following reconstruction. They ranged from 60% in primates down to 13% in rabbits compared to their normal contralateral ACL. A-P laxity following patellar tendon ACL autografts in animal models has ranged between 156% and 600% of the normal knee in primates, canines, and goats[1,6,15,16,21]. How much these values could be improved upon if the animals could truly comply with the post-operative rehabilitation program is, of course, totally conjectural and probably some improvement could be attained if animals could follow a post-operative rehabilitation protocol. At the present time, we do not know what the ultimate failure loads and the stiffness values for reconstructed ACLs are in humans and we do not know the time frame within which they return toward normal.

The devitalized and devascularized ACL does not undergo a change in biomechanical properties if anatomic position, orientation, and strain distribution along the collagen fibers are maintained in a goat model according to Jackson et al[17]. These findings suggest that the decrease in biomechanical properties of ACL grafts may not be the result of revascularization and healing during rehabilitation, but rather improper positioning and tensioning of the graft. We studied the relationship between anterior-posterior knee laxity and the structural properties of autogenous patellar tendon grafts used to replace the ACL in canines one year after reconstruction[6]. As anterior knee laxity increased, the ultimate failure load and linear stiffness values of the graft decreased. The clinical significance of this study is that knee laxity measurements demonstrating an increase in anterior translation of the tibia relative to the femur during graft healing may indicate that the graft has developed weakened and reduced structural properties.

From the observations made on the animal models of ACL reconstructions, one must be concerned about early and aggressive rehabilitation activities. It could be construed that such early rehabilitation efforts may, in fact, elongate or even fail a healing ACL graft. The investigations demonstrating the prolonged and incomplete improvement in the biomechanical function of ACL grafts in the animal models should caution us about rapid and

aggressive rehabilitation until more is known about how the biomechanical behavior of human ACL reconstructions are affected by various rehabilitation programs.

In-Vivo Biomechanical Investigations

Functional braces are used to treat instability of the knee after injury to the anterior cruciate ligament. They are also used to prevent intra-articular injury and protect healing ACL grafts; however, the extent to which a brace can produce these effects is unclear. Thus, we performed an investigation of the effect of functional braces on ACL strain in human subjects with uninjured knee ligaments and normal muscle function[3]. None of the functional braces produced a deleterious increase in anterior cruciate ligament strain; a finding in contradiction to our earlier investigation of braces using the cadaver model. For low anteriorly directed shear loads applied to the tibia, bracing provided a protective strain-shielding effect on the ACL compared to the unbraced condition, but strain-shielding did not occur at the higher anterior shear loads expected to occur during athletic activities. Some of the braces produced a strain-shielding effect on the ACL for internal-external torque of the tibia.

In an effort to develop an objective database for prospective investigations on the effect of rehabilitation on healing grafts, we have measured the strain behavior of the anteromedial bundle of normal ACLs[7]. Strain has been measured with a Hall Effect Strain Transducer (HEST) and more recently a Differential Variable Reluctance Transducer (DVRT, MicroStrain Co., Burlington, Vermont). The summary of the amount of strain produced by various rehabilitation activities is provided in Table 1. ACL strain values were found to be dependent on knee flexion angle and muscle activity for: 1) active flexion/extension motion; 2) isometric quadriceps contraction; 3) simultaneous contraction of quadriceps and hamstrings; and 4) squatting activities. Many investigators suggest that open kinetic chain activities produce greater ACL forces than closed kinetic chain activities[13,19,20,28,36,37]. Thus, the use of squatting and other closed kinetic chain activity is advocated by many who promote early vigorous rehabilitation. Our investigation measuring the strain produced in squatting with and without a sport cord would indicate that higher strains are produced by this activity than previously reported. This demonstrates the danger of taking the literature at face value and not performing direct measurements to validate the effect of rehabilitation activities on strain, which correlates to the stress which must be withstood by a healing ACL.

We measured the elongation behavior of ACL grafts in human subjects at the time of surgery and at one year follow-up. We demonstrated that, at the time of implantation, local elongation behavior of an ACL graft was not significantly different in comparison to the local elongation behavior measured in a series of normal control ACLs[4,5]. One year following the installation of a bone-patellar tendon-bone autograft, we remeasured the elongation behavior in the reconstructed ACL and demonstrated a trend toward greater elongation within the healed ACL than was seen at the time of implantation[4]. This would indicate that factors including rehabilitation occur during healing that may adversely alter the end results of ACL reconstructions.

TABLE 1

A rank ordering of different rehabilitation activities based on the peak strain value developed during the activity.

ACTIVITY	PEAK STRAIN
Isometric quadriceps @ 15° (to 30 Nm of extension torque)	4.4%
Squat with Sportcord	4.1%
Active Range of Motion with a 45N weight boot	3.8%
Lachman Test (150N of anterior shear)	3.7%
Squat without Sportcord	3.4%
Active Range of Motion	2.8%
Simultaneous quadriceps & hamstrings contraction @ 15°	2.8%
Isometric quadriceps @ 30° (to 30 Nm of extension torque)	2.7%
Anterior drawer (150N of anterior shear)	1.8%
Isometric hamstrings @ 15°	0.6%
Simultaneous quadriceps & hamstrings @ 30°	0.4%
Passive Range of Motion	0.1%
Isometric quadriceps 60° - 90° (to 30 Nm of extension torque)	0.0%
Simultaneous quadriceps & hamstrings 60° & 90°	0.0%
Isometric hamstrings @ 30°, 60°, and 90° (10 Nm of flexion torque)	0.0%

Our investigations of the biomechanical behavior of normal and reconstructed ACLs in humans has led us to be concerned about current rehabilitation methods. Those who use any rehabilitation activity which loads the healing ACL in the early post-operative period must understand that significant strains are imparted to the healing ligament. Although no one knows what strains are deleterious to the ACL, physicians developing their own ACL reconstruction post-operative protocols should realize that these structures are being loaded and there is a potential for damage to the healing tissues if overzealous or too early application of rehabilitation activities occurs.

At the present time, our main concern is that current rehabilitation protocols advocated are not based on truly validated research data. The lack of randomized clinical trials evaluating the ultimate outcome of rapid and aggressive rehabilitation compared to more conservative and lengthy rehabilitation must occur before we can fully answer the question of *which* activities can be safely prescribed and at what time they can be instituted. We

fear that the present utilization of rapid rehabilitation may be based more on the pressures of marketing than on the evaluation of scientific data. It is unfortunate that outcome studies requiring expensive epidemiologic investigations and relatively prolonged periods of time must be performed before we can understand which activities are safe and when they can be prescribed. The dilemma that ACL rehabilitation provides for the physician, and more importantly for his/her patients, stresses the value of outcomes research based on solid epidemiologic grounds. We must be extremely critical in our analysis of studies which advocate one rehabilitation program over another. Most are based on biased, poorly controlled, and defective epidemiologic research. Only when all orthopaedists fully understand the need for appropriate outcomes research incorporating well designed randomized clinical trials and demand their utilization will we be able to attain the goal of devising the ultimate universally acceptable ACL reconstruction protocol. Unfortunately, it is going to take time, effort, and financial support to develop the necessary investigations to determine what is the ideal ACL rehabilitation program. The title of this article asked the question, "What do we really know about rehabilitation following anterior cruciate reconstruction?" The answer has to be that, "At the present time, we know very little about the effects of rehabilitation on the healing ACL graft."

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THE RESPONSE OF THE FLEXION-RELAXATION PHENOMENON IN THE LOW BACK TO LOADING

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ABSTRACT

Fick[7] hypothesized in 1911 that the erector spinae muscles are not active when the trunk is in the fully flexed position. This effect was later called the flexion-relaxation phenomenon (FRP) and is believed to be the result of the ligaments and other passive elements of the spine taking over the load of the muscles. This study examined the effect of loading on the EMG activity of five males and five females during postures of standing at 45°, 90°, and full flexion. The results showed major differences in the relationship between the electromyographic signal (EMG) of the erector spinae and loading for the four postures. The erector spinae muscles did not activate in positions of full flexion (or even 90° for some subjects) for loading as high as 50% of their maximum voluntary contraction, suggesting that alternative muscles are being activated and that the passive tissues may be put under higher loads than originally thought in these positions. The results suggested that the FRP could be used as a biofeedback tool to illustrate to workers that their muscles are not turning on in the fully flexed positions, and therefore, these positions should be avoided.

Key Words: Electromyography, low back pain, flexion-relaxation phenomenon.

INTRODUCTION

The electromyographic activity of the dorsal muscles are anatomically related to the force in the muscles (Anderson et al.[2], Basmajian and DeLuca[5] & Pope et al.[22]). It has been established that electromyographic activity increases both with an increase of flexion angle and an increase in external loading at a fixed flexion angle (Anderson et al.[3,4], Morris et al.[18], Schultz et al.[24]).

One of the most common activities is forward flexion, yet it is a complex event. According to Carlsöö[6], the first fifty degrees of flexion occurs within the lumbar spine and the remainder by rotation of the pelvis. In extension the reverse happens, pelvic rotation followed by lumbar spine extension. Carlsöö[6] and Okada[20] have found that flexion is initiated by muscles that stabilize the pelvis and lock the hip joints (gluteus maximus, gluteus medius and hamstrings). Erector spinae activity increases with flexion to a point where it decreases completely (Allen[1], Floyd and Silver[8], Golding[10], Grieve[11], Morris et al.[19], Pauly[21], Valencia & Monroe[26]).

Flexion-relaxation, or a cessation of activity in the erector spinae muscle group, is generally thought to occur as a result of the passive tissue of the back (ligaments, fascia, disk, facets etc.) taking over the load for the muscles. If this is indeed the case, then a loss of muscular control in the trunk would be occurring in these bent over postures, suggesting that they should be avoided. However, investigators have recently suggested that when the loading on the trunk becomes enough, muscles activate even in the fully flexed postures in order to protect the passive tissues (Schultz[25]). Floyd and Silver[9] suggested that the phenomenon was due to stretch reflex inhibition.

The study is concerned with the action of the erector spinae musculature when a pull is performed during which the loading is gradually increased from 0-50% of a maximum voluntary contraction (MVC). Four different postures of 0° (standing), 45°, 90° and full flexion were tested as shown in Figure 1.

METHODS

Ten subjects, five male and five female, aged 18-40 years volunteered to participate in the study. None of them had any significant history of low back pain or present illness. All subjects were consented and no compensation was offered for participation in the study.

A metal frame was used to keep the subject in the correct postures for the testing. During the 0° posture (standing), a vest was worn which was connected to a rope and load cell. The other three postures were performed pulling up on a handle as shown in Figure 2. During these postures the length of the cable connected to the handle was controlled in such a way as to allow the subject to hold the desired posture during the pull. If the subject went out of a range of +/- 10° of the testing posture recorded by the inclinometer during a pull, the computer escaped and the trial was not recorded.

The subject performed two trials of MVC for each posture. The highest value in these two pulls was taken as the MVC value. After two MCV pulls, one trial of increasing a pull from a 0 load value to 50% of the MVC

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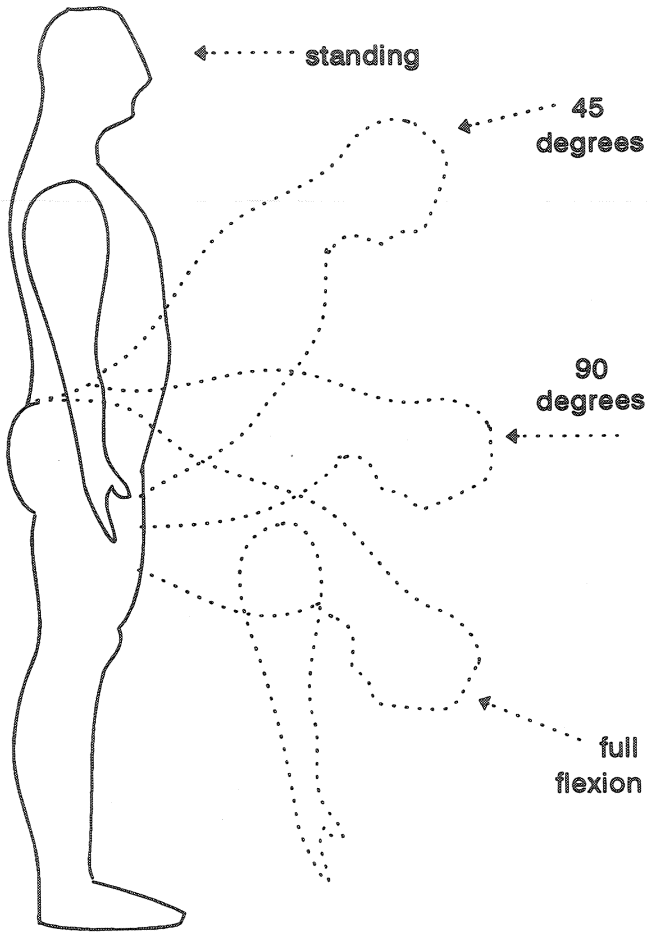


Figure 1. Four different testing postures

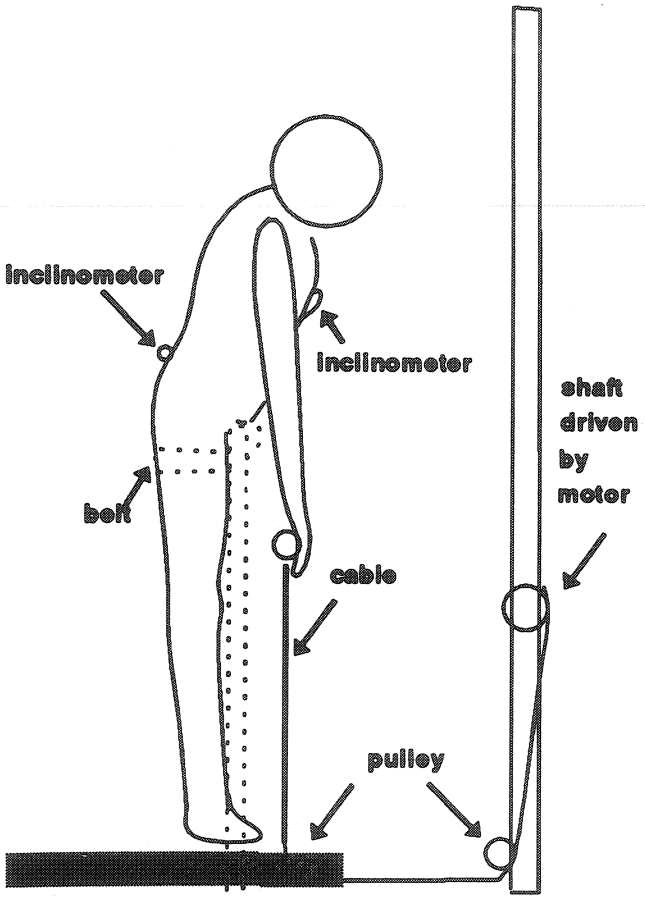


Figure 2. Subject in testing frame

load value was recorded. A biofeedback system of tones was used to signal to the subject the amount they were pulling. Electromyographic activity of the erectors spinae was recorded bilaterally by Davicon electrodes (with a gain of 1000) during the 0-50% MVC trials at the level of the third lumbar vertebrae, approximately 3 cm. from the midline of the spine. Palpation was done by using the level of the iliac crest as level with the L4/L5 interspace.

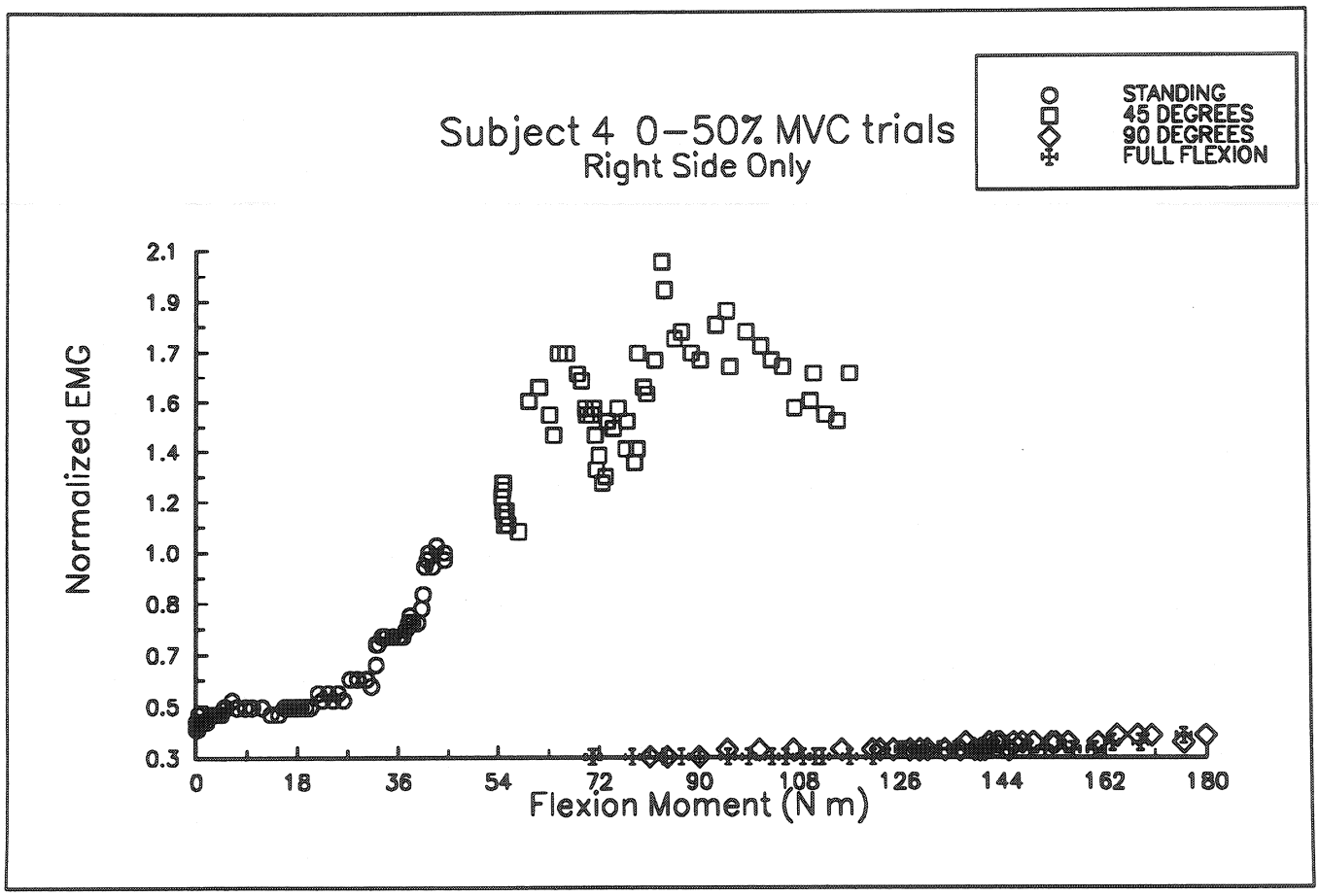
The EMG signal was amplified (gain of 3.365) in the power supply and a 100 ms RMS conversion was performed on the signal before recording by the computer at 20 Hertz. A fluid-filled Spectron inclinometer with a linear range of 120 degrees was used for the angle measurements. The inclinometer was mounted on the sternum with velcro straps (Haig et al.[12]). The readings from the inclinometer were recorded simultaneously with the EMG readings.

RESULTS

For comparisons to be made between subjects, a normalization technique was performed on the EMG readings. This consisted of dividing all the EMG values by the value of the EMG activity at the 50% MVC load in the standing position. An EMG value corresponding to the 50% MVC load was used instead of the full MVC EMG value because the EMG is still in the linear range at the 50% MVC load. The standing posture was used for normalization instead of the flexed postures to minimize the effect of body segment weights on the pull.

Calculations of body segment weights were done using the following values: 36% of body weight (BW) as the weight of the trunk above L3, 9% of BW as the weight of the two arms and 5% of BW as the weight of the head and neck. The mass center of the trunk above L3 was estimated as 30% of the distance between L3 and the ear in the upright standing position (Magnusson[17]). The distance from the muscle to the center of the L3 vertebral body was taken from the work of Kumar[15].

The individual segment weights were then multiplied by their respective moment arms. The moment arms were determined using the anthropometric data collected during the testing. The resultant values for flexion moment were then plotted against the normalized EMG activity as shown in Graphs 1 and 2.



Graph 1 Subject #4 right sided EMG vs. flexion moment

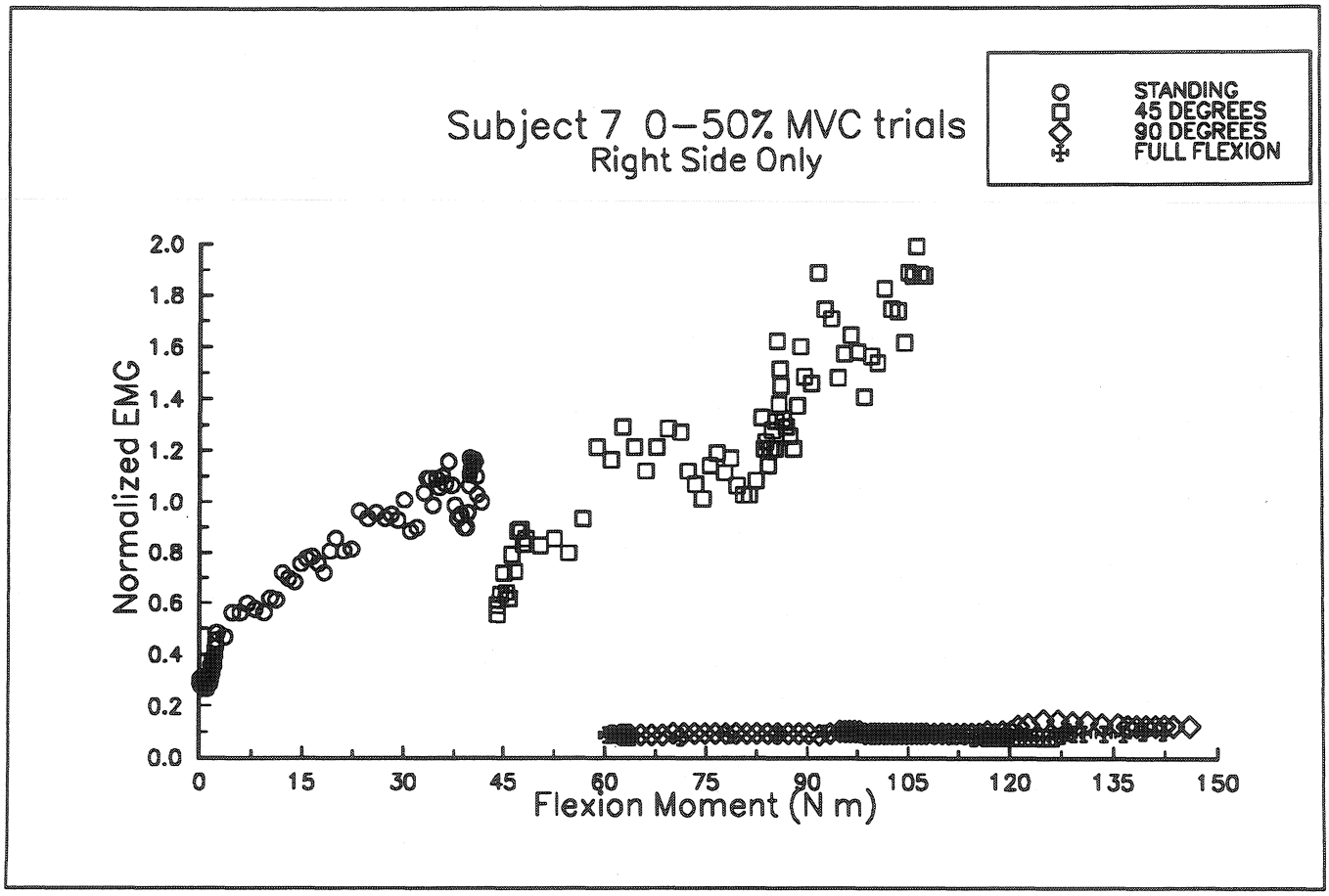
DISCUSSION

From Graphs 1 and 2 of the 0-50% MCV trials, it can be observed that a higher flexion movement is achieved in the flexed postures than in the standing posture. This was due in part because of the larger moment arms for the body segments in the flexed positions and also due to the fact the subjects showed a greater ability to produce force in the flexed postures.

The normalized EMG values for the subjects stay close to zero in the fully flexed posture and 90° posture, even for values as high as 50% MVC, indicating that muscles other than the erector spinae are generating the torque. These findings agree with those of Floyd and Silver[9] who found that the erector spinae remain inactive in the initial stages of heavy weight lifting, but disputes the findings of Schultz et al.[25] who reported that the erector spinae muscles would turn on in full flexion to compensate for any increase in loading over that which is caused by the weight of the upper body. Schultz et al.[25] also suggest that a similar relationship exists between EMG/Load in the back regardless of the flexion angle. From the graphs, it appears that a different pattern of EMG activity in relation to force occurs in the 90° and full flexed postures than in the 45° and standing postures. This changing relationship for the most flexed postures suggests that a mechanism is present to relieve the loading from the muscles that is not present in the slightly flexed postures. Kippers & Parker[14] have also shown that the FRP would occur later in the bending cycle when additional weight was carried, suggesting that it would take longer for the ligaments to take over for the muscles.

Portney and Morin[23] demonstrated that the hamstrings stay active during the flexed postures which could suggest that these muscles play a role in relieving the erector spinae muscles. The gluteus muscles relax on full flexion and the abdominal muscles are only active during the first few degrees of flexion. Another possible relief mechanism is suggested by Hukins et al.[13] and Macintosh et al.[16] by which the thoracolumbar fascia is used to enclose the erector spinae muscles and thereby increase their efficiency.

The results suggest that the passive mechanisms of the trunk are under greater stress than originally thought in



Graph 2 Subject #7 right sided EMG vs. flexion moment

the fully flexed postures. The flexion-relaxation phenomenon could possibly be used to train workers by illustrating to them that the nonmuscular parts of the their spine are at risk for injury in these fully flexed postures. This technique could also be used as biofeedback in lifting in combination with angle, so that when angle is increased and muscle activity drops substantially the wearer would be warned with a tone.

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ACTIVITY VS. REST IN THE TREATMENT OF BONE, SOFT TISSUE AND JOINT INJURIES

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For at least 250 years physicians have recognized that the loading and movement of musculoskeletal tissues caused by physical activity alters these tissues and the structures they form, and may affect healing; yet the appropriate role of activity in the treatment of injuries has been a subject of controversy. Some of the most experienced and knowledgeable physicians and students of the musculoskeletal system taught that early controlled activity promotes healing and accelerates restoration of function, while others advanced the opposite view. The opponents of treatment of injuries with activity argued that absolute rest allows healing to proceed at the maximum pace, and that early use of injured musculoskeletal tissues increases inflammation and disrupts repair tissue, thereby delaying or preventing healing. A series of investigations conducted over the last several decades helped resolve this controversy thereby improving treatment of musculoskeletal injuries and defining an important area for future research.

The purpose of this paper is to clarify the roles of activity and rest in the treatment of musculoskeletal injuries. It reviews the development of the concepts of activity and rest as treatments of musculoskeletal injuries, and then compares the effects of activity, that is, loading and motion of tissues, and active muscle contraction, with the effects of rest. In particular it summarizes recent studies of cell and tissue responses to repetitive use, the specific responses of normal bone, dense fibrous tissues, cartilage and muscle to increased and decreased use, and the effects of activity on bone, soft tissue and joint healing.

ACTIVITY VS. REST

Two of the most widely recognized contributors to orthopaedics, Nicolas Andre and Julius Wolff, were among those who argued that activity benefited normal tissues. In his thesis, first presented in 1723, Nicholas Andre (1659-1742) noted that moderate exercise strengthens and shapes the musculoskeletal tissues. He advocated "action" as a more important treatment than "rest." In the latter part of the 19th century, Julius Wolff (1836-1902) described the ability of bone to adapt to changes in repetitive loading, and stressed that the adaptation of bone to changes in use occurred "according to mathematical law."

At approximately the same time, a French Orthopaedist, Just Lucas-Championniere (1843-1913) [Figure 1], went beyond the concepts of Andre and Wolff to argue that activity benefited injured tissues. He taught that movement accelerated healing, and that enforced rest injured cartilage, ligaments and muscles. He also observed that slight movement at a fracture site promoted healing rather than retarded it, and advocated massage treatment of fractures and joint injuries.

Given the observations and recommendations of Lucas-Championniere it is reasonable to ask why physicians have not included early controlled activity as a critical part of the treatment of musculoskeletal injuries for at least 100 years, and why more effort has not been directed towards investigating the effects of activity on healing of the musculoskeletal tissues and refining the clinical application of controlled activity to the treatment of injuries. The answers to these questions lie to some extent in the widely accepted teachings of a talented and influential group of investigators and physicians from Great Britain. In the 1700s John Hunter (1728-1793) prescribed "rest" as the routine treatment of "disablements" of the human motor system, a practice that John Hilton (1807-1878) strongly supported in the 1800s. Hilton considered long continuous rest the most powerful treatment a surgeon

Figure 1. Just Lucas-Championniere (1843-1913), French Orthopaedist who advocated treatment of musculoskeletal injuries with activity and taught that enforced rest damaged normal tissues.

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could bring to the aid of "disordered tissues," and noted that he had never seen long-continued rest produce harm. Despite the fame and influence of Hunter and Hilton, Hugh Owen Thomas (1834-1878) [Figure 2], during his long and successful career in Liverpool, became the strongest and most effective advocate of rest as the optimal treatment of musculoskeletal injuries. He believed that the only way a surgeon could promote healing was by giving an injured part rest, and that an overdose of rest was impossible. He taught that rest must be "enforced, uninterrupted, and prolonged," and observed that forced early motion stimulated inflammation that led to adhesions. The contrasting teachings of Hugh Owen Thomas and Just Lucas-Championniere show why clinical experience alone cannot form a sound foundation for a comprehensive approach to treatment of injuries or diseases. Both individuals were observant, experienced clinicians, but because they had limited information concerning the structure, composition and function of the musculoskeletal tissues and the healing of these tissues, they could not study the responses of the tissues to rest or activity, and they had limited ability to measure the outcomes of treatment and conduct controlled clinical investigations. For these reasons, clarification of the role of activity vs. rest in the treatment of injuries awaited advances in the studies of the musculoskeletal tissues.

Figure 2. Hugh Owen Thomas (1834-1891), Orthopaedist from Liverpool who taught that musculoskeletal injuries should be treated by prolonged enforced rest.

MECHANISMS OF TISSUE RESPONSE TO REPETITIVE LOADING AND MOTION

Most investigations of the effects of repetitive loading and motion focus on isolated tissues and cells, yet activity also has transient and persistent systemic effects including alterations in cardiovascular function, tissue perfusion, metabolism, and hormonal balance[30, 65, 75, 89, 101, 127, 145]. Although the influence of these systemic changes on local tissue responses to repetitive loading has not been extensively studied, they may influence the local response of tissues to repetitive use, possibly by altering the sensitivity of the tissues to cyclical loads. For this reason predicting the effects of activity on tissues in vivo from studies of the effects of loading and motion on cells and tissues in vitro must be done with caution. Nonetheless in vitro investigations provide insight into the mechanisms of the tissue responses to activity.

Recent studies of local effects of repetitive loading have identified a variety of cell and tissue responses. They have shown that repetitive loading of various types and intensities influences cell shape and cell synthetic and proliferative functions[13, 19, 22, 39, 40, 81, 114, 129]. Furthermore, they show that loading alters the alignment of the matrix macromolecules[57, 99, 12], that the matrix transmits loads to cells, and that cells can realign the matrix macromolecules in response to these loads[58, 81, 99]. The response of the tissues to loading varies among tissues and may vary with age[29, 120, 149], that is, tissues from skeletally immature individuals may be more responsive to increased use than tissues from older individuals.

The local mechanism of bone, tendon, ligament and cartilage response to loading consists of cells detecting tissue strains and responding by modifying the tissue. Experimental studies show that cells may detect tissue strain either directly through deformation of the cells, or indirectly through alterations in the matrix due to deformation of the tissue. Cyclic stretching or compression of mesenchymal cells can align intracellular microfilaments along the axis of tension, change cell shape[7, 83] and alter synthesis of DNA, matrix molecules and prostaglandins[19, 56, 60, 61, 90, 103, 110, 122, 129, 161]. Deformation of the matrix can alter matrix macromolecular organization, fluid flow, streaming currents, pressure gradients or electrical fields. These matrix alterations can influence cell function[56, 59, 96, 103]. By altering matrix macromolecular organization, matrix deformation may provide tissues with a mechanism of recording and averaging transient strains thereby giving the cells a more

sustained and coherent stimulus[128]. Loading of a tissue also can affect local vascular perfusion and diffusion through the matrix thereby altering the flow of nutrients and metabolites[15].

The local mechanisms of skeletal muscle response to changes in activity differ from those of connective tissues: dense fibrous tissue, bone and cartilage[20, 33, 44, 133]. The connective tissues consist primarily of mesenchymal cells and an extracellular matrix, while skeletal muscle consists of two components: an elaborate extracellular matrix synthesized and maintained by connective tissue cells like those found in fibrous tissues, and innervated muscle cells or myofibers[24]. The connective tissue component of skeletal muscle has a critical structural role in maintaining the tissue organization and stability[33]. In addition it contributes to the passive mechanical properties of muscle including resisting excessive elongation of the myofibers[116]. Both myofibers and muscle connective tissue cells respond to changes in muscle activity and injury. Presumably, the muscle connective tissue cells, like the cells in dense fibrous tissues, respond to changes in tissue loading and motion with alterations in cell proliferation and synthetic activity that change the organization, composition and mechanical properties of the extracellular matrix. Unlike the connective tissue cells, myofibers respond to persistent changes in the activity primarily with changes in cell structure, volume and function. The mechanisms of their response to activity remain unclear, but it appears that they respond to both stretching and repetitive active contraction.

RESPONSES OF SPECIFIC TISSUES

Studies of individual tissues show that maintenance of normal bone, dense fibrous tissue, cartilage and muscle require a minimal level of repetitive use. This minimal level varies among tissues and individuals, but activity below this level adversely alters the tissues and can eventually cause irreversible changes. The intensity and frequency of activity above the minimal level necessary to cause an adaptive tissue response also varies among tissues and individuals. In general the tissues of younger individuals appear to be more responsive. Bone and skeletal muscle have more dramatic and obvious responses to increased and decreased use, but the dense fibrous tissues and cartilage can also respond to changes in level of activity. Activity also influences healing of these tissues, but the effects vary considerably and in general remain less well understood than the effects of activity on normal tissues.

Bone

Decreased Use of Normal Bone

Immobilizing a limb in a cast or placing a patient in skeletal traction for a prolonged period of time causes bone resorption to exceed bone formation[139]. Osteoclasts resorb trabecular and cortical bone, and osteoblasts fail to replace enough bone to maintain the mass and strength of the tissue. Decreased activity may not produce readily detectable changes in bone volume, shape and strength, but prolonged immobilization of a limb will cause radiographic changes including decreased density of cancellous bone, loss of trabeculae, thinning and increased porosity of cortical bone. Regular contraction of the muscles of an immobilized limb may decrease the loss of bone[31]; but without weight bearing, bone mass declines to less than half the normal value after 12 weeks[82,139]. These alterations decrease bone strength and increase the probability of fracture. Regaining bone density after prolonged decreased use, even with vigorous activity, can require many months, even in children. In some individuals, especially older people, bone density may never return to its previous level.

Increased Use of Normal Bone

Persistent increases in cyclic loading of bone cause bone formation to exceed bone removal and can result in dramatic increases in bone density, volume and strength. In 1864, Sedillot found that removing the tibial diaphysis in dogs caused the fibula to increase in size sufficiently to compensate for the loss of the tibia[100]. A more recent study of pigs provided an equally dramatic example of the ability of bone to adapt to increased loads[55]. Resection of the ulnar diaphysis increased the compressive strain on the radius by two to two and one-half times its normal value. This led to a rapid increase in the diameter of the radius such that within three months the cross sectional bone area of the radius approached the value for the radius and ulna combined, and the compressive strain in the radius had decreased to nearly the normal value. Repetitive loading in vigorous physical activities can produce similar, although less impressive, effects[34, 36, 37, 88, 102]. For example, professional tennis players develop increased bone density, cross sectional area and diaphyseal diameter in the humerus of their dominant arm[36, 71].

Use of Injured Bone

Although fractures heal in rigidly immobilized unloaded limbs, optimal fracture healing appears to require at least some cyclical loading of the repair tissue. Loading a fracture site stimulates bone formation while decreased loading slows fracture healing[106, 126]. Limb denervation also can retard fracture healing, possibly by diminishing loading of the fracture or by inhibiting the effect of growth factors that require activation by neurotransmitters[117]. In contrast, exercise can increase the rate of repair[64], possibly through loading of the fracture. Experimental work, in particular the investigations of Kenwright, Goodship and colleagues, shows that early or almost immediate loading and movement, including induced micromotion at

long bone fracture sites, may promote fracture healing[54, 76-79], observations that support Lucas-Championniere's teachings. Clinical studies also show that early or even immediate controlled loading of long bone fractures does not impair, and may promote, fracture healing[38, 97, 125].

Dense Fibrous Tissues (Tendon, Ligament and Joint Capsule)

Decreased Use of Normal Dense Fibrous Tissue

Decreased loading of dense fibrous tissues that normally resist tension (tendon, ligament and joint capsule) alters matrix turnover so that with time, matrix degradation exceeds formation, the newly synthesized matrix is less well organized, and tissue stiffness and strength decline. Specifically prolonged limb immobilization decreases the glycosaminoglycan and water content and the degree of orientation of the matrix collagen fibrils, and may increase collagen cross linking and decrease collagen mass of the dense fibrous tissues[1-4, 6, 9-11, 148, 154, 156, 160]. The duration of decreased loading necessary to produce significant changes probably varies among tissues and individuals, but most studies show marked alterations of the tissues after six weeks of immobilization. However, in one study of rabbit patellar tendons, only three weeks of stress shielding decreased tendon tensile strength to nine percent of the control value[160].

The degree of decreased loading and motion necessary to cause these changes also remains uncertain, but one study indicates that dense fibrous tissues may be less sensitive to decreased activity than bone. Allowing active joint motion in dogs while preventing weight bearing for eight weeks decreased bone density, but did not cause resorption or weakening of the knee ligaments[82]. These results suggest that maintenance of bone structure and mechanical properties requires weight bearing, but loading due to active joint motion may be sufficient to maintain the composition and mechanical properties of the periarticular dense fibrous tissues at least for two months.

Decreased loading also alters ligament, and presumably tendon and capsular insertions into bone[26, 105, 152, 154]. The extent and severity of the alterations depend to some extent on the type of insertion. In some tendon, ligament, or joint capsule insertions (called direct insertions) most collagen fibrils pass directly into the bone matrix through a series of well defined zones that include the substance of the tendon, ligament or joint capsule, a zone of fibrocartilage, a zone of calcified cartilage and the bone[152]. In other insertions (called indirect or periosteal insertions), many of the collagen fibrils join the periosteum and relatively few fibrils pass obliquely into the bone matrix[152]. The cruciate ligament tibial and femoral insertions provide examples of direct insertions, and the tibial insertion of the medial collateral ligament provides an example of a periosteal insertion. Decreased ligament loading due to immobilization usually produces more extensive change in the periosteal type of insertion. In these types of insertions, subperiosteal osteoclasts resorb much of the bony insertion of ligaments subjected to prolonged immobilization. This leaves the ligament attached primarily to periosteum. In the direct type of insertion, resorption occurs around the insertion but relatively little resorptive activity occurs within the insertion.

The cruciate and medial collateral ligaments of the knee provide examples of the difference in the response of direct and indirect insertions to immobilization. Prolonged immobilization causes bone resorption around the periphery of the cruciate ligament insertions, but only limited resorptive activity beneath the insertion site and in the zone of mineralized fibrocartilage[104, 105]. In contrast, prolonged immobilization causes significant diffuse resorption of the bony part of tibial insertion of the medial collateral ligament[85, 152, 154]. These changes, particularly those in the periosteal type insertions, weaken the bone ligament junction significantly within six to eight weeks.

Following resumption of normal joint use, cells in the insertion site begin to form new bone and restore the structure and mechanical properties of the insertions toward normal, but complete restoration of the insertion site structure and strength following six to eight weeks of immobilization requires a longer period of active loading[9, 159]. Six to eight weeks of activity following immobilization of dog knees left ligament insertions significantly weaker than normal insertions, and the available evidence suggests that complete restoration of normal ligament insertion structure and mechanical properties requires up to one year of activity[85, 105, 154]. Muscle contractions alone probably will not prevent the changes due to decreased ligament loading since in one experiment isotonic exercises during immobilization did not prevent weakening of ligament insertions[105].

Increased Use of Normal Dense Fibrous Tissues

Experimental studies show that repetitive exercise can increase the strength, size, matrix organization and possibly collagen content of tendons, ligaments and their insertions into bone[1, 9, 25, 26, 96, 99, 135-137, 141-144, 153, 157, 159, 162, 163]. Application of tension to cultured tendons increased protein and DNA synthesis[129], and an in vivo study showed that increased loading alone can cause adaptation of dense fibrous tissue[159]. Insertion of a pin underneath rabbit medial collateral ligaments increased the load on the ligaments by 200 to 350%, and over 12 weeks significantly increased the strength of the bone ligament complex.

Aging decreases ligament stiffness and strength and may decrease the adaptive response to repetitive loading[29]. In one experiment a life long training program did not improve the mechanical properties of canine medial

collateral ligaments or flexor tendons or prevent age related deterioration of the dense fibrous tissue mechanical properties[149]. From this work it appears that age related changes in ligaments may eventually negate the potential benefits of training.

Dense fibrous tissues respond not only to changes in intensity and frequency of loading but to changes in the type of loading. Tendon regions regularly subjected to tension during normal activities differ from regions regularly subjected to compression in terms of tissue structure, matrix composition and cell synthetic activity[8, 51, 95]. Tendon regions subjected primarily to tension consist of linearly arranged dense collagen fibrils and elongated cells and have a lower proteoglycan content, different proportions of proteoglycan types and a higher rate of collagen synthesis than regions subjected to compression as well as tension[51, 84, 95, 146, 147]. Tendon regions subjected primarily to compression consist of a network of collagen fibrils separated by a proteoglycan containing matrix and more rounded cells than those found in tension bearing regions; and the cells of these regions synthesize larger proteoglycans than the cells of the regions subjected primarily to tension[95]. These differences may be caused, at least in part, by differences in the type of loading[52]. Subjecting tendons to compression increased the hyaluronic acid and chondroitin sulfate content while applying tension to the same tendon decreased the glycosaminoglycan content[51]. Like tendons, ligaments vary in thickness, matrix composition and water content among different ligaments and among regions of the same ligament[47]. Presumably, some of these variations result from adaptation to differences in loading.

Use of Injured Dense Fibrous Tissue

Experimental work shows that controlled loading applied at the optimal time during repair of dense fibrous tissue injuries can promote healing[11, 25, 26, 32, 46, 49, 50, 67, 115, 135-137, 140, 155, 158]. Tensile loading of tendon repair tissue appears to cause the repair cells and matrix collagen fibrils to line up parallel to the axis of tension[13, 16]. Lack of tension leaves the repair tissue cells and fibers disoriented. Loading may also alter the rate of tendon repair[49]. Three weeks following injury, surgically repaired tendons treated with early mobilization had twice the strength of repaired tendons treated with immobilization[50]. Twelve weeks following injury, repaired tendons treated with early mobilization had greater strength than repaired tendons treated with an initial period of immobilization. Controlled loading and motion soon after injury can accelerate ligament repair by increasing the wet and dry weight of injured ligaments, improving matrix organization and inducing more rapid return of normal tissue DNA content, collagen synthesis and strength[11, 48, 92, 140].

Excessive or uncontrolled loading of injured tissues disrupts repair tissue, causes further damage and may delay or prevent repair. In a study of medial collateral ligament healing in rats, forced exercise increased the strength of ligament repair tissue in stable knees[32]. In unstable knees, forced exercise did not increase the stiffness and strength of the repair tissue but increased joint instability. Another study of the effects of anterior cruciate ligament transection showed that temporary immobilization of the knee prevented the development of osteophytes suggesting that early motion following injury may have increased the joint instability[111]. For this reason loading and motion treatment of dense fibrous tissue injuries must be carefully controlled. Furthermore, the optimal motion and loading treatment probably differs among the types of dense fibrous tissues, the types of injuries and among patients. For example, the optimal timing and intensity of loading and motion treatment of a clean laceration of a digital extensor tendon in a child may differ from the optimal loading and motion treatment of a crushing muscle-tendon avulsion of the Achilles tendon in an adult.

Articular Cartilage

Decreased Use of Normal Articular Cartilage

Persistent decreases in loading and motion of a synovial joint cause articular cartilage changes that parallel the changes in the periarticular dense fibrous tissues: chondrocytes change their synthetic activity, cartilage proteoglycan concentration decreases, matrix organization may decrease and the mechanical properties deteriorate[17, 18, 28, 42, 43, 45, 53, 62, 63, 66, 72, 74, 80, 108, 109, 113, 118, 119, 121, 130, 131, 134, 138]. Although loading of an immobilized joint by repetitive muscle contraction may help preserve the cartilage[31], the maintenance of normal synovial joint structure, composition and function requires both loading and motion[112].

Cartilage alterations occur soon after a persistent decrease in joint use. Forty days following experimental tibia fractures in dogs the articular cartilage of the operated limb had a significantly lower glycosaminoglycan concentration[108]. Presumably the decrease in glycosaminoglycan concentration resulted from decreased loading and motion of the joints due to the fracture. Cast immobilization of a dog limb also damaged articular cartilage[74, 80, 109, 113]. Six weeks or more of cast immobilization decreased cartilage thickness, uronic acid content and proteoglycan synthesis and diminished the ability of proteoglycans to form aggregates. Cessation of immobilization followed by ambulation in a pen for three weeks reversed the changes. Treadmill exercise after cessation of immobilization prevented the reversal indicating that intense and frequent loading of the damaged cartilage impeded repair[109].

A study comparing the effects of six weeks of immobilization of dog knees using external fixators with the effects of six weeks of immobilization in long leg casts suggests that the rigidity of joint immobilization influences the severity of the joint damage[18]. External fixators rigidly immobilized the knees, but long leg cast immobilization allowed eight to 15 degrees of motion. Cartilage water content increased 7% in both groups of knees, but hexouronate concentration decreased 23% in the joints treated with casts and 28% in the joints immobilized by rigid external fixators. The rigid fixators also produced more severe depression of proteoglycan synthesis and proteoglycan loss, and impaired cartilage recovery. Within a week after remobilization, joints treated with long leg casts had recovered near normal hexouronate content, but rigidly immobilized joints showed little or no evidence of recovery of hexouronate content.

Continued immobilization of joints eventually causes irreversible damage including contracture of periarticular dense fibrous tissues and muscles that act across the joint, loss of articular cartilage and obliteration of the joint cavity by fibrofatty tissue[42, 45]. Once the fibrofatty tissue fills the joint, attempts to forcefully restore motion tear the intra-articular tissue, often in a different plane than that of the original joint cavity, and avulse fragments of remaining articular cartilage[42, 43].

The time of immobilization necessary to irreversibly damage a synovial joint probably varies among joints and species. Most animal studies suggest that controlled remobilization can reverse the damage caused by a month or more of immobilization. In rat joints, remobilization reversed changes due to 30 days of immobilization, but 60 days of immobilization caused irreversible changes[43]. Two weeks of immobilization of rabbit knees did not cause any detectable permanent changes, but after six weeks some joints had developed contractures[45]. In dog knees, six days of immobilization decreased proteoglycan synthesis 41% and three weeks of immobilization caused loss of proteoglycan aggregation. Two weeks of active motion restored proteoglycan aggregation to normal[113]. Another study of dog joints showed that 15 weeks of remobilization improved but did not completely restore the mechanical properties of dog articular cartilage subjected to 11 weeks of cast immobilization[74].

Increased Use of Normal Articular Cartilage

Increased loading and motion of articular cartilage, up to a certain level, may increase matrix synthesis relative to matrix degradation, at least in skeletally immature animals. In one series of investigations the effects of regular running in dogs depended on the distance the animals ran. Moderate running (four kilometers/day five days a week for 40 weeks) increased cartilage thickness, proteoglycan content and indentation stiffness[50, 111, 144, 162, 163]. A period of more strenuous running (20 kilometers/day five days a week for 15 weeks) decreased cartilage thickness and proteoglycan content[91, 111, 149]. Longer term low-impact strenuous running (40 kilometers/day for up to one year) decreased cartilage proteoglycan concentration and indentation stiffness and stimulated remodeling of subchondral bone, but these animals did not develop degenerative joint disease[14, 107]. These studies suggest that a limited period of increased use may alter articular cartilage composition and mechanical properties, but it does not accelerate joint degeneration. They also suggest that synovial joint tissues, especially in skeletally immature individuals, may be able to adapt to increased use.

Use of Injured Articular Cartilage

The effects of early loading and motion on injured cartilage vary with the type of cartilage injury[23, 25, 28]. Differences in the type of tissue damage and the repair response separate acute cartilage injuries into three types[23, 25, 28]: 1) loss or abnormalities of the matrix macromolecules without disruption of the tissue; 2) disruption of cartilage without injury to subchondral bone; 3) disruption of cartilage and subchondral bone. Chondrocytes can restore lost proteoglycans if the collagen matrix of articular cartilage remains intact and if enough chondrocytes remain viable. Chondrocytes cannot repair disruptions of the tissue like chondral fractures or cartilage lacerations. Following cartilage injury they briefly increase their synthetic and proliferative activity, but they do not migrate to the site of injury or produce new cells and matrix that fill the tissue defect. Disruption of subchondral bone along with cartilage causes hemorrhage and initiates inflammation and repair by cells from the bone and the bone blood vessels. A fibrin clot forms in the tissue defect. Mesencyhmal cells migrate into the clot and produce repair tissue that usually fills the bone defect and most of the chondral defect. The cells in the chondral portion of the defect then produce repair tissue that usually has a matrix with a composition intermediate between fibrocartilage and articular cartilage[23, 25, 28].

The available evidence indicates that controlled early movement prevents cartilage degeneration following joint injury and may facilitate healing. The observations that prolonged joint immobilization and unloading injure articular cartilage, that cyclic loading increases chondrocyte synthetic activity and that resumption of use following joint immobilization improves articular cartilage composition and mechanical properties suggest that controlled loading and motion may stimulate repair of cartilage damage limited to loss of matrix proteoglycans. Furthermore, in one study active and passive motion following experimental depletion of proteoglycans stimulated restoration of matrix proteoglycans[151], but there is no evidence that joint use promotes repair of injuries that disrupt the cartilage

without damaging subchondral bone. Early motion during the repair and remodeling phases of healing following osteochondral injuries can decrease or prevent adhesions and immobilization-induced deterioration of uninjured cartilage, and studies of the effects of early passive motion treatment on experimental osteochondral injuries indicate that passive motion improves the initial quality of cartilage repair tissue[123, 124].

Despite the necessity of loading and motion for maintenance of articular cartilage, premature or excessive loading and motion may delay healing or disrupt cartilage repair tissue[5, 25, 28, 109, 150]. Following injuries associated with depletion of matrix proteoglycans, repetitive intense loading of cartilage, especially impact loading, before the chondrocytes restore the matrix proteoglycan content, may cause further damage[25, 27]. Guinea pig knees subjected to chemical injury developed cartilage fibrillation and osteophytes after three weeks of unrestrained active joint use; immobilization for three weeks prevented fibrillation and osteophyte formation[150]. Running on a treadmill for three weeks following prolonged immobilization of dog knees prevented reversal of the immobilization induced changes in cartilage proteoglycans[109]. Early loading and motion may also damage the repair tissue that forms following osteochondral injury. Examination of the effect of abrading the femoral heads of dogs showed that protection of an abraded surface from loading allowed formation of cartilage repair tissue[5]. Areas subjected to heavy loading formed little or no repair tissue.

Skeletal Muscle

Decreased Use of Normal Skeletal Muscle

Decreased use of skeletal muscle rapidly causes easily detectable changes in muscle volume, structure and function[12, 21, 35, 41, 93]. Within weeks of a reduction in frequency or intensity of activity, myofiber and myofibril volumes and oxidative capacity decrease causing decreases in muscle mass and strength. A decrease in intramuscular capillary density and an increase in intramuscular connective tissue volume relative to myofiber volume accompany these changes in the myofibers[73]. Rigid immobilization produces more rapid and severe loss of muscle structure, volume and function than a decrease in the frequency or intensity of activity. Muscle protein synthesis decreases within six hours of cast immobilization of a limb[21]. Two weeks of cast immobilization decreases muscle fiber size and causes loss of myofibrils and with increasing length of immobilization, mitochondria enlarge, lose their cristae and disintegrate[35]. Eventually the muscle cells contain only amorphous protein, vesicles and fragments of membranes. As the myofibers degenerate, fibrous tissue and fat become a progressively larger proportion of the tissue.

Changes in muscle volume and function accompany these structural alterations. Six weeks of cast immobilization decreased the weight of cat muscles nearly 25%, and 22 weeks of cast immobilization decreased muscle weight nearly 70%[35]. The ability of these muscles to generate tension decreased as muscle weight decreased. In humans six weeks of cast immobilization for treatment of forearm fractures had a similar effect on muscle strength: adductor pollicis muscle maximal voluntary contraction decreased 55% and maximal electrically evoked contraction decreased 33%[41].

Increased Use of Normal Skeletal Muscle

Persistent increases in use also change the structure, functional capacity and often the volume of skeletal muscle[20, 94, 132, 133]. The specific adaptive changes in muscle depend on the pattern of increased use. Patterns that produce different muscle responses include[33]: low-tension high-repetition use that primarily increases muscle endurance; high-tension low-repetition use that primarily increases muscle strength; and, stretching that primarily increases muscle strength. Initially muscle may respond to a training program with rapid changes in structure and function, but as adaptation occurs, the rate of change decreases and eventually the muscle reaches a stable state.

Repetitive low-tension high-repetition exercise, like walking, running, cycling or swimming, performed for 30 to 60 minutes at a time, increases the capacity of muscle cells for sustained effort. This type of endurance training increases the number and size of muscle cell mitochondria, muscle glycogen concentration and the proportion of muscle cells identified as having high oxidative capacity[33, 98]. These changes can double the muscle oxidative capacity[33, 98]. Strength training programs usually consist of repetitive high-tension low-repetition muscle use. These programs increase muscle strength and usually volume, primarily by causing cell hypertrophy - that is, increasing the number of myofibrils. Strength training programs generally do not increase muscle oxidative capacity. Stretching accelerates muscle protein turnover and can cause hypertrophy and increase strength[33].

Use of Injured Muscle

The effects of activity on muscle healing depend to some extent on when activity begins following injury. Immediate mobilization of injured muscles may increase scar formation and interfere with orderly regeneration of myofibers[70], but mobilization following a short period of immobilization produces more rapid disappearance of the hematoma and inflammatory cells, more extensive, rapid and organized myofiber regeneration, and more rapid increase in tensile strength and stiffness[68-70, 86, 87]. In contrast, prolonged immobilization following injury produces muscle atrophy and poor organization of the regenerating myofibers[70, 86, 87]. These results suggest that after

a brief period of rest, controlled use of an injured muscle will produce the optimal healing.

SUMMARY AND CONCLUSIONS

One of the most important advances in the treatment of musculoskeletal injuries has come from understanding that controlled early resumption of activity can promote restoration of function, and that treatment of injuries with prolonged rest may delay recovery and adversely affect normal tissues. In the last decade of the nineteenth century two widely respected orthopaedists with extensive clinical experience strongly advocated opposing treatments of musculoskeletal injuries. Hugh Owen Thomas in Liverpool believed that enforced, uninterrupted prolonged rest produced the best results. He noted that movement of injured tissues increased inflammation, and that, "It would indeed be as reasonable to attempt to cure a fever patient by kicking him out of bed, as to benefit joint disease by a wriggling at the articulation." Just Lucas-Championnier in Paris took the opposite position. He argued that early controlled active motion accelerated restoration of function, although he noted that mobility had to be given in limited doses. In general, Thomas' views met with greater acceptance in the early part of this century, but experimental studies of the last several decades generally support Lucas-Championneir. They confirm and help explain the deleterious effects of prolonged rest and the beneficial effects of activity on the musculoskeletal tissues. They have shown that maintenance of normal bone, tendon and ligament, articular cartilage and muscle structure and composition require repetitive use, and that changes in the patterns of tissue loading can strengthen or weaken normal tissues. Although all the musculoskeletal tissues can respond to repetitive loading, they vary in the magnitude and type of response to specific patterns of activity. Furthermore, their responsiveness may decline with increasing age. Skeletal muscle and bone demonstrate the most apparent response to changes in activity in individuals of any age. Cartilage and dense fibrous tissues also can respond to loading, but the responses are more difficult to measure. The effects of loading on injured tissues have been less extensively studied, but the available evidence indicates that repair tissues respond to loading and, like immature normal tissues, may be more sensitive to cyclic loading and motion than mature normal tissues. However, early motion and loading of injured tissues is not without risks. Premature or excessive loading and motion of repair tissue can inhibit or stop repair. Unfortunately, the optimal methods of facilitating healing by early application of loading and motion have not been defined. Nonetheless, experimental studies and newer clinical investigations document the benefits of early controlled loading and motion in the treatment of musculoskeletal injuries, and orthopaedists should consider controlled activity as part of the optimal treatment of musculoskeletal injuries.

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PRIMARY CEMENTED TOTAL HIP ARTHROPLASTY: FIVE TO TWELVE YEAR CLINICAL AND RADIOGRAPHIC FOLLOW-UP

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ABSTRACT

A retrospective clinical and roentgenographic study was completed on 131 primary cemented total hip arthroplasties with a minimum of five years follow-up (mean, seven years; range, five to twelve years). Second generation cement technique including plugging of the medullary canal, cement gun filling, and pressurization of the canal was used. Acetabular cement was also pressurized.

The total mechanical failure rate of the acetabular components was 18.4% compared to that of the femoral components which was 3.1%. There was a significantly higher incidence of acetabular component failure in rheumatoid arthritis patients (38.9%) compared to a preoperative diagnosis of primary osteoarthritis (14.1%) ($p=0.013$). Yet there were no rheumatoid arthritis patients in the femoral component revision group. There were no differences in revision rates for metal-backed versus nonmetal-backed cups ($p=0.113$).

The average thickness of the proximal medial cement mantle was 2.8 millimeters in the loosening group and 5.4 millimeters in the nonloosening group ($p=0.333$). All failures occurred in those patients whose proximal medial cement mantle was less than five millimeters. The authors strongly endorse the use of hybrid total hip arthroplasty and emphasize the need for meticulous surgical technique especially in obtaining a cement mantle of sufficient thickness in the proximal medial aspect of the femur.

INTRODUCTION

Modern cementing techniques have been evolving since the mid-1970's as a result of multiple research efforts. Lee, Ling, and Wrighton reported results of their research on bone cement preparation in 1973[14], and Amstutz et al. introduced the concept of plugging the intramedullary canal in 1976[2]. At about the same time Miller et al. studied the interface between the polymethylmethacrylate and living cortical bone[16], and Weinstein et al. reported on the effects of high pressure insertion upon the mechanical properties of the acrylic material[26]. In 1978 Oh and Harris presented data regarding pressurization of cement in the femoral canal[19] and, with Bourne, reported on the use of a femoral cement compactor and rubber dam to improve bone-cement pressurization in the proximal area of the femur[20]. These second generation advances have led to improved femoral component fixation. Several long-term follow-up studies have reported excellent results employing these advances[12,22].

In contrast to the femoral component, the failure rate of the acetabular component has not improved[17]. With the cementing technique of the late 1960's and early 1970's, it has been estimated that 40% to 50% of cemented acetabular components are loose[10]. In addition to the application of modern cement technique in acetabular component fixation, metal-backed acetabular components were thought to produce a more uniform distribution of stress[6, 25], and subsequently lead to decreased incidence of aseptic loosening of the cup.

Second generation cement techniques were first used by the senior author in 1979. In this study we will report the results of these primary cemented total hip arthroplasties (THA) followed from five to twelve years.

MATERIALS AND METHODS

Between November, 1979 and December, 1986, 192 primary cemented THAs were performed in 163 patients at Indiana University. Follow-up data could not be obtained on a total of 61 hips (41 due to inadequate follow-up, 13 due to advanced age or infirmity of the patients, and death in the case of seven patients). Therefore, 108 patients with 131 THAs (68% of the total group) were followed for a minimum of five years. Patient demographic characteristics are shown in Table I. Demographic characteristics of the dropouts did not differ from those for whom minimum five year follow-up was available.

There were 17 cases of failed surface replacements (13%) in the study group. These failed surface replacements were considered a primary case on the femoral side and a revision case on the acetabular side. Thus there were 114 primary hips on the acetabular side and 131 primary hips on the femoral side.

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TABLE I.
DEMOGRAPHIC CHARACTERISTICS OF STUDY PATIENTS

Total Number of Patients	108
Total Number of Hips	131
Gender	
Male	40 (31%)
Female	91 (69%)
Average Age (years, range)	65 (22-85)
Average Follow-up (months, range)	84 (60-144)
Diagnosis	
Primary Osteoarthritis	79 (60.3%)
Secondary Osteoarthritis	10 (7.6%)
Rheumatoid Arthritis	19 (14.5%)
Avascular Necrosis	6 (4.6%)
Failed Surface Replacement	17 (13.0%)

TABLE II.
TYPES OF IMPLANTS USED IN PRIMARY CEMENTED THA

ACETABULAR COMPONENTS

Metal-backed (n = 61)	Nonmetal-backed (n = 70)
56 MC-1	54 HD-2
4 HD-2	16 HC-1

FEMORAL COMPONENTS
52 HD-2
32 HS1N
21 HS2P
12 HS2N
13 OMNIFIT

HD-2 acetabular and femoral components are products of Howmedica, Rutherford, NJ. All other components are products of Osteonics, Allendale, NJ.

A variety of implants were used on both the femoral and acetabular sides (Table II). All stems were made of cobalt chrome and were of a similar design (i.e., straight with rounded corners medially). All stems, with the exception of the 21 HS2P, had collars. All stems were cemented using second generation techniques including plugging of the canal, retrograde filling of the canal with a cement gun, and further pressurization of the cement into the proximal femur. No attempt was made to reduce the porosity of the cement through centrifugation or vacuum mixing. The acetabular components were also implanted with pressurized cement using a balloon pressurization system to achieve interdigitation of the cement into the cancellous bone. Whenever possible (i.e., most commonly in the primary or secondary osteoarthritis cases), subchondral bone was retained, and multiple, one-quarter inch diameter drill holes were then made in the acetabulum.

Radiographic results were evaluated by comparing an anteroposterior radiograph of the pelvis and lateral view of the proximal femur made in the immediate postoperative period with similar radiographs made at follow-up or with the radiograph made just before the hip was revised. Each radiograph was taken in a standardized orientation and was evaluated taking radiographic magnification into consideration. On the femoral side we analyzed the thickness of the proximal medial cement mantle, the amount of cement below the tip of the proximal medial cement mantle, the amount of cement below the tip of the implant, the position of the implant relative to the femoral canal, and radiolucencies. Zonal analysis for the femoral component was used as described by Gruen et al.[9]. In assessing femoral component fixation, three categories of loosening (definite, probable, and possible) were used as defined by Harris et al.[11]. On the acetabular side we analyzed radiolucencies and socket inclination. We used the criterion as reported by Mulroy and Harris that all sockets which showed a continuous radiolucent line or had migrated were considered loose[17].

Clinical results regarding degree of pain and walking capacity were evaluated using the uniform clinical rating system developed by Johnston et al. of the Hip Society[13].

Data analysis included descriptive statistics and chi-square analyses to determine if there were any statistical differences in revision rates with regard to use of metal- versus nonmetal-backed components, of males versus females, and of osteoarthritis versus rheumatoid arthritis patients. Statistical analyses were performed using CSS:STATISTICA software (Statsoft, Tulsa, Oklahoma).

RESULTS

Acetabular Component Mechanical Failures

Of the 114 primary acetabular components, 11 were revised for aseptic loosening, two of which had been revised prior to five year follow-up. An additional 10 components with minimum five year follow-up were found to be radiographically unstable. Therefore, a total of 21 of the 114 acetabular components have failed, yielding a total mechanical failure rate of 18.4%. There was no significant difference in the incidence of acetabular component mechanical failure in male (9.4%) versus female (21.2%) patients ($p = 0.138$). There was a significant difference between the diagnostic categories of primary osteoarthri-

tis versus rheumatoid arthritis with regard to mechanical failure rates. The primary osteoarthritis group had a mechanical failure rate of 14.1%, whereas the rheumatoid arthritis group failure rate was 38.9% ($p=0.013$). Although not included in the mechanical failure rate of primary acetabula, it should be noted that there were two radiographically unstable and no revised cups in the group of 17 failed surface replacements. The mechanical failure rate of the failed surface replacement group did not differ significantly from the osteoarthritis group. There were 57 metal-backed and 57 nonmetal-backed acetabular components in the primary acetabular group. The incidence of revision of the metal-backed components was three (5.3%) compared to eight (14.0%) of the nonmetal-backed ($p=0.113$). In addition, there was no difference between the total mechanical failure rate for metal-backed (15.8%) versus nonmetal-backed (21.1%) components ($p=0.251$).

Femoral Component Mechanical Failures

Of the 131 primary femoral components with a minimum five year follow-up, three required revision for aseptic loosening (2.3%). One additional case was judged radiographically to be definitely loose at 11 year follow-up, hence our total mechanical failure rate was 3.1%. All four stem failures occurred in HD2 stems, however this stem design was the most frequently used stem in this series. There was no significant difference in the femoral component mechanical failure rate in male (5.0%) versus female (2.2%) patients ($p=0.391$).

Radiographic Results

The proximal medial cement mantle measured less than two millimeters in five hips (3.8%), from two to five millimeters in 70 hips (53.4%), from six to 10 millimeters in 48 hips (36.7%), and greater than 10 millimeters in eight hips (6.1%). The average mantle thickness was 5.4+/-2.5 millimeters in the nonloosening group and 2.8+/-1.9 millimeters in the aseptic loosening group ($p=0.033$) (see Table III). All failures occurred in those patients with a proximal medial cement mantle of less than five millimeters ($p<0.0075$).

The average cement mantle below the tip of the prosthesis was 25.0+/-15.8 millimeters in the nonloosening group and 16.7+/-17.6 millimeters in the aseptic loosening group. There was no statistical difference in mantle thickness below the tip of the prosthesis between the aseptic loosening and nonloosening groups.

The majority of stems were in a neutral orientation (65.9%), and there was no relationship between stem orientation and component loosening.

On the femoral side 84% had no radiolucent lines at the bone-cement interface. One patient had a complete radiolucent line, and the remaining 16% demonstrated radiolucencies in one or more zones.

TABLE III.
FEMORAL COMPONENT
ROENTGENOGRAPHIC RESULTS (N=131)

	Group	
	Nonloosening (n = 122)*	Aseptic Loosening (n = 4)
Proximal and Medial		
Cement Mantle		
Average (mm)	5.4+/-15.8	2.8+/-1.9
0-4mm (n)	42	4
>5mm (n)	80	0
Cement Mantle		
Below Tip of Implant		
Average (mm)	25.0+/-15.8	16.7+/-17.6
0-5 (n)	15	1
6-30mm (n)	75	1
>30mm (n)	32	2

* = poor quality of five radiographs precluded accurate determination of cement mantle thickness

On the acetabular side the average socket inclination was 41.8+/-6.3 degrees in the nonloosening group and 43.0+/-6.5 degrees in the failed group with no statistically significant difference noted.

Clinical Results

Not all clinical assessment measures were available on all hips, therefore clinical results are reported as valid percentages, based only on those cases with available values. Minimum follow-up was five years in all cases, and the average follow-up for the cases with valid clinical data did not differ from the total group. There were 102 hips with no pain (83%); 15 with mild pain (12%); five with moderate, activity-limiting pain (4%); and one with severe pain (1%). Of the six patients with activity-limiting pain one was noted to have an unstable acetabular component, one had a trochanteric non-union, and no cause could be determined in the other cases. Seventy-five patients (81%) reported being able to walk for an unlimited amount of time; three patients (3%) could walk between 30 and 60 minutes, three (3%) between 11 and 30 minutes, three (3%) between two and 10 minutes, and nine (10%) could walk only two minutes or less. Twelve of those with limited ability to walk were limited or unable to walk for reasons other than the hip (four rheumatoid arthritis,

three knee osteoarthritis, two sciatic nerve palsy, one claudication, one contralateral hip OA, and one polio).

DISCUSSION

Several clinical studies have reported the importance of the proximal medial cement mantle[3, 4, 8, 15, 18, 23]. Beckenbaugh and Ilstrup reported that failure to obtain good packing of cement on the medial side resulted in a twofold or greater increase in femoral loosening[3]. Nobel et al. reported the optimum cement mantle is distinctly asymmetric and that thin cement carries with it a high risk of fragmentation, particle generation, and osteolysis[18]. Llinas et al. also noted that a thicker mantle (i.e., one greater than 10 millimeters) was associated with femoral loosening[15]. In a large series of primary cemented THAs using first generation techniques, Ebramzadeh et al. recently stated that femoral stems with a two to five millimeter thick proximal medial cement mantle had a better outcome than stems with either a thicker or thinner cement mantle[8].

Sixty-three percent of the cemented hips in our series had a proximal medial cement mantle of five millimeters or greater, with all failures in cases of less than a five millimeter cement mantle. However, we have 42 (34%) cases which are now radiographically stable and have less than a five millimeter cement mantle. We also have eight hips whose proximal cement mantles are 10 millimeters or greater, and none of these hips have shown evidence of loosening either clinically or radiographically. Our study indicates that cement mantle thickness is a critical aspect in cemented total hip arthroplasty, and based on our findings, we now recommend a proximal cement thickness of five millimeters or more. However, the cement mantle should be thin enough to provide optimum loading of the proximal femoral cortex yet thick enough to avoid cement fracture. The exact thickness required to accomplish these goals may vary and is likely dependent upon a number of factors including stem design, size, and position.

We were surprised by the relatively high failure rate of our cemented acetabular components with what were considered to be modern cementing techniques. One possible reason for the high failure rate was that we used multiple small drill holes in the acetabulum. Subsequently Amstutz has reported that fewer large and deep fixation holes are more beneficial than smaller and more numerous holes in obtaining durable fixation[1]. We were especially disturbed by the failure rate in our RA population. Severt et al reported a revision rate of 7% with another 13% loose by radiographic analysis in a group of 75 RA hips followed for an average of 7.4 years[24]. Their failure rate included revision of four acetabular components and one femoral component. The one revision of the femoral component occurred 12.3 years postoperatively. Our rheumatoid population had a high failure rate in the acetabular component and no failures of the femoral component.

In a study of 40 rheumatoid arthritis patients with uncemented total hip arthroplasties reported by Cracchiolo et al., none had required revision after an average follow-up of 3.7 years and none were pending[7]. We have a series of 91 cementless acetabular components followed for a minimum of five years that show much better results than this group of cemented components (3.3% mechanical failure rate)[5]. Our cementless group were younger (average age of 49), and although there were only four rheumatoid arthritis hips in the study group, there have been no acetabular component failures in rheumatoid arthritis hips. Therefore, due to the lower acetabular failure rates, we have switched to a cementless socket independent of femoral fixation in all patients regardless of age.

Our series had an equal amount of metal-backed versus nonmetal-backed acetabular components. In contrast to a recent report by Ritter et al.[21], there was no significant increase in failure rate of metal-backed components in our series. In fact the actual failure rate was less than that for the nonmetal-backed ones. Differences may be related to differences in the types of implants used in each series.

Harris et al. reported a 1.7% incidence of loosening of the femoral component at an average follow-up of 74 months in 117 hips using modern cementing techniques[12]. Russotti et al. reported a similar series of 251 hips followed between five and seven years with a loosening rate of 1.2%[22]. We believe our current data with a loosening rate of 3.1% is in keeping with the low failure rate reported by others.

Although the vast majority of patients had no pain and were able to walk for an unlimited amount of time, it should be noted that approximately 15% reported some degree of pain or limited walking ability. While some limitations were attributed to causes other than their hips, some cases with well-fixed implants reported pain and/or limited walking ability. In addition, we had a large number of hips which had been lost to follow-up or for whom recent clinical data was unavailable, and we cannot assume that those hips are necessarily all functioning well. This suggests that factors other than fixation stability may influence pain and function and bears further study.

Based on this data in a group of patients with a mean age of 65 years, the authors strongly endorse the use of hybrid total hip arthroplasty. We continue to emphasize the need for meticulous surgical technique with particular attention to cement mantle thickness in the proximal medial aspect of the femur.

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THE SURGICAL APPROACH TO TOTAL HIP ARTHROPLASTY: COMPLICATIONS AND UTILITY OF A MODIFIED DIRECT LATERAL APPROACH

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INTRODUCTION

A surgical approach for total hip arthroplasty (THA) must meet several requirements. It should provide wide exposure to the acetabulum and proximal femur to satisfactorily prepare the bony beds for implantation. The approach should be useful for the wide array of deformities seen in arthritis of the hip, and be extensile to improve exposure in difficult cases. Minimal trauma should be inflicted on surrounding muscles, tendons and ligaments. The sciatic nerve and femoral neurovascular bundle should be protected and preserved. Hip replacement should be performed in an efficient manner to lessen the risk of infection and thromboembolism, and hasten postoperative recovery. Finally, the approach cannot be associated with complications or untoward side effects.

Many basic surgical approaches and modifications have been described for total hip arthroplasty. Each approach has certain advantages and disadvantages, and no one approach completely satisfies all requirements. The choice of surgical approach is based on many considerations, including but not limited to: the size and muscularity of the patient, the number of assistants and type of retractors available, previous surgery and incisional scars, the need for increased postoperative inequality, etc. The most important factor is the experience and bias of the surgeon, and clearly a thorough knowledge of both surface and deep anatomy is required for any approach.

The anterolateral approach was first described by Watson-Jones in 1935 in his treatise on the treatment of femoral neck fractures. Mueller popularized this approach for total hip arthroplasty for the purpose of avoiding trochanteric osteotomy.[40] The approach is most commonly performed in the supine position with the affected buttock elevated. A straight, curved or V-shaped incision is made over the trochanter and the fascia lata is incised. The interval between the tensor fascia lata and gluteus medius is developed; thus there is no true internervous plane. It is usually necessary to release the anterior fibers of the gluteus medius tendon to avoid excessive retraction on this muscle. After the reflected head of the rectus femoris is divided, an anterior capsulectomy and femoral neck osteotomy are performed. A posterior capsulectomy with release of the short external rotators is usually necessary for exposure and mobility of the proximal femur.[40]

The dangers of the anterolateral approach include injury to the femoral nerve, artery or vein by excessive or prolonged anterior retraction. The superior gluteal nerve may be divided if dissection is carried too far proximally. This should rarely be necessary in routine THA, and the denervation of the tensor fascia lata has uncertain significance. The advantages of this approach include its utility in most primary THA's with excellent visualization of the acetabulum and femur and low postoperative rate of instability. Disadvantages include its lack of extensibility, the need to dissect on both sides of the hip joint, and the often excessive release or retraction of the abductor muscles necessary for exposure.

Described initially by Ollier in 1881, the lateral transtrochanteric approach was popularized by Sir John Charnley for THA to provide wide exposure and allow advancement of the abductor muscles during reattachment.[18] Great controversy exists regarding the necessity for an osteotomy and its advantages. Most primary THA's can be performed without osteotomy, but this approach is still popular for revision surgery and for reconstruction of the dysplastic hip. The patient may be placed supine with the buttock elevated or in the lateral decubitus position. A straight or slightly curved incision is centered over the trochanter, and the fascia lata is incised. The osteotomy is performed after identification and freeing the borders of the gluteus medius, and elevation of the origin of the vastus lateralis. The osteotomized fragment is reflected proximally and a complete capsulectomy is performed. Again, no true intervenous plane is employed. The trochanter may be advanced during closure to improve abductor muscle function and soft tissue tension. The major advantages of this approach include the wide exposure achieved, the preservation of the abductor musculotendinous fibers and the ability to advance the abductors. The disadvantages include an increased operating time and

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blood loss, postoperative bursitis from trochanteric wires, and the possibility of trochanteric non-union. Non-union without migration is usually asymptomatic. However, migration occurs in between 2 and 15% of cases, and will lead to loss of abductor function, a limp, and potential instability of the hip. Therefore, reattachment of the trochanter is a critical step in this approach.

The posterolateral approach was first described by Langenback in 1874, for the purpose of draining pyarthroses of the hip.[40] The approach was later modified by Kocher and others, then popularized in North America by Gibson. Moore advocated the use of a more inferiorly placed incision into the buttock to insert femoral endoprostheses, and the approach was thus named "Southern Exposure".[40] The procedure must be performed in the lateral decubitus position. Most commonly, the incision courses along the posterolateral border of the femur and greater trochanter, then curves posteriorly towards the posterior superior iliac spine. The fascia lata is incised and the fibers of the gluteus maximus are split. The short external rotators are released prior to a posterior capsulectomy and posterior dislocation of the femoral head. There is no true internervous plane in this approach, but the gluteus maximus is not significantly denervated and the dissection is behind the superior gluteal nerve-innervated abductor muscles. The principle danger of this approach is injury to the sciatic nerve which must be protected during dissection of the posterior hip capsule. The advantages of this approach include its reproducible anatomy and exposure, and the avoidance of the abductor musculature. The major disadvantages include the need to perform the procedure in the lateral decubitus position, limited extensibility, and difficulty in knowing the exact position of the pelvis during reconstruction. The posterolateral approach has been associated with the highest incidence of postoperative instability after THA.[50]

The anterior approach of Smith-Peterson reached its greatest utility for the performance of cup arthroplasty. The approach utilizes the superficial interval between the sartorius and the tensor fascia lata muscles and the deep interval between the rectus femoris and gluteus medius muscles. Thus, it is truly an internervous approach, between the femoral and superior gluteal nerves. The approach is most commonly used today for pelvic osteotomies, hip fusions and biopsies. Many variations of this approach have been described to increase exposure and improve its versatility, including transection of the tensor fascia lata or gluteus medius, osteotomies or extensive stripping off the pelvis. Despite these attempts, this approach provides inadequate exposure and has very little usefulness in performing THA.

The medial approach was first described by Ludloff in 1908. It employs the interval between the adductor longus and gracilis muscles. It is used primarily for the treatment of congenital dysplasia of the hip and to approach the iliopsoas tendon and lesser trochanter. It has no role in THA.

The direct lateral or transgluteal approach was apparently first described by Kocher in 1903.[28] McFarland and Osborne "suggested an improvement on Kocher's method" in 1954, noting the direct functional continuity of the tendinous periosteum of the gluteus medius and vastus lateralis.[34] They recommended swinging forward these muscle bellies after their release, like a "bucket handle". When it was not easy to peel the tendons from bone, they recommended taking a few flakes of trochanteric bone adhering to the tendons. Hardinge popularized the direct lateral approach in the modern era. In his description in 1982, he recommended incising this combined tendon directly over the trochanter, and carrying the dissection posteriorly into the gluteus medius fibers. The combined tendon was then sutured into bone and onto itself during closure.[15] This has become the standard direct lateral approach discussed in most textbooks and articles. McLauchlan described the Stracathro approach, whereby anterior and posterior slices of trochanter are elevated with the gluteus medius. He reported excellent results in over 2000 THA's performed through this approach.[35] Anterior modification, employing just an anterior trochanteric osteotomy, was described by Dall in 1986. He stated that this partial osteotomy leaves intact the posterior gluteus medius and its thick tendon.[8] Finally, Frndak et al recently reported excellent clinical results using an abductor muscle "split", which also leaves the posterior gluteus medius intact, but does not require an osteotomy.[12] Extensile versions of this approach have also been described for the purpose of revision surgery.[13,19]

Thus, there have been many modifications of the direct lateral approach since its original description. These l ateral approaches have been studied in several ways recently, including the relevant anatomy,[25] abductor function,[1,16,36,39,47] and heterotopic ossification.[23,48] There is certainly no consensus regarding the utility or complications of any or all of these approaches. Direct lateral approaches have been blamed for a high prevalence of limp, heterotopic ossification and hemorrhage.[3,33,43,48] Others have reported normal abductor function, and generally satisfactory results when compared to other approaches.[12,23,36] To our knowledge, a comprehensive review of any direct lateral approach used in a large series of patients does not exist in the literature.

Discouraged with an unacceptably high rate of THA dislocation using the posterolateral approach, the senior authors turned to a direct lateral approach for THA in 1985. After a short period on the learning curve, incorporating slight modifications, the approach described in this

paper has been used exclusively for all primary THA and most revision THA at our institution since 1987. This report reflects our experience with a modified direct lateral approach in primary THA in a large consecutive series of patients with a minimum two year follow-up.

For the purposes of this report, 770 consecutive primary total hip arthroplasties were reviewed. The complications considered potentially attributable to the approach included postoperative instability, limp, heterotopic ossification (HO) and nerve palsy. Direct measures of the utility of the approach included its applicability to a wide array of problems seen in primary THA without the need for further exposure, as well as the average duration of surgery. Utility, without untoward effects, was assessed using clinical results as taken from the Harris hip rating and AAOS-Hip Society rating forms. Component placement was recorded as an indirect measure of the adequacy of exposure.

The pertinent results will be outlined here, and described in detail later. Of the 770 hips, there have been three known dislocations, for an overall prevalence of instability of 0.4%. Excluding those who died or were lost to follow-up, there were two dislocations of 712 THA's that were followed for greater than two years, for a prevalence of instability of 0.3%. A moderate or severe limp from any cause was present in 10% of patients at two year follow-up, and in 4% of a subgroup of patients with only unilateral osteoarthritis of the hip (Charnley A). Heterotopic ossification developed in 34% of hips. It was functionally limiting in only seven patients. A total of four partial sciatic nerve palsies occurred in this series.

It was never necessary to convert to a trochanteric osteotomy or perform a concomitant posterior capsulectomy to gain exposure. The duration of surgery, including patient transfers and prepping and draping, has averaged one hour and thirty-eight minutes for primary THA using this approach. Acetabular and femoral component placement was considered excellent in over 90% of patients.

As this review will show, this modified direct lateral approach has greatly diminished the potentially devastating complication of postoperative instability in our experience. It has been associated with an acceptable level and severity of limp and heterotopic ossification. Excellent exposure can be achieved, allowing accurate placement of components in an efficient manner.

Operative Technique

The technique described here varies significantly from many previously described lateral approaches to the hip. Therefore, the approach will be described in some detail. The approach is very similar to the Translateral Abductor Muscle "Split" described by Frndak et al.[12]

Preoperative templating is carried out to estimate limb length inequality and approximate acetabular and femoral component sizes. The patient is transferred to the lateral decubitus position, nonaffected hip down on an inflatable bean bag. Supplemental taping is used to secure the patient. The hip and leg are prepped and draped free, and a sterile pouch is made on the assistant's side, anterior to the patient. A straight lateral skin incision is made midway between the anterior and posterior dimensions of the greater trochanter, equidistant cephalad and caudad to the tip of the trochanter (Fig. 1). The fascia lata is incised between the muscle bellies of the tensor fascia lata and the gluteus maximus (Fig. 2). The trochanteric bursa is incised and the anterior and posterior borders of the gluteus medius and the vastus lateralis are identified. Blunt retractors are used to separate the muscle fibers of the gluteus medius at its anterior-middle one-third junction, up to three cm cephalad to its insertion (Fig. 3). Care is taken to protect the inferior branch of the superior gluteal nerve as it courses between the gluteus medius and minimus muscles. Electrocautery is used to split and detach the combined tendon and periosteum of the gluteus medius and vastus lateralis. This division is carried anterior to the trochanter to leave behind a posterior tendinous cuff for later suturing. Distally, the incision curves posteriorly at the vastus ridge and taken in line with the fibers

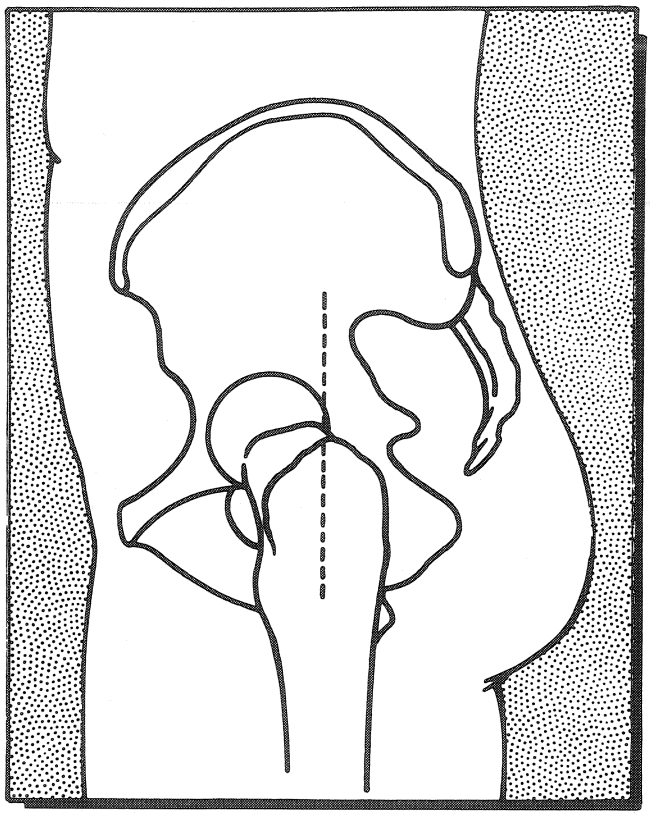

Figure 1
Illustration of the skin incision, centered over the trochanter.

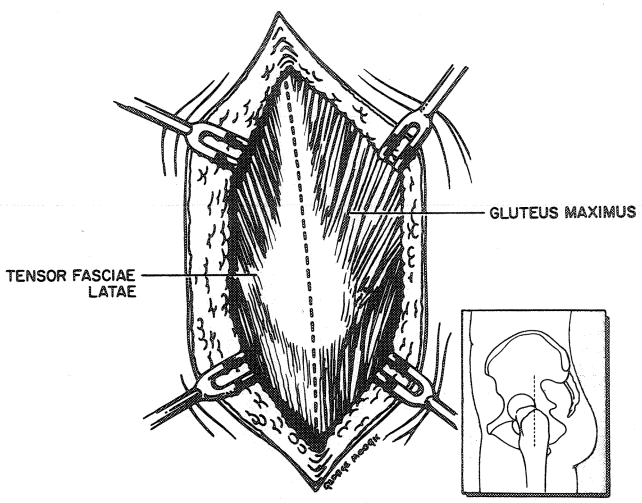

Figure 2
The incision in the fascia lata, between the insertion of the tensor fascia lata and gluteus maximus muscles.

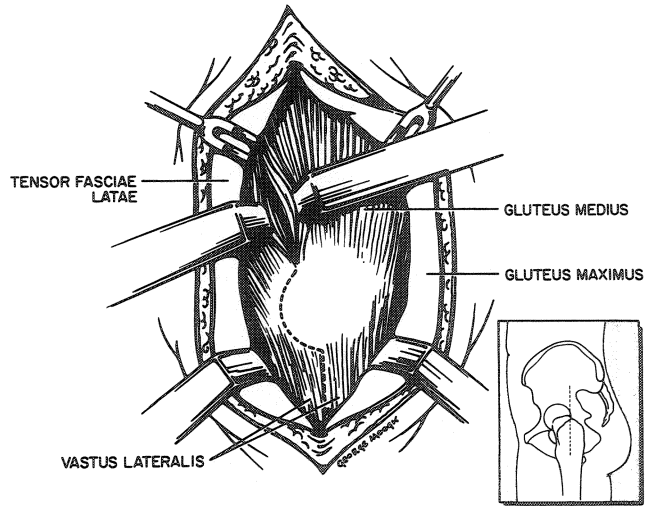

Figure 3
Blunt retractors are used to spread the fibers of the gluteus medius at its anterior-middle one-third junction. The combined tendon/ periosteum is divided anterior to the trochanter, and the fascia of the vastus lateralis posterior to or at the midline.

of the vastus lateralis. Two points of bleeding may be encountered. First is the ascending branch of the medial circumflex artery behind the trochanter. Second is the transverse branch of the lateral circumflex artery in the vastus lateralis. Both arteries are easily cauterized. Under direct vision, the gluteus minimus is divided in line with its tendinous fibers (Fig. 4). A plane between the gluteus minimus and anterior capsule is easily found proximally. Blunt dissection with scissors is carried out to the acetabular rim, identifying and cutting the reflected head of the rectus femoris, as the leg is externally rotated. The origin

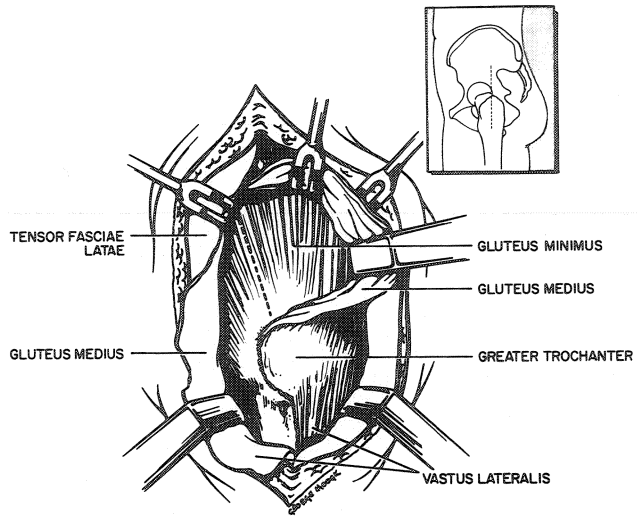

Figure 4
Division of the gluteus minimus is done in line with its fibers, under direct vision and limited to three cm from its insertion.

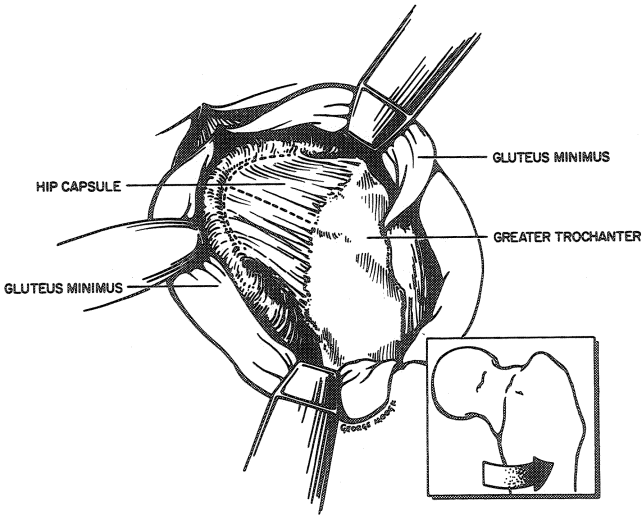

Figure 5
Exposure of the anterior capsule for capsulectomy.

of the vastus lateralis is elevated from the intertrochanteric line, and medially to the lesser trochanter as necessary. A blunt-tipped retractor can be carefully placed over the anterior acetabular rim or alternatively, a sharp-tipped retractor is placed into the anterior-superior ilium. With adequate exposure of the anterior capsule, an anterior capsulectomy is performed (Fig. 5). A smooth Steinmann pin is placed in the ilium and a mark made on the greater trochanter for leg length determination. Dislocation of the femoral head is achieved by external rotation, flexion and adduction, while pulling the head from the acetabulum using a bone hook. The leg is brought over into the sterile

Figure 6
Positioning of the leg for femoral neck osteotomy and canal preparation.

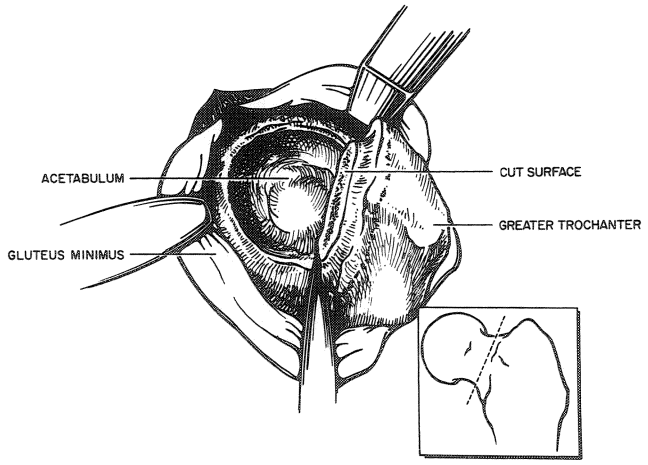

Figure 7
Acetabular exposure requires an anterior-superior retractor, an inferior retractor that holds the femur posterior, and a posterior soft tissue retractor.

pouch to perform a femoral neck osteotomy (Fig. 6). One may then elect to prepare the femur or place the leg back on the operating table and move to the acetabulum. For acetabular preparation, a Hohman retractor is placed in the acetabular notch beneath the transverse acetabular ligament (Fig. 7). Posterior retraction is generally adequate by externally rotating the leg and use of a soft tissue retractor. Rarely is a posterior rim retractor required.

If limb length and femoral offset are restored after placement of components, there is generally no tendency to subluxation with a full range of motion. The positions of maximal external rotation in extension and internal rotation in 90 degrees of flexion are particularly important to assess.

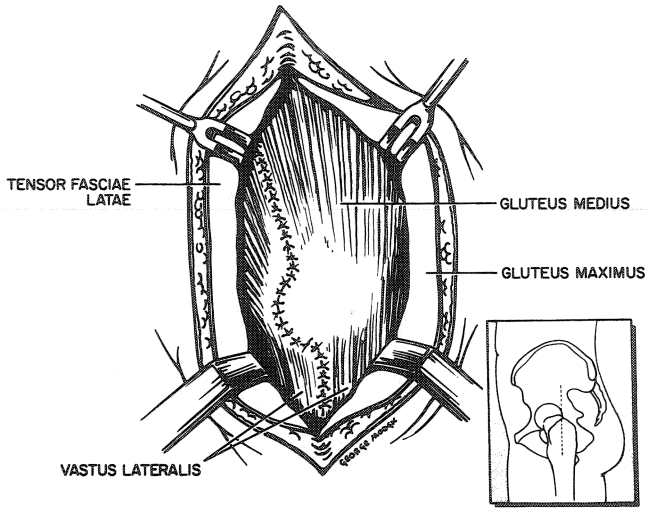

Figure 8
Closure is carried out in layers, with reapproximation of the combined tendon and periosteum of the gluteus medius and vastus lateralis.

Careful attention to the detail of closure of the muscular layers is paramount to the success of this approach. A heavy absorbable suture is used to reapproximate the divided gluteus minimus. Interrupted, heavy absorbable suture is used to draw up and reapproximate the anterior flap of gluteus medius and vastus lateralis to the posterior tendinous cuff. We feel this tight soft tissue closure is critical in preventing postoperative abductor weakness. This suture line is then carried proximally into the muscle fibres of the gluteus medius and distally, closing the fascia of the vastus lateralis (Fig. 8). The fascia lata, subcutaneous tissues and skin are closed in the usual fashion.

Postoperative Rehabilitation

A pillow is placed between the patient's legs until they are awake in the recovery room. Braces and/or splints are not used. Ambulation is begun the next day. For the first six weeks, patients are instructed on crutch-walking, progressing to full weight-bearing as tolerated. They are cautioned to avoid excessive flexion of the hip and to avoid crossing their legs. Abduction exercises are allowed with gravity removed. From six weeks forward, they are advanced from crutches to a contralateral crutch or a cane, full weight-bearing. Abduction exercises are performed against gravity and with resistance up to four kg. in addition to hip flexion and straight leg raising exercises. Patients are generally released from physiotherapy and the use of a cane at three months and are allowed to progress to full activity at that time.

MATERIALS AND METHODS

Seven hundred and seventy primary total hip arthroplasties were performed at the University of Western Ontario

DEMOGRAPHICS

	Hips	Patients	F/U Average
	770	697	3.6 yrs (2-6.5)
Died	46	45	≥2 yrs 712
LTF	12	12	≥3 yrs 514
Clin/X-ray	697	615	≥4 yrs 369
Clinical	712	640	≥5 yrs 183
Gender	394 F	318 M	≥6 yrs 43
Dx (%)	OA 83	RA 6	
	ON 4	CDH 3	

Table 1

Hospital, between October 1987 and January 1992. The period of study reflects a time after the learning curve of using this approach, but allows a minimum two year follow-up. However, our experience with this approach before and after these dates has been similar. All surgeries were performed under the supervision of two senior surgeons (CHR,RBB) using the described modified direct lateral approach. Forty-five patients with 46 hips died prior to two year follow-up, and 12 patients with 12 hips were lost to follow-up and could not be contacted. Therefore, 712 THA's in 640 patients had a 2 to 6.5 year review with an average follow-up of 3.6 years. These hips form the basis for the clinical portion of this review. Twenty-five patients could be contacted by phone only. Therefore 687 hips had both clinical and radiographic review. Hips were placed in 394 females and 318 males. The average age of patients at last follow-up was 64.3 years with a range of 19 to 87 years. The diagnosis leading to hip replacement was osteoarthritis in 83%, rheumatoid arthritis in 6.3%, osteonecrosis in 4.2% and CDH in 2.8%. Contemporary implants were used in all patients; 65% of hips were hybrids. (Table 1)

Postoperatively, patients were followed at six weeks, three months, six months, one year and yearly thereafter. Clinical information had been recorded using the Harris Hip rating[17] with transition to the AAOS/Hip Society rating form after the recommendation of Johnston et al.[26] Because of this transition and lack of uniformity between various scores,[4] reporting will focus on individual parameters such as pain and limp. The criteria for the presence and severity of limp was based on the recommendations of the AAOS/Hip Society.[26] Patients were not divided into Charnley functional classes.[6] However, a subset of 230 patients known to have only unilateral osteoarthritis of the hip were evaluated separately.

All intraoperative, postoperative and follow-up complications were recorded prospectively in a computer data bank. In addition, the hospital charts and serial x-rays were available for review on all patients. The 25 patients who had failed recent appointments were contacted by telephone and queried specifically regarding hip dislocation, pain or other problems with the hip replacement.

Radiographs were reviewed by two of us (BM/NN) without knowledge of the clinical results. Acetabular inclination was measured from the interteardrop line. No attempt was made to measure component version. Femoral component alignment was referenced from the axial alignment of the proximal femur and was considered to be neutral if it fell within three degrees of being colinear. Heterotopic ossification was graded according to the classification of Brooker et al.,[2] and divided into A and B functional subtypes as per the modification of Maloney et al.[31]

No specific measures for HO prophylaxis were used in this series. Radiation therapy is not readily available at our institution, and anti-inflammatory medications were considered contraindicated during the Coumadin prophylaxis used in the majority of these patients.

A computer data bank is used in our operating room to record information regarding specific procedures. Operative time is defined as the duration the surgeon is involved in patient care, including patient transfers, positioning, prepping, draping and closure. This information has been recorded for all surgeries for the past 3 1/2 years, for the purpose of quality assurance.

Statistical analysis was carried out with an analysis of variance and Chi-squared tests to determine the relations between demographic variables, HO and clinical outcomes.

RESULTS

Complications

Of the entire group of 770 THA's, there have been three dislocations for a prevalence of instability of 0.4%. All three dislocations were posterior in direction and occurred without major trauma. One dislocation, in a patient with high riding CDH, became recurrent and required a revision to a longer neck femoral component and reattachment of the anterior flap of the gluteus medius, with a satisfactory outcome. The second patient dislocated stooping over in a flexed position while vomiting. The femoral neck had a long skirt thought to be partly responsible for the dislocation (Fig. 9). He had a satisfactory outcome with one closed reduction. A third patient dislocated his hip two months postoperatively and had a successful closed reduction and satisfactory outcome prior to his death, one year following total hip arthroplasty. Therefore, of the 712 hips with a minimum two year follow-up, there have been two known dislocations (prevalence = 0.3%). No other reports of THA instability

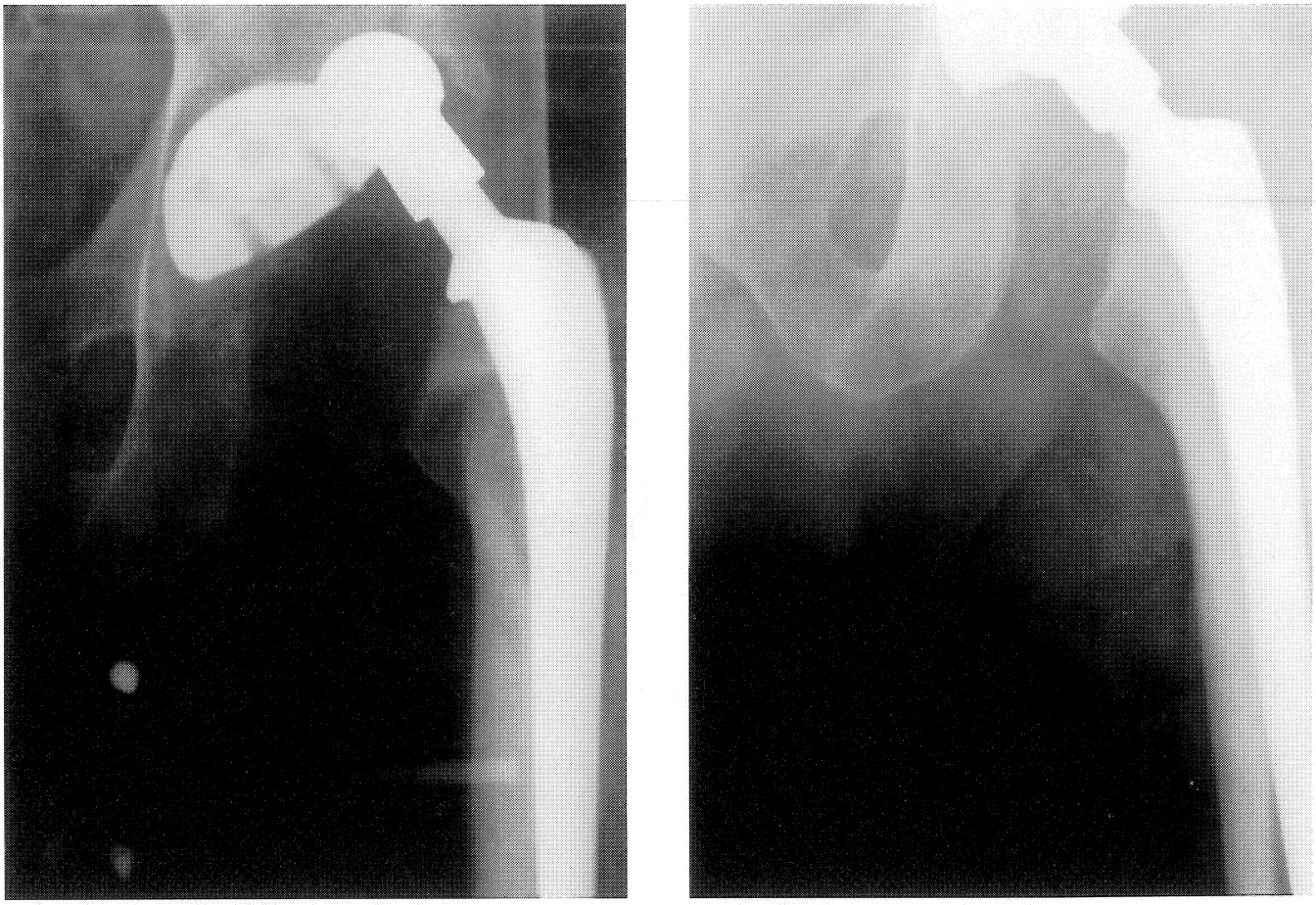

Figure 9
Dislocation occurred 2 years post-op while stooping over and 9b) relocation of THA.

in the form of subluxation or dislocation have been reported or recorded for any of these patients, over the length of follow-up studied.

Parenthetically, 178 revision THA's were performed during the same time period using a similar modified direct lateral approach. Of these hips, there have been only two known dislocations for a prevalence of 1.1%.

Limp was recorded as absent, slight, moderate or severe as graded by the AAOS/Hip Society recommendation. The prevalence of a moderate or severe limp in the entire patient series decreased from 12% to 10% from the one to two year follow-up but then increased to 21% at five year or greater follow-up. Similarly, the need for more than part-time cane use decreased from 9% to 7% from years one to two and then increased to 13% at five year or greater follow-up (Table 2).

In the subset of 230 Charnley type A patients who are the subject of a separate study,[29] limp was evaluated after a Six-Minute Walk. A moderate or severe limp was present in 4% at two year follow-up, gradually increasing to 11% at five year or greater follow-up. Again, the need for more than part-time cane use increased from 1% at two years to 8% at greater than five year follow-up (Table 3).

LIMP/WALKING AIDS (OVERALL)

Yr Follow-up	Mod/Severe Limp (%)	≥ Cane Use (%)
1	12	9
2	10	7
3	14	8
4	17	13
5	21	13
6	21	12

Table 2
The prevalence of moderate or severe limp and the need for more than part-time cane use at each length follow-up, for all patients with minimum 2-year follow-up.

LIMP/WALKING AIDS (CHARNLEY A)

Yr Follow-up	Mod/Severe Limp (%)	≥ Cane Use (%)
1	3	3
2	4	1
3	6	2
4	10	2
5	12	8
6	6	0

Table 3
The prevalence of limp, and need for more than part-time cane use for the 230 patients with unilateral hip osteoarthritis, evaluated after a timed six minute walk.

HARRIS HIP RATING (OVERALL)

Yr Follow-up	No Pts.	Average	% G + E
1	395	93	90
2	370	94	92
3	223	94	93
4	149	93	87
5	89	91	82
6	23	94	100

Table 5
Harris Hip rating, average and percentage good and excellent results at each length of follow-up, for the entire patient series.

HETEROTOPIC OSSIFICATION

Brooker	0	66%
	I	26
	II	5
	III A	1.8
	B	0.8
	IV A	0
	B	1 pt

Table 4
Heterotopic ossification, according to Brooker et al (2) and modified by Maloney et al (31) for the 687 hips with minimum 2-year radiographic review.

Heterotopic ossification was present to some degree in 34% of hips. It was Brooker Grade I in 25.7%, grade II in 5.3% and grade III in 2.6%. Only one patient in the series had apparent ankylosis (Grade IV). Of the 19 patients (2.8%) who had grade III or IV HO, seven were functionally limited (type B) in ascending stairs, sitting or donning shoes and socks (Table 4).

In the series, there were four partial sciatic nerve palsies, as discussed later. There were no femoral nerve or vascular injuries.

Utility

This approach was utilized for every primary THA performed during the period of study. In the entire series, it was never necessary to convert to a trochanteric osteotomy to improve exposure nor was it necessary to perform a concomitant posterior capsulectomy.

The average duration of surgery for primary THA over the past 3.5 years has been 1 hours and 38 minutes, including patient positioning, prepping and draping, and transfers.

As stated, both the Harris Hip rating and the AAOS/Hip Society rating were used to assess clinical results in these patients over the length of follow-up reported here. Approximately one-half of patients had serial numerical Harris scores at each length of follow-up, as seen in Table 5. The remaining patients were not given a cumulative "score", but the individual parameters of pain, limp, etc., as taken from the AAOS/Hip Society form are reported here. The Harris score averaged 94 at two year follow-up, decreasing to 91 at five years. Ninety-two percent of patients had good and excellent results at two years, compared to 82% at five years (Table 5).

Each of the 230 patients with unilateral hip osteoarthritis had serial Harris Scores. At two years, the average score was 96, with 97% good and excellent results. The average score decreased to 93, with 86% good and excellent results at five years (Table 6).

For the entire series, no or slight pain was present in 93% of hips at two years, with an average pain score of 42 out of 44. The average score decreased to 40, with 88% of patients having no or slight pain at five years (Table 7).

The average acetabular angle in this series was 40.3 degrees with a standard deviation of 6.4 degrees (range 20-65 degrees). Therefore, socket inclination was between 34 and 47 degrees in 95% of THA's. The femoral component was placed in neutral in 90% of patients, varus in 3% and in valgus in 7%.

Statistical analysis revealed a significantly higher Harris hip rating in patients with osteoarthritis and CDH compared to osteonecrosis and rheumatoid arthritis ($p<0.0001$). A significantly lower hip rating was found with advancing age ($p<0.0001$) and length of follow-up

HARRIS HIP RATING
(CHARNLEY A)

Yr Follow-up	Average	% G + E
1	96	95
2	96	97
3	96	94
4	95	92
5	93	86
6	97	100

Table 6
Harris Hip rating for the 230 patients with unilateral hip osteoarthritis.

PAIN RATING
(OVERALL)

Yr Follow-up	Average (of 44)	% N or Sl
1	42	92
2	42	93
3	41	90
4	40	88
5	40	88
6	41	89

Table 7
Pain score, average and percentage who had none or slight pain, for all patients with minimum 2-year follow-up.

($p = 0.046$). The presence of heterotopic ossification did not significantly affect the hip rating score ($p = 0.3$).

Heterotopic ossification was significantly more common in males ($p < 0.001$), and was not affected by the type of fixation ($p = 0.6$).

DISCUSSION

The current era of investigation in total joint arthroplasty has focused on biomaterials, implant fixation and the avoidance of particulate debris and osteolysis. Although these issues are of paramount importance to the long term functioning of total hip arthroplasty, it should be remembered that a well performed arthroplasty with accurate placement of components is the first prerequisite for satisfactory results. In addition, the avoidance of complications and untoward effects is critical to the success of any surgery, and especially in total hip arthroplasty.

For example, a dislocation might be a simple, one-time occurrence requiring only a closed reduction, bracing and modification of physiotherapy. The morbidity to the patient is minimal in this case and cost to the system is less than $2,000.00 Cdn at our institution. However, complications such as nerve palsies, thromboembolism and decubiti can occur in up to 40% of dislocations and may compromise results.[10] If the dislocation becomes recurrent and a revision is necessary, the morbidity is excessive[5] and the cost is generally greater than $20,000.00 Cdn. if the procedure and rehabilitation are uncomplicated. Therefore, it seems imperative to avoid complications that are potentially attributable to the surgical approach and are associated with excessive morbidity and medical cost.

In this regard, we felt the need to convert from a posterior to a lateral approach in order to limit the rate of postoperative instability in total hip arthroplasty. The approach described here differs from many other direct lateral approaches in several ways. First the patient is placed in the lateral decubitus position, allowing direct downward visualization of the relevant anatomy. Secondly, only the anterior one-third of the gluteus medius is split in line with its muscle fibers, and this is done using blunt retractors and not sharply using a scalpel or electrocautery. Third, the incision is taken anterior to the greater trochanter into the combined tendon and periosteum of the gluteus medius and vastus lateralis, allowing a tight soft tissue closure. Fourth, division and elevation of the vastus lateralis is carried out posteriorly, to avoid the anteromedially directed nerve supply. Finally, the split in the gluteus medius and minimus is limited to three cm cephalad to the greater trochanter and this is done under direct vision to avoid injury to the superior gluteal nerve and artery. Currently, the approach described here is used for all primary THA's and most revision THA's at our institution. We have been very satisfied with the ability to avoid most complications as discussed below.

Dislocation

The acceptable rate of postoperative instability following THA has not been established. Woo and Morrey reported an incidence of 3.2%, more than twice as common using the posterior versus the anterolateral approach.[50] The incidence in primary THA was 2.4%. Khan reported an incidence of 2.1% unaffected by the surgical approach.[24] Lewinnek et al reported a prevalence of 3% using a posterior approach.[30] McCollum and Gray were able to decrease the rate of dislocation to 1.14% using the posterolateral approach with careful positioning of components.[33]

The likelihood of recurrent instability following an initial dislocation has ranged from 33% to 59%.[9,10,24,38] The functional cost of recurrent dislocations has been studied

by Chandler et al, who found that patients had a much worse outcome one year following the initial dislocation.[5] The majority of patients with recurrent instability will require an operation, most commonly a revision of one or both components.[10,50] Daly and Morrey reported successful eradication of the instability in only 61% of hips following reoperation for recurrent postoperative instability.[9]

The prevalence of dislocation after direct lateral approaches is not well known. Scheck et al reported two dislocations of 67 THA (3%) using the "Kocher-McFarland" direct lateral approach.[43] Frndak reported one dislocation of 65 hips using their muscle "split" approach.[12]

We have observed a postoperative dislocation in only 0.4% of all primary THA's performed during the period of study, with a similar prevalence of 0.3% of the hips with minimum two year follow-up. As would be predicted, two of the three hips were treated successfully closed and one required a reoperation. Uncharacteristically, two of three dislocations occurred late, approximately two years after the index procedure. We might attribute the lack of postoperative instability to two or more factors. Because the posterior capsule is left intact and the anterior structures, excluding the capsule, are preserved and approximated anatomically, a tight soft tissue envelope is created during closure. In addition, correct acetabular component positioning is not difficult using this approach in the lateral decubitus position, even if the patient rolls forward or backward, as the surgeon is afforded direct downward vision of the pertinent anatomical landmarks. Well over 95% of the acetabular components in this series were within the "safe zone" of inclination of 30 degrees to 50 degrees as described by Morrey.[38] Appropriate acetabular component version was probably achieved in a similar percentages of cases, but this measure was not taken from the radiographs as we feel it is often inaccurate. Other factors such as patient compliance and skilled nursing and physiotherapy personnel are obviously important. The prevalence of 0.4% in primary THA and 1.1% in revision THA is less than other published reports and is certainly within acceptable limits for postoperative instability. This approach has tremendously limited the morbidity and additional medical cost we previously experienced while using a posterior approach.

Abductor Weakness

Abductor weakness has remained a persistent concern in using direct lateral approaches. Orthopaedic texts typically describe the Hardinge modification, stating there is a risk of gluteal weakness and the approach threatens to denervate a large mass of gluteal muscle.[18,22,40] Abductor weakness may result from three sources in direct lateral approaches. The superior gluteal nerve (SGN) may be injured directly or through traction. The suture line in the abductors may dehisce postoperatively during rehabilitation. Finally, the portion of abductors that is elevated and retracted may be defunctionalized and not recover. Baker and Bitounis found electromyographic (EMG) evidence of SGN injury in 10 of 29 hips operated through a Hardinge approach and that this finding correlated with a limp.[1] Svennson et al reported dehiscence of the abductor suture line of greater than two cm in one-third of patients after the Hardinge approach, and that limp correlated with a separation of greater than 2.5 cm.[47] In the clinical setting, McCollum and Gray found the lateral approach to cause a postoperative limp and be time consuming.[33] Callaghan et al found a significant association of postoperative limp with the direct lateral approach compared to the posterolateral approach, using the Porous Coated Anatomic total hip system.[3] Heekin et al later found the difference not significant in the same patients.[21]

On the other hand, Hardy and Synek reported normal abductor power and EMG studies after a direct lateral approach in seven patients.[16] Horwitz et al found no difference in limp or abductor strength in a randomized clinical trial of the Hardinge and Transtrochanteric approaches.[17] Minns et al reported that the strength of the abductor muscles recovered equally after these two approaches and was comparable to the non-operated side.[36] Frndak et al demonstrated a normal Trendelenburg test and no limp attributable to the approach in 50 patients undergoing 65 THA's using their modified direct lateral approach.[12]

In this series, we observed a moderate or severe limp in 10% of patients at two years, increasing to 21% at five years or greater. Similarly, 7% of patients required more than part time cane use at two years, increasing to 13% at five years or greater. Generally, this limp has been attributed to other conditions such as contralateral hip disease or ipsilateral knee or ankle arthritis, limb length inequality or neurologic disorders. In the subset of 230 patients with unilateral osteoarthritis of the hip, the prevalence of moderate or severe limp after a timed six-minute walk was a modest 4% at two years, increasing to 12% at five years. The increasing prevalence of limp over time is most likely a sign of advancing age with the development of coexistent conditions such as spinal stenosis or polyarticular arthritis. Some THA's have also deteriorated due to early aseptic failure.

Clearly, a thorough knowledge of the anatomy of the superior gluteal nerve and abductor muscles is necessary prior to proceeding with this approach. Jacobs and Buxton showed in cadavers that the superior gluteal nerve most commonly courses between the gluteus medius and minimus, and runs at least five cm cephalad to the tip of the trochanter. Therefore, division of the gluteus medius

should be kept within this safe zone and preferably done bluntly and under direct vision. Retraction of the gluteus medius will allow direct visualization for division of the gluteus minimus. Elevation of only the anterior one-third of the gluteus medius and minimus limits the defunctionalization of the abductors postoperatively allowing quicker mobilization, perhaps limiting the incidence of postoperative limp. Close attention to a tight soft tissue closure is also critical. Using these techniques, abductor weakness and limp is not a problem in the great majority of patients undergoing primary THA using this approach.

Heterotopic Ossification

Heterotopic ossification has been reported in between 8 and 90% of total hip replacements, and rated severe in between 1 and 24%.[27,45] Severe HO has been associated with increased pain, decreased range of motion and ultimate failure of the THA. Although there are methods of preventing HO with low dose radiation therapy and anti-inflammatory medication,[20,41,45] the best course is to eliminate factors responsible for HO. Many authors have reported the surgical approach to be an important factor. Morrey et al reported a higher incidence and more severe grades of HO following the anterolateral and lateral approaches compared to the posterior approach.[37] Errico and Fetto reported a higher incidence of HO after the transtrochanteric lateral compared to the posterolateral approach.[11] Horwitz et al observed HO more commonly using the direct lateral than the transtrochanteric approach, but this was not clinically significant.[23] Testa and Mazur demonstrated similar results in a non-randomized series of patients.[48] Scheck found HO was more common following a lateral approach when compared to reports of other approaches.[43] Finally, Martell found HO present in 70% of patients undergoing uncemented THA using a direct lateral approach.[32] From these reports, it seems HO may be more common after lateral approaches, but the clinical significance is unclear.

In our series less than 3% of patients had grade III or IV HO, and this was clinically significant in only seven of the 687 patients studied (1%). A distinct form of HO occurs after this modified direct lateral approach, consisting of bone spicules emanating from or around the greater trochanter, presumably arising from the elevated combined periosteum and tendon of the gluteus medius and vastus lateralis (Fig. 10). Of note, the prevalence and severity of HO was similar in cemented, hybrid and cementless THA. This finding is in contradiction to that of Maloney et al, who reported that HO occurred more commonly after cementless stem insertion, and agrees with the report of Rockwood and Horne.[31,42]

This relatively low occurrence of HO might be attributed to careful, blunt in-line fiber spreading of the gluteus medius and tissue protection during acetabular femoral canal preparation. It might help dispel the belief that HO is more common after lateral approaches, given that HO prophylaxis was not used in these patients.

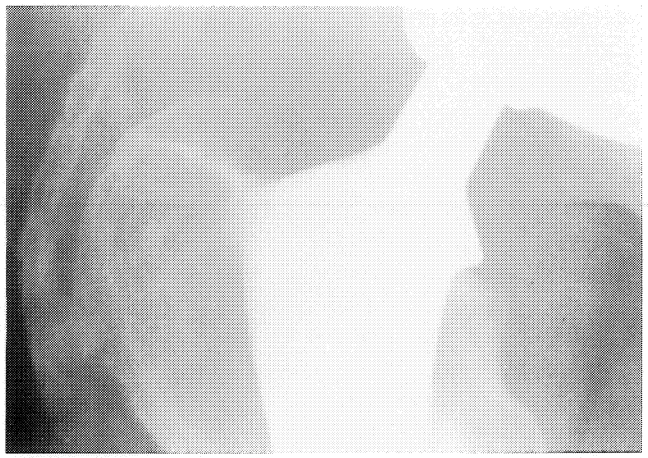

Figure 10
Typical appearance of HO following this approach.

Nerve Palsy

The reported incidence of femoral or sciatic nerve palsy following total hip arthroplasty is between 0 and 3%.[49] Schmalzried et al reported a 1.3% incidence after primary THA and 5.2% after primary THA for CDH. They reported that all patients with postoperative nerve palsies had decreased walking ability at last follow-up.[44] Even patients with partial recovery may have a compromised result and ongoing neurogenic pain. Four nerve palsies occurred as the result of 712 THA's reported here that had a minimum two year follow-up. All palsies were partial neuropraxias of the sciatic nerve, and all showed some recovery at last follow-up. Each palsy was thought due to retraction, and none occurred in a patient who had significant lengthening or had the THA done for CDH. Whether these palsies could have been avoided, or the incidence lowered using a different approach, is difficult to assess.

Utility

Measures of utility of a surgical approach are difficult to define. Those reported here, including applicability in THA, OR time, hip rating and pain scores deserve comment, but may only have usefulness if compared directly to other approaches. Regarding applicability, this approach has proven reliable and predictable in accessing the hip and is currently the approach used for all primary and revision THA's at our institution, including those for CDH. The average OR time of one hour, thirty-eight minutes has been comparable to that of a posterior approach, and is considered acceptable at our teaching institution. The finding that greater than 90% of acetabular and femoral components were positioned well is support

for the adequacy of the exposure using this approach. Finally, although hip rating scores are not valid measures of the success of THA, it appears that no untoward effects such as pain or decreased walking ability could be attributed to the approach. It has been our observation, supported by statistical analysis here, that hip scores and walking ability (as judged by a limp and the need for walking aids) deteriorate over time, as patients become older and more debilitated. This should be remembered when evaluating patients longitudinally in this manner.

Disadvantages

There are severe potential disadvantages of this modified direct lateral approach. The skin incision is generally longer than that required for a posterior approach. One or two surgical assistants are required, depending on the size of the patient and expertise of the surgeon. A sterile pouch must be maintained. If the anatomy is poorly understood, the SGN is in danger, and the femoral neurovascular structures can be injured by excessive dissection or retraction. Finally, trochanteric bursitis may be more common than with other incisions not coursing over the trochanter, an issue not addressed here.

Several limitations to this study exist. It is a retrospective review and is subject to the observations and interpretations of the reviewers. No information is available for the 12 patients lost to follow-up, who potentially have had complications. However, the 98% retrieval (712/724) of available hips is excellent, and even if some of those hips lost to follow-up had complications, it would not likely change the significance of the results. This is a relatively short term follow-up, and a longer period of time will be required to exclude some complications, such as late instability.[7] Finally, this report reflects the experience of two senior surgeons who have supervised over 1000 THA's via this approach at one institution, with nursing and ancillary personnel who are familiar with the procedure and rehabilitation. The results may not be applicable to other circumstances.

CONCLUSION

In conclusion, we describe a modified direct lateral approach for use in primary THA's and most revision THA surgeries. This approach provides excellent exposure and allows accurate placement of components in a timely fashion. In our experience, it has greatly diminished the potentially devastating complication of postoperative instability and is associated with an acceptable incidence of postoperative limp, heterotopic ossification and nerve palsy. A thorough knowledge of the relevant anatomy and surrounding neurovascular structure is a requisite prior to proceeding with this approach. However, with careful technique and attention to detail, a satisfactory outcome can be achieved in nearly all patients.

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OUR EXPERIENCE WITH DUAL ENERGY X-RAY ABSORPTIOMETRY (DEXA) AND THE WISCONSIN HIP

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INTRODUCTION

More than 30 years ago, Sir John Charnley laid the foundation for current total hip replacement with his monumental work on low friction arthroplasty[2]. Numerous variations and modifications in design followed, reflecting the emerging knowledge of implant design, metallurgy, biomechanics, and chemistry.

Failure of THA, due to loosening of aseptic components with associated osteolysis, was first reported in the 1970s and continues to be the major long-term complication of the procedure. Loosening of cemented prosthetic components led many orthopedic surgeons and scientists to investigate the feasibility of alternative fixation methods for prosthetic devices while others perfected cement techniques. Investigations in the late 1970s led to the development of a wide variety of porous coated implants. Basic science work has provided an understanding of the many issues concerning the use of porous materials and their ability for fixation by means of tissue ingrowth.

All hip implants cause remodeling of the surrounding bony tissue. Grossly accelerated bone remodeling and huge loss of mineral in the proximal femoral cortex have been demonstrated in animals models with some cementless implants. In humans, the remodeling changes that are observed around some cementless femoral stems tend to appear in a shorter period of time and can be more severe than those observed around cemented stems[1,13]. This potentially adverse bone remodeling, causing bone loss around the cementless prosthesis, is thought to be the result of diminished stresses in the bone secondary to stress shielding. Bone loss can have potentially deleterious effects and can present formidable problems for eventual revision. A number of risk factors for bone loss have been identified clinically; they include the patient's age, gender, pre-existing osteopenia, extent of the implant porous coating, and the diameter of the stem[3]. A stem causing minimal atrophy is probably advantageous. A thorough understanding of the biological adaptation between the bone-prosthetic interface will assist in the success of a particular prosthetic component.

Previous efforts to quantify bone resorption around femoral stems have been troublesome and inexact. Plain radiographs, quantitative computed tomographic scanning, and routine dual photon absorptiometry are neither sensitive, specific nor precise for the determination of quantitative changes of peri-prosthetic bone mineral density. Analysis of plain roentgenograms provides only a subjective impression of bone remodeling and does not allow for precise quantification of resorption. Changes in density must be greater than 30% to be observed with any certainty. West and colleagues, using qualitative radiographic densitometry, examined the magnitude of error for variables such as film lot, exposure settings, target distance, field variability, and femoral rotation[16]. Small changes in each of these variables result in densitometric differences of 9-21%, and these errors accumulate as several factors vary at once. Serial radiographs on implanted patients at intervals of several days to weeks varied by more than 50%.

A semiquantitative evaluation of bone resorption has been developed by Engh and colleagues; this method provides data on factors influencing bone remodeling[3]. The authors note that their method is an approximation, and comment that resorption below the detection threshold cannot be accurately quantified. This method is insensitive, non-specific, and imprecise for the determination of quantitative changes in peri-prosthetic bone mineral density.

The original application of DXA was for the diagnosis and monitoring of metabolic bone disease and for assessing fracture risk in osteoporotic patients. The primary regions of interest for these applications are the femoral neck and lumbar spine. Recently our team and others have utilized dual energy x-ray absorptiometry (DXA) to precisely quantify the changes in peri-prosthetic bone density after THA[5-11]. This application of DXA allows monitoring of the degree and rate of bone response in THA patients.

Dual energy x-ray absorptiometry is a technique that uses x-ray absorption to determine the amount of bone in specified skeletal regions. The instrument uses a narrowly collimated x-ray beam which is filtered to allow two energies to be emitted. These two energies attenuate differently in soft tissue and bone, and the transmitted radiation is measured by a scintillation detector. The x-ray beam is passed through the proximal femur region in a rectilinear scan pattern caudad to cephalad. The amount of bone in the beam path is calculated as bone mineral content (BMC) in grams. BMC is then divided by the projected area of the region scanned, and this is reported

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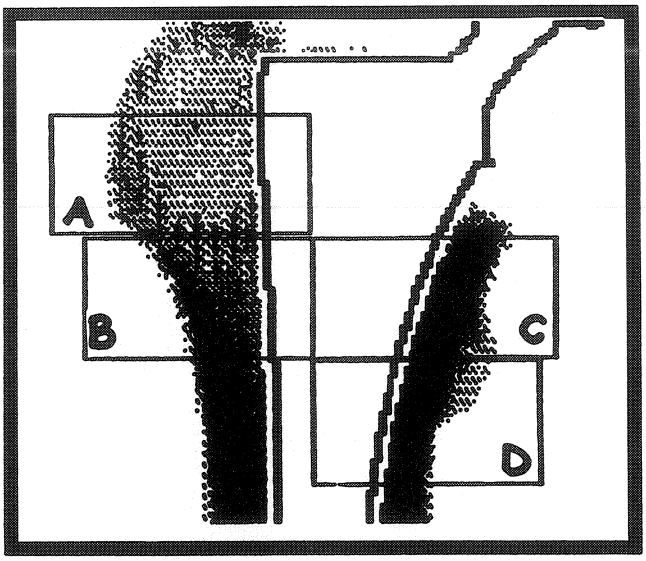

Figure 1. Regions of interest A-D: The midpoint of the lesser trochanter is the reference point; all regions are two cm in height.

as the bone mineral density (BMD) in g/cm^2. Thus, BMD provides an area density representing bone concentration in a given region, corrected for the size of that region. The DXA output is therefore similar to the AP projection in conventional radiography where a three-dimensional structure is imaged in two dimensions. The radiation dosage to the patient is small, less than five mrem per scan, allowing for repeat measurements with little hazard. A more detailed description has been given elsewhere[7].

MATERIALS AND METHODS

Bone mineral data were acquired and analyzed with an orthopedic software package (Lunar DPX, Madison, WI). This software allows for determination of BMC in determined regions of interest. The metal prosthesis is removed from analysis using a proprietary segmentation algorithm based on the metal's x-ray attenuation. Additionally, a one millimeter offset from the implant edge is invoked to insure complete removal of all metal components; this offset also eliminates any effect due to extreme density change ("partial volume effect") at the bone-implant interface.

For our studies, four regions of interest (ROIs) were distinguished with the midpoint of the lesser trochanter as the reference point (Figure 1). An anatomical landmark was chosen over an implant-based landmark to eliminate measurement error which might arise in subsequent scans with possible changes in implant position. Each ROI is two centimeters in height and includes all the bony points between the implant edge and the periosteal bone edge. Two lateral ROIs were selected: (A) in the greater trochanter and (B) distal to the greater trochanter; the two medial ROIs were (C) superior to and (D) inferior to the midpoint of the lesser trochanter. The ROIs correspond approximately with Gruen zones IA, IB, VIIA, and VIIB. When we began our work, DXA acquisition and analysis programs were only available for the proximal regions. Currently, the software now allows for determination of BMD based on all Gruen zones.

Before commencing clinical studies, accuracy and precision of the technique was established. Accuracy was assessed by scanning bone phantoms of known densities with a prosthesis overlying the bone phantom. We discerned no difference between pairs of scans with the implant present versus implant absent from the regions of interest. Furthermore, no effect of implant type on measured BMD values for the four densities of material was observed. The measured values were not different from expected values, with measurement errors well below 1% for all densities, and there were no differences in accuracy among the different densities.

Next, precision was assessed under three conditions: (a) in bone phantoms; (b) in cadaver femora, implanted *ex vivo,* measured with no position changes between each scan; and (c) in patients who had undergone THA, remeasured with repositioning between scans. Precision error, determined as % coefficient of variation (%CV; standard deviation/mean) of repeated measurements, was $< 0.6\%$ in the bone phantoms and $< 1.5\%$ in the cadaver femora. In the patient group, four ROIs were defined and the average precision error with repositioning was 3.0%. The precision error for BMD *in vivo* was greater than *ex vivo* (cadaver) estimates. This increased precision error *in vivo* is probably due to variable patient position and nonhomogeneous distribution of soft tissue. Little difference in precision was found between ROIs although the distribution and amount of cortical and cancellous tissue varies among regions.

With the proof that DXA has both the accuracy and precision necessary to detect and quantify peri-prosthetic bone mineral density, we commenced a study using DXA to determine the course of bone remodeling around a femoral stem, specifically the Wisconsin Hip System. This is a titanium alloy stem with a proximal plasma sprayed coating. A more detailed description of the stem is provided by Scerpella and colleagues[14].

Two patient groups were recruited and followed per protocol for two years. All patients utilized the same implant type (Wisconsin Hip System; Biomet, Warsaw, IN). The first patient group was composed of individuals scheduled to undergo THA (32 patients, 34 hips) and the second patient group included those individuals with a pre-existing THA of one to six years duration (57 patients, 61 hips). This provided a mixed longitudinal, cross-sectional study design for evaluation of long-term changes.

All patients had disabling disease of the hip that had failed to respond to non-operative treatments.

RESULTS

Changes in BMD were examined as absolute and percent changes from baseline (pre-operative or initial measurement) for each patient. Additionally, the relationships between BMD response and age, weight, stem size, and disease were also examined. Expected gender differences in height and weight were accounted for in the statistical analyses. Age at time of surgery was not different between groups and the distribution of underlying disease was similar. There were also no obvious differences between the groups for the distribution of prosthesis size. Clinical outcome, examined by Iowa Hip Scores, showed that post-surgical assessment was greater than the pre-operative assessment. This level of satisfaction continued with on-going follow-up. There were no serious complications nor surgical failures reported in this patient population. Excellent five year survival rate and minimal thigh pain was reported by the patients. Proximal femoral remodeling occurred resulting in a net bone loss for these patients.

In the first patient group, those scheduled for THA, pre-operative femoral bone mineral densities were determined for both hips in patients prior to surgery. Interestingly, BMD of the diseased femur was determined to be significantly lower (~4-6%; $p<0.02$) than that of the contralateral femur. Therefore, we concluded that the contralateral femur should not be used as a benchmark for postoperative comparisons. Subsequent measurements of this patient group were made within two weeks after surgery, then at one, three, six, 12, and 24 months. The relative change in BMD was similar for all four regions. Immediately after surgery, BMD increased in all regions (6-11%). Next, there was a reduction in bone mineral values that continued for six months, followed by a plateau through the second postoperative year. At three months, the typical BMD loss from baseline was 4-10%, and at six months, 11-21%. Little further decrease was observed between six and twelve months. The relationships between BMD and gender, age, height, weight, body mass index, prosthesis size, and original diagnosis were also examined. Weight was a consistently positive variable; no other variables were significant when weight was included in the model.

In the second patient group, those patients who had already undergone THA, little change was observed during the two year follow-up, regardless of the length of time since surgery. Observed BMD changes in this group did not exceed 3%. Moreover, there was no observed regional response. To better understand the individual variability in bone mineral values and skeletal response, associations with gender, age, height, weight, body mass index, prosthesis size, and disease were examined. While BMD values for gender and disease were different, the rate of change in BMD was not influenced by either. Additionally, stem diameter did not significantly alter BMD values.

DISCUSSION

In an interesting study, Engh and colleagues measured the bone mineral content of five patients at autopsy who had had an AML prosthesis for 7-84 months[5]. They demonstrated a mean decline of 7-52%; the region adjacent to the proximal one-third of the femur had the greatest mean decrease in bone mineral content. This region with the greatest decrease is also the region with the greatest difference between the stiffness of the implant and the stiffness of the peri-prosthetic bone. Although we also observed a decline in the proximal one-third of the femur, our measured decline was not as great as that reported with the AML stem.

Our study is unique because it demonstrates the two year bone response in patients with recent and pre-existing THA. The two patient groups can be viewed as a continuum from immediate postoperative response through eight years post-surgery. Immediately after surgery, an increase in BMD was observed in all four regions of interest. This increase then returned nearly to the baseline values by the first month. Others have also reported similar findings in human and canine models. Van Rietbergen and colleagues demonstrated an initial postoperative increase in BMD when using an iterative computer model to analyze remodeling in an animal model[15]. The origin of this interesting and puzzling initial increase was further investigated by us.

Using seven pairs of human cadaver femora, we examined the effects of femoral component implantation and femoral component composition on BMD measurements[12]. We observed no effect of the femoral component composition (titanium alloy or cobalt chromium) on the measurement of BMD. Further study demonstrated that reaming and broaching of the femoral canal induced an eight percent decrease in BMD when compared to pre-implantation values. This decrease observed after reaming and broaching was eliminated when a femoral stem was pressed fit into the femur.

These results do not adequately explain the demonstrated increase in BMD observed in patients two weeks after surgery nor do they justify the 11% increase measured in dogs[10]. Most probably, we hypothesize that the increased BMD measurement observed immediately postoperative might be accounted for by rotational differences of the femur by the DXA scan when comparing preoperative to immediate postoperative scans, thereby increasing the BMD measurement. Conversely, the authors of the canine study attribute the increased BMD to partial

volume effects due to the relative thinness of the femoral cortex[10]. Regardless, it is interesting that the decline in BMD observed after reaming and broaching was eliminated after press-fitting the femoral prosthesis. We speculate that this effect may be due to the compacting of trabeculae into the endosteal surface of the medullary cortical bone. Dual energy x-ray absorptiometry allows for the quantitative assessment of bone mineralization. The ability to measure peri-prosthetic bone mineral density over time and in a number of regions provides the clinician with accurate, precise, and objective information on the performance of the femoral stem. While DXA will not replace the standard methods for diagnosis of bony ingrowth or prosthesis-related phenomena such as subsidence and osteolysis, we do believe that the data obtained by this technique will enhance the understanding of bone tissue adaptation around the hip prosthesis. Clinical application of this technique may prove to have better prognostic value in the early diagnosis of adverse remodeling responses.

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MULTIPLE DRUG RESISTANCE IN OSTEOSARCOMA

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INTRODUCTION

Osteosarcoma is a mesenchymal neoplasm in which the malignant cells produce an osteoid matrix. Morphologic classification of these tumors is based on the degree of osteoid production, the presence of coexisting cartilaginous or fibrous stroma, the presence of a round cell component, and the degree of vascularity[1,2]. Although the histologic appearance of osteogenic sarcoma can vary extensively, diagnosis usually is not difficult[1,2]. With the exception of parosteal and well differentiated variants, osteogenic sarcomas are aggressive malignancies and without aggressive chemotherapy and ablative surgery, prognosis is very poor[3]. With ablative surgery alone, long term survival has been approximately 10%; however, with the advent of neoadjuvant chemotherapy and modern surgical approaches, survival has increased to 52-87%[4,5]. Despite progress in the treatment of this tumor, approximately 25% of patients do not respond to aggressive therapy, and most of those succumb to distant metastatic disease[6].

The strongest predictor of clinical outcome with current therapeutic modalities is the degree of necrosis induced by preoperative chemotherapy, as identified histologically in the surgical resection specimen[4,5]. At present, factors which reliably predict therapeutic response are lacking, although some authors believe that chondroblastic tumors and tumors which occupy more than a third of the bone require more aggressive chemotherapy[7]. Many of the ongoing investigations of osteosarcoma have therefore focused on the identification of factors which are predictive of poor response to current preoperative treatments with the aim of developing alternative protocols and improving response.

Recent evidence suggests that one mechanism of chemotheraputic resistance in many tumor types is nonspecific removal of cytotoxic drugs from tumor cells by the membrane pump known as P-glycoprotein[8]. This ATP-dependent membrane protein has broad specificity, and has been detected in normal tissue types and human cancers[8-10]. P-glycoprotein expression has been identified in human sarcomas[10-12], and Chan et al reported a strong correlation between P-glycoprotein expression and poor prognosis in childhood rhabdomyosarcoma[10]. A recent study has demonstrated P-glycoprotein mRNA expression in some osteosarcomas and an inverse correlation with relapse-free and overall survival[13].

In the current study we have evaluated the expression of P-glycoprotein in 21 cases of osteogenic sarcoma in an attempt to determine if its expression correlates with chemotherapy resistance and is predictive of a poor response to conventional therapy. We present immunohistochemical and *in situ* hybridization data on P-glycoprotein expression before and after chemotherapy and correlate the results with histologic type, histologic response to chemotherapy, and patient outcome.

MATERIALS AND METHODS

Twenty-one cases of osteosarcoma were retrieved from the surgical pathology files of Strong Memorial Hospital in Rochester, New York. Clinical records on all patients were reviewed. Immunohistochemical studies were performed on the intial biopsy in all cases, on viable tumor from the resection specimens in eight cases, and on tissue from pulmonary metastases in three cases. Tissue from all cases had been formalin fixed and decalcified in a mixture of formaldehyde and formic acid (Decalcifier, Surgipath, Richmond, IL) prior to routine histologic processing and paraffin embedding. Sections for immunohistochemistry and *in situ* hybridization were cut at 5μ and mounted on poly-L-lysine-coated slides.

Immunodetection of the MDR gene product P-glycoprotein was performed by the biotin-streptavidin method[14] using the C219 antibody (mouse monoclonal; Signet Laboratories, Inc., Dedham, MA) at a dilution of 1:20.

Images of the immunostained microscope slides were digitized using a videocamera (Hitachi VK-C350) mounted on an Olympus BH2-RFCA microscope using the 20X objective. The images were captured in 32 bit PICT format using Colorsnap software (Computer Friends, Inc., Portland OR) on a Macintosh IIci microcomputer. The immunostaining was digitally enhanced using Adobe Pho-

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TABLE I: Clinical Data and P-Glycoprotein Status of Initial Biopsy

PT.	SEX	AGE	TUMOR SITE	HISTOLOGY	C219	TREATMENT	STATUS
1	M	50	Rt. hemipelvis	Low grade osteosarc w/ focal chondroid diff.	+	Resection	NED
2	F	10	Facial bones posteior orbit	High gr. osteosarc	+	POG protocol 8651; ifosphamide, VP-16, carboplatinum taxol	DOD
3	F	65	Left proximal tibia	High gr. osteosarc	–	Resection; Ifosphamide	DOD
4	F	7	Rt. proximal humerus	High gr. osteosarc	–	POG protocol 8651, resection	NED
5	F	74	Rt. pelvis	Pagetic osteosarc	+ +	Palliative radiation	DOD
6	F	25	10th rib, chest wall tumor	Parosteal osteosarc	–	Resection	NED
7	M	36	Rt. distal femur	Parosteal osteosarc	–	Resection, bone grafting	NED
8	F	13	Rt. proximal humerus	High gr. osteosarc	–	POG Protocol 8651, resection	DOD
9	F	11	Left femur	High gr. osteosarc	–	POG protocol 8561, resection, Ifosphamide	AWD
10	M	17	Pelvis	Small cell osteosarc	+	POG protocol 8561	DOD
11	M	16	Rt. distal fibula	High gr. epithelioid osteosarc	-	POG protocol 8651, resection, metastatectomy	NED
12	F	18	Rt. proximal humerus	High gr. osteosar.	+	Memorial Sloan-Kettering protocol; resection	NED
13	M	30	Pelvis, left humerus	High gr. osteosarc	–	POG protocol 8651, resection	NED
14	F	16	Left femur	High gr. osteosarc	–	CCSG protocol 782; resection	NED
15	M	61	Rt. maxillary sinus	High gr. telangiectatic osteosarc	+	Radiation	NED
16	F	15	Distal femur	High gr. telangiectatic osteosarc	+	POG protocol 8561, resection	NED
17	F	78	Rt. hip	Pagetic osteosarc	–	None	DOD
18	F	9	Left proximal femur	High gr. chondroblastic osteosarc	-	POG 8651; resection	DOD
19	M	78	Rt. humerus	High gr. osteosarc	–	None	DOD
20	F	10	Left tibia, rt. humerus	High gr. chondroblastic osteosarc	-	POG 8651, resection	DOD
21	M	19	Distal left tibia	High gr. chondroblastic osteosarc	+ +	POG 8651, amputation	DOD

Key:Treatment: POG (Pediatric Oncology Group) protocol 8651: High dose methotrexate, adriamycin, cis-platinum; Memorial -Sloan Kettering protocol= Methotrexate, vincristine, adriamycin, bleomycin, cyclophosphamide, actinomycin-D, cytoxan ; CCSG (Children's Cancer Study Group) protocol 782 = Methotrexate, bleomycin, cyclophosphamide, actinomycin-D, adriamycin, cis-platinum.

C219 staining: (-) = no staining; (+) = staining in <50% tumor cells; (+ +) = Staining in >50% tumor cells.Status: NED = no evidence of disease; AWD = alive with disease; DOD = dead of disease.

toshop (Adobe Systems, Inc., Mountain View, CA) software by converting the image to an indexed color table format and remapping the shades of red characteristic of the immunoperoxidase color reaction product to black for the corresponding pixels.

In situ hybridization was performed using a modified digoxigenin-11-dUTP labeled nonradioactive technique (Genius™ kit, Boehringer-Mannheim, Indianapolis, IN) with immunodetection using an antidigoxigenin antibody as previously described[15]. A 30 base oligonucleotide probe to the multidrug resistance gene-1 mRNA (MDR-1 antisense

probe) and a complementary 30 base control sense MDR-1 probe were chemically synthesized and used in this study. The sequence of the oligonucleotide antisense probe was: C C A A C C A G G G C C A C C G A C T G C C C A C T C T G C .

A full length cDNA MDR-1 probe and the oligonucleotide MDR-1 probe were labeled with ^{32}P and used for northern blotting of mRNA from kidney, adrenal, and an osteosarcoma specimen to confirm specificity of the oligonucleotide used in the *in situ* hybridization experiments.

RESULTS

The clinical data are summarized in Table I. The 21 patients studied had tumors of the following histogenic subtypes: nine conventional high grade osteosarcomas, three chondroblastic osteosarcomas, two telangiectatic osteosarcomas, two parosteal osteosarcomas, two Pagetic osteosarcomas, one epithelioid osteosarcoma, one small cell osteosarcoma, and one low grade osteosarcoma. There were six femoral, five humeral, four pelvic, three tibial, two facial bone, one fibular, and one rib lesion. Patients ranged from seven to 78 (average 31) years old; eight were males and 13 females. Two patients with Pagetic osteosarcoma and one additional patient who refused recommended therapy were treated palliatively, and all three died of their disease. One low grade and two parosteal osteosarcomas were treated by surgical resection alone, and one unresectable telangiectatic maxillary sinus osteosarcoma was treated with radiation therapy. The remaining 14 patients were treated with the conventional combination of surgery and chemotherapy. At a minimum follow-up time of two years (range = two to ten years), ten of the 21 patients studied (52%) were without evidence of disease. Of the 14 patients who underwent chemotherapy, three of five of the patients with MDR1-negative tumors have no evidence of disease (60%). However, only three of nine (33%) of the patients with MDR1-positive tumors remain disease free.

At initial biopsy, eight of 21 tumors (38%) were positive immunohistochemically for P-glycoprotein using the C219 monoclonal antibody, with only two (9.5%) exhibiting strong expression (staining in over 50% of the cells). In general the P-glycoprotein was expressed in poorly differentiated areas lacking osteoid matrix production, as well as in areas of chondroid differentiation. P-glycoprotein immunoreactivity was rarely observed in cells in areas of mature tumor bone formation. Of the strongly staining tumors, one was a chondroblastic osteosarcoma and one a Pagetic osteosarcoma, and both of these patients died of their disease. An additional patient with a chondroblastic osteosarcoma which was initially negative demonstrated strong staining in the tumor following neoadjuvant chemotherapy (Table 2). The two low grade parosteal sarcomas were both negative for P-glycoprotein. All the other specimens which were positive for P-glycoprotein expression demonstrated only moderate staining (<50% of

TABLE II: Histologic Response and P-Glycoprotein Status Before and After Chemotherapy

PATIENT	SITE	DRUG TREATMENT	C219 PRE	C219 POST	TUMOR NECROSIS
8	Rt. proximal humerus, rt. lung	POG protocol 8651	–	+	80%
9	Left femur	POG protocol 8651, Ifosphamide	–	NVT	100%
11	Rt. distal fibula	POG protocol 8651	–	+	50%
12	Rt. proximal humerus Left pulmonary metastasis.	Memorial Sloan-Kettering protocol	+ +	NVT NVT	100% 100%
14	Left femur	CCSG protocol 782	ND	–	70-80%
18	Left proximal femur	POG protocol 8561; Cyclosporine	–	+ +	80%
20	Left tibia	POG protocol 8651, Ifosphamide/Mesna, Cyclosporine, Carboplatinum Etoposide	-	+	50%
21	Distal left tibia Rt. pulmonary metastasis.	POG protocol 8651, Actinomycin-D, Bleomycin, Cytoxan	+	+ +	amputation before chemo

Key:Treatment: POG (Pediatric Oncology Group) protocol 8651: High dose methotrexate, adriamycin, cis-platinum; Memorial -Sloan Kettering protocol= Methotrexate, vincristine, adriamycin, bleomycin, cyclophosphamide, actinomycin-D, cytoxan ; CCSG (Children's Cancer Study Group) protocol 782 = Methotrexate, bleomycin, cyclophosphamide, actinomycin-D, adriamycin, cis-platinum.

C219 staining: (-) = no staining; (+) = staining in tumor cells; NVT = no viable tumor ; ND = not done.

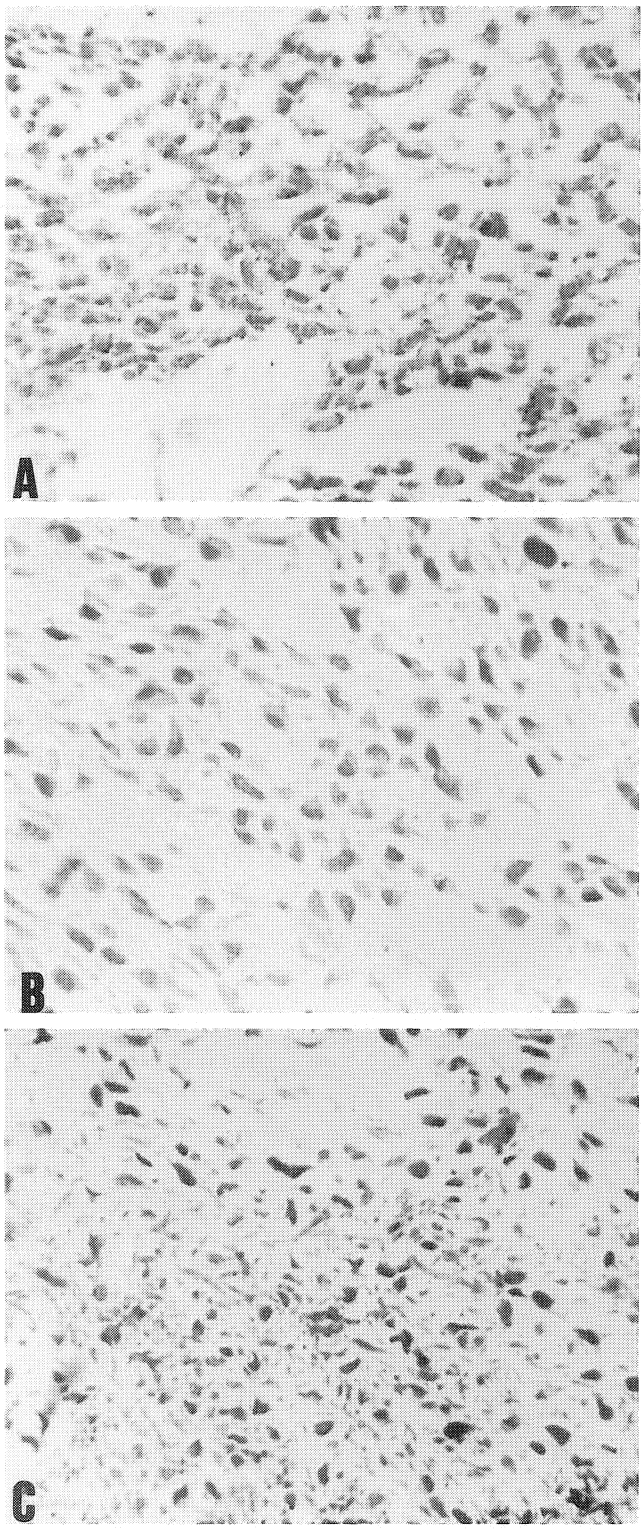

Figure 1. Immunohistochemistry for P-glycoprotein using C219 monoclonal antibody on osteosarcoma before and after chemotherapy. (A) Biopsy of osteosarcoma (Patient #18), negative control with omission of primary antibody. (B) Biopsy immunostained with C219. Note absence of staining similar to the negative control in 1A. (C) Resection specimen of same patient after two cycles of neoadjuvant chemotherapy. Note the induction of P-glycoprotein expression as evidenced by the positive staining with C219. Magnification = 200x.

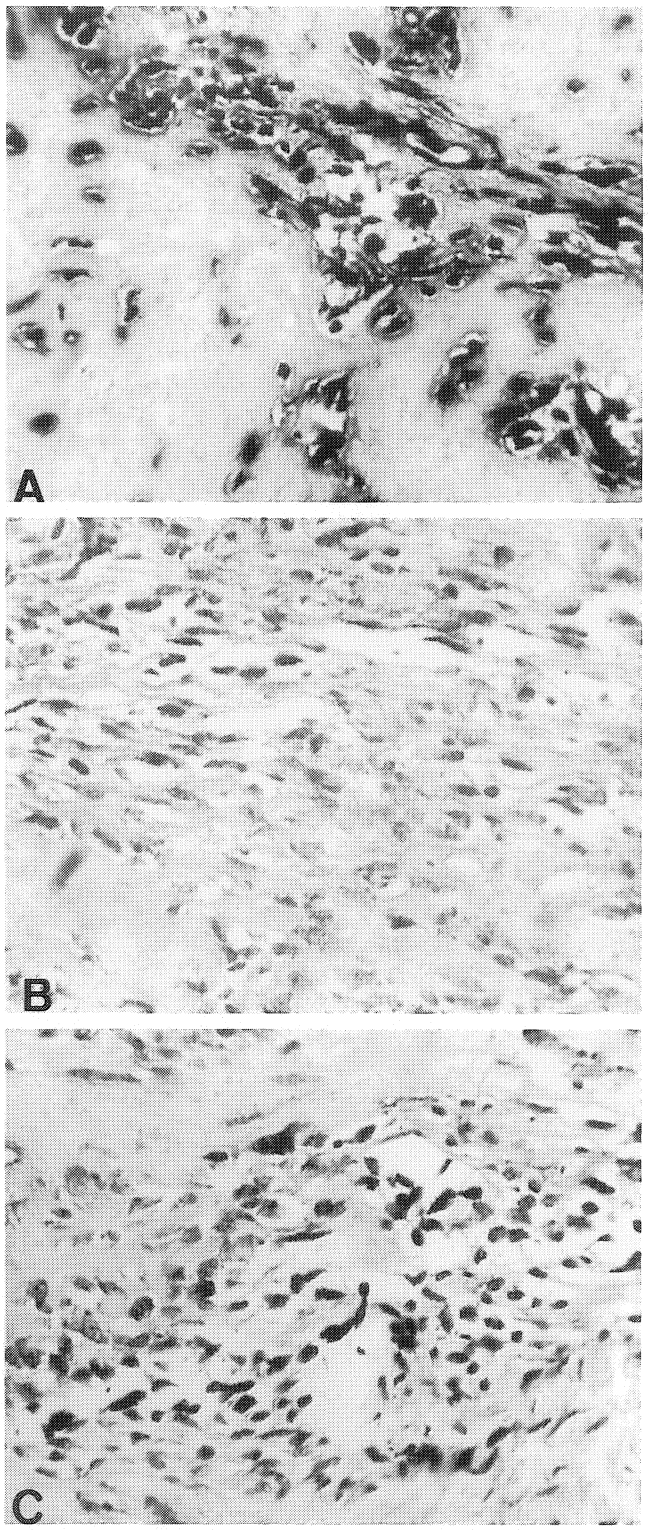

Figure 2. *In situ* hybridization with MDR1 cDNA probe. (A) Resection specimen of osteosarcoma (Patient #18), after two cycles of neoadjuvant chemotherapy, hybridized with a polydT probe as a positive control to demonstrate preservation of mRNA in the specimen. Note positive staining of all the cells. (B) Same resection specimen hybridized with a negative control sense probe sequence complementary to the DNA (not the mRNA) sequence for MDR1. Note that there is minimal background staining. (C) Resection specimen hybridized with MDR1 probe. Note strong staining in the cells of this tumor indicating presence of the mRNA for MDR1 after the preoperative chemotherapy. Magnification = 200x.

cells). In eight patients tissue was available for analysis from both the biopsy and following neoadjuvant chemotherapy and resection (Table 2). In four of these patients whose tumors were initially negative for MDR1 at biopsy, the specimen was positive at resection, suggesting either inducibility of the drug resistance mechanism or selection of subpopulations of drug resistant tumor cells by the preoperative exposure to chemotherapy. All of these tumors demonstrated poor responses to chemotherapy as judged by tumor necrosis of only 50-80%. One patient with a P-glycoprotein positive tumor at biopsy, however, showed no viable tumor at resection. Of the four patients who demonstrated induction of P-glycoprotein expression during neoadjuvant chemotherapy, three died of metastatic disease and one developed pulmonary metastases one year after completion of chemotherapy, but has been without evidence of disease for three years following pulmonary resections. Figure 1 demonstrates immunohistochemical results in patient #18, with no staining at biopsy (Figure 1B) as compared to the negative control (Figure 1A), but positive staining for P-glycoprotein after neoadjuvant chemotherapy (Figure 1C).

To confirm that the immunostaining represented MDR1 rather than a cross-reacting protein such as MDR2, *in situ* hybridization was carried out on six of the osteosarcomas using an oligonucleotide probe specific to MDR1, as well as with a complementary control probe. The results correlated with the immunohistochemistry and confirmed presence of mRNA for MDR1 only in those specimens which stained positively using the C219 P-glycoprotein antibody. Figure 2 shows *in situ* hybridization results for the resection specimen illustrated in Figure 1. Poly dT was used as a control probe to verify the presence of mRNA in the tissue specimen (Figure 2A). The negative control sense probe shows a low background level of staining (Figure 2B), and Figure 2C shows the expression of the induced mRNA for MDR1. The initial biopsy specimen for this patient was negative for MDR1 mRNA

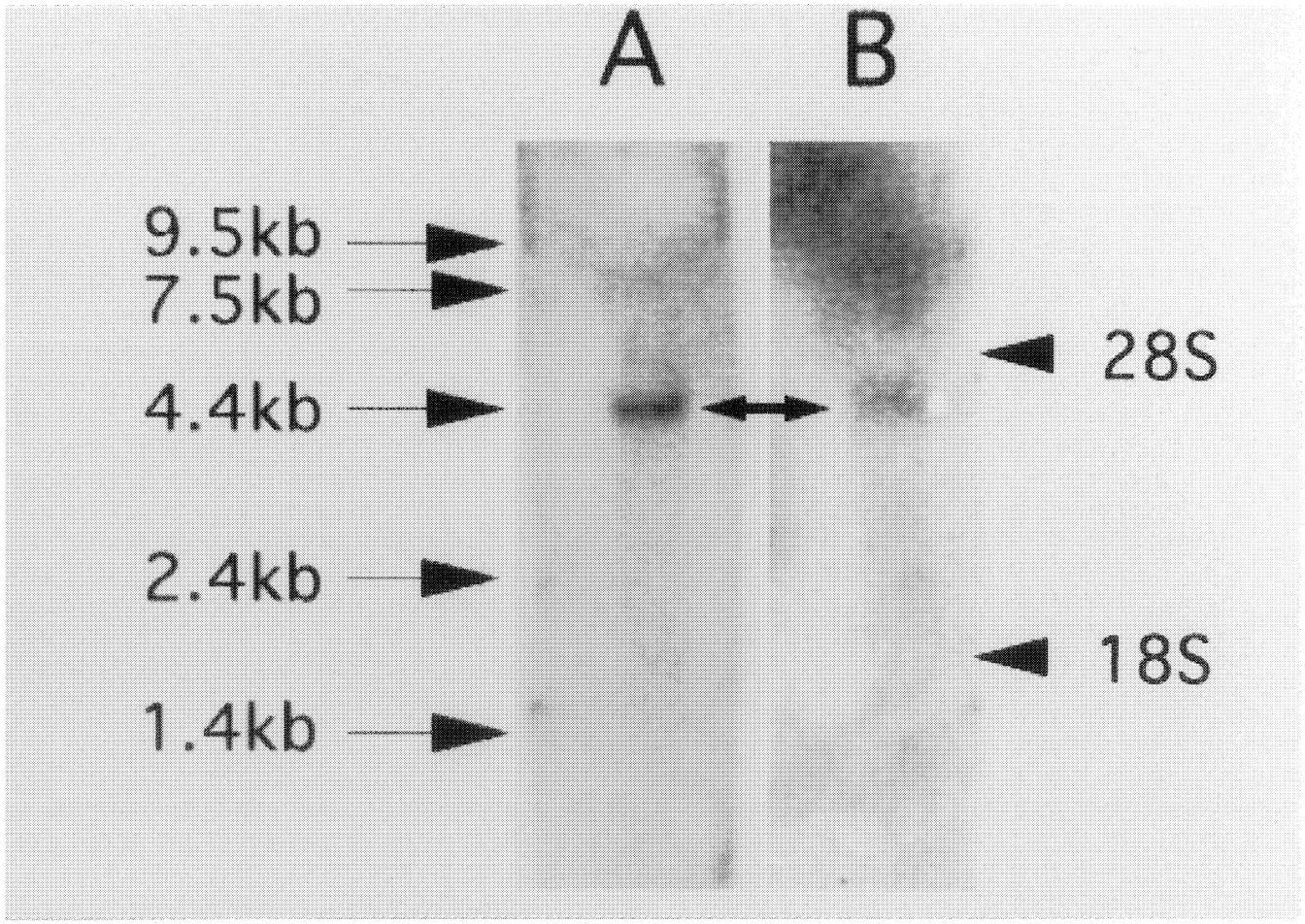

Figure 3. Northern blot verification of cDNA oligonucleotide probe used for *in situ* hybridization. The molecular weight markers are shown on the left and the ribosomal RNA molecular weights on the right. Both lanes contain total RNA from kidney, which expresses P-glycoprotein. Lane A was hybridized with a full length cDNA for MDR1, and demonstrates the expected 4.5 kb transcript. Lane B was hybridized with the oligonucleotide cDNA, demonstrating recognition of the same transcript.

(not shown), corresponding to the immunohistochemical findings. The specificity of the oligonucleotide *in situ* hybridization probe was further confirmed by northern analysis of mRNA using a full length cDNA probe and the oligonucleotide probe comparatively, with demonstration of the expected 4.5 kb transcript of MDR1 (Figure 3).

Analysis of three metastatic lesions was also conducted and in all three, P-glycoprotein was found to be expressed by both immunohistochemistry and *in situ* hybridization. An example is shown in Figure 4A (negative control) and 4B (C219). Although the red immunoperoxidase stain is readily apparent in color, it may not be well visualized in black and white photographs, depending on the relative levels of the hematoxylin counterstain and the reaction product. Therefore Figure 4 is image enhanced using digital color mapping as described in METHODS. The immunoperoxidase reaction product indicating presence of P-glycoprotein is represented by the black granular pattern (Figure 4B) and is absent in the control (Figure 4A). The *in situ* hybridization was also positive for MDR1 in this specimen (not shown).

One patient failed treatment and developed metastatic disease to the right humerus after completion of her chemotherapy (patient # 20). The patient was treated

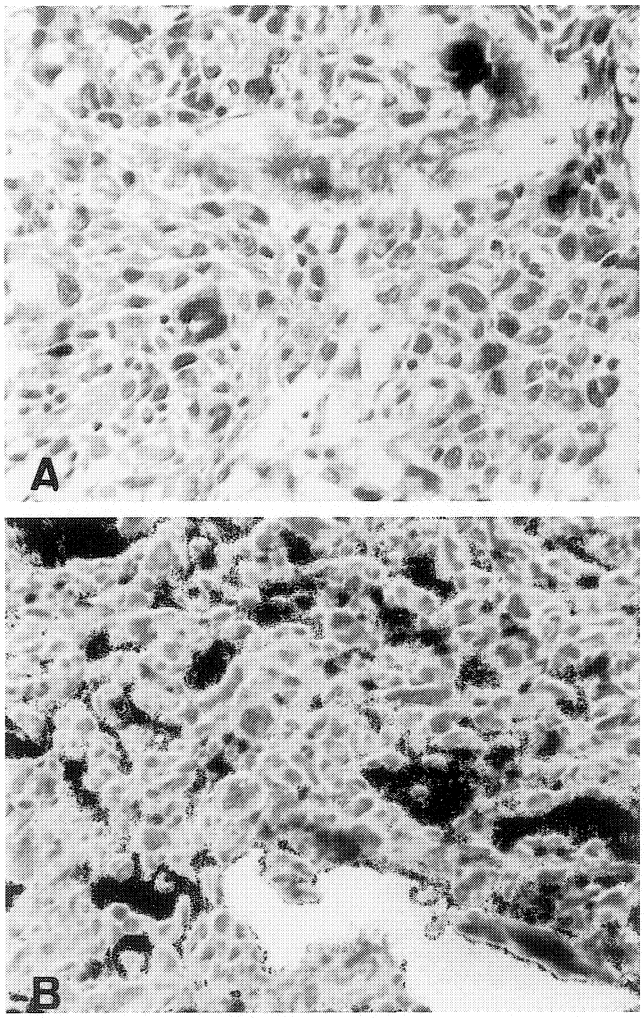

Figure 4. Immunohistochemistry of a pulmonary metastasis of osteosarcoma (patient #12) for P-glycoprotein. (A) Negative control with omission of the C219 primary antibody, with minimal staining. (B) C219 immunohistochemistry, digitally enhanced using color mapping as described in METHODS to demonstrate localization of P-glycoprotein in the metastatic tumor in a gray scale image. The black granular appearance represents the reddish immunoperoxidase reaction product corresponding to P-glycoprotein location. Magnification = 200x.

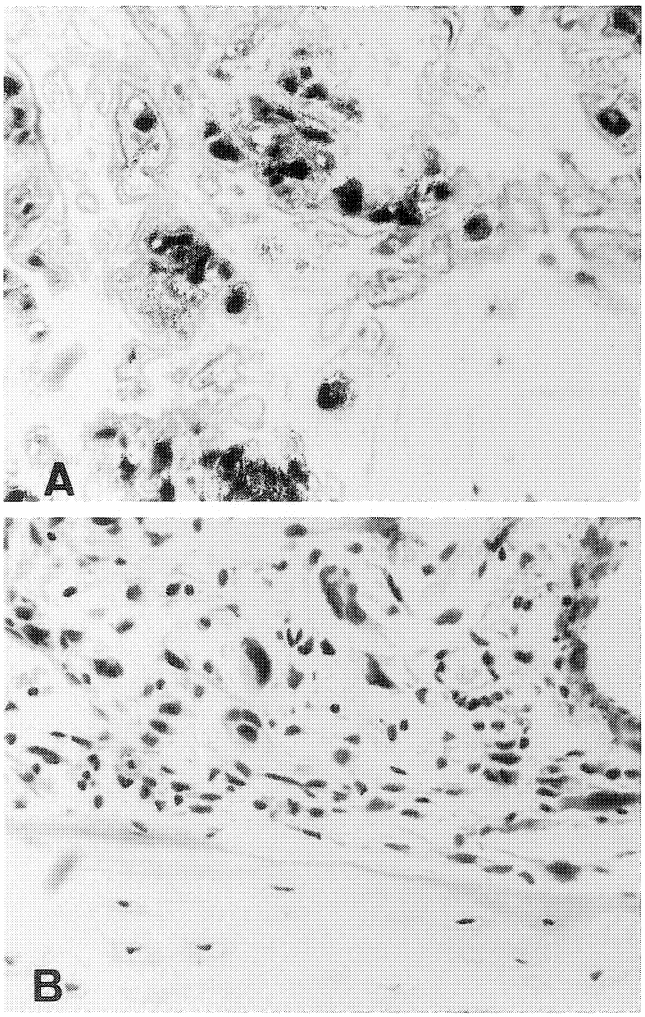

Figure 5. Immunohistochemistry of metastatic osteosarcoma before and after repeat chemotherapy with cyclosporine A as a P-glycoprotein inhibitor. The patient (#20) presented with a tibial osteosarcoma treated with neoadjuvant chemotherapy and below knee amputation. After completion of 1 year of adjuvant postoperative chemotherapy, the patient presented with a proximal humeral metastasis. The biopsy, immunostained with C219 for P-glycoprotein and digitally enhanced, is shown in (A). The patient was treated with two cycles of repeat similar chemotherapy with addition of cyclosporine A and the humeral metastasis resected. The resected specimen immunostained and digitally enhanced is shown in (B), showing no P-glycoprotein expression in the remaining viable tumor cells, with 50% of the specimen being necrotic. Magnification = 200x

with repeat chemotherapy with the addition of cyclosporine A as an MDR1 inhibitor, followed by resection of the proximal humerus and prosthetic reconstruction after two cycles of therapy. Biopsy of the humeral metastasis prior to chemotherapy demonstrated intense P-glycoprotein expression (Figure 5A), and there was no evidence of necrosis. However, after chemotherapy plus cyclosporine A there was minimal expression in the resected specimen (Figure 5B), 50% of which was necrotic, suggesting selective chemotherapeutic cytotoxicity in the MDR1 positive cells of the tumor. The presence of the remaining MDR1 negative cells may indicate existence of other operant drug resistance mechanisms.

DISCUSSION

Despite the advent of adjuvant chemotherapy and limb salvage surgery in osteosarcoma, long term survival rates remain disappointing in the 50-70% range[4-6] due to metastatic disease. The discovery of drug resistance mechanisms such as P-glycoprotein (MDR1) suggests a possible reason for failure of chemotherapy in some patients[13,16,17]. The present study indicates that approximately 38% of osteosarcomas express P-glycoprotein, and that an additional 20% may be induced to express the protein after neoadjuvant chemotherapy. The incidence of expression agrees with previous reports using other methods[13]. The immunohistochemical results using monoclonal antibody C219 were confirmed by highly specific *in situ* hybridization studies. As might be expected, osteosarcomas with known poor responsiveness to chemotherapy (Pagetic and chondroblastic osteosarcomas)[7,17,18] exhibited strong expression of P-glycoprotein. Conversely, low grade tumors such as parosteal osteosarcoma did not express the protein. Overall disease-free survival in this study was 52%, similar to other reported series[4-7]. Sixty percent of the MDR1-negative patients who were treated with chemotherapy remain disease free versus 33% of the MDR1-positive patients, suggesting a negative correlation between MDR1 expression and survival. This is consistent with prior pilot studies reported in the literature[13,17]; however, the small sample size in the present study necessitates a cautious interpretation of the data.

While the mechanism of induction of drug resistance is unknown, a likely possibility is clonal selection of cell populations expressing MDR1. The four patients in which P-glycoprotein expression was induced showed poor responses to chemotherapy in terms of percentage tumor necrosis, and all experienced metastases, suggesting that induction of MDR1 in initially negative tumors may be a poor prognostic sign. In contrast, the two patients who had P-glycoprotein negative biopsies which remained negative after chemotherapy did not develop metastases and have remained free of disease. This confirms previous reports which suggest a role of MDR1 in modulating responsiveness of osteosarcoma to chemotherapy[13,17].

In addition the findings of the patient treated with cyclosporine A as an MDR1 inhibitor suggested a partial effect of this approach in enhancing chemotherapeutic efficacy in drug resistant tumors. Renal and immunotoxicity of cyclosporine A severely limits its usefulness, but other less toxic and more promising MDR inhibitors are currently under development and may prove useful in treatment of drug resistant sarcomas.

Due to the small number of patients with differing histogenic types of osteosarcoma in the present study, the findings are by no means conclusive. Further studies of MDR1 expression in osteosarcoma are needed to determine its real significance regarding chemotherapeutic responsiveness. However, the preliminary results presented in this study suggest that: (1) a significant percentage of osteosarcomas express MDR1 as demonstrated by both protein and mRNA detection; (2) expression of MDR1 in osteosarcoma treated with chemotherapy appears to negatively correlate with overall survival of these patients; (3) MDR1 is inducible in some osteosarcomas by exposure to neoadjuvant chemotherapy, and induction may signify a poor prognosis; (4) MDR1 is expressed in metastatic osteosarcoma; (5) the chemotherapeutic response as judged by tumor necrosis appears to correlate negatively with induction of MDR1; (6) MDR1 inhibitors may render previously resistant osteosarcomas at least partially responsive to chemotherapy; and (7) MDR1 is preferentially expressed in the dedifferentiated and chondroid areas of osteosarcomas. These findings provide a framework for future, more extensive, studies involving larger numbers of patients to better define the role of multidrug resistance gene expression in osteosarcoma treatment and prognosis.

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THE REGISTRY OF BONE SARCOMA A HISTORY

Edward F. McCarthy, M.D.

There have been many national cooperative efforts led by panels of physicians, usually pathologists, to formulate nomenclature of particular diseases. Most of these efforts have dealt with neoplastic diseases, and their goal has been to correlate specific histologic features with a name and a prognosis. Examples of such panels are The Early Malignant Melanoma Panel, the Wilm's Tumor Study Group, and the Non-Hodgkin's Lymphoma Pathologic Study Group. These cooperative efforts to formulate nomenclature have their origin in the vision of one energetic surgeon, Ernest Codman, who, in 1921, established the Registry of Bone Sarcoma. Working under the auspices of the American College of Surgeons, Codman's goals were to record living patients with bone sarcoma, to revise inadequate existing nomenclature, and to learn the behavior of these neoplasms. The project lasted many years and was a great success. Not only did the Registry accomplish Codman's three goals, it achieved other further reaching effects. As the first national prospective study, it provided a model for studies of other diseases. Also, because many hospitals contributed to the Registry, it helped spearhead the movement toward hospital standardization. Finally, because the Registry depended on the working together of surgeons, pathologists, and radiologists, cooperative practice became fundamental to the treatment of bone diseases.

Ernest Codman (1869-1940) was a Boston surgeon with a special interest in bones (Figure 1). By 1897, only a year after Roentgen had discovered x-rays, Codman was emphasizing the importance of this tool in the clinical management of patients with bone disease[13]. In 1909 he had described the triangle of reactive periosteal bone adjacent to bone tumors that bears his name[2]. Codman was also a founding member of the American College of Surgeons, formed in Chicago in 1913[12].

In 1920 Codman had a patient with what he thought was a bone sarcoma. The family of this patient gave Codman a $1,000 gift to find out if any patients survived a bone sarcoma and, if so, what treatment they had. The treatments available at that time were amputation, x-rays, radium, and Coley's toxin. Coley's toxin, used from the early 1890s until World War II, was a sterilized suspension of streptococci cultures which, when inoculated into patients, was believed to enhance their resistance to neoplasms.

Figure 1. Ernest Codman (1869-1940). Courtesy of the National Library of Medicine.

Codman began his $1,000 study by writing a letter to every member of the American College of Surgeons, then about 4,000. The letter began as follows:

> Dear Doctor: Have you any living cases of bone sarcoma? I include in this question, recent cases which are now under treatment and also any cases which you may consider as having recovered[3].

The response was a surprise. One hundred and seventy one members responded immediately and wrote descriptions of patients they believed to have bone sarcoma. In

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Figure 2. James Ewing (1866-1943). Courtesy of the National Library of Medicine.

Figure 3. Joseph Bloodgood (1867-1935). Courtesy of the National Library of Medicine.

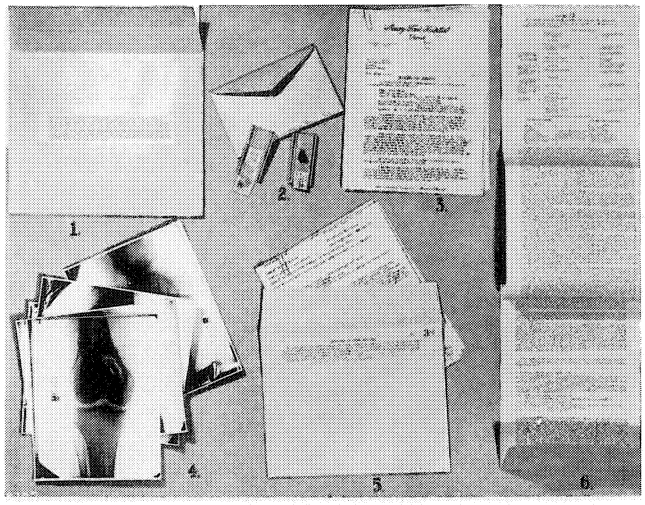

Figure 4. The various materials of one case. Reprinted with permission of Surgery, Gynecology & Obstetrics, now known as the Journal of the American College of Surgeons.

addition, 345 members also wrote to show their support of the study and suggested that such studies be made of other surgical diseases.

Because of this enthusiastic response, Codman was able to persuade the Regents of the American College of Surgeons to establish the Registry of Bone Sarcoma on June 7, 1921. Fifteen hundred dollars was appropriated by the College to continue the work[7]. Codman invited two other experts in bone diseases, James Ewing and Joseph Bloodgood, to work with him. James Ewing (1866-1943) was a pathologist in New York, at that time working at Cornell University (Figure 2). He had already published his book, *Neoplastic Diseases*[8], and he had just described the entity, diffuse endothelioma of bone, a malignant tumor which immediately (to his great protests) bore his name[9]. Joseph Bloodgood (1867-1935), a surgeon and director of surgical pathology at Johns Hopkins in Baltimore, also had an interest in bone tumors. (Figure 3). He had already published his observation based on his own cases and those he culled from the literature, that "giant cell sarcoma" behaved as a benign tumor[1]. Thus, the three physicians in charge of the Registry of Bone Sarcoma, were the country's most respected experts on bone tumors.

Codman continued to solicit cases of bone sarcoma from the members of the College. Only living patients could be registered. Surgeons sent the clinical history, details of the physical examination, radiographs, and histologic material (preferably wet tissue) to the Registry's headquarters at 227 Beacon St. in Boston[4]. The diagnosis and method of treatment was also submitted. The Registry sought yearly follow-up on each case and thus became the first national prospective study.

submitted. The collection was dormant during World War II, and in 1953 the entire collection, finally closed, was presented to the Armed Forces Institute of Pathology in Washington[15].

The patient whose family gave Ernest Codman $1,000 to start his project eventually died and was found to have metastatic carcinoma, not a bone sarcoma. But the gift has benefited bone tumor patients ever since.

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THE SURGICAL TREATMENT OF CONGENITAL SPINE DEFORMITY: GENERAL PRINCIPLES AND HELPFUL HINTS

Robert B. Winter, M.D.

INTRODUCTION

Since a high percentage (75%) of congenital spine deformities are progressive, and only a tiny percentage of these (+/-5%) are responsive to brace treatment, a very large percentage of congenital spine deformities require operative treatment. There is little disagreement with the above statement, but there is a large variability as to which operative procedure should be used, and at what age the surgery should be done.

CONGENITAL LORDOSIS

Congenital lordosis is always due to a posterior defect of segmentation involving several vertebral levels combined with active anterior growth plates[13]. If detected early before significant deformity occurs, the optimal treatment is an anterior fusion of all involved segments plus one segment above and below. There should be no fear of "stunting the child's spine growth" since the posterior bar cannot elongate, only cause deformity. Any loss of vertical spine growth is a fault of the pathologic process and not the fault of the surgeon.

Patients presenting with significant deformity (in whom correction is desired), require a combined anterior and posterior approach. In the anterior approach the surgeon removes the discs plus some bone on each side of the disc to create an anterior wedge osteotomy. This automatically removes the pathologic anterior growth plates.

Posteriorly, the laminar synostosis must be osteotomized at the same levels as the anterior osteotomies. Correction is achieved by pulling the apical segments back to a strong rod using Luque wires. In the thoracic spine, one should strive for 20° to 30° of kyphosis, and in the lumbar spine for 40° of lordosis[19].

Distractive instrumentation should be used carefully as these patients have a very high frequency of tethered spinal cords. Electronic spinal cord monitoring as well as the more optimal wake-up test should be utilized.

CONGENITAL KYPHOSIS

As with congenital lordosis, congenital kyphosis is completely refractory to brace treatment. The natural history results in a high frequency of paraplegia[12]. This is particularly true of formation-type defects. The primary goal of treatment is therefore prevention of paraplegia.

For formation-type defects, the best treatment is early detection and early posterior fusion. Early means before age five and kyphosis less than 50° (supine). Casting should be used post-operatively and the fusion mass augmented six months later. Early posterior fusion allows any existing anterior growth to continue, and slow but steady correction of the kyphosis occurs due to this "epiphysiodesis" effect[14].

Unfortunately, most formation-type congenital kyphoses do not present to the surgeon this early. For the more advanced deformities, both anterior and posterior fusions are mandatory with careful attention to a radical anterior release of contracted ligaments, anterior strut grafting and posterior shortening with compression-type instrumentation.

If the patient presents with a partial paraplegia, anterior spinal cord decompression must be added to the anterior fusion. Laminectomy is absolutely contraindicated.

For segmentation-type congenital kyphosis, a posterior fusion will stop progression of deformity but will not give correction. If correction is desired, anterior osteotomies of the congenital bar are done first, followed by posterior fusion with compression instrumentation[6].

CONGENITAL SCOLIOSIS

Congenital scoliosis is far more common than either congenital lordosis or congenital kyphosis. Since a large number of these are progressive and few are responsive to bracing, surgery is the mainstay of treatment. The problems revolve around which surgery and when[15].

There are four main types of surgery to be considered: (a) Posterior spine fusion (with or without instrumentation), (b) combined anterior and posterior spine fusion (with or without posterior instrumentation), (c) convex anterior and posterior hemi-arthrodesis and epiphysiodesis, and (d) hemivertebra excision and fusion.

Posterior Spine Fusion

This remains the "gold standard" of surgical treatment. On a world-wide basis, thousands of patients have been successfully treated in this manner. For a good result the spine is carefully exposed by a meticulous subperiosteal technique. It is always necessary to fuse the entire measured curve, and usually one vertebra above and one below. Metallic markers should be placed at both ends of

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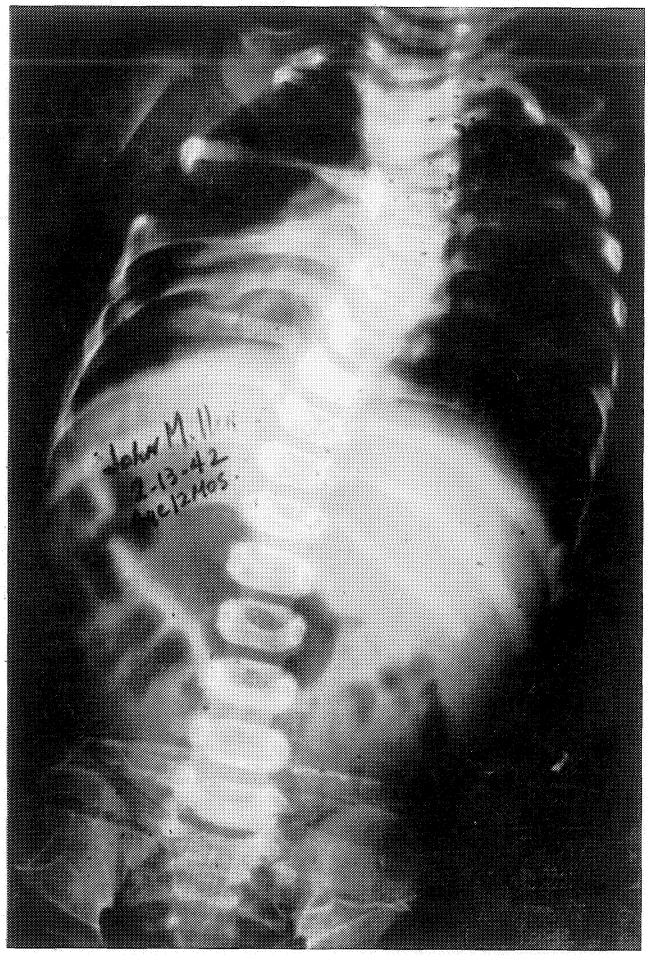

Figure 1-A This 12 month old male was seen elsewhere in 1942 with a 30° scoliosis due to a unilateral unsegmented bar on the left and healthy tissues on the right side. No treatment was given.

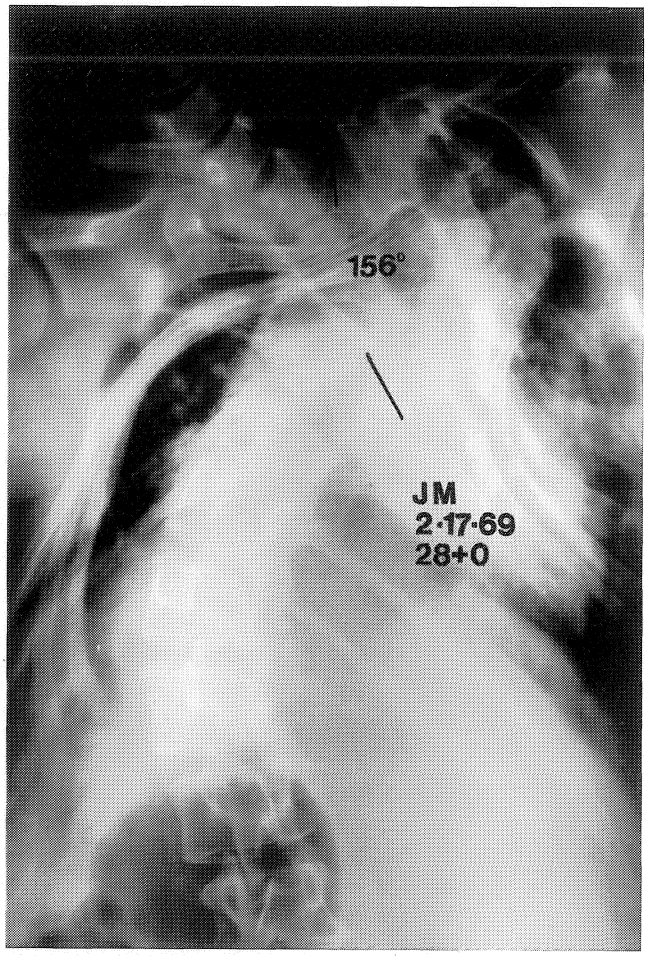

Figure 1-B When seen by Dr. John H. Moe in 1969 at the age of 28, he was in terminal cor pulmonale and died just a few days after this x-ray. The type of progression must be prevented by early fusion.

Figure 1(A-B). is reproduced with permission from *Congenital Deformities of the Spine* by R.B. Winter M.D., Thieme Stratton, NY 1983.

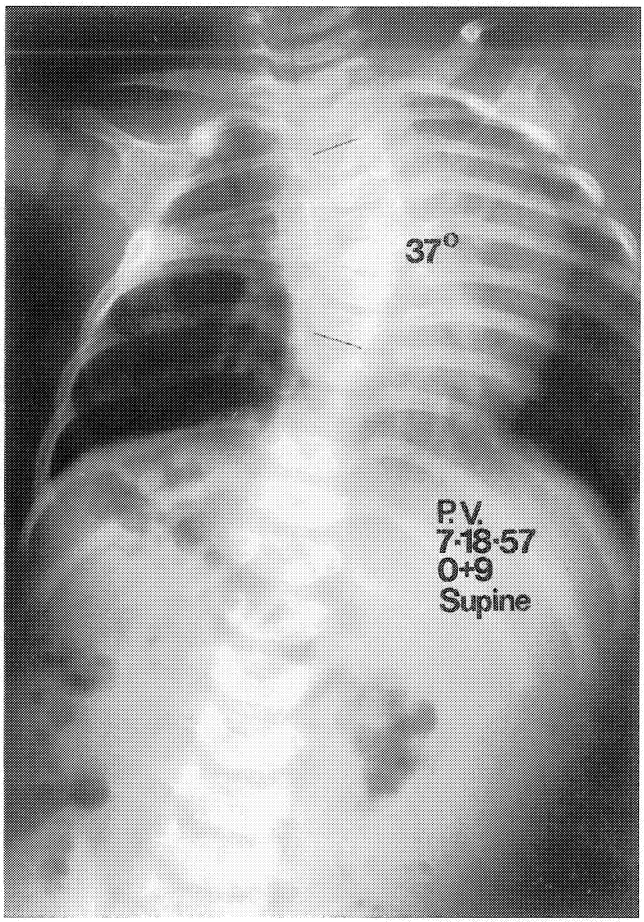

Figure 2-A This nine month old child was seen at Gillette Children's Hospital in 1957 with a virtually identical 37° scoliosis due to a unilateral unsegmented bar. He had a posterior spine fusion C_7-T_9 at age 12 months by Dr. Moe.

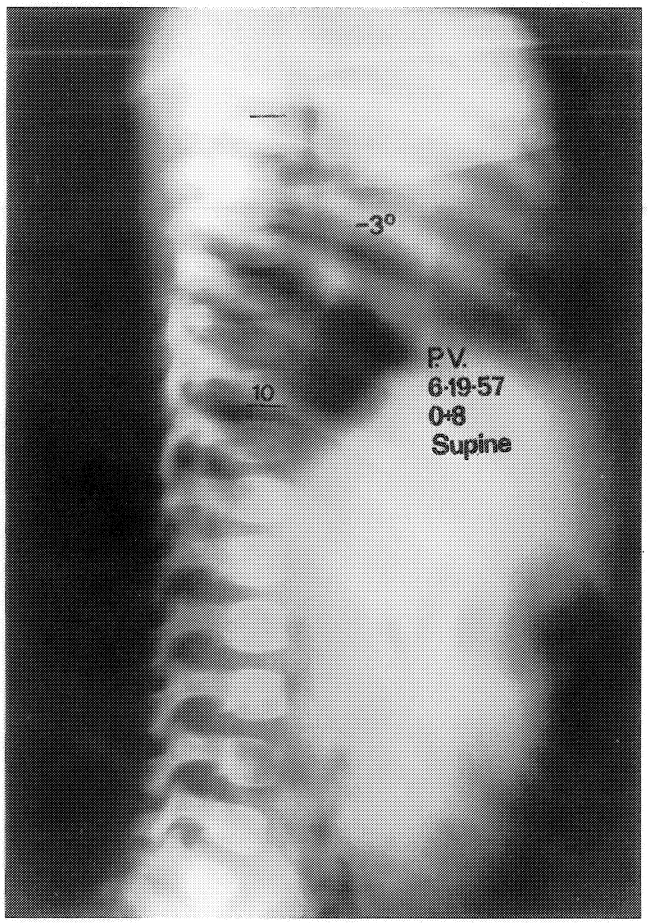

Figure 2-B A lateral view at the same time showed a very flat thoracic spine. Will posterior fusion only lead to progressive lordosis?

Figure 2(A-D) is reproduced with permission from *Congenital Deformities of the Spine* by R.B. Winter, M.D., Thieme Stratton, NY 1983.

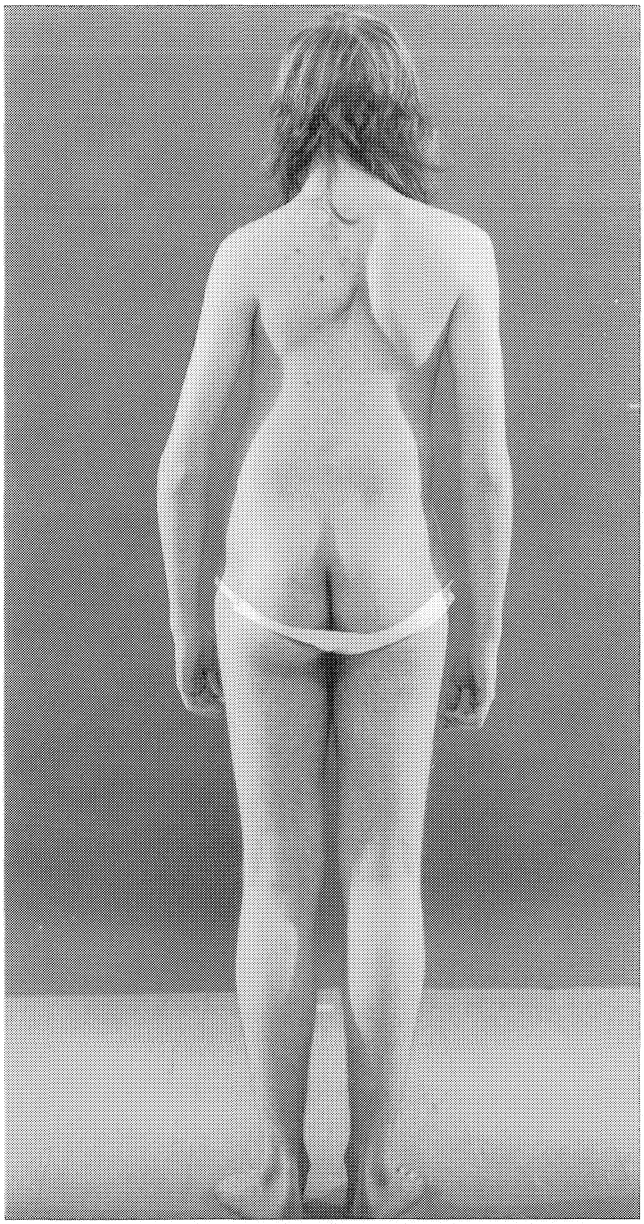

Figure 2-C A posterior photograph at age 20, 19 years after his fusion. Although his torso-leg proportions are not normal, they are only minimally disturbed.

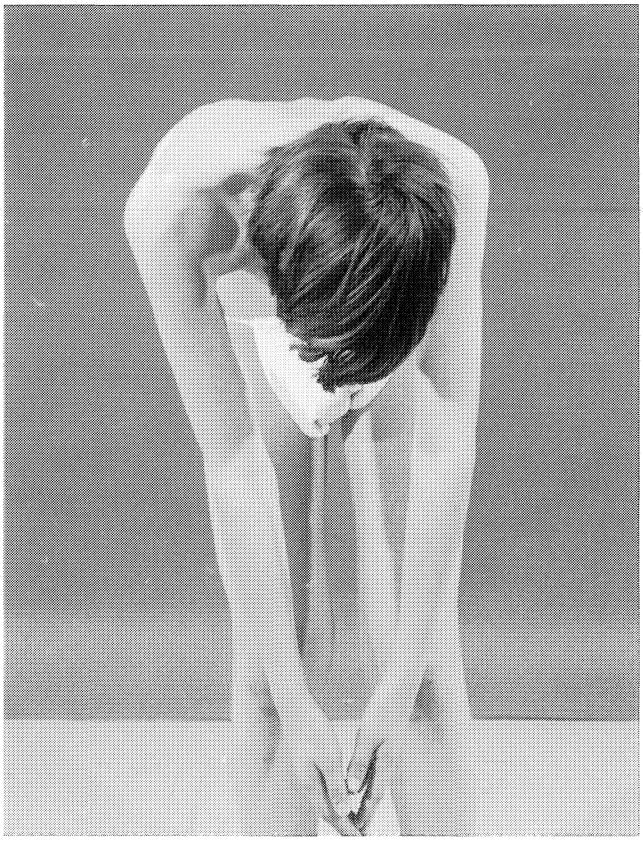

Figure 2-D A forward bending photograph at age 20 shows no rotational prominence.

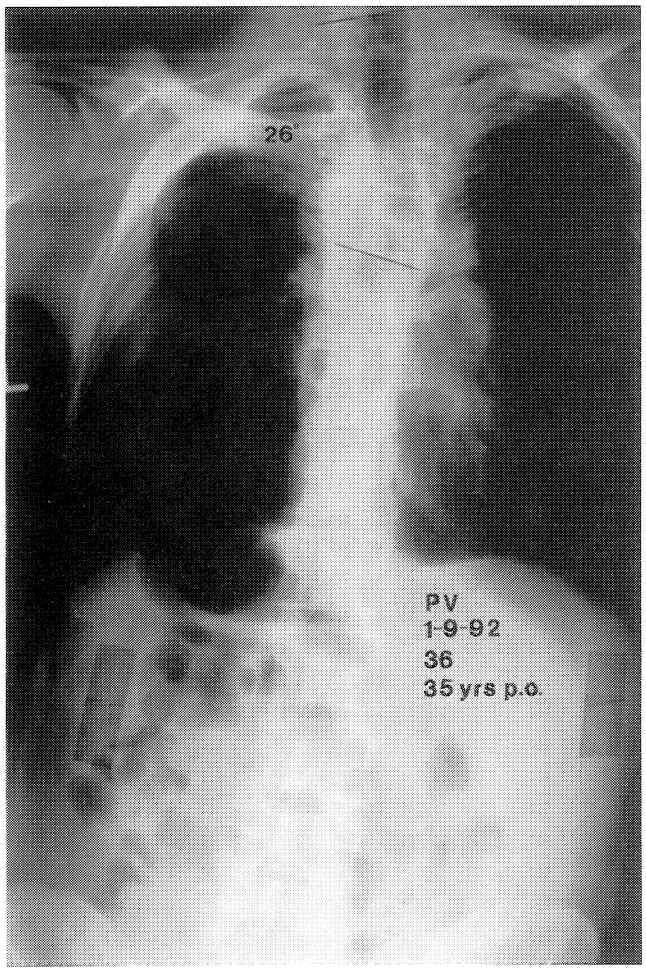

Figure 2-E A long-term follow-up at age 36 shows the scoliosis to measure 26° (correction was achieved by a postoperative cast).

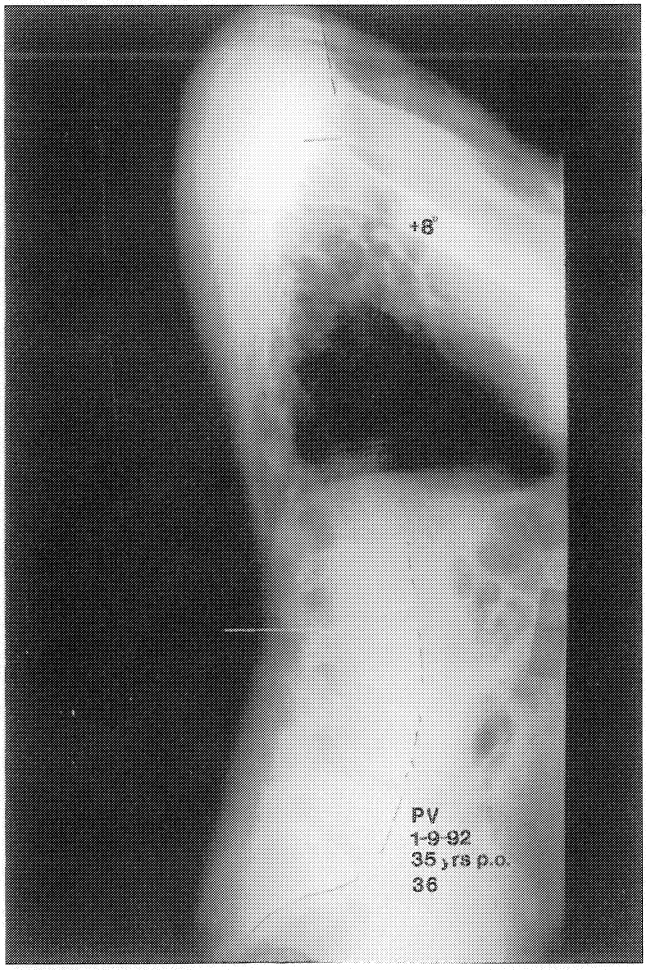

Figure 2-F A lateral view at age 36 shows a persistently flat thoracic spine, but slightly improved from preoperatively. This long-term follow-up was obtained because he came in with a herniated disc, not because of any problem with his scoliosis or old fusion.

the planned fusion area and a radiograph taken in the operating room to be sure the proper levels have been exposed. For idiopathic scoliosis only one marker is needed as the vertebrae are easy to count, but for congenital scoliosis counting can be quite difficult so two markers are best.

After exposure, any existing facet joints should be excised, the entire exposed area deeply decorticated with a gouge, and liberal bone graft added from the iliac crest. Allograft can be used, but parental or sibling bone should also be considered.

If no instrumentation is used, correction is achieved postoperatively with a cast or brace. Instrumentation can be used during surgery, but it must be remembered that patients with congenital spine deformity have a high prevalence of dysraphic lesions (49%) and the highest frequency of operative paraplegia of all etiologies of curvature. Despite the "modern" trend to use instrumentation in virtually all scoliosis operations, the surgeon should think twice about using it due to the risks involved.

For young children in which no instrumentation is used, the post-operative brace or cast program can be either on bedrest or ambulatory. If a curve is very stiff, the cast or brace isn't going to produce much correction, so ambualtory care is appropriate (why keep a child in bed for four months for 5° of correction?). If, however, the curve is flexible, there is risk that major correction can be achieved in the horizontal position but lost if ambulatory. In such cases four months at bedrest is not an unreasonable price to pay for a life-long benefit of good correction. (Figure 1, [J.M.] (Figure 2, [P.V.])

What about the so-called "crankshaft" phenomenon? Won't there inevitably be a bending of the spine into increasing lordosis and rotation due to the early posterior fusion and continued anterior growth? This is true for young idiopathics (infantile and juvenile), but *not* for congenitals since the anterior growth can be so deficient in the congenital patient. In the only three publications when late bending was analyzed[5,10,16], only 15-20% of patients showed late bending.

Who is going to show late bending (the crankshaft effect)? It is those patients with healthy anterior growth plates. These can be seen on ordinary radiographs or, if needed, tomograms or MRI scans. Another trick is to see whether the patient is showing rotation as part of the natural history. If they are, they will continue to rotate after the posterior fusion. (Figure 3, [D.Z.])

Combined Anterior and Posterior Fusion

The use of this combined procedure has several advantages: (a) elmination of the crankshaft effect, (b) a higher percent correction due to the multiple disc excisions, and (c) a lower rate of pseudarthrosis. To these must be added the relative risk of the anterior approach. At the present time we operate on all of our combined fusions under the same anesthetic so there is no risk related to extra anesthetics. We have experienced very few complications related to the anterior approach except when performing thoracotomies in patients who have major compromise of their pulmonary function (FVC under 40% of normal)[8].

In doing the anterior approach, we perfer to use the talents of skilled pediatric surgeons. The spine is approached via a pure thoracotomy, thoracolumbotomy or pure lumbotomy depending on the area to be fused. The segmental vessels are systematically ligated or cauterized (we have never seen a paraplegia due to vessel ligation), the vertebra and disc exposed subperiosteally, the disc and cartilage endplates removed, and the fusion performed. Depending on the area and pathology, either rib strut grafting or disc space chip grafting is done.

Once the anterior incisions are closed, the patient is turned prone onto the scoliosis frame and is reprepped and redraped. The posterior procedure is then performed as described above, either with or without instrumentation. (Figure 4, [J.B.])

Hemi-Epiphysiodesis (Convex Growth Arrest)

This is not a new concept, the first case being reported by MacLennon in 1922[7]. Recent reports are available from various centers in Minneapolis and St. Paul[18], Paris[2], and Birmingham, England[1].

The concept is simple. Why fuse and destroy the growth potential still existing in the concavity of a curve? Would it not make more sense to fuse only the growth centers on the *convexity* of the curve, the ones that are producing the patient's problem? The concept is perfectly valid *provided there is concave growth tissue*. Thus the indications for this procedure are (a) too much convex growth, (b) some concave growth, and (c) no kyphosis (if present it will be aggravated by the anterior part of the fusion).

The technique is simple, the spine being exposed anteriorly as described above, but only the convex one-half of the disc and endplate is excised and fused. Posteriorly only the convex side is exposed (subperiosteal stripping of the concavity will result in a spontaneous fusion) and bone grafted. A corrective cast is applied at the end of the procedure. Casting is maintained for six months with changes as needed. Usually nothing is required after that.

Careful follow-up to the end of growth is critical. We have seen several cases in which an excellent result was seen for five to seven years and then lost at the time of the pubertal growth spurt. The parents must always be warned of this as they may grow weary of "routine" check ups and disappear from the clinic at just the wrong time.

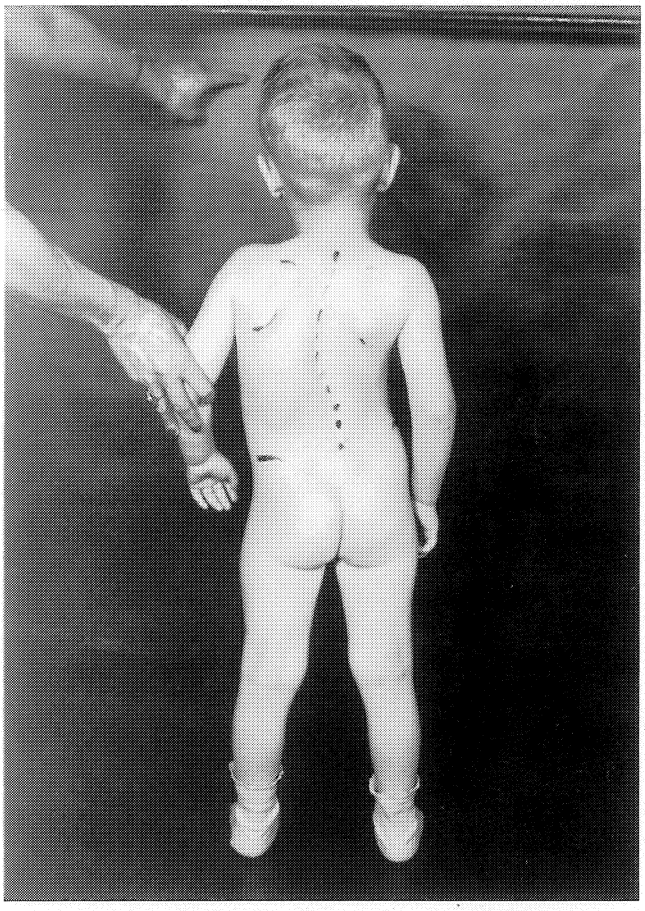

Figure 3-A This three year old boy was seen at Gillette in 1950. There were no health problems other than the curvature which had been noted to be quite progressive.

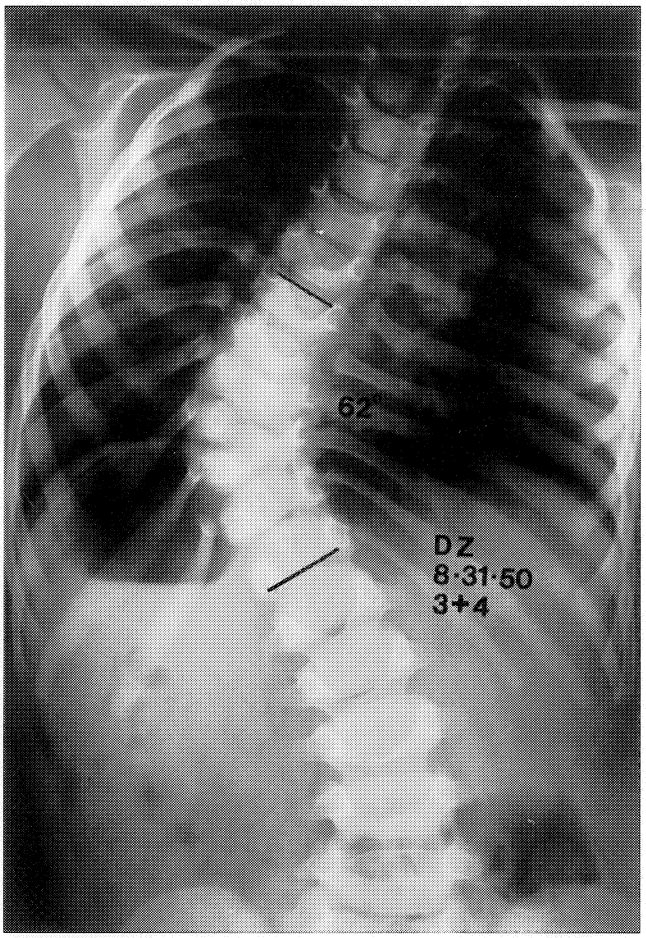

Figure 3-B He had a 62° scoliosis due to a hemivertebra at T9 on the left. He was treated with serial casts for two years and then had a posterior spine fusion from T5 to T12 with Risser cast correction, six months of bedrest and one year of casting.

Figure 3(A-F) is reproduced with permission from *Congenital Deformities of the Spine* by R.B. Winter M.D., Thieme Stratton, NY 1983.

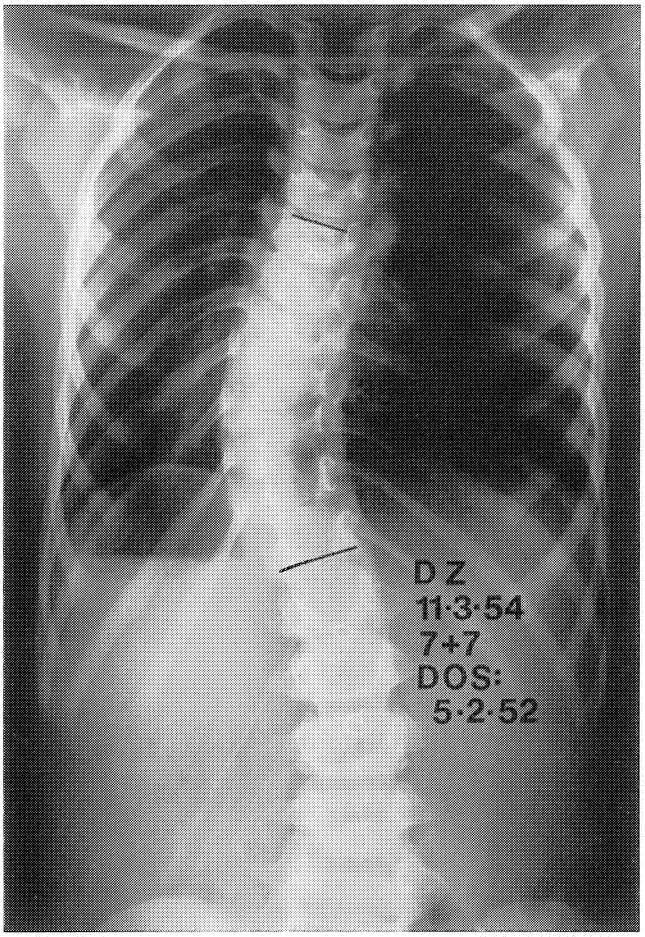

Figure 3-C This x-ray was done in 1954 at the age of seven years, two years after the surgery. The fusion is solid at 35° and his balance is excellent (a good example of why most hemivertebrae do not need excision).

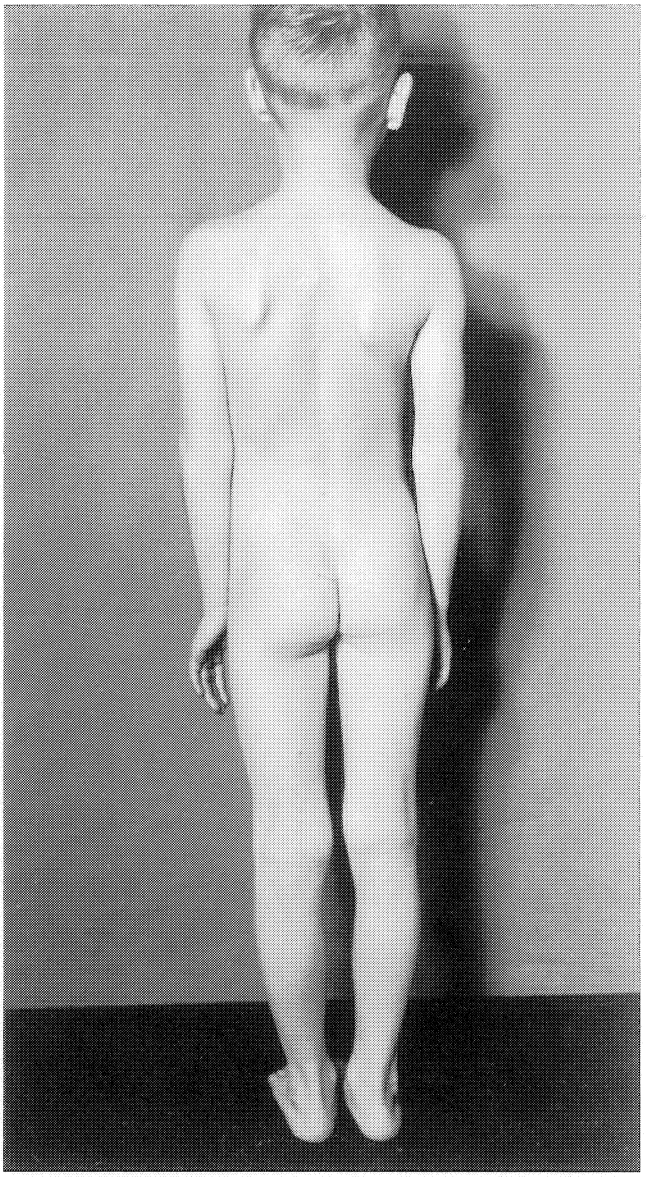

Figure 3-D A photograph at the same time showing the excellent status two years after the surgery.

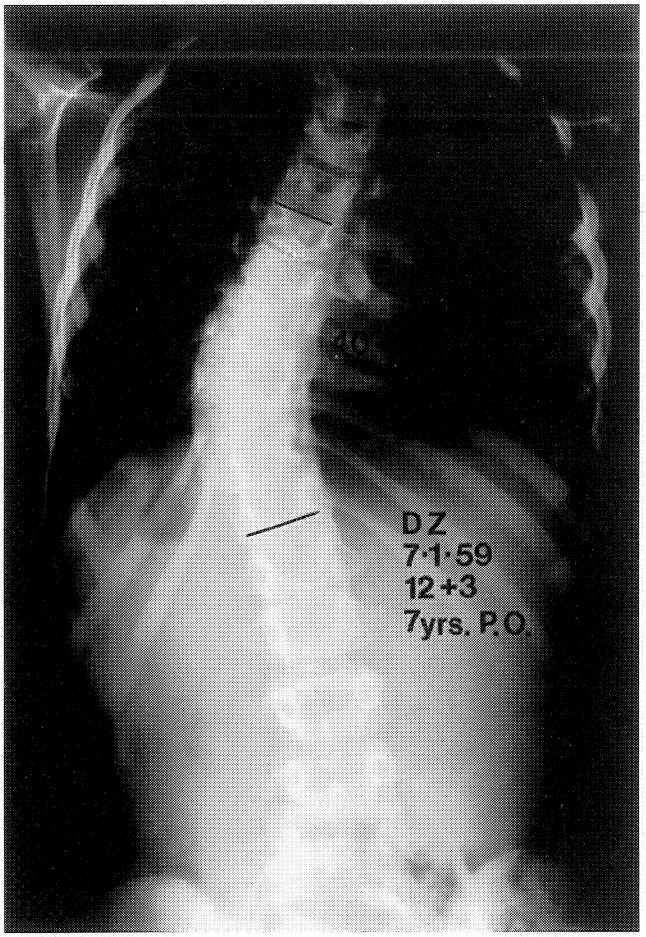

Figure 3-E The x-ray at age 12, seven years after the fusion, shows deterioration. Although the curve measures 40°, only 5° worse, the vertebrae above and below the ends of the fusion are now in the main curve whereas previously they were in compensatory curves. This is part of the "crankshaft" effect.

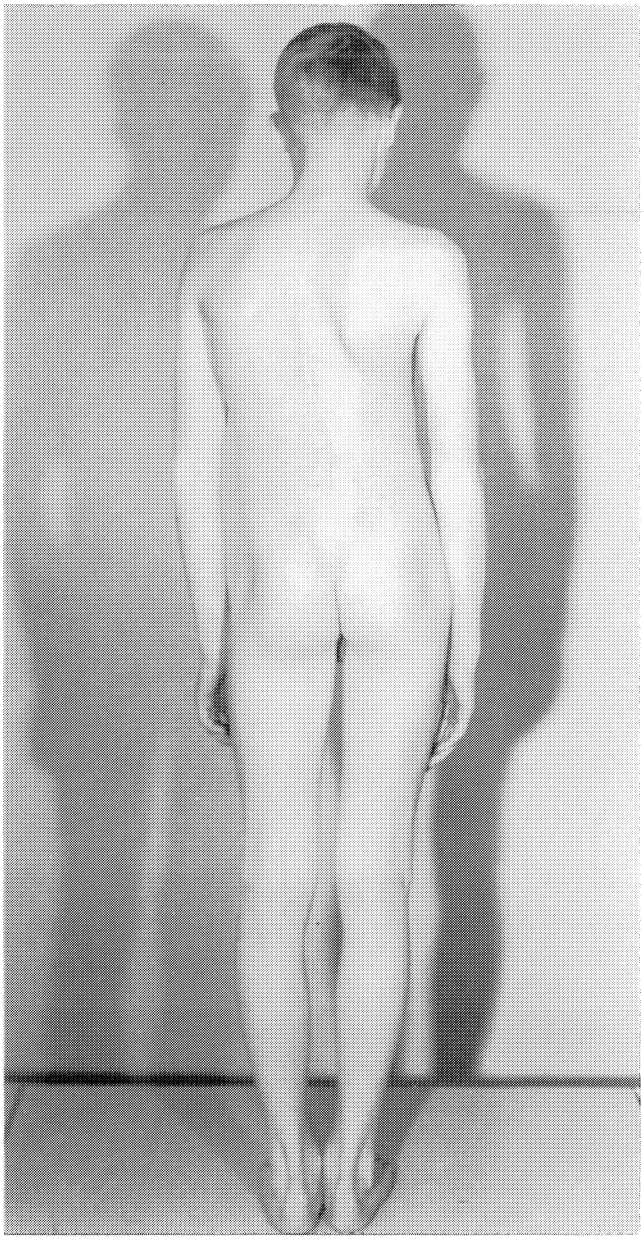

Figure 3-F The clinical photograph shows the loss of good compensation due to the rotatory phenomenon. This is a classic example of the "crankshaft phenomenon". If operated on in 1995, we would do both an anterior and posterior fusion at age three, thus preventing such problems.

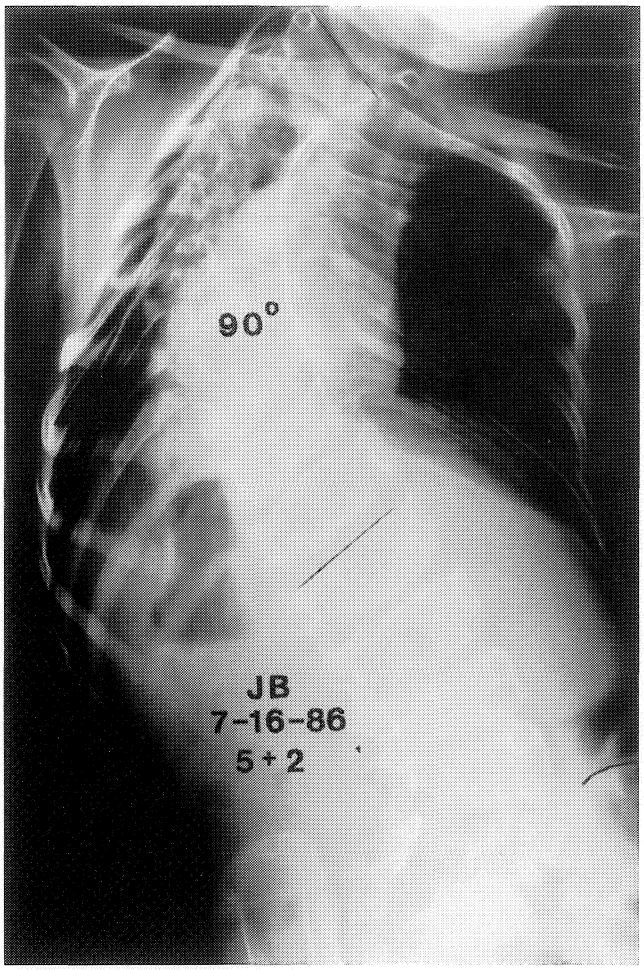

Figure 4-A This five year old girl was seen elsewhere with a 90° scoliosis, a wide interpedicular distance in the lumbar spine and a lumbar scar from a repaired meningocoele at birth.

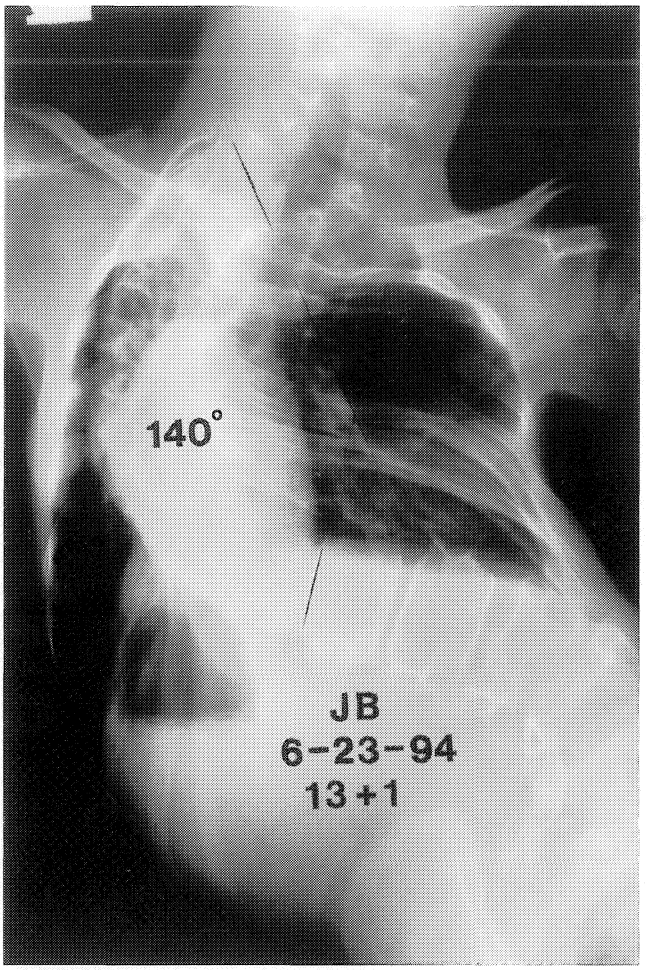

Figure 4-B When seen by the author at age 13, the curve had increased to 140° and her vital capacity had declined to only 23% of normal.

Figure 4(A-J) is reproduced with permission from *Congenital Deformities of the Spine* by R.B. Winter M.D., Thieme Stratton, NY 1983.

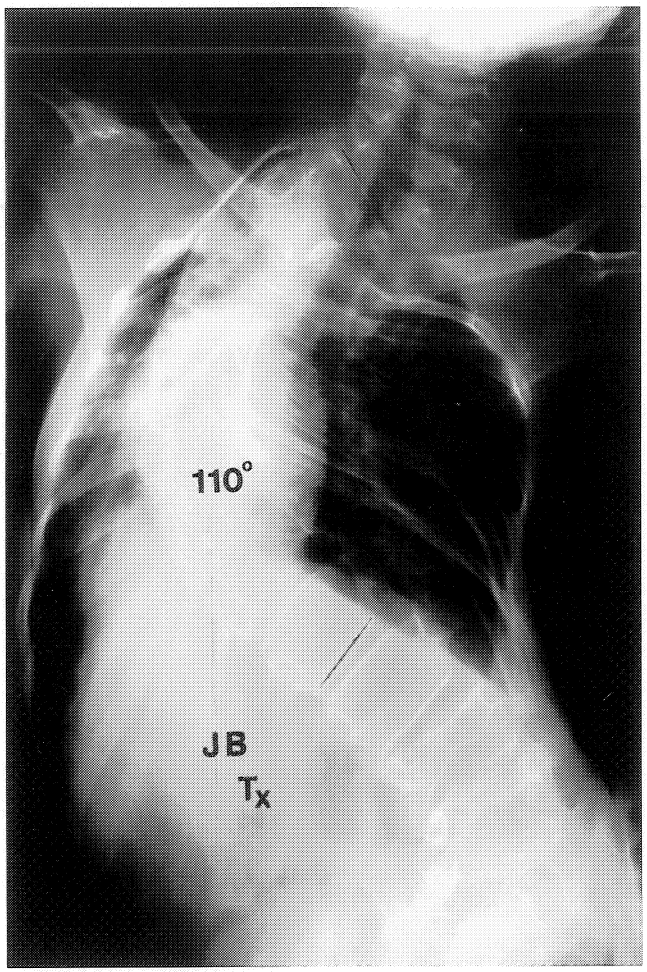

Figure 4-C A supine maximal traction film showed the curve to be correctable only to 110°.

Figure 4-D An MRI showed a Chiari Malformation (the cerebellar tonsils are below the foramen magnum).

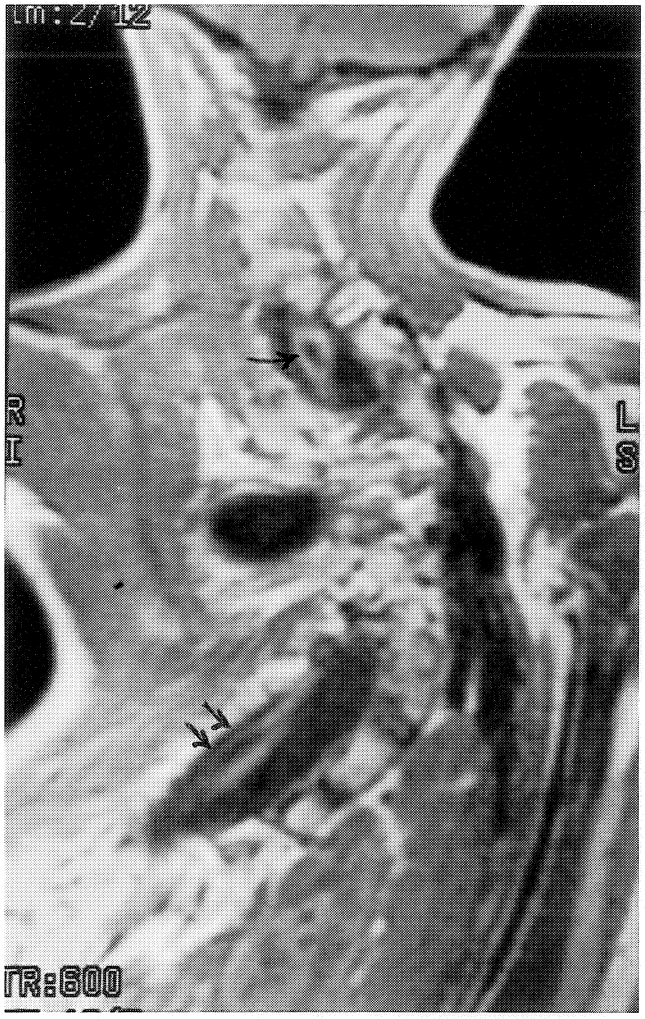

Figure 4-E The MRI also revealed a syrinx of the spinal cord at the cervico-thoracic junction as well as a diastematomyelia at the thoracolumbar junction.

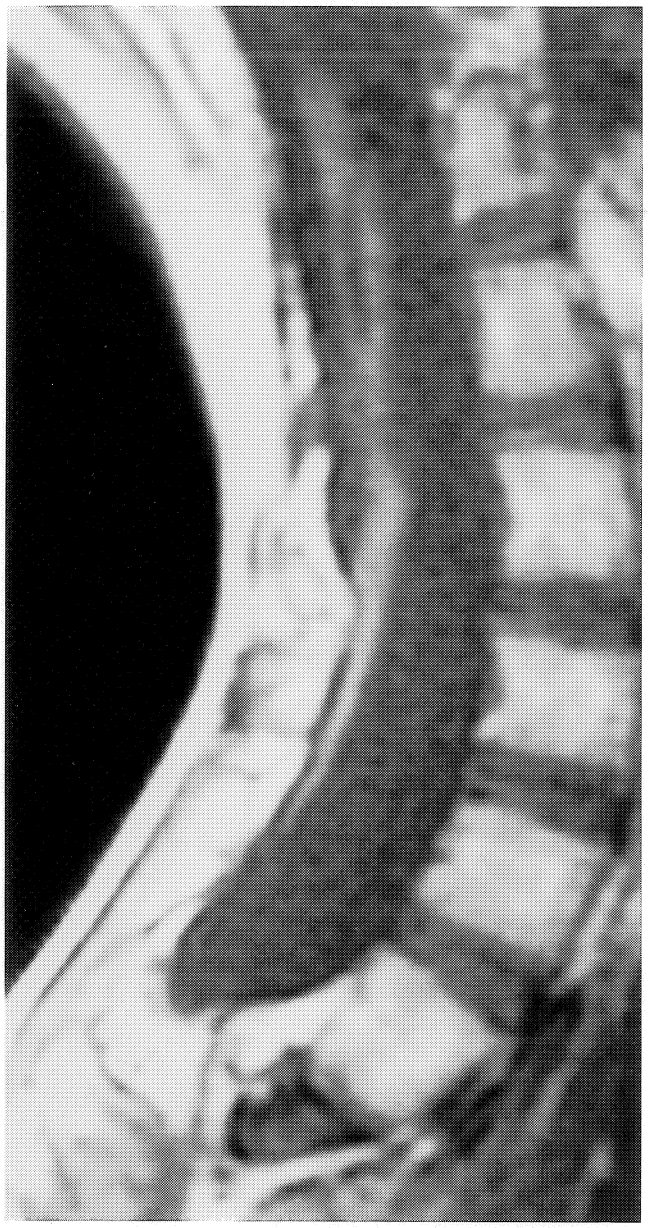

Figure 4-F This sagittal cut of the MRI shows the diastematomyelia as well as a tight filum terminale distally.

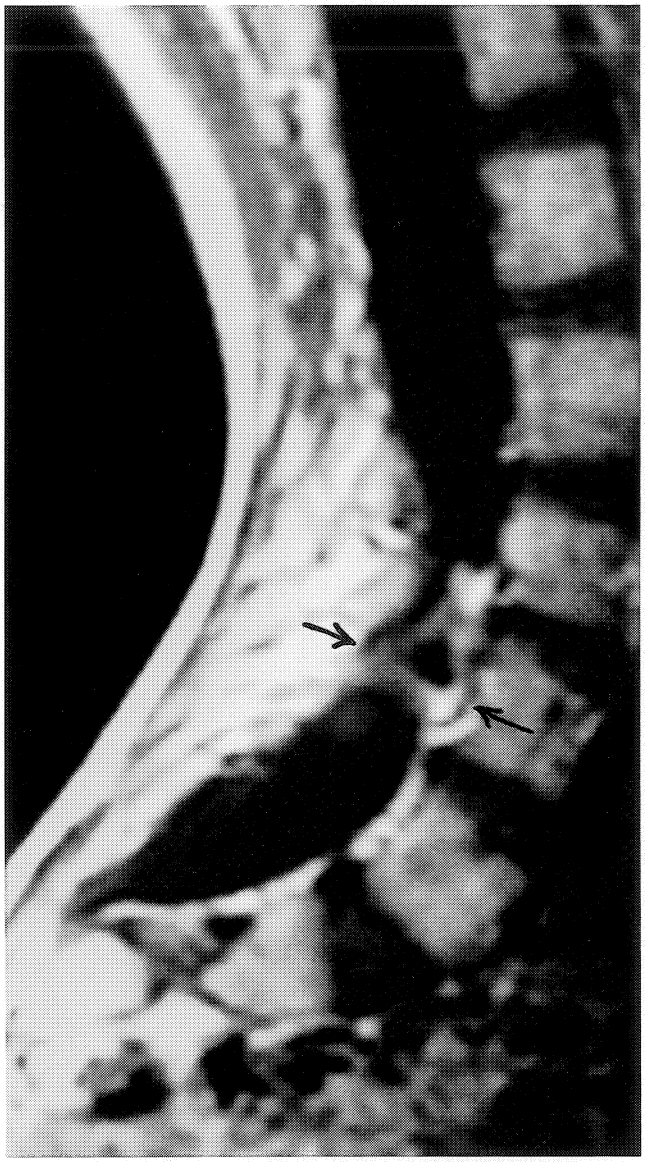

Figure 4-G The sagittal cut of the MRI shows the midline spur of the diastematomyelia.

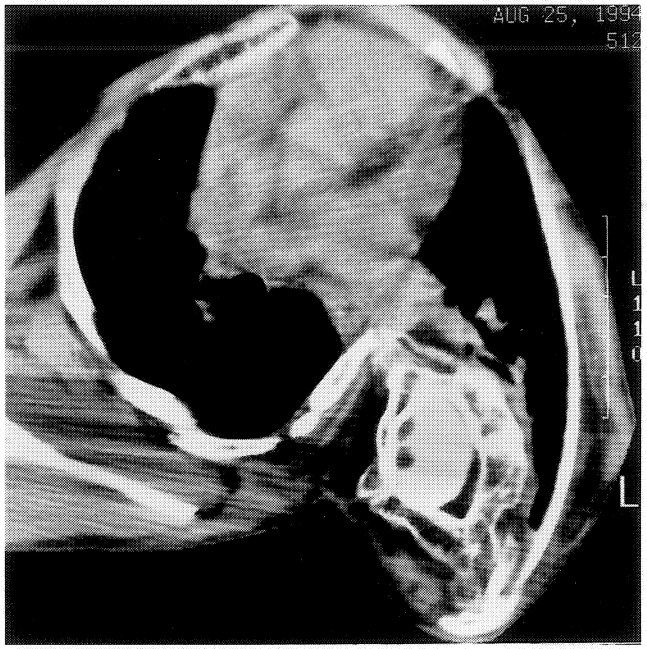

Figure 4-H This axial cut of a CT myelogram shows the severe rotation of the spine with the vertebral laminae 90° from normal. The diastematomyelia is readily seen. Note the uselessness of rib resection for a severe rotational problem like this.

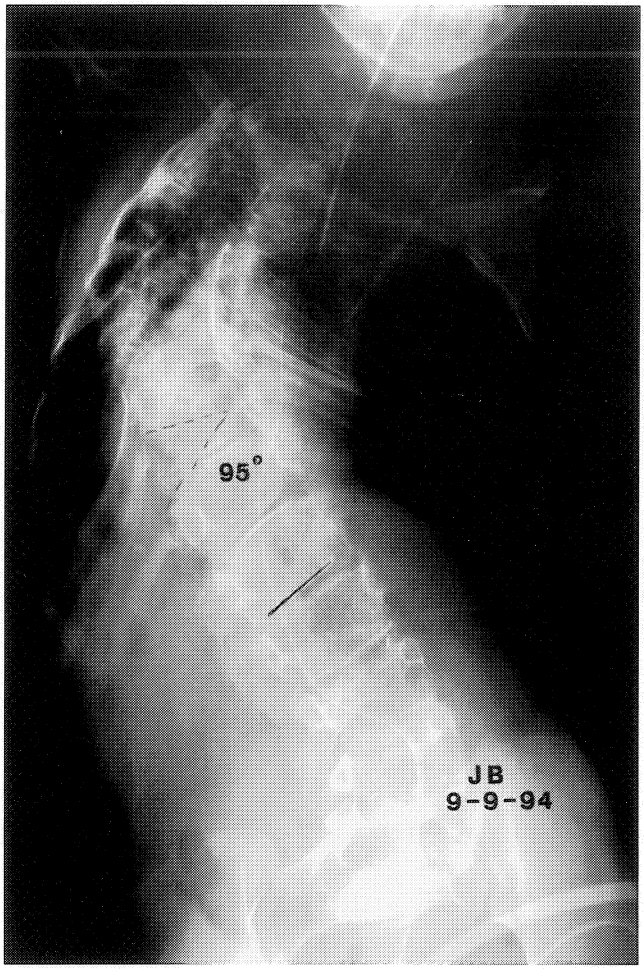

Figure 4-I Treatment consisted of 1) removal of the spur and release of the tight filum, 2) anterior fusion T6-L4 with a wedge resection at T12 (see dotted lines), 3) halo application, 4) two weeks of halo-gravity traction, 5) posterior spine fusion C7-L4 with apical wedge resection T12, and 6) application of a halo-Milwaukee brace.

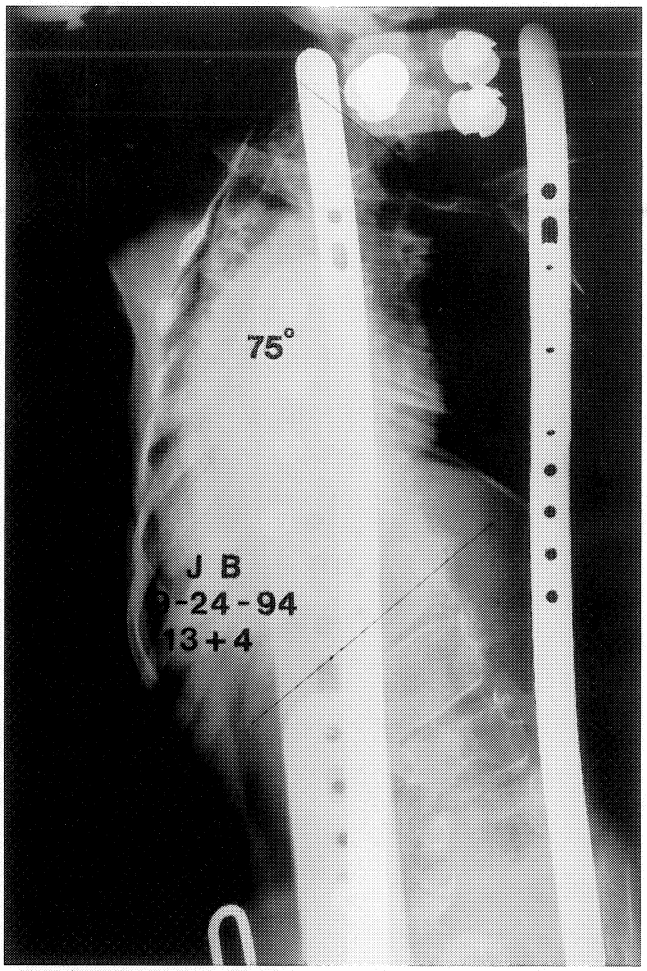

Figure 4-J At the time of discharge from the hospital, with additional correction using the halo-Milwaukee brace, the curve is 75°, no neurologic complications had occurred, and her vital capacity was already better than pre-operatively despite the anterior approach. This correction has been fully maintained.

Hemivertebra Excision

This is not a new procedure, being first done by Royle in Australia in 1921[9]. The early pioneers had many problems and complications so that it was not until 1960 that Leatherman began to revive the procedure. His success was directly related to the ability to perform high quality anterior spine surgery and the availability of Harrington rods with which to correct and stabilize posteriorly. His concept that it was often better and safer to shorten the convexity than to lengthen the concavity was a major advancement.

The indication is a short, rigid curvature, the apex being the hemivertebra. It must be a situation in which the less complex methods described above will not achieve an adequate alignment.

The anterior approach can be either a pure thoracotomy, thoracolumbotomy, or lumbotomy depending on the level to be resected and fused. Anteriorly, the hemivertebra is identified, the discs above and below removed, and the majority of the hemibody excised quickly. Once the posterior cortex is the only part remaining, the spinal canal is entered in the center of the hemibody cortex and the hole enlarged in all directions using a rongeur and/or curettes. Finally the foramena above and below the pedicle are opened, leaving only the pedicle itself. The anterior one-half of the pedicle should be removed via the anterior approach using Kerrison rongeurs and fine end-biting Lempert rongeurs. The major problem in the anterior part of the surgery is bleeding from the epidural veins. This must be managed with thrombin-soaked gelfoam, cottonoids, and bipolar cautery. The anterior surgery may also involve disc excision above or below (or both) the hemivertebra excision area. Whether or not this is done depends on the length of the curve, since the whole length of a curve should always be fused.

Posteriorly, the curve is exposed, the correct level identified (usually by x-ray) and the posterior half of the hemivertebra excised. This is done by removal of the ligamentum flavum above and below the hemi-lamina, the hemilamina itself, the transverse process, and the posterior half of the pedicle. This is easy if the anterior portion of the pedicle is adequately excised[15].

If the bones are large enough, some type of instrumentation can be used to close down the wedge created by the hemivertebra excision. This can be a compression system using a hook on the lamina above and another on the lamina below. When closing the gap, the two exiting nerve roots should not be compressed.

The goal of surgery is not a total closure of the gap, but rather the achievement of balanced alignment. There is often a secondary (compensatory) curve above the hemivertebra curve which must be analyzed carefully. If it has a structural component, total correction of the primary curve is ill-advised. As shown by Holte et al[4] in their review of 37 patients with hemivertebra excision, spontaneous improvement of the secondary curve was almost always seen on long-term follow-up.

As noted previously, these patients must be followed on a regular basis until the end of growth as problems can develop later, especially at the time of the pubertal growth spurt.

CONCLUSIONS

Much of the mystery associated with congenital spine deformities has disappeared over the past 25 years. This was due first to studies of the natural history so that we knew which patients would get into trouble and which ones would not. Secondly, we were able to analyze the results of treatment by the pioneers such as Risser and Moe, so that we knew when braces and posterior fusion alone would or would not work. Finally, another generation of spine surgeons such as Hodgson, Leatherman, Harrington, and Stagnara advanced our techniques via anterior approach, hemivertebra excision, instrumentation, and spinal cord monitoring.

Along with these milestones of manangement we must not forget what we have learned about the total evaluation of the patient. Thanks to the MRI we can now readily evaluate the entire neural axis for the many lesions which may be lurking there. We know to evaluate the genitourinary system, heart, limbs, auditory system, and the family history.

The essence of management of congenital spine deformity is to detect it early, analyze it thoroughly, and to never allow it to progress to a severe deformity. Severe deformities must be *prevented*, not corrected[3].

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CHIROPRACTIC MANIPULATION: AN HISTORICAL PERSPECTIVE

James C. Krieg, M.D.

Some of the earliest indications of body manipulation were noted in the Kong Fou Document, written around 2700 B.C., brought to the Western world by French missionaries. Greek papyrus dating back to 1500 B.C. gave instructions in using maneuvers of the lower extremities to affect low back pain.

Evidence of manipulation being used for various conditions has been seen in the writings of the ancient Japanese, Indians of Asia, Egyptians, Babylonians, Syrians, Hindus, and Tibetans. It has been practiced in Tahiti for centuries. (Fig.1)

The history of spinal manipulation in America predates the arrival of Europeans. Hieroglyphics of ancient North Americans depict "back walking," the manipulation of the spines of sick individuals with the feet of others. The Polynesian Island natives had children walk on the backs of the infirmed. This practice was witnessed by explorers of the 1500's.

While the origins of "bone setting" are unknown, the practice has existed in many societies, including early America. The practitioners of bone setting had no formal training. Often their art was a mixture of religion and superstition, rather than any scientifically based practice.

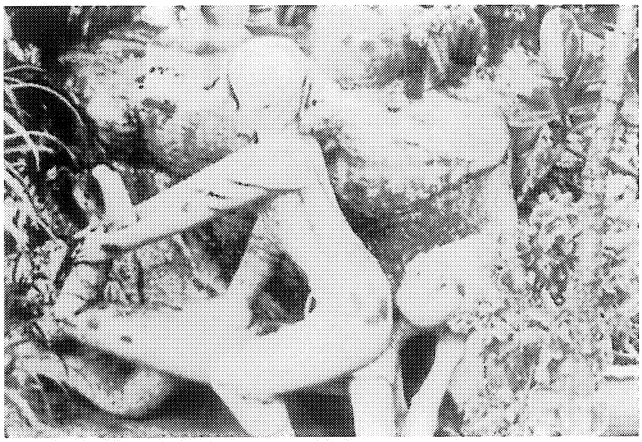

Figure 1.
Statue located in Bangkok, ca. 1275-1300 A.D. The figures depict a right SI joint manipulation

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In fact, some spoke of dislocations where none were possible, or of small bones that became out of place, where none existed.

This led to a general mistrust of the manipulations by the practitioners of conventional medicine. Despite this, the methods crept into the practices of many medical practitioners.

The first formal training in manipulation came with the birth of Osteopathic Medicine in 1874. It was Andrew Still, the founder of Osteopathy, who first espoused the science of joint manipulation. At the time, Still was a respected medical practitioner, and this led some credibility to what had previously been, in the eyes of many, sheer quackery.

Although they manipulated all joints, the pioneers of osteopathic methods felt that the spine was the foundation of their craft. The "spinal lesion" was the source of all disease. The lesion is described most often as the "immobilization of a joint in a position of normal movement," i.e. a locked joint. The locked joint can interfere with the extra-articular circulation, rendering the individual susceptible to every variety of illness. They referred to this as "lowered vitality."

When discussing the development of spinal manipulation and the birth of chiropractic, it is only fair to do so in the milieu of conventional medicine at the turn of the century. Some milestones to recall are the first description of Pasteur's germ theory in the 1860's. At that time, Lister's concept of antiseptic surgery was not yet fully accepted. The 1880's saw the discovery of the tuberculus bacilli. X-rays were first introduced in the United States in the 1890's. Medical Schools did not have formal requirements regarding premedical training until 1919.

Chiropractic was invented by Daniel David Palmer. (Fig. 2) Mr. Palmer was born in 1845 in Port Perry, a little Canadian town near Toronto. He moved to the U.S. at a young age. He held several jobs, including grocer and teacher in Letts, Iowa. To gain extra money, he studied phrenology, the science of the brain. While lecturing on the subject he met Paul Caster, an internationally known magnetic healer. Caster explained his science to Palmer as such, "I devised a method where, by rubbing and slapping the entire body of a sick patient, I imparted my magnetism. It cured the sick."

Palmer was so impressed that he became a student of Caster and quickly set up a practice in Burlington, Iowa as a magnetic healer. His practice did poorly, as Burlington already had a magnetic healer, his mentor, Paul Caster. So Mr. Palmer packed his bags and moved his practice up the Mississippi River to Davenport. His practice improved,

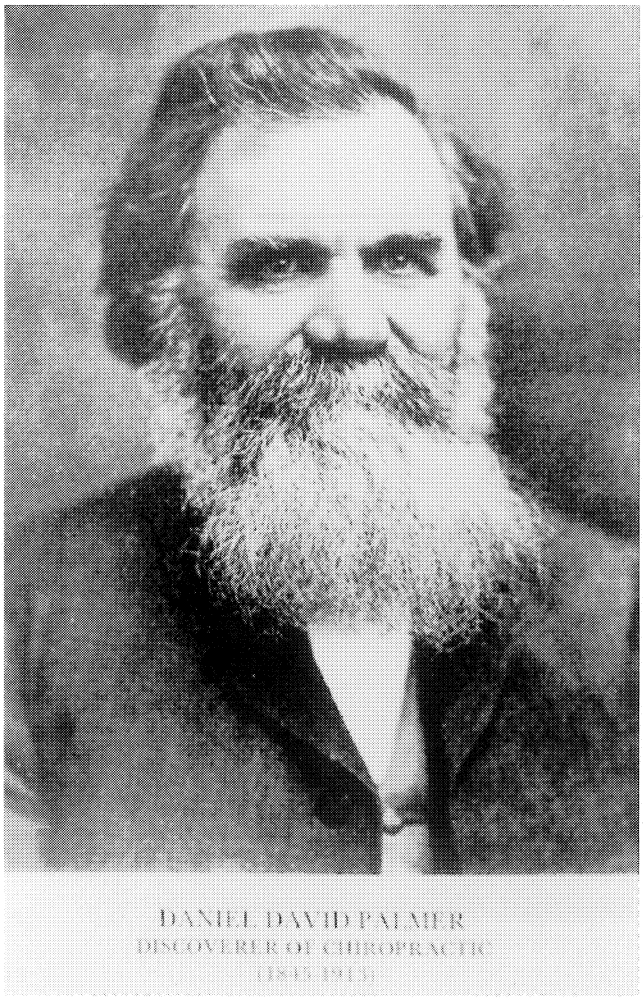

Figure 2.
Daniel David Palmer, father of chiropractic

but he still required supplemental income to raise his family. He began to raise goldfish for cash. In fact, Mr. Palmer developed a new method of shipping the fish in low volume, high surface area containers that to this day are the industry standard in shipping live fish.

What has been heralded as the "Great Discovery" occurred in 1895. Mr. Palmer was working late one night and struck up a conversation with Harvey Lillard, his deaf janitor. Inquiring as to the cause of Lillard's deafness, Mr. Palmer learned that seventeen years prior, Lillard sustained an injury to his neck. He stooped over, and heard and felt a snap in his neck. At that moment he went suddenly deaf. In addition, from that time on, he noticed a lump on the back of his neck. Mr. Palmer, felt that the bump on the neck and the deafness were somehow related. For three days he gave the bump thrusts. On the third day, Lillard jumped up, yelling, "Doc! Doc! I hear!" Thus was born the Science of Chiropractic.

Figure 3.
The Palmer home and site of the original Palmer Infirmary and Chiropractic School.

Mr. Palmer soon expanded this success and applied his method to all manner of ills. He began looking for bumps to push on in people with a variety of conditions. His practice grew, and along with it his income.

Soon after his great discovery, Mr. Palmer dubbed his method "Chiropractic." It comes from the Greek words cheiro and practikos, roughly translated to "done by hand." The name was meant to serve as a distinction between his method and that of conventional medicine, with its pills and early concepts of surgery.

Three years after discovering chiropractic, Mr. Palmer founded the Palmer Infirmary and Chiropractic School. (Fig. 3) As the first training institution for the chiropractic method, it was started at the urging of Mr. Palmer's son, Bartlett Joshua. (Fig. 4)

Bart was only 17 when his father started the Palmer School. He was one of four students in the first graduating class. Upon graduation he changed his name to B.J. Palmer. He traveled to several towns in Michigan and West Virginia, having various troubles forming practices.

In 1903, B.J. returned to Davenport at his father's request. Mr. Palmer's practice was horribly in debt and the school was failing. B.J. bought out the practice and the school. In 1905, B.J. incorporated the Palmer School of Chiropractic under the laws of Iowa as an educational institution. Meanwhile, Mr. Palmer left town broke and despondent. He went back to Letts, Iowa, where he soon fell in love and married. His wife, Molly, convinced him to return to Davenport.

B.J. and his dad always had a competitive relationship. This intensified upon Mr. Palmer's return to Davenport when he saw that both B.J.'s practice and the school were flourishing. He was infuriated. He attempted to regain control of both, and B.J. let him regain control over the school. However, his father remained bitter and his

Figure 4.
Bartlett Joshua Palmer, D.C., Ph.C.

previously poor business practices grew even worse. The school once again was led toward financial ruin.

Matters came to a head in 1906. B.J. and his father were charged with practicing medicine without a license. Mr. Palmer was indicted first, for reasons that remain unclear. In fact, B.J. never stood trial. His father, on the other hand, was tried and convicted in Scott County v. D.D. Palmer. He was fined five hundred dollars. At sentencing, Mr. Palmer angrily addressed the court. He condemned them for convicting him of a charge he did not believe. He was subsequently incarcerated in the Scott County jail. After 17 days, against his father's wishes, B.J. paid the fine and had him released. This served to widen the rift between father and son. B.J. bought out his father's share of the business once again, and they parted ways for the last time.

With his father out of the picture, B.J. set about in earnest to advance his practice, the Palmer School and the field of chiropractic. He advanced his techniques in a series of books on the subject. (Fig. 5) He wrote that his father

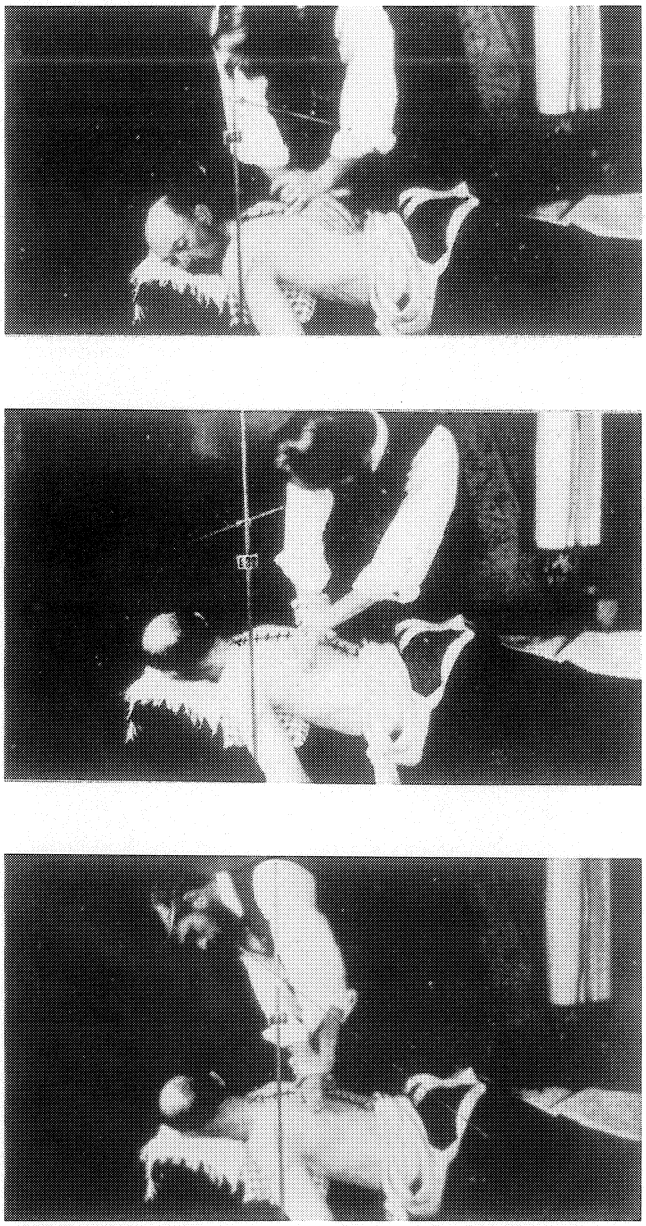

Figure 5.
B.J. demonstrates his technique of manipulation in The Science of Chiropractic, Vol. I-V.

stumbled upon the art of chiropractic, and began to develop it into a science. However, he advanced the science and elevated it to a philosophy. He declared himself the first Ph.C., or Philosopher of Chiropractic.

The science of chiropractic was based on three principles. Adjustment of the spine was similar to that described by osteopaths, with some technical differences. Palpation was the means by which areas requiring adjustment were identified and described. Nerve-tracing was the other key to diagnosis. It involved tracing one's symptoms to the level of subluxation causing them. These nerves were the mediators of "Innate Intelligence," a natural life force that

represented the ability and desire of the body to heal itself, or return to its normal state of homeostasis.

Subluxation of the spine occurs in one of a combination of six directions. The science of chiropractic, based on the subluxations present in the spine, was proven by B.J. using the extensive osteology collection at the Palmer School.

The philosophy of chiropractic was set forth by B.J. as well. He wrote, "Therapeutics is wrongly based. It needs one vast revolution. This is the mission of chiropractic- the first non-therapeutical theological philosophy." Palmer believed that life, death, and disease, described as the "intermediate," were insufficiently explained by the current science ("the knife") or religion ("preaching the gospel").

This void was filled by chiropractic. He aimed to bridge the spiritual and corporeal.

In promoting chiropractic, he drew sharp distinctions between his science and the science of conventional medicine. He reiterated the risks of anesthesia, blood loss, and the unpredictable results often associated with early surgery. In 1909 he introduced the use of X-rays which served to mainstream chiropractic. In 1913 states began to license chiropractors.

B.J. held advertising crucial to the development and spread of chiropractic. He taught advertising and patient management skills to his pupils. He encouraged them to offer free consultations (X-ray fees excluded, of course) in order to generate patients. He espoused the use of full body length X-rays with elaborate explanations given to patients to account for their varied complaints. After all, the patients needed to understand their disorder in order to see the need for repeated adjustments.

On a more personal level, he began to use the emerging media of radio as a means of advertising his own practice and his school. He purchased and developed WOC in Davenport, and WHO in Des Moines. He later affiliated with NBC in order to gain national exposure. It was as owner of WOC that he first met Ronald Reagan. He was Reagan's first employer in what was to become a long and illustrious acting career. (Fig. 6)

In the 1930's chiropractic came under the scrutiny of John Nugent. He reviewed chiropractic schools, attacking the weaker ones. In 1935 he headed the National Council on Chiropractic Examining Boards. This movement became known as "Nugentism." In 1942 the Council issued its first report. Twelve schools, including the Palmer School, received "provisional approval." In 1946 this list was narrowed to four schools. Notably absent from the list was Palmer's program. One of the standards set by Nugent's Council was a four year curriculum, each year to include at least nine months of study. Palmer had an eighteen month course of study until 1958. B.J. and

Figure 6
Ronald Reagan behind the microphone at WOC.

Nugent differed on this and many other subjects, including the advisability of requiring college training prior to embarking on a career in chiropractic. B.J. often had disdain for the college educated.

At the same time Nugent was scrutinizing the educational institutions of chiropractic, there was essentially no regulation of the daily practice of the science. Partly as a result of B.J.'s push to advertise, the mid 1900's were marked by a virtual explosion of unusual devices, they had names such as the Polysine Generator, the Chromoray, the Neurocalometer, and the Electroencephaloneurementimpograph. (Fig. 7) The Neurocalometer's problem was that in FDA testing the device proved unable to distinguish a well person from a corpse. This was the impetus for the new, improved Neurocalometer which claimed that it would not be confused in discerning the living from the dead.

As a result of these and other fantastic claims, the division and animosity between chiropractic and conventional medicine worsened. Claims of practicing medicine

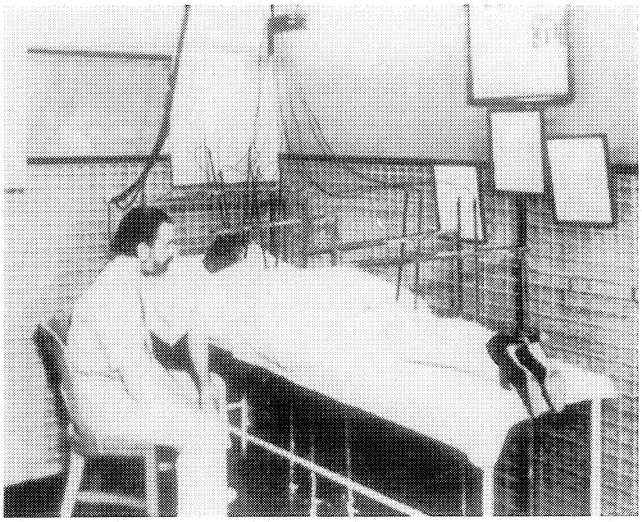

Figure 7
B.J. demonstrates the electroencephaloneuromentimpograph

without a license became commonplace. Many chiropractors were prosecuted, and some imprisoned.

Many within the field of chiropractic recognized the problems that the far fetched claims of their colleagues were causing. As a result, many began to tone down their rhetoric. In effect, a field that had its roots in being unconventional sought to become more mainstream. Less was heard about Innate Intelligence and the ability of manipulation to cure diabetes, heart disease, and other medical conditions. More was focused on the claim that manipulation could aid in treating ailments of the spine.

On October 1, 1976, Chester Wilk and four other chiropractors brought suit against the American Medical Association, American Hospital Association, American Academy of Orthopaedic Surgeons, five other medical associations, and four individuals. The defendants were charged with violating Section 1 of the Sherman Antitrust Act—conspiring to eliminate chiropractic through refusal to associate professionally with chiropractors. The case went to trial in Chicago, in December 1980. The original jury found for the defendants, after the judge implied to them that a defendant can escape the Sherman Act by acting in a public interest. On appeal, the Seventh Circuit Judge ruled that the decision was in error, but refused to overturn it based on a legal interpretation. The case was ordered back to trial. In the second trial, Wilk had to prove that the primary effect, rather than intent, of the defendants had been to restrict competition. As a result, the defendants had to prove that they not only acted out of public interest but that, by their actions, the public had been served.

The key evidence in the case was produced by Mr. Throckmorten, general counsel of the Iowa Medical Society. He had devised a plan to curb chiropractic in Iowa. He actively shared this with his counterparts in other states. This led to Throckmorten's appointment as Chairman of the AMA Committee on Quackery. At that time the AMA was part owner of the Joint Commission on Accreditation of Hospitals (JCAH), the American College of Physicians (ACP), the American College of Surgeons, and the American Hospital Association. This meant that Throckmorten and his policies received a great deal of credibility. This led to chiropractors being denied access to hospital facilities.

In August, 1987 a federal judge ruled in favor of Wilk based on the strong opposition the AMA held toward chiropractic without evidence. The AMA, ACS, and American College of Radiology were found guilty. The AAOS, JCAH, and ACP were found not guilty. The case was upheld on appeal in 1990.

As a result of Wilk v. AMA, the AMA was required to mail a letter to all of its members, and those of the codefendant groups, stating that opposition to chiropractic was against the principles of the AMA. Chiropractors could no longer be denied access to health care facilities or third party payers. This case was a turning point in the history of chiropractic.

The modern practice of chiropractic is a far cry from the early science of the Palmers. Chiropractic is now an accepted form of treatment in many elements of our society. Third party payers recognize and compensate for chiropractic treatment. A recent study by the RAND Corporation (Shekelle, 1994) verified, by meta-analysis, that chiropractic manipulation can be an effective treatment for acute low back pain, without radiculopathy, of less than one month duration. Cost of treatment is comparable, per episode, to treatment by orthopaedic surgeons. (Shekelle, 1995).

While many chiropractors have clung to their roots, and continue to search for subluxations that are responsible for various medical conditions, the majority have focused their attention on the treatment of back pain. While this may be causing a rift within the field, it is certainly leading to more and more mainstream acceptance of spinal manipulation. The future of chiropractic, while uncertain, seems to be headed far beyond the expectations of D.D. Palmer when he first cured Harvey Leggett of his deafness, or the ambitions of B.J. when he incorporated the Palmer School of Chiropractic.

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THE "SAGGING ROPE SIGN" IN AVASCULAR NECROSIS IN CHILDREN'S HIP DISEASES - CONFIRMATION BY 3D CT STUDIES

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ABSTRACT

Growth disturbance of the proximal femoral epiphysis and physis secondary to avascular necrosis (AVN) in a variety of children's hip disorders produces changes in the femoral head and neck that make radiographic interpretation difficult. The enlarged overhanging femoral head produces radiographic markings on the femoral neck which are sometimes confusing. These have sometimes been misinterpreted as growth arrest lines. Apley and Wientroub reintroduced Perkins' description of the "sagging rope" sign in AVN of the femoral head, and Clarke clarified that this puzzling radiographic transverse metaphyseal line overlying the femoral neck in fact represents the margin of the femoral head rather than a growth arrest line. Their report was made after studying plain and stereoscopic radiographs alone. Our review of 23 cases of femoral head AVN in children, documented by 3 dimensional computerized tomographic (3D CT) radiographs of the femoral head and pelvis, confirms Clarke's view of the nature of the "sagging rope" sign. These sophisticated radiographic studies provide new detail and understanding of head-neck relationship in AVN which allows better planning for surgical correction of hip disorders in children.

INTRODUCTION

Damage to the capital epiphysis and physis of the proximal femur secondary to AVN leads to a short, broad femoral neck and a flattened capital epiphysis. The "sagging rope" sign (Fig. 1), originally observed by George Perkins, (and published by Apley and Wientroub[1] in 1981) can be observed in certain cases of Legg-Perthes' disease, AVN following treatment of developmental dysplasia of the hip (DDH), and in other miscellaneous causes of AVN in children.

The "sagging rope" sign describes a distally convex radiopaque line noted on anteroposterior plain radiographs

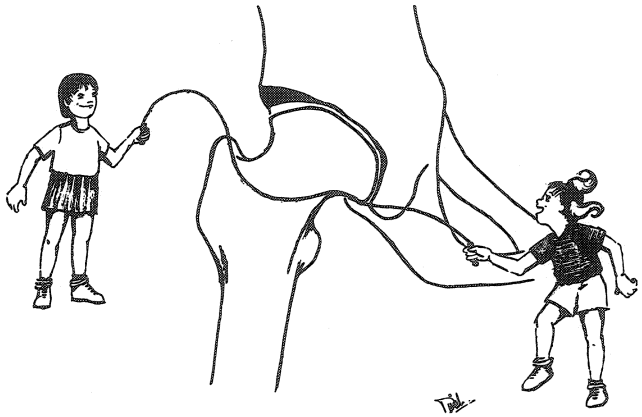

Figure 1 Depiction of "sagging rope" sign: a concept proposed by Perkins to define the lower margin of the femoral head in AVN in children. The radiopaque line, which resembles a loosely held jump rope, represents the margin of the true femoral head.

of the hip in children with AVN. The line is seen overlying the femoral neck and extends laterally from the inferior border of the neck for a variable distance, frequently reaching the superolateral border of the neck. Usually the line is curved and sags at its center but is sometimes almost straight.

The etiology of this line has been argued with some suggesting that it might represent a Harris growth arrest line[5]. Apley and Wientroub[1] noted the radiographic finding in severe cases of Legg-Perthes' disease, DDH with AVN, and other less common epiphyseal dysplasias and suggested that its presence indicates damage to the growth plate with a marked metaphyseal reaction. They also described that the line seems to have its origin in the distal edge of a band of rarefaction in the metaphysis.

However, Clarke et al.[3] presented a different interpretation concluding that the line is a radiological shadow cast by the edge of a severely deformed head. They studied this line by stereoscopic anteroposterior radiographs, intraoperative radiographs using needle markers, and radiographs of the excised femoral head and neck.

The development of sophisticated imaging technology (3D CT) allows imaging of complex hip disorders in clear three dimensional format that allows better understanding of the pathoanatomy and pathomechanics of hip disorders. The technology allows ready evaluation of complex morphology and deformity of the femoral head, neck, and acetabulum

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from many different angles and perspectives. Subtractive techniques allow the femoral head and acetabulum to be studied separately.

In this paper we will present our evaluation and confirmation of the "sagging rope" concept in 18 children (23 hips) with AVN using 3D CT data.

MATERIALS AND METHODS

From June 1990 to October 1994, we performed 3D CT studies on 23 hips in 18 children with complex femoral head deformity related to AVN. The etiology of the AVN in these patients included Legg-Perthes' disease (11 hips-11 patients), epiphyseal dysplasia (10 hips-5 patients) and AVN following treatment of DDH (2 hips-2 patients). Eleven hips in nine patients demonstrated the "sagging rope" sign on plain radiographs (Legg-Perthes' disease, six hips in six patients; DDH, three hips in two patients; epiphyseal dysplasia, two hips in one patient).

The mean age at 3D CT evaluation was 12 years and 6 months (ranging from 7 years 1 month to 20 years 4 months). The CT images were obtained using a General Electric scanner. The data were stored on nine-track magnetic tapes and analysed by the Cemax 5000 (Cemax Medical Products, Mountain View, CA, U.S.A.), and Cemax VIP (version 1.7 Beta, release 1.3) which take volumetric data to produce 3-D images in any desired plane for analysis.

RESULTS

"Sagging rope" sign on plain radiograph:

In the anteroposterior view (Fig. 2A), the line extends laterally from the inferior border of the neck for a variable distance, frequently reaching the superior border; usually the line is curved, sagging at its center, but occasionally it is almost straight[1]. Because the overlying bone may occur both anteriorly and posteriorly, two separate lines can sometimes be observed.

"Sagging rope" sign in 3D CT studies:

In all cases, failure of growth in the epiphysis and the proximal femoral physis led to broadening and shortening of the femoral head and neck with relative overgrowth of the greater trochanter. The characteristic features of the femoral head on 3D CT which could not be easily recognized on plain radiographs included: a) the magnitude of the broadened femoral head b) the portion of femoral head protruding in an anterolateral-inferior direction which acts as a non-weight bearing area and an obstacle for internal rotation of the femoral head c) the shape of the anterolateral-inferior margin of the flattened femoral head which overhangs the femoral neck and exactly coincides with the radiopaque line known as the "sagging rope" sign on the plain radiograph (Fig. 2B) d) a groove in the femoral head (Fig. 2C) made by impingement of the softened

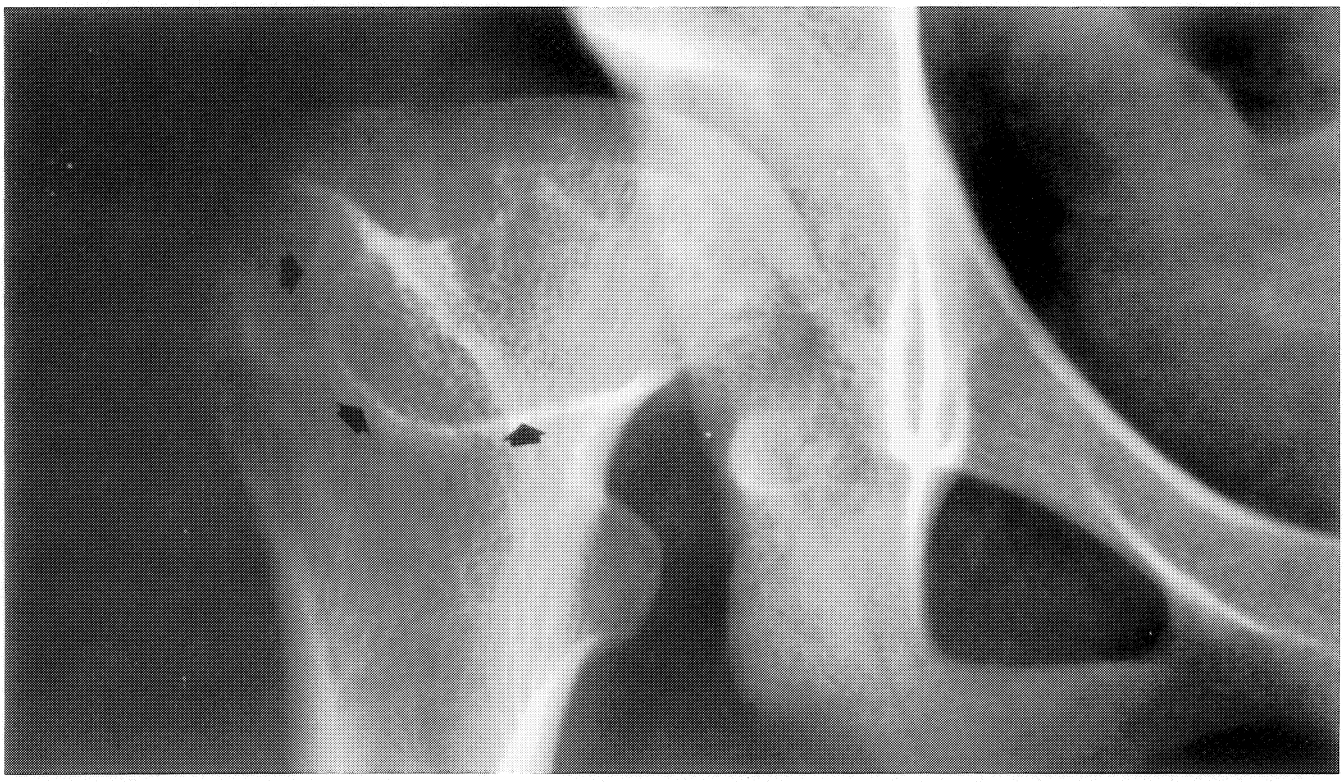

Figure 2A The "sagging rope" sign on the plain AP radiograph of the right hip in a 13 year old girl with late healing Legg-Perthes' disease.

Figure 2B A 3D CT scan of right hip corresponding to Figure 2A. The anatomy is clearly defined. The head is flattened and the proximal femur externally rotated. The border of the anterolateral-inferior head margin (arrows) coincides with the position of the "sagging rope" sign as noted on the plain radiograph.

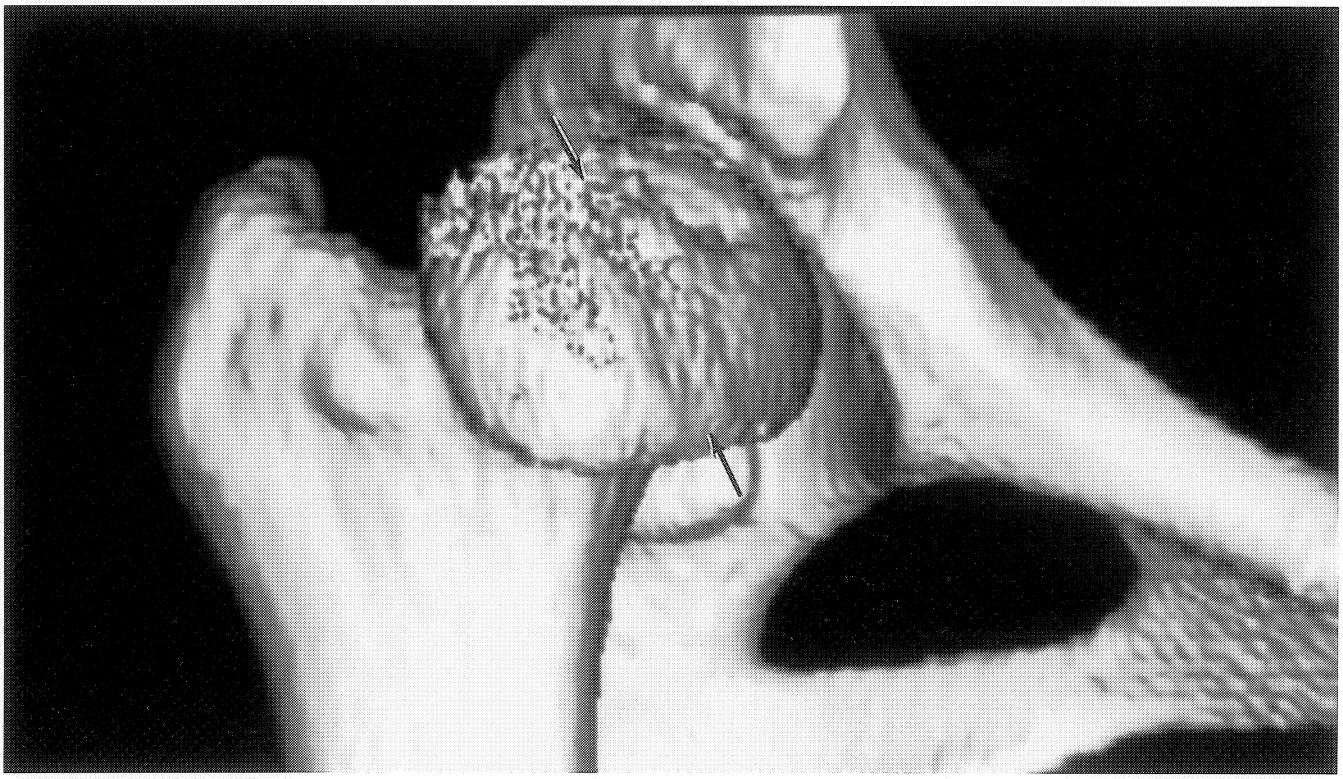

Figure 2C Another 3D CT scan of the same right hip, rotated 36 degrees. This view demonstrates a groove (arrows) in the deformed head produced by impingement of the anterolateral femoral head against the rim of the acetabulum.

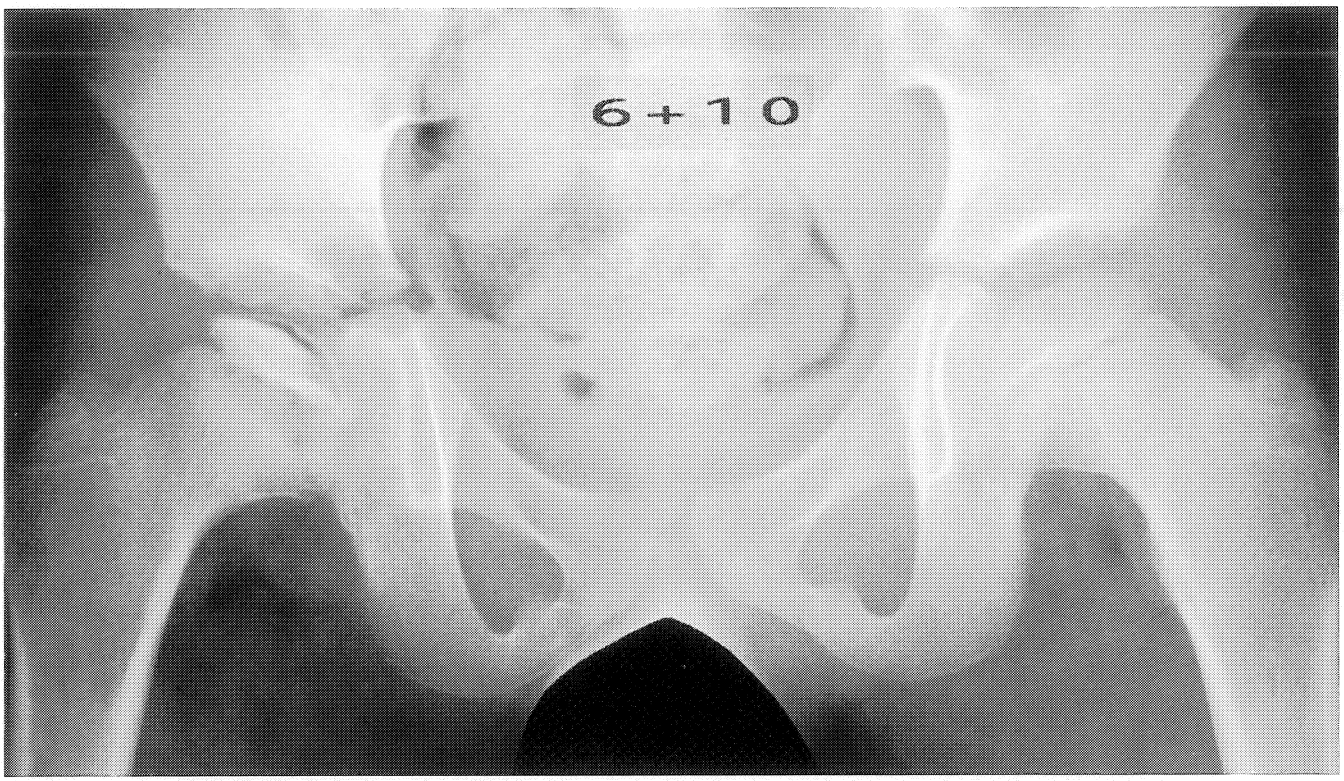

Figure 3A Initial plain AP radiograph of the pelvis in a 6+10 year old child with severe Catterall group III Legg-Perthes' disease of the right hip.

femoral head on the anterosuperior rim of the acetabulum. The acetabular rim divides the flattened femoral head into a more congruous posteromedial-superior portion and a protruding anterolateral-inferior portion which cannot be contained in the acetabulum. Not all femoral heads demonstrated this groove however.

The head and neck deformity noted in AVN likely develops during the primary healing process after major vascular insult when the femoral head is in a biologically plastic state. Compression force on the soft and vulnerable capital femoral epiphysis can deform the head and produce an anterolateral portion which is no longer contained within the acetabulum. As a consequence of this head deformity, the posteromedial-superior portion of the head persists as the true articulating head with the adjacent neck and femur rotating externally resulting in a functional retroversion. This leads to an external rotation deformity in both severe Legg-Perthes' disease and DDH complicated by AVN.

Careful comparision of the "sagging rope" sign on plain radiographs with corresponding structures on the 3D CT scan clarify that the line noted on plain radiographs represents the margin of the overlying deformed femoral head, most commonly an anterolateral-inferior overhang. In less deformed heads, the line may be nearly straight and does not reach the superior border of the neck. Also in some cases a double line is noted which represents an overhanging of both the anterior and posterior femoral head margins. This is readily confirmed by 3D CT studies. In fact the the overhang is circumferential in the damaged femoral head, but the "sagging rope" phenomenon is only demonstrated on the anteroposterior view which shows the anterior and posterior overhang.

CASE REPORTS

Case 1. A six year old girl who developed Legg-Perthes' disease was initially treated with a containment orthosis for one year. At 13 years of age she complained of increasing pain and limp in her right side. She presented with an out-toeing gait on the right and was noted to have an externally-rotated right leg when examined in the supine position. The plain radiographs showed a coxa magna with head extrusion and a distinct "sagging rope" sign which extended from the inferior border of the neck medially to the superior border laterally, crossing the intertrochanteric line. She also had markedly decreased articulo-trochanteric distance due to relative coxa vara (Fig. 2A). A 3D CT study showed a severely deformed, flattened and extruded femoral head with an externally rotated femur. The anterolateral-inferior margin of the flattened femoral head exactly coincided with the shape and site of the "sagging rope" sign as noted on the plain radiographs (Fig. 2B,C).

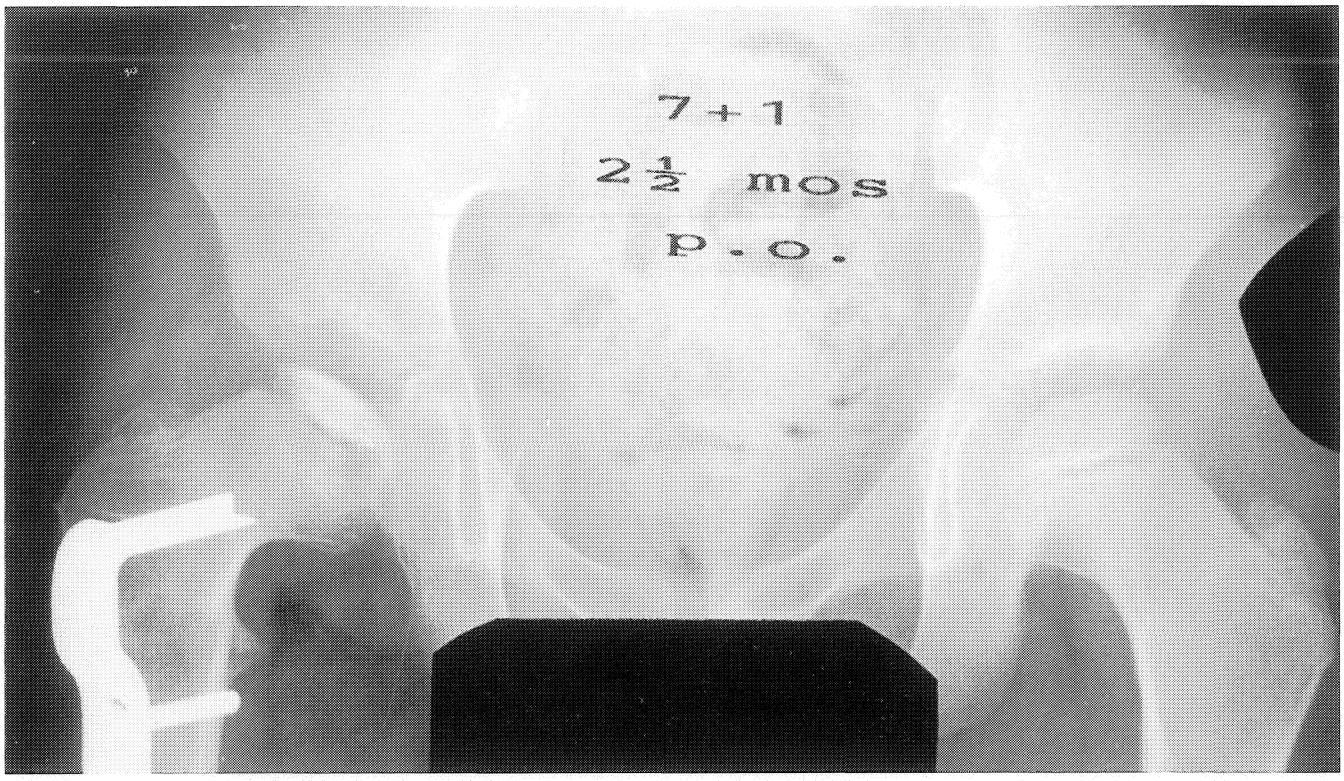

Figure 3B Plain AP radiograph taken 2.5 months after proximal femoral varus, slight extension osteotomy. This early radiograph suggests satisfactory containment of the femoral head.

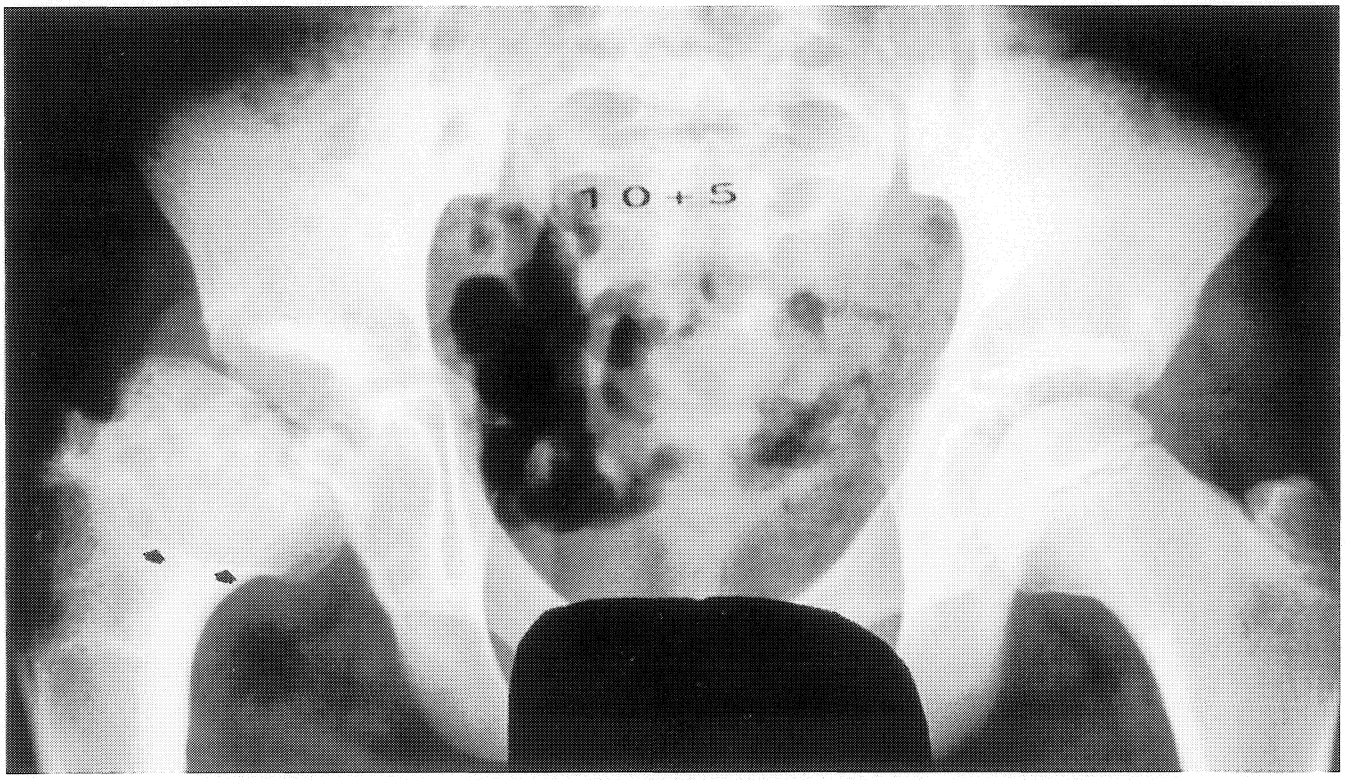

Figure 3C Plain AP radiograph, 3.5 years following operative containment. The patient now has increased pain, decreased abduction, and the clinical signs of hinge abduction. This radiograph demonstrates a widened, enlarged femoral head and neck with a positive "sagging rope" sign (arrows).

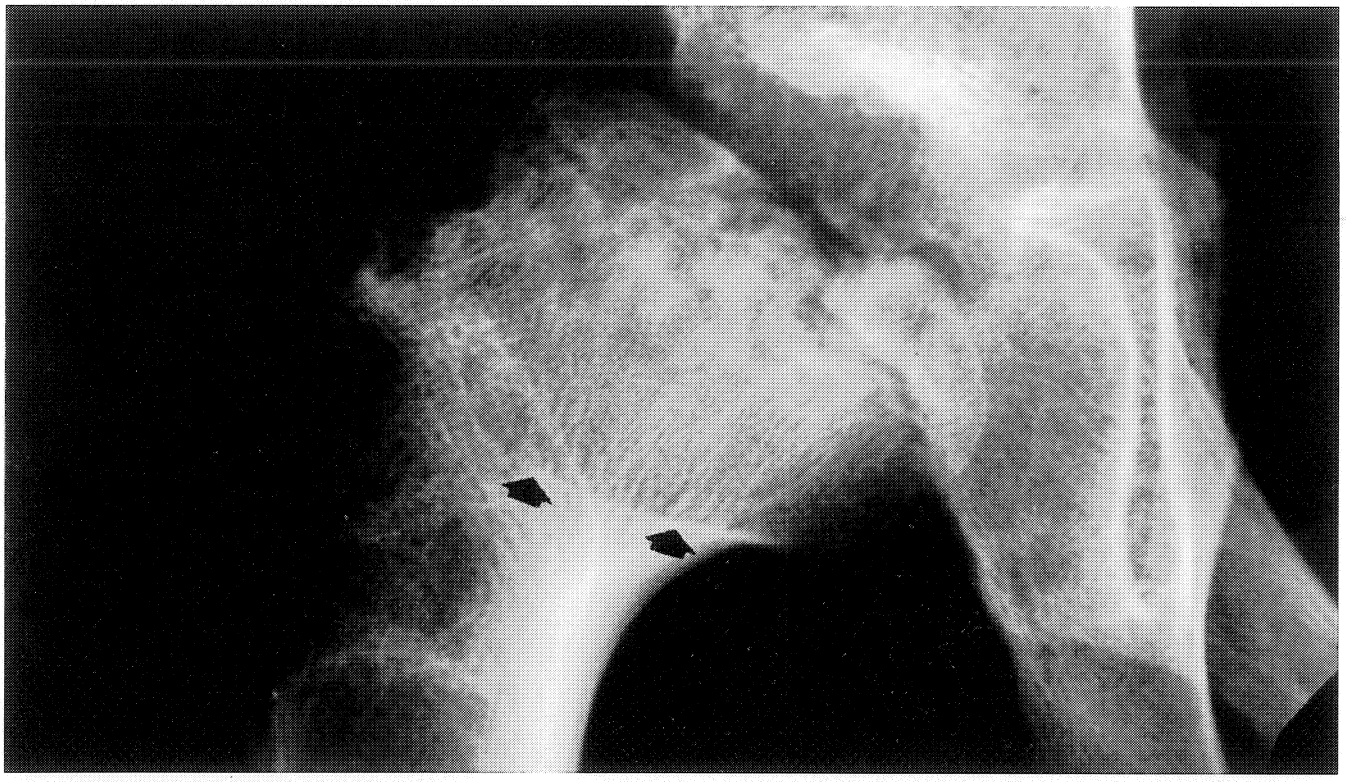

Figure 3D Detailed view of same radiograph.

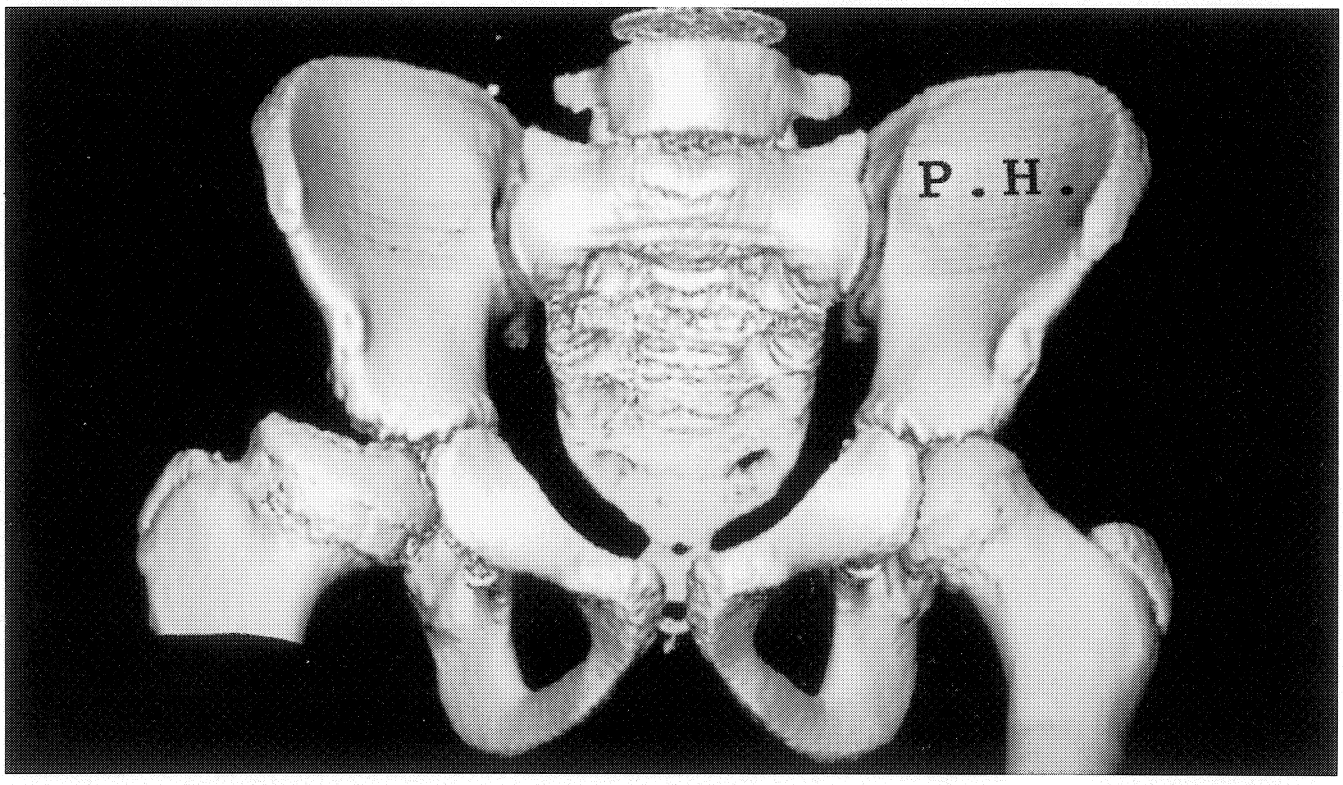

Figure 3E A 3D CT scan taken at the same time shows a flattened, saddle shaped femoral head with marked extrusion and mild external rotation of the proximal femur.

Case 2. A 6-year 10-month old boy developed relatively severe Legg-Perthes' disease (Fig. 3A) and after traction, adductor tenotomy, and Petrie casts to mobilize the hip, was treated with a varus-slight extension osteotomy of the proximal femur (Fig. 3B). He initially did well but at age ten years (three years after initial containment surgery), he developed increasing pain, a progressive limp, and was noted to have decreased hip abduction in extension. Radiographs at this age showed flattening and widening of the femoral head and neck with a typical "sagging rope" sign (Figs. 3C, D). A 3D CT study (Figs. 3E, F) revealed a markedly enlarged saddle shaped femoral head which was leading to hinge abduction. The protruding anteroinferior portion of the head coincided with the shape and site of the "sagging rope" sign noted on the plain radiograph. A femoral valgus osteotomy and shelf acetabuloplasty were performed which relieved his pain and improved his hip abduction (Figs. 3G, H).

Case 3. A 7-year 6-month old girl presented with a history of DDH which was treated with spica cast reduction (without prior traction) in Pakistan at age nine months. On examination at age seven years in our clinic, she had a left abductor lurch and positive Trendelenburg test. Plain radiographs revealed mild acetabular dysplasia, coxa magna, and a short "sagging rope" sign on the right hip which had mild AVN. On the left hip, there was marked flattening of the femoral head due to severe AVN.

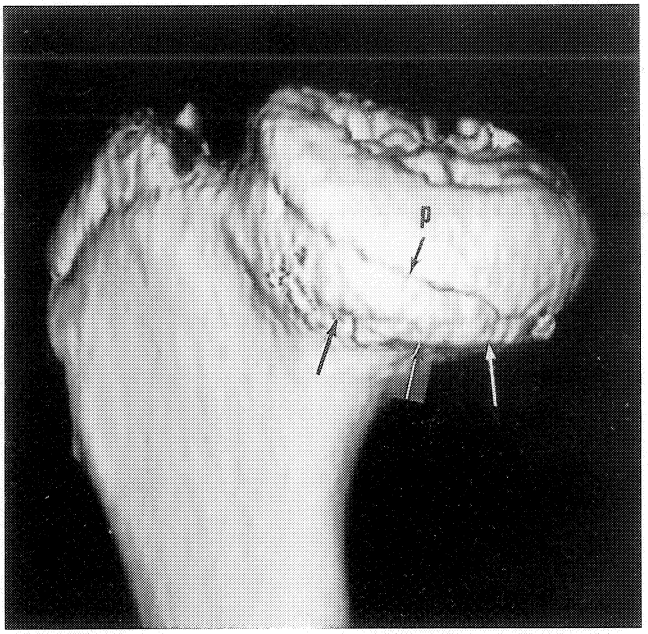

Figure 3F Detailed view of femoral head with acetabulum subtracted. Both the physis (p) and the margin of the head (arrows-"sagging rope") are apparent.

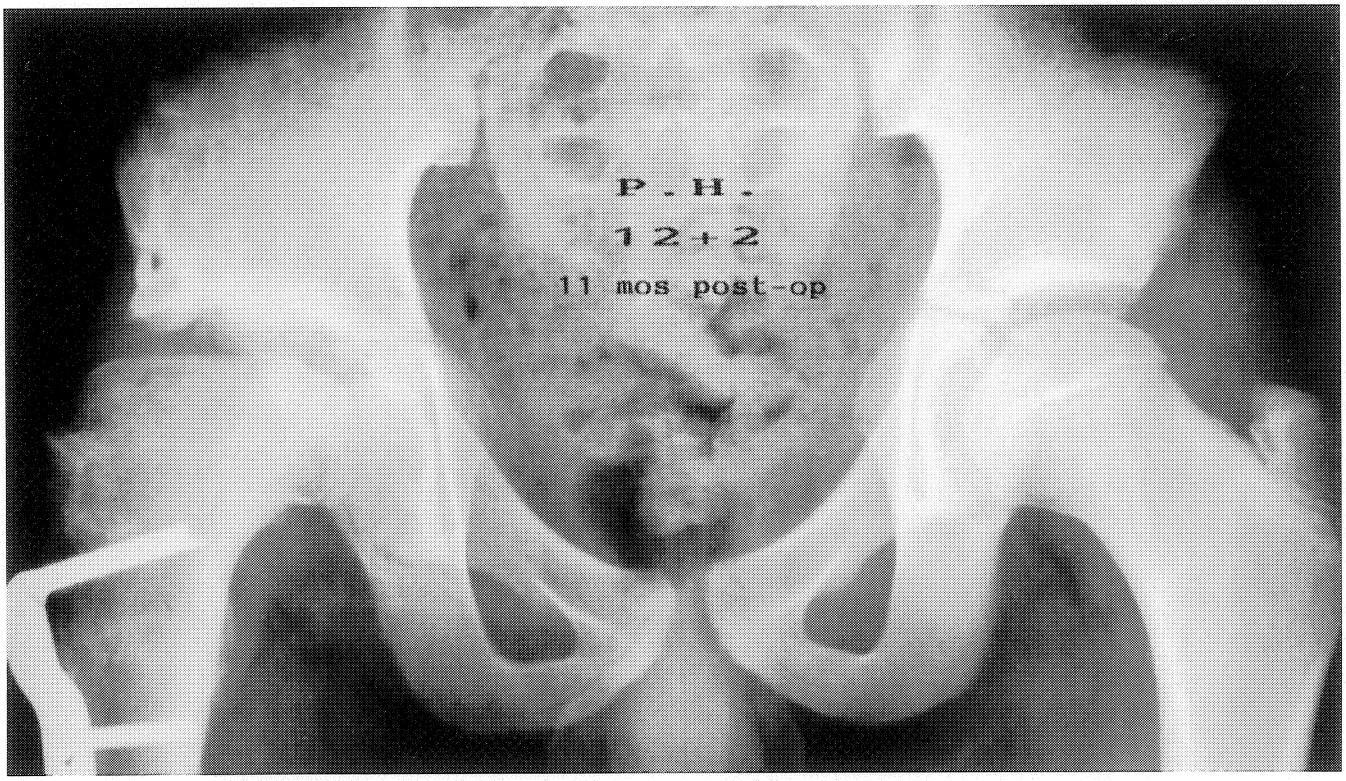

Figure 3G Plain AP radiograph following corrective valgus osteotomy plus shelf acetabuloplasty performed to correct hinge abduction and to provide femoral head coverage. The patient now has improved motion and no hip symptoms.

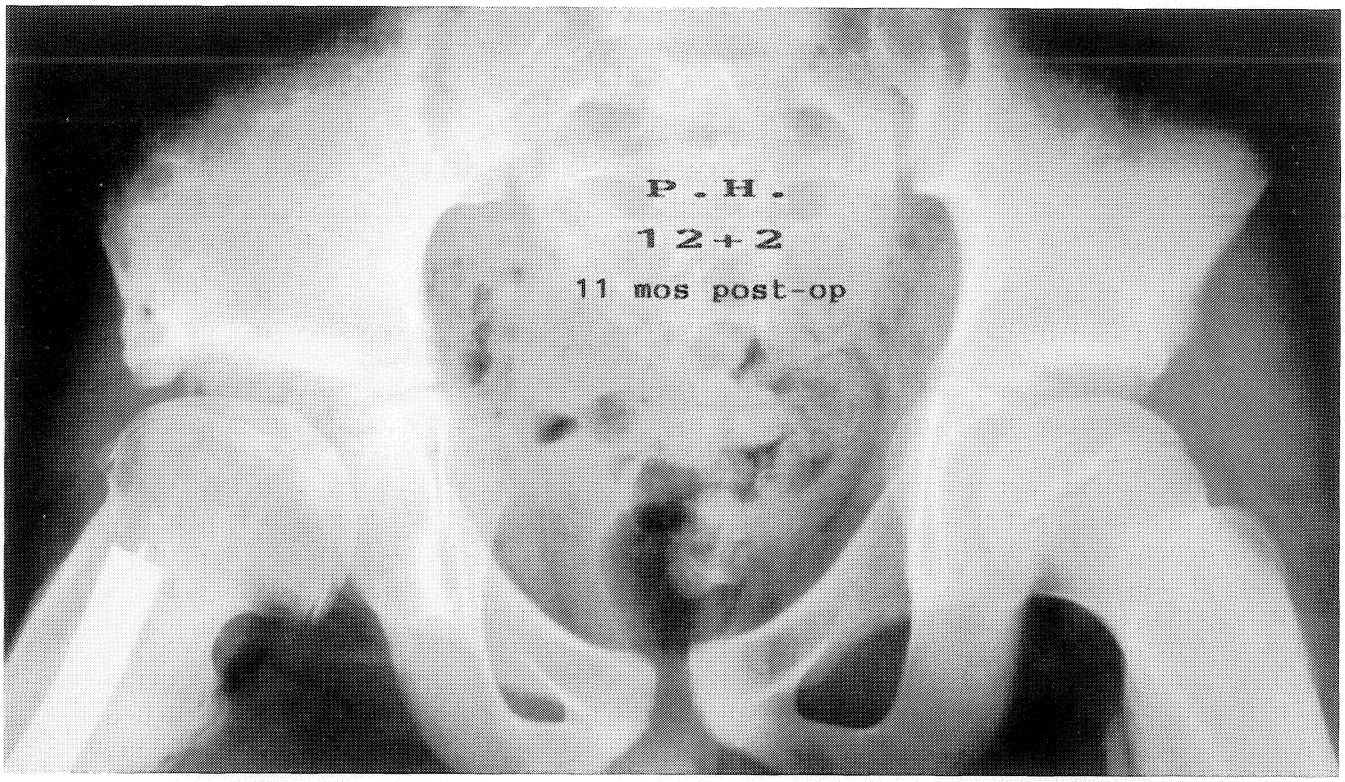

Figure 3H Frog view-as in Fig. 3G. The lateral view of the femoral head clearly depicts the shape of the enlarged femoral head (coxa magna).

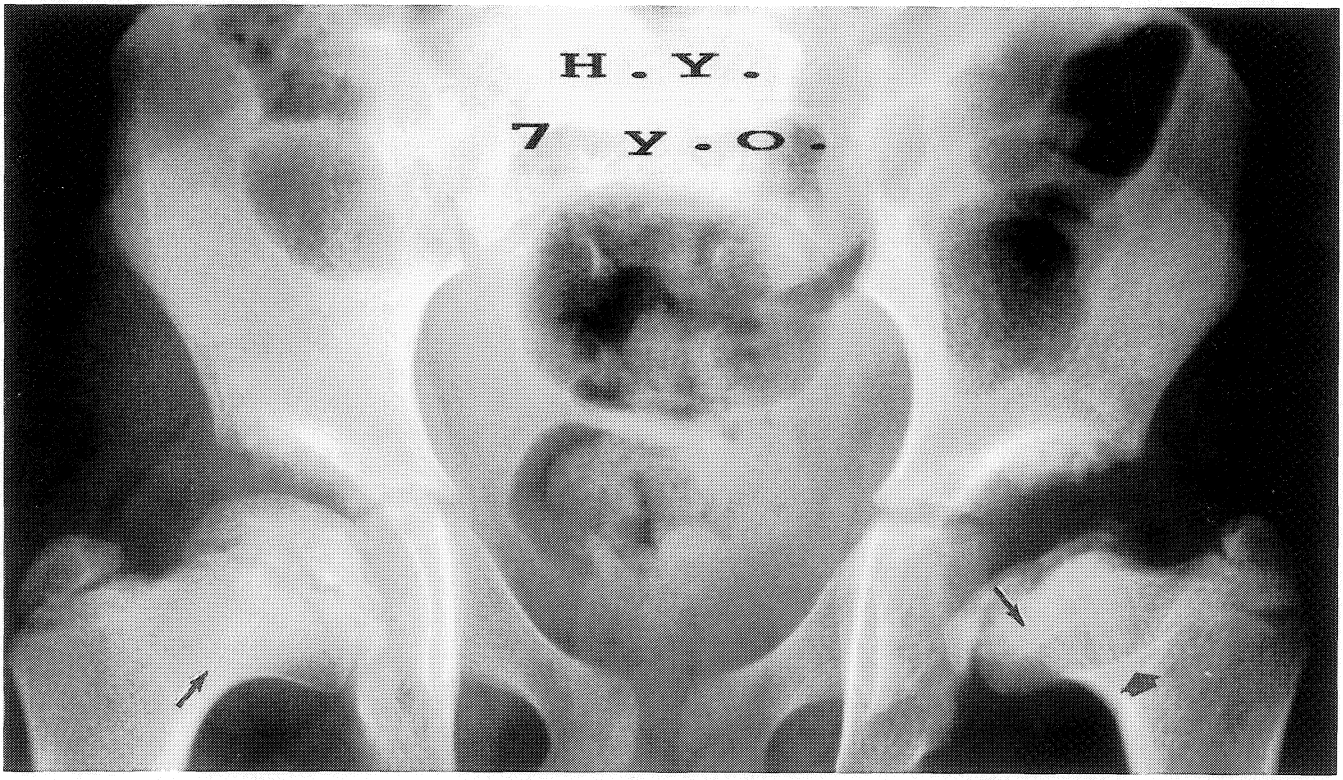

Figure 4A Plain AP radiograph in a seven year old child who had bilateral DDH reduced and maintained in a hip spica at age nine months in Pakistan. The film shows bilateral acetabular dysplasia and coxa magna with a mild right side and a more clearly demarcated left side "sagging rope" sign. The left side has a double "sagging rope" sign demonstrating both the anterior (small arrow) and posterior (large arrow) margins of the overhanging femoral head. The coxa vara and head deformity are characteristic of AVN.

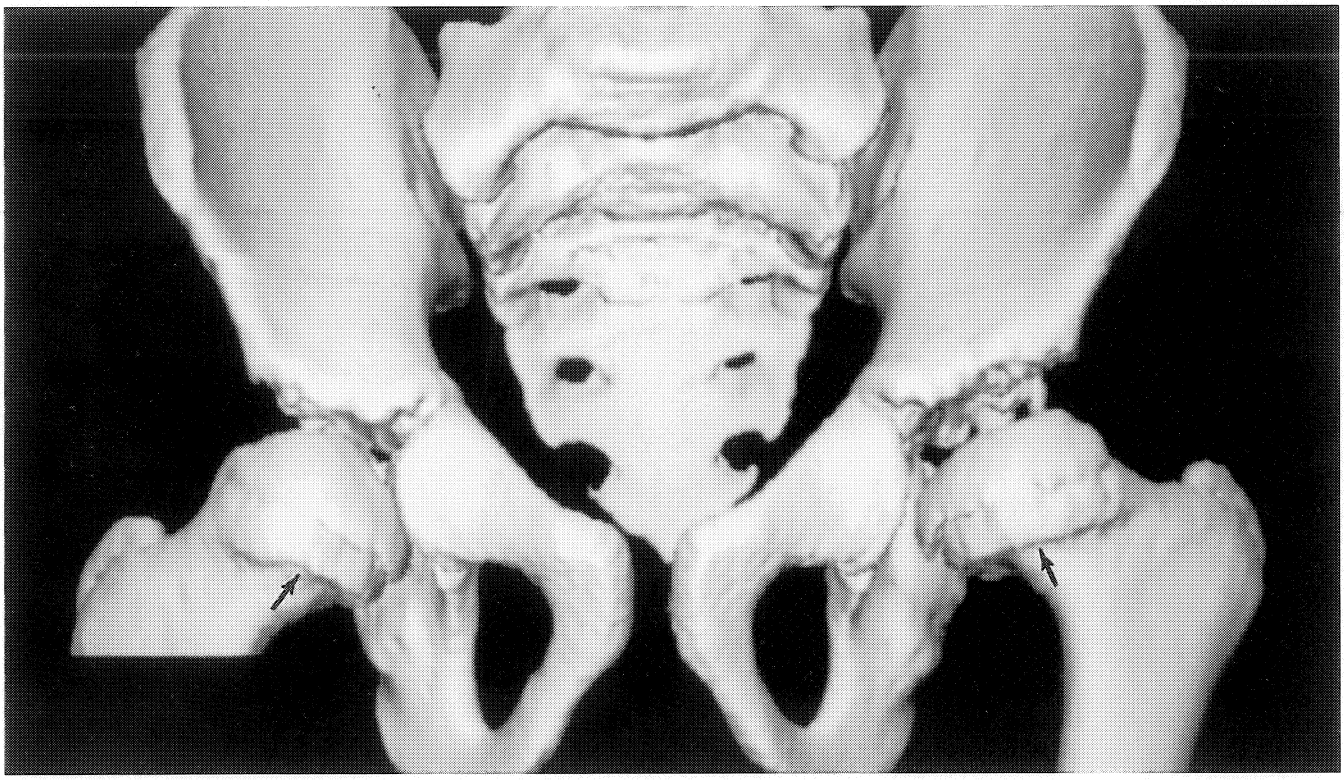

Figure 4B A 3D CT scan taken at the same time showing acetabular dysplasia, a flattened femoral head, and a protruding anteroinferior metaphyseal margin (arrow) of the femoral head on the left hip. The right side also demonstrates a mild protruded metaphyseal margin (arrow).

The radiographs demonstrated a double "sagging rope" sign with each line slightly curved but not reaching the superior border of the neck (Fig. 4A). A 3D CT study revealed the exact nature of the abnormal head shape with epiphyseal damage more severe posteriorly with some anteromedial sparing (Fig. 4B). The site and shape of the inferior radiopaque line on the plain radiograph, which sags downward in its central portion, coincided with the posteroinferior head margin as noted on the 3D CT studies. The superior, nearly straight, "sagging rope" sign on the plain radiograph coincided with the anteroinferior head margin on the 3D CT study (Figs. 4C, D).

DISCUSSION

The use of 3D CT imaging technology in this study confirms the studies of Clarke et al.[3] who determined that the "sagging rope" sign in AVN represents the femoral head margin overlying the metaphysis (femoral neck). This is a clearly different etiology from Harris growth arrest lines[5] which represent temporary cessation of normal physeal growth but not AVN.

The "sagging rope" sign is clearly the radiologic result of a deformed femoral head which overlies the femoral neck. It can be seen in Legg-Perthes' disease, AVN which follows treatment of DDH, and other causes of childhood AVN of the hip. The peak incidence of Legg-Perthes' disease occurs in mid-childhood with a cycle of reconstitution that takes two to five years, thus a significant amount of growth continues in the deformed head. The effect of continuing growth and partial premature closure of the epiphyseal line can influence the final femoral head shape. This phenomenon is also seen in other conditions with cartilage necrosis.

Apley and Wientroub[1] thought the length of the "sagging rope" sign was related to the extent of the ischemic damage or the extent of the metaphyseal response to that damage. They suggested a resemblance to Harris growth arrest lines[5]. Clarke et al.[3] refuted Apley and Wientroub's concept and concluded that the line represents the anterolateral edge of the severely deformed femoral head.

Hoffinger et al.[6] also supported the study of Clarke et al. and emphasized that any metaphyseal cyst-like changes proximal to this line might actually be epiphyseal changes superimposed on the metaphysis. This has been subsequently disproven by others who used MRI and CT studies to demonstrate that the so-called metaphyseal cysts in Legg-Perthes' disease are truly within the metaphysis. Hoffinger et al.[7] then restudied the matter and clarified that some metaphyseal cysts are truly within the neck (metaphysis).

Our 3D CT analysis of the "sagging rope" sign confirms the findings of Clarke et al. Clearly the thin radiopaque

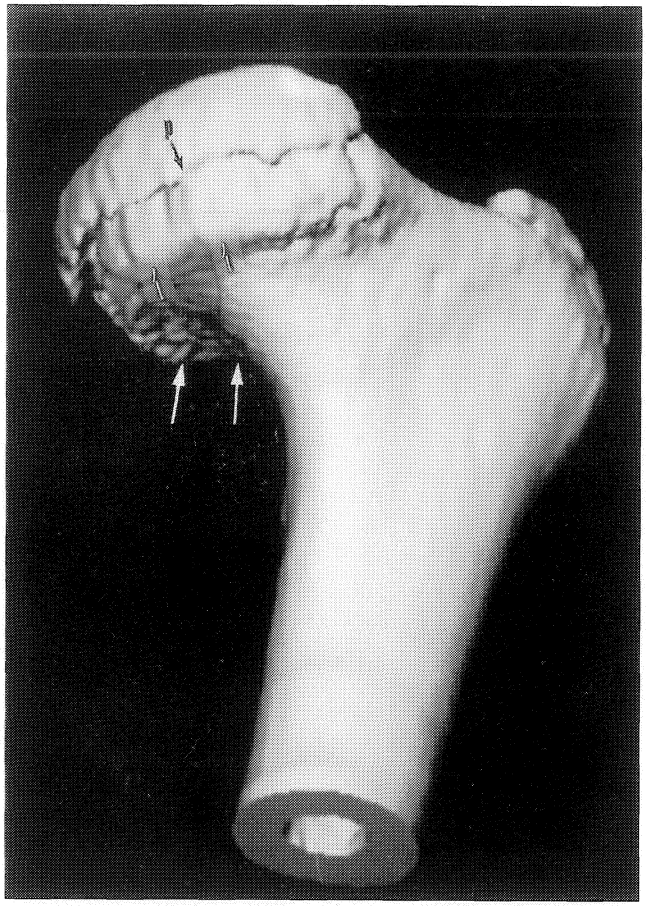

Figure 4C The 3D CT scan of the subtracted left femur viewed from anteriorly (with slight upward tilt) clearly demonstrates both the physeal margin (p) and the "sagging rope" sign (arrows). This "sagging rope" margin corresponds to the superior most line on the plain radiograph (Fig. 4A) which is the anterior margin of the femoral head overhang (short arrows). The posterior margin or overhang, as depicted by white arrows, corresponds to the larger inferior line on the plain radiograph (large arrow-left hip-Fig. 4A).

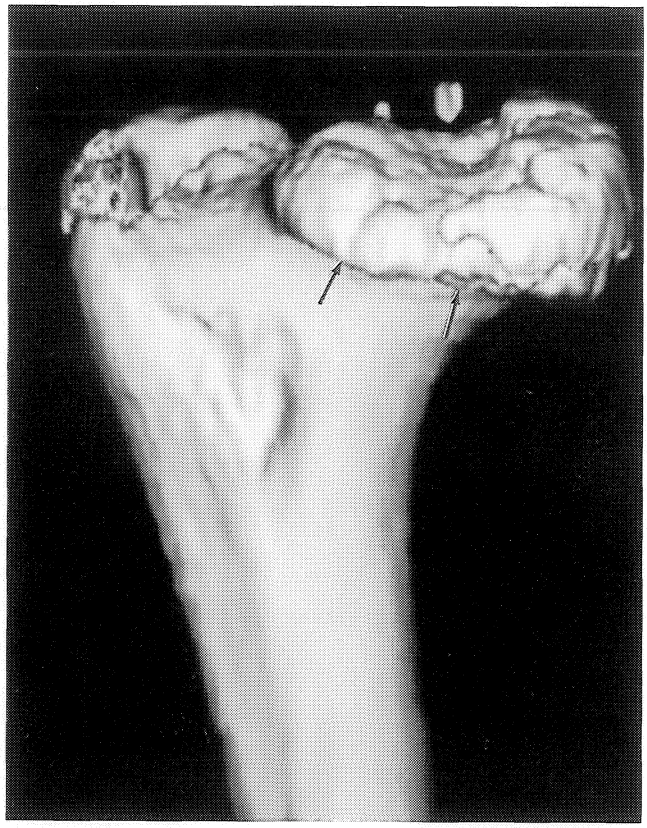

Figure 4D The 3D CT scan of the subtracted left femur viewed from behind demonstrates epiphyseal irregularity (cartilage not visualized) and a "sagging rope" sign (arrows). This posterior overhang corresponds with the larger inferior "sagging rope" sign depicted in the plain radiograph (left hip-Fig. 4A).

line noted on plain radiograph represents the margin of the deformed femoral head and not a metaphyseal response in femoral neck. By use of 3D CT analysis we were also able to learn more about the femoral head-acetabular relationship in childhood AVN and its relationship to the externally rotated limb posture commonly seen in AVN. It has been shown that remarkably early in the pathologic process of Legg-Perthes' disease, an anterolateral segment of the femoral head protrudes from the confines of the acetabulum[2,4]. Snow et al.[8], in a two dimensional CT study, reported anterior impingement of the femoral head as a late phenomenon of Legg-Perthes' disease. Our 3D CT studies confirm this phenomenon, clarifying that the anterolateral-inferior protrusion of femoral head acts as the obstacle for internal rotation of the femoral head as a late sequelae of Legg-Perthes' disease. In addition our studies suggest that many Legg-Perthes' patients develop a functional retroversion with the posterosuperior segment of the head remaining as the true articulation with the acetabulum and the anterolateral-inferior prominence leading to an external rotation deformity of the entire distal femur.

The presence of the "sagging rope" sign has considerable prognostic significance confirming that the disease has been severe and the physis partially damaged[1]. Our study adds further insight into this relationship.

We noted two types of "sagging rope" sign. In one type the line extends from the inferior border of the neck medially to the superior border of the neck laterally with a large curve crossing the intertrochanteric line, deeply sagging at its center. This type of line represents a severely deformed head with anterolateral-inferior protrusion and a resulting increased external rotation posture of the distal femur and limb.

In the second type we noted a short, relatively straight line, nearly parallel to the intertrochanteric line which does not reach to the superior border of the neck. This type of line is associated with a moderately deformed head and a more mild and early disease process than the first type. This type of line, associated with a milder degree of AVN, can be the result of anteroinferior or posteroinferior

overhang of the femoral head. In some cases both the anterior and posterior "sagging rope" sign can be seen together in the same hip.

CONCLUSION

The radiographic appearance of a "sagging rope" sign in the proximal femoral metaphysis of children with Legg-Perthes' disease, AVN secondary to DDH, and other conditions causing AVN in children confirms the presence of significant head enlargement and deformity. The head deformity is the result of head flattening due to compression force on a soft and vulnerable capital femoral epiphysis. The subsequent anterolateral-inferior protruded portion of the femoral head produces the typical radiographic "sagging rope" sign. The development of an associated externally rotated femur due to the functional femoral retroversion that occurs when the protruded head becomes bifid produces a deeper "sagging rope" sign on the plain radiograph.

The clarity provided by 3D CT images of femoral head deformity in AVN allows both a better understanding of prior conceptions regarding radiographic imaging and, in addition, provides the opportunity for new understanding of the pathomechanics of the hip in AVN.

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TECHNIQUES FOR CELL AND TISSUE CULTURE MECHANOSTIMULATION: HISTORICAL AND CONTEMPORARY DESIGN CONSIDERATIONS

Thomas D. Brown, Ph.D.

Although specific transduction pathways remain elusive, there is now overwhelming evidence that mechanical stimuli play a major role in regulating many aspects of cellular activity, particularly in the musculoskeletal[24] and cardiovascular[59] systems. The last several years witnessed intensive scientific study of cellular mechano-response and/or mechano-transduction, much of it involving *in vitro* preparations. A wide variety of cell, tissue, and organ culture preparations were introduced for that purpose.[10,37,51,56,63]

Much of this *in vitro* work was facilitated by the development of mechanical devices intended to deliver prescribed loading or distension stimuli to culture systems. Historically, the experimental apparatus used in these mechano-stimulatory culture studies was usually devised by investigators whose main focus was on biology rather than on mechanics. Until very recently - arguably, even now - the ability to deliver unconfounded and well characterized mechanical stimuli to culture systems lags far behind the sophistication of the biochemical and molecular biology tools used to measure the response. As in any area of research, confusion about the intrinsic stimuli delivered in a given experiment obviously limits the generality of conclusions which are drawn and hinders formulation of hypotheses unifying the observations of individual investigators. A review of the pertinent literature reveals a pattern of superb ingenuity in devising new techniques to apply mechanical stimuli of various sorts, but little in the way of attention to characterizing those stimuli on a rigorous basis.

Pioneering *in vitro* mechano-stimulatory work was done in the 1930's by Glucksmann[21], who devised several clever biologic loading models. In one compression model, endosteal cell cultures from embryonic chick tibiae were grown on explanted intercostal muscle preparations to which the two neighboring ribs were left attached. Over a period of several days, the intercostal muscle tissue degenerated and the ribs drew closer together, causing compression of the interposed endosteal cell culture mass. Another biologic compression technique involved interposing bone rudiment "barriers" to impede culture mass expansions. Glucksmann also devised a technique for studying the effects of local distraction, which was induced by surface tension in hanging-drop cultures. Bassett's group[4], whose interests were in both electrical and mechanical stimuli, also worked with hanging-drop cultures. They described an auto-compaction technique whereby compression was achieved during transfer of an embryonic chick tibial cortex culture mass between successive suspension clots. Alternatively, they achieved tensile inputs by stretching their cultures over a sequence of progressively larger silicone rods during the growth periods. Of course, characterization of the mechanical stimuli in these early preparations was restricted to qualitative description.

The era of quantitation of mechanical input dates from the work of Rodan and his collaborators, who studied a variety of cell and explant preparations. Notable innovations included pneumatic piston application of compressive force to chick embryo long bones mounted in a tuberculin syringe barrel[44], hydrostatic pressurization of suspensions of isolated cartilage or bone cells[6,43], and tensile loading of rat calvarial cells seeded and cultured on stretched collagen ribbons[64]. Working within a more conventional cell culture regime, Somjen and her colleagues[50] achieved tensile inputs (initially of unspecified magnitude, but later quantified[5]) by using orthodontic screws to distract two semi-circular slabs of acrylic glued to the exterior base of standard plastic culture dishes. Concurrently, Meikle et al.[34] devised a conceptually related tensioning technique involving (quantified) spring-loading of partially-split plastic substrates upon which they mounted organ cultures of cranial sutures from newborn rabbits.

Until recently, hydrostatic pressurization was the most frequently used means for inducing compressive loading of cell, tissue or explant cultures[2,6,9,27,30,33,57,59]. The advantages of this approach include the relative simplicity of the equipment involved, the spatial homogeneity of the stimulus, the ease (via manifolding) by which multiple specimens are loaded simultaneously, and the straightforward means by which static and/or transient inputs are accurately quantified. Unlike the case for direct physical contact[52], there is no potential for impediment of culture-to-medium fluid or metabolite exchange due to physical blockage or local culture compaction by a platen. Also, the loading achieved is independent of the degree of adhesion between the culture and its substrate. One cited disadvantage, however, is that gas phase pressurization to

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levels necessary for physiologic culture stresses substantially alters pO2 and pCO2 in the liquid culture medium, requiring compensatory medium treatment steps[39]. Also, perhaps more significantly, the *in vivo* stress states of most musculoskeletal tissues are appreciably non-equiaxial. To overcome these disadvantages, a number of groups accept the trade-offs (and usually much greater technical difficulty) associated with direct platen loading[11,12,13,17,18,23,46,53].

Devices involving controlled distension of deformable substrates have many advantages and are now in widespread use. The roots of this approach trace back to the simple static loading devices constructed by Somjen et al.[50] and by Meikle et al.[34]. A great jump in sophistication occurred with the work of Leung et al.[32], who devised a plunger/linkage arrangement for a series of small loading frames, wherein oscillatory linear displacements were input to clamps attached to the ends of rectangular elastin substrate membranes prepared from bovine aortic tissue. Nominal strains of 10% were delivered at just below one Hz, for periods of up to 56 hours, with marked effects on protein and DNA synthesis by rabbit aortic smooth muscle cells seeded on the elastin strips. However, because of grip end-effects and the anisotropy and geometric irregularity of the natural elastin substrate, local strains were probably very heterogeneous. A technically improved but conceptually similar arrangement was later used by Ives et al.[28], whose interests were on both substrate distension and medium fluid shear stress effects. They substituted a simple spring-loaded pulley/cable arrangement for the complex piston/linkage system, and as a substrate used an artificial material (polyetherurethane urea) which was cast into precise rectangular strips of 0.2 mm thickness. Dewitt and colleagues[16] also used a motor/cam arrangement to achieve cyclic tension, but opted to apply their loadings directly to clamped chondrocyte culture sheets (i.e., no substrate). While platen-to-platen deformations could be kept precisely uniform, their no-substrate approach is obviously limited to situations involving intact culture sheets. Also, the mechanical stimulus is unavoidably confounded by the need to remove the culture from its initial "growth" flask, and to mount it within the grips of the mechanical testing flask.

Murray and Rushton[35] formed a series of four rectangular culture wells by sealing Permanox slabs to a polycarbonate base sheet, which was in turn tensioned by an outrigger arm linked to a stepper motor-driven lead screw. A computer was programmed to deliver motor command signal pulses resulting in "ramped square wave" inputs involving strain rates of 0.01 sec-1 for multi-hour periods. They did not report substrate strain measurements within their culture wells, but local structural reinforcement by the relatively large Permanox well sides suggests that substrate strains within the wells were very inhomogeneous, and probably much smaller than the overall average strain in the base sheet. Another rectangular-well device, but one lending itself to much better quantitation of input strains, is that recently introduced by the Ulm group[36]. They use individually cast silicone rubber dishes which are gripped by brackets attached to cams driven by a DC motor. Optical measurements of grids ruled on the base of a calibration dish demonstrate an impressively homogeneous distribution of both axial and transverse (Poisson effect) strains. Jones et al.[29] used two distinct systems. One was a four-point bending arrangement using rectangular culture plates made either of glass or polycarbonate, suspended within a nutrient fluid bath in a 40x40 mm silicone rubber culture well. This system is noteworthy in that it permitted study of either tensile or compressive strains (or both), depending on the side(s) of the substrate plate being loaded. Also, this system included strain gauge readout of the instantaneous substrate strain, which was verified as being reasonably homogeneous over the entire culture area. Their second system, designed to avoid macroscopic motion of target cells in order to facilitate microscopy and electrophysiological measurement, used a plastic ribbon substrate distended by two symmetrically-moving plates driven by motorized cams.

At present, devices in which strains are imposed by distensions of deformable circular substrates represent the most widely used class of mechano-stimulatory systems. The first report of a device of this type was by Hasegawa et al.[25], who studied DNA and protein synthesis in rat calvarial bone cell cultures. They used a standard Petriperm culture dish whose bottom was induced to deform by being pressed against a convex template by a static weight. Both a single-dish version and 20-dish version of this system were developed. These investigators noted that the imposed distensions could in principle be controlled by template curvature. However, while the specific template geometry and static weight used in their experiments were reported, the strain level input to the cultured cells was neither measured nor estimated. Their rather simplistic approach to mechanical analysis was typified by the (incorrect[60]) assertion that stretching was uniform throughout the dish base because the platen was "uniformly curved".

Flexible-bottomed circular cell culture plates designed deliberately for mechanical stimulus studies were first introduced in 1985 by Banes et al.[3]. These investigators used a PC-based programmable loading device (the precursor of the present Flexercell system) to induce culture strain by means of vacuum cyclically applied to the underside of the plates. Pertinent parameters of system performance (vacuum magnitude, waveform, maximum stretch,

frequency, duty cycle, etc.) were reported. Because of its programmability and relative ease of set-up and operation, the system lent itself to a wide range of applications. Several units were soon fabricated for use by investigators affiliated with the developers' research group, and the system was commercialized in 1987. As of the date of this writing, over 90 units are in service. Biologic applications of this system initially outpaced rigorous mechanical characterization, although several engineering studies recently appeared to redress this imbalance. These include experimental measurements of the radial strain distribution on the substrate culture surface[19], a linearized quasistatic isotropic finite element model of substrate strain anisotropy and heterogeneity[20], a dynamic and geometrically nonlinear finite element model of the substrate plus nutrient medium[41], and a combined experimental/computational characterization of hyperelastic constitutive behavior of the substrate[40].

Another differential pressure flexible-membrane system, driven by positive pressure rather than by vacuum, was introduced by the bioengineering group at the University of Pennsylvania[61]. Circular membranes cut from 100μm polyurethane sheets were clamped peripherally by O-rings, and deflected by solenoid valve mediation of pressure in a central reservoir. To their credit, these investigators very thoroughly characterized the major aspects of their system's mechanical performance, including static calibration of pressure versus deflection at the membrane center (pole), optical probe measurements of transient membrane pole deflections, silicone rubber castings of the membrane deflection contour, and experimental validation of a closed-form analytical expression relating pole deflection to radial strain. The system has subsequently seen service in a number of cell culture applications by this group, primarily in the cardiovascular area[22,62]. A modified version of this device was developed by the orthopaedic group at that same institution using a motor-driven reciprocating pump, polyurethane (Pellethane) membranes, polysulfone culture well walls, and a redesigned arrangement for clamping the periphery of the membranes[7].

Under quasistatic differential pressure, the radial strain distribution across a peripherally tethered circular membrane is approximately homogeneous[60], albeit prestrain-dependent[8]. The circumferential strain, however, varies from zero at the periphery to a maximum (equal to the radial strain) at the pole. The inherent strain heterogeneity and anisotropy in differentially pressurized membrane systems recently motivated alternative approaches, most notably platen abutment. Of course, achieving strain isotropy and homogeneity depends upon appropriate platen geometry and platen/membrane interface kinematics. It is noteworthy that in several earlier abutment systems involving spherical cap or flat-ended platens, achieving homogeneous and equi-biaxial membrane strains was not a stated design objective[1,25,55].

Working independently, both Schaffer et al.[49] and Hung and Williams[26] recently devised circular ring platens which peripherally stretch a central portion of the membrane by means of a lubricated interface (idealized as frictionless) between the platen and the membrane. The fractional area of the initial membrane surface experiencing homogeneous equi-biaxial strain necessarily diminishes during the loading pulse (i.e., ever more of the membrane slips radially outward over the frictionless platen ring as the platen advances axially). However, all points on the membrane which remain inside the platen contact ring experience nearly equibiaxial and homogeneous strain, a very important advance.

Futher concerns involve fluid/substrate interactions. Macroscopic culture displacement in a direction transverse to the (unloaded) substrate plane is a common attribute of both differential-pressure and platen-abutment systems. Peak displacement magnitudes in the multimillimeter range are common, the specifics depending on system design and desired culture strain. As the substrate and culture layer oscillate, the nutrient fluid medium overlying the culture layer must also displace. The associated fluid motions impart both normal and shear stresses to the culture layer. The normal stresses (inertial) arise primarily in reaction to the imposed fluid accelerations, whereas the shear stresses (viscous) arise primarily due to velocity gradients within the medium.

Very little is known about the nutrient medium fluid dynamics in these mechano-stimulatory culture systems, which is perhaps not surprising given the limited mechanical characterization usually accorded these devices. However, as noted by Schaffer et al., "Ultimately, fluid flow and shear stress must be considered as potential transduction mechanisms for deformation induced cell responses in any cell deformation system." For 10% peak strains in their particular system, which required five mm transverse displacements of the substrate membrane, those investigators estimated (viscous) fluid shear stresses on the order of 10 dynes/cm^2 (0.5, 6.0, and 17 dynes/cm^2 at 1, 5, and 10 Hz, respectively), values which are well into the range sufficient to cause changes in cell shape and in prostaglandin production[48]. No corresponding estimates for (inertial) normal stresses were reported; however, these are not difficult to estimate. Inducing five mm peak sinusoidal displacements for a five mm thick mass (typical medium depth) having a density of 1 gm/cm^3, requires peak transverse normal stresses of 19.7, 493, and 1970 dynes/cm^2 for frequencies of 1, 5, and 10 Hz, respectively.

Clearly, the potential for nutrient medium fluid effects to impart confounding stresses to the culture layer depends on the specifics of the experiment being conducted (i.e., cell type, apparatus design, stimulus frequency, substrate strain, etc). In the extreme limit of very slow loading frequencies and/or very small peak strains, this phenomenon may not be physically or biologically consequential. However, the thresholds involved are presently uncertain, and may be disturbingly low. For example, Olesen et al.[38] demonstrated that shear stresses as small as 0.70 dynes/cm^2 could half-maximally activate (K+) ion selective channels in the membranes of cultured bovine aortic endothelial cells. (The entire activation range was 0.2 to 17 dynes/cm^2). Reich et al.[42] showed that cultured osteoblasts underwent 6- to 12-fold elevations in levels of cAMP (an important second messenger) when subjected to fluid shear stresses in the range of 0.1 to 2.5 dynes/cm^2. And Lansman et al.[31] recorded rapid and substantial responses from several types of cation-specific stretch activated membrane ion channels for suction pipette pressure differentials in the range of 1.3 to 2.7 dynes/cm^2.

To date, most culture work dealing with fluid interactions (including computational fluid dynamics models[15,47]) involves cardiovascular cells and tissues[37]. However, there is good reason to suspect that musculoskeletal cells such as osteoblasts may respond analogously, as they possess many of the same (plausible) mechanoreceptors[14]. Indeed, Reich et al.[42] recently showed that osteoblasts in culture are three times more sensitive to fluid flow stimulation than are human vascular endothelial cells. However, regardless of whether or not the transduction and response mechanisms turn out to be similar, there is virtually no doubt that mechanical stimulation of musculoskeletal cell cultures will remain an important research area for the forseeable future. Indeed, given the emerging evidence for a possible mechano-stimulatory role of high-frequency strain components *in vivo*[45,54], we may witness an increase in the number of *in vitro* studies using loading paradigms that are potentially susceptible to confounding mechanical effects from the fluid medium.

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DEVELOPMENT OF THE OSTEOBLAST PHENOTYPE: MOLECULAR MECHANISMS MEDIATING OSTEOBLAST GROWTH AND DIFFERENTIATION

Jane B. Lian, Ph.D.
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ABSTRACT

The formation of bone tissue involves multiple activities of the osteoblast. The combined application of molecular, biochemical, histochemical and ultrastructural approaches has defined stages in the development of the osteoblast phenotype with each subpopulation of cells exhibiting unique morphologic and functional properties in relation to the ordered deposition of the mineralized bone extracellular matrix (ECM). Peak levels of expressed genes reflect a maturational sequence of osteoblast growth and differentiation characterized by three principal periods: proliferation, ECM maturation and mineralization. A plethora of new information in the past several years provides the basis for insight into molecular mechanisms regulating the development and activities of differentiating osteoblasts. These new concepts will be discussed within the context of understanding cellular responses of bone tissue. To be considered are the following: 1) maturational stages of the osteoblast reflected by the selective expression of transcription factors (e.g., oncogenes, cyclins, homeodomain proteins) and phenotypic genes that provide signals for differentiation through the osteoblast lineage; 2) role of the extracellular matrix in mediating osteoblast growth and differentiation; 3) osteoblast stage specific responses to physiologic mediators (e.g., growth factors and hormones); 4) the developmentally regulated expression and selective responses of osteoblast phenotypic genes are supported by cooperative, synergistic and/or antagonistic activities at multiple basal and enhancer or suppressor sequences in gene promoters; and 5) deregulation of these control mechanisms in transformed osteoblasts and osteosarcoma cells.

I. INTRODUCTION

Understanding the factors regulating bone growth, the continued remodelling of bone throughout life and the regeneration of injured tissue are basic biological questions and concerns of today's clinician for the treatment of bone related disorders. Practical applications in orthopedics include knowledge of bone formation and resorption events related to abnormalities in skeletal development, fracture repair, metabolic bone diseases and implant stability. To allow for a rational intervention of these processes clinically, one must gain knowledge of the mechanisms that regulate tissue formation, maturation and stability. One fundamental approach has been to isolate the bone cells which in culture exhibit tissue-specific metabolic responses and biosynthesis of structural components of bone. From these studies, several classes of factors have been identified that allow us to define regulatory mechanisms operative in control of growth and differentiation of the cell osteoblasts and/or osteoprogenitors. These include but are not restricted to bone morphogenic proteins[27], cell growth factors[23], hormones[98], cytokine modulators[57] and mechanical physical forces[22,136]. It is also recognized that a broad spectrum of physiologic mediators of bone formation have differential and highly selective effects on the numerous cells involved in osseous tissue formation and turnover. A clear understanding of effects on osteoblasts is somewhat compromised by species differences or the experimental system, although such variations are now being appreciated as related to the stage of cellular maturation or differentiation which impacts on the responsiveness of the osteoblast to physiologic modulators of bone cell functions.

The focus of this review is a description of the sequelae of events associated with osteoblast growth and the progression of differentiation as related to formation and organization of bone tissue by normal diploid cells derived from fetal bone *in vitro*. For each maturational stage, characteristic activities and responses to physiologic mediators of osteoblast growth and differentiation will be described. The signalling pathways and molecular mechanisms mediating development of the osteoblast phenotype will be described as these approaches provide a basis for development of specific modes of therapeutic intervention in the treatment of skeletal disorders.

II. DEVELOPMENT OF THE OSTEOBLAST PHENOTYPE

For many years, bone was defined anatomically and examined largely in a descriptive manner by ultrastructural analysis and by biochemical and histochemical methods[21,123,139]. These studies provided the basis for our understanding of bone tissue organization and orchestration of the progressive recruitment, proliferation and

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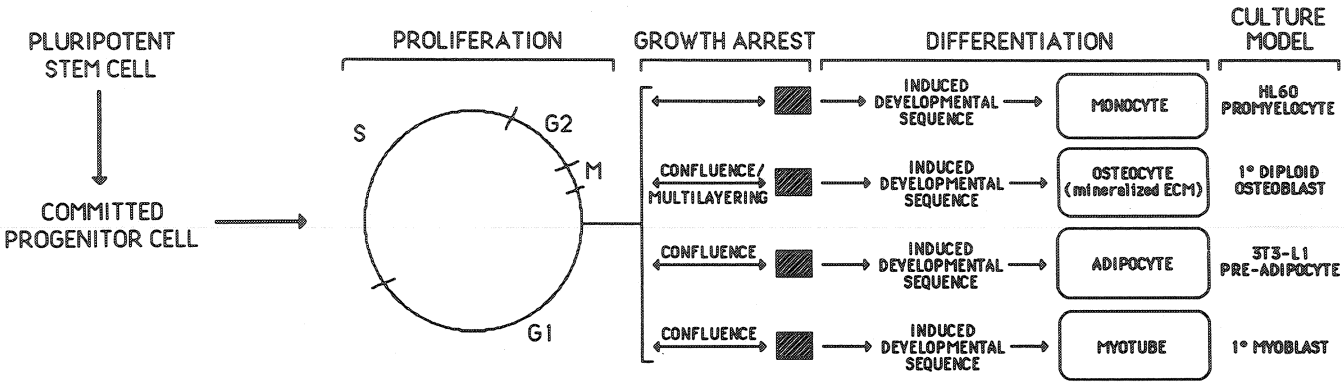


Fig. 1. Schematic representation of the events associated with progressive expression of monocyte, granulocyte, osteoblast, adipocyte, and myotube phenotypes. Initially the cells (HL-60 promyelocytic leukemia cells, primary cultures of embryonic calvarial osteoblasts, 3T3-L1 preadipocytes, or myoblasts) actively proliferate, expressing cell cycle and cell growth-regulated genes as well as genes encoding extracellular matrix proteins. After growth arrest, a developmental sequence involving the sequential and selective expression of genes that results in the differentiated cell and tissue phenotype occurs. Completion of the proliferation period marks an important transition point where expression of tissue-specific genes, often functionally coupled to the down-regulation of proliferation, is initiated.

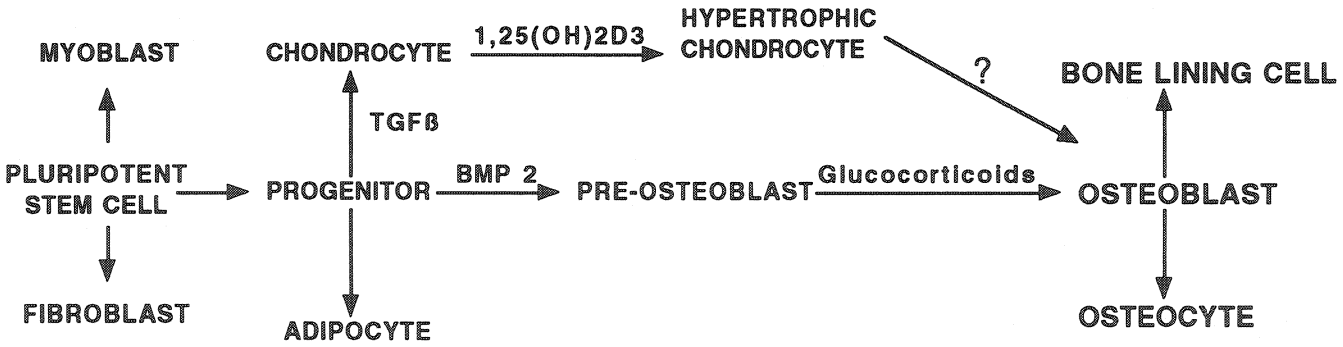


Fig. 2. The osteoblast differentiation pathway. Progression through the osteoblast lineage from a pluripotent mesenchymal stem cell which has multiple options is illustrated. Several physiologic mediators including, but not limited to, transforming growth factor b (TGFb), the bone morphogenic protein 2 (BMP-2) and glucocorticoids, which have been documented to influence progression through the chondrocyte or osteoblast phenotype, are indicated. A question mark placed between the hypertrophic chondrocyte and osteoblast reflects recent reports which have indicated the hypertrophic chondrocyte can further differentiate to an osteoblast-like cell expressing genes observed in mature osteoblasts. The cuboidal osteoblast that synthesizes bone matrix will further differentiate to either an osteocyte when enveloped in mineralized matrix or to a flattened lining cell on a quiescent surface of mineralized bone. Each of these subpopulations of osteoblasts exhibit different properties and express osteoblast phenotypic genes to varying extents (see text for details).

differentiation of the various cellular components of bone tissue. Now, complemented by an increased knowledge of molecular mechanisms that are associated with and regulate expression of genes encoding phenotypic components of bone and those which may control the progressive development and maturation of the bone cell phenotype, our understanding of bone cell and tissue differentiation is rapidly expanding.

It has been recognized that defining mechanisms operative in the development and maintenance of the osteoblast phenotype necessitates comprehensive knowledge of cell growth and tissue-specific genes expressed with regard to: 1) the time course and extent of expression; 2) temporal vs. functionally coupled relationships; 3) control of gene expression at both transcriptional and post-transcriptional levels; and 4) signalling pathways and macromolecules that integrate the activities of physiological regulatory mediators involved in lineage development of the osteoblast.

A functional relationship between cell growth and the initiation and progression of events associated with differentiation has been viewed as a fundamental question by developmental biologists for more than a century. In the case of bone, as observed with other systems (Figure 1), the relationship of growth and differentiation must be maintained and stringently regulated, both during development and throughout the life of the organism to support tissue remodeling. Understanding biological regulatory mechanisms that support bone cell development within the context of the proliferation/differentiation relationship provides a viable basis for addressing skeletal disorders and particularly bone cell cancer, where aberrations in the proliferation/differentiation relationship may facilitate both diagnosis and evaluation of targeted therapy.

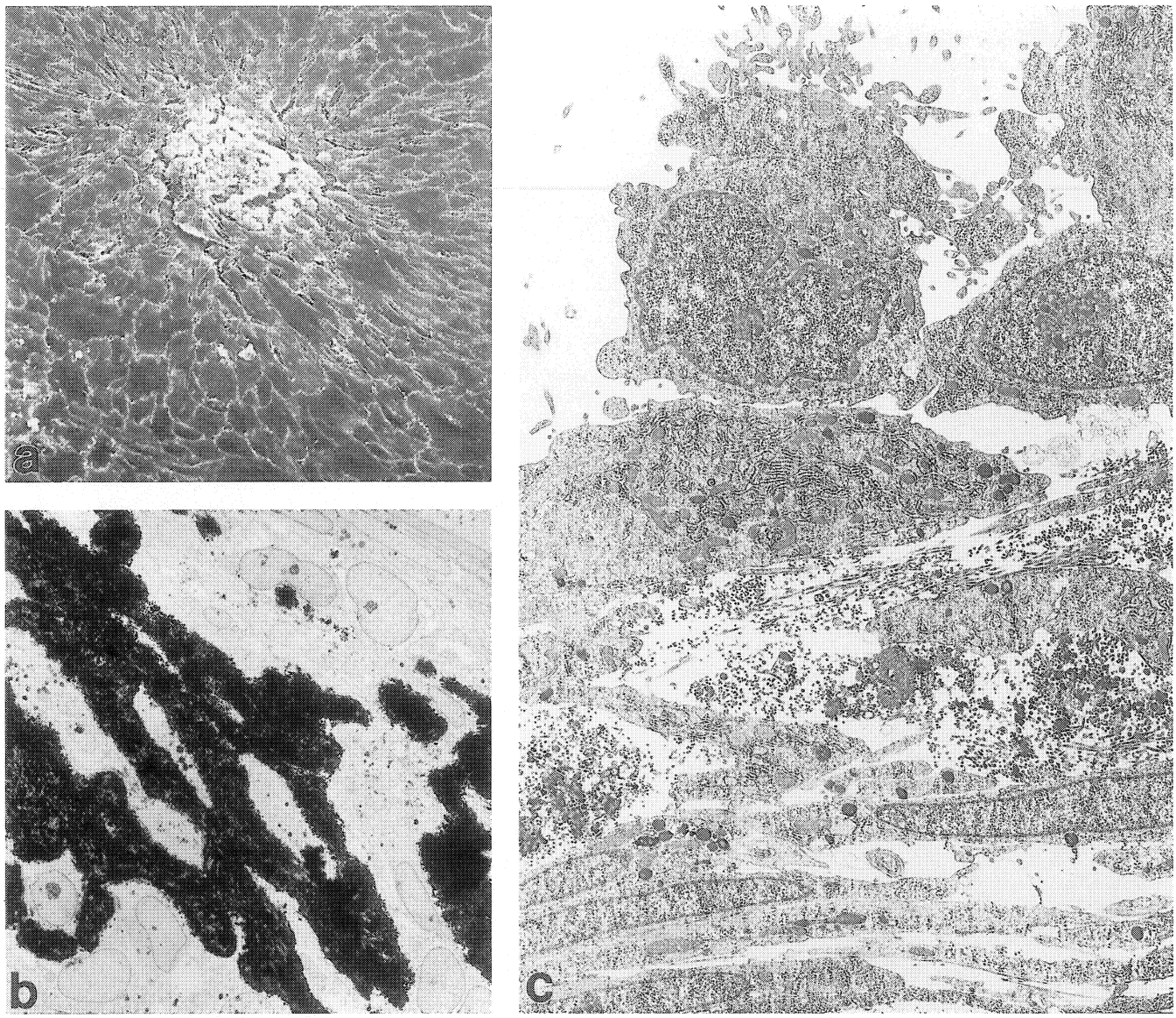


Fig. 3. Morphology and ultrastructure of fetal rat calvaria-derived osteoblast cultures. (a) Scanning electron micrograph showing cuboidal osteoblasts both at monolayer confluency and in multi-layers forming a typical bone nodule having a mineralized extracellular matrix, 100X. (b) Low power transmission electron micrograph of an undemineralized sectioned bone nodule to illustrate the mineralized extracellular matrix surrounding osteoblasts. Mineral deposits are hydroxyapatite crystals associated with collagen fibers, 500X. (c) Transmission electron micrograph of a demineralized nodule in cross-section to reveal the orthogonal layers of collagen interspersed between osteoblasts. Note the large cuboidal surface osteoblast having a large central nucleus rich in ribosomes and with extensive Golgi, 8000X.

It is now generally accepted that the progenitor stem cell of the osteoblast is a pluripotent mesenchymal fibroblast which prior to commitment can develop as an osteoblast, chondrocyte or other phenotypes[46]. An important aspect of bone cell biology is to experimentally address the regulatory events related to the recruitment and commitment of pluripotent mesenchymal cells into the developmental pathway which initially restricts their options for specialization to either the osteoblast and chondrocyte pathways and subsequently to solely the osteoblast phenotype (Figure 2). Potential cell culture systems to study growth and differentiation of progenitors include recent use of bone marrow cultures which offer the possibility of examining events associated with stem cell differentiation to osteoblasts[28,45,86,135,191]. Particularly successful has been culture of human derived marrow cells that can be induced to differentiate to osteoblasts producing a bone like matrix by the synthetic glucocorticoid, dexamethasone, or by the bone morphogenic protein, BMP-2[51,76].

A. The ordered expression of genes during development of the osteoblast phenotype

The development of methods for culture of normal diploid calvarial-derived osteoblasts under conditions which support development of a tissue-like organization[16,141] (Figure 3) similar to embryonic bone provided the basis for experimentally addressing the proliferation/ differentiation relationship within the context of physiological regulation[131]. By trypsin-collagenase digestion of fetal rat calvaria, a population of cells from the third sequential digest will express significant levels of osteoblast phenotypic markers including alkaline phosphatase, osteopontin and osteocalcin mRNA[4,131]. When placed into culture these bone cell genes are downregulated and nearly every plated cell initiates proliferation as indicated from ^{3}H thymidine autoradiography and *in situ* hybridization studies using the H4 histone gene as a probe which is coupled to DNA synthesis (Figure 4A). Only a few osteocytes released, having a distinct morphology, will not reinitiate proliferation[178]. The osteoblasts proliferate forming multilayers of cells as sheets[48,72,78] or focal nodules[4,6]. When proliferation ceases, alkaline phosphatase levels increase sufficiently for histochemical detection. An ordered deposition of mineral is initiated within the extracellular matrix of these nodules resulting in the development of a bone tissue-like organization, with an orthogonal arrangement of collagen layers between osteoblasts and a mineralized extracellular matrix (Figure 3).

The sequential expression of cell growth and tissue-specific genes has been mapped by immunocytochemical methods[4,108], Northern blot analysis[9,131] and *in situ* hybridization[100,141] during progressive development of the bone cell phenotype from a proliferating cell to a mature osteocytic cell in a mineralized Type I collagen extracellular matrix. This temporal sequence of gene expression has defined three distinct periods: growth (proliferation) and extracellular matrix biosynthesis; extracellular matrix development, maturation and organization; and extracellular matrix mineralization (Figure 4B).

During the first 10 to 12 days of culture following isolation of fetal rat calvarial-derived osteoblasts, a period of active proliferation is reflected by mitotic activity with expression of cell cycle (e.g. histone) and cell growth (e.g. c-myc, c-fos, and c-jun) regulated genes. These genes encode proteins that support proliferation by functioning as transactivation factors in the case of c-myc and c-fos and as proteins that play a primary role in packaging newly replicated DNA into chromatin in the case of histones. Modifications in expression of proliferation related genes, e.g. c-fos or c-src expression *in vivo* (in transgenic animals), results in altered bone formation[58,75,147,158] indicating the importance of their regulated expression during the proliferative period for control of cell growth as well as for control of genes later during osteoblast development that directly involve bone cell differentiation. This concept is further supported by evidence for the selective expression of fos and jun related family members through the course of osteoblast differentiation[114].

During this proliferation period, and fundamental to development of the bone cell phenotype, several genes associated with formation of the extracellular matrix (Type I collagen, fibronectin, and TGFβ) are actively expressed and then gradually decline with collagen mRNA being maintained at a low basal level during subsequent stages of osteoblast differentiation. The accumulation of collagen contributes, in part, to the cessation of cell growth. Immediately following the down-regulation of proliferation, proteins associated with bone cell phenotype are detected. For example, alkaline phosphatase enzyme activity and mRNA are increased greater than 10-fold. At this time, a differentiation-specific histone gene is expressed[30,160]. During the immediate post-proliferative period (from 12 to 18 days), the extracellular matrix undergoes a series of modifications in composition and organization that renders it competent for mineralization. As the cultures progress into the mineralization stage, all cells become alkaline phosphatase positive histochemically (Figure 3). Histochemical detection of APase is considered one of the earliest phenotypic markers of the osteoblast lineage. In heavily mineralized cultures, cellular levels of alkaline phosphatase mRNA decline (Figure 4B). At this time maximal levels of collagenase gene expression are observed and may relate to a remodelling of the matrix to support tissue organization and mineral deposition[154]. Apoptotic cells are also detected suggesting programmed cell death may provide a mechanism for regulating the number of surface osteoblasts that further differentiate to osteocytes[102].

With the onset of mineralization, several other bone-expressed genes are induced to maximal levels, paralleling the accumulation of mineral. These are bone-synthesized proteins known to associate with the mineralized matrix *in vivo*[40,43,61,189] including bone sialoprotein[119], osteopontin and osteocalcin[48,131]. Osteopontin is expressed both during the period of active proliferation (at 25% of maximal levels), decreases post-proliferatively and exhibits induction at the onset of mineralization, achieving peak levels of expression during mineralization (days 16 to 20). This pattern of osteopontin expression has been observed in other osteoblastic developmental systems[49,165] and may reflect multiple functional properties. Increased osteopontin expression can occur following serum stimulation of quiescent fibroblasts, oncogene transformation or phorbol ester treatment of fibroblasts[31]. Here one can speculate that proliferation or tumorigenic related functions of osteopontin may be related to control of relationships be-

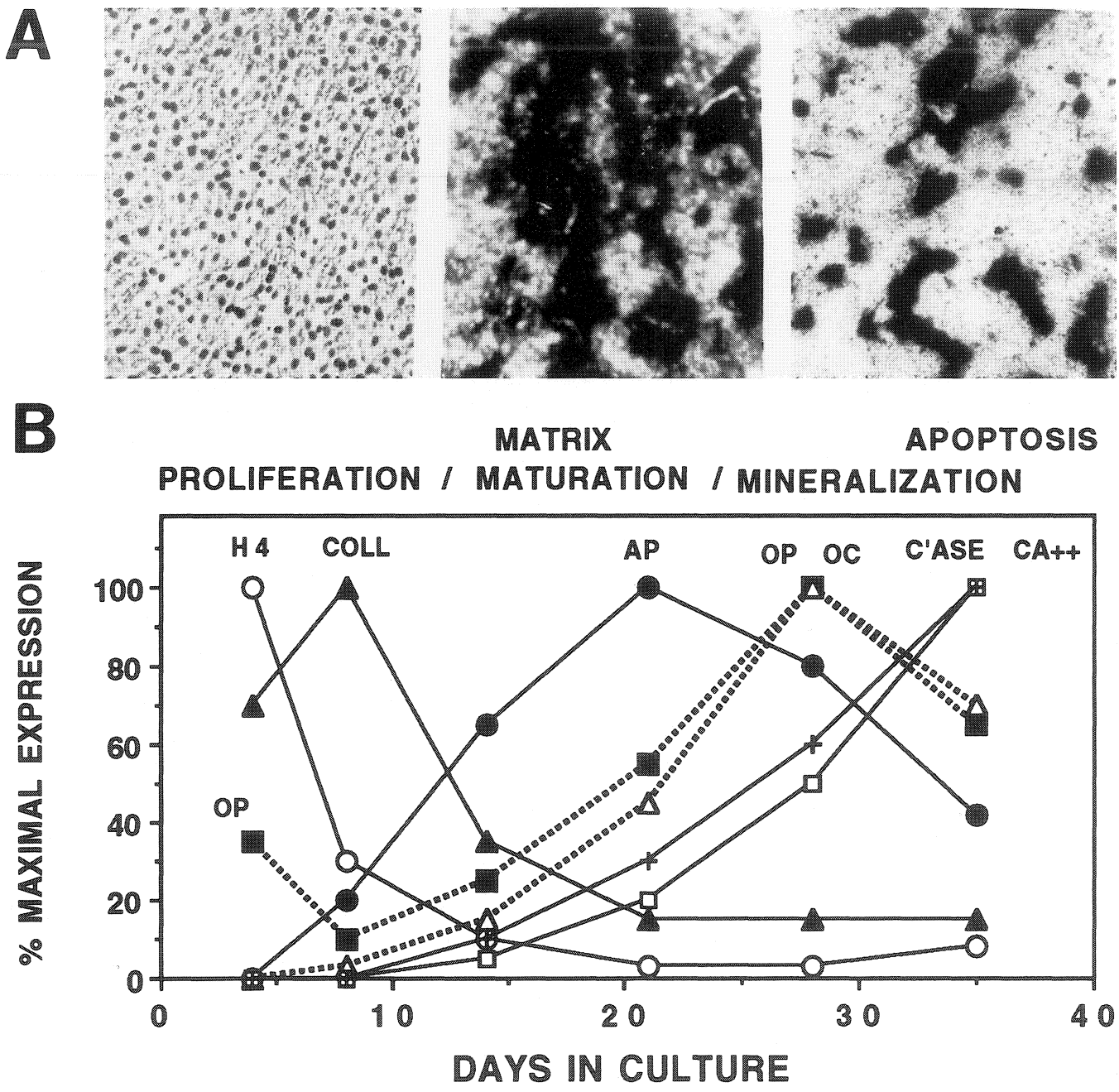


Fig. 4 The osteoblast development sequence. (A) Histochemical staining of fetal rat calvaria derived osteoblast cultures during the development of in vitro formed bone-like tissue. Left panel, tritiated thymidine autoradiography illustrating the proliferation period; middle panel represents alkaline phosphatase staining demonstrating nearly every cell is positive; and the right panel represents a typical von Kossa silver stain plate revealing mineralized bone nodules throughout the culture dish, 10X. (B) Temporal expression of cell growth and osteoblast phenotype related genes during 35 days of culture. Cells were harvested on the indicated days and total cellular RNA prepared for assay of various transcripts by Northern blot analysis. The resulting blots were quantitated by scanning densitometry and the results plotted relative to the maximal expression of each transcript. Conditions and origin of the probes are detailed in Owen et al., 1990 and Shalhoub et al., 1992. In the growth period, histone H4 collagen (COLL), and osteopontin (OP) are shown. The peak levels of alkaline phosphatase mRNA (AP) represent the matrix maturation period. In the mineralization period, osteopontin (OP) and osteocalcin (OC) reach their peak levels. The increase in mRNA transcripts of OC and OP during the culture period reflect calcium (Ca++) deposition. The increase and peak levels of collagenase (C'ASE) are related to remodeling or editing of the extracellular matrix. Apoptotic cells are observed during the mineralization period (see text for details).

tween cells and extracellular matrices, particularly in light of the arg-gly-asp containing sequence that mediates cell attachment[130]. Consistent with high levels of osteopontin expression during the mineralization period are the calcium binding properties of this acidic glycoprotein containing O-phosphoserine[53]. Several studies indicate osteopontin interact with osteoclasts implicating this phosphoprotein in the resorption process[115,116,144].

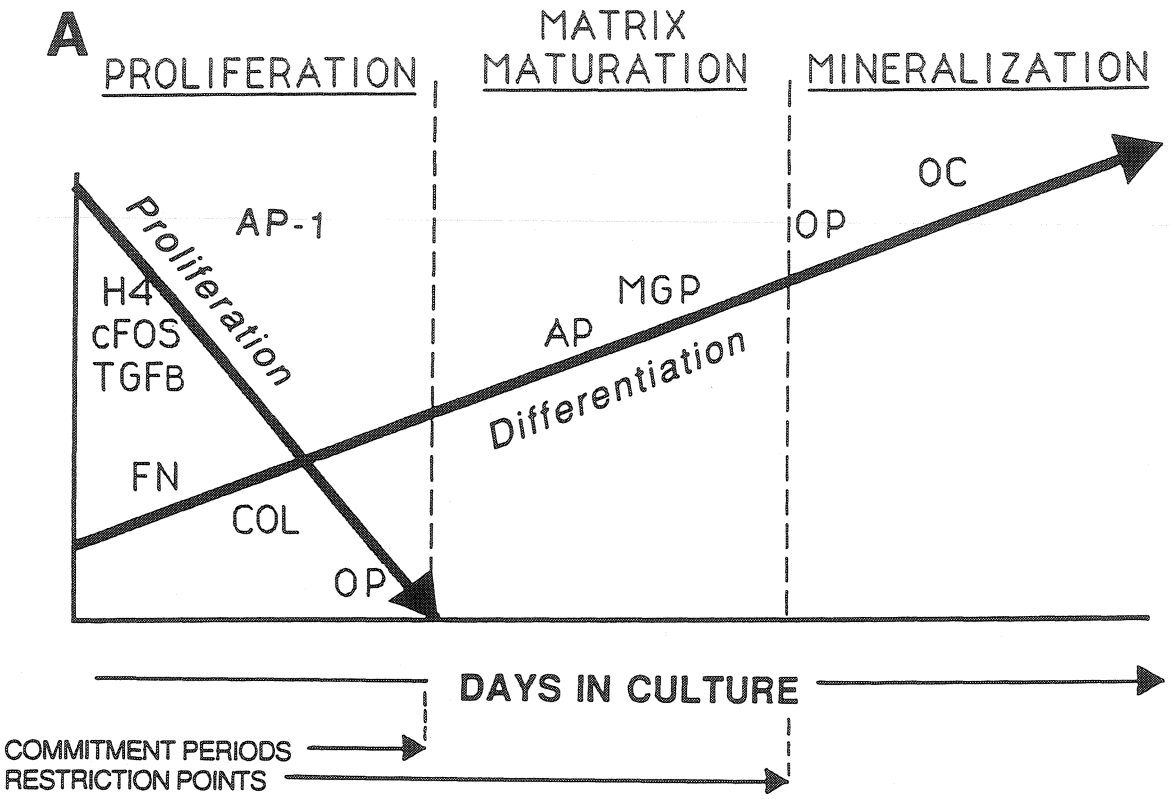
The vitamin K-dependent protein, osteocalcin (bone Gla protein), in contrast to osteopontin, is expressed only post-proliferatively with the onset of nodule formation. This 5.7kD calcium-binding protein, characterized by 3-gammacarboxy-glutamic acid residues (Gla), binds tightly to hydroxyapatite and is maximally expressed with mineralization of the extracellular matrix *in vivo*[61] and *in vitro*[131]. Osteocalcin mRNA and synthesis correlates (0.92) to calcium deposition *in vitro* in rat osteoblast cultures[4], similar to expression and protein accumulation in the bone extracellular matrix *in vivo*[61,187]. Several modifications of culture conditions of fetal rat calvarial derived osteoblasts[131] demonstrate that induction of high osteocalcin and osteopontin mRNA levels are dependent upon formation of a mineralized extracellular matrix. However, post-natal derived cells or osteoblasts from more mature bone exhibit osteocalcin expression in non-mineralizing cultures. Several studies suggest osteocalcin may contribute to either regulation of mineral deposition or turnover of the mineral phase in bone. *In vitro* osteocalcin is an inhibitor of mineral nucleation[19,146]. *In vivo* increased synthesis by pharmacologic doses of $1,25(OH)_2D_3$ results in undermineralization[64], while absence of osteocalcin accumulation in bone (induced by warfarin anticoagulants) leads to punctate calcifications[39,68]. Other studies demonstrate osteocalcin serves as a bone matrix signal that promotes osteoblast differentiation and acivation demonstrated in several biological assays *in vivo* [33,55,56,89,93,185] and *in vitro*[10,29,90,99]. Thus, expression late in the osteoblast development sequence[91,94] reflects osteocalcin as a marker of the mature osteoblast, consistent with a possible role for the synthesis and binding of osteocalcin to mineral for participation in bone resorption related events. Clinically, serum osteocalcin levels reflect bone turnover[92], and the gene is regulated by hormones (e.g. $1,25(OH)_2D_3$) and growth factors (e.g. TGFβ) involved in bone turnover (see next section).

Analysis of these osteoblasts at the single cell resolution by *in situ* hybridization for expressed genes indicates that the temporal pattern of gene expression does not occur synchronously in all cells[140,141] but is related to tissue organization. For example, osteocalcin expressing cells are found only within mineralizing nodules; in contrast, alkaline phosphatase positive cells occur between nodules. The biological relevance of the osteoblast culture system as a model for bone cell differentiation is supported by a sequence of gene expression (cell growth and osteoblast related genes) that is similar to the pattern of gene expression and tissue distribution determined during fetal calvarial development *in vivo*[192] and in neonatal bones[104,126,148,187]. The significance of the osteoblast developmental sequence is that it provides a framework for evaluating aberrations in osteoblast growth or differentiation responses in bone disorders and allows for development of targeted therapeutic approaches.

Several striking examples illustrate therapeutic approaches that can be extrapolated from an understanding of the osteoblast development sequence. The effects of substances including caffeine[8], warfarin[39,68] and dioxanes[1], which have caused abnormalities in skeletal development were examined in cultured osteoblasts[11,52,170]. Each inhibited the osteoblast developmental sequence *in vitro*, but by impinging on different regulatory mechanisms. In other studies, it has been shown that potential defects in bone formation *in vivo* can be reiterated through the osteoblast *in vitro*. For example, osteoblast cultures established from calvaria of two rat osteopetrotic mutants, the tl/tl and op/op, show alterations in expression of genes and nodule formation. For the tl mutant derived osteoblasts, the developmental sequence is abbreviated compared to cells from normal littermates[74]. Mineralization occurs prematurely in the osteoblasts derived from osteopetrotic calvaria, and some of the abnormalities in the developmental pattern of osteoblast genes expressed *in vivo*[152] that contribute to the sclerotic features of the disease are retained *in vitro*[74].

B. Two transition-restriction points during development of the osteoblast phenotype characterize the proliferation/differentiation relationship.

The sequential and stringently regulated expression of genes that define three principal periods of osteoblast phenotype development (proliferation, extracellular matrix development and maturation, and mineralization) is schematically illustrated in Figure 5 as a reciprocal and functionally coupled relationship between proliferation and differentiation. Two transition points are key elements of this temporal expression of genes that support cell growth and differentiation: the first transition point, at the completion of the proliferation period when genes for cell cycle and cell growth control are down-regulated and expression of genes encoding proteins for extracellular matrix maturation is initiated; and the second, at the onset of extracellular matrix mineralization. These transitions have been experimentally established[131] and functionally defined as restriction points during osteoblast differentiation to which developmental expression of genes can proceed but cannot pass without additional cellular signalling[reviewed in 163,164]. Thus, establish-



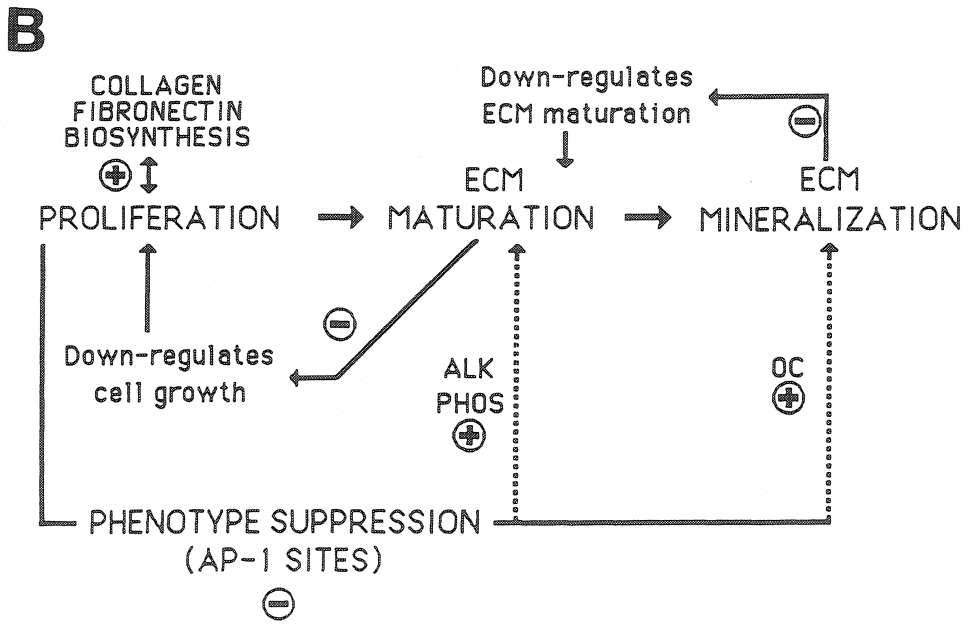


Fig. 5. Reciprocal and functionally coupled relationship between cell growth and differentiation-related gene expression. (A) These relationships are schematically illustrated as arrows representing changes in expression of cell cycle- and cell growth-regulated genes (proliferation arrow) and genes associated with the maturation (differentiation arrow) of the osteoblast phenotype as the extracellular matrix develops and mineralizes in normal diploid cell cultures. Here, the three principal periods of the osteoblast developmental sequence are designated within broken vertical lines (proliferation, matrix development and maturation, and mineralization). These broken lines indicate the two experimentally established principal transition points in the developmental sequence exhibited by normal diploid osteoblasts during the progressive acquisition of the bone cell phenotype. The first is at the completion of proliferation when genes associated with matrix development and maturation are up-regulated, and the second occurs at the onset of extracellular matrix mineralization. (B) A series of signalling mechanisms are illustrated whereby the proliferation period supports the synthesis of a Type I collagen-fibronectin ECM, which continues to mature and mineralize. The formation of this matrix down-regulates proliferation, and matrix mineralization down-regulates the expression of genes associated with the ECM maturation period. The occupancy of AP-1 sites in the osteocalcin and the alkaline phosphatase gene promoters by Fos-Jun and/or related proteins are proposed to suppress both basal and vitamin D-induced expression before upregulation post-proliferatively (phenotype suppression).

ing the basis of cellular competency for progression toward development of the mature osteoblast phenotype necessitates identification of the signalling pathways operative at the developmental transition points by which genes are selectively activated and/or suppressed. The absence during the proliferation period of expression of genes observed in post-proliferative mature osteoblasts is called "phenotype suppression." The model is supported by binding of regulatory factors abundant in proliferating osteoblasts (e.g. oncogenes[94,95,114] encoded or helix-loop-helix proteins[118,129]) to regulatory elements of genes expressed later in development (see Section IV).

By abbreviating or extending either the proliferation or differentiation period, one can determine which genes associated with extracellular matrix biosynthesis, maturation or mineralization are prematurely upregulated or delayed in initiation of expression. The biochemical modifications that include inhibition of proliferation, decreased extracellular matrix biosynthesis, delayed extracellular matrix mineralization, and accelerated differentiation by glucocorticoid on culture in collagen matrices provided support for several signalling pathways that promote differentiation. Inhibition of proliferation upregulates expression of genes that are expressed only during progression of the osteoblast developmental sequence up to the stage where mineralization is initiated (e.g. alkaline phosphatase and osteopontin but not osteocalcin). Additionally, there is evidence for the concept that expression of at least a second set of genes is not directly coupled to the down-regulation of proliferation, but rather to development of the more differentiated osteoblast in a mineralized matrix. Inhibition of collagenous extracellular matrix formation prevents induction of alkaline phosphatase levels and mineralization. In the absence of mineralization, osteopontin and osteocalcin are not induced to high levels and alkaline phosphatase does not decline. From these studies, one can postulate that proliferation is functionally related to the synthesis of a bone specific extracellular matrix and that the maturation and organization of the extracellular matrix contributes to the shutdown of proliferation. This then promotes expression of genes that render the matrix competent for mineralization, a final process that is essential for complete expression of the mature osteoblast phenotype. The onset of extracellular matrix mineralization and/or events earlier during the mineralization period may be responsible for the down-regulation of genes expressed during extracellular matrix maturation and organization. Clearly, in this model the development of an extracellular matrix is integrally related to the differentiation stages. This relationship is evident from a series of studies in which cells were cultured at various concentrations of ascorbic acid[131]. With resulting higher levels of collagen synthesis and accumulation of the extracellular matrix, proliferation ceases at a lower cell density, and alkaline phosphatase mRNA levels and enzyme activity per cell are greater. Thus, there is a contribution of signals from the extracellular matrix that promotes progressive differentiation of the osteoblast, and this is indicated from findings in other cell culture systems[4,42,142]. This working model for a functionally coupled relationship provides a basis for understanding aberrations in skeletal development and the consequences of intervention by factors that effect bone formation and turnover.

A complementary experimental approach substantiating the support and/or inductive effect of the collagen extracellular matrix in osteoblast differentiation is culturing primary diploid osteoblasts on Type I collagen film or in a collagen gel[2,112]. Here, with rat osteoblasts, we observe an accelerated progression of osteoblast phenotype development[103] indicated by early and enhanced expression of alkaline phosphatase and osteocalcin. This is in agreement with the studies of Reddi and coworkers[184] demonstrating induction of osteocytic cells from osteoprogenitors when grown on matrigel. Thus, our working model provides a basis for addressing whether particular stages of osteoblast differentiation exhibit selective responsiveness to actions of hormones and other physiological factors that influence osteoblast activity as well as other questions related to molecular mechanisms associated with bone formation.

III. GROWTH FACTOR AND HORMONE MODIFICATIONS ON DEVELOPMENT OF THE OSTEOBLAST PHENOTYPE

A. Windows of Responsiveness for Altering the Course of Osteoblast Differentiation

Hormonal and growth factor modulation of osteoblast growth and differentiation is also illustrated by several striking examples, including the steroid hormones, glucocorticoids, and 1,25(OH)2D3, the active vitamin D metabolite. From an historical perspective, it is well known that vitamin D anabolically and catabolically modulates bone cell metabolic activities[64,110,190], and more recently it has become apparent that this occurs through selective expression of a series of vitamin D responsive genes[reviewed in 96,98]. Vitamin D treatment of osteoblasts alters the level of gene expression to one that reflects a more mature differentiated cell. For example, with short term exposure (up to 48 hours), proliferation is down regulated with collagen and alkaline phosphatase mRNA levels while osteocalcin, matrix Gla protein and osteopontin are upregulated. However, chronic treatment of rat osteoblasts with 10^{-8}M $1,25(OH)_2D_3$, if initiated during the proliferation period, can block differentiation of osteoblasts (Figure

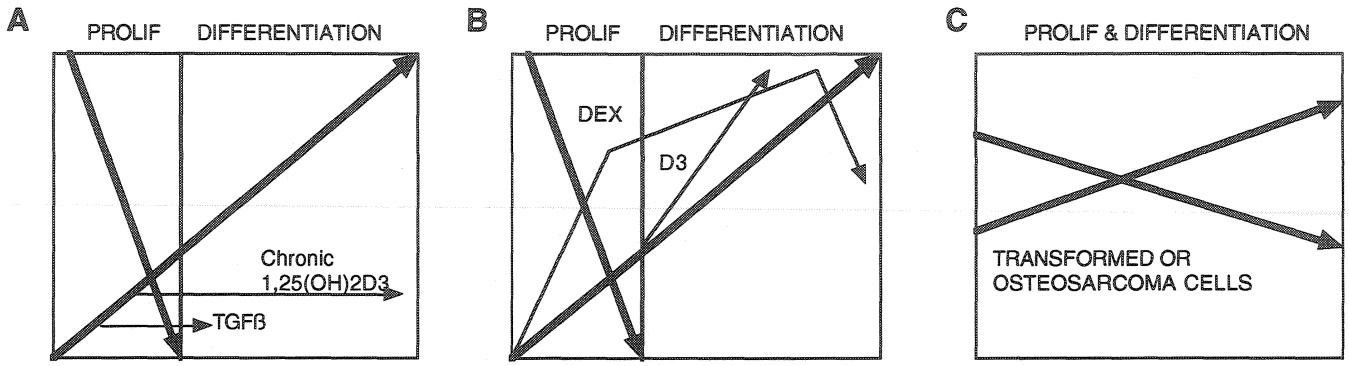


Fig. 6. Modifications of the growth differentiation relationship by growth factors, hormones and in osteosarcoma cells. (A) Inhibition of differentiation is indicated by treatment of fetal rat calvaria osteoblasts during the proliferation period. The mitogenic effects extend the proliferation period and irreversibly alter the phenotype development. Exposure of proliferating osteoblasts to the active metabolite of vitamin D expression inhibits proliferation and downregulates collagen and alkaline phosphatase, blocking differentiation. (B) Induction of differentiation by exposure of proliferating osteoblasts to glucocorticoids, represented by dexamethasone (DEX) or by acute exposure of the cultures in the post-proliferative period to 1,25(OH)2D3 (D3). (C) The deregulation of the relationship between growth and differentiation in transformed osteoblasts or osteosarcoma cells is illustrated. The proliferation vector reflects the continuous expression of cell growth and expression of cell cycle- and proliferation-related genes. In contrast to normal diploid cells, the constitutive expression of osteoblast differentiation phenotype markers in transformed cells in the absence of the two developmentally important transition points (cessation of proliferation and mineralization) observed in normal diploid cells. In osteosarcoma cells, cell growth and tissue-specific gene expression occur concomitantly.

6). Here the down-regulation of collagen and alkaline phosphatase gene expression by vitamin D prevents formation and mineralization of the bone extracellular matrix. Thus, there is a consequential absence of expression of the mature osteoblast phenotype genes such as osteocalcin and osteopontin which are coupled to mineral deposition.

The proliferating osteoblast *in vitro* (analogous to the osteoprogenitor cell *in vivo*) is highly responsive to a phenotype modification, as also illustrated by the effects of glucocorticoids[24]. Glucocorticoids promote differentiation of progenitor cells to the osteoblast phenotype[86] and accelerate the differentiation time course of rat osteoblasts *in vitro*. Dexamethasone, a synthetic glucocorticoid, increases the number of mineralized bone nodules in primary fetal rat calvarial osteoblast cultures[15]. In subcultivated cells, the effect is even more pronounced. Glucocorticoids stimulate the growth of cells competent to progress through the osteoblast developmental sequence. In the absence of dexamethasone, passaged osteoblasts lose the ability to differentiate. This responsiveness diminishes when cells reach confluency indicating the importance in targeting the proliferating cell. However, there is a limited capacity of the cells for this reinitiation of osteoblast growth and differentiation. It is likely that glucocorticoids push the cells to terminal differentiation, depleting the pool of proliferating uncommitted cells.

The molecular mechanisms associated with glucocorticoid mediated osteoblast differentiation are not clear[153,167]. Early response genes (e.g., cfos) are induced. Osteopontin responds rapidly and expression is increased by dexamethasone during the proliferation period. Alkaline phosphatase and osteocalcin are upregulated parallel to an increase in the number of bone nodules and earlier induction of mineralization compared to non-dexamethasone treated cultures. Whether some of the relationships between genes that are coupled or functionally related have been altered due to direct modulation by glucocorticoids or whether the accelerated differentiation is secondary to other modifications in osteoblast developmental parameters remains to be established.

TGFβ1 is a principal mediator of cell growth and differentiation[reviewed in 27] which regulates bone matrix formation and turnover *in vivo*[14,109,124]. However, TGFβ1 has been shown to inhibit, in a dose dependent manner, development of the osteoblast phenotype in cultures of chick periosteal cells[73] and fetal rat calvarial derived cells[3,20,60]. This observation appears inconsistent with (a) several *in vivo* studies demonstrating local application of TGFβ1 stimulates bone formation and (b) knowledge that osteoblasts produce TGFβ1 [147,131]. The discrepancy is easily reconciled. *In vivo*, numerous cell types are present in the local bone environment that are targets for TGFβ1. Synergistic effects on local factors produced by non-osseous cells that stimulate osteoblast activity are not present in the more homogeneous osteoblast preparations isolated for *in vitro* studies. Secondly, *in vitro*, TGFβ1 mRNA levels are highest during the proliferating period and downregulated post-proliferatively during nodule formation[131]. Another level of regulation is production of protein in a latent form[32]. Thus, the addition of active TGFβ1 peptide to bone cells *in vitro* reveals effects on the osteoblast phenotype not appreciated from *in vivo* studies. Harris et al.[60] (1994) reported that TGFβ1 also inhibited

BMP2 expression in these fetal rat calvarial cell cultures implicating this bone morphogenic protein, as well as the bone matrix related proteins, as components of the TGFβ1 inhibition of osteoblast differentiation. Post-proliferative osteoblasts and second passage cells that are accelerated to differentiate by dexamethasone are refractory to the inhibitory effects of TGFβ1[20] emphasizing the window of responsiveness to physiologic mediators for phenotype modifications in proliferating osteoblasts.

B. Selective Responses are Related to the Stage of Osteoblast Maturation

Not only do hormones and growth factors influence the osteoblast growth and differentiation relationship, but responsiveness of a particular gene to a physiologic regulator is a function of the developmental stage of the osteoblast. This is illustrated by several examples. Several studies reported differential stimulation of alkaline phosphatase by vitamin D, dependent upon the basal level of expression in the ROS 17/2.8 cell[44,107,159]; $1,25(OH)_2D_3$ exerts either stimulatory or inhibiting effects on collagen synthesis in various cell lines and culture systems[26,41,85]. In the normal diploid rat osteoblast cultures at different stages of phenotype development, from the proliferation period to the mature osteocyte-like cell in the mineralized matrix, we observed pleiotropic effects on several vitamin D regulated genes between immature and differentiated osteoblasts[50,133]. For example, histone H4, collagen, and alkaline phosphatase are down-regulated in proliferating osteoblasts, but in mature osteoblasts in a mineralized matrix, an upregulation is observed. The selective effects of the hormone are illustrated by a change in morphology of osteoblasts on the surface of a mineralized nodule, with no effect on internodular cells[140]. This observation may be relevant to the selective functional activities of osteoblast populations *in vivo*. *In vivo* $1,25(OH)_2D_3$ can promote differentiation of osteoclasts and mediates bone resorption through activities on the osteoblast. Lining cell osteoblasts must retract from the bone surface and secrete factors for osteoclast activation. Other osteoblasts need to be involved in bone formation activities. The release of local active growth factors or cytokines to stimulate osteoblast proliferation is one such mechanism to increase or recruit a local osteoblast population to the resorption site.

Confirmation of this concept of developmental responsiveness of the osteoblast is also observed in relation to glucocorticoid effects[153,175]. Osteopontin and alkaline phosphatase are increased 20-30 fold greater in alkaline phosphatase negative cells compared to mature osteoblasts. Growth factors also exhibit differential effects in modulating cellular activities depending on the cell phenotype, stage of maturation and level of gene expression[25,54,145]. Fibroblast growth factor (αFGF) can stimulate bone formation *in vivo*[113,120], and *in vitro* can promote osteoblast differentiation of marrow progenitor cells in conjunction with dexamethasone[125] or bone organ culture[25]. However, exposure of osteoblast cultures to αFGF can block differentiation via its mitogenic effects and induction of collagenase[122,145,169] and inhibit collagen expression in mature MC3T3-E1 cells[70].

In summary, these findings support the concepts that (1) a proliferating osteoblast-like cell is selectively sensitive to phenotype alterations by steroid hormones and growth factors; and (2) genes exhibit developmental stage-specific responses reflecting subtle differences in the cohort of transcription factor complexes regulating the cognate promoter regulatory elements. Glucocorticoids, $1,25(OH)_2D_3$ and TGFβ have irreversible and sustained effects that modify the progression of differentiation of proliferating cells of the osteoblast lineage. Several questions are raised regarding the relevance of these *in vitro* observations to physiologic and therapeutic effects *in vivo*. Considerations need to be given to osteoblast subpopulations as well as to dose and timing or duration of hormone exposure. More fundamental questions are related to defining the specific mechanisms operative in proliferating cells that allow for such dramatic phenotypic alterations. Possibilities include the involvement of early response genes and modifications in transcription factors by hormones and growth factors, e.g. the oncogenes[94,95,132], homeobox genes[66,101,173] and helix-loop-helix proteins[118,129,168]. Each of these classes of transcription factors is regulated by steroid hormones and modulates bone-specific gene expression reflecting a cascade of mechanisms contributing to phenotypic modifications.

IV. ADDRESSING MOLECULAR MECHANISMS MEDIATING OSTEOBLAST GROWTH AND DIFFERENTIATION

Proliferation is a fundamental requirement for developmental establishment and renewal of tissues. A broad spectrum of signalling mechanisms, which integrate and amplify growth-related regulatory cues, regulate the expression of genes requisite for proliferation and cell cycle control. Equally important are the regulatory cues in proliferating cells that allow for exit from the cell cycle and commitment to a phenotypic lineage. Consequently, the modularly organized promoter elements of genes which support the onset and progression of proliferation provide a blueprint for growth control within the context of responsiveness to mediators of proliferative status. These include, but are not restricted to, cytokines, growth factors and steroid hormones. To define these molecular mechanisms, we have focused on characterization of the transcription factors regulating the promoters of two genes; the histone gene which is tightly coupled to DNA synthesis and the osteocalcin gene which is developmen-

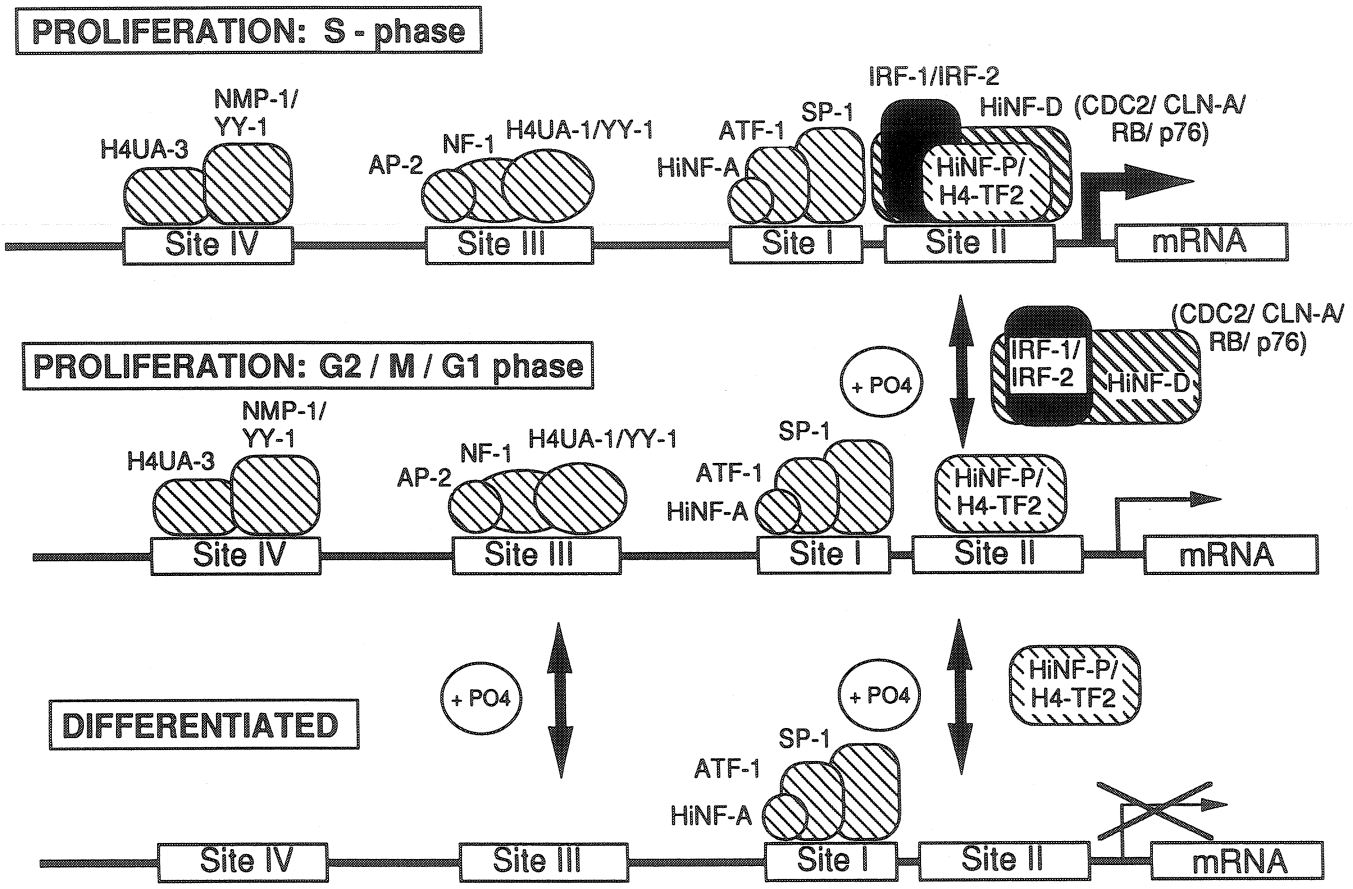


Fig. 7. Regulation of histone gene expression during osteoblast growth and differentiation. Organization of the human histone H4 gene promoter regulatory elements (Sites I-IV) is illustrated. The transcription factors which exhibit sequence specific interactions with these domains are indicated during the S phase of the cell cycle when the gene is actively transcribed (top panel). Site II contributes to cell cycle regulation of transcription, Site IV binds a nuclear matrix protein complex (NMP-1), while the protein-DNA interactions at Sites III and I support general transcriptional enhancement. The Site II transcription factor complex is modified by phosphorylation during the G1/G2/ mitotic periods of the cell cycle resulting in lower levels of transcription. The lower panel (differentiated cells) illustrates complete loss of transcription factor complexes at Sites II, III, and IV following exit from the cell cycle with the onset of differentiation. Assembly of the Site II complex during S phase involves cyclin A, the cyclin dependent kinase cdc2, an RB related protein and IRF2 growth regulatory factors, reflecting integration of phosphorylation mediated control of histone gene expression.

tally regulated and a tissue specific marker of differentiation.

The regulatory sequences are established in gene promoters by one or more criteria that include: (1) demonstration of an influence on transcriptional activity by deletion, substitution or site specific mutagenesis *in vitro* and *in vivo*; (2) identification and characterization of sequence specific regulatory element occupancy by cognate transcription factors *in vitro* and *in vivo*; (3) modifications in protein-DNA interactions as a function of biological activity; and (4) consequential modifications in functional activity following overexpression or suppression of factors which exhibit sequence-specific recognition for regulator domains.

A. The Histone Gene Promoter is a Paradigm for the Integration of Regulator Signals Mediating Cell Cycle Control and Proliferation/ Differentiation Interrelationships.

From a biological perspective, an understanding of growth control necessitates defining the stringent regulation of molecular parameters associated with competency for initiation of proliferation and progression through the cell cycle[12]. Regulatory parameters have been defined that mediate both initiation of proliferation and cell cycle progression[155]. The emerging concept is that the cyclins and cyclin-dependent kinases are responsive to regulation by the phosphorylation-dependent signalling pathways associated with activities of the early response genes which are upregulated following mitogen-stimulation of proliferation[reviewed in 71,69,80,106]. Cyclin-dependent phosphorylation is functionally linked to activation and suppression of both p53 and Rb-related tumor suppressor genes which

mediate transcriptional events involved with passage into S phase. The activities of the cyclin-dependent kinases are downregulated by a series of inhibitors designated CDI's and mediators of ubiquitination which signal destabilization and/or destruction of these regulatory complexes in a cell cycle-dependent manner. Particularly significant is the accumulating evidence for functional interrelationships between activities of cyclin-cdk complexes and growth arrest at G1 and G2 checkpoints where competency for cell cycle traverse is monitored[37,38,128,156], editing functions are operative, and decisions for continued proliferation, growth arrest or apoptotic cell death are executed[188].

The histone gene promoter is a paradigm for understanding molecular mechanisms related to cell cycle-mediated transcriptional control[reviewed in 160,162]. Transcription of the gene is constitutive throughout the cell cycle, upregulated at the onset of S phase and completely suppressed in quiescent cells or following the onset of differentiation[13,36] (Figure 7). Consequently, activity of the promoter is responsive to regulatory signals which contribute to transcriptional competency for cell cycle progression at the G1/S phase transition point and to transcriptional downregulation postproliferatively. The modularly organized promoter regulatory elements of the histone H4 gene promoter and the cognate transcription factors have been characterized within the context of cell cycle dependent regulatory parameters[138,143,176,177,179,180] (Figure 7). There is a direct indication that the cell cycle regulatory element exhibits phosphorylation-dependent modifications in transcription factor interactions which parallel and are functionally related to cell cycle as well as growth control of histone gene expression. The S phase transcription factor complexes assembling at the H4 promoter include cdc2, cyclin A, and RB related protein and IRF-2[181,183], reflecting an integration of phosphorylation-mediated control of histone gene expression, enzymes involved in DNA replication, as well as growth stimulation and growth suppression at the G1/S phase transition point.

B. The Osteocalcin Gene is a Paradigm for Integration of Regulator Signals Mediating Developmental and Hormonal Regulation of Bone Formation.

Influences of promoter regulatory elements that are responsive to basal and tissue-restricted transactivation factors, steroid hormones, growth factors and other physiologic mediators has provided the basis for understanding regulatory mechanisms contributing to developmental expression of osteocalcin, tissue specificity and biological activity. These regulatory elements and cognate transcription factors support postproliferative transcriptional activation and steroid hormone (e.g. vitamin D) enhancement at the onset of extracellular matrix mineralization during osteoblast differentiation. The bone-specific osteocalcin gene is organized in a manner which supports responsiveness to homeostatic physiologic mediators and developmental expression in relation to bone cell differentiation (Figure 8).

A series of elements contributing to basal expression[91] include a TATA sequence (located at -42 to -39) and the osteocalcin box (OC box), a 24 nucleotide element with a CCAAT motif as a central core. Both are required for rendering the gene transcribable[62,77,172,173]. The OC box is a highly conserved regulatory sequence required for basal expression of the rat, mouse and human OC genes. The OC box additionally serves a regulatory function in defining the threshold for initiation of transcription and contributes to bone tissue-specific expression of the osteocalcin gene[62]. However caution must be exercised in attributing tissue-specific transcriptional control to a single element. Contributions of multiple sequences appear to be operative in tissue-specific regulation thereby providing opportunities for expression of the osteocalcin gene in bone under diverse biological circumstances.

Two osteocalcin gene promoter regulatory domains which exhibit recognition for transcription factors that mediate developmental pattern formation are an MSX homeodomain protein binding site within the OC box[62,66,173] and an AML runt homology sequence protein binding site[161,182]. The AML sites also bind an osteoblast restricted nuclear matrix protein complex (NMP-2),[17] and our preliminary studies indicate an AML related protein is present in osteoblasts[161,182]. These sequences may represent components of regulatory mechanisms that contribute to pattern formation associated with bone tissue organization during initial developmental stages and subsequently during tissue remodelling. Involvement of other homeodomain-related genes that are expressed during skeletal development in control of osteoblast proliferation and differentiation is worthy of consideration. These include, but are not restricted to, the families of Dlx and PAX[59,83,101,157] genes.

Multiple glucocorticoid responsive elements (GRE) with sequences that exhibit both strong and weak affinities for glucocorticoid receptor binding have been identified in the proximal promoter[5,63,166]. Interactions of other transcription factors with the proximal glucocorticoid responsive elements which include NF-IL6 have been reported[174], further expanding the potential of the OC gene to be transcriptionally regulated by glucocorticoids. A distal GRE (nt -697 to -683) is in close proximity to an AP-1 site. It is reasonable to consider that the OC gene GRE'S may be selectively utilized in a developmentally and/or physiologically responsive manner.

The vitamin D responsive element (VDRE) functions as an enhancer[20,34,79,111,117,171]. The VDRE transcription

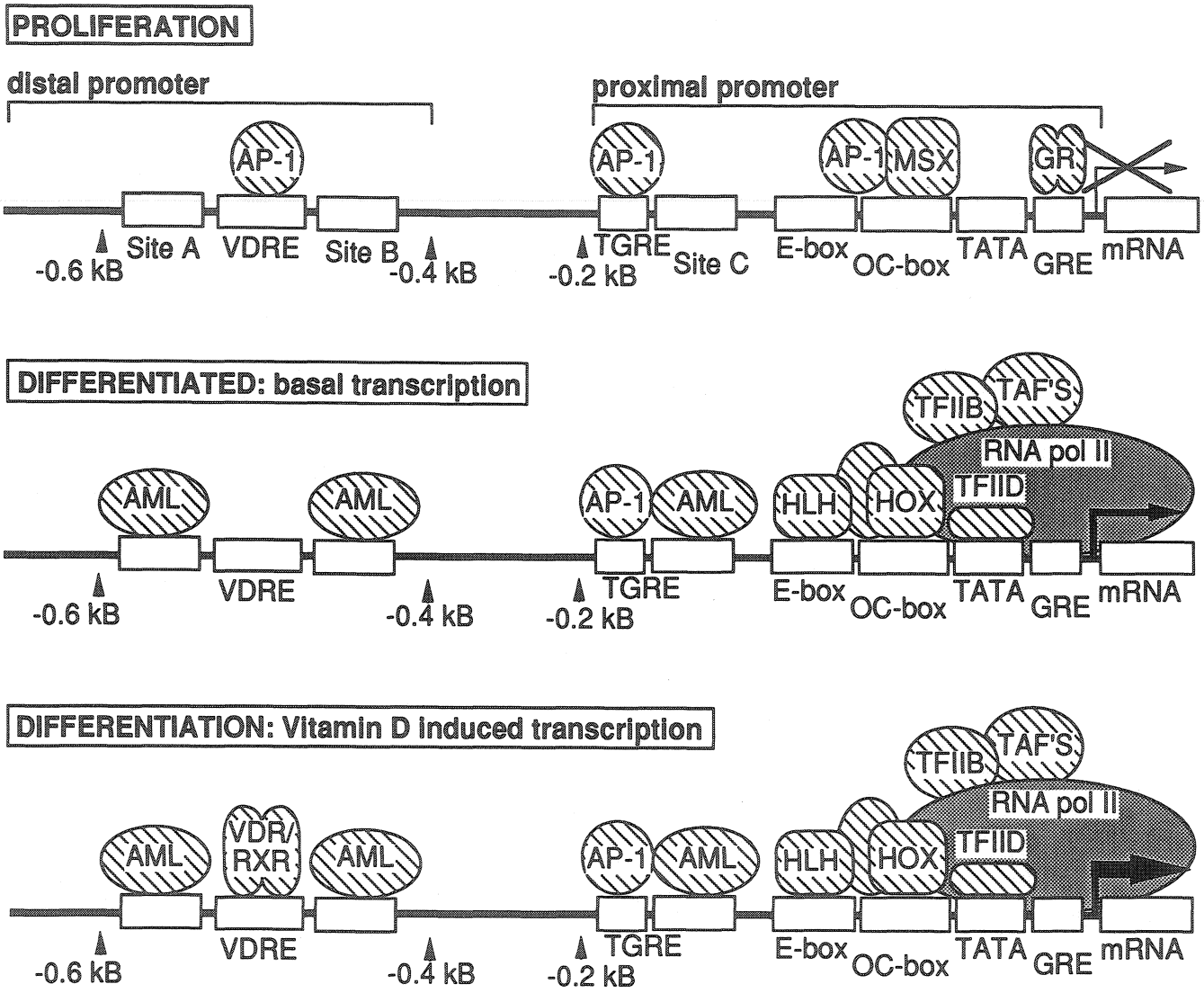


Fig. 8. Regulation of osteocalcin gene expression during osteoblast growth and differentiation. The regulatory domains within the initial 700 nucleotides 5' to the transcription start are indicated. In the proximal promoter, several classes of transcription factors are represented which bind to key regulatory elements. The OC Box is the primary tissue specific transcriptional element that binds both homeodomain proteins (MSX), oncogene encoded proteins forming heterodimers at AP-1 sites or a cryptic tissue-specific complex (not shown). Helix-loop-helix protein (HLH) bind to the contiguous E Box motif. Three nuclear matrix protein binding Sites (A, B and C) interact with an AML related transcription factor. Several glucocorticoid response elements (GRE) are indicated as well as the vitamin D response element (VDRE), which is a primary enhancer element. Additional AP-1 sites are indicated that overlap either the TGFb response element (TGRE) or the VDRE. The combined and integrated activities of overlapping regulatory elements and associated transcription factors provide a mechanism for developmental control of expression during osteoblast growth and differentiation. Occupancy of the elements by cognate transcription factors parallels and is functionally related to either (a) suppression of transcription in proliferating osteoblasts (top panel); (b) activation of expression in differentiated cells (middle); and (c) enhancement of transcription by vitamin D (lower panel).

factor complex appears to be a target for modifications in vitamin D mediated transcription by other physiologic factors including TNF-α[84] and retinoic acid[18,82,105,149,150]. Additional regulatory sequences include an interferon response domain[121], an NFkB site reported to be involved in regulation mediated by TNFα,[88] a series of AP-1 sites[35,94,137] (one of which mediates TGFβ responsiveness[7]), an E box[168] that binds HLH containing transcription factor complexes, and a sequence in the proximal promoter that binds a multi subunit complex containing CP1/NR-Y/CBF-like CAAT factor complex[174].

The overlapping and contiguous organization of regulatory elements, as illustrated by the TATA/GRE, E Box/AP-1/CCAAT/homeodomain, and TNFa/VDRE AP-1/VDRE, provide a basis for combined activities that support post-proliferative expression and responsiveness to physiologic mediators[reviewed in 96-98]. Additionally, hormones modulate binding of transcription factors other than the cognate receptor to non-steroid regulatory sequences. For example, vitamin D induced interactions occur at the basal TATA domain,[134] and $1,25(OH)_2D_3$ upregulates MSX-2 binding to the OC box homeodomain motif and supports increased MSX-2 expression[65,66,173]. It is this complexity of OC gene promoter element upregulation that allows for hormone responsiveness in relation to either basal levels of expression or other activities.

V. DEREGULATION OF GROWTH-DIFFERENTIATION RELATIONSHIP IN TRANSFORMED OR OSTEOSARCOMA CELLS

In several transformed osteoblasts and osteosarcoma cell lines such as the ROS 17/2.8 rat osteosarcoma cell line, there is a deregulation of the sequential pattern of gene expression observed in diploid osteoblasts. A relaxation of control mechanisms permits sequentially expressed genes in diploid osteoblasts to be expressed simultaneously during proliferation, as reflected by concomitant expression of the histone H4 gene and tissue specific genes including alkaline phosphatase, osteopontin, and osteocalcin[164]. It should be emphasized that, while in normal diploid osteoblasts some genes (e.g. osteocalcin, osteopontin) are expressed or induced to high levels only at the onset of extracellular matrix mineralization, the genes in osteosarcoma cells are expressed in the absence of a bone-like extracellular matrix. Perturbations are implicated in the signalling mechanisms that interface the down-regulation of cell growth and induction of genes that support extracellular matrix maturation and specialization with those that control gene expression associated with extracellular matrix mineralization. Our understanding of how gene responsiveness to regulators of osteoblast growth and differentiation is compromised in osteosarcoma cells can thereby provide insight into molecular mechanisms that are deregulated.

Transcriptional control of the H4 histone gene is strikingly modified in osteosarcoma cells. An abrogation of the cell cycle and proliferation-regulated changes in transcription factor binding to the histone promoter elements, most notably at the cell cycle regulatory element by nuclear extracts from tumor cells, is observed[67]. Enzymatic dephosphorylation of nuclear extracts results in loss of HiNF-D-site II interactions and increased electrophoretic mobility of the site III protein-DNA complex in normal cells. Therefore, involvement of phosphorylation at these two histone gene promoter elements is implicated[81]. Indeed, specific phosphorylation events (kinase activities) play a key role in cell cycle progression e.g. cdc2 regulation of the cyclin gene[127]. Thus, for a tumor cell, continual traverse of the cell cycle may be associated with modifications in the level of transcription factor phosphorylation or the utilization of specific phosphorylation sites. The observations are not unique to the ROS 17/2.8 cell, but a comparison of several tumor cell lines revealed similar differences when compared to their normal diploid counterparts. The identical relationship has been shown in WI38 (normal fibroblasts) compared to the transformed HeLa cell line[177].

The post-proliferative and developmental expression of osteocalcin in normal diploid osteoblasts and its regulation by steroid hormones only when osteocalcin expression is ongoing postproliferatively has been well documented. We have proposed that AP-1 sites which overlap the basal regulatory CAAT-containing element, the OC box, and the vitamin D responsive element (VDRE), bind the nuclear proto-oncogene encoded fos-jun protein complex as a mechanism by which osteocalcin expression and vitamin D modulation is suppressed in normal actively dividing cells[94,133]. In ROS 17/2.8 cells, osteocalcin expression occurs in the presence of AP-1 activity in contrast to the diploid cells. To understand osteocalcin expression in proliferating tumor cells, we have examined the transcription factor complexes at basal regulatory sequences and at the vitamin D responsive element of the osteocalcin gene promoter. In normal diploid osteoblasts, nuclear extracts from proliferating cells and in post-proliferative osteocalcin expressing cells exhibit differences in protein-DNA interactions. In contrast, the tumor cell nuclear extracts from proliferating or confluent cultures are similar and support protein-DNA interactions that are strikingly different than those of the normal osteoblasts[18]. These differences are found at each of the basal elements and the VDRE[20,151].

We can speculate that the deregulation of growth control in osteosarcoma cells may reflect modifications in the activity of tumor suppressor genes[reviewed by 87,186]. Alternatively, or together with the loss of stringent growth control, there may be modifications in the regulatory sequences and/or in the factors that control the

progressive expression of tissue-specific genes and their response to cell growth or morphogenic regulatory factors. While the specific molecular mechanisms remain to be established, by further understanding the deregulation of growth in bone tumors, we can anticipate gaining additional insight into control of the tightly coupled relationship between proliferation and development of the osteoblast phenotype.

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DIFFERENCES IN LIGAMENTA FLAVA AMONG SOME MAMMALS

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The ligamenta flava connect the laminae of adjacent vertebrae and extend from the midline over the interlaminar spaces to the roots of the articular processes reinforcing the articular capsules. The ligamenta flava are rich in elastic fibers and, although they have been extensively studied, their function in the mechanics of the spine has not been clearly delineated. Schmorl[13] indicated that in man "the ligamenta flava serve to restrain the mobility of the apophyseal joints". Rolander[12] suggested that their function was simply " to give the vertebral canal a smooth, dorsal covering in all positions of the spine". Nachemson and Evans[8] studied the mechanical properties of the third lumbar ligamentum flavum in men and concluded that the ligament "serves as a highly specialized tissue in protecting the nerve roots from mechanical impingement and also prestressing the disc providing some intrinsic stability to the spine". Fasana[3,4] indicated that in the vervet monkey the ligamenta flava are the strongest of all the ligaments of the spine and provide a "control mechanism for the gradual governing of the vertebral column; after flexion and lateral bending of the spine the ligamenta flava facilitate the return of the rotated vertebrae to the neutral position".

To further understand the possible significance of the ligamentum flavum in spinal movements and posture we have studied the morphology and the elastin and collagen content of these ligaments in the low thoracic and lumbar spines of various animals. Mammals with flat backs and limited spinal mobility in these spinal segments such as the goat and sheep as well as mammals with arched backs and greater spinal mobility such as the monkey and cat were studied.

MATERIALS AND METHODS

We dissected the caudal half of the thoracic spine and the lumbar spine from the following young adult animals: three dogs, two goats, three sheep, two cats, three New Zealand rabbits, and three vervet monkeys (Cercopithecus Sabaeus). On removal, segments of the spinal column were fixed in 10% formalin, decalcified in 5% formic acid solution, cut in sagittal, frontal and coronal planes, embedded in paraffin, sectioned at seven micromillimeters and stained with H and E, Verhoeff-vanGieson, Masson trichrome and PAS. The ligamenta flava are best seen from their anterior aspect, after severing the pedicles and opening the vertebral canal.

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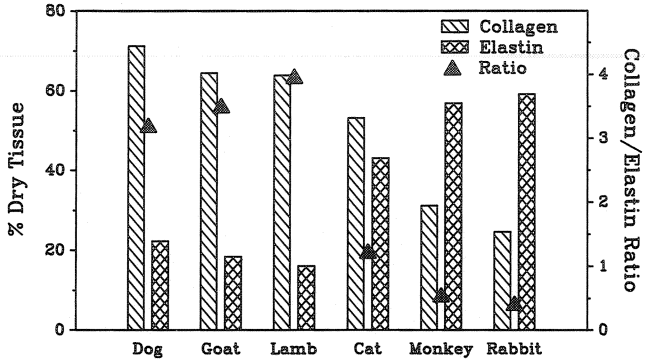

Figure 1
Elastin and collagen content of ligamenta flava of some mammals.

The ligamenta flava to be used for biochemical analysis were carefully dissected out of their laminar insertions, defatted in acetone and minced with a sharp knife. They were then hydrolyzed in 6 NHCL at 130° for five hours, dried, and redissolved in water. Hydrolysates were purified by passage through a Sep-Pak cartridge. Aliquots of the purified hydrolysate were used for hydroyproline, pyridinoline and desmosines determination. Vittorio Pedrini developed a technique for the rapid analysis of collagen and elastin crosslinks in small samples of ligament. The HPLC technique previously used for the quantitation of the collagen pyridinoline (Pyr) crosslinks[2,10] was applied to the study of the polyfunctional crosslinking amino acids desmosine (Des) and isodesmosine (Ide) characteristic of elastin. Des and Ide were used to quantify elastin in the liagmenta since their amount is fairly constant in mature elastin[17]. The results of the biochemical slides were published in the Transactions of the Orthopaedic Research Society[9]. See Figure 1.

RESULTS

In all mammals studied, the ligaments insert into the low border and lower anterior surface of the lamina above and into the upper and posterior surfaces of the lamina below (Fig. 2). There is a minimal interval in the midline between the right and left ligamenta flava where small vessels may be seen. The ligaments extend laterally, cover the capsule of the facet joints and reach the vertebral foramina. The lateral extension of the ligamentum flavum is thinner than the interlaminar portion (Figs. 3 and 4).

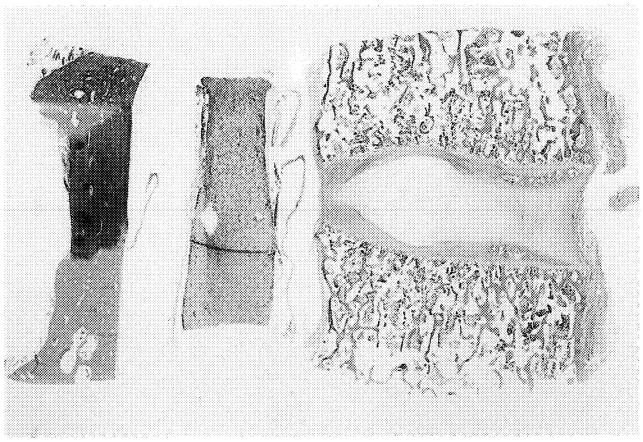

Figure 2
Sagittal section of the spinal column at the level of the second lumbar intervertebral disc of a young adolescent vervet monkey. We see part of the vertebral bodies adjacent to the disc, the spinal cord and the thick ligamentum flavum attached to the laminae. Verhoeff-vanGieson, x 6.

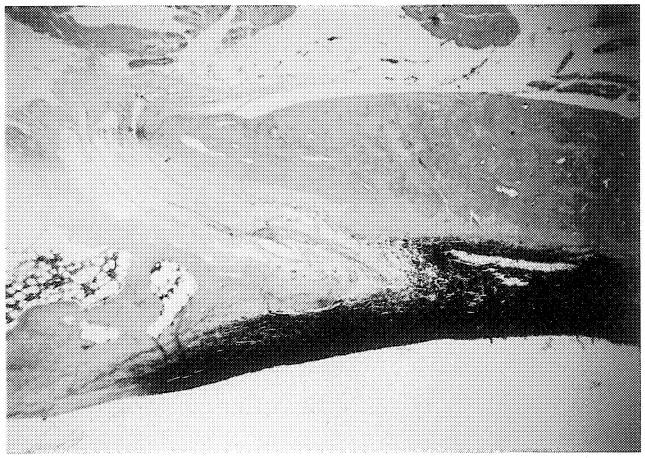

Figure 3
Transverse section of the vertebral arch and facet joint of the tenth thoracic vertebra of a rabbit. The ligamentum flavum covers the capsule of the facet joint and inserts into the articular process. Verhoeff-vanGieson, x 40.

The thickness and color of the ligamenta flava vary among the mammals studied. Ligaments are thick and yellow in the monkey, rabbit, and cat and relatively thin and whitish in the goat, sheep and dog. In the rabbit and cat the ligamenta flava are about two mm thick throughout the areas of the spine studied. The ligaments are only 1.5 mm thick in sheep and goat and in the large dogs studied, the ligamenta were two mm thick.

In the lower thoracic and upper lumbar spines of the vervet monkey, the ligamenta flava extend into the interspinous spaces, in part replacing the interspinous ligaments. At the midline in the interspinous spaces of the thoracolumbar junction, the ligamentum flavum in the monkey can be nine mm thick; the ligament is usually five mm thick in the lower lumbar area.

Figure 4
Transverse section of the vertebral arch of the fourth lumbar vertebra of a young monkey showing the insertion of the ligamentum flavum into the articular process. The elastic ligament covers the collagenous joint capsule. A nerve-vascular bundle is seen close to the insertion site. Verhoeff-vanGieson, x 40.

With the light microscope we observed that the ligamentum flavum in the monkey and in the rabbit consists mostly of elastic fibers with lesser amounts of collagen fibers and very few elongated cells (Figure 5). In the interlaminar portion of the ligament the fibers are arranged more or less parallel and longitudinally along the main axis of the spine. They are obliquely oriented in the lateral and capsular portions of the ligament. Some fibers bifurcate and some crisscross, forming a "scissorial lattice"[4]. In the cat the collagen fibers are slightly more numerous than the elastin fibers (Fig. 6), and in the dog there are more collagen fibers than elastic fibers (Fig. 7). In the thin ligamenta flava of the sheep and goat, the collagen fibers are predominant; the elastic fibers appear thick and wavy and not taut as in the mammals with thick ligaments (Fig. 8).

Figure 5 Sagittal section of the ligamentum flavum between the first and second lumbar vertebrae of a young vervet monkey. Verhoeff-vanGieson, x 40.

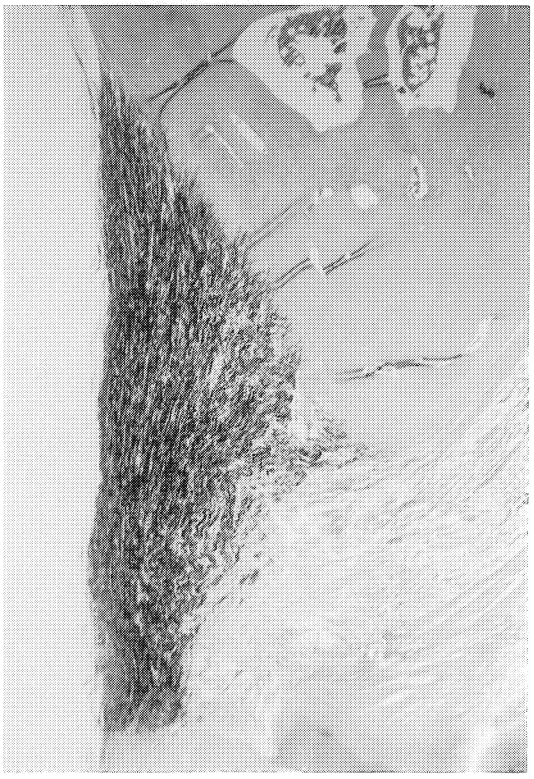

Figure 6 Sagittal section of the ligamentum flavum between the laminae of the second and third lumbar vertebrae of a cat. Verhoeff-vanGieson, x 40.

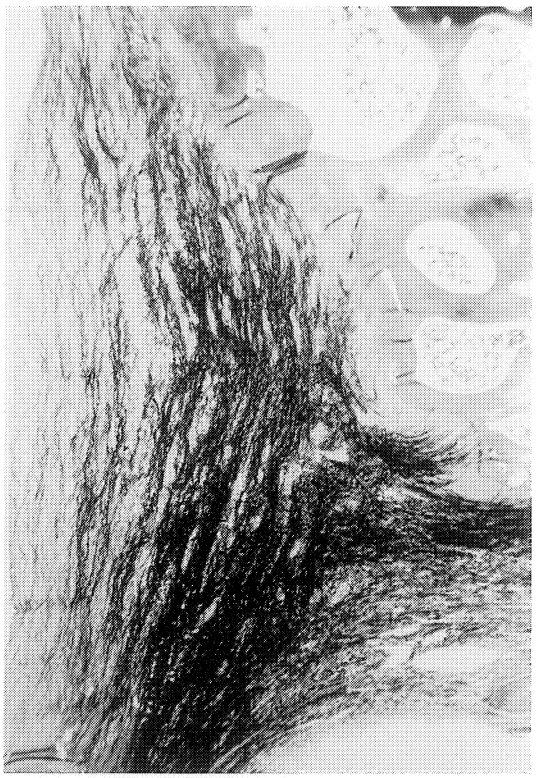

Figure 7 Sagittal section of the ligamentum flavum between the lamina of the second and third lumbar vertebrae of a dog. Verhoeff-vanGieson, x 40.

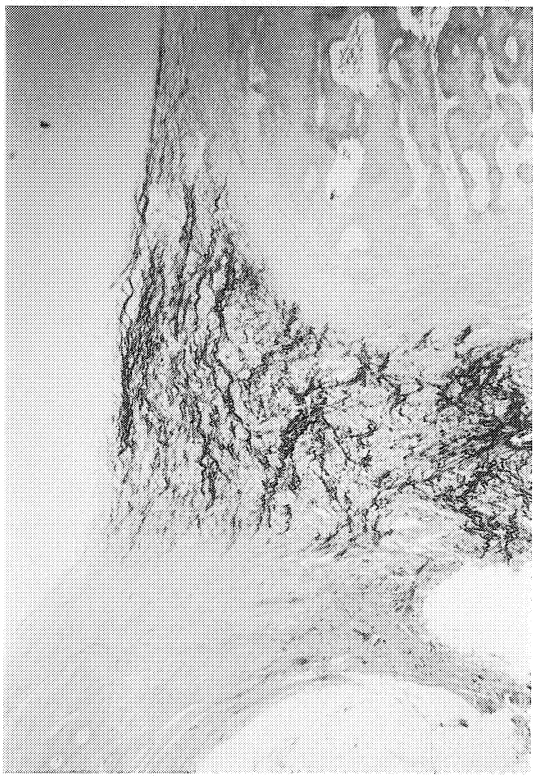

Figure 8 Sagittal section of the ligamentum flavum between the second and third lumbar vertebrae of a sheep. Verhoeff-vanGieson, x 40.

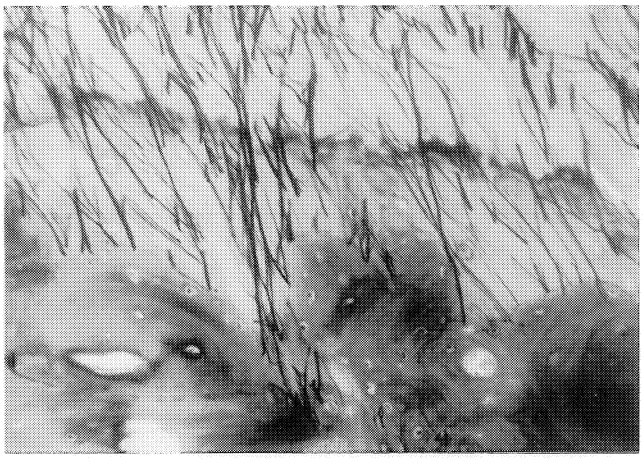

Figure 9
Insertion of a lumbar ligamentum flavum of a monkey into the spinal process. The dark "blue line" separates the fibrocartilaginous zone (above) from the mineralized fibrocartilage. Some elastic fibers cross these zones and insert into bone. Verhoeff-vanGieson, 265.

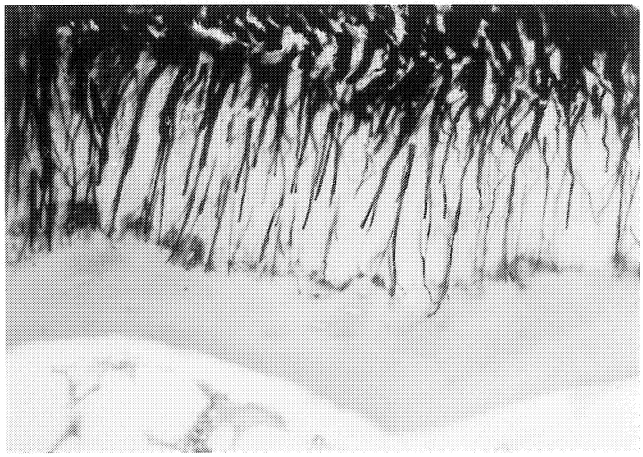

Figure 10
Insertion of a lumbar ligamentum flavum of a monkey into the lamina. The blue line appears to be in contact with the bone. Thus the zone of mineralized fibrocartilage is very thin and not clearly discernible. Many elastic fibers cross the fibrocartilaginous zone to insert into bone. Verhoeff-vanGieson, x 265.

In all mammals studied, the ligamenta flava insert directly into bone without interposed periosteum. The ligament insertion has been divided into four zones: ligament, fibrocartilage, mineralized fibrocartilage and bone[1,14]. The thickness and morphology of these zones is similar in all species studied. The elastic and collagen fibers continue in parallel fashion into the fibrocartilaginous zone where the collagen fibers are more abundant. The cells in the fibrocartilaginous zone are rounded, lined up in rows of two to four cells, and tend to resemble cartilage cells. The ground substance is PAS positive. The strongly basophilic "blue line" separates this zone from the mineralized fibrocartilage. Many elastic fibers terminate in the

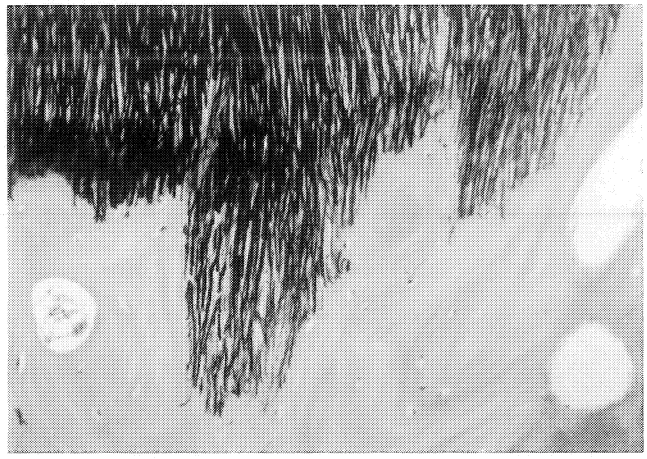

Figure 11
Jagged and uneven insertion of a lumbar ligamentum flavum of a monkey into a lamina. The fibrocartilaginous and mineralized fibrocartilage zones are almost absent. Verhoeff-vanGieson, X 265.

mineralized fibrocartilage, although some manage to reach and insert into the bone (Figs. 9 and 10). The area of contact between the laminar bone and fibrocartilage is very uneven and jagged and may contain thin areas of newly formed bone (Fig. 11).

At the site of the facet joints the ligamentum flavum adheres to the joint capsule. Some of the thick elastic fibers of the ligamentum flavum cross into the mostly collagenous joint capsule (Fig. 4).

Elastin content varies greatly in the ligamenta flava of different mammals and correlates inversely with their collagen content[11]. Within the same animal species, in the lower thoracic and lumbar spinal segments sampled, the composition of the ligamentum flavum changed very little within the spinal location (lower thoracic vs lumbar; right vs left). We did not study, however, the ligaments of the cervical and upper thoracic spines. The content of elastin and collagen in the ligaments as determined biochemically, correlated well with what was observed with the light microscope in the tissue slides with the Verhoeff-vanGieson stain. There was much more elastin than collagen in the ligaments of the rabbit and monkey, and equal amounts in the cat. There was less elastin than collagen in the dog, and much less in the goat and sheep.

DISCUSSION

Elastin fibers are present in abundance in tissues where a high compliance and elastic recoil are necessary. Dorsoventral flexibility of the lower thoracic and lumbar spines varies among the animals studied: Flexion-extension of these segments of the spine is very limited in the goat and sheep. It is less limited in the dog and is quite free in the monkey, rabbit and cat. A remarkable degree of forward flexion of the lower thoracic spine may be observed in the rabbit, cat and monkey when sitting. We observed a direct

correlation between the degree of dorso-ventral flexibility of the spine and elastin content of the ligamenta flava in the mammals studied. The ligaments in the caudal half of the thoracic spine and in the lumbar spine of the goat and sheep have less than 20% of elastin and over 60% of collagen. In the rabbit and the monkey, the ligamenta flava have about 60% of elastin and 30% of collagen. Collagen-elastin ratio is slightly over one in the cat and it is three in the dog with less dorso-ventral flexibility.

Of the animals in our study, the vervet monkey has the highest mobility in its entire spine. Their ligamenta flava are the strongest of all the vertebral ligaments, are rich in elastin, and extend into the interspinous spaces from T4 to the sacrum, replacing in part the interspinous ligaments[3,4]. The vervet monkey often walks and climbs with an upright posture and sits on the tarsus and metatarsus of the hindlegs and on the ischial tuberosities for long periods of time. In this sitting posture there is a marked kyphosis at the lower thoracic spine. The monkeys have prehensile hands and feed with their hands. Their ligamentum nucha is very atrophic.

The sheep and goat, as most ungulates, have an extremely large ligamentum nucha which extends from the upper cervical vertebrae and the occiput to the very large spinal processes of the upper thoracic vertebrae and supports most of the weight of the head while grazing. The ligament is composed largely of elastin, thus conserving energy during prolong periods of feeding[5,6,15].

The ligamenta flava are in permanent longitudinal tension. The interlaminar part of the ligamentum flavum is the only one of the posterior elements that prestresses the intervertebral disc. In man with normal or moderately degenerated discs, Nachemson and Evans found that the L3-L4 ligamentum flavum prestresses the disc by a force ranging from 1500 grams in the young to 400 grams in the aged. The ligament creates an intradiscal pressure of 0.70 kg per cm^2 in the upright position[8].

Our observations support the hypothesis advanced by Mungai[7] that "the variations in the elasticity and elastic fiber content is related to the amount of postural tension put on the ligaments". The ligamentum flavum appears to have an important role in the control of vertebral motion and in providing intrinsic stability to the spine. Ungulates with long legs and a need to feed from the ground have a large elastic ligamentum nucha that controls their long neck and head motions with little energy expenditure[6]. Primates feed with their hands while sitting; they have practically no ligamentum nucha and the ligamenta flava is presumably to help maintain the sitting posture and control intervertebral movements while saving muscular energy. When mammals like the dog, cat and rabbit run with a leaping-gallop, the spine bends and stretches with the lower thoracic vertebrae serving as the center of these movements. In these motions, the ligamenta flava assist the powerful back musculature[6]. The cat and the rabbit often sit with an arched back; the elastin content of their ligamenta flava is close to that of the vervet monkey and much higher than in the dog.

SUMMARY

The ligamenta flava of the thoracolumbar spine of mammals with great spinal mobility have a larger content of elastin than in animals with little spinal motion. The elastin content is also higher in the ligamenta flava of mammals with arched backs and prolonged sitting posture than in nonsitting mammals with the vertebral column in the shape of a flat bow. The ligamentum flavum appears to be important; a) in the control of intervertebra movements, b) in providing intrinsic stability to the spine in the sitting and standing postures and c) in maintaining a smooth surface in the posterior wall of the spinal canal and neural foraminae.

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MECHANORECEPTOR ENDINGS OF THE CERVICAL, THORACIC, AND LUMBAR SPINE

Robert F. McLain, M.D.
Kamshad Raiszadeh, M.D.

INTRODUCTION

Ligaments and periarticular connective tissues are traditionally thought of in terms of their structural characteristics and their function as mechanical restraints. Although the possibility that these tissues have neurosensory functions was advanced by a number of authors over the years, it was not until the 1980's that Brand and others reintroduced this notion and presented convincing evidence in its support[1,2,3,4,8,18,26,28]. Although this work focused primarily on the articular tissues of the peripheral joints[9,13,14,22], recent studies show that the same considerations pertain in the spine and may play an important role in determining mechanical and functional stability, susceptibility to degenerative disease, function of protective muscular reflexes, and incidence and severity of back pain[11,25,31,37]. The presence of mechanoreceptive nerve endings in the facets of the cervical spine confirms that, at least in this segment of the spine where motion and head position are key functions, the position of the facets and their connective tissues is under surveillance by the central nervous system. This paper reports the results of subsequent analysis of facets in the thoracic and lumbar spinal segments and discusses the significance of these findings in light of neurophysiological studies carried out in our laboratory.

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MATERIALS AND METHODS

Investigators have identified mechanoreceptive nerve endings in a number of spinal tissues, but receptor types and density distributions have not been carefully analyzed. Although recent electrophysiological studies demonstrated proprioceptive endings in facet and paraspinous connective tissues, histological confirmation of location and receptor type was not done[11,37]. This study was

Table 1

Type	Morphological Features	Average Dimensions	Location	Probable Functional Characteristics	Other Eponymous or Descriptive Designations
Type 1	Globular receptors. Round, oval, or "bean shaped", thinly encapsulated, usually found in clusters.	40-100μm in length	Found in fibrous capsule of joint, and in peri-articular ligaments and tendons. Usually in superficial layers of dense connective tissue.	Mechanoreceptor. (Slowly adapting, low threshold afferent ending).	Ruffini ending. Golgi-Mazzoni ending. Meissner corpuscle. Basket or spray-type ending.
Type II	Cylindrical corpuscles with thick laminated encapsulations, and central axon core. Parent axon may be bifid or trifid, entering at one terminal of the cylinder.	μm in length, and 100 μm in width.	Found in deeper layers of fibrous capsule, at junctions of fibrous tissue and fat, and in fat pads. Often accompanied by vascular leash. Oriented with connective tissue fibers in dense capsule or ligament.	Mechanoreceptor. (Rapidly adapting, low threshold afferent ending).	Pacinian corpuscle, Vater-Pacinian corpuscle. Modified Pacinian corpuscle. Paciniform corpuscle. Meissner corpuscle. Golgi-Mazzoni body. Bulbous corpuscle. Club-like ending.
Type III	Fusiform corpuscles with a thin capsule surrounding a densely arborizing nerve terminal. Fine neuritis form meshwork visible at higher magnification.	Up to 600 μm in length, and 100 μm in width.	Found in ligaments and tendons, as well as dense fibrous connective tissue of joint capsule.	Mechanoreceptor. (Very slowly adapting, high threshold afferent).	Golgi ending, Golgi-Mazzoni corpuscle.
Type IV	Unmyelinated free nerve endings and unencapsulated plexuses.	0.5 - 1.5 μm in diameter.	Found in all peri-articular and intra-articular tissues except for cartilage.	Nociceptor. (Non-adapting).	

performed to determine the distribution of mechanoreceptive elements in the facet capsules of normal human subjects to compare the density of receptors in cervical, thoracic, and lumbar segments, and to classify these receptors according to the classification of Freeman and Wyke[12].

Thirty-six facet capsules were harvested from the cervical, thoracic, and lumbar spines of eight normal human subjects. Specimens were taken from the spines of seven patients treated for fracture or dislocation, harvesting only those capsules from uninjured segments undergoing fusion for adjacent trauma, and from one cadaver, a victim of trauma. The mean age of the subjects was 32 years (range 15-60 years), and all capsules were harvested from facets judged to be free of degenerative disease on both radiographic and direct visual inspection. No patient had any systemic disease that might be associated with neuropathy or facet arthropathy.

Facet capsules were sharply excised using scalpel and fine forceps, taking care not to crush or distort the tissue. The entire dorsal capsule was harvested in each case, but the volar portions of the capsule and the interface with the ligamentum flavum were not taken. Tissues were processed for histological examination using a modified gold-chloride technique described by DeAvila et al[8]. Twenty-five micron sections were mounted on standard glass slides, de-paraffinized, and cover-slipped with Permount. No post-staining was necessary.

All sections were analyzed using an Olympus BH-2 light microscope. Encapsulated endings were classified according to Freeman and Wyke (Table 1). To be included in this analysis each ending had to meet three criteria: 1) Each receptor had to demonstrate evidence of encapsulation; 2) Each had to have a morphology consistent with previously described receptors; 3) Each had to be identifiable as an encapsulated receptor on serial sections without evidence of artifact. In most cases a parent axon could also be identified, confirming the structure as a nerve ending and eliminating the possibility of misidentifying a structural artifact or vascular element. Elements which met two of

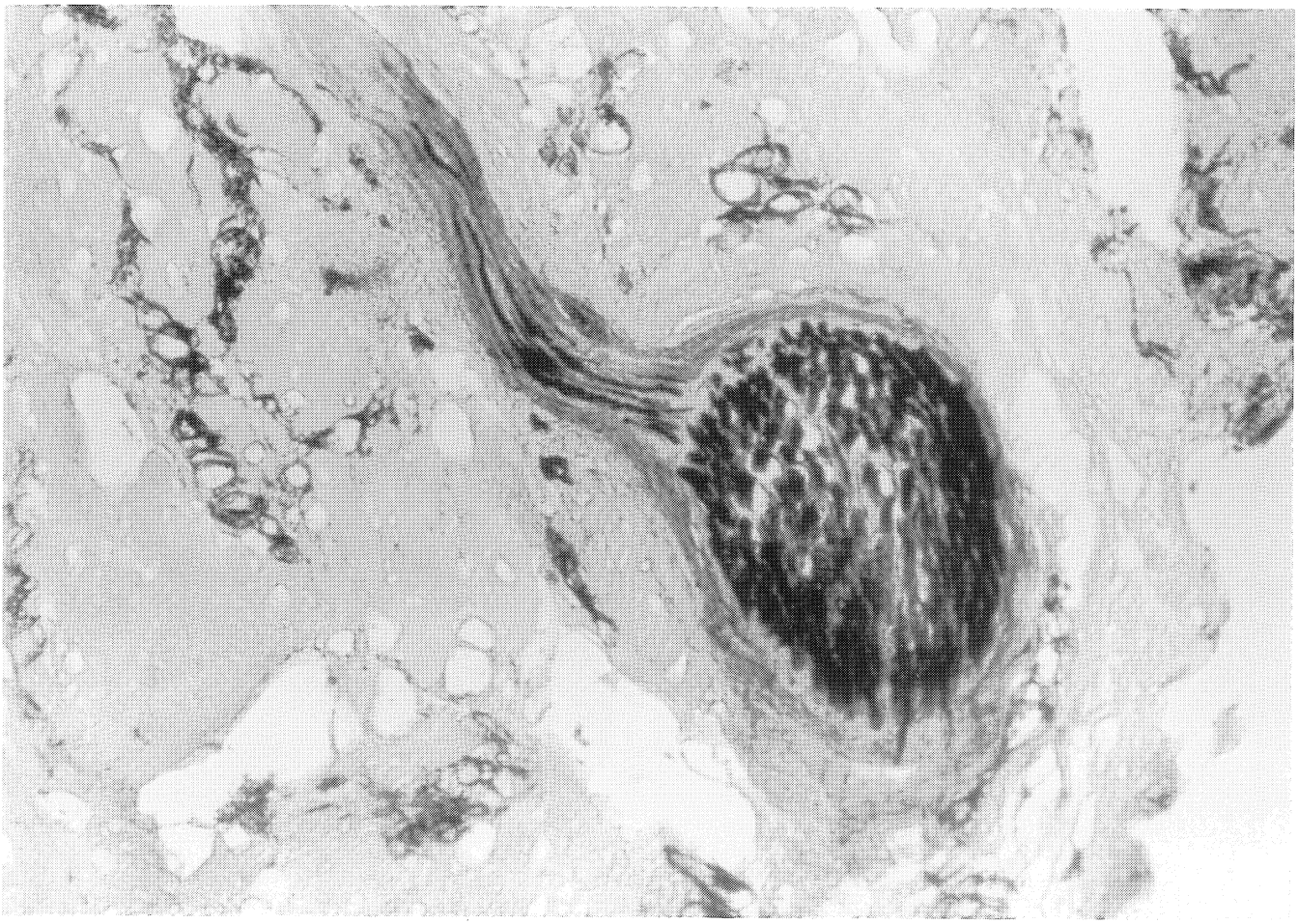

Figure 1. Cross-section of a large nerve entering the facet joint capsule near the junction of the capsule proper and the insertion of paraspinous musculature. The large nerve bundle follows the periphery, giving off smaller branches (arrow) which penetrate deeper into the capsule. These branches then ramify into fine axons and, finally free nerve endings or mechanoreceptive nerve endings.

the above three criteria were encountered and noted, but these were not included in the classification.

RESULTS

Facet capsules at all spinal levels were well supplied with large and small neural elements and with small arterioles and capillaries. The transitional regions between the capsule proper and the insertions of the paraspinous musculature were richly innervated with large and small nerves penetrating from the peripheral margin into the densest portion of the capsule. This was particularly characteristic of the broad lumbar and cervical capsules, and less so of the smaller and thinner thoracic tissues (Figure 1). Fine myelinated and unmyelinated fibers were present in every specimen, and no difference in density could be seen from segment to segment. These fine nerves resembled those described by DeAvila et al: myelinated axons demonstrated a dense, black axon core surrounded by a myelin "clear space" delineated from the surrounding matrix by a very thin line of dark gray neurolemma; unmyelinated axons demonstrated a single black line with a delicate, granular quality[8].

Histological analysis identified encapsulated nerve endings in over 80% of cervical facet capsules, 60% of the lumbar specimens, but only 35% of thoracic capsules. Most cervical capsules contained one or two distinct encapsulated endings; in all, 36 mechanoreceptive endings were found in 21 cervical facets. In contrast, thoracic facet capsules only occasionally contained a single receptor, with two receptors found among seven specimens. The lumbar facets contained an intermediate density of encapsulated endings, with single receptors found in five of eight specimens. Parent axons could be identified for the majority of these endings. Parent axons ranged from three to five microns in diameter.

Type I, non-paciniform endings were found in capsular specimens from both cervical and lumbar segments but were not numerous. Type I mechanoreceptors were usually found in the loose areolar tissue at the margins of the capsule. While previous investigators noted that Type I receptors are often found in clusters, this study noted they were always solitary endings and never found in clusters. These endings measured 35-50 microns in diameter with a slightly ovoid shape and a well defined capsule.

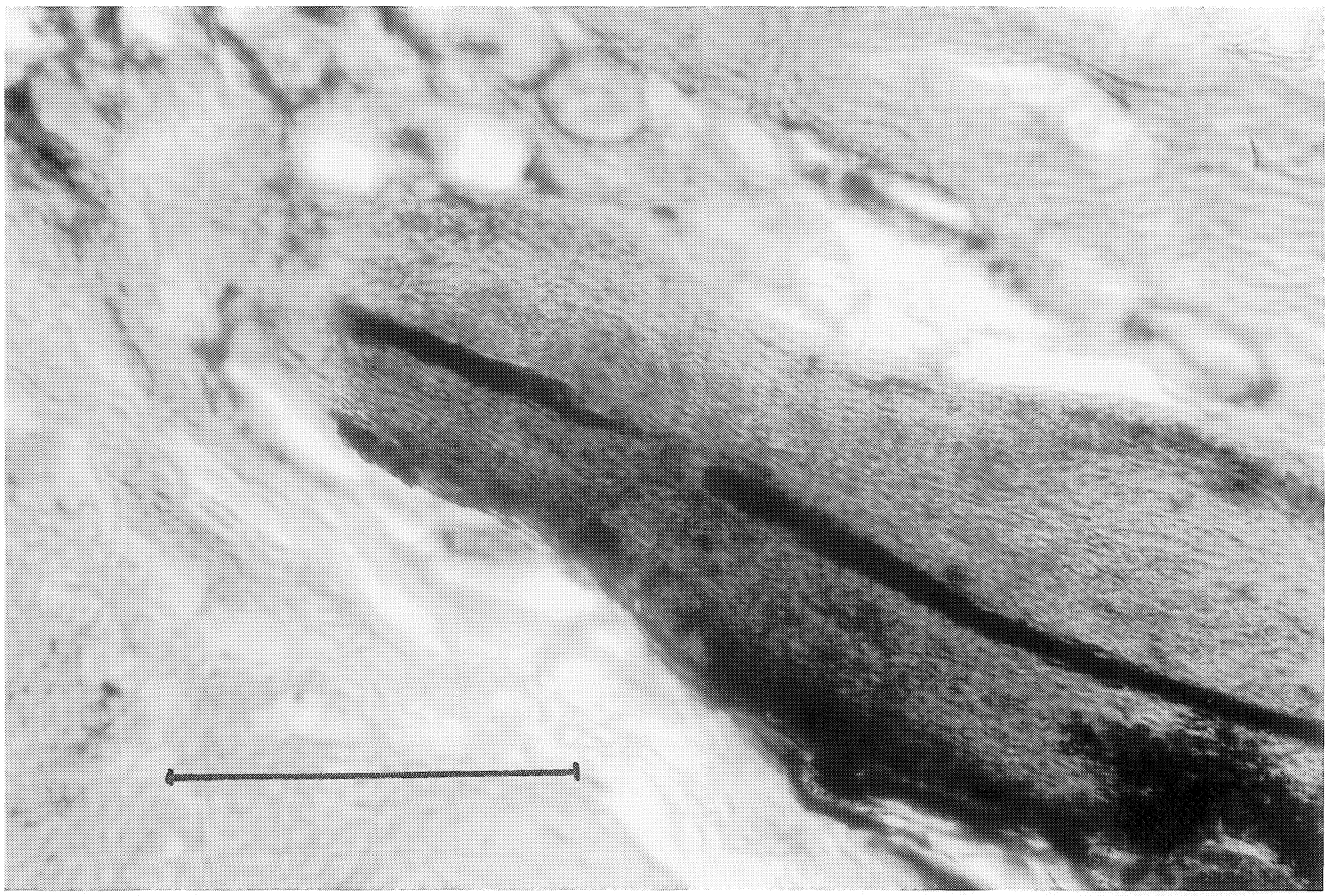

Figure 2. Type II mechanoreceptor from a lumbar facet capsule, showing the dense black central axon core surrounded by a thickened, multilaminar capsule. Ending resides in the dense connective tissue within the substance of the joint capsule, but is surrounded by a small quantity of fibrofatty connective tissue. (Bar = 30 microns).

Type II, paciniform receptors were the most common type found among the spinal facets and were found at all segmental levels. These large receptors, similar in appearance to those described originally by Polacek, varied considerably in size and shape (Figure 2). The largest of the Type II endings measured 500 microns in length.

All of these endings were characterized by a distinct, black central axon core surrounded by a thick capsule made up of numerous lamellae. Cross-sections through the capsule revealed concentric layers of faintly pink staining material alternating with thin gray lines of gold chloride stain at the interface between lamellae (Figure 3). Type II receptors were found in dense, fibrous capsular tissues, often oriented along thin clefts in the collagen matrix. These clefts usually contained a small amount of fibrofatty tissue as well as microvasculature and the parent axon supplying the nerve ending.

Type III endings were uncommon and were only found in a few capsular specimens. These receptors were found at the junction of the dense fibrous capsule and the loose areolar, subsynovial tissue. These large endings contained a fine reticular mesh-work of tiny neurites within a thin, amorphous capsule.

Unencapsulated Type IV nerve endings were identified in all capsular specimens but varied in density from individual to individual. These free nerve endings are thought to be nociceptive in nature[20,23] and were present in all spinal segments. As these elements are ubiquitous, their numbers were not recorded for individual specimens. Type IV endings were found within the dense fibrous capsule as well as the loose areolar and fibrofatty tissues at the margins of each specimen.

Receptors were occasionally encountered which could not be identified according to previous classification schemes. One such encapsulated ending was isolated from the subsynovial portion of a lower cervical facet capsule (Figure 4). This receptor appeared thinly encapsulated with a tortuous coil of neural elements forming a discoid body. Serial sections confirmed the discoid shape consisting of numerous coils of thickened neurites embedded in a granular stroma, and demonstrated a parent axon, aligned

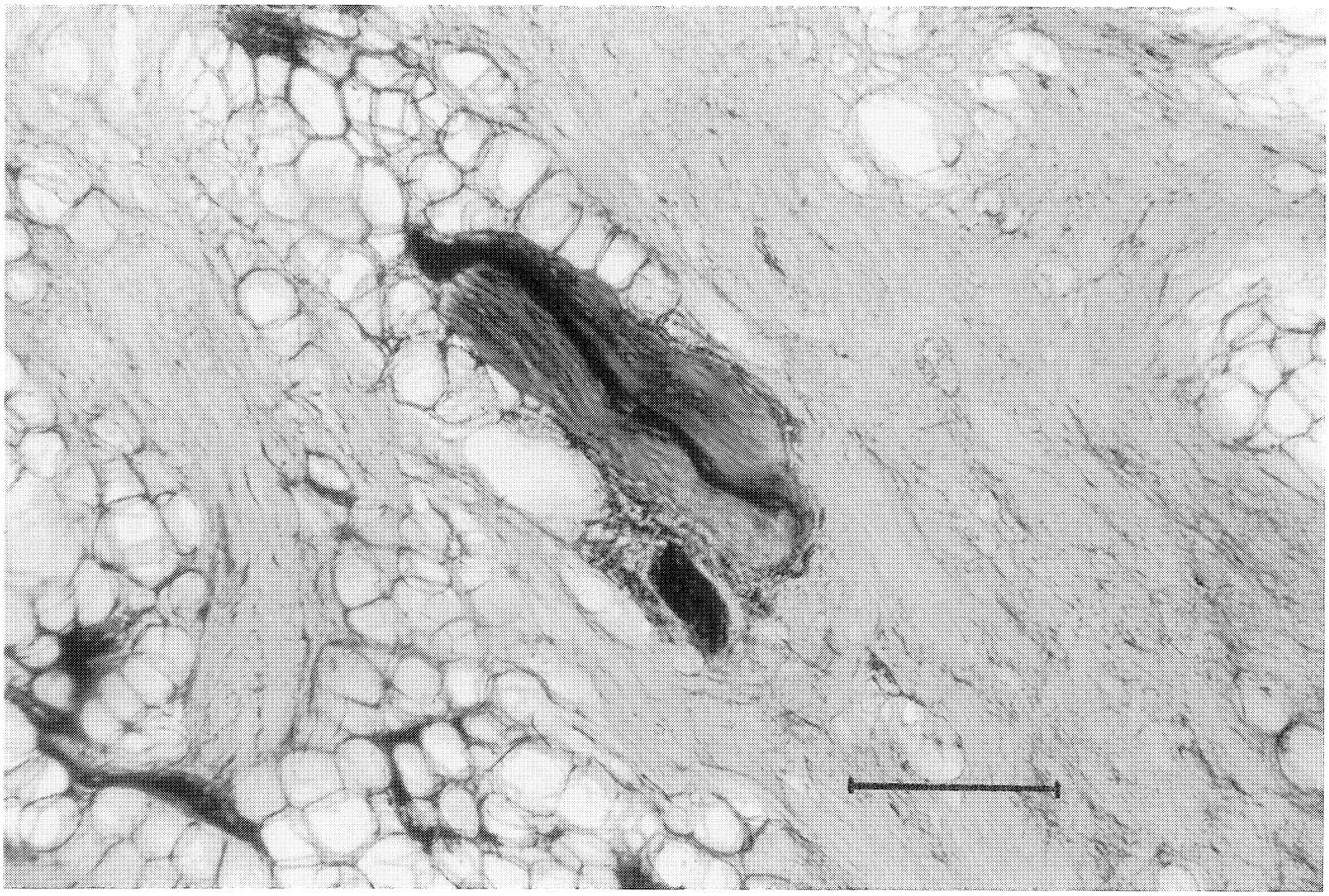

Figure 3. Type II (Paciniform) receptive ending from cervical spine facet joint. Central axon core is contained within a thick lamellated capsule. Serial sections showed this receptor to be approximately 150 microns in length. (Bar = 50 microns).

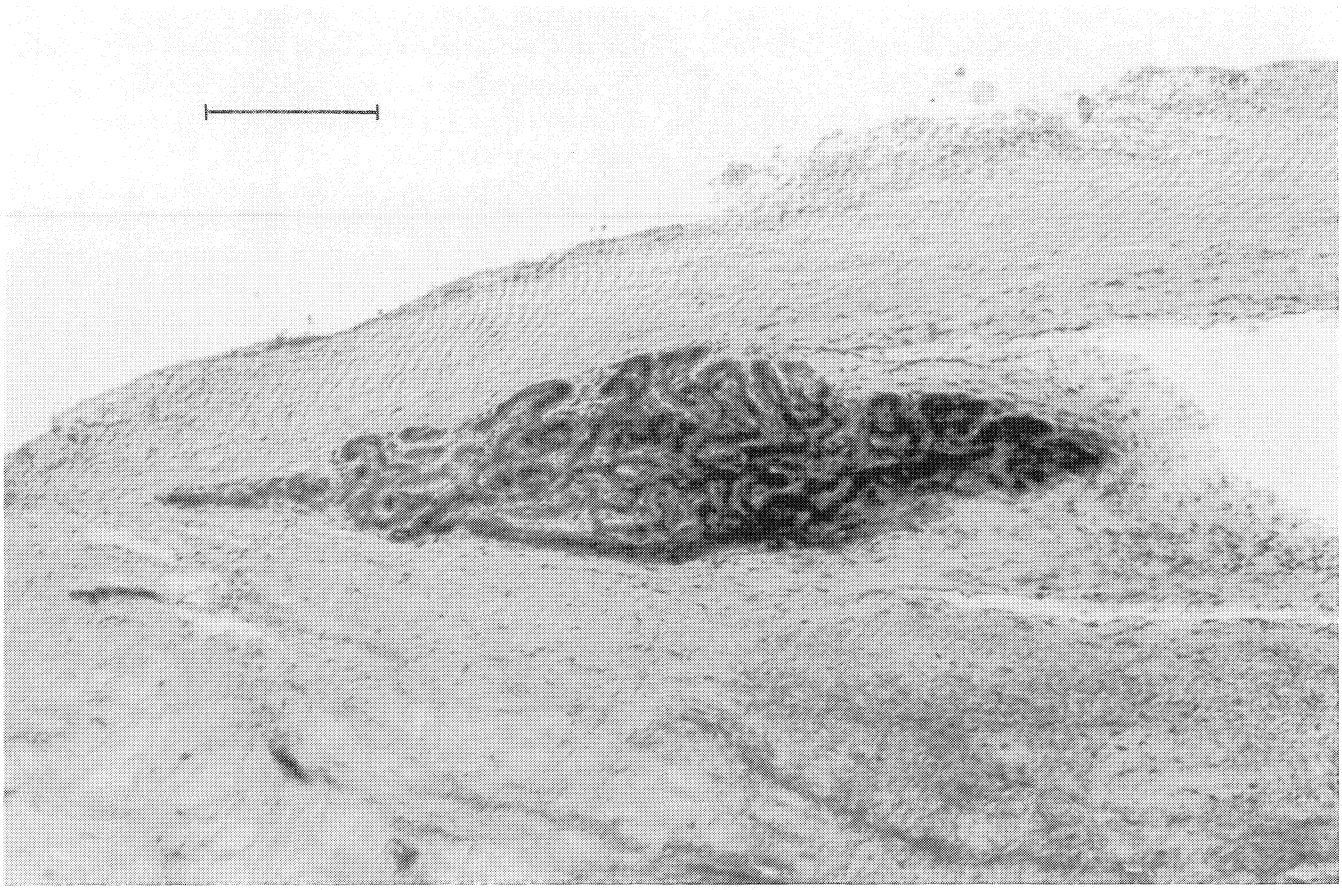

Figure 4. Cross-section of discoid receptive ending located in subsynovial portion of human facet joint capsule. Serial sections reveal a parent axon entering from the left pole. (Bar = 50 microns).

along the collagen bundles, entering the structure at one pole. This structure has not previously been described to our knowledge.

DISCUSSION

Facet capsules at all levels of the spine appear to have at least a small population of mechanoreceptive endings in residence. The cervical regions contain the greatest density and diversity of endings which, considering the proprioceptive and reflexive demands placed on the neck, makes sense. The thoracic spine, which is relatively rigid and unable to contribute much to balance or position, contains only a sparse population of endings. The lumbar spine appears to contain an intermediate number of endings. This information adds to the growing fund of knowledge concerning spinal innervation, and it substantiates a neurosensory role for articular connective tissue of the spine similar to that proposed for peripheral articulations.

Freeman and Wyke documented the presence of encapsulated and unencapsulated receptors in a number of spinal tissues during their analysis of the posterior elements of the spinal column, published in 1967, but they did not comment on the density of the receptors found or on the distribution of the different receptor types among the various tissues studied[12]. Most recently, Giles and Harvey found nociceptive nerve endings in the capsular tissues of the human facets, first in the capsule itself and later in the synovial lining of the facet capsule[15,16]. Gronblad et al identified numerous fine nerve endings traveling with the microvasculature of the synovial plica, and occasionally saw free nerve endings within the synovium, confirming Giles' work[21]. None of these investigators, however, specifically identified encapsulated nerve endings within the substance of the normal facet capsules. Furthermore, each of these studies focused on the lumbar spinal segments, to the exclusion of the thoracic and cervical segments.

The nerve endings found in this study were morphologically consistent with the description given by Freeman and Wyke and others for mechanoreceptors of cat, dog, simian, and human articular tissues[12,27,34,36]. All four receptor types were represented in these normal capsular tissues, though Type III receptors were rare. None of the endings identified in this study resembled the "spray-like" endings seen in human fibular collateral ligaments[8] or the putative "Pacinian", "Golgi Tendon Organ", or "Ruffini"

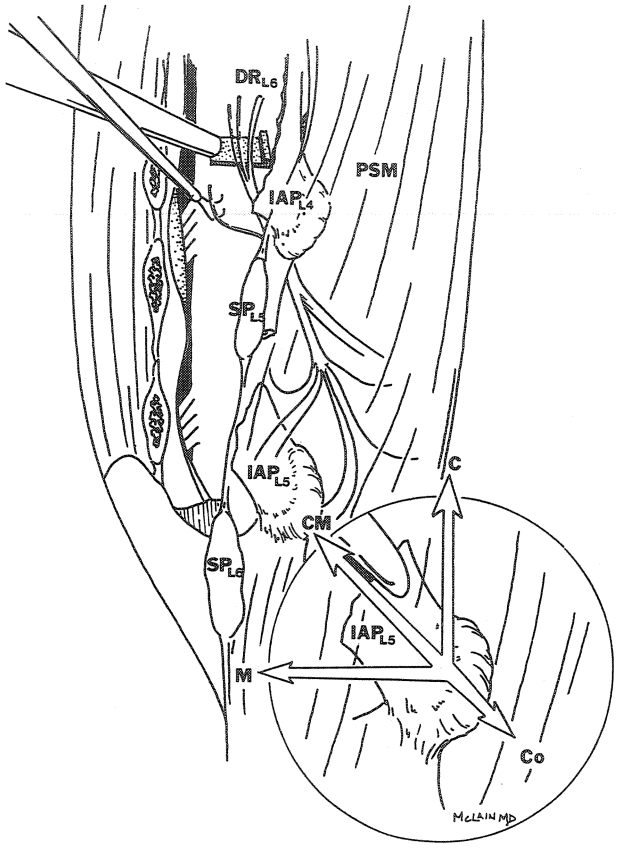

Figure 5A. Experimental set-up for analysis of mechanosensitive nerve endings in and around the capsule of the lumbar facet joint of the cat. The paraspinous muscles (PSM) have been stripped away on the left hand side, but are undisturbed on the right. A wide laminectomy has been performed at L4 and L5, leaving the inferior facet of L5 (IFL5) with its soft-tissue attachments intact. The dura has been opened to reveal the spinal cord and dorsal roots. A bipolar electrode records impulses transmitted cranially through the L6 dorsal root fibers (DRL6). Inset picture shows the jaw of fine rongeur applying cranial (Cran), craniomedial (CM), medial (Med), and compressive (Comp) loads to the inferior articular process of L5.

endings described in studies of the human anterior cruciate ligament[34]. Rather, these endings conformed closely to the descriptions advanced by O'Connor et al, of Types I, II and III endings found in dog and cat periarticular tissues[26,27,28]. Moreover the Type II, or Paciniform, receptors seen in this study closely resembled those receptors originally described by Polacek[33], particularly with respect to the broad encapsulations typical of simian receptors. Receptors in the current study demonstrated thick, concentric capsules with many lamellae similar to those seen in Macaque monkeys, and considerably thicker than seen in the typical Type II receptors of dogs or cats[12,27,33,36]. Whether this similarity has phylogenetic or functional significance is unknown.

The location of the single, discoid receptor identified in this study suggests a mechanoreceptive function as does the complex neural morphology. This receptor does not fit any classification scheme, and does not appear similar to either the "spray-like" endings of Polacek[32] or DeAvila et al[8]. Although Ruffini-like receptors have been shown to vary considerably in their morphology depending on the tissues they inhabit, the size of this discoid receptor is an order of magnitude greater than that commonly attributed to Type I receptors.

The small number of receptive endings encountered in the facet capsules suggests that these receptors have relatively large receptive fields, and that one or two endings are sufficient to monitor the area of the facet capsule. Recently completed neurophysiological studies support this contention, and suggest that a few receptors may be sufficient to monitor not only the facet capsule, but the broad expanse of connective tissues surrounding the facet, both adjacent and remote[31]. These studies clearly show that receptors within and adjacent to the capsule are highly sensitive to facet joint motion and are capable of producing a graduated neural discharge relative to directional changes in capsular tension providing, in essence, directional sensitivity (Figure 5A & B). At the same time we were able to show that receptors at some distance away from the manipulated facet remained exquisitely sensitive to joint motion and direction of pull. These findings suggest either a neural interconnection between receptors within the facet capsule and those in the surrounding musculature, or an indirect transmission of forces applied to the capsule through adjacent ligaments, muscle, and/or fascia, to the remote receptors which actually responded. In either case, the complexity of the neural network in the spine is sufficient to provide a highly integrated level of feedback to the central nervous system regarding position, motion, strain, and muscular activity within the back. O'Connor et al showed in the knee that when sensory disruption is superimposed on joint instability, the rate of articular degeneration is accelerated, compared to either injury alone[29]. Disruption of this proprioceptive system in the spine through surgical intervention, trauma, illness or aging, could seriously impact protective muscular reflexes and balance which may be responsible for preventing injury or for limiting dysfunction in the face of injury[7,10,30,35].

Finally, it is likely that encapsulated endings contribute to pain perception in addition to their proprioceptive functions, particularly with respect to motion outside the extremes of normal joint excursions. Substance P immunoreactivity was identified in free nerve endings in all areas of the body but also in some encapsulated endings, including those within the posterior longitudinal ligament[19,24]. This suggests that at least some putative mechanoreceptors are capable of nociception as well.

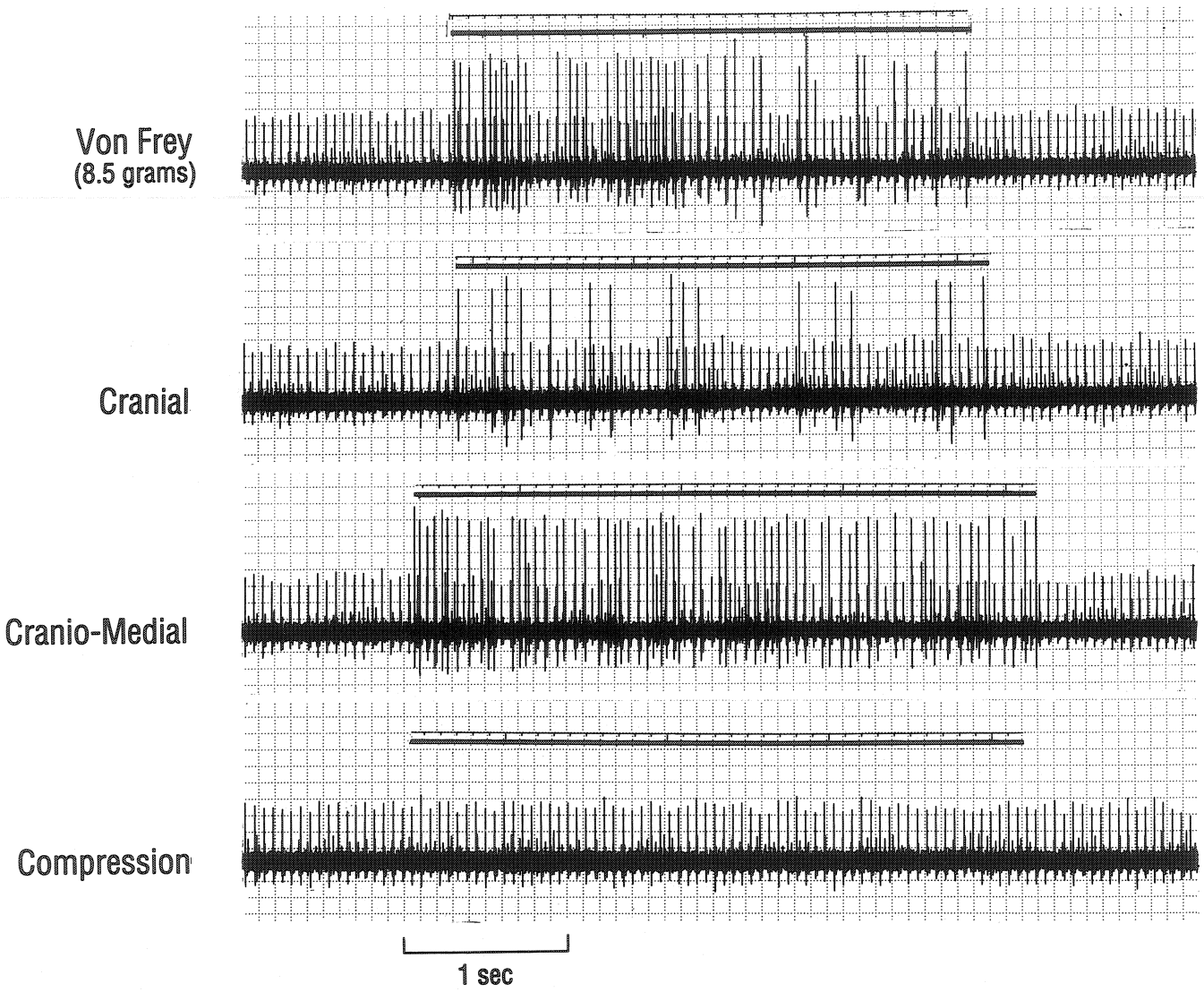

Figure 5B. Single afferent recording from a mechanosensitive ending (large discharge spikes) in the capsule of the L5-L6 facet of a normal adult cat. Recordings were obtained using a bipolar microeletrode, recording resting activity and activity during four modes of stimulation. The top record shows an abrupt increase in discharge activity during stimulation of the receptive field with a von Frey probe. Line two shows a moderate increase in activity of the index ending with 1.0 kg load applied in cranial distraction. Line three shows a marked increase in receptor activity when the same load is applied in the craniomedial direction. Line four demonstrates that there is no activity in this ending when compressive force is applied to the facet joint. The solid bar reflects the duration of stimulus in each case.

Whether the receptors identified in the current study are active in pain production at the extremes of spinal motion is not known.

CONCLUSIONS

The presence of neural elements within the facet joint capsules proves that these tissues are observed by the central nervous system, and the fact that the receptors identified are mechanosensitive suggests that the mechanical state of the spine is monitored through these capsules. Previous neurophysiological studies support this contention and suggest a highly integrated network of nerve endings and connective tissues capable of communicating changes in joint tension or compression both directly to the CNS and indirectly to spinal receptors remote from the actual facet. All four receptor types were identified in the current specimens including Types I-III mechanoreceptive and Type IV nociceptive endings. If different receptor types do respond to different ranges or states of joint excursion[5,6,17], then these receptors are likely to play important roles in proprioception, protective muscular reflexes, joint pain caused by excessive motion, and generalized pain caused by intrinsic or extrinsic stimuli.

The predominance of receptors in the cervical spinal facets is consistent with the greater mobility of this segment of the spine, and with its need to accurately position the head in space and coordinate muscular activity

to protect it from injury. The presence of previously unidentified receptors suggests that there is more diversity in the mechanoreceptive system than previously recognized.

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PROPRIOCEPTION IN THE ANTERIORLY UNSTABLE KNEE

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I. INTRODUCTION

Despite the anterior cruciate ligament (ACL) being the most frequently injured knee ligament[22], the literature suggests a wide range of resulting dysfunction and discrepant treatment. Dysfunction consists of limitation of activities of daily living and recreational activities due to pain, swelling and "giving-way" of the knee[35]. Two distinct, yet not mutually exclusive, viewpoints may account for dysfunction following ACL injury. In the "structural paradigm" , dysfunction results from lack of restraint to anterior subluxation of the tibia on the femur [8,11,15,19,20,21,25,26,30,31]. In the "neurosensory paradigm", dysfunction results from loss of critical sensory input[1,3,6,7,13,24,39,40]. That is, neural pathways originating in the ACL contribute to a sense of "proprioception" , allowing for reflex or supraspinal initiation of stabilizing muscle contraction about the knee.

Proprioception, in its strictest sense, is an awareness of limb location in space[42], reflected by the ability to reproduce limb position. Today this definition is often expanded to include the awareness of limb movement. When proprioceptive sense is lost, as might occur with injury to the ACL, one would be less able to detect limb movement. In 1989, Barrack et al.[3] used latency to detection of passive motion as a measure of proprioception. He used this to demonstrate a proprioceptive deficit in a group of patients with unilateral, isolated, complete ACL tears.

We instituted this study to confirm and extend the findings of Barrack et al. We additionally addressed the issue of dysfunction following injury by identifying the severity of symptoms and degree of functional impairment. Lastly, we explored the possibility that separate populations of mechanoreceptors may be stimulated at different rates of extension of the leg, producing varying degrees of proprioception. Therefore, we proposed the following hypotheses: 1) normal joint movement sense (proprioception) becomes abnormal following disruption of the ACL; 2) dysfunction of the knee correlates with poor proprioceptive ability; and 3) proprioceptive ability depends upon the rate of extension of the knee.

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II. MATERIALS AND METHODS

We identified potential subjects from records of all patients with torn ACL's seen in the Orthopaedic Clinics at the University of Iowa Hospitals and Clinics from January 1, 1987, to March 1, 1990. We selected nine test subjects aged 18-40 years using the following inclusion criteria: 1) positive anterior drawer sign; 2) positive Lachman's sign; 3) positive pivot shift test; and 4) anterior subluxation of the tibia on the femur of at least 3 mm greater than the contralateral normal knee, as measured by the KT-1000 arthrometer at 89 N. The screening process excluded patients with clinical evidence of other major ligament or meniscal injury, those with a history of significant injury to the contralateral knee, and patients in whom ligamentous reconstruction had been performed. Patients with minor meniscal tears were not excluded as long as the injury was not located near the periphery of the meniscus where mechanoreceptors may exist. Only one subject underwent arthroscopy which included resection of the ACL stump and a partial lateral meniscectomy. All test subjects were at least three months post injury and demonstrated at least partial return to recreational activities in order to adequately establish the function of their knee. We recruited fifteen normal subjects, aged 18-40 years from University students and staff.

The examiner assigned each subject a knee-function score according to the Cincinnati Rating System, which evaluates symptoms of pain, swelling, giving-way, and function as related to overall activity level, stairs, jumping or twisting activities, walking and running[36]. This rating scheme served two important functions: first, it allowed us to distinguish subjects functioning well from those functioning poorly after a reasonable recovery period; secondly, it allowed us to control for variability in functioning in our statistical analysis.

The testing apparatus was similar to that used by Barrack et al.[3]. We seated subjects in a custom designed chair reclined to 60 degrees from horizontal for comfort. They wore blindfolds and noise-reducing headphones to decrease visual and auditory cues. Their legs hung freely over the edge of the seat, 4-6 cm proximal to the popliteal fossa. Schuco air splints which covered the feet and ankles, and blood pressure cuffs which covered the thighs were inflated to 20 mmHg to decrease cutaneous sensation. Since it was imperative that motion about the knee be passive, we used surface electromyography to monitor the

muscle activity of the vastus lateralis and lateral gastrocnemius. If muscle activity was detected, that particular trial was repeated. Both legs were passively suspended by wires attached to custom made cloth socks which covered the air splints. These wires coursed through a pulley and connected to a 12V D/C servo-motor with tachometer. An IBM PC/AT compatible computer drove the servo-motor at the appropriate RPM's depending on the desired angular velocity and the length of the subject's leg (center of knee joint to the bottom of the heel). The resulting angular velocities were 0.5 degrees/second and 5.0 degrees/second. The threshold, in degrees, to detection of passive motion about the knee joint constituted the measurement of joint movement sense. This was calculated by multiplying the reaction time and the appropriate angular velocity.

The pulley system was adjustable so that the leg could move through its natural arc. We chose a starting position of 40 degrees of flexion from the horizontal. Several investigators have demonstrated that during normal gait the knee rotates through approximately 0-65 degrees of flexion[27,29,33,34]. Therefore, differences in proprioception detected at 40 degrees of flexion may emphasize findings of dysfunctional gait. Additionally, use of this range of motion allowed comparison with the study of Barrack et al.[3].

We studied all individuals in an identical manner. All subjects had both knees tested. We instructed the subjects that at a random time, 5-30 seconds after a tap on the shoulder, one of their legs would begin to extend. They had an "off" button to press when they detected motion about their knee joints. After two practice runs at each velocity on each leg, we conducted the actual test consisting of twenty repetitions, five on each leg at each velocity. We varied both the velocity and the leg in a random fashion.

As an estimation of muscle mass, we measured thigh circumference 15 cm proximal to the lateral joint line. This was undertaken to determine whether proprioceptive differences may be due to loss of muscle spindles from muscle atrophy which often accompanies knee injuries.

Repeated measures analysis of variance was used to analyze the data. The model used one between-subjects factor (ACL deficient vs. control subjects) and two within-subjects factors: side (injured vs. noninjured in ACL deficient subjects and right vs. left in controls) and speed of motion (0.5 degrees/second vs. 5.0 degrees/second). "Systat" software was used to make correlations between threshold difference (injured - noninjured) and thigh circumference difference, KT-1000 arthrometer difference, Cincinnati Rating System scores, and time since injury.

III. RESULTS

The control group did not show a statistically significant difference in proprioception threshold between right and left knees at 0.5 degrees/second or 5.0 degrees/second (Table 1, Fig. 1). Likewise, the ACL deficient group demonstrated no significant difference in threshold between injured and noninjured knees at either speed. In addition, we observed no significant difference between the control and test groups at either speed.

TABLE 1
ANALYSIS OF VARIANCE

	MEAN THRESHOLDS	P-VALUE
Injured	3.197 ± 1.609	0.639
Noninjured	3.302 ± 1.878	
Left	3.354 ± 1.464	0.639
Right	3.448 ± 2.065	
Injured	3.197 ± 1.609	0.820
Controls	3.354 ± 1.464	
0.5 DEG/SEC	2.002 ± 1.790	0.001
5.0 DEG/SEC	4.690 ± 1.433	

THRESHOLDS TO DETECTION OF MOTION

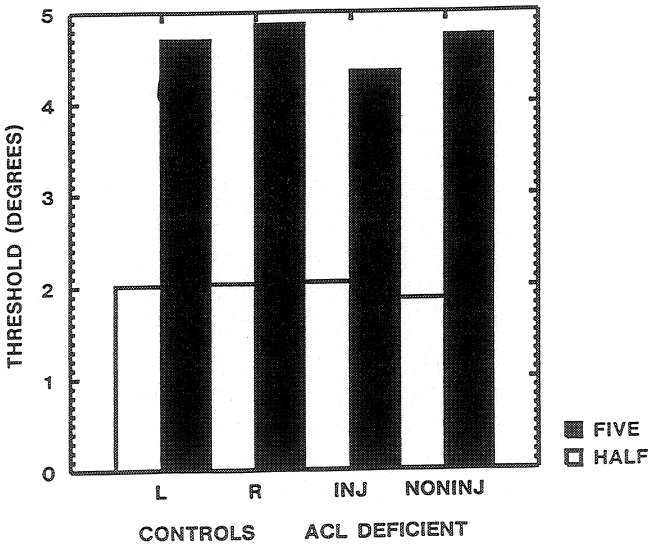

Figure 1

When comparing rates, however, both the control and the ACL deficient groups demonstrated significantly higher proprioception threshold with extension of the knee at 5.0 degrees/second when compared to knee extension at 0.5 degrees/second ($F = 88.99$, $p = .001$).

ACL deficient subjects were an average of 8.7 months post injury. KT-1000 arthrometer testing demonstrated an injured to noninjured mean difference of 6.3 mm (range 3 to 12.5). The injured knees' mean score on the Cincinnati Rating System was 75 (range, 54 to 90). All noninjured and control knees received a perfect score (100 points).

Although a few correlations approached significance (thigh circumference difference -0.472, Cincinnati Rating System -0.400), none were statistically significant (Table 2).

TABLE 2
CORRELATION WITH THRESHOLD DIFFERENCE
(INJURED - NONINJURED)

PARAMETER	0.5 DEG/SEC	5.0 DEG/SEC
Thigh Cir Diff	0.017	-0.472
KT-1000 Diff	-0.051	0.145
Time Since Inj	-0.133	0.100
Function Score	-0.400	-0.183

IV. DISCUSSION

The neurosensory concept of joint function is not a new one. In the mid-19th century, mechanoreceptors were identified in the pericapsular tissue[28,38]. By the turn of the century, an important role for joint mechanoreceptors was conceptually well established by Sherrington[41]. It wasn't until the mid-20th century, though, that investigators began to establish a more precise indication of the contribution of these joint afferents to locomotor function. In the 1940's and 1950's electrical impulses were detected in the cerebelli[2] and post-central gyrus[32,37] of decerebrate cats in response to joint movement. In 1944, Gardner[16] showed that Ruffini mechanoreceptors located in the posterior capsule of the cat knee were associated with the reception of proprioceptive impulses. In 1964, Freeman and Wyke[14] discovered large, dense arborizations of myelinated nerve fibers at the attachments of ligaments. Subsequent were the findings of reflex muscular responses to stimulation of articular nerves in the cat[17] and changes in reflex muscular tension following articular nerve sectioning[9].

Proprioception changes occur under a variety of conditions. Investigators have documented a decline in proprioception attributable to normal aging. Measuring the ability to reproduce from memory the perceived resting position of knees, Kaplan et al.[23] found that elderly women demonstrated decreased static position sense compared to younger women. Athletic training also affects proprioception. Barrack et al.[4] noted that a group of professional ballet dancers performed better than controls on a test of detection of passive motion about the knee, but did worse than controls when reproducing joint angle. They suggested that ballet dancers differed from controls due to different neural mechanisms, different joint laxity or superior muscle development. Articular disease, but not total joint arthroplasty, adversely affects joint position sense. A group of postoperative total knee arthroplasty patients who had osteoarthritis or rheumatoid arthritis showed a marked decline in proprioception compared to controls, but showed no difference between their operated and unoperated knees[5]. The authors concluded that a marked decline in proprioception is associated with degenerative joint disease, but that total joint replacement did not lead to a further decrease in sensation. Similarly, sixteen patients studied prior to and following total hip replacement with capsulectomy demonstrated no decline in joint position sense[18].

Several studies suggest that ligaments may be important in joint position sense. For example, Freeman et al.[13] noted that ligamentous injury to the foot and ankle leads to proprioceptive deficits. Their definition of proprioception deficit consisted of subjective observations of a modified Rhomberg's test and/or the patient's perceived instability. They concluded that the incidence of proprioceptive deficit and the symptom of "giving way" could be reduced by coordination exercises.

Recently, mechanoreceptors have been reported in the human ACL[24,39,40]. Kennedy et al.[24] and Schultz et al.[39] postulated their role in proprioceptive reflex arcs which protect the knee from deformation beyond its anatomical limits. Using latency to detection of slow passive extension of the knee, Barrack et al.[3] identified a proprioceptive deficit in 11 patients with a documented complete ACL tear.

Our first hypothesis, that normal joint movement sense (proprioception) becomes abnormal following disruption of the ACL, is not supported by our findings of no change in threshold to detection of passive motion between ACL deficient and normal knees. Our findings are contradictory to the findings of Barrack et al.[3] who showed a decrease in proprioception in ACL deficient knees when joint movement senses was measured at 0.5 degrees/second. This discrepancy may be explained by one or more of the following: 1) our nine subjects or Barrack et al's eleven subjects may not be representative of a larger group; 2) our ACL deficient groups may not be comparable because all of Barrack et al's subjects underwent arthroscopy with resection of the ACL stump while only one of our test subjects had a similar procedure. Since there is a tendency to select more severely injured knees for arthroscopy, their test group may have been biased toward more severe joint injuries. Likewise, because we did not visu-

alize the ACL in most cases, some of our subjects may have had only partial ACL tears with preservation of some neural structures; 3) our instructions to the subjects or some unidentified experimental conditions may have differed; and 4) the ACL may not significantly contribute to knee joint proprioception, at least in some patients, particularly since innervation is variable.

Our second hypothesis, that dysfunction of the knee correlates with poor proprioceptive ability, is also not supported by the data. This suggests that: 1) the Cincinnati Rating System is not a sensitive method for detecting proprioceptive dysfunction, or 2) latency to detection of passive motion measured experimentally at 0.5 degrees/second and 5.0 degrees/second does not relate to dysfunction in activities of daily living. Perhaps testing at even faster rates closer to physiologic speeds (upper limits of which reaches 200-400 degrees/second)[43] may show differences, or 3) our patient population may be insufficiently impaired to exhibit abnormal proprioception.

Lastly, we hypothesized that proprioceptive ability in the knee depends upon the rate of extension of the knee. Our data showing an increased threshold to detection of motion at 5.0 degrees/second compared to 0.5 degrees/second supports this hypothesis. Two explanations may account for this: 1) separate populations of mechanoreceptors in the ACL are stimulated at different rates of extension of the knee, providing different proprioceptive information; or 2) other periarticular receptors (including muscle spindles) may be selectively activated at higher speeds.

Thigh circumference was shown not to correlate with the difference in proprioception threshold between the injured and noninjured knees. Since thigh circumference was used as a measure of muscle mass, it follows that muscle mass did not affect proprioceptive ability. This is supported by the finding that the morphology of muscle spindles does not change with muscle fiber atrophy[10]. We do not, however, suggest that muscle spindles contribute to movement sense.

In our attempts to replicate Barrack et al's data, we encountered several inherent limitations common to both studies. First, innervation of the ACL is likely variable. Some subjects may rely more heavily on ligamentous afferents than other subjects. Therefore, while some ACL deficient subjects showed increased thresholds individually, there was no significant increase in threshold when evaluating the group as a whole. Second, supraspinal processing of afferent signals may vary from person to person depending on level of concentration, degree of athletic ability, genetics or other unknown variables. Third, while ACL deficiency can be confirmed by both clinical criteria and arthroscopic findings, it is technically more difficult by either method to exclude and control for small yet significant capsular and/or collateral ligament tears which may contribute to proprioceptive loss. Fourth, measurements of knee laxity by the KT-1000 arthrometer are subject to inter-and intraobserver variability[12]. We attempted to eliminate interobserver variability by having one experienced person make many (6 of 9) of the measurements.

In addition to the limitations common to both studies, several of our control and test subjects reported a vibratory sensation in their toes, heel or the back of their knee when the motor was engaged. It is possible that some subjects may have been responding to this vibration sensation instead of, or in addition to, a movement sensation; thus confounding potentially real differences.

V. CONCLUSIONS

In the population studied and with the method we employed to measure proprioception, we found no evidence of proprioceptive loss with ACL injury. We noted no significant correlation between poor proprioceptive ability and dysfunction of the knee as measured by the Cincinnati Rating System. We did, however, detect differences in proprioceptive ability at varying rates of extension of the knee.

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RESULTS

Bone Length. The tibiotarsus (TT) and femur (F) of controls grew longitudinally 33.2 and 21.6 mm respectively between 8 and 12 weeks of age, and 9.3 and 5.9 mm between 12 and 14 weeks. No further longitudinal growth was seen in the bones of the controls between 14 and 20 weeks of age (Table I).

At eight weeks of age the runner TT was 13 percent shorter and the F 12 percent shorter than age matched controls. By 12 weeks of age the difference in length had been reduced to 9 percent for TT and 7 percent for F, and at 14 weeks both bones had reached approximately 95 percent the length of the control bones. After 14 weeks there was no further increase in the length of the control bones, but the runner bones continued to grow, reaching 98 percent of the length of age matched controls at 20 weeks. The differences between the runners and the control bones were statistically significant ($p<.05$) at all ages except for the femur at 20 weeks of age (Table I).

Bone Cross-Section Area. At eight weeks of age control TT bones had reached 60 percent of their final cross-sectional area and the F 72 percent. By 12 weeks these values had increased to 95 percent TT and 100 percent F. In contrast, at eight weeks the runner TT had reached only 52 percent of its final radial growth and the F 54 percent. By 12 weeks, these values increased to 95 percent TT and 96 percent F. Hence, the radial growth rate was delayed in the runner bones. Further, similar to length, the runner TT and F approached the radial growth of the control bones by 14 weeks but remained 12.4 percent (TT) and 5.4 percent (F) smaller than controls at 20 weeks of age (Table I).

Cortical Area. The increase in total cross-sectional area was paralleled by a proportional increase in cortical area for both the runners and controls with the percent of the total cross-sectional area occupied by cortical bone decreasing approximately 5-8 percent from 8 weeks to 20 weeks of age. At all ages studied, the absolute value for the cortical bone area in runners never reached the control value; therefore, the actual amount of cortical bone in the runners compared to control bones remained less than 100 percent at maturity (20 weeks). However, when the cortical area was calculated as the percent of its own total cross-sectional area, the TT cortex of runners was proportionally larger than controls at all ages, whereas the F cortex was increased only at eight weeks (Table I).

In order to determine if the runner bones, which were delayed in both length and radial growth at the young ages, were proportionally normal, length/cross-sectional ratios were determined at each age group for both the control and runner bones. Total cross-sectional diameter and cortical cross-sectional diameter, defined as the diameter of a circle equal to the cortical cross-sectional area, were used in calculating these ratios. The length-total cross-section diameter ratio was significantly smaller ($p<.05$) in the runner TT compared to age matched controls at eight weeks of age. All other length-total cross-section diameter ratios were similar in runners and controls. The length-cortical cross-section diameter ratio was significantly smaller ($p<.05$) in the 8- and 12-week TT and 8-week F runners compared to age matched controls. All other length-cortical diameter ratios were similar between runners and age matched controls (Table II).

Collagen Nonreducible Crosslinks. Lysylpyridinoline (LP) and hydroxylysylpyridinoline (HP) represent two of the major intermolecular crosslinks of both avian and mammalian bone collagen. While the HP crosslinks are present in mature collagen of many types of connective

TABLE II

LENGTH-CROSS SECTION DIAMETER RATIOS OF CONTROL AND EXERCISED TIBIOTARSUS (TT) AND FEMUR (F)

	Control TT	Runner TT	Control F	Runner F
8 Wk-length/total D.	16.37 ± 1.29	*15.18 ± 0.57	10.33 ± 0.71	10.10 ± 0.22
8 Wk-length/cortical D.	22.98 ± 1.96	*20.98 ± 1.27	15.54 ± 0.72	*14.67 ± 0.56
12 Wk-length/total D.	16.86 ± 1.27	15.78 ± 1.26	10.40 ± 0.14	10.45 ± 0.53
12 Wk-length/cortical D.	24.93 ± 1.32	*22.95 ± 2.24	16.32 ± 0.53	16.44 ± 0.73
14 Wk-length/total D.	16.69 ± 0.55	16.49 ± 0.77	10.72 ± 0.19	10.65 ± 0.34
14 Wk-length/cortical D.	26.04 ± 1.23	27.75 ± 1.29	17.16 ± 1.01	17.59 ± 0.94
20 Wk-length/total D.	16.88 ± 1.05	17.75 ± 0.22	10.83 ± 0.39	11.06 ± 0.44
20 Wk-length/cortical D.	25.72 ± 1.33	26.75 ± 0.99	17.57 ± 0.66	17.65 ± 0.39

Data = mean ± S.D.
*Significantly different from age matched controls ($p<.05$)

TABLE III

PYRIDINOLINE CROSSLINKS
(20 Wk Chickens)

	TIBIOTARSUS				FEMUR		
Animal#	HP	LP	Total	Animal#	HP	LP	Total
CONTROLS	Res/Mole Collagen				Res/Mole Collagen		
1	059	.153	.212	1	.051	.105	.156
2	.085	.196	.281	2	.045	.117	.162
3	.078	.135	.213	3	.075	.132	.207
4	.087	.140	.227	4	.072	.114	.186
5	.060	.135	.195	5	.051	.101	.152
6	.091	.138	.229	6	.051	.093	.144
Mean	.077	.150	.226	Mean	.058	.110	.168
S.D.	.014	.024	.029	±S.D.	.013	.014	.024
RUNNERS							
7	.056	.125	.181	7	.071	.109	.180
8	.062	.129	.191	8	.076	.087	.163
9	.075	.174	.249	9	.076	.126	.202
10	.068	.156	.224	10	.074	.131	.205
11	.087	.116	.203	11	.062	.093	.155
12	.048	.131	.179	12	.066	.121	.187
13	.061	.133	.194	13	.063	.101	.164
14	.071	.168	.239	14	.052	.128	.180
Mean	.066	.142	.208	Mean	.068	.112	.180
S.D.	.012	.021	.027	S.D.	.008	.017	.018

tissues, the LP crosslinks are present only in mineralized tissue, and it has been suggested that they might represent a specific metabolic marker of bone turnover[6]. The number of pyridinoline crosslinks in the TT and F of 20-week-old animals did not differ significantly between the controls and runners. However, in the TT , the control group demonstrated a slightly higher value (0.226 residues/M collagen) than the runners (0.208 residues/M collagen). In the F, the reverse was true with the runners indicating 0.180 residue/M collagen compared to 0.168 in the control group. In both the control and runner groups the TT indicated a significantly greater number of residues/M collagen than the F. Lysylpyridinoline was the predominant form of pyridinoline crosslinks by a ratio of nearly 2:1 (Table III).

DISCUSSION

The effects of exercise on adult mammalian bones are well documented and such studies indicate increased cortical thickness[9, 21] and increased density of the bones[15]. Mature avian bone responds to disuse or to the application of moderate dynamic loads in a manner very similar to mammalian bone. Non-loaded bones show cortical thinning, intracortical porosis and some subperiosteal new bone formation, while extensive subperiosteal and endosteal new-bone formation without any remodeling within the preexisting cortex is observed in moderately loaded bones[18].

The response of immature bone to exercise has received very little attention in spite of data indicating that its adaptation does not parallel that of mature bone. In 1977 Kiiskinen reported that intensive training decreased the volume and length of the femur of growing mice[11]. A reduced rate of growth was also found in junior high school athletes playing a strenuous and long season of interscholastic basketball[19], and retarded growth of the lower extremities of children submitted to strenuous physical labor has also been reported[10].

Our data indicate that strenuous exercise delays the linear and radial growth of TT and F of male chickens with the degree of stunting greatest in the youngest group. Further, at the younger ages the runners' bones were not proportionally normal in regard to length/cross-section relationships.

At skeletal maturity (20 weeks), the length of the runner long bones were nearly normal, but the total cross-sectional area of the TT was 12.4 percent smaller than that of age-matched controls and 5.4 percent less in the F. Since the initial degree of radial growth delay in the two bones of the 8-week-old runners was similar, the better recovery of the F could be related to the amount of growth expected of the bone and/or to a lesser effect of stress on the femur. The total cross-sectional area of the femur in the 8-week-old controls is 32 percent larger than that of the TT. To fulfill its physiological function, the F

needs only to increase by 39 percent between 8 to 20 weeks of age, compared to 66 percent for the TT. Likewise, the femoral cortex needs to increase by only 22 percent between 8 to 20 weeks compared to 40 percent for the TT. Our observations in the strenuously exercised avian growing bone suggest that the osteogenic response observed in the adult animal apparently is suppressed or overcome in the young bone by other factors (e.g. hormonal changes induced by strenuous exercise) having a pronounced negative effect on bone growth. Previously we found that the tarsusmetatarsus (TMT) of these same 8- and 12-week old runners had a significantly smaller total cross-sectional area, but the percent of the total cross-sectional area comprised by cortical bone was significantly greater in the runners. Further, the runners had decreased bending stiffness, energy to yield, and energy to fracture compared to bones of age matched controls, therefore suggesting that our experimental conditions not only altered the bone mass but also the mechanical quality of the bones [12]. Our present data indicate that at 8 and 12 weeks of age the runners also had smaller TT and F total cross-sectional areas, but at 12 weeks of age the TT cortical bone cross-sectional area had normal values while the F cortical bone area remained 17 percent smaller in the runners than in the control animals. These data suggest a distal to proximal gradient associated with the impact forces related to running. After 12 weeks of age the TT continued to increase in radial growth (periosteal), but no further proportional increase in cortical bone (endosteal) growth occurred. In fact, medullary cavity expansion increased slightly in the runners reducing the amount of cortical bone from 48 percent to 45 percent while in the control TT cortical bone area, it remained proportionally at approximately 42 percent of the total cross-sectional area. Therefore, on a percent basis the TT of runners maintained a larger cortical bone area than control animals. In the femur, the total cross-sectional area continued to grow between 12 and 14 weeks of age in both control and runner animals, but the medullary cavity also expanded proportionally thereby maintaining a cortical bone area equal to 40 percent of the total cross-sectional area. At maturity (20 weeks), we found the F collagen to be less cross-linked than the TT suggesting a distal to proximal impact force gradient associated with running on the long bones. Further, the TT cross-sectional area was significantly smaller in runners compared to controls as also occurred in our previous study involving the TMT. In contrast, the femur had reached nearly normal morphometric values at 20 weeks of age. Therefore, the TT appears more stunted relative to growth and composition than the F, and the TMT was previously found biomechanically to be markedly younger in runners than in controls. These data suggest that the distal bones are affected by the running regime to a greater extent than proximal bones. Li et al[23] have also indicated that there are marked differences regarding the effect of strenuous exercise on immature tibia and metatarsal bones in the rat, suggesting that local loading and bone specific responses are important in modulating the effects of immature bone to strenuous exercise. While further studies are needed to determine the mechanism of the bone growth suppression observed, it appears erroneous to assume that data obtained from adult tissue are also applicable to young growing bone.

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THE SENSITIVITY OF JOINT AFFERENTS TO KNEE TRANSLATION

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ABSTRACT

The cruciate ligaments contain mechanoreceptors which putatively contribute to knee function and dysfunction. However, the interpretation of studies showing neural responses to traction loads applied to the cat cranial cruciate ligament (CCL - analogous to the anterior cruciate ligament in humans) depends upon demonstrating that non-CCL periarticular receptors are not stimulated. We assessed the capability to rigidly fix the knee against traction loads applied to the feline CCL. The tibia and femur were fixed either with clamps or Steinmann pins. Motion of the bones was monitored with liquid metal strain gauges (LMSG) and the activity of the posterior articular nerve (PAN) was recorded while traction loads of up to 20-30 N were applied to the CCL. Joint afferents recorded from the PAN were insensitive to the CCL loads in the rigidly fixed preparation. Motion of the proximal tibia and distal femur was less than 100 micrometers for both methods of fixation, with neither method demonstrating more rigid fixation. In contrast, we observed vigorous discharges with focused light pressure on the capsule and under conditions allowing 200-500 micrometers of tibial displacement on the femur. This suggests that clinically undetectable instability may give rise to aberrant mechanoreceptor activity contributing to dysfunction.

Keywords: Mechanoreceptors; anterior cruciate ligament; posterior articular nerve; cat

INTRODUCTION

The role of ligament mechanoreceptors in motor control has considerable biological and clinical importance[1, 4, 11, 13, 18, 20, 25]. The histologic presence of mechanoreceptors in ligaments and experimentally documented physiological responses to stimulation strongly suggest an important role in motor control. Clinically, variable (but sometimes excellent) recovery of untreated patients with complete tears of the structurally important anterior cruciate ligament (ACL), as well as variable recovery in surgically restored ACL's, suggests a function of the ligament beyond a structural one, leading some to postulate a neurosensory function[6, 7, 30]. The high incidence of ACL injury[23] and controversies surrounding treatment of these injuries argue for establishing a clear understanding of the sensory role of this ligament.

Several investigators have experimentally explored the role of ligament mechanoreceptors in cats by recording reflexes or afferent nerve responses to pressure or traction on the intact CCL while fixing the tibia and femur[20, 26, 28, 29]. The *in vitro* importance of these responses depends upon whether or not the applied stimuli are similar to those which might occur *in vivo*. Thus, it is important to know whether the displacements occurring in those experiments, and the loads applied could occur *in vivo*, and under what circumstances.

Further, each of the above investigators assumed that the reported responses occurred only as a result of mechanical stimulation of receptors in the CCL. However, other periarticular tissues contain sensitive mechanoreceptors[2, 3, 5, 9, 10, 16, 17, 27], and one cannot presume a priori that the sorts of fixation used are sufficiently rigid to insure that the recorded responses do not result from non-CCL receptors.

We conducted the following study to determine the amount of tibio-femoral displacement which would result in mechanoreceptor activity, and whether two kinds of femoral and tibial fixation were sufficiently rigid to prevent stimulation of various periarticular receptors in response to tugging on the intact CCL.

MATERIALS AND METHODS

One male and two female adult cats were obtained, housed and treated following The United States Public Health Service approved guidelines. The cats were anesthetized with Ketamine administered intramuscularly (25 mg/kg) and alpha-chloralose administered IV (60 mg/kg loading dose, 20 mg/kg/hr maintenance), and placed on ventilatory support. Rectal temperature was maintained at approximately 37 degrees C. The anterior aspect of the knee was exposed to gain access to the CCL. A long parapatellar incision was made after which the patellar tendon was detached from the tibial tubercle with the tendon and patella reflected proximally. After excising the underlying fat pad, a loop of Dacron suture material was passed around the CCL for applying traction loads to the ligament.

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After exposure of the CCL, the animal was placed prone in a rigid frame, with the right hip extended (Figure 1). The iliae were secured with screws. The frame of one cm by one cm square steel stock provided two vertical struts; one for a clamp to grip the femur and one for a clamp to grip the tibia. The tibia and femur were secured approximately 10-15 degrees short of full extension using compression clamps with serrated jaws that gripped the exposed bone. These clamps were positioned as close as possible to the joint. After data were obtained using this apparatus, the serrated jaws were replaced with grooved clamps that held Steinmann pins (3.2 mm diameter). One Steinmann pin was driven through each of the bones and secured by identical clamps on each side of the bone.

Motion of the femur and tibia relative to the clamps holding the serrated jaws or Steinmann pins was measured using liquid metal strain gauges (LMSGs)[8]. One strain gauge was affixed to the tibia within a few millimeters of the tibial plateau and one to the femur at the center of the condyles. The other ends of these gauges were secured rigidly at the bases of the clamps that held the respective bones.

The tibial nerve was exposed in the popliteal fossa and the posterior articular nerve (PAN) was identified and exposed[11, 12, 24] under a dissecting microscope for multi-unit recording. Extracellularly recorded action potentials were obtained from the whole PAN or from smaller teased bundles using platinum bipolar hook electrodes immersed in warmed paraffin oil confined to the space in the posterior fossa formed by exposing the PAN. Action potentials were amplified by a Grass P511 AC preamplifier with bandpass filtering of 300-10KHz. Amplified signals were connected to a loudspeaker for audible monitoring during the experiments.

The CCL was stimulated by exerting traction via a Dacron loop attached to a hand-held force transducer (Grass FT03 and Grass P122 DC amplifier). Traction was usually exerted perpendicular to the table surface, although pulls directed off this axis were also employed in attempts to influence PAN discharge. Traction was performed with the two clamping systems fixed as rigidly as possible, then with the clamps or pins variably loosened. Light pressure on the joint capsule was applied by a two mm glass rod with a smooth, rounded end.

All signals were stored on magnetic tape with a bandwidth of DC-2250 Hz. These signals were digitized subsequently using a 12 bit analog-to-digital converter and a personal computer. The PAN signal was digitized at 12.5 samples/second and the force and position signals digitized at 400 samples/second. The action potential spikes in the PAN signal that could be reliably distinguished from noise were marked for their time of occurrence using an interactive graphical analysis program. The inverse of the period between adjacent discharges was calculated and plotted over time to yield plots of discharge frequency.

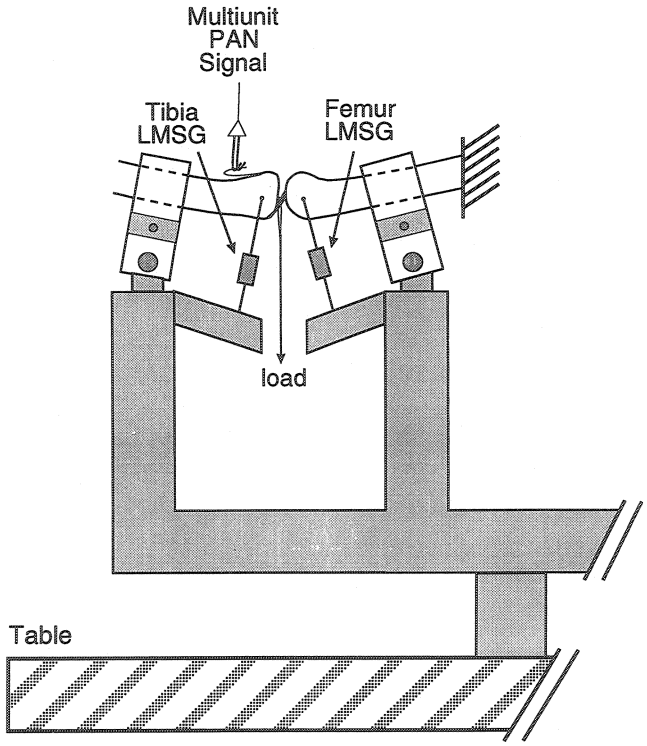

Figure 1. Schematic of the apparatus.

RESULTS

With tightened clamps the knee joint and frame were visibly rigid for loads of 15-20 N (approximately one-half body weight) applied to the CCL through the loop of suture. These loads yielded LMSG shortening of 0-75 micrometers and 0-60 micrometers relative tibio-femoral displacement when the serrated jaws clamped the bones (Figure 2; left). In one animal no displacement was registered when tightly clamped; in the other two animals 15 N loads yielded movements of about 30-50 micrometers. Steinmann pin fixation resulted in roughly comparable displacements with comparable loads (Figure 2; right).

Joint receptors were insensitive to the motion (i.e., up to 60 micrometers) of fully clamped or pinned bones when tugging on the CCL (Figure 3). The background discharge frequency of the PAN spikes was unaffected by the CCL loads or small displacements during traction on the CCL (Figures 3 and 4). Repeated application and release of these CCL loads failed to reveal either increased or decreased PAN discharge rates while the load was held constant, or while the load was changing. Strong, brief tugs that saturated the force transducer also failed to affect PAN discharge (Figure 4). Evidence for altered discharge rates in the multi-unit signal also was not heard when the signal was amplified and fed to a loudspeaker

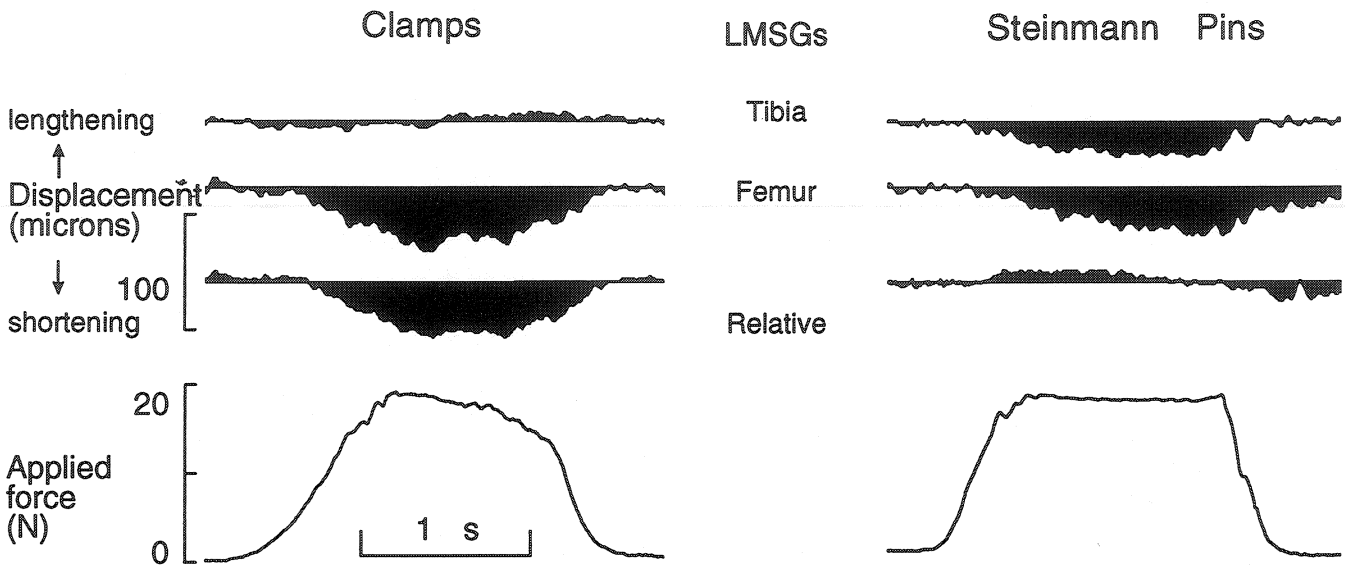

Figure 2.
Signals from the LMSGs during application of traction on the CCL. Tibial motion was somewhat greater with the single Steinmann pins than for the clamps, but less than 50 micrometers. Relative motion (third trace from top) was computed by subtracting the femoral displacement from the tibial displacement.

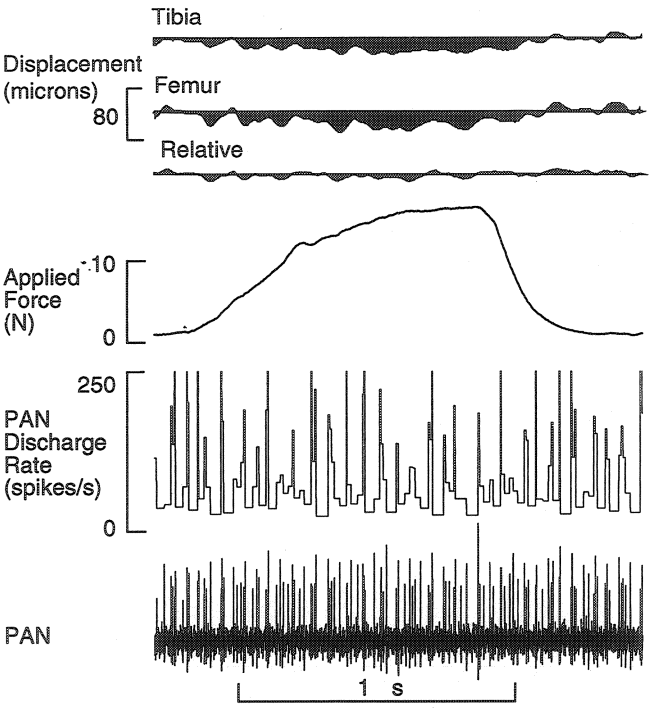

Figure 3.
Signals obtained during a single trial during which the CCL load was increased steadily to about 17 N with less than 10 micrometer relative tibiofemoral displacement. The raw, multi-unit PAN signal is the lowermost trace. Instantaneous PAN discharge rates above background were not observed.

during the experiment or later during formal analysis.

In contrast, PAN discharge increased with gentle probing of the joint capsule with a glass rod, and when CCL loads of about 6 N were applied while the clamp holding the tibia was loosened slightly (Figure 5). Under the latter conditions the tibia visually moved forward (and rotated) relative to the femur with tibial LMSG lengthenings of over 500 micrometers while the femoral LMSG remained stable. However, the increased discharge patterns began with as little as 20-30 micrometer LMSG lengthenings, indicating substantial sensitivity of pericapsular receptors.

DISCUSSION

Given that several reports in the literature[9,19,21,28] document substantial sensitivity of CCL mechanoreceptors to direct stimulation, it is important to know the relevance of that sensitivity to the displacements of the tibia relative to the femur which stimulate receptor activity. It is also important to know whether that degree of displacement could have caused the stimulation of non-CCL mechanoreceptors, thus confounding the interpretation of those studies.

Several issues must be noted prior to interpreting the results of this experiment. First, the actual loading of the CCL under these conditions is unknown: the measured load is in fact distributed to various ligaments and other periarticular soft tissues. The actual load in the CCL in our experiments would lie between the measured load and the load on the CCL if the tibia were displaced anteriorly on the femur similar to an amount recorded. Similarly, it is

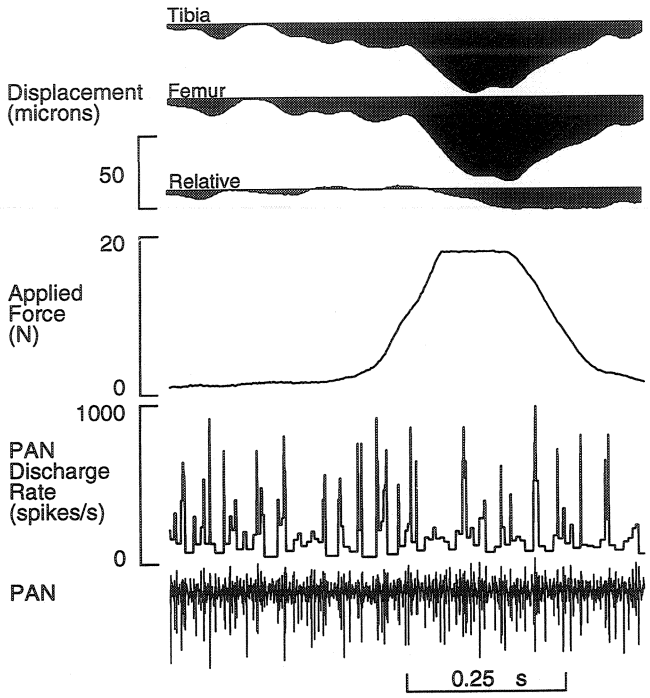

Figure 4.
A brief, strong tug was applied to the CCL with the tibia and femur clamped. The force transducer saturated at about 18 N.; the relative tibio-femoral motion was about 20 micrometers with no increase in background PAN discharge rates.

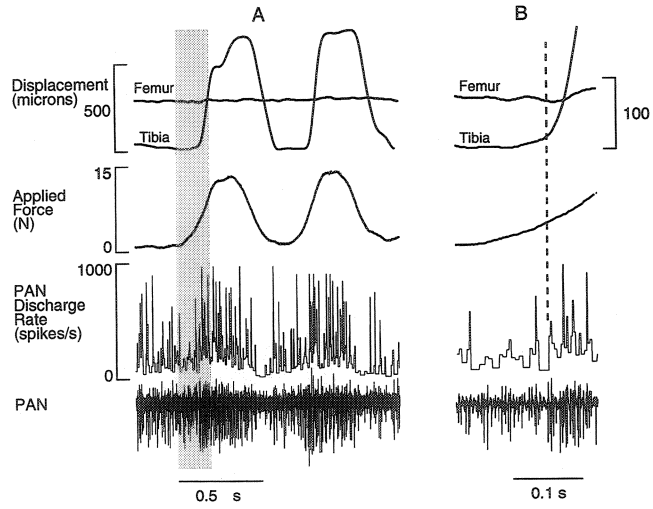

Figure 5.
Signals obtained when two brief pulls were applied to the CCL after the tibial clamp was slightly loosened. The right panel represents an expanded portion of the shaded region shown on the left. The upward deflection of the prestressed LMSG indicates the visually observed external rotation of the tibia on the femur. Enhanced discharge was observed with as little as 20-40 micrometer LMSG shortening.

difficult to a priori determine the loads applied to the CCL via a loop which will excite non-CCL periarticular afferents, although both posterior capsule afferents[16] and CCL afferents[9] are exquisitely sensitive to direct loads in the order of tiny fractions of a Newton.

Second, while we did not specifically identify CCL receptors, a large number of periarticular afferents were very sensitive both to light pressure and CCL tension great enough to cause visible motion of the tibia. Thus, we can presume that the recording techniques were adequate for periarticular receptors whose specific locations remained unidentified. The consistent failure of CCL loads to alter discharges in these afferents supports our interpretation that the employed fixation mechanically isolated joint afferents from CCL stimulation.

Third, the failure to alter PAN activity by CCL stimulation with rigid fixation does not necessarily contradict previous reports of CCL afferents that were recorded from the PAN. Both Cole et al.[9] and Krauspe et al.[21] reported experiments in which no afferents were identified (the means of stimulation in these two experiments differed although the recording methods were similar). Cole et al.[9] reported a total of 19 CCL afferent recordings in 20 cats, while Krauspe et al.[21] reported 26 recordings in 11 cats. The failure to demonstrate CCL afferents in this experiment with rigid fixation may be related to one of several factors. First, there appear to be a relatively small number of CCL afferents in the PAN[14,15]. Second, the positioning of the electrodes relative to the locations of only a few CCL axons may not have been optimal. Furthermore, it is entirely possible that some innervation of the CCL comes from either the medial or lateral articular nerves (Gomez-Barrena et al.[14]), neither of which were sampled. Third, a loop about the CCL may in fact apply relatively little load to the CCL depending upon the relative motion of the tibia to the femur (see discussion above). However, demonstration of CCL afferents was not the point of our experiment.

Finally, while our method of recording displacements did not allow determination of rotation of the tibia on the femur nor separation of translation and rotation, the method of slightly loosening the clamps of the chosen configuration would allow very little tibial translation, while it would allow tibial rotation. The fact that we could observe slight external rotation of the tibia relative to the fixed femur, and the fact that the LMSG lengthened, rather than shortened attests to rotational motions. Further, while we cannot precisely determine the degree of rotation, we can be assured that it is very slight since increased discharge began with only 20-30 micrometer displacement of the laterally attached tibial LMSG.

Several reports document physiological responses in the PAN to mechanical stimulation of the intact CCL[19,28].

These reports indicate that steady traction on the cruciate ligaments in the range of 5-10 N induces tonic changes in muscle spindle sensitivity. We designed this study in part to determine whether the sort of tibial and femoral fixation used in past experiments was adequate to avoid inadvertent stimulation of non-CCL periarticular mechanoreceptors, particularly during slow or steady pulling loads applied to the CCL. The ease with which we achieved functionally (i.e., failure to stimulate receptors) rigid knee fixation strengthens the interpretation of Johansson and colleagues that their experiments demonstrated reflexive modulation of muscle spindle sensitivity from CCL afferents. This modulation of spindle sensitivity may be important for the control of muscles that cross the knee joint during posture and voluntary movement and supports theories of an important sensory role for the ACL. Nevertheless, ligamento-fusimotor reflexes must be assessed in awake, behaving animals to ensure that these reflex connections are not weakened or gated by descending control signals during locomotion.

The ligatures used to apply the ligament loads were feared by Johansson and colleagues[19, 20] to be a potential source of stimulation of meniscal afferents in their experiments. In the current study meniscal afferents were obviously not excited when the knee was clamped, even though we routinely found such afferents in the PAN that are exquisitely sensitive to mechanical stimuli (forces in the range of 0.05 N applied with a 2 mm rounded probe[9]). Hence, based on the present data, and with the care described by Johansson and colleagues, inadvertent stimulation of meniscal mechanoreceptors by the Dacron loop around the CCL does not appear to be an important source of artifact. This may not be true when the menisci are compressed from muscle activation, when bearing the animal's weight, or if the leg is clamped with the joint compressed.

The observation that stimulation of many periarticular receptors occurs with relatively small amounts of motion when the clamps were loosened raises an interesting possibility in regard to clinical observations: while the loss of ACL afferents may deleteriously affect function in ACL-deficient patients, so might the 'unexpected' stimulation of many non-ACL receptors during small (i.e., non-visible), yet abnormal translations of the tibia on the femur. This observation of the sensitivity of receptors may explain why patients with minor or even clinically undetectable instability (but perhaps in the range of 0.5-1.0 mm) complain of giving way or more vague symptoms of instability. Presumably, unexpected discharge of even a few periarticular receptors may contribute to these sensations. Microstimulation of single afferents innervating joint regions of the human hand evoke specific sensations of joint displacement or innocuous deep pressure sensations[22]. Restoring structural stability with a reconstruction may turn off these deleterious signals, thus enhancing function. However, it is equally possible that these additional signals could in some way replace lost ACL signals, leading to a sort of "neural adaptation." This might explain why some patients function well with nonoperative treatment.

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CURRENT STATUS OF WALKING ORTHOSES FOR THORACIC PARAPLEGICS

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Spinal cord injury (SCI)[1] patients classified as paraplegics are confined to a wheelchair for a prolonged period of time, which they use as their sole mode of transportation. Prolonged sitting, however, results in compounded medical, physiologic, social, and psychologic problems that severely compromise the patient's health and quality of life. Pressures sores, decreased bone-density in the legs, increased risk of fracture, bowel and bladder stagnation, urinary tract infection, deteriorating cardiopulmonary and circulatory conditions, spasticity, and joint contractures are the most common problems of wheelchair-bound paraplegics.

Spasticity is a most debilitating problem, since it requires muscle relaxation for suppression. Muscle relaxants may cause generalized depression and reduce patients' ability to deal with the usual stress of daily living. This may ultimately result in the patient feeling detached from society. Unfortunately, at present, there is no practical orthosis that allows paraplegics to stand and walk independently for periods considered useful or even exercise.

A long leg brace (LLB), such as a rigid knee, ankle, and foot orthosis (KAFO) that requires significant consumption of energy for ambulation, provides limited walking function. Unfortunately, long-term evaluations have shown that this orthosis is soon abandoned by most patients, although a few use it for exercise.

The Reciprocating Gait Orthosis (RGO) developed at Louisiana State University (LSU) in the 1970s was first used in pediatric patients with severe musculoskeletal disabilities of the lower extremities (e.g. spina bifida, muscular dystrophy, sacral agenesis, osteogenesis imperfecta, and limited cases of cerebral palsy). During the late 1970s and through the 1980s, successful applications were made to SCI patients, mostly paraplegics, although some quadriplegics with residual upper extremity function also benefited. Since 1983, approximately 5,000 RGO units have been made and applied in the United States, Canada, Great Britain, The Netherlands, France, Israel, Australia, and South Africa. At present, the RGO is fully covered by Medicare/Medicaid, private insurers, and by the health authorities of the various countries.

Although initial results with the RGO in SCI patients were encouraging, the orthosis has several limitations, especially the high energy cost of ambulation compared with healthy subjects or wheelchair transportation. To reduce that energy cost, we developed (in 1983) a simple but effective and practical electrical muscle stimulation (MS) unit to power the RGO during walking.

Requirements for Simple Locomotion

Four distinct biomechanical factors are involved in the most simple human locomotion: standing upright, swinging one leg, simultaneously pushing off with the other while maintaining balance and stability.

The swing phase of one leg is a relatively complex function requiring activation of the hip, knee, and ankle in the flexion mode. For the most elementary swing phase, however, hip flexion is the minimal requirement for the "stiff-leg" walk (i.e., extended knee and rigid ankle). This type of stiff-legged locomotion, however, requires some lateral sway and an elevation of the trunk so that the foot clears the floor as the leg moves from the posterior (toe-off) to the anterior (heel-strike) position.

The contralateral push-off is accomplished by hip extension of that leg accompanied by knee extension and ankle plantarflexion. Considering the elementary "stiff-knee" gait, only hip extension is required. The isolated swing of one leg without a contralateral push-off, however, will result in zero forward progression (known as "wheel spinning"), which underscores the importance of hip extension.

The issue of balance and its stability requires that the trunk's center of gravity be positioned within a prescribed region between the feet, which allows a certain amount of anterior-posterior and lateral sway but preserves balance. Shifting the projection of the trunk's center of gravity out of that region will upset the balance and may cause a fall if not corrected fast enough.

Design Rationale for Muscle Stimulation Power

In our experience over the last ten years, we noted that most patients can achieve reasonable locomotion with the

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LSU-RGO alone (i.e., without MS). Why, then, employ MS power to complicate the system?

Isolated upper body work consumes much more metabolic energy per kilogram of body mass of active tissue than the combined work of the upper and lower body. This, added to the fact that the legs are paralyzed and the trunk muscles are very active during locomotion with the RGO alone (without MS), results in excessive energy expenditure and stress on the arms. By using MS to power the RGO, we can produce strong enough contractions of the large thigh muscles to provide the swing and push-off functions while simultaneously creating combined upper and lower body work, thereby reducing the overall energy cost of locomotion. An additional advantage is the reduction in work by and stress on the spinal and arm muscles produced by the swing/push-off in the absence of MS. This is very important to the design concept, as will become obvious when the system evaluation is considered.

The rationale for designing a practical hybrid locomotion system is, therefore, based on biomechanical, physiological, ergonomic, surgical/medical, and realistic factors. The design itself should allow for several other important factors that are the foundation of orthotics/prosthetics practice-i.e., function, ease of donning/doffing the device, safety, reliability, independence of assistance in operation, cost, and cosmesis. These factors are addressed in the following sections.

The LSU-RGO maintains upright posture and balance, and electrical muscle stimulation of the rectus femoris of one leg simultaneously with the stimulation of the contralateral hamstrings will provide hip flexion and extension, respectively, for successful locomotion.

The LSU-RGO

The Louisiana State University-Reciprocating Gait Orthosis (LSU-RGO) is a passive mechanical orthosis generally categorized as an HKAFO (hip, knee, ankle, foot orthosis). It consists of a polypropylene AFO splint that is custom-made to the size of the patient and worn inside the shoe. Its function is to give stability to the ankle joint to allow balanced upright posture. From each AFO, two aluminum uprights extend on the lateral and medial sides, terminating in bilateral knee joints. Two additional uprights extend from each knee joint, the lateral one terminating in a hip joint, while the medial upright extends only two-thirds of the way along the thigh. A polypropylene posterior cuff connects the medial and lateral thigh uprights, while anterior velcro straps insure that the thigh stays in position. An additional upright extends from each hip joint along the lateral aspects of the trunk to just below the axilla. Two velcro straps, one posterior and one anterior, connect the proximal ends of the uprights to insure proper placement of the trunk.

The knee joint was specifically redesigned for applications in SCI patients. Our experience shows that nearly all paraplegics suffer from significant hamstring contractures. Attempts to stand from a seated position with the aid of muscle stimulation or with arm strength alone does not result in full knee extension. To allow the patient to remain upright and prevent his collapse into the wheelchair, we incorporated a ratchet knee joint that would freely move into extension but not return into knee flexion. This important feature allows the patient to remain upright even when the knee is flexed 10° to 25°. After the first step, the shear force developed at the knee with heel strike fully extends the knee and locks the joint in position for the desired duration of locomotion. For sitting, specially designed posterior bales are engaged by the edge of the chair, which unlocks the ratchet mechanism and allows the knee to flex freely. The bales are spring-loaded, which causes the ratchet mechanism to be engaged as soon as they are removed from the edge of the chair. The patient does not have to use his arms for locking or unlocking the knee joint.

The hip joints of the RGO are connected to each other with two stainless steel cables guided inside a low-friction conduit. The cables function to satisfy two objectives: first, to prevent simultaneous hip flexion of both hips and consequent collapse of the patient (this allows the patient to remain upright with no energy expenditure and without using the upper extremities for support for prolonged periods of time); second, to force transmission from one hip to the contralateral one in order to make reciprocal movement of the legs possible. If one hip goes into flexion, force is transmitted via the cables to create a contralateral hip extension, a reciprocal motion identical to the swing of one leg simultaneously with contralateral push-off.

The reciprocal mechanism may be disengaged to allow simultaneous flexion of both hips for purposes of sitting down. This is accomplished by the patient pressing a small pin that disengages the reciprocal mechanism. The pin, however, is spring loaded and will engage the cables automatically if the patient stands and extends his or her hips sufficiently. The pin is also equipped with two locking positions, one at full hip extension and the second at 20° hip flexion. Hip flexion of 20° shifts the center of gravity forward so that the patient can walk up a handicapped ramp. This position of partial hip flexion also allows patients with some hip flexion contracture (which is common after prolonged sitting) to stand up in two stages. Standing or hip extension may easily be locked in the 20° position, relieving the patient's upper extremities from providing antigravity support. The patient can then attempt to extend the hip further into the fully extended position.

locomotion in the RGO (with or without stimulation). This can result primarily from muscle stretching, range-of-motion exercise, or stimulation alone, as was reported by Kralj et al. Stimulation alone is important in reducing or eliminating spasticity and, consequently, the antispastic medication. The effect of electrical stimulation on spasticity, however, lasts only a short while, with a gradual return of spasticity three to four days following the last application.

Contractures of the hip, knee, and ankle joints were initially regarded as contraindications, but as long as the joints are not ossified, application of MS and/or locomotion with the RGO significantly decreases the contracture and increases the joints' range of motion. Continuation of the locomotion with the RGO powered by muscle stimulation consolidates the gains, but they can be quickly lost if the patient does not ambulate for two to three weeks.

Long periods of sitting in the wheelchair accelerate weight gain. We accept overweight, motivated patients who often lose weight rapidly as soon as they begin to walk. This could not be attributed to the MS alone, but rather to the locomotion and the high rate of metabolic energy consumption it requires. These patients are eventually good walkers despite the initial hardship.

Patients who begin locomotion relatively soon after injury have a rapid reversal of muscle atrophy. Patients who begin even two decades after injury can have equal improvements, but they require longer periods of MS therapy. The late-starting patients have greater initial difficulties to overcome because of deficiencies of their cardiopulmonary systems.

Patients with injuries at T-1 to T-11 are easier to rehabilitate, although we accept patients with lesions above and below the range. One patient had complete lack of sensory and motor function below T-1 and incomplete damage up to the C/5-6 level. After several weeks of arm-hand strengthening he was accepted to the program, and three years later, he was one of the best users. However, high lesions that completely affect the arms and hands are contraindications.

Patients with lesions below T-11 have partial or complete damage to the lower motor neurons and therefore do not respond to stimulation. Such patients are, as a rule, better walkers with the RGO alone, especially if some hip flexion is available.

The pre-existing pressure sores and some skin lacerations heal rapidly once stimulation and locomotion are initiated. We suspect that the improvement in the lower extremities is the result of stimulation, muscle hypertrophy, revascularization, and increased metabolism.

Experience shows that acceptance to the program should not be limited to certain patients but should be open to the general paraplegic population. Hardship and perseverance are required by some patients with severe deficiencies, but success is possible.

RGO Fitting and Training

Each patient undergoes three to four weeks of perambulatory training (three one-hour sessions per week) to develop trunk balance and to strengthen arm and shoulder girdle muscle, back extensors, and abdominal muscle. The object of this perambulatory training is to reduce contractures, maximize the strength and control of any innervated muscles, increase the strength of the arms and shoulders (essential for ambulation in the RGO), and retrain the patient to control the trunk's center of gravity-a function gradually lost after prolonged sitting in the wheelchair. Another purpose is to improve the patient's cardiopulmonary condition and endurance.

The importance of this perambulatory training can be gauged from the fact that patients who successfully complete it become good users of the RGO relatively quickly, whereas patients who do not participate have a low acceptance rate even after prolonged ambulatory training.

Our patients are fitted with a custom RGO by a certified orthotist who has prior experience with this orthosis. The RGO uprights and cables are properly calibrated so that, for at least one minute, the patient can stand fully balanced and stable without holding on to anything. Additional care is taken to align the leg uprights to that circumduction or scissoring is completely eliminated.

Following the initial fitting, each patient receives six weeks of training: three-hour sessions each day for three days a week learning to put on and take off the RGO, walk on level surfaces, sit and stand, and make corners and full turns. All training is provided by a registered physical therapist with extensive previous experience with the RGO.

Patients with injuries at T1 and/or incomplete damage to the low cervical levels receive an additional three weeks of arm strengthening before beginning RGO training.

The proper fitting and calibration of the RGO by an experienced orthotist is essential for its success. The alignment of leg members, symmetry, proper tension in cables, adjustment of thoracic straps, and other factors make an enormous difference in the ability of the patient to use and accept the orthosis.

Muscle Stimulation Therapy

Each patient receives six weeks of MS therapy to the quadriceps and hamstrings muscles. The therapy consists of three weekly sessions lasting up to 40 minutes each. The object is to reverse thigh muscle atrophy and increase strength. A pair of carbon-impregnated surface electrodes are placed over the hamstrings and another pair over the quadriceps of each leg. The patient is raised with a

specifically designed hydraulic lift while sitting on a narrow seat, similar to a bicycle seat, with free space around the legs. A specially designed, four-channel electrical stimulator delivers 0.5 ms rectangular pulses at a rate of 20 pulses per second to one quadriceps and the contralateral hamstrings. This results in a hip flexion, contralateral hip extension and knee flexion and simulates swing and push-off phases of the gait cycle. The stimuli are then switched to the contralateral muscles.

Initially, the stimuli are applied for one minute at a rate of 0.3 steps/sec (i.e., a swing and a contralateral push-off are held for three seconds before reversing the stimuli to the muscles of each leg). A ten-minute rest is given to the patient following another minute of the "walking-like" session.

The stimulation therapy is increased by two minutes per session as the muscles become conditioned. In the final two weeks of the stimulation therapy, the patients are given two 20-minute sessions around a ten minute rest period. A 25 N weight is wrapped around the ankles to load the movement and to improve strength and fatigue resistance of the thigh muscles. During the last two weeks of training, the stimulus cycle is increased to one step/sec-i.e., the patient performs swing and contralateral push-off 60 times per minute.

During therapy, patients' heart rates are monitored with an earlobe sensor to check for excessive stress. Some patients demonstrate a rapid increase in heart rate during the first week of MS therapy. If the heart rate increases over 140 beats per minute, the patient is lowered to the supine position and closely monitored for 20-25 minutes until the heart rate returns to normal. Occasionally, additional preconditioning is prescribed on the tilt table to allow the cardiovascular system to adjust to the upright posture.

Gait Training with MS-powered RGO

Once a patient completes the six weeks of gait training with RGO and the simultaneous MS therapy, an additional six weeks (three-hour sessions thrice weekly) of gait training with the MS-powered RGO is given to develop skill and improve performance in level walking when using MS for the thigh muscles.

ENERGY CONSUMPTION

Protocol

Instrumentation for patients consists of a nose clip and a mouthpiece from which two flexible tubes are connected to a volume spirometer containing oxygen mounted on a rolling cart. The cart is pushed along after the patient during locomotion. The tubes are mounted on a light-weight plastic shoulder harness to allow the patient to move his head freely during locomotion. Expired, excess O_2 consumption during each breath and overall 0_2 consumption are recorded.

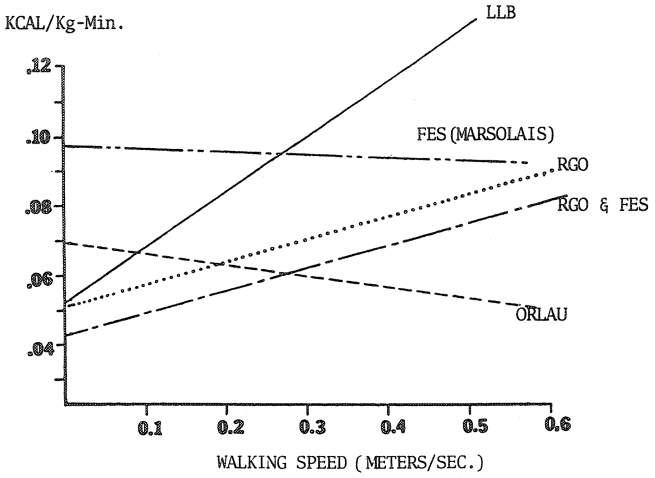

Figure 1

Initially, the patient stands quietly for five minutes to establish basal heart rate and energy consumption at rest. The patient is then instructed to walk a level, straight 30-meter track at a speed set by a metronome. At the end of the track, the final heart rate and total O_2 consumption is measured. Following a 20-minute rest, the metronome speed is changed and the procedure is repeated. Walking speeds are set at random to prevent bias errors. Before the next trial is initiated, the patients' heart rates must return to within ± 3 beats/min. of the original resting heart rate.

Patients are instructed not to eat for three to four hours before coming to the clinic and another hour and a half without food is allowed to elapse before the trial begins. Each patient is also instructed to walk a 30-meter distance at a comfortable speed. Two such trials are performed by each patient and are included in calculating the average preferred walking speed of all the patients. The preferred walking speed of a group of six patients with T-1 to T-10 injuries is 0.2 m/sec.

Results

The energy cost of a new orthotic device is meaningful only if it is compared to that of a well-known device, such as the LLB, that is available as an option for the same patient category. The data in figure 1 compares five systems. The energy expenditure in kcal/kg-min against walking speed is shown. The lowest energy cost is associated with the MS-powered RGO at walking speeds from 0 to 0.27 m/sec. Ranking second in energy expenditure per minute is the RGO, which displays a nearly parallel curve to the RGO and MS, but shifted 0.01 kcal/kg-min upward. The energy expenditure associated with the LLB climbs quickly as walking speed increases; it

is ranked third for walking speeds ranging up to 0.1 m/sec. The HGO demonstrates a rapid decline in energy cost as walking speed increases; it has a lower cost than the LLB at 0.1 m/sec and is even lower than the RGO and MS-powered RGO at 2.0 and 0.27 m/sec, respectively.

If 0.2 m/sec is the preferred walking speed for daily activities, a ranking of the five types of walking aids would put the RGO and the MS first, with the lowest energy cost, the RGO and HGO second and third, the LLB fourth, and the Marsolais FES, with the highest energy cost, fifth.

Heart Rate

Figure 2 displays the mean and standard deviation of the pooled pre- and post-trials heart rate for the RGO and MS-powered RGO, and the heart rate date for the LLB and the Marsolais FES as obtained from the literature. Heart rate data for the HGO are not available in the literature.

The mean pre-trial heart rate (HR) for patients using the MS-powered RGO was 88 beats/min (standing quietly) and the post-trial heart rate (HR) was 119 beats/min, a 35.2% increase. For the RGO, the HR rose from 86 beats/min at rest (standing) to 131 beats/min post-trial, a 52.3% increase. For the LLB and Marsolais FES systems, the comparable increases (from the seated positions) were 87.5% and 101.25%.

By the amounts indicated in Figure 2, the addition of MS power to the RGO resulted in lower HRs at the end of a walk of at least 30 meters, compared to the HRs of the same patients using the RGO alone, the LLB, and Marsolais FES system. The lower HR from walking in the MS-powered RGO reflects the low stress associated with this device, confirming the advantages of a walking aid in which a passive mechanical orthosis is coupled with MS of the leg muscles.

Cost

An important factor in the use of orthotic devices is cost. The RGO has been available commercially since the mid-1970s from Durr-Fillauer Orthopaedics, Inc., of Chattanooga, Tennessee. At present, its cost, including the hardware shipped from the manufacturer, assembly by a local orthotist, and custom fitting (casting, alignments, calibration, etc.), is $4,200. The cost of the rolling walker necessary for ambulation is $155, and the custom-built stimulator is $1,200. The total cost of the hardware is therefore $5,555.

The success of an orthosis, as determined by patient acceptance, depends on the quality of training in its use. In our experience, the training proved to be a most important element in acceptance. Well-trained patients became routine users; poorly trained patients (primarily those not from New Orleans who could spend only a limited time as

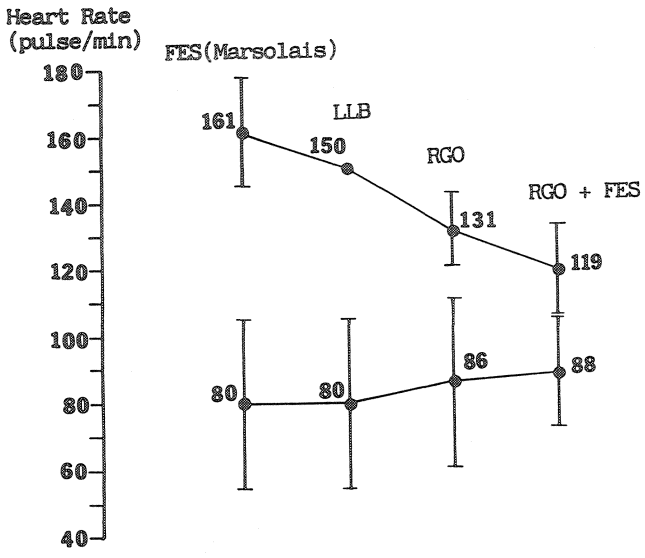

Figure 2

outpatients) were not frequent users. The training requires at least six weeks of supervised and guided ambulation by a physical therapist at the rate of three weekly sessions. The cost of this gait training averages $1,200, although it varies with the patient's age, weight, sex, level of injury, duration of disability, and motivation. Some patients need only two to three weeks of gait training; in difficult cases, up to 15 weeks is required. The latter cases involve patients with joint contractures, high level of injury, high levels of spasticity, weight problems, and advanced age (oldest patient: 62 years old at rehabilitation).

Therapy to reverse muscle atrophy adds to the costs: three weekly sessions that last for an average of six weeks cost an average of $2,500.

Overall, the average cost of the rehabilitation comes to $9,255, which is reasonable compared to other orthotic or prosthetic devices. A below-knee prosthesis, for example, costs between $1,800 and $4,000; an above-knee prosthesis costs between $3,200 and $10,000, excluding gait training.

Reliability-Maintenance

The RGO has become more reliable over the years. Based on experience with a large number of patients, the RGO, if used daily, requires approximately two service visits per year. Less frequent users require an average of one service visit every two years, a frequent equivalent to that of other prosthetic devices that are routinely applied, such as above- and below-knee prosthetics. Repairs normally occur during the gait-training period when the brace is new and occasionally needs calibration to optimize its performance. A broken cable or a fractured AFO are usually attributable to the patients' weight, and can be

immediately replaced with heavy-duty components that can last satisfactorily for many years.

Conclusions

Compared to other currently available options including mechanical or the MS orthosis, the use of the RGO powered by brief electrical stimulation of the thigh muscles to initiate the gait cycle of thoracic paraplegics results in a substantial reduction of energy expenditure. The advantages of such a hybrid orthosis, combined with the appropriate training, can provide selected paraplegics with an alternative to wheelchair transportation. It has added potential benefits of preventing osteoporosis and pressure sores, improving cardiopulmonary, kidney, bladder, and circulatory functions, as well as improving the patients' outlook.

To date, we have fitted 700 patients with the RGO and over 27 patients with the MS-powered RGO and followed them nearly three years. We had two failures, patients who abandoned the program before training was completed due to social problems. The remaining patients are regular users daily or at least three times a week. They use it in the workplace, in daily walking exercise or as a means of home ambulation for a total of 40 hours weekly. Others who do not use it daily will use it for such special occasions as going to church or social gatherings for at least 12 to 15 hours per week.

Patients are trained to don or doff the orthosis either in bed or when seated. This procedure normally takes 15 to 20 minutes when performed without help. This does not bother patients, but they are disappointed that the brace has to be taken off to perform bathroom functions. This requirement is the result of the RGO's inability to perform hip abduction; lack of this function also limits a patient's ability to get in and out of a car or bed without help. We have designed, and are now testing, a hip abduction joint that will remove this limitation, but many other limitations still exist: the inability to safely walk up stairs or on uneven surfaces of dirt, grass, or gravel. Current work indicates that improvements in function are possible and would increase acceptance of the orthosis as a routinely worn accessory.

The successes and failures of researchers over the decades have taught us invaluable lessons which have helped us develop a reasonably practical walking orthosis. We consider it practical as patients can use it without assistance in the home, workplace, school or other environments; it is commercially available and has a reasonable cost; and it was found useful by many outside of our group. This is the first time an orthosis with such features is available. Still, it is primitive when compared to healthy legs. Rather than frustrate us, this should motivate us to more aggressive research efforts.

We have relied heavily on the physiologic and engineering work of others and on the basis of recent developments in our laboratory, we see the potential for significant advances in control of muscles in a mode similar to that used in voluntary contraction. There is now good progress in obtaining basic information on how agonist and antagonist muscles coactivate or co-contract about a joint; we are studying the feasibility of using EMG as a force feedback in a closed-loop MS-control scheme. Completing this research and development will take many years, but the expected results will be worth the wait. In the meantime, a reasonable and practical orthosis is available as an alternative to the wheelchair.

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RATIONALE FOR CLASSIFICATION OF FLEXION VS EXTENSION STRAIN IN ACUTE LOW BACK PAIN

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People experiencing acute low back pain (less than one month) are subjected to a myriad of treatment protocols as well as diagnostic tests. These treatments range from bedrest and medications to chiropractic adjustments, therapeutic injections, and surgery. Diagnostic tests include radiographs, CT, myelogram, and MRI. These tests and procedures are all quite costly, probably unnecessary, and, in fact, make some people worse[1]. The large number of treatment options demonstrates the lack of consensus regarding the appropriateness of these various protocols. Geographic regional variation of the use of these various procedures would seem to indicate that the procedure performed depends partly on where you live[4].

There is, however, a growing body of research and literature which specifically compares these disparate treatment protocols as well as their outcomes. Most (90%) of acute low back pain patients recover in four weeks. For these patients, conservative treatment is as effective as any other treatment[2]. Evidence indicates that an important factor in conservative management involves providing accurate information to patients regarding an explanation of their problem and recommendations on methods for symptom control and limiting recurrence. Providing this information may reduce use of medical resources and speed recovery. Failure to receive an explanation of the problem results in patient dissatisfaction, increased use of diagnostic tests, and patients seeking treatment from other professionals[5].

This paper provides a rationale and guide for explaining diagnostic conclusions, as well as recommendations for control of symptoms and recurrence. The explanation must be believable and understandable. While it is most often not possible to identify a specific cause for painful symptoms, an explanation of the likely reason for their condition can be provided. A thorough history interview and physical exam to rule out serious pathology (infection, tumor, neurologic deficit, etc) should always be done. In the absence of "red flags", the likelihood of a rapid recovery should be affirmed. Vocabulary should include terms the patient can understand. Models, pictures, and drawings are often helpful in making the explanation understandable.

Classification of acute low back pain into flexion vs extension strain provides a guide for presenting an explanation and recommendations during the first four weeks of conservative treatment. Low back pain is most often caused by flexion strain from either repetitive or sustained lumbar flattening or reduction of lordosis. Most people report that sitting often produces their symptoms, though stooping and bending are also painful. Screening maneuvers during the physical exam include forward and backward bending in standing and lying (supine and prone) positions. In these positions the sensation of pain during flexion movements, compared to much less or no pain with extension movements, indicates a flexion type of strain. Flexion movements will tend to increase patients' symptoms and extension will relieve their symptoms. Diagrams and/or spine models may be used to show that flattening of the lordosis, as in a slouched sitting position, produces a flexion strain on the posterior longitudinal ligament (PLL). (Fig. 1) The PLL is the most sensitive structure in the spine for pain. The greatest number of nociceptive nerve endings have been identified in the PLL[8]. Strain of the PLL produces a burning, aching type of low back pain. If it becomes too painful, there will be reflex muscle guarding pain as well. This muscular pain can be a more intense, sharper pain. The flexion strain position may also produce a compressive force in the intervertebral discs. Most people are aware of "slipped discs" and usually have some

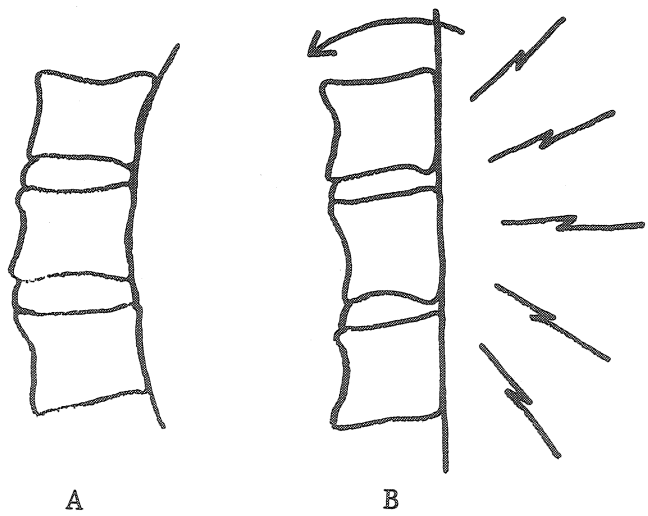

Figure 1
A. Diagramatic representation of normal lumbar lordosis and posterior longitudinal ligament (PLL).
B. Representation of reduced lumbar lordosis with compressive force on discs and flexion strain on PLL producing pain.

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frame of reference when discussing them. It is therefore appropriate to explain to the patient that they have no evidence of herniation upon physical examination and that many asymptomatic people have bulging or herniated discs[3].

If, however, the standing and lying flexion/extension tests indicate pain reproduction during extension movements that are relieved by flexion, extension strain is the most likely problem. Extension strain implicates the facet joints as the pain generators. Extension movements tend to compress or load the lumbar facet joints. Patients with extension type pain may have increased lordosis and describe their symptoms as being more prominent in standing and when arising from sitting activities. Sitting and sidelying with the knees flexed feels comfortable. Additional screening in the standing position involves single-leg stance with back extension on each side. Often one side will be more painful than the other. If by history and physical exam, extension strain is suspected, a Larson instability test may be done to differentiate facet pain from pain associated with a pars defect. The Larson sign involves having the patient lie prone comfortably (usually with 1-2 pillows under the abdomen). Pressure is exerted downward on the spinous processes at the level to reproduce the patient's pain. This procedure is repeated with the patient actively performing back extension. Testing is positive when there is pain in the relaxed position which disappears in the active extension position. This test has a sensitivity of 90% in painful patients with spondylolysis[7]. Pars interarticularis defects usually present as extension strain when painful. The rationale for the Larson test arises from the assumption that active extension stabilizes a pars defect but not pain from a symptomatic facet.

Recommendations for symptom control should follow the rationale of the problem explanation. The recommendations should be succinct to avoid confusion. Treatment instructions should be conveyed with reassurance that the patient's active participation will be the key to recovery. An understandable explanation and reasonable recommendations promote compliance with the home treatment. Provision should be made for the "what if" situation. Patients should be given instructions on who to contact "if" symptoms worsen or the treatment results in adverse effects.

Recommendations for a flexion strain include passive lumbar extension positions and movements as well as instruction on how to maintain a lumbar lordosis in sitting and lifting. The focus of the exercise should be on reducing flexion strain, particularly of the PLL. The use of cold packs for the relief of muscle guarding pain can be beneficial when applied in the prone position. Aerobic activity is encouraged. If aerobic exercise equipment is used (bicycle, stair machine, skier, etc), lumbar lordosis should be protected throughout the exercise.

Recommendations for extension strain would involve flexion exercises. Supine stretching with knees to chest and pelvic tilt exercises are encouraged, as well as advice regarding some flattening of the lumbar lordosis throughout daily activities. Prone lying over 1-2 pillows and application of cold packs helps reduce muscular pain. Again, aerobic activity is encouraged with a reminder to maintain a slight flattening of the lordosis during exercise.

In summary, most people with acute low back pain will improve to nearly normal within four weeks, regardless of the type of treatment offered. Often, a reasonable explanation of probable causes of their pain and expected recovery will relieve anxiety and improve compliance with a home exercise program. This paper describes a rationale for classification of flexion vs extension strain which is understandable to most patients and serves as a guide to determining an appropriate exercise program.

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ACETABULAR FRACTURES CLASSIFICATION OF LETOURNEL AND JUDET— A SYSTEMATIC APPROACH

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T. Turbett, B.S.
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INTRODUCTION

The acetabulum is a complex structure and fractures in this region can be difficult to classify radiographically. In clinical practice and research the classification method of Judet and Letournel is most widely used. We found a significant learning curve associated with classifying these fractures using this method. Accurate classification of every case requires an experienced observer and prolonged study of excellent x-rays. Thus, we developed a systematic approach by which the inexperienced observer can learn to recognize fracture patterns in the majority of cases. This approach is intended as an aid to understanding a well accepted classification which will shorten the

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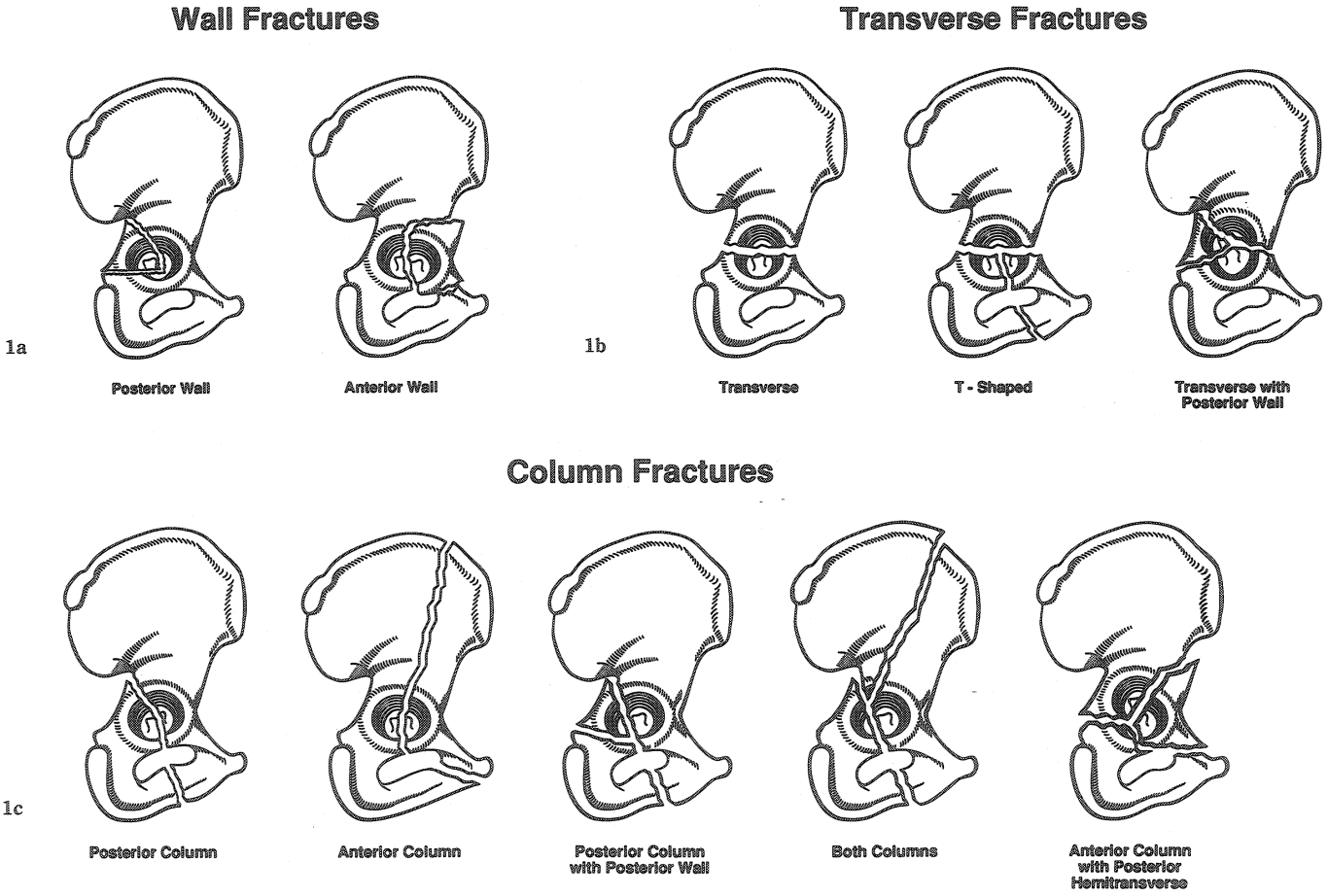

Figure 1a-c
Drawings demonstrating the acetabular fracture patterns as described by Judet and Letournel. They are grouped into wall fractures (1a), transverse fractures (1b), and column fractures (1c). (Reprinted, with permission, from: Acetabular Fractures: A Systematic Approach to Classification. Journal of Emergency Radiology, Jan/Feb 1995.)

learning curve associated with classifying these fractures by the method of Judet and Letournel.

I. JUDET AND LETOURNEL CLASSIFICATION

The anatomic classification of acetabular fractures was established by Judet in 1964 and was slightly modified by Letournel. This classification was developed prior to computed tomography and was based on A/P and oblique x-rays. Ten fracture patterns were divided into two groups consisting of five elementary and five associated fracture types. We propose regrouping these into three primary fracture patterns: Wall, Transverse, and Column, each with unique recognizable radiographic features (Fig. 1a,b,c).

II. ANATOMY

Skeletal anatomy

Understanding the columns of the acetabulum is critical to accurately use this fracture classification. From its lateral aspect, the acetabulum forms an inverted Y, one limb forming the anterior column and one the posterior column[2] (Figure 2). The anterior column is the anterior and superior portion of the hemipelvis. It extends from the iliac crest to the symphysis pubis and includes the anterior wall of the acetabulum. Think of it as the portion of a brittle model that would break from a twist to the anterior superior iliac spine and anterior wall of the acetabulum. The posterior column is the posterior and inferior portion of the acetabulum. It begins at the superior gluteal notch and descends through the acetabulum, obturator foramen, and inferior pubic ramus and includes the posterior wall of the acetabulum, ischial spine and ischial tuberosity. Think of it as the portion of a brittle model that would break from a twist to the ischial tuberosity and posterior wall of the acetabulum.

Radiographic Landmarks

Three radiographic views should be obtained to evaluate acetabular fractures. These are the anteroposterior (AP) and two 45° oblique Judet views (obturator oblique (OO) and iliac oblique (IO)) (Figure 3a,b,c). The AP radiograph

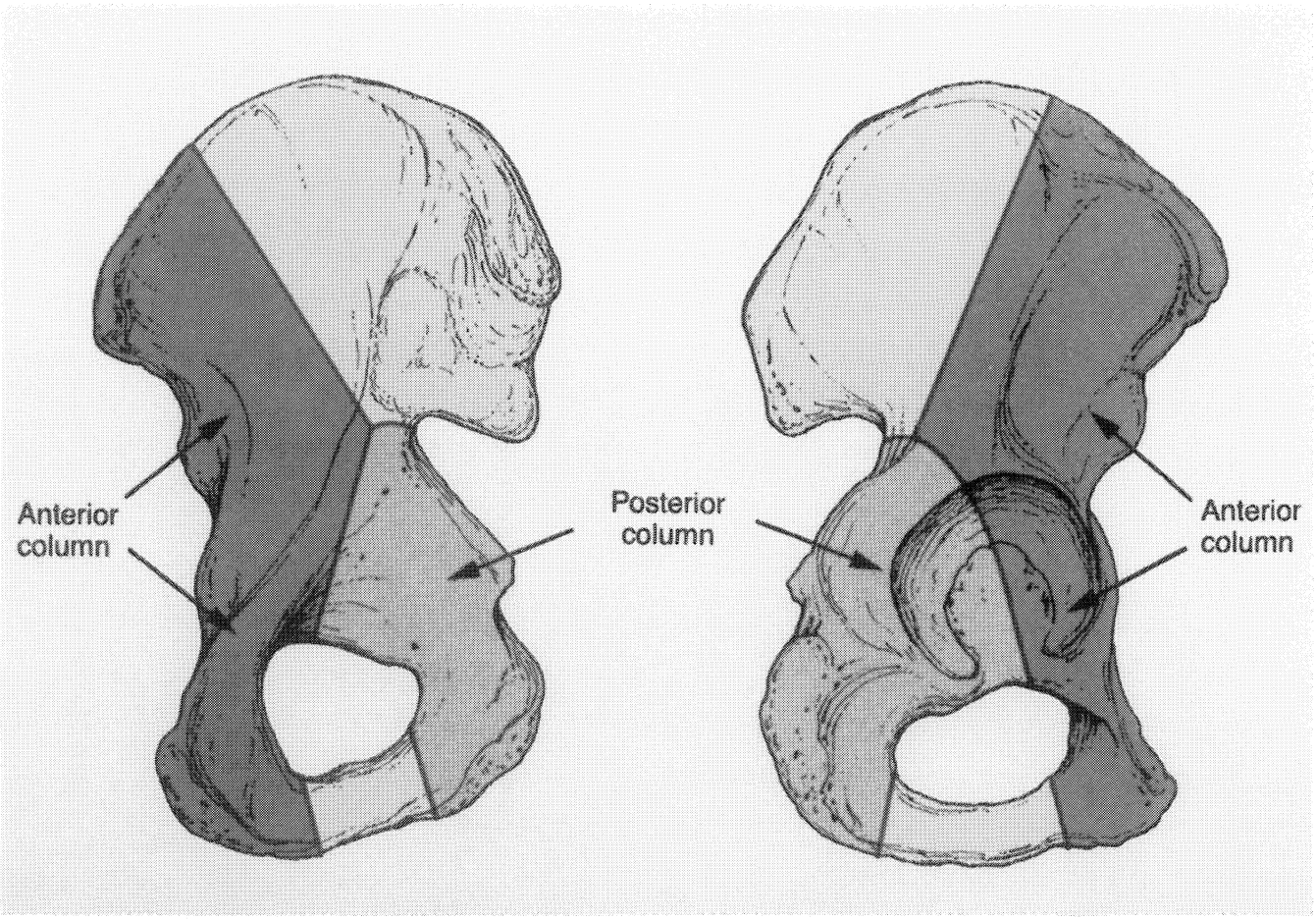

Figure 2 Drawing demonstrating the extent of the anterior and posterior columns on the inner and outer aspects of the bone. (Reprinted, with permission, from: Browner, Jupiter et al: Skeletal Trauma, Vol 2, p.900. Philadelphia, W.B. Saunders, 1992.) Note that the anterior column is mostly superior, and the posterior column is mostly inferior.

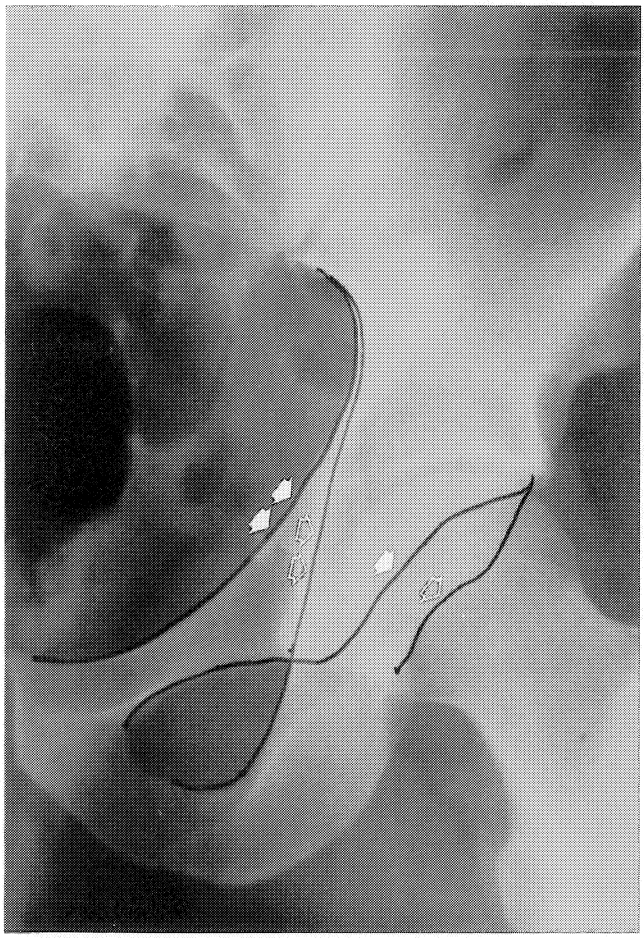

Figure 3a-g
Radiographs and CT cuts demonstrating the normal radiographic landmarks of the acetabulum. These three radiographs and four levels of CT cuts should be examined in each case.

Figure 3-a On the anteroposterior radiograph, note the posterior wall (single, hollow white arrow), the anterior wall (single, solid white arrow), the iliopectineal line (double, solid white arrows) and the ilioischial line (double, hollow white arrows).

demonstrates the following four landmarks: the iliopectineal line (IP), the ilioischial line (II), the anterior rim of the acetabulum, and the posterior rim of the acetabulum (Figure 3a). The boundary of the II line starts at the greater sciatic notch and runs along the course of the ischial spine to the posterior border of the obturator foramen.[1] The line usually begins proximally with the IP line, with which it appears to blend. The IP line extends along the "radiologic" pelvic brim to the superior border of the symphysis pubis.[1] The anterior wall of the acetabulum begins at the external border of the roof but is more horizontally oriented than the posterior border and is superimposed on the shadow of the posterior wall. The line follows a curved path to become continuous with the superior border of the obturator foramen. The posterior wall is visualized as a straight line that is continuous superiorly with the beginning of the outline of the articular

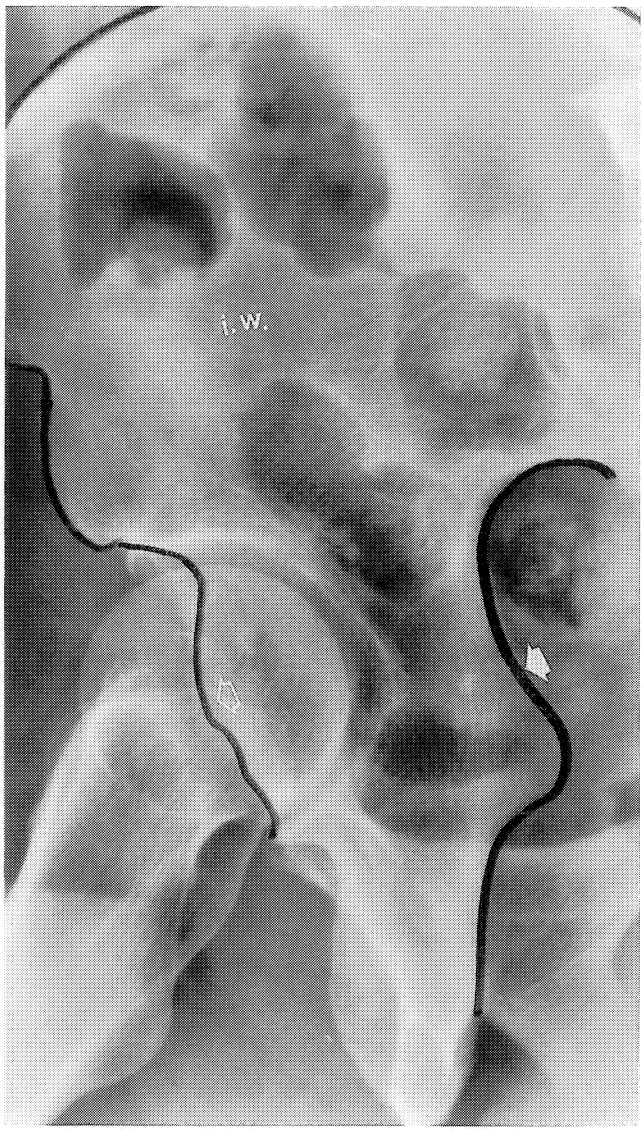

Figure 3-b The iliac oblique radiograph demonstrates the iliac wing (i.w.), posterior column (solid white arrow) and the anterior wall (hollow white arrow). The superior portion of the PC is well demonstrated.

surface and inferiorly overlies the outline of the upper margin of the ischial tuberosity.

The 45° IO view is taken with the fractured acetabulum rotated away from the x-ray tube. It shows the iliac wing in its largest dimension and profiles the greater and lesser sciatic notches and the anterior rim of the acetabulum. The superior portion of the posterior column is best visualized on this view (Figure 3b). The 45° OO view is taken with the fractured acetabulum rotated toward the x-ray tube. It shows the obturator foramen in its largest dimension and profiles the anterior column and posterior rim of the acetabulum. The inferior portion of the anterior column is best seen on this view (Figure 3c). For maximal information full 45° oblique views are necessary (on the OO, the tip of the coccyx should be over the femoral head).

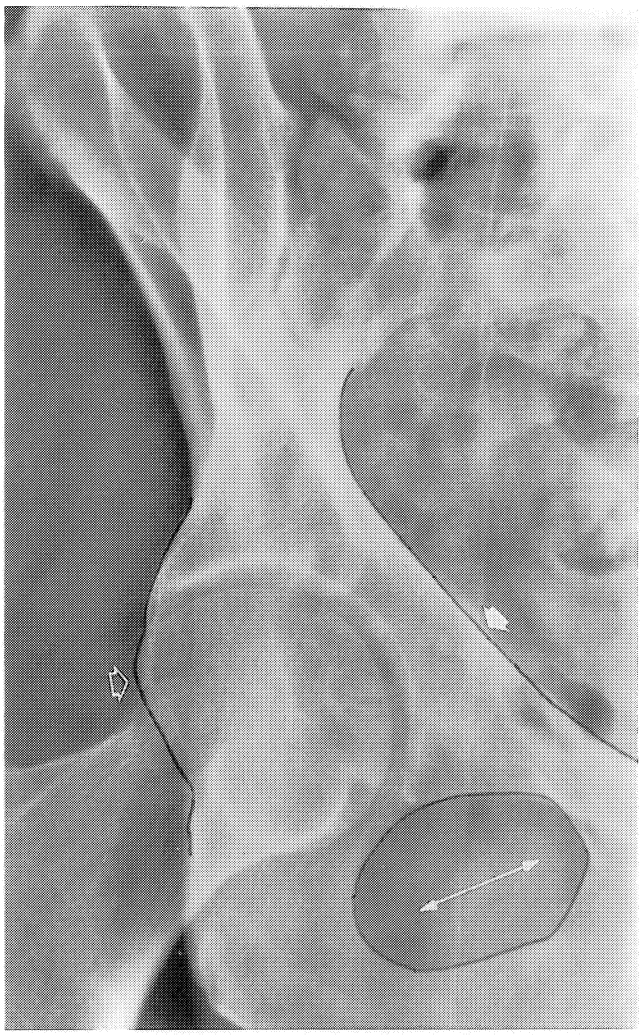

Figure 3-c The obturator oblique radiograph demonstrates the obturator ring (double-headed arrow), the anterior column (solid white arrow), and the posterior wall (hollow white arrow). It demonstrates the inferior portion of the anterior column. Scrutinize this view for breaks into the obturator ring.

Figure 3-d This proximal CT cut at the level of the SI joint will show a fracture of the AC. Note the SI joint (hollow white arrow) and the iliac wing (solid white arrows).

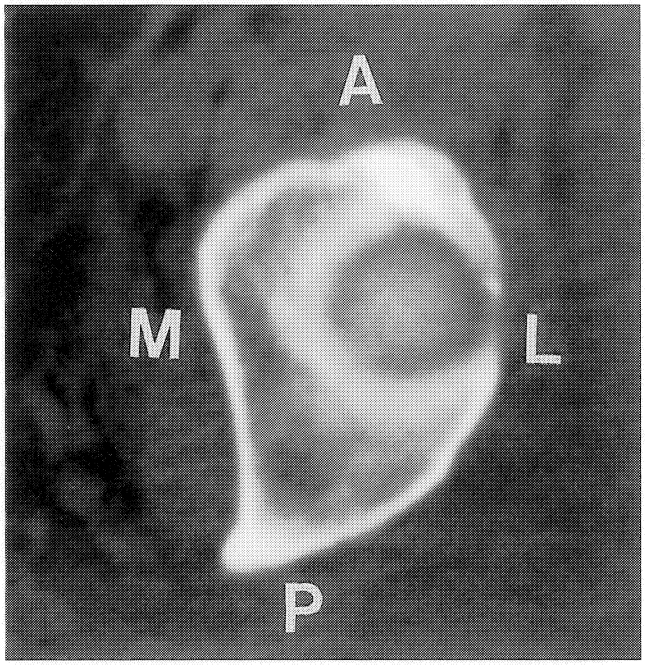

Figure 3-e An axial CT cut at the level of the dome. Note the anterior, posterior, medial and lateral borders of the acetabular dome.

Computed Tomography

Computed tomography (CT) is useful for evaluating the orientation of the main fracture line (transverse vs column), the location and size of wall fractures and for evidence of marginal impaction around major fracture lines. In addition, it can be used as an aid to accurate fracture classification. An axial CT will conclusively determine the presence or absence of an anterior column fracture into the iliac wing and the presence or absence of a break in the obturator ring indicating a T- type or column fracture. Familiarity with axial CT sections through the pelvis and acetabulum is required to obtain this information.

Study the axial CT cuts in four locations: the iliac wing, the superior dome, through the acetabulum at the level of the anterior and posterior walls, and at the level of the inferior acetabulum near the entrance to the obturator ring. The iliac wing should be seen from the ASIS to the SI joint (Figure 3d). The presence of a fracture line in this area indicates a fracture of the anterior column and the absence of a fracture usually means that there is not an anterior column fracture; an exception to this would be an

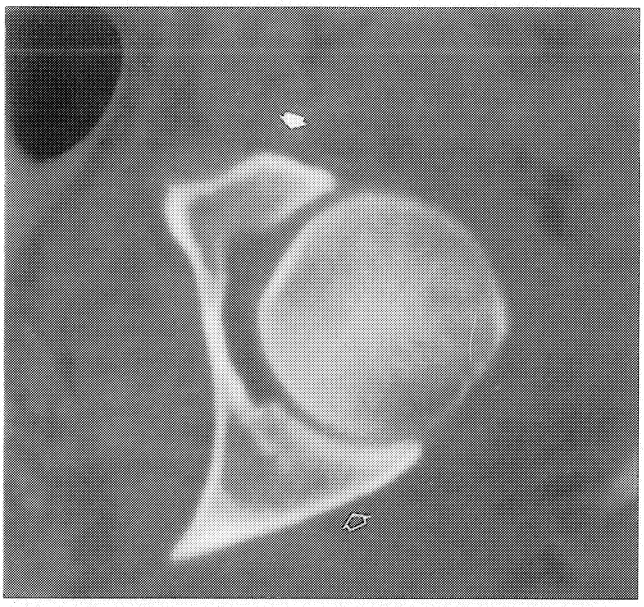

Figure 3-f Further caudally, note the anterior (solid white arrow) and posterior (hollow white arrow) walls. This CT cut is at the mid-level of the joint.

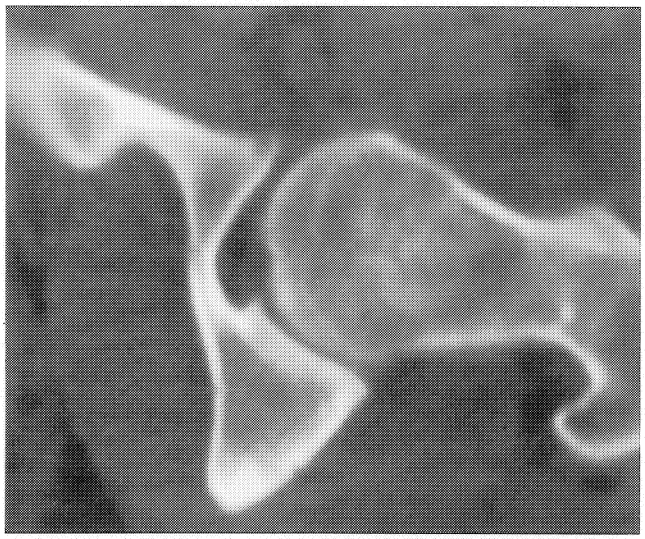

Figure 3-g The inferior portion of the acetabulum just before entering the obturator ring is visualized on this cut. A break in the quadrilateral plate at this level indicates a fracture extending into the obturator ring.

unusual low fracture of the anterior column which does not reach this level. The superior dome has a typical appearance with anterior, posterior, medial and lateral borders (Figure 3e). A fracture line from anterior to posterior in this region indicates a transverse fracture pattern. A medial to lateral fracture line indicates a column fracture pattern. Evaluate the anterior and posterior walls at the level of the middle of the joint (Figure 3f). Finally, the inferior acetabulum, just before the entrance to the obturator ring, should be evaluated for a fracture in the quadrilateral plate at this level (Figure 3g). The presence

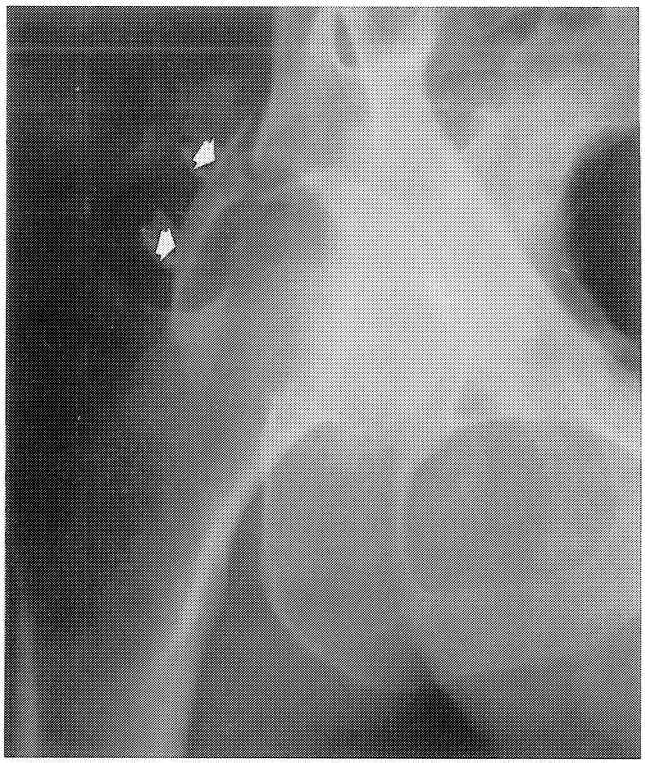

Figure 4a-b Radiographs and CT of a posterior wall fracture. Figure 4-a Posterior wall fracture can be seen on the obturator oblique (solid white arrows).

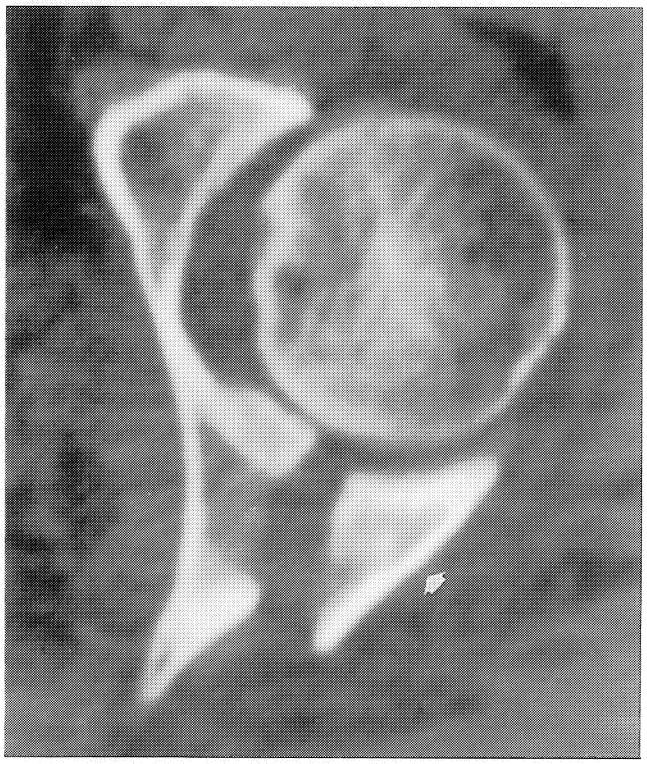

Figure 4-b The CT scan through the joint demonstrates the large posterior wall fragment (white arrow).

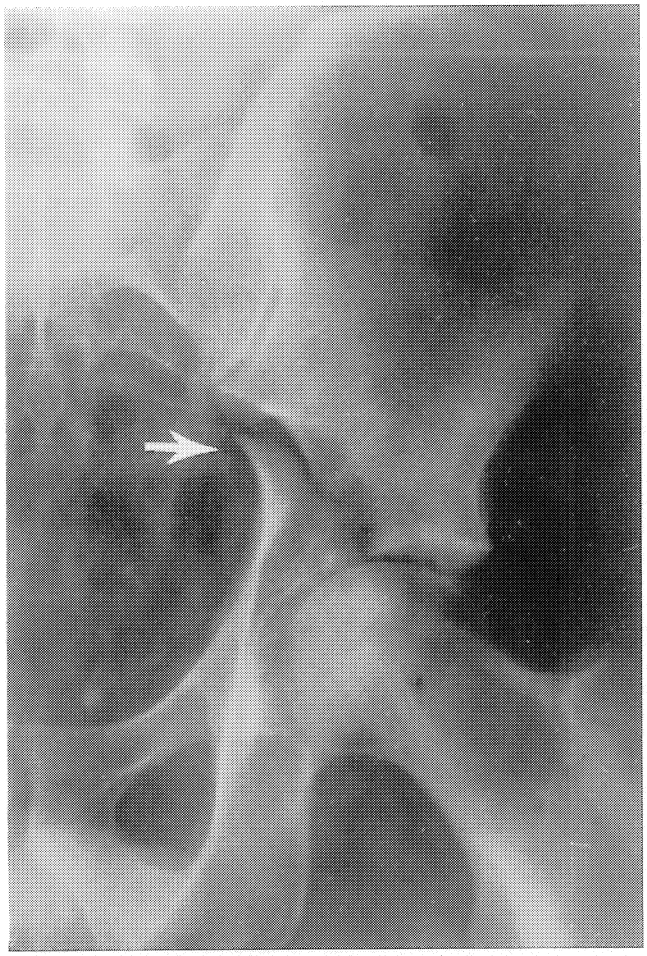

Figure 5a-b Radiographs and CT of a displaced transverse acetabular fracture.

Figure 5-a A moderately displaced transverse fracture is seen on the AP radiograph. Note the disruption of the IP and II lines (large white arrow). The obturator ring is intact (this would be checked on the OO and CT at the inferior acetabulum), eliminating a T-type fracture pattern.

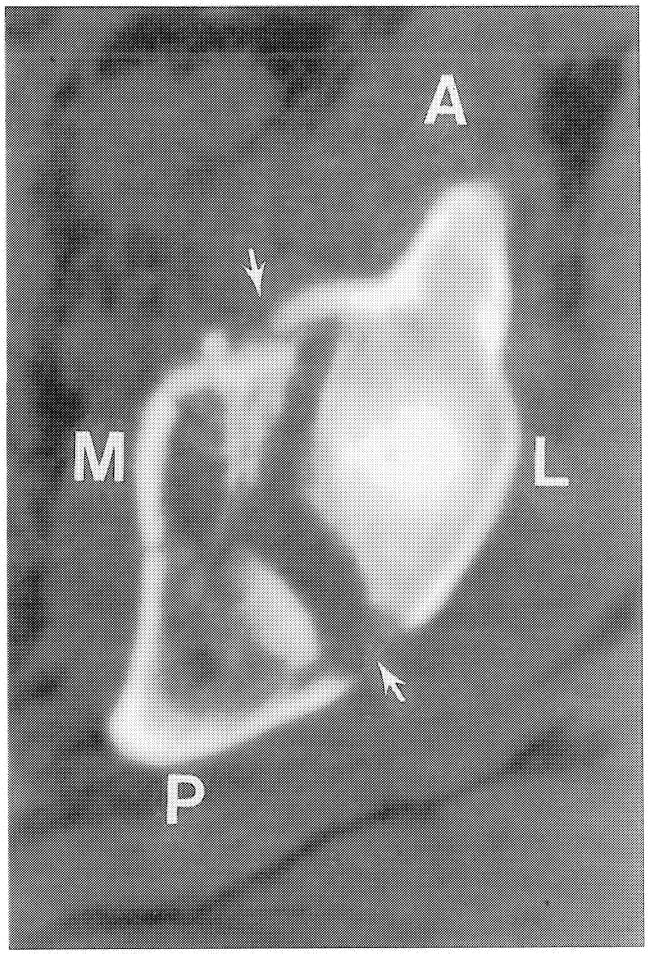

Figure 5-b Note the classic anterior to posterior fracture pattern on the CT cut through the dome (white arrows), indicating a transverse fracture rather than column fracture.

of a fracture here indicates a column fracture pattern (most commonly posterior column) or a T-shaped transverse fracture.

III. THE THREE BASIC PATTERNS

Wall fractures

Posterior wall fractures are extremely common and anterior wall fractures are extremely rare. In the large series of acetabular fractures presented by Letournel, anterior wall fractures comprised only 1.9% of all fracture types.[1] Therefore, we will concentrate on the identification of the posterior wall fracture. Posterior wall fractures are best seen on the OO view (Figure 4a) and on the CT through the level of the center of the joint (Figure 4b). This shows the typical appearance of a posterior wall fracture. Learn to recognize it because it frequently occurs in association with other patterns. If isolated, the II and IP lines should not have crossing fracture lines, the obturator ring should not be broken and there should not be a fracture into the iliac wing. The presence of any of these findings indicates that the posterior wall is associated with another pattern.

Transverse

Transverse fractures divide the acetabulum into a top and bottom half (Figure 5a). The fracture line runs from the front to the back of the pelvis through the acetabulum. The ilioischial and iliopectineal lines will be disrupted. *Note that disruption of these lines therefore does not necessarily imply a column fracture pattern.* The iliac wing is intact and part of the weight bearing dome remains intact with the proximal hemipelvis. Since the fracture line runs from anterior to posterior the CT scan will frequently demonstrate an anterior to posterior fracture line through the dome (Figure 5b). The obturator ring will be fractured

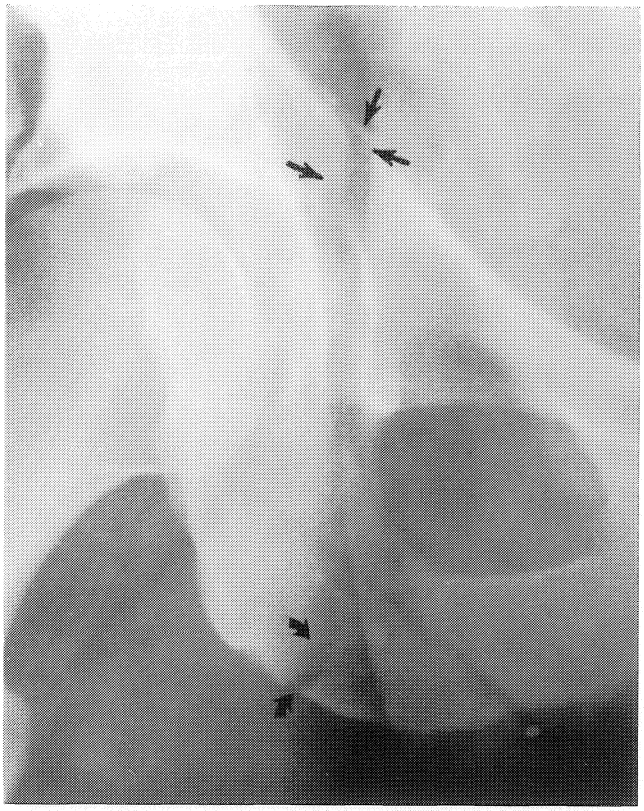

Figure 6a-d Radiographs and CT's of a T-shaped acetabular fracture.

Figure 6a The AP pelvis film suggests disruptions of both the II and IP lines (narrow black arrows) and a break in the inferior portion of the obturator ring (wider curved black arrows).

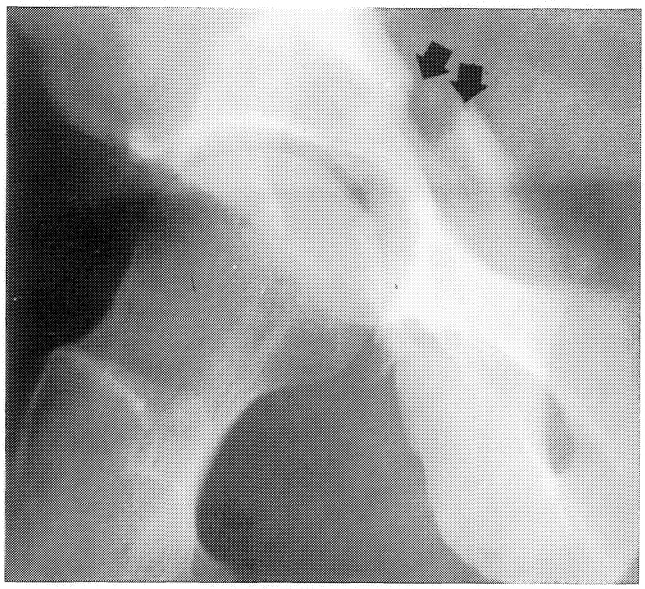

Figure 6b The IO confirms a posterior fracture (black arrows).

only in the transverse variant called the T-type fracture (Figure 6a,b,c,d). There are three fracture types that demonstrate an underlying transverse pattern. These include simple transverse (Figure 5a,b), transverse with posterior wall, and the T-type fracture (Figure 6a,b,c,d). In the T-type the bottom half of the transverse is split by a longitudinal fracture line dividing the obturator ring. Look for a fracture into the obturator ring on the OO radiograph and on the CT at the inferior acetabulum just before entering the ring. The transverse posterior wall is a posterior wall fracture associated with the other features of a transverse.

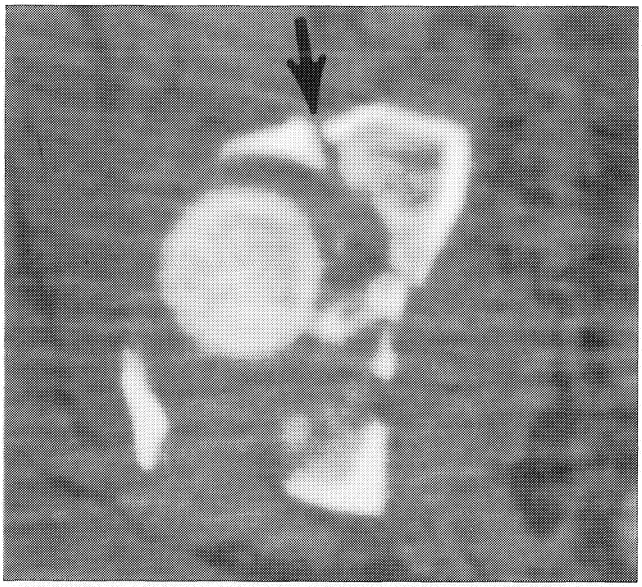

Figure 6c The CT cut near the dome shows an anterior fracture line (black arrow) and suggests a general anterior to posterior fracture configuration, indicating a transverse pattern.

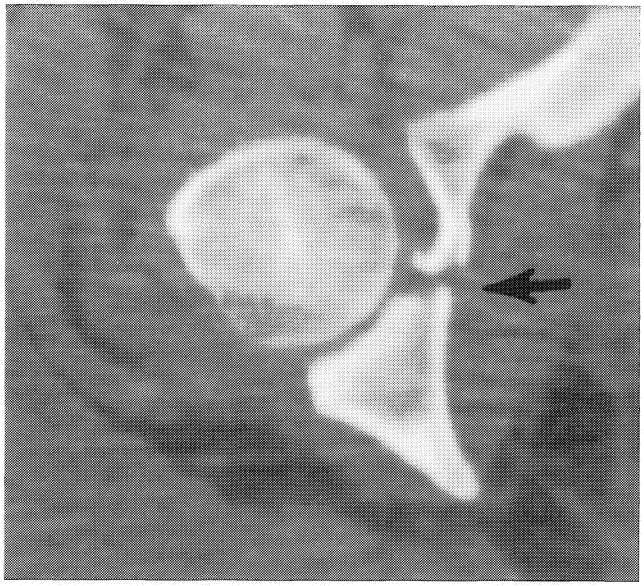

Figure 6d The CT at the inferior acetabulum confirms a quadrilateral plate fracture into the obturator ring.

Figure 7a-f Radiographs and CT of a both column acetabular fracture.

Figure 7-a The AP pelvis demonstrates interruption of the II and IP lines (large black arrows). The fracture of the obturator ring and ilium are also seen (small black arrows) which occur together only with a BC fracture.

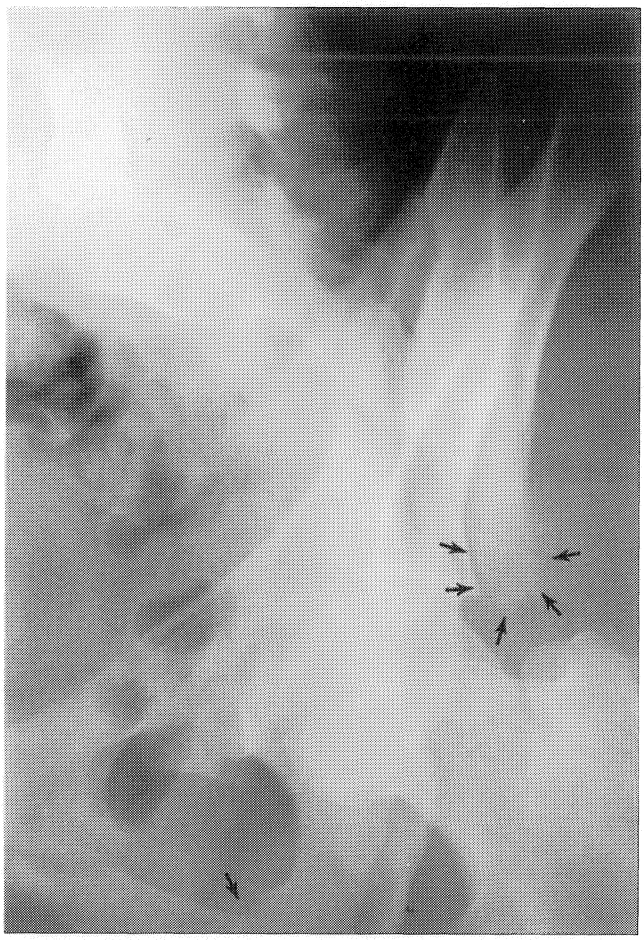

Figure 7-b The obturator oblique accentuates the obturator ring fracture. (small single arrow). This is an excellent example of a spur sign (multiple black arrows).

Column

Column fractures divide the acetabulum into front and back halves by fracture lines that are generally located in the coronal plane. There are five fracture types that demonstrate an underlying column fracture pattern; anterior column (AC), posterior column (PC), posterior column with posterior wall (PCPW), both column (BC) and anterior column-posterior hemitransverse (ACHT).

In fractures of the AC, a segment of the anterior acetabulum of variable size is fractured along with an anterior-superior segment of the innominate bone extending from the middle of the superior pubic ramus below to any point above as far back as the mid part of the iliac crest.[1] Radiographic hallmarks of most AC fractures include a fracture line extending above the acetabulum through the iliac wing and disruption of the IP line occasionally seen in several planes. Examine the proximal CT cut where this fracture line is well seen (Figure 7d).

On this CT cut the AC fracture will have a medial to lateral orientation indicating a coronal fracture line indicative of a column fracture pattern. *The presence or absence of this fracture rules in or out an AC fracture since none of the other acetabular fracture patterns create a fracture extending to the level of the sacro-iliac joint.* A low AC fracture is an exception to this rule. When the AC fracture is isolated, the IO will not show a posterior fracture line.

PC fractures must have a fracture of the obturator ring and disruption of the II line. The fracture into the obturator ring is best seen on the obturator oblique radiograph and on the low CT cut through the bottom of the acetabulum demonstrating a fracture of the quadrilateral plate (Figure 7f). The obturator ring fracture should involve the ischium or the inferior pubic ramus since the superior pubic ramus can be disrupted by an AC fracture. If it is an isolated PC fracture the OO will not demonstrate an anterior fracture line through the IP line, and the proximal CT cut will demonstrate the iliac wing to be

Figure 7-c The iliac oblique x-ray reveals a fracture of the iliac wing (black dots and arrow).

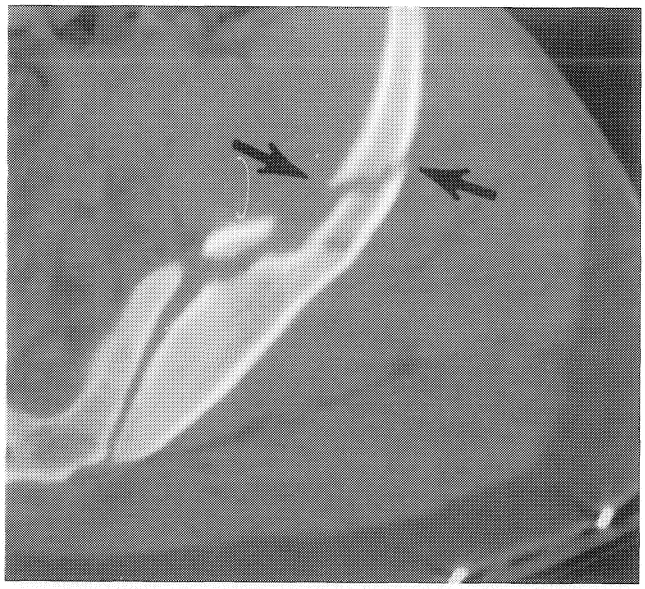

Figure 7-d A proximal CT cut demonstrates a fracture of the iliac wing (large black arrows).

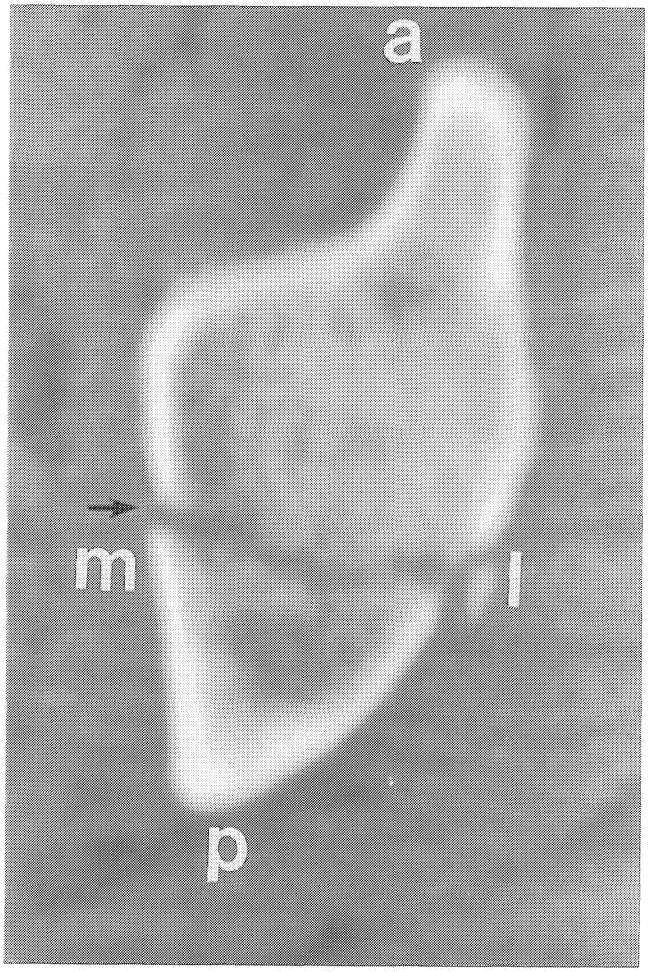

Figure 7-e More caudally, a fracture pattern typical of column fractures is seen traversing from medial to lateral through the weight bearing dome (small black arrow).

intact. Both AC and PC are coronal fracture patterns, so they will have medial -to- lateral major fracture lines on the CT scan.

The features of the BC fracture pattern deserve extra emphasis as this is a common fracture pattern and is initially difficult to interpret. It has the features of both an AC and PC fracture (Figure 7a,b,c,d,e,f). *This is the only fracture pattern with both an iliac wing fracture and a low break in the obturator ring.* Similar to a transverse pattern, both the II and IP lines will be disrupted (Figure 7a). The entire articular surface is separated from the intact iliac wing which is the iliac side of the sacro-iliac joint. For all other patterns a portion of the acetabular articular surface will remain with the nonfractured iliac wing. The pathognomic "spur sign" should be looked for laterally on the OO or CT (Figure 7b and 7f). This is the distal extension of the unfractured iliac wing which tapers to a spur. The CT scan will demonstrate a medial-lateral fracture pattern through the dome (Figure 7e). Since both columns rotate medially together with the femoral head, secondary radiographic

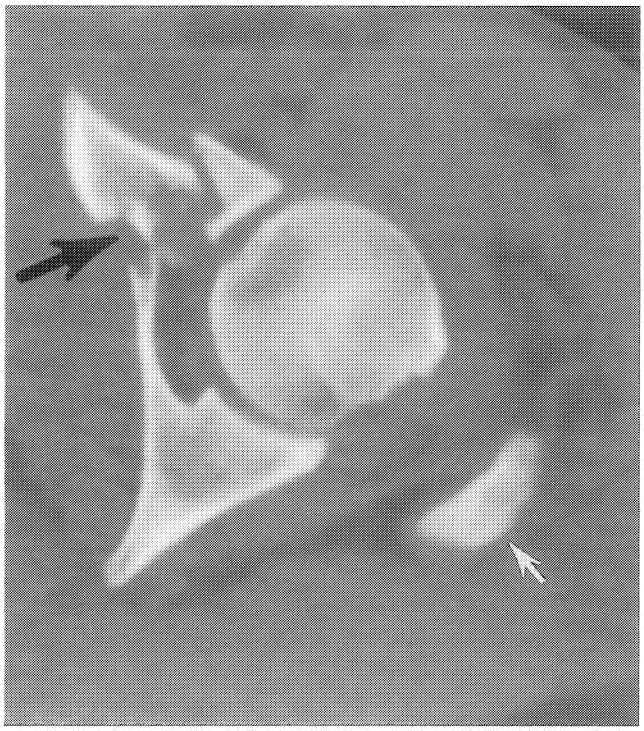

Figure 7-f The spike of iliac wing (the spur sign on the obturator oblique x-ray) is nicely seen on the CT scan at the joint level (white arrow). A fracture of the quadrilateral plate extending to the obturator ring is also seen (black arrow).

congruence will often be observed between the femoral head and acetabular fracture fragments despite the fracture displacement (Figure 7a,b,c).

III. The Systematic Approach

The following steps are designed to systematically evaluate acetabular fracture radiographs for the purpose of assigning each fracture to one of the ten groups. The initial goal is to classify the fracture into one of three major patterns: *column, transverse or wall.* Once these features have been recognized, then address the associated fractures (wall fractures or hemitransverse patterns.) These steps should be followed as outlined below.

Evaluate for a column fracture pattern in step 1 and 2, for a transverse pattern in step 3, and for a wall fracture in step 4. Combine these steps to classify the majority of the fractures accurately.

1) Is the iliac wing broken (obturator oblique, high CT scan)? yes: either AC or BC or ACHT. Be aware of a low AC fracture that could be missed on the CT at the level of the SI joint.
2) Is the obturator ring broken with breaks in the ischium or inferior pubic ramus (obturator oblique, CT through bottom of acetabulum)? yes: PC, BC or T - type (see # 3 regarding Transverse patterns). Beware that an AC fracture breaks the obturator ring at the superior pubic ramus only.
   >> If #1 and #2 are both yes, then BC is the only possible pattern (look for spur, no weight bearing dome with acetabulum, secondary congruence, and med-lat CT fracture pattern.)
   >> If #1 no and #2 yes, then PC or T-type is the diagnosis. Look at the obturator oblique and the CT cuts at the level of the dome and the mid-joint for an anterior fracture line; yes - T - type, no - PC.
   >> If #1 yes and #2 no, then AC or AC posterior hemi-transverse is the diagnosis. Look at the posterior column on the iliac oblique for a crossing posterior fracture line; yes - ACHT, no - AC.
3) Are the II and IP lines both broken with fractures exiting on the obliques both anteriorly and posteriorly? This indicates BC, ACHT or one of the three transverse variants.
   >> If #3 is yes: and #1 is no, must be one of the transverse patterns (rules out BC and ACHT); if #2 is yes, then must be a T-type: if #2 is no, then transverse only.
4) Is there a posterior wall fracture? (obturator oblique, CT through mid joint)
   >> If #4 is yes and if #1, 2, or 3 yes, then PW associated with above diagnosis if #'s 1, 2, and 3 no, then PW.

Application of the above four steps should be tested in the previous cases presented. Once you are familiar with these steps, try the unknown case presented in figures 8a-e.

SUMMARY

After a background understanding of the classification of Judet and Letournel and the radiographic anatomy of the pelvis, the majority of acetabular fractures are readily classified by utilizing the steps as outlined above. We feel that a systematic, stepwise approach to classifying acetabular fractures into larger groups and then subclassifying these groups will help simplify the application of the Letournel and Judet classification. Try using this method, and your ability to classify these fractures will improve.

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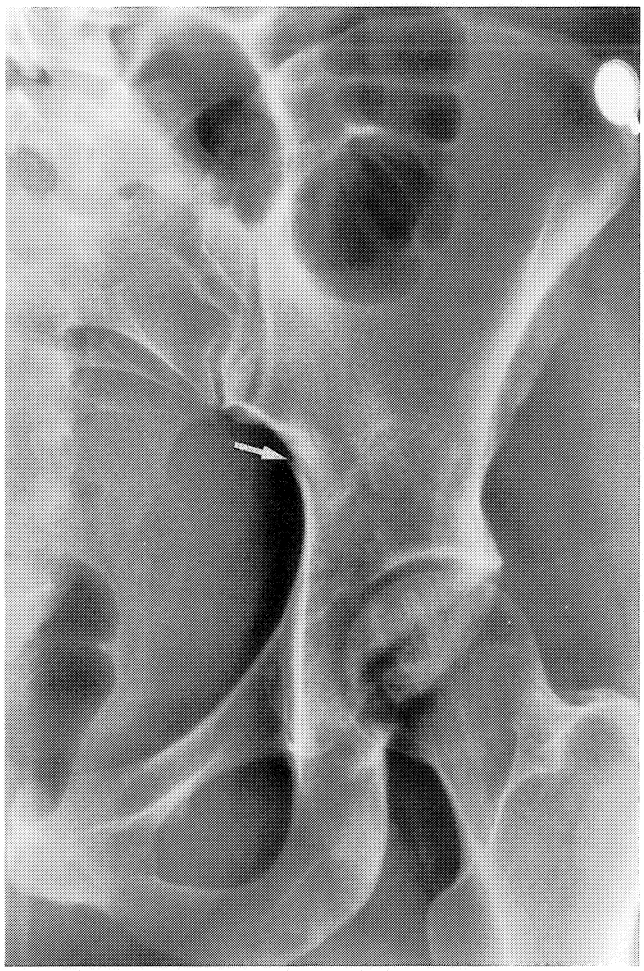

Figure 8a

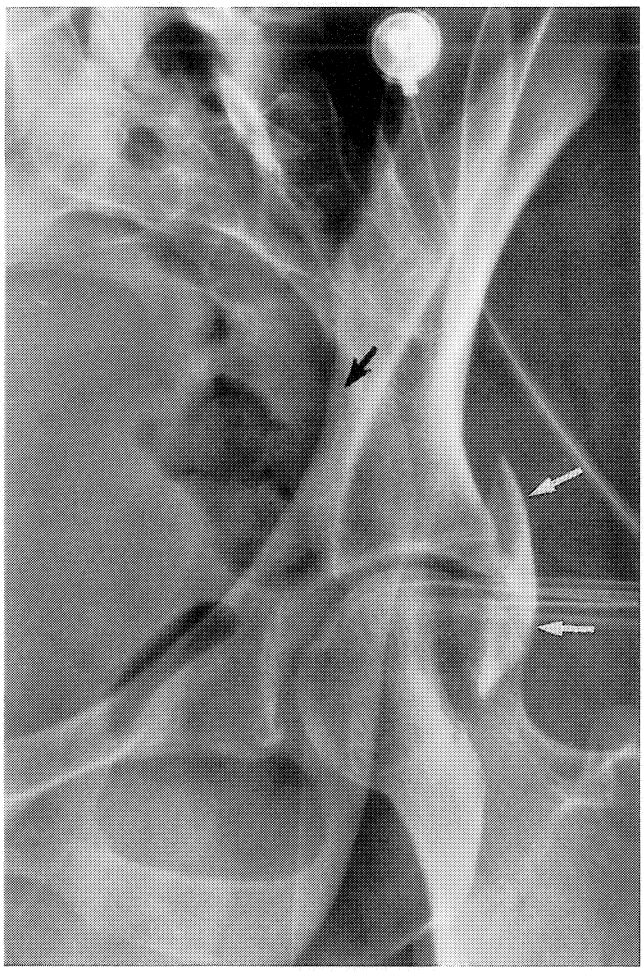

Figure 8b

Figure 8a-e Radiographs and CT scan of "unknown case".

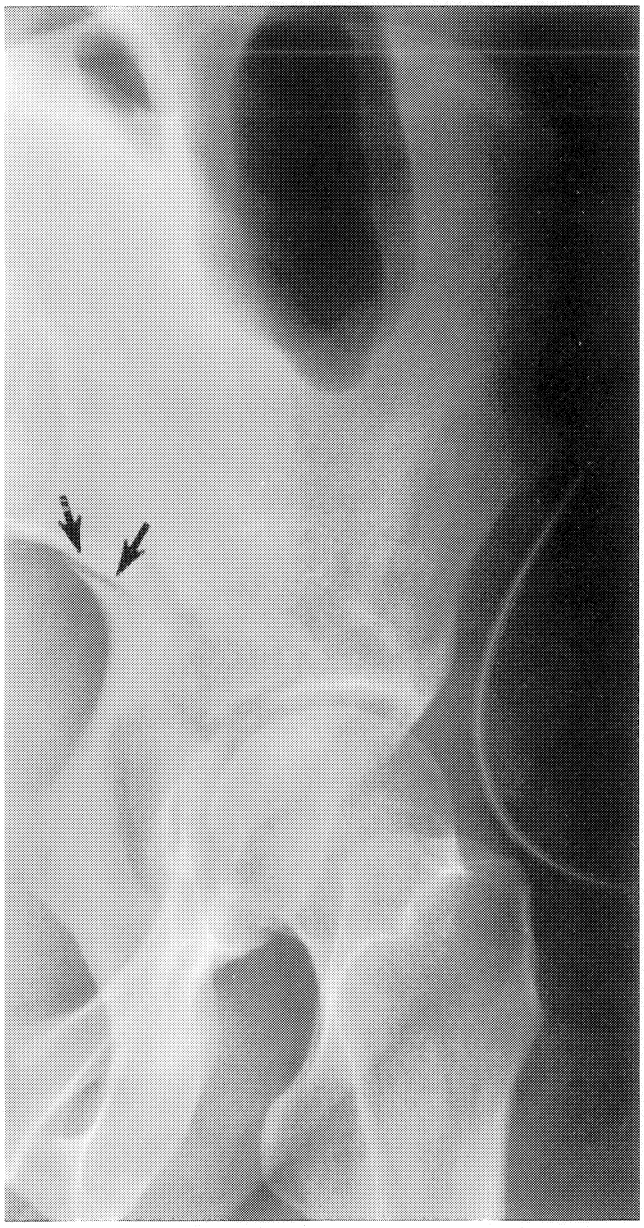

Figure 8c

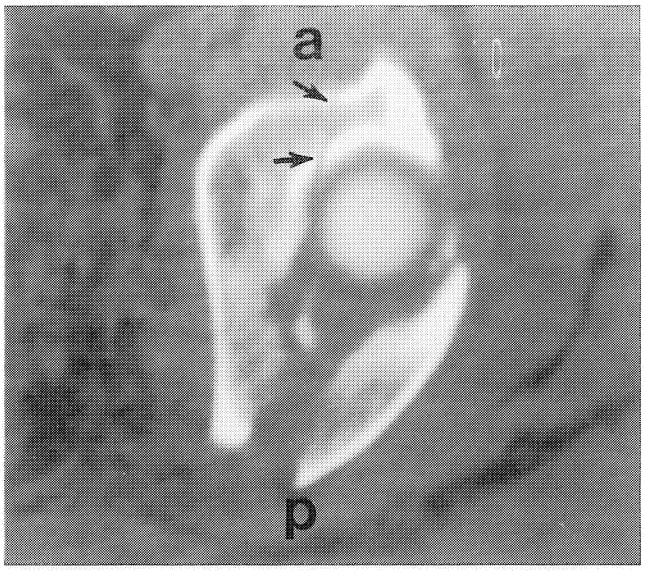

Figure 8d

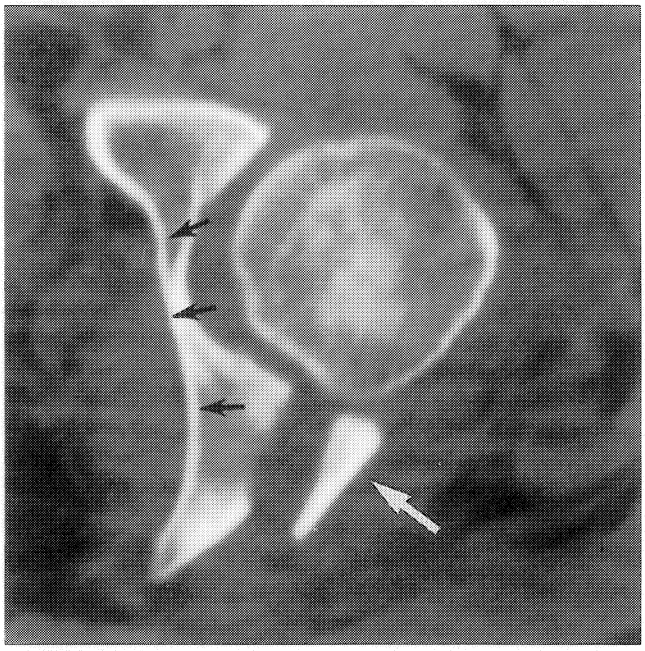

Figure 8e

LEGEND APPENDIX

Answer to unknown Figure 8a-e.

a) The AP pelvis shows a proximal fracture at the sciatic notch where the II and IP lines merge (white arrow).

b) The OO shows a PW fracture (white arrows) and a hint of an anterior fracture (black arrow). The obturator ring is not fractured.

c) The IO shows a posterior fracture line in the sciatic notch (black arrows).

d) The CT cut through the dome shows a displaced posterior fracture line and a nondisplaced anterior fracture line (black arrows).

e) The CT cut low through the acetabulum shows the bottom of the PW fracture (white arrow), and confirms that there is no break into the obturator ring (black arrow).

Systematic Approach

1) Is the iliac wing broken (would confirm on proximal CT cut)? - no
2) Is the obturator ring broken? - no
3) Are the II and IP lines both broken? - yes (check 8d)
4) Is there a PW fracture? - yes

Diagnosis

Transverse PW. The major fracture line posteriorly must go either into the obturator ring (PCPW) or anteriorly transverse PW.

AN ARTICULATED ANKLE EXTERNAL FIXATION SYSTEM THAT CAN BE ALIGNED WITH THE ANKLE AXIS

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ABSTRACT

Aligning an articulated ankle external fixator with the ankle axis located using a mechanical axis finder has been shown to preserve normal ankle joint kinematics while the fixed hinge device is attached. However, several problems exist preventing the clinical application of this finding for fractures of the tibial plafond. We initiated a series of studies to resolve these issues. First, the accuracy of the mechanical axis finder in biological systems was quantified by comparing it to that of a computationally derived helical axis. Second, a prototype fixator design was developed in the biomechanics lab to increase the versatility of intraoperative fixator placement. Finally, a radiographic method of locating the ankle axis was developed which is based on talar morphology independent of the fractured tibia. The prototype fixator has been accurately aligned along the ankle axis in cadaveric specimens using this method.

Open reduction and internal fixation (ORIF) is the accepted method of treatment for tibial plafond fractures. It holds the advantage of sufficient fracture fixation to permit early joint motion. Good results have been reported using this method[3,11], but some authors have reported complication rates up to 50%[2,4,9,10,14]. The wide surgical approaches required, in conjunction with preexisting soft tissue injury, are thought to significantly increase the risk of soft tissue complications. In response to these problems, many investigators are beginning to utilize external fixation as an alternate treatment modality.

One external fixation system which has shown particularly good results is a monolateral cross-ankle articulated fixator (Orthofix SRL., Verona, Italy) which allows motion at the ankle joint as the plafond fracture is healing (Figure 1)[1,8,12]. The fixator is applied with two pins distally, one in the talus and one in the calcaneus, and two pins proximally in the tibia. The distal clamp is attached to the fixator body by a uniaxial hinge that is centered over the medial side of the talus. The current clinically recommended application technique aligns the hinge along a horizontal ankle axis. The hinge is released post-operatively and the patient performs passive and active motion.

The current technique for applying the articulated external fixator requires the imposition of a non-physiologic (horizontal) axis at the ankle. This abnormal axis of rotation may lead to altered joint kinematics, decreased range of motion and possibly to changes in the contact forces at the joint surfaces.

We have quantified the degree of alteration of the normal kinematics of the ankle with three different fixator orientations by performing a biplanar kinematic analysis of cadaveric ankles[5]. The fixator applications simulated a horizontal axis (the configuration currently used), an ap-

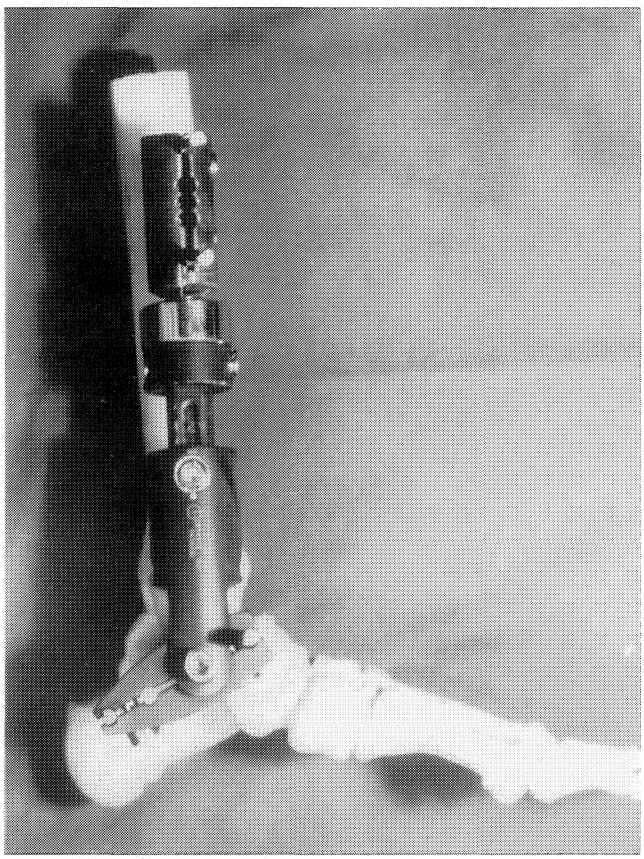

Figure 1. The Orthofix articulated ankle external fixator aligned with the current clinically recommended hinge orientation.

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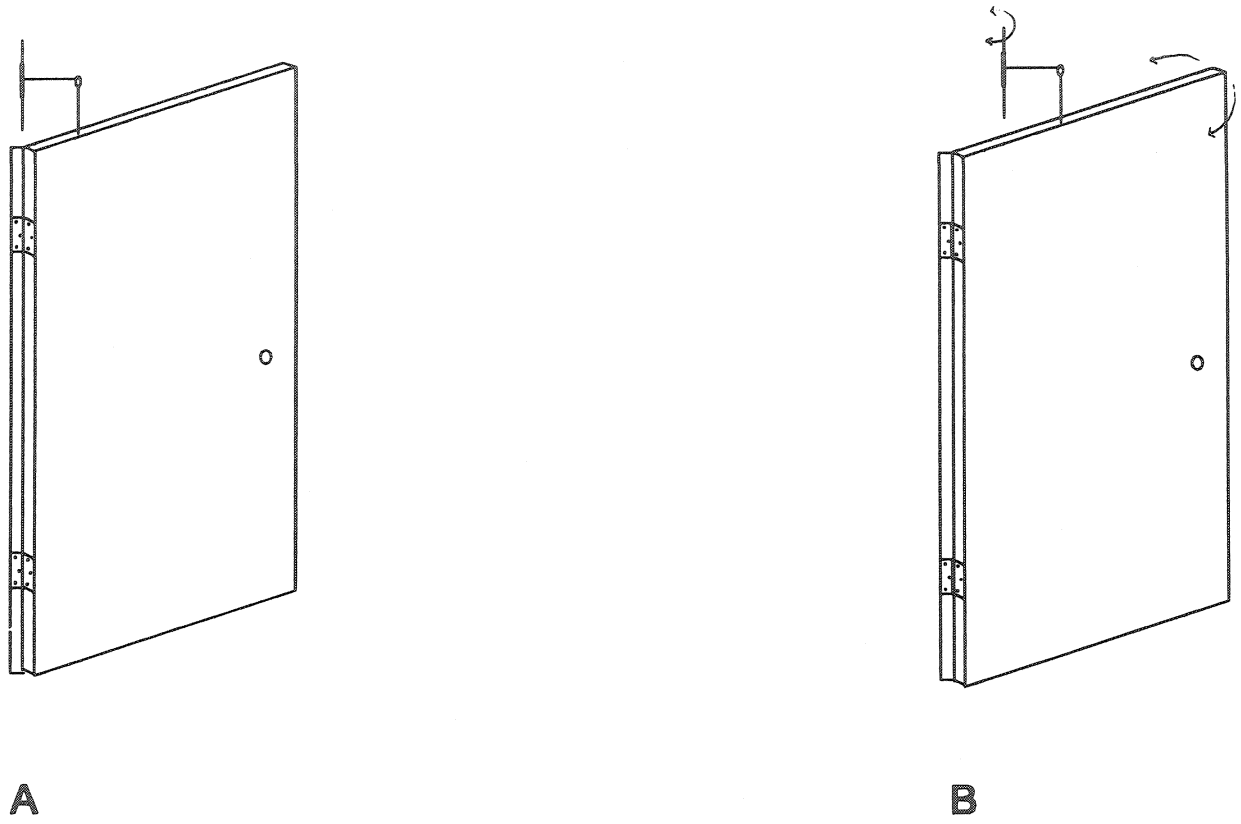

Figure 2. If the axis finder is aligned with the hinge of a door (a), the axis pin will rotate about itself as the door is opened and closed. If, however, the axis finder is not aligned with the hinge (b), the pin will move in an arc as the door is opened and closed.

proximate ankle axis described by Inman[7], and an axis located using a new mechanical axis finder[6,13]. The current clinical application technique, which approximates a horizontal ankle axis, significantly disturbed normal ankle joint motion and decreased the total range of motion possible. Aligning the fixator with the average ankle axis described by Inman resulted in significant differences from normal motion about one of three possible rotational axes. With the fixator hinge applied along the axis determined by the axis finder, ankle motion was not altered from normal. This result indicated that applying a fixator aligned along the true ankle axis might have significant clinical advantages.

The axis finder is a mechanical device described by Hollister et al.[6]. It works on the principle that if a pin is attached to a body undergoing fixed-axis rotation in alignment with the axis of rotation, the pin will rotate about its own axis as the joint is rotated. If, however, the pin does not lie on the joint's rotational axis, its tip will describe an arc as the joint rotates. This principle can be visualized by thinking of the joint as a door hinge (Figure 2). If a pin is attached to the door such that it is coincident with the hinge of the door, the pin will appear to rotate about itself as the door is opened and closed. However, if the pin is attached eccentrically from the door hinge, and/or if the pin is not aligned parallel to the hinge, it will describe an arc as the door is opened and closed.

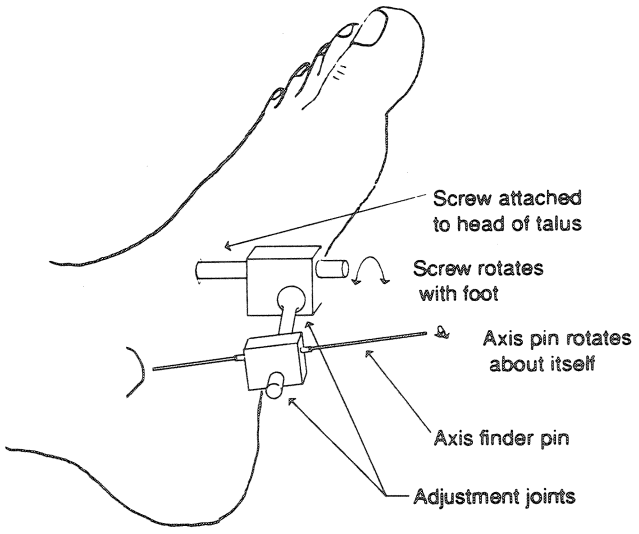

Figure 3. When used on the ankle joint, the axis finder is attached to the head of the talus and the axis pin is adjusted until minimal motion occurs.

Table 1. The angular disparity between the calculated helical axis and the axis finder for the hinge model and cadaver ankle.

	20° PF → neutral	neutral → 10°DF	20° PF → 10° DF
hinge model	2.74° (0.42)	4.06° (0.26)	2.36° (0.35)
cadaver ankle	9.88° (0.72)	10.94° (1.42)	9.10° (0.25)

In the case of the ankle joint, motions of an adjustable pin attached to the talus are monitored as the ankle is moved (Figure 3). This is best done by looking down the long axis of the pin. If the pin is coincident with the ankle's axis of rotation, no pin motion will be apparent. If the pin is not aligned with the ankle's axis of rotation, the end of the pin will either describe an arc or ellipse. The pin must then be adjusted in a direction perpendicular to its arc of observed motion to orient it coincident with the ankle's axis. Through a series of iterative adjustments of the axis finder pin, one can locate the axis of rotation of the joint.

At the completion of this kinematic study, a number of hurdles remained before the goal of clinically aligning a fixator hinge along the ankle axis could be realized for fractures of the tibial plafond. Some of these issues were addressed in a series of additional studies described here. First, the accuracy of the axis finder was investigated in order to determine the reliability of its use in biological systems; second, alternate fixator design prototypes were developed to increase the ease and versatility of intraoperative hinge placement; and third, a radiographic method was developed for locating the ankle axis.

Accuracy of the axis finder

In theory, the axis finder is able to precisely locate the axis of rotation of a simple hinge joint. However, the ankle joint does not behave as a simple perfect hinge, and therefore some error in the location of the ankle axis by the axis finder is unavoidable. This error, along with its ramifications for fixator hinge orientation, was quantified and addressed.

A series of biplanar radiographic analyses were conducted in order to compare the experimentally determined axis finder ankle axis to a computationally defined helical axis. A surrogate hinge model of the foot was designed and instrumented with tantalum marker beadlets for formal biplanar radiographic analysis. The axis finder was attached and adjusted until it was visually aligned with the hinge axis of the model. Biplanar radiographs were exposed and the three-dimensional locations of the model and the axis finder endpoints were computed. From these locations, the three dimensional helical axis about which the model was rotating was computationally determined. The vectoral dot product of this helical axis and the axis finder axis was used to determine the angular disparity between these two axes. Subsequently, a similar procedure was used to determine the angular disparity between the computed helical axis versus the axis finder axis in two cadaver specimens.

The axis finder was able to consistently locate the axis of rotation of the hinged surrogate model to within 4° in all cases. In the cadaver ankles, the axis finder was able to approximate to within 10° the true axis of rotation of the ankle, as defined by the computationally determined helical axis (Table 1). Even though the axis finder was only able to locate the "true" ankle axis to within 10°, the kinematic study suggests that the ankle still moves well with the fixator aligned along the axis finder axis. Gross observations on several cadaver specimens indicated that the axis finder does not locate a unique axis, but instead finds a locus of axis orientations, all of which show minimal pin movement. When the fixator hinge is aligned with any of these axes, the normal kinematics of the ankle are not altered within the sensitivity of the kinematic measurements described above.

Redesign of the distal fixator clamp

With the current commercially available fixator, the hinge can be oriented only in line with the distal fixator pins. Anatomic constraints require that these pins be placed horizontally, parallel to the dome of the talus, thus in effect prescribing a non-physiologic orientation of the fixator rotation axis. In order to allow the fixator to be aligned with the physiologic ankle axis, the distal clamp was redesigned to allow much more freedom in its placement.

The first design modification was to replace the rigid distal clamp with a ball joint, similar to that which attaches the proximal clamp to the fixator body (Figure 4a and 4b). This modification allowed the distal clamp to be angulated at least 17° relative to the fixator body. With this modification, the distal clamp could be angulated enough to allow the fixator hinge to be aligned with the physiologic ankle axis. However, this required that the fixator screws be parallel with the ankle axis, a situation which is technically difficult to achieve. Even if the screws could be reproducibly aligned parallel to the fixator axis, they would often have to be inserted in a manner which would disrupt either the talonavicular or subtalar joints.

The next step was to redesign and modify the fixator hinge and screw-clamp mechanisms. The major design criterion here was to allow the screws to be inserted into the talus and the calcaneus in the recommended horizontal orientation while allowing the fixator hinge to be indepen-

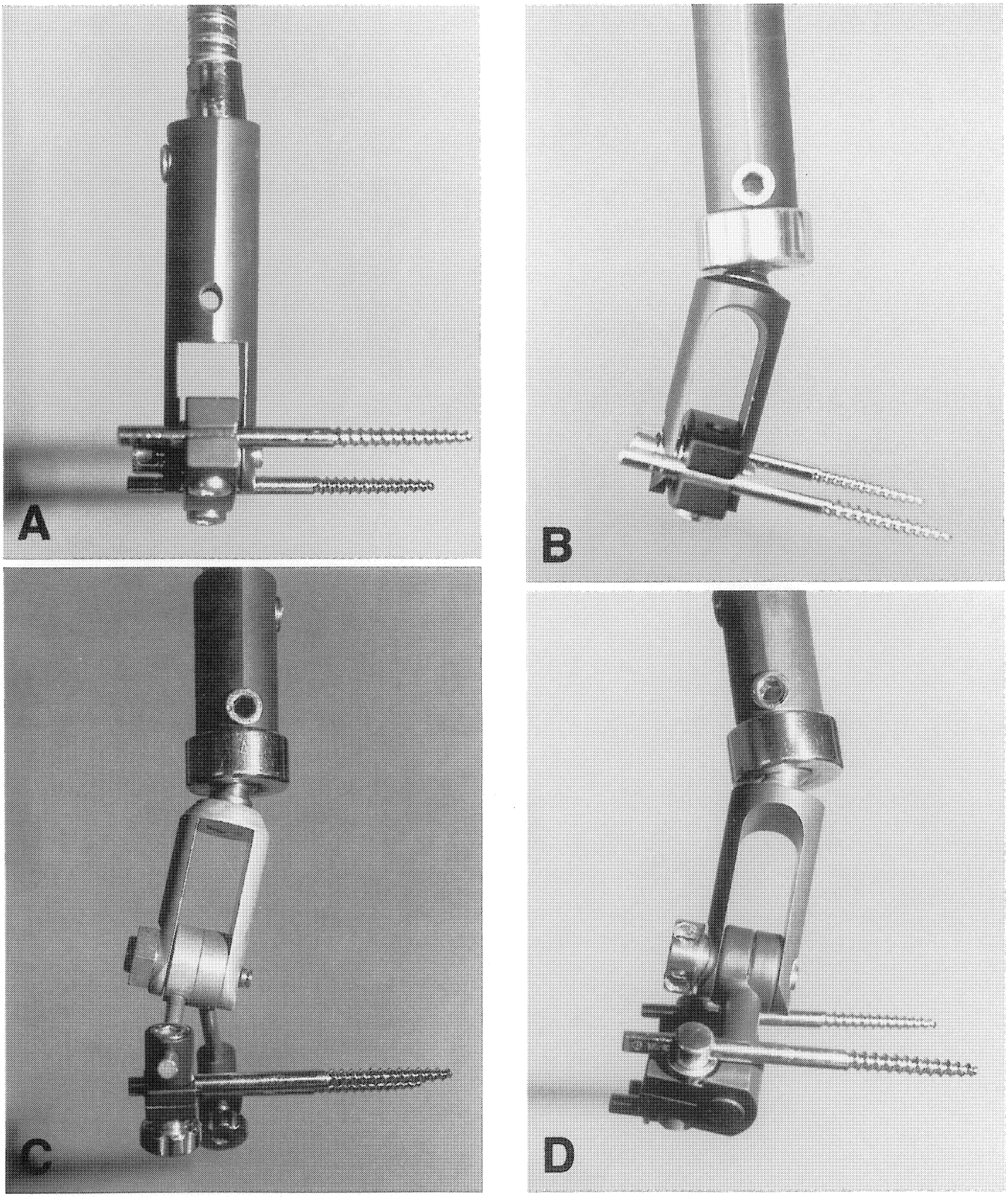

Figure 4. The evolution of the distal clamp. The original rigid distal clamp (a) only allowed the hinge to be oriented along a horizontal axis. The first design modification added a ball joint in place of the rigid clamp (b). This allowed the distal clamp to be angulated 17° with respect to the fixator body. The next modification was to add accessory joints at the screw-clamp interfaces and a screw within a screw joint at the fixator hinge. The in-house prototype (c) and the Orthofix version (d) are shown.

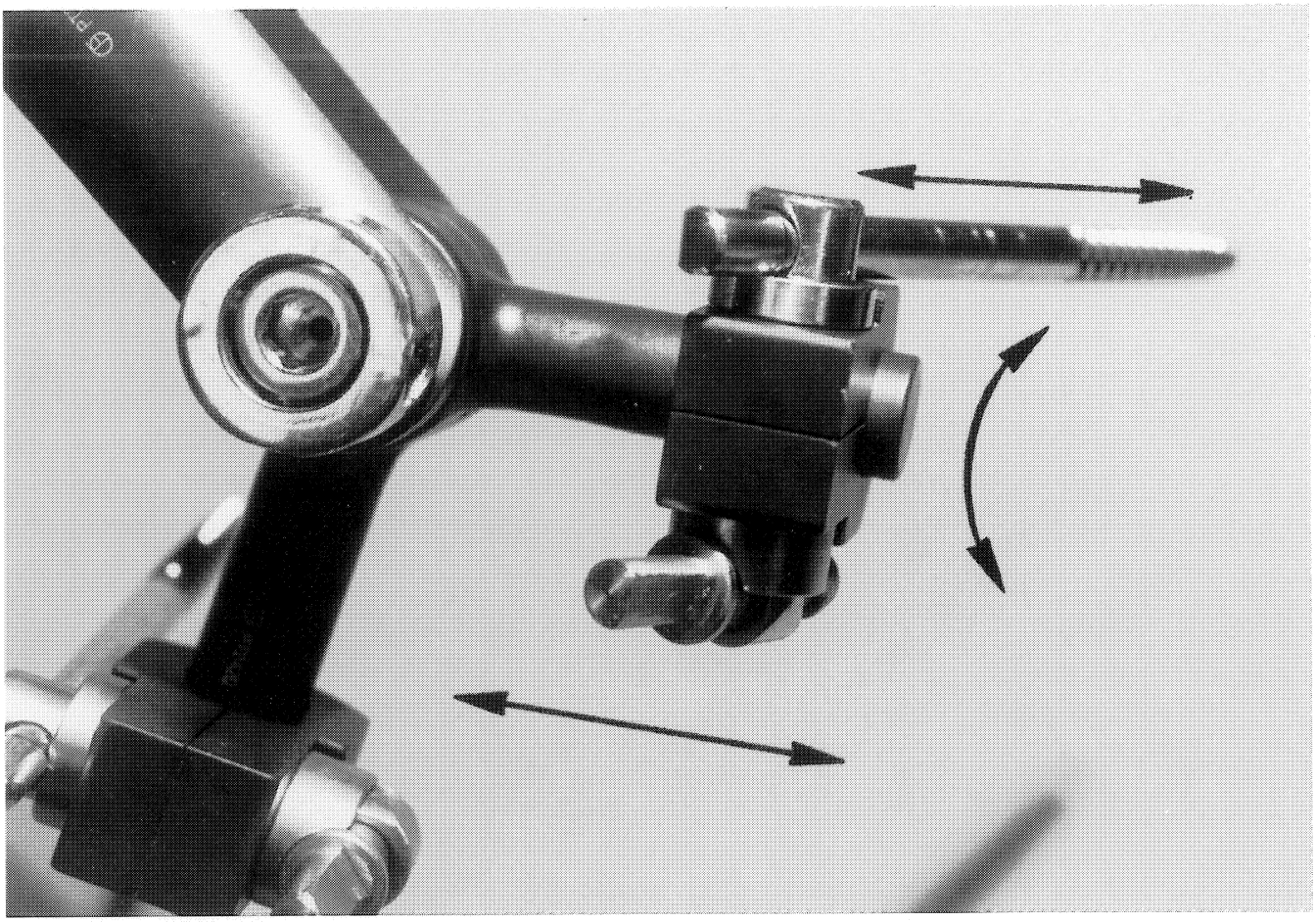

Figure 5. The new screw clamp design allows the clamp to be independently adjusted in the three planes shown. These additional degrees of freedom allow the fixator hinge to be aligned with the axis of the ankle independent of the screw orientation.

dently aligned with the axis of rotation of the ankle joint. To accomplish this, accessory joints were introduced at the junction between each of the fixator screws and the screw clamp (Figure 5). These accessory joints have three degrees of freedom and allow the hinge to be aligned with the axis of the ankle, independent of the orientation of the fixator screws. Additionally, the entire clamp is allowed to slide along the arm of the fixator in order to adjust the hinge position relative to the talar screw.

To allow additional surgical freedom in the placement of the talar and calcaneal screws, an additional joint was added to the distal clamp. This joint is at the junction between the two arms and allows the angle between each of the arms to be changed relative to each other (Figure 6). This modification allows greater freedom in the placement of the calcaneal fixator pin. This necessitated the development of a double locking mechanism (i.e., a screw within a screw), one for the two arms of the fixator clamp and one for the main ankle articulation.

An in-house prototype of the new distal clamp was fabricated (Figure 4c) and tested on several cadaver specimens. Initial success in the application of the fixator, and the resulting improvement in ankle motion, prompted Orthofix to build a refined prototype that conformed more closely to the existing Orthofix external fixation system (Figure 4d). In addition, the refined prototype incorporated standard Orthofix screw clamps, which were not available for the in-house version of the fixator. This refined prototype has also been successfully tested on several specimens.

Radiographic determination of the ankle axis

Plafond fractures usually involve extensive comminution of the distal articular surface of the tibia. This invariably results in the disturbance of the normal anatomy and dynamics of ankle motion. All methods currently available to locate the axis of rotation of the ankle, including the axis finder, implicitly rely on normal ankle anatomy and kinematics. If the normal anatomy is severely compromised, the kinematics will be altered, and there is no way to recover the pre-fracture rotation axis, regardless of whether one uses a malleolar-based axis definition or an axis-finder-based axis definition.

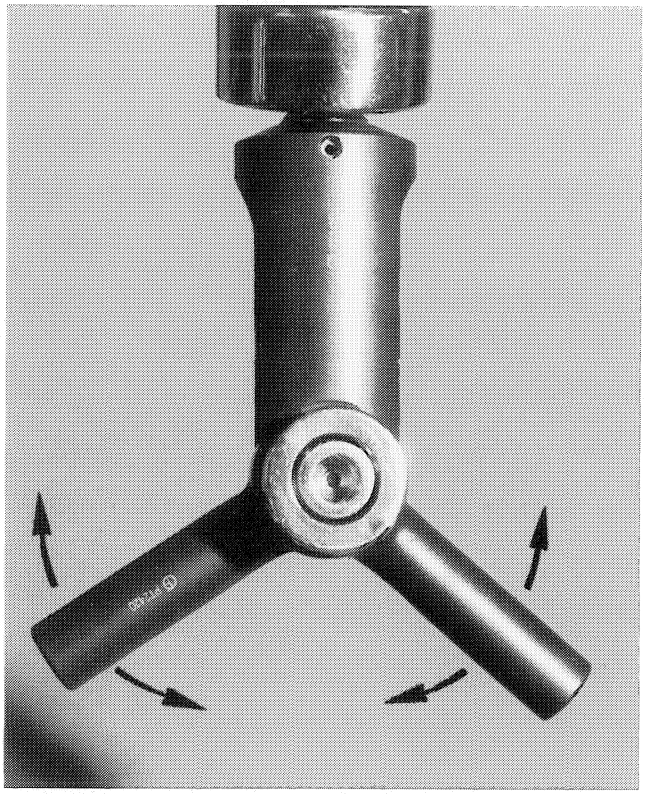

Figure 6. An additional joint was added at the junction between the clamp arms. This modification allows the arms to be positioned independent of each other, allowing greater freedom in the placement of the calcaneal fixator pin.

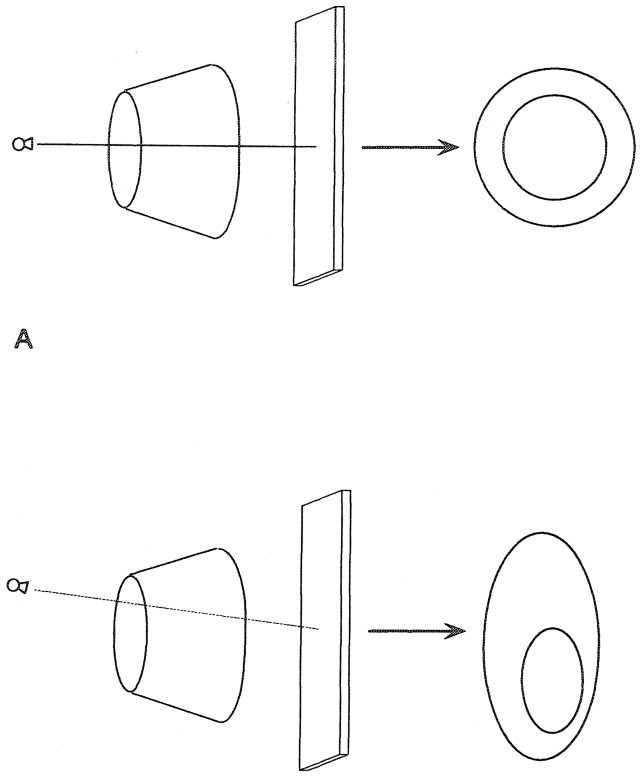

Figure 7. If a truncated cone is exposed to an x-ray beam along the long axis of the cone (a), the resulting image will be two concentric circles. If, however, the truncated cone is exposed to an eccentrically oriented beam (b), the resulting image will be two non-concentric ellipses.

Fortunately, although plafond fractures often involve significant injury to the distal tibia, the talus is usually spared from significant bony damage. Theoretically, a method of locating the ankle axis based solely on the talus would allow the orientation of the fixator hinge axis to be determined independent of the damaged tibia, and therefore would have application to fractures of the tibial plafond.

It was noted by Inman[7] that the trochlea of the talus was not shaped as a cylinder, as previous authors had stated, but rather as a segment of a cone. The base of this cone is located on the lateral side of the talus, and the apex of the cone is on the medial side. Inman postulated that the long axis of this cone was the axis of rotation of the talus in the mortise. More recently, Singh et al. made use of talar anatomy when using an axis finder to locate the ankle axis[13]. Serial magnetic resonance images of the talus were obtained in a plane perpendicular to the axis of rotation, as inferred by the axis finder. They then fit a circle to the arc of the talar trochlea apparent on each of the slices. The center of this circle was found to be reasonably coincident with the mechanically determined axis of the ankle joint.

If a radiograph is exposed along the long axis of a truncated conical segment, a double shadow representing two concentric circles appears (Figure 7a). The inner shadow depicts the surface nearest the apex of the cone, and the outer shadow depicts the surface nearest to the base of the cone. If a radiograph is exposed at an angle to the long axis of the cone, these two shadows will be non-concentric and will form ellipses (Figure 7b). A radiograph exposed along the long axis of this cone will result in segments of two concentric circles with their common center being coincident with the cone's axis. In the case of the ankle, by using this concept in reverse (i.e., by locating that specific position of the talus which casts concentric radiographic double shadows), one should be able to locate the axis of rotation of the ankle joint.

Six cadaveric specimens were used to test this hypothesis. The axis of rotation of the ankle was first determined on each using an axis finder. Then a radiograph of the ankle joint was exposed with the central beam of the fluoroscope aligned coincident with the axis finder pin. In all cases, the expected double arc was located, although in many cases only small segments of the arcs were visible (Figure 8). The distance between the circle segments was variable ranging from 5 - 10 mm. The center of the two

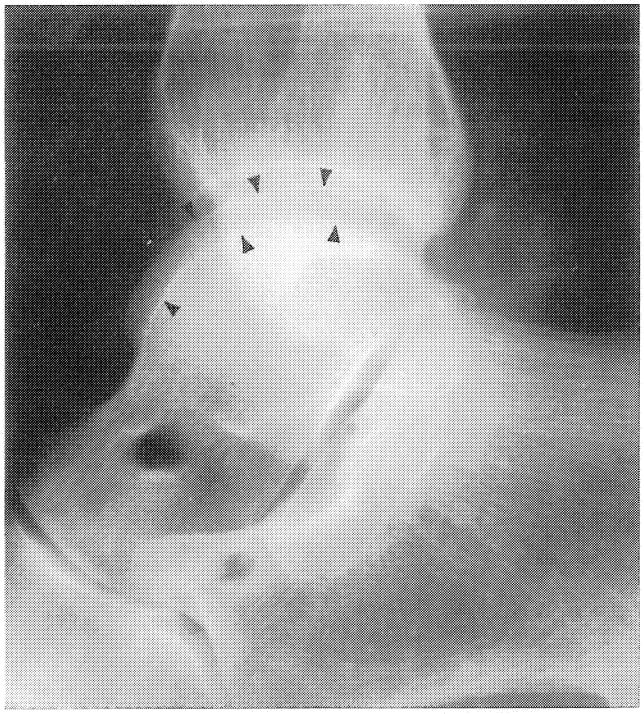

Figure 8.
Fluoroscopic image of the talus aligned with the axis of rotation of the ankle. Notice the double shadow of the talar dome.

arcs was within five millimeters of each other, indicating that the arcs were segments of two concentric circles. As expected, the tips of the medial and lateral malleoli were superimposed upon one another.

With the radiographic appearance of the ankle axis quantitatively defined relative to the talus, the next task was to locate the axis of rotation of the talus, independent of the axis finder. Using fluoroscopy, the characteristic double shadow was located on the same cadaveric specimens. This was accomplished by placing the ankle in the fluoroscopic field such that a lateral image of the talus was exposed. By manipulating the ankle in an iterative process, the image of the talus in its double shadow formation was obtained. The center of the circle formed by the two arcs was then located, and an axis positioning guide (i.e. the axis finder) was attached via a previously inserted talar pin. The positioning guide was adjusted until it was coincident with the fluoroscopic beam and was then locked into place. At this point, the pin of this positioning guide was coincident with the radiographically determined axis of rotation of the ankle joint.

In order to determine if this orientation was similar to that previously obtained using the axis finder, the ankle was moved and the amount of motion in the axis positioning pin was observed. The amount of pin motion was similar to that observed when locating the axis using the axis finder alone. Prototype fixators were then applied along the radiographically determined axis of rotation. The total range of motion qualitatively and quantitatively appeared unaffected relative to the unrestricted ankle.

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THE LEATHER ANKLE LACER

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ABSTRACT

The purpose of this study was to evaluate the efficacy of a leather ankle lacer for treating painful problems of the ankle and hindfoot. The evaluation involved patient self assessment, clinical examination and radiographic determination of the effectiveness of the ankle lacer. Overall, patients had moderate pain relief with significant but not complete restriction of motion. Based on this study and our clinical experience, we find the leather ankle lacer to be a compliant and comfortable treatment strategy for patients with painful ankle and hindfoot problems who desire some retained motion.

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INTRODUCTION

Arthritis of the ankle and hindfoot are common problems. Initial treatment typically involves activity modification and use of oral anti-inflammatory agents. If these measures fail, bracing to reduce motion and unload the affected joints may be considered. Currently, the most popular approaches typically involve fabrication of a rigid polypropylene ankle foot orthoses (AFO). Although this method is generally well tolerated, it can cause difficulties related to excessive restriction of motion, skin irritation or gradual fitting problems secondary to leg atrophy. At the University of Iowa, we have used a custom-molded leather

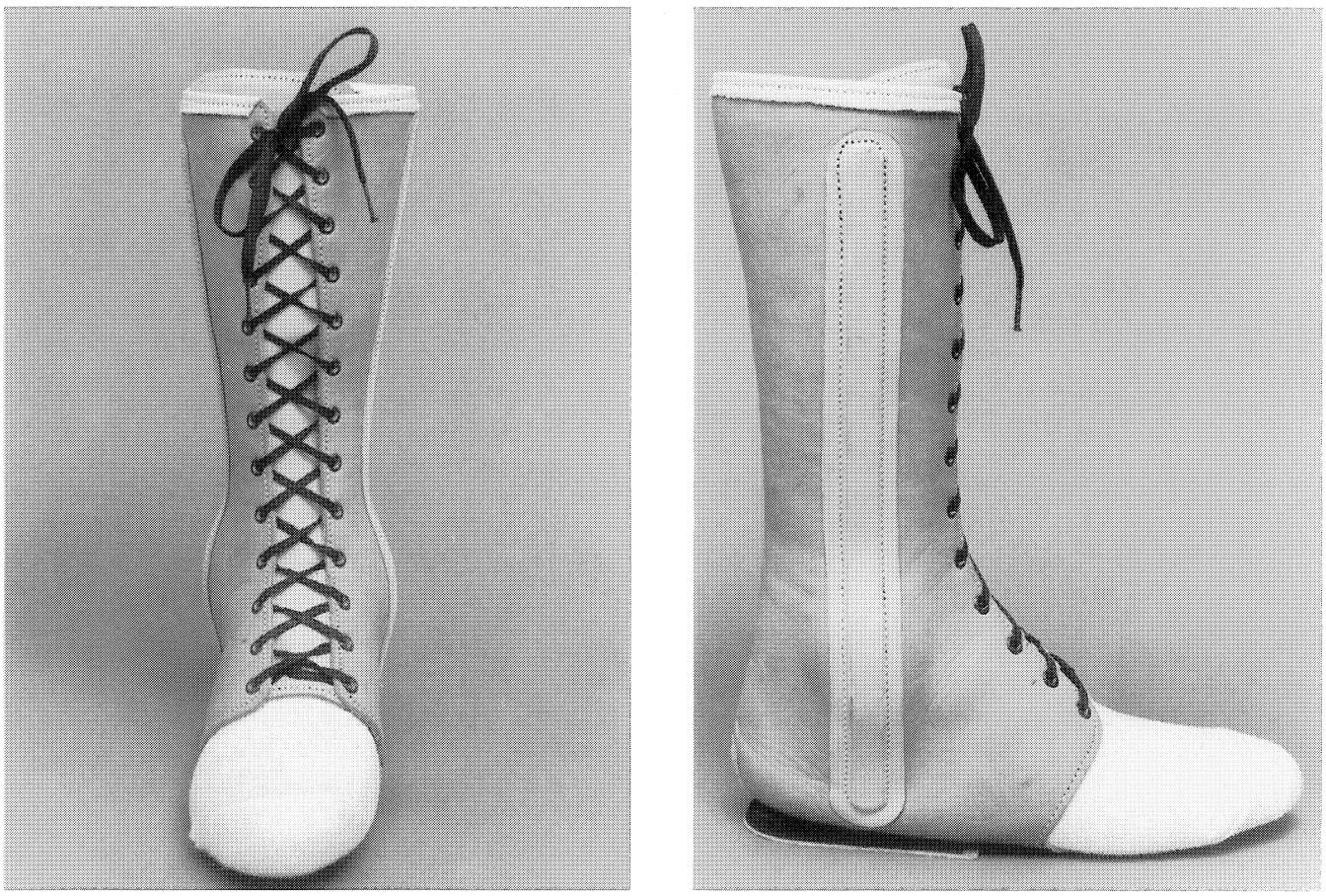

Figure 1A & B The leather ankle lacer. Medial and lateral metal stays restrict motion in the transverse plane.

ankle lacer to treat selected patients with problems of the ankle or hindfoot. (Fig. 1) At our institution, this device has been used for over fifty years since Jordan first described the application of leather bracing to treat problems of the ankle.[1] Today the leather ankle lacer remains a viable alternative to modern synthetic braces because of its intrinsic compliance and low interface sheer. We decided to undertake the present study to assess the lacer's efficacy with pain relief and restriction of motion.

Fabrication of the Custom-Molded Ankle Lacer

The impression of the foot and ankle is carefully taken with consideration given to the amount of anticipated correction or accommodation. Generally, the ankle rests in slight pronation with compensatory forefoot supination. Complete correction of the deformities may not be possible and usually is not well tolerated by the patient. Following the negative impression, a positive model is made and modified in a usual manner with careful attention paid to overall cylindrical reduction in circumference to provide loading on the leg.

Smooth molding leather is soaked in water, secured to the model and allowed to dry completely. Soft lining leather is stretched under the molding leather and covered with a plastic wrap that acts as a barrier. Once dry, the leather is cut off the model anteriorly, making room for the tongue to be added later. Eyelets or Velcro roller loops are added. The metal stays are added to the medial and lateral sides of the lacer, carefully contoured to produce the desired support. Leather stay covers are glued over the metal stays.

Trimlines generally resemble those of other AFO's: mid-metatarsal head, neck of the fibula, and slightly above the apex of the gastrocnemius muscle bellies posteriorly. Polyethylene or mesh wire may be substituted for the metal stays for a more general support. Both materials are "sandwiched" between the two leather layers.

MATERIALS AND METHODS

Subjects

This study involved five patients from the University of Iowa Hospitals and Clinics who were presently using the leather ankle lacer. Prior to participation, all patients signed an informed consent form approved by the institution's Human Subjects Review and Radiation Protection Committees. There were three women and two men, having a mean age of 66 years and range 53-79 years. Seven braced feet were examined with the average length of lacer wear being 5.5 years. Basic subject data are presented in Table 1.

TABLE 1

Patient History

	Age	Sex	Weight	Length of Brace wear (Yrs)	Medical Condition
1.	79	F	170	10	Subtalar Instability
2.	5	F	140	5	Rheumatoid Arthritis
3.	78	F	170	1	Ankle DJD
4.	62	M	194	5	Ankle Instability
5.	58	M	200	7	Ankle Instability

Subjective Evaluation

A subjective evaluation of the brace was done by a written questionnaire and personal interview. The patients were asked about their level of pain and their ability to function both with and without use of the lacer. Subjects were also questioned regarding the extent to which they wore the lacer and their daily activity level. The cosmetic appearance and comfort of the lacer was also queried. The patients were requested to rate their overall satisfaction with the leather ankle lacer.

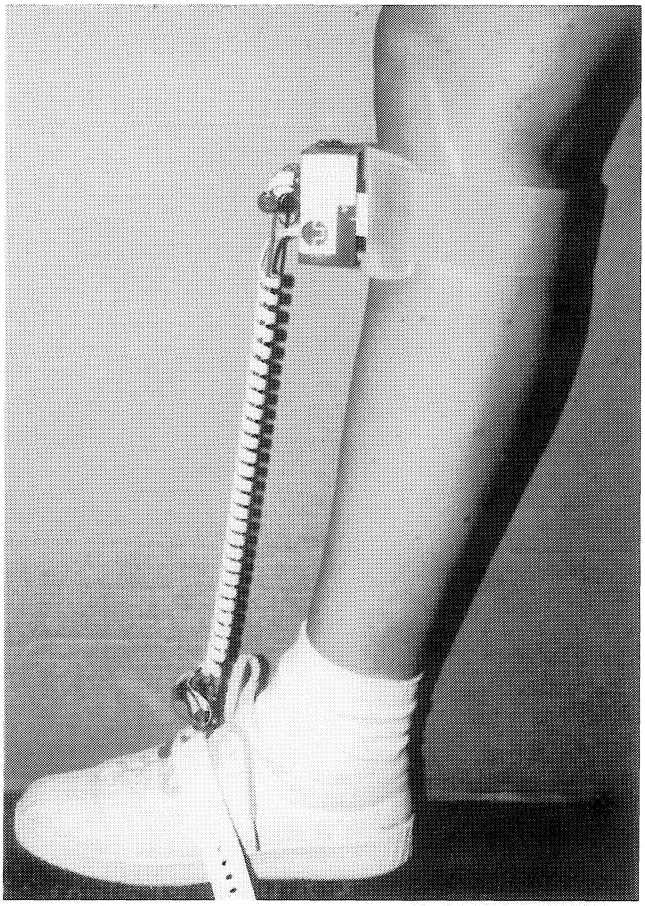

Figure 2 Three dimensional electrogoniometer consists of two orthogonally mounted potentiometers.

Physical Examination

The condition of the skin underneath the brace was examined, noting the presence of any calluses or ulcers. Calf atrophy was determined by measuring the calf circumference 10 cm below the medial knee joint line. Range of motion of the ankle and subtalar joints was measured with a clinical goniometer.

Three Dimensional Electrogoniometry

A three dimensional electrogoniometer, constructed from mutually perpendicular potentiometers, was used to measure motion. (Fig. 2) Patients were instructed to maximally flex, extend and rotate their ankles. Motion was measured with and without use of the lacer. The reliability of the method was determined by comparing electrogoniometric measurements to those made from radiographs.

Radiographic Analysis

Sagittal plane motion was also determined radiographically. Four separate lateral X-rays were taken by a standard protocol of each foot and ankle. (Fig. 3) Radiographs were taken in maximum flexion and maximum extension, both in and out of the lacer. From these lateral X-rays, we measured motion in the ankle, hindfoot and midfoot. Ankle motion was determined by changes in the tibiotalar angle. The tibial axis was defined by a line drawn between the medial and lateral cortex parallel to the long axis of the bone. The talar axis was determined by the method of Digiovanni et al.[2] Hindfoot motion was measured by changes in the talocalcaneal angle. The calcaneal axis was defined by a line drawn tangent to its inferior surface. Midfoot motion was determined by changes in the talo-first metatarsal angle. The first metatarsal axis was defined by a line longitudinally bisecting its shaft.

To reduce the error of measurement, lines were drawn on each X-ray three separate times by two different examiners. The mean differences between flexion and extension values were used to indicate the sagittal plane motion. The differences between braced and unbraced angles represented the restriction of motion from the lacer.

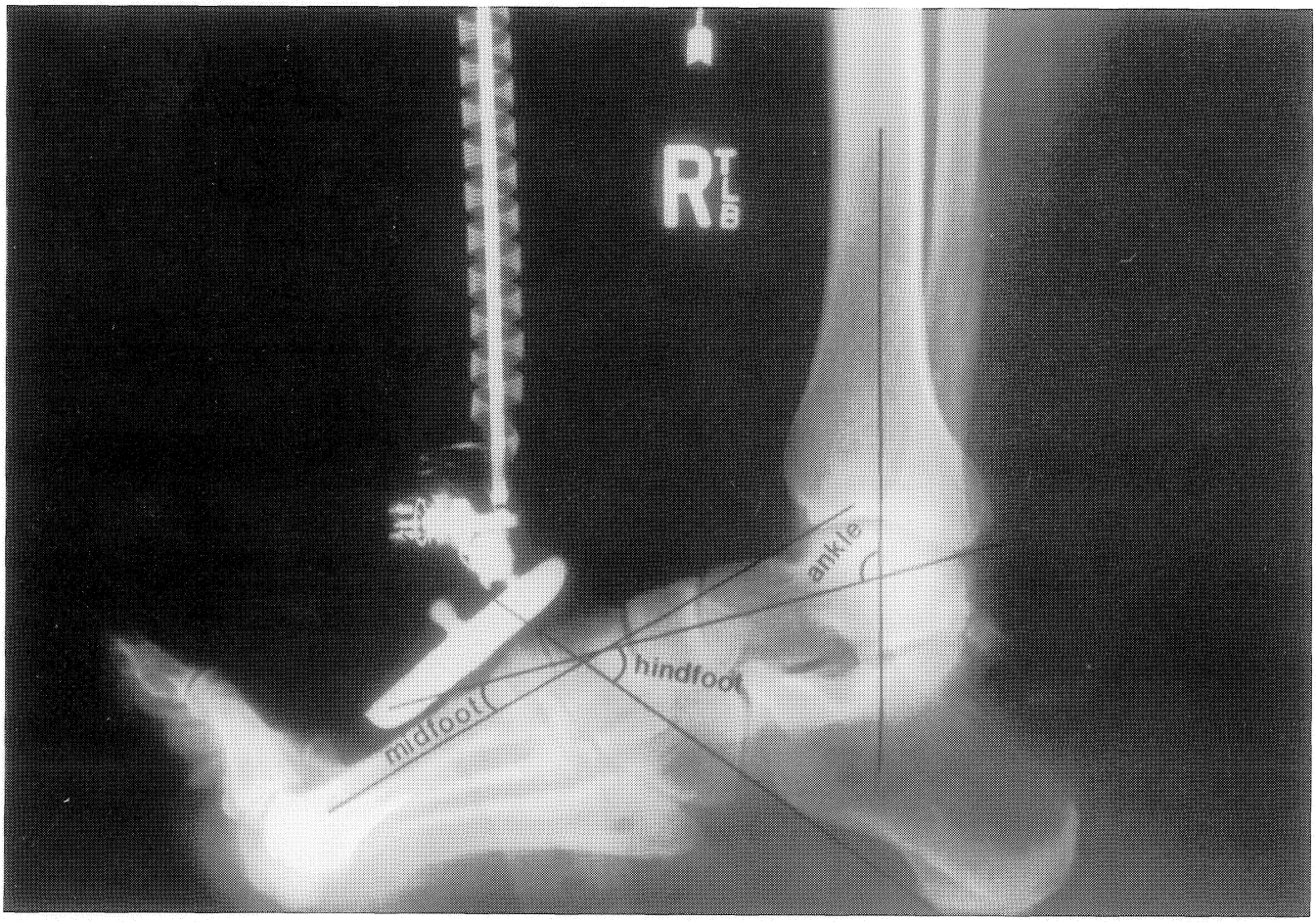

Figure 3 Lateral radiograph demonstrating 1) technique for making angular measurements of the ankle, hindfoot and midfoot, and 2) simultaneous positioning of the electrogoniometer.

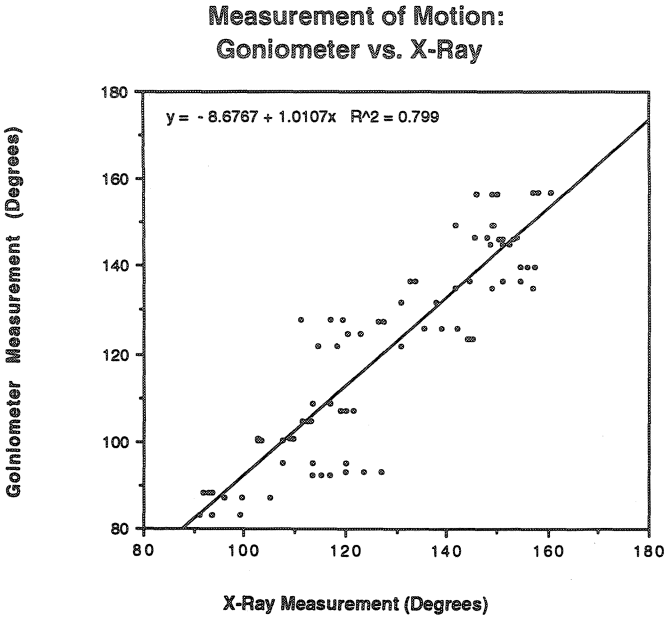

Figure 4 Correlation between sagittal plane motion measurement by electrogoniometer and by radiographic technique. R2 value of 0.79 suggests good validity of the noninvasive, goniometric technique.

RESULTS

Subjective Evaluation

The lacer was reported to relieve pain in all cases. Pain was reduced but not eliminated. The ability of the patient to function in various situations was difficult to assess due to their general low level of activity. In the majority of cases, patients utilized the lacer throughout the entire day. Twenty percent of patients found the lacer very comfortable while the remaining 80% found it somewhat comfortable. Sixty percent of patients added their own padding in order to provide improved comfort. Only 40% of the patients found the lacer to be cosmetically acceptable. Despite these cosmetic concerns, 60% of patients rated themselves as extremely satisfied and 40% as moderately satisfied. No patients were dissatisfied.

Physical Examination

The lacers were well tolerated by the skin in all cases. We found no areas of erythema or ulceration. Compared to the uninvolved side, there was an average 2.2 cm atrophy in the calf circumference of the involved leg (n=3). The clinical goniometric measurements of ankle and subtalar motion showed no significant difference between the uninvolved and involved side when the brace was not worn.

Three Dimensional Electrogoniometry

The three dimensional goniometric measurement of total sagittal plane motion was compared in each case to the radiographic measurement of that motion. The correlation between these measures was strong ($R^2 = 0.79$), suggesting the validity of the electrogoniometric technique and its potential clinical utility. (Fig. 4)

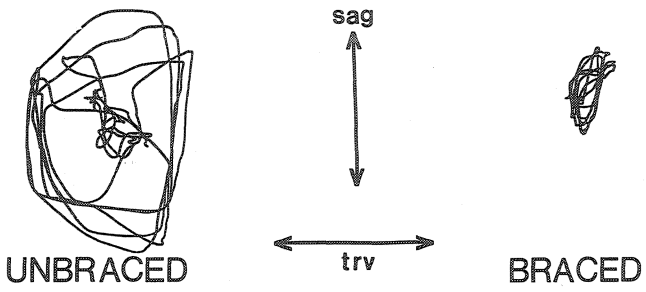

Figure 5 An example of an X-Y plot of electrogoniometrically measured transverse and sagittal plane motion. Note the marked decrease in global foot and ankle motion with use of the leather ankle lacer.

With use of the brace, all patients showed decreased motion in both the transverse (axial) and sagittal planes. A typical example of a patient's motion unbraced and braced is shown in Figure 5. The electrogoniometer was especially helpful in measuring motion in the transverse plane which cannot be fully examined by conventional radiography. A 70% restriction in transverse plane motion was found with use of the leather lacer ($p = .002$). (Fig. 6)

Radiographic Results

The radiographic results showed a significant decrease in sagittal plane motion in the braced ankle and hindfoot. The midfoot motion was not significantly reduced with use of the leather ankle lacer. (Table 2) The largest reduction

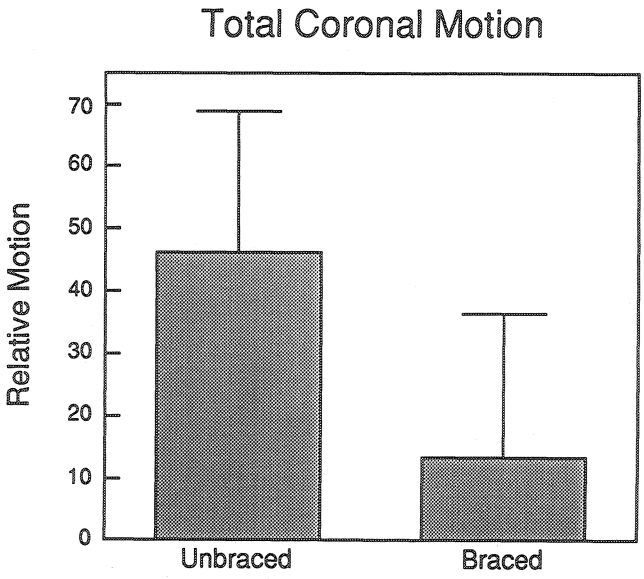

Figure 6 Transverse plane ankle and hindfoot motion was reduced an average 70% with use of the lacer.

TABLE 2

Radiographic Results

Region	Mean Angle (deg) Unbraced	Mean Angle (deg) Braced	Standard Deviation Unbraced	Standard Deviation Braced	Mean Angle T-Test Result	Mean Angle Difference (deg)
Ankle	34.9	25.9	20.9	18.8	p=0.001	8.9
Hindfoot	8.8	4.5	5.1	3.8	p=0.001	4.4
Midfoot	8.4	7.7	4.2	4.4	p=0.64	0.7

in motion occurred at the tibiotalar joint where motion was reduced an average of 8.9 degrees, representing a 26% reduction from the maximal amount of unbraced ankle motion. The decrease in sagittal motion at the subtalar joint was 4.4 degrees, representing a 50% reduction in unbraced motion.

DISCUSSION

The findings of this study confirm our clinical experience with use of the leather ankle lacer. The lacer is generally well tolerated and affords pain relief, motion restriction, and functional improvement. Although the amount of pain relief was only moderate, it was consistent. This may reflect a selection bias, since we only evaluated long-term users of the lacer. Patients who were dissatisfied with its use might not have met our inclusion criteria. The degree of motion restriction was also moderate. In the sagittal plane we found an average 26% decrease in motion at the ankle joint, 10% decrease in the subtalar joint and negligible change in the midfoot. The effect on transverse plane motion was more profound. With use of the electrogoniometer, we found an overall 70% decrease in motion. These data suggest that, in terms of motion restriction, the best indication for use of the leather ankle lacer is for patients with ankle or hindfoot hypermobility in the transverse (axial) plane. In our practice, the leather ankle lacer is primarily prescribed as an alternative to transverse plane rigid polypropylene ankle-foot orthoses. The lacer tends to provide sufficient stability while still allowing some motion. Unlike the rigid AFO's, the lacer allows changes in calf volume and may help unload the hindfoot when standing.[3] The paucity of skin problems makes this device particularly helpful when bracing patients on long-term corticosteroids, with vasculitis or fragile skin.

Acknowledgments

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THE MANAGEMENT OF SEVERE AVASCULAR NECROSIS FOLLOWING SLIPPED CAPITAL FEMORAL EPIPHYSIS BY TRANSTROCHANTERIC ROTATIONAL OSTEOTOMY
Results of Successful Treatment in Two Cases with Longterm Follow-up

Mark C. Cullen, M.D.
Alvin H. Crawford, M.D.

ABSTRACT

We present two cases of unstable slipped capital femoral epiphysis complicated by avascular necrosis that were successfully treated with transtrochanteric anterior rotational osteotomy. These two cases both had severe avascular necrosis and were felt to be unsalvageable. We recommend this surgical technique as a viable alternative to other forms of treatment in this selected patient population.

INTRODUCTION

Slipped capital femoral epiphysis is a disorder of unknown etiology where by weakening of the perichondral ring allows progressive displacement of the epiphysis relative to the metaphysis along an open growth plate. The treatment goals in slipped capital femoral epiphysis are: stabilization and prevention of further slippage; stimulation of early physeal closure; and prevention of avascular necrosis of the femoral head, chondrolysis, and osteoarthritis. Avascular necrosis of the femoral head is the most devastating complication associated with the treatment of slipped capital femoral epiphysis. Avascular necrosis is rare in the untreated slip, but has been reported after almost all forms of treatment[1,3-15,17,19-22].

Factors associated with the development of avascular necrosis in slipped capital femoral epiphysis include: delay in diagnosis; amount of the displacement; treatment method and pin placement. Loder[12] has reported that "unstable slips" are associated with a 50% incidence of avascular necrosis. Recognizing this association is the first step in treating this devastating complication. The management of this complication must be individualized due to varying degrees of avascular necrosis and the lack of consistent good results with different treatment methods. In severe cases of avascular necrosis, current treatment options include: restricted weight-bearing, arthrodesis and joint replacement. Arthrodesis is an unacceptable option to most children in this age group, while arthroplasty in adolescents is fraught with complications of revision in the future.

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SURGICAL INDICATIONS AND TECHNIQUE

Avascular necrosis of the femoral head is usually localized to the anterosuperior aspect of the femoral head. The posterior and inferior aspects of the head retain normal cartilage even in the most advanced cases. The transtrochanteric rotational osteotomy rotates the femoral head anteriorly around the axis of the neck resulting in rotation of the necrotic articular surface out of the weight bearing area and transmission of weight bearing forces through the intact posterior articular surface[18]. This form of osteotomy can be applied to the treatment of avascular necrosis, osteoarthritis, deformities of slipped capital femoral epiphysis and Perthes' disease of the hip. Preoperative radiographs and hip arthrogram as outlined by Sugioka[18] are necessary to assess the posterior articular cartilage and predict the postoperative radiographic appearance of the femoral head. A surgical success rate of 93% can be anticipated when the ratio of transposed intact femoral articular cartilage to the acetabular weight-bearing area is greater then 36%[18].

The surgical technique and results of the transtrochanteric anterior rotational osteotomy in the treatment of avascular necrosis of the femoral head has been previously described in detail by Sugioka[18]. The patient is placed in the lateral recumbent position and an oblique approach to the hip is utilized. An osteotomy of the greater trochanter is used to facilitate hip joint exposure. The short external rotators and quadratus femorus are transected and the capsule is exposed anteriorly and posteriorly. Care is taken during this aspect of the procedure to avoid injury to the posterior column branch of the medial femoral circumflex artery which lies above the lesser trochanter. This vessel is easily visualized during transection of the external rotators and quadratus femorus. The joint capsule is incised circumferentially along the acetabular rim. In preparation for the transtrochanteric osteotomy, two K wires are placed through the surface of the trochanter both anteriorly and posteriorly in a plane perpendicular to the femoral neck axis. An X-ray is taken to confirm the

appropriate position of the planned osteotomy. A transtrochanteric osteotomy is made approximately 10 mm distal to the intertrochanteric crest at right angles to the longitudinal axis of the neck. Near the base of the lesser trochanteric process, the osteotomy is angled 90° cephalad. Upon completion of the osteotomy, the iliopsoas tendon is released to facilitate rotation of the proximal fragment. The femoral head is then rotated anteriorly. The rotation angle of the femoral head is measured as the angle between the two pins previously placed. The femoral head is then fixed in position with metallic screws or pins. The greater trochanter is shortened and stabilized into position. Postoperatively the patient is kept non-weight bearing until satisfactory healing occurs.

Case #1

J.W. was an 11 year old female who had an acute unstable slipped capital femoral epiphysis (Figure 1A) treated with in situ pin fixation in January, 1981. This surgery was complicated by pin penetration and she went on to further slippage. In April, 1981 she underwent pin removal and refixation. She later developed a painful left hip and x-rays revealed evidence of avascular necrosis with femoral head collapse. Her femoral head continued to subluxate and collapse with further pin penetration (Figure 1B). Her pins were subsequently removed in August, 1981.

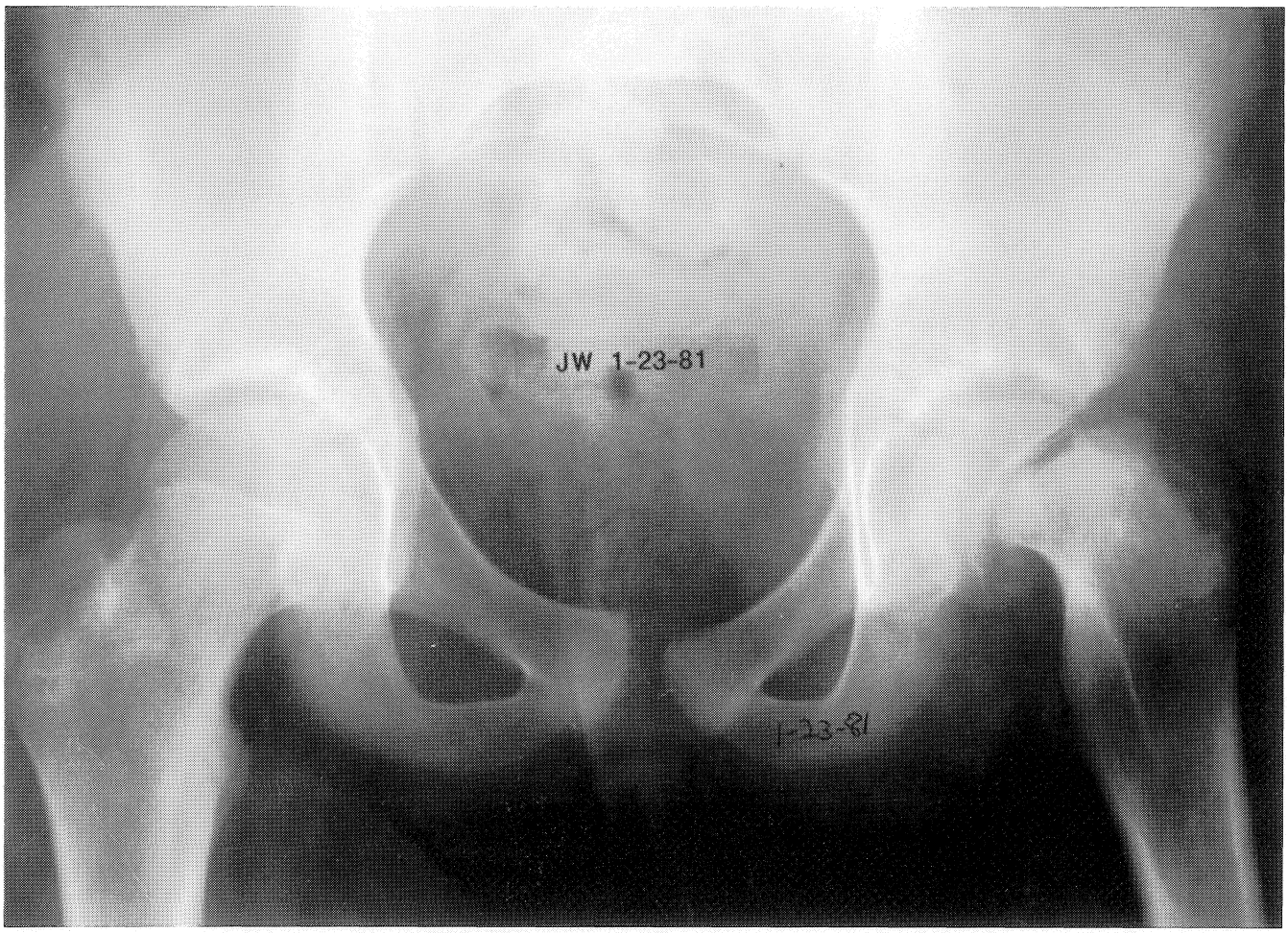

Figure 1 Eleven year follow-up of 11 year old child (J.W.) who presented with an acutely unstable slipped capital femoral epiphysis, developed avascular necrosis and was treated by Sugioka osteotomy.
Figure 1A. Initial x-ray showing acutely unstable left slipped capital femoral epiphysis.

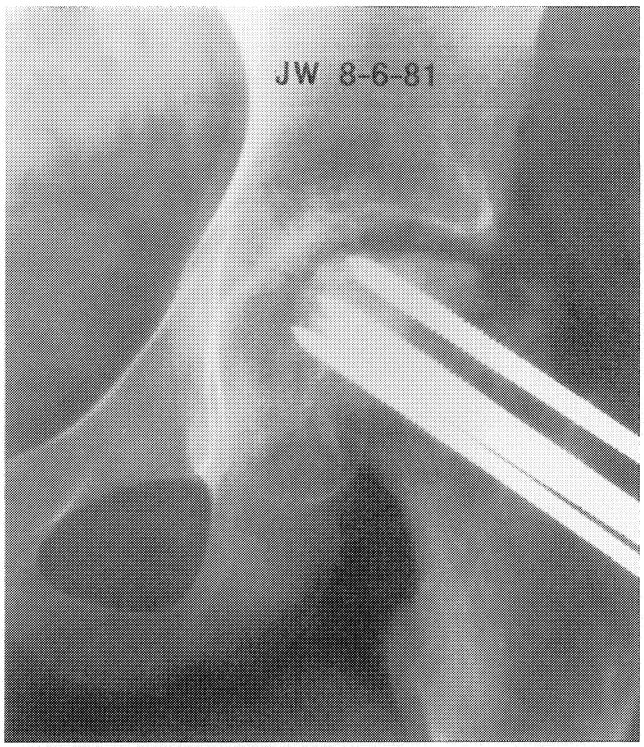

Figure 1B. AP x-ray seven months later showing head flattening and sclerosis indicating avascular necrosis

The patient was referred to CHMC in March, 1982 for evaluation of her chronic left hip pain and decreased range of motion. Physical examination at that time revealed an obese female with a 1.5 cm leg length discrepancy and hip motion of extension 0°, flexion 60°-70° with marked external rotation of 60°, no internal rotation, and a fixed external rotation deformity of 30° with external rotation of 30°-70°. She demonstrated a marked externally rotated trendelenberg gait with a short leg component on the left side. Radiographs at this time revealed segmental avascular necrosis (Figure 1C,D).

In May, 1982 she had a transtrochanteric anterior rotational osteotomy (Figure 1E). Prior to discharge her left hip motion was extension/flexion 0°-35°, internal/external rotation 5°-10°, and abduction 40°. She was discharged to home on strict bedrest in Buck's traction for six to eight weeks. She was readmitted in July, 1982 for physical therapy. Her range of motion continued to progress and at follow up in December, 1982 was noted to have a leg length discrepancy of 3.2 cm. She had contralateral Blount stapling of her distal femoral, proximal tibial, and proximal fibular epiphyses for treatment of her leg length discrepancy in January, 1983.

Her hip motion deteriorated over the next few months and an arthrogram was done in June, 1983 which revealed findings consistent with adhesive capsulitis. Her femoral head appeared revacularized on follow up x-ray. Due to

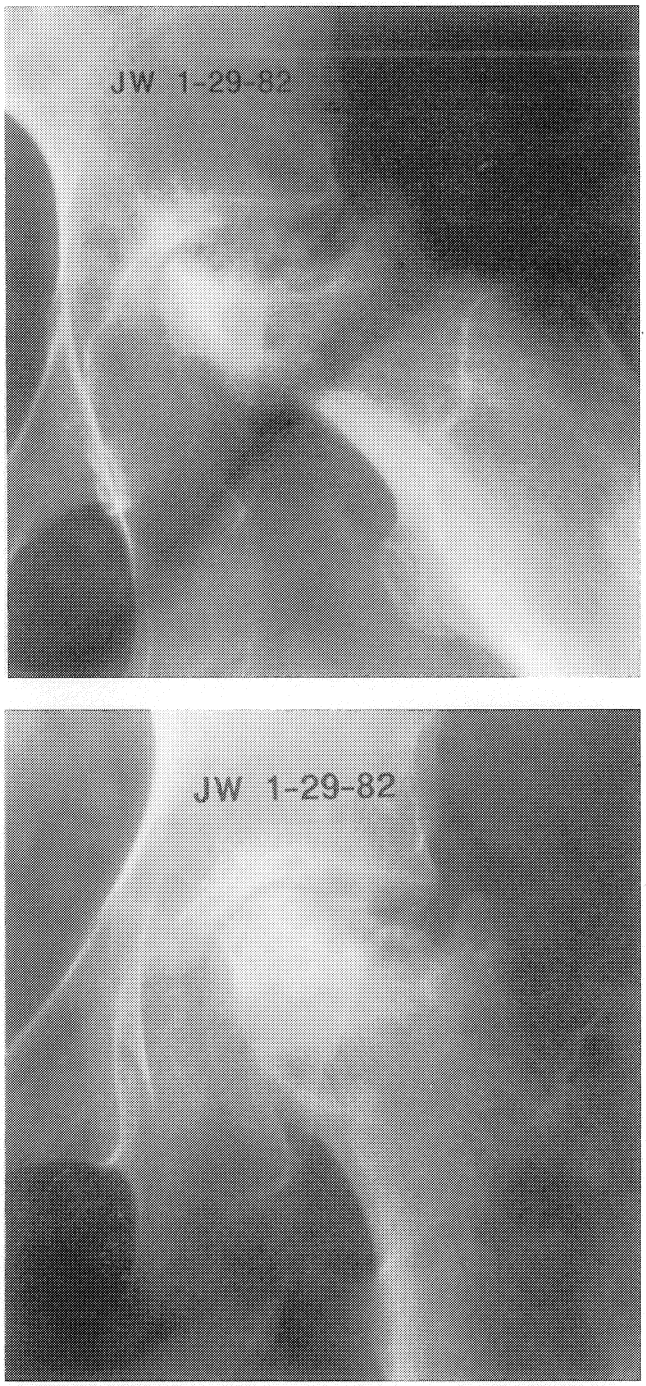

Figure 1C,D. AP and frog x-ray taken at presentation to CHMC following removal of pins showing severe superolateral head deformity with acetabular notching of the femoral head.

her limited range of motion (extension/flexion 0°-30°, internal/external rotation 0° and abduction of 10°), she underwent subtotal capsulectomy[16] and cheilectomy in June, 1983. Her motion improved and was recorded as extension/flexion 15°-86°, adduction/abduction 0°-5°, and internal rotation/external rotation 0°. She was discharged with home CPM and physical therapy. Her weight bearing

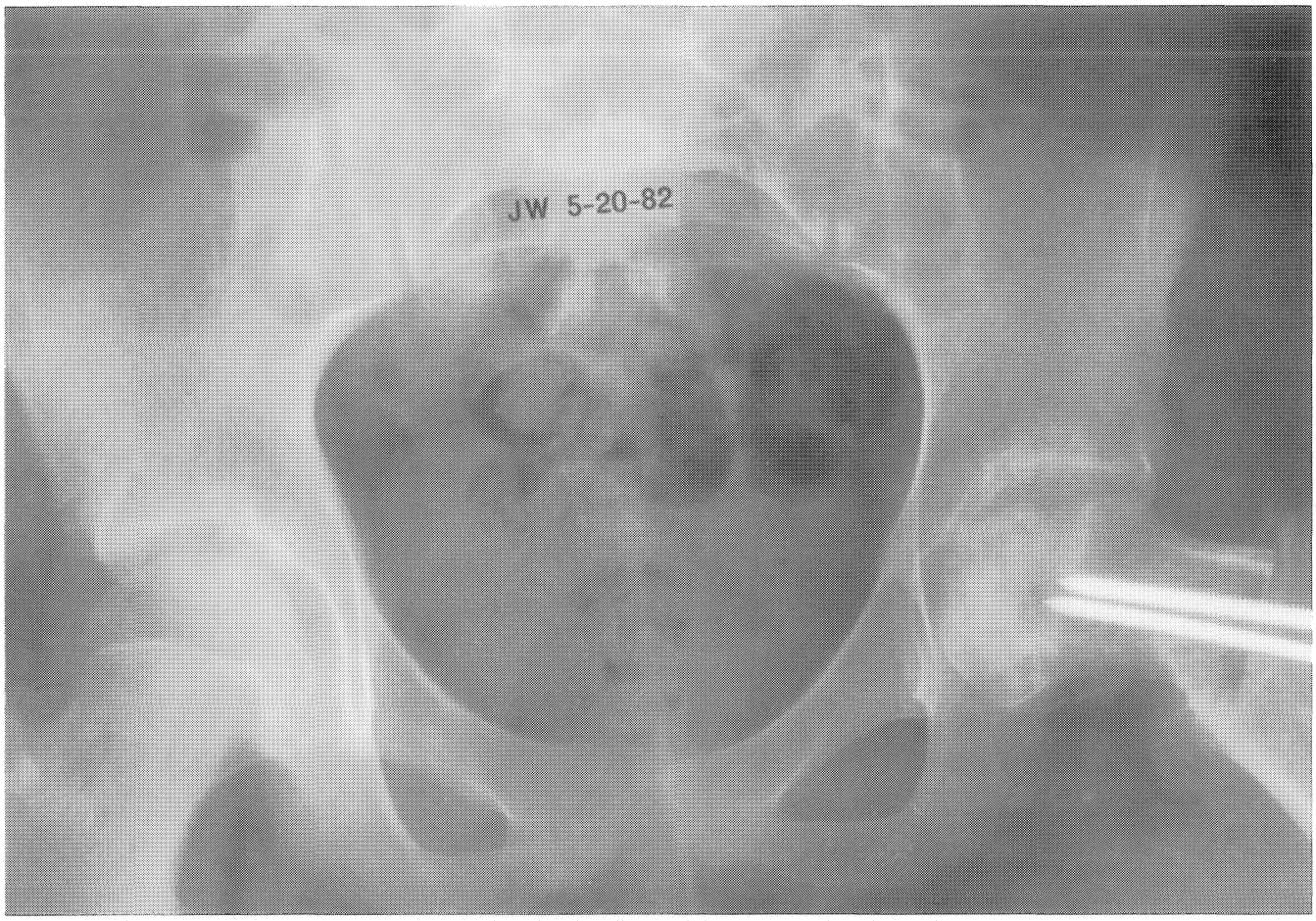

Figure 1E. Immediate postoperative AP x-ray showing transtrochanteric rotational osteotomy performed 16 months after initial slip.

status at this time was partial weight bearing. She was gradually advanced to full weight bearing with a cane. She has been seen at yearly intervals until 1993 (Figure 1F,G) with essentially no change in her hip motion and complete correction of her leg length discrepancy. She is tolerating moderate activity with minimal fatigue at the end of the day.

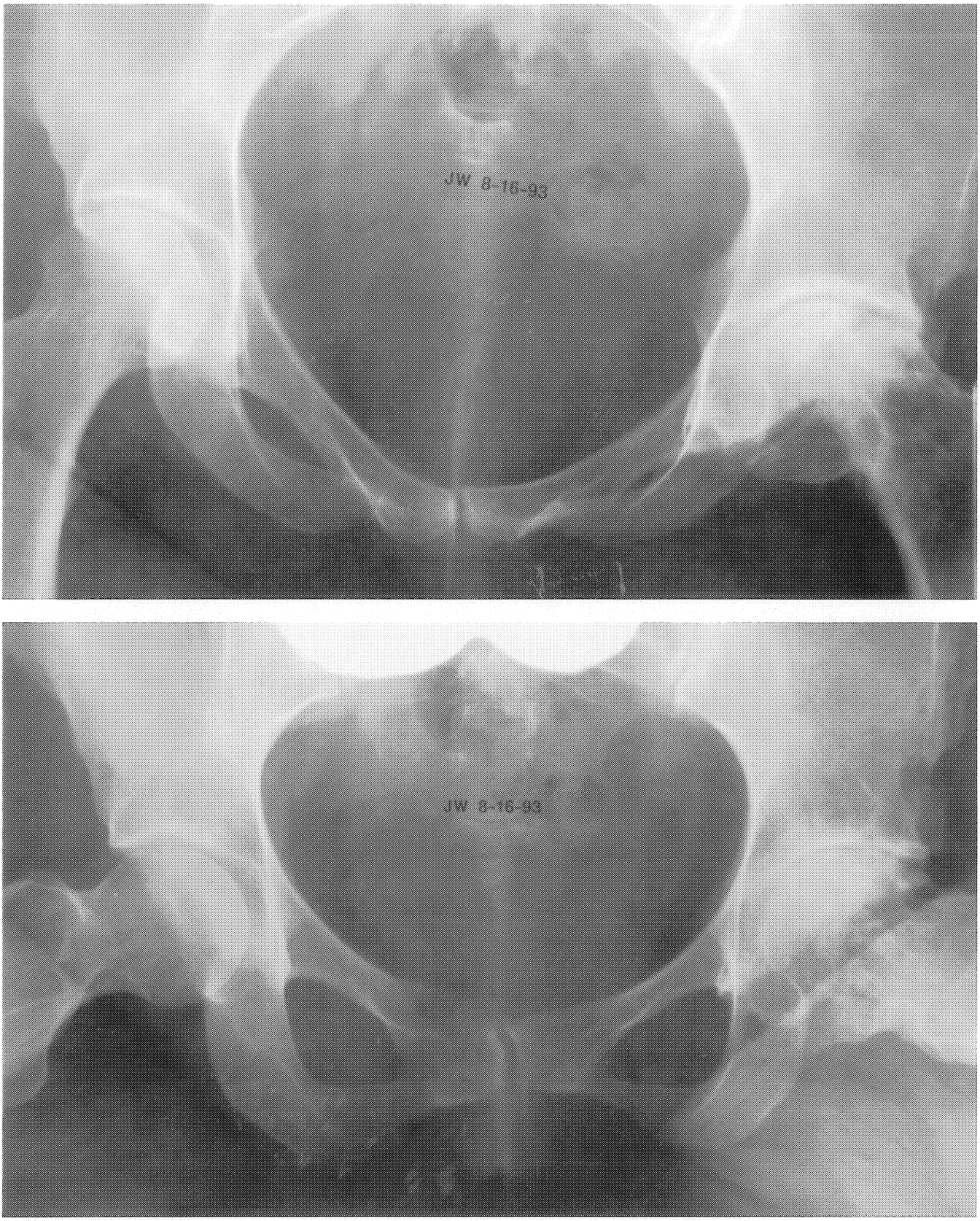

Figure 1F,G. AP and frog x-ray 11 years following transtrochanteric osteotomy showing revascularization of the femoral head, joint space preservation and hip range of motion.

Case #2

C.F was a 12 year old white female of normal stature for her age who developed right hip pain and on radiographs was noted to have sustained an acute on chronic unstable slipped capital femoral epiphysis of her right hip in June, 1988. She was treated with anatomic reduction and in situ fixation with two cannulated screws. The patient did well until approximately five months postoperatively when she developed increased right hip pain, decreased hip range of motion, and a limp. Radiographs at that time revealed avascular necrosis of the femoral head. The patient was referred to CHMC for treatment in January, 1989 following removal of screws. Physical examination at that time revealed right hip motion of extension/flexion 0°-90°, internal rotation/external rotation 0°-30°, abduction 35°, and no obvious gait abnormality. Radiographic examination revealed segmental avascular necrosis with collapse and subluxation of the right femoral head (Figure 2A). The posterior superior aspect of the femoral head appeared to be well vascularized.

Sugioka osteotomy of her right hip was performed in January, 1989 (Figure 2B). Postoperatively she was placed in CPM for six days and on the seventh postoperative day was placed in a spica cast. The spica cast was removed in February, 1989 and CPM reinstituted. She was admitted in April, 1989 for three days of physical therapy. She had no complaints and her hip motion was recorded as extension/flexion 0°-90°, internal rotation/external rotation 10°/30°, and adduction/abduction -5°/30°.

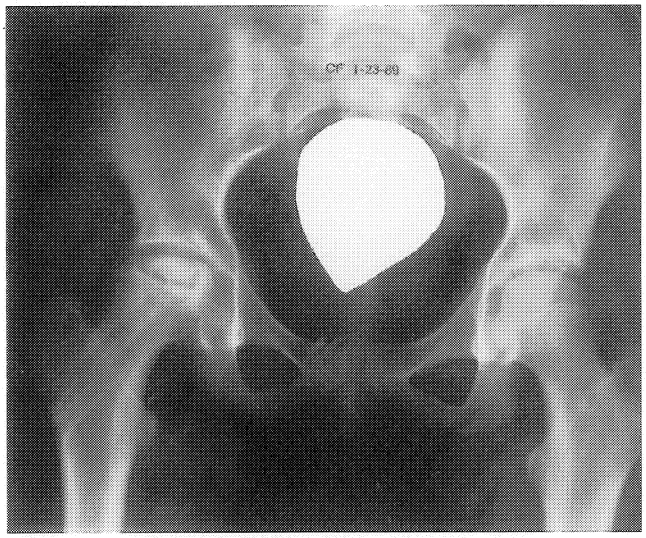

Figure 2 Four year follow-up of 12 year old child (C.F.) who presented with avascular necrosis following treatment of an acutely unstable slipped capital femoral epiphysis that was salvaged using Sugioka osteotomy.
Figure 2A. AP x-ray showing segmental collapse following anatomic reduction of an acutely unstable slip treated by cannulated screw fixation. The screws were removed prior to presentation to CHMC.

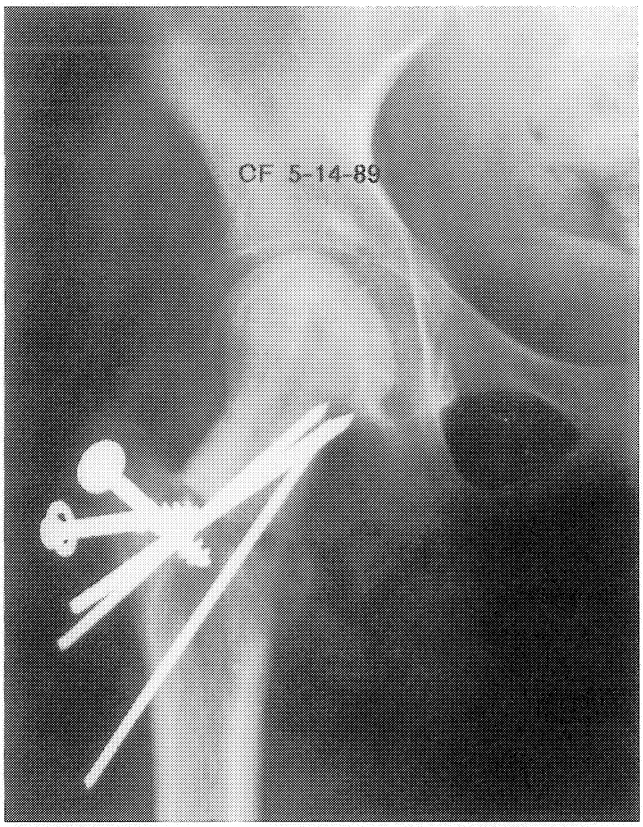

Figure 2B. Immediate postoperative x-ray of right hip following Sugioka osteotomy.

She was admitted in July, 1989 for elective removal of hardware. She continued to do well and was seen in follow up at one year in January, 1990. She had no complaints and physical exam revealed right hip motion of extension/flexion 0°-90°, adduction/abduction 20°-40° and a 5° external rotation deformity with internal rotation/external rotation of 0°-25°. She continued to have motor weakness with flexion 4/5, extension 4/5, abduction 4-/5 and adduction 4+/5. She was advanced to 25% weight bearing with crutches .

She was advanced to full weight bearing over the next year and was seen in follow up 23 months after her osteotomy in December, 1991. At this time the child was noted to have improved range of motion and symmetric motor strength bilaterally. She was instructed to perform activity as tolerated but to avoid exertional activity requiring excessive hip loading. She was last seen in follow-up 3 1/2 years after surgery in July, 1993 (Figure 2C,D), at which time she weighed 275 lbs and was tolerating moderate activity with minimal hip pain.

Discussion

The current recommended treatment of slipped capital femoral epiphysis is single pin fixation in situ[13]. This technique attempts to minimize the complications of pin

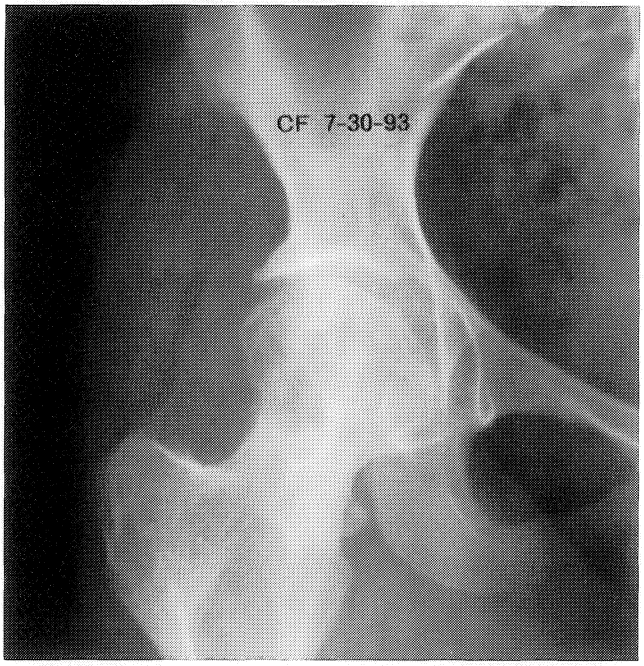

Figure 2C,D. AP and frog x-ray taken three years later showing revascularization of the femoral head, adequate joint space and full range of motion

penetration and avascular necrosis associated with the use of multiple pins. Verner[20] reported 100% (3/3) incidence of avascular necrosis in single pin fixation of severe slips and 0% (0/15) in mild and moderate slipped capital femoral epiphysis. O'Beirne[14] reported 1/1 case of AVN in a severe slip in their series of 18 patients treated with single pin fixation. Koval[14] reported two cases of AVN in 2/6 severe slips and 2/12 acute slips in 60 patients treated with single pin fixation. Aronson[2] reported no cases of AVN in nine severe slips and 1/8 acute slips in 58 patients. Ward[21] reported no cases of AVN in nine severe slips and two acute slips in 53 patients treated with single pin fixation. These recent studies indicate that the incidence of avascular necrosis has dropped dramatically with the institution of single pin fixation for slipped capital femoral epiphysis.

The greatest risk of avascular necrosis is still associated with acute and severe slips. The incidence of avascular necrosis in 25 cases of severe slips pinned in situ in these five studies was 25% (7/28) while the incidence in acute slips was 14% (3/22). These results clearly indicate that, although single pin fixation has greatly reduced the incidence of avascular necrosis in mild and moderate slips, avascular necrosis remains a difficult problem in the treatment of acute and severe slips of the femoral capital epiphysis. It is our belief that the terminology of acute vs chronic as a definition does not predict the risk of avascular necrosis as well as the unstable slip where there is loss of intimate contact of the epiphysis and metaphysis. We feel that classifying slips as stable or unstable gives a better prediction of the overall risk of avascular necrosis[3]. This terminology has recently been supported by Loder[12]. These authors reported a 47% incidence of AVN in unstable slips and no cases of AVN in stable slips[12].

The natural history of patients with avascular necrosis after treatment for slipped capital femoral epiphysis was not well documented in the literature until a recent review of cases from the Campbell Clinic by Krahn[11]. Their review of 264 patients revealed 36 patients (11%) who developed avascular necrosis. Twenty-two patients (24 hips) were available for long term follow-up. Analysis revealed three distinct groups of patients. Group 1 (4 patients) had early femoral head collapse and required early joint reconstruction during adolescence. Group 2 (5 patients) had progressive degenerative changes and required reconstruction as young adults and Group 3 (15 patients) have not required reconstruction. Over 2/3 of the patients in this study had poor clinical results and 38% required early reconstruction. Avascular necrosis following an acute or acute on chronic slip had a worse prognosis and required adolescent reconstructive surgery in 2/2 acute and 2/7 acute on chronic slips. Chronic slips required early reconstruction in only 1/11 patients suggesting a more benign course of slow degeneration. The incidence of early joint replacement in this retrospective review would be much higher using today's liberal indications for total joint arthroplasty.

We present two cases of slipped capital femoral epiphysis complicated by avascular necrosis that were successfully salvaged using the transtrochanteric rotational osteotomy of Sugioka. Avascular necrosis of the femoral head is usually localized to the anterosuperior aspect of the

femoral head. The posterior and inferior aspects of the head retain normal cartilage even in the most advanced cases. The transtrochanteric rotational osteotomy rotates the femoral head anteriorly around the axis of the femoral neck resulting in rotation of the necrotic articular surface out of the weight bearing area and transmission of weight bearing forces through the intact posterior articular surface[18]. Preoperative radiographs and hip arthrograms as outlined by Sugioka[18] are necessary to assess the posterior articular cartilage and predict the ultimate post-operative radiographic appearance of the femoral head. A surgical success rate of 93% can be anticipated when the ratio of transposed intact femoral articular cartilage to the acetabular weight-bearing area is greater then 36%[18].

To our knowledge, these two case reports are the first in the literature using this procedure for the salvage of avascular necrosis of the femoral head following treatment of slipped capital femoral epiphysis. The Sugioka osteotomy is a technically demanding procedure and should only be attempted by skilled surgeons familiar with this surgical procedure. The results of these two cases of previously catastrophic hip problems followed for 3 1/2 to 11 years are encouraging. We are optimistic that this procedure offers a better alternative than arthrodesis and arthroplasty and encourage pediatric orthopaedic surgeons to consider the transtrochanteric rotational osteotomy of Sugioka as a salvage procedure for selected cases of slipped capital femoral epiphysis complicated by severe avascular necrosis.

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SEPTIC KNEE FROM ILIZAROV TRANSFIXATION TIBIAL PIN

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INTRODUCTION

Ring fixators with small transfixion wires (the Ilizarov method) are effective in the treatment of acute trauma and late reconstruction of the leg. Transfixion wires need to be placed with careful attention to anatomy to avoid complications. Safe placement of proximal tibial transfixion wires requires extracapsular positioning. This anatomic detail has not been emphasized in the literature. This case report illustrates knee joint infection as a sequelae of pin penetration of the capsule. Furthermore the capsule attachment to the proximal tibia is defined by radiographic imaging and cadaveric dissection.

Case Report

A 35 year old man presented with a severe posttraumatic deformity of his right leg and foot due to a motorcycle wreck 16 years previously. He sustained an open tibial shaft fracture and a right talus fracture. He had plate fixation of his tibia with acute shortening of five cm probably due to extensive comminution and bone loss. He had 50 degrees of hindfoot equinus with severe ankle and subtalar arthrosis, most likely from avascular necrosis of the talus. He also had severe loss of muscle mass and function in the superficial and deep posterior compartments of the leg from acute muscle trauma or residual from compartment syndrome. He had no signs of chronic infection and was transportationally functional primarily with a bicycle. He had chronic ankle and hindfoot pain and callouses over the metatarsal head plantar surfaces where he was bearing all weight. He also had poor ambulation due to the short limb which was only partially compensated by the equinus position (Fig. 1).

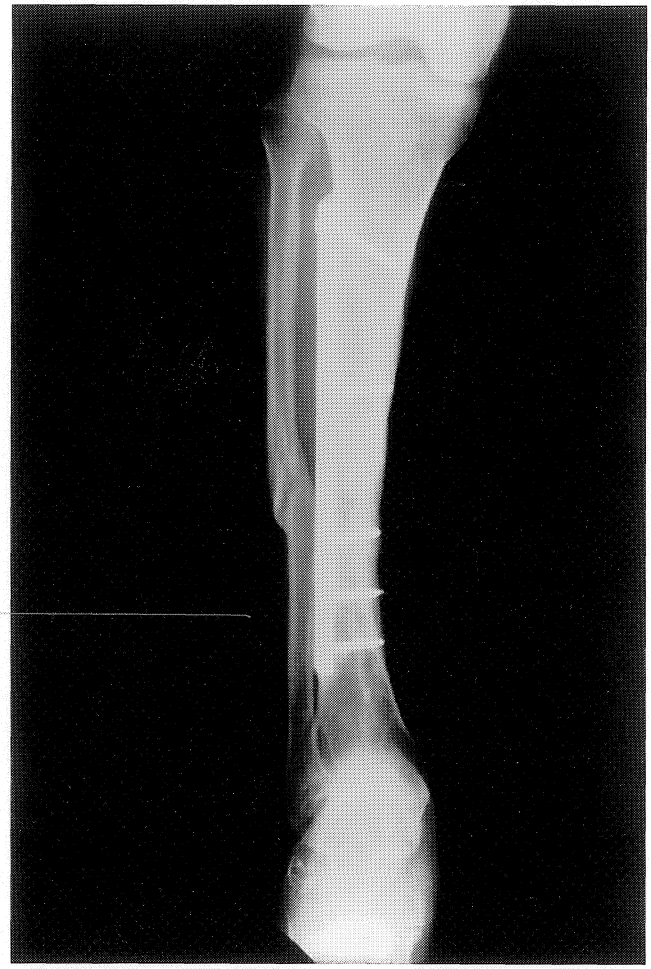

Figure 1. The patient's original tibial shaft fracture had been treated with a plate and screws with a resultant five cm shortening. He also had ankle and subtalar arthrosis and hindfoot equinus.

Staged correction began with correction of the equinus. The patient was taken to the operating room where the plate and screws were removed, and a talus and tibial closing wedge osteotomy was performed to correct the hindfoot equinus and obtain a good cancellous surface for ankle fusion. A retrograde GSH nail was placed across the arthritic subtalar joint and resected ankle joint and locked proximally and distally (Fig 2). Both joints fused, and the patient recovered uneventfully though with a persistent five cm leg length discrepancy.

Stage 2 of the reconstruction consisted of Ilizarov lengthening to correct the leg length discrepancy. The patient received antibiotic prophylaxis, and a four ring Ilizarov external fixator frame was used with eight tensioned transfixion wires. The fibula was osteotomized, and a proximal tibial metaphyseal corticotomy was performed

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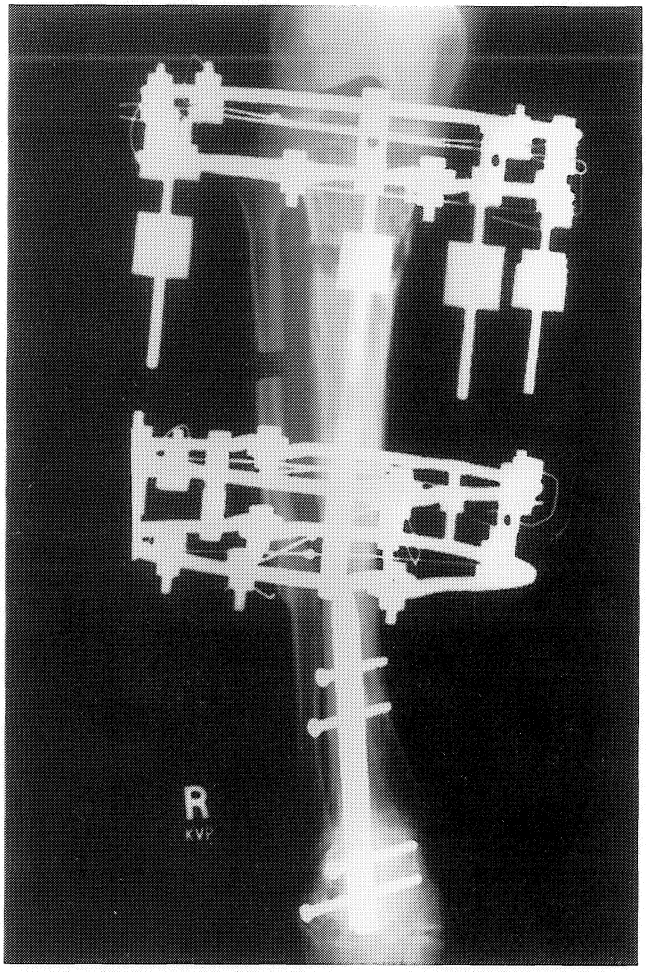

Figure 2. The patient's plate fixation was removed, and a closing wedge osteotomy was performed to correct the equinus deformity. A locking retrograde GSH nail was placed across the subtalar and ankle joints for fusion as demonstrated in this lateral radiograph.

Figure 3. An AP radiograph of the patient's right tibia and fibula are shown with the Ilizarov fixator in place. Proximal pin #1 (with a lateral olive) traversed the tibia from 80 degrees (10 degrees anterior of straight lateral) to 280 degrees (10 degrees anterior of straight medial), where 0 or 360 degrees around the circumference of the leg is straight anterior. Pin #1 was eight mm distal to the tibial articular surface and therefore did not penetrate the knee joint capsule. Proximal pin #2 traversed the tibia from 45 degrees (halfway between anterior and lateral) to 250 degrees (20 degrees posterior of straight medial). Pin #2 was six mm distal to the tibial articular surface and therefore penetrated the knee joint capsule posteromedially.

to preserve the periosteal and endosteal blood supply. Two of the rings were placed proximal to the corticotomy site and two were distal (Fig 3). The patient tolerated the procedure well without initial complications.

A five day post-operative period without placing tension on the fixator was observed to allow the first stage of fracture healing to begin. The distraction was begun on the fifth post-operative day at the rate of 0.25 mm four times a day for 40 days. A 1 cm residual leg length discrepancy was planned to allow easier ambulation with the fused ankle and hindfoot. The patient was distracted 36 mm, and then distraction was slowed to 0.5 mm per day secondary to patient discomfort. Pin tracts were clean and carefully cared for throughout the lengthening with no pin tract infection clinically.

The patient was re-admitted 30 days post-operatively with knee pain. The knee was swollen, warm, erythematous, and tender. Joint aspiration revealed cloudy fluid with 120,000 WBCs, and culture grew Streptococcus agalactiae. The patient was immediately taken to the operating room for arthroscopic irrigation and debridement and placed on a cephalosporin post-operatively. The knee was clinically better for 36 hours, but the knee infection recurred as evidenced by reaccumulation of fluid and pain. The two most proximal transfixion wires were removed, and knee joint irrigation revealed a continuity between the joint and the most proximal posteromedial pin tract. Injection fluid arthroscopically instilled into the joint drained out the posteromedial pin tract despite a six mm distance between the pin tract and the articular surface. The other three pin tracts from the two removed wires did not communicate with the joint. The pin tracts were

Figure 4. After removal of the Ilizarov fixator, the distracted corticotomy site was spanned by maturing regenerate bone.

debrided, and the articular surfaces were noted to be normal arthroscopically. Because of loss of stability from removal of two wires, the frame was stabilized by addition of a new half-pin into the proximal tibia attached to the proximal ring. The patient was placed on penicillin and discharged to home with antibiotics for a total of four weeks. The knee joint infection resolved and did not recur again.

Lengthening was re-initiated one week after discharge. This was limited by consolidation of the distraction gap, and lengthening was stopped at 41 mm. Four weeks later the external fixator was removed, and the patient was placed in a brace. At four months he returned to full activity and the regenerate bone had matured (Fig 4).

ANATOMY

Five cadaveric knee dissections were reviewed to determine the location of knee joint capsule attachment to the proximal tibia. Average distance from the tibial capsule attachment to the proximal tibial articular surface was eight mm posteromedially and 11 mm posterolaterally. Anteriorly, the distance was shorter before attaching to the tibia, averaging three mm.

Magnetic resonance images of 11 knees with T1 and T2 weighted coronal and sagittal views were reviewed. Measurements showed a distance of 7.6 mm from articular surface to capsule insertion medially. Laterally we measured an average distance of 7.5 mm from articular surface to tibial capsule insertion.

DISCUSSION

The Ilizarov method has been used since 1951 to correct long bone and joint deformities and to lengthen limbs[9]. The method makes use of tensioned transfixion wires attached by pins to an external fixation frame to provide compressive or distractive forces to the bone while maintaining limb stability and mobility. This form of external fixation has all the risks of large half pin external fixation as well as some special risks. We report a new complication and a technique for preventing the complication.

Deep infections and wire tract infections are reported in cases using the Ilizarov method. However a literature search of Medline articles from 1980-1994 revealed no articles discussing joint infection as a complication of Ilizarov lengthening[1,2,3,4,5,6,7,8,11,12,13,14,15,16]. The skin and exposed wires are obviously not sterile. Pin tract infections are common and can result in pin loosening or chronic osteomyelitis[10]. In this case report the direct communication of the posteromedial proximal pin tract with the knee joint was demonstrated during joint lavage. Furthermore the infection recurred when the pin was left in place but resolved promptly and completely after pin removal and pin tract debridement. The absence of clinical signs of pin tract infection before or during the knee joint infection suggests that mere penetration of the capsule may be sufficient to cause joint infection.

The use of Ilizarov-type frames in intra-articular fractures of the tibia has recently gained popularity. Wires are commonly placed even closer to the joint than with lengthening or transport frames. This closer proximity to the joint increases the risk of capsular penetration.

The exact attachment site of the knee joint capsule to the proximal tibia is not a detail mentioned in anatomy texts. It is also not identified or mentioned in Ilizarov technique manuals or cross-sectional anatomy diagrams. We found the capsule to attach to the anterior half of the proximal tibia just three mm below the articular surface. Posterolaterally the capsule inserts 11 mm from the joint, but transfixion pins generally avoid this area as it contains the common peroneal nerve. Posteromedially the capsule attachment is eight mm distal to the joint. This is the region of greatest risk of joint penetration using current insertion suggestions. This case report implicated the

posteromedial pin as the cause of joint infection. The posterior capsule attachment is difficult to measure due to the presence of the posterior collateral ligament, but transfixion pins are not recommended in this location due to risk of injury to the tibial nerve or popliteal artery.

Knowledge of the anatomy of joint capsule attachment to the tibia is necessary to avoid pin penetration of the capsule with its risk of knee joint infection. As demonstrated by cadaveric dissection and magnetic resonance imaging review, a distance of nine mm from the tibial articular surface is required for pin placement to avoid penetration of the capsule in the posteromedial quadrant. In the anterior half of the tibia, pins can be placed as close as four mm to the articular surface without penetrating the capsule.

CONCLUSION

Knee joint infection can occur as a result of proximal tibial transfixation pins penetrating the knee joint capsule. This complication can be effectively treated by pin removal, pin tract debridement, arthroscopic irrigation of the knee, and intravenous antibiotics. However, early consolidation of the regenerate bone may result as a consequence of knee joint infection during lengthening. To prevent this complication, pins placed in the proximal tibia should not penetrate the capsule. This can be accomplished by avoiding the proximal three mm of tibia anteriorly and the proximal eight mm of posteromedial tibia during pin placement.

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REGIONAL LIDOCAINE ANESTHESIA WITHOUT EXSANGUINATION FOR OUTPATIENT MANAGEMENT OF UPPER EXTREMITY FRACTURES

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William M. Hayes, M.D.†
Roger Cornwal††

Upper extremity fractures are perhaps the most common fractures managed by the orthopedic surgeon. The majority can be managed on an outpatient basis. Hematoma block is frequently used because of its ease of administration and its safety. It does not afford the same level of pain relief given by intravenous lidocaine injection[7,17]. Intravenous lidocaine anesthesia was first described by Bier in 1908[1]. The senior author has used intravenous lidocaine anesthesia for the closed treatment of upper extremity fractures for more than twenty years. The technique to be described gives a superior level of anesthesia which allows multiple attempts at reduction of the fracture without discomfort.

The technique has been described previously[3,7,12,17]. The modifications described here will include: no exsanguination of the affected limb, scalp vein needle for injection, reduced dose of lidocaine, and finally, the use of a sugar tong splint following reduction[5,6,13].

To date, no known complications of this technique have occurred. Patient compliance has been excellent. No additional anesthesia has been required to accomplish acceptable reduction. The pain relief afforded the patient during the fracture reduction without the need for limb exsanguination makes this procedure the authors' preference for treatment of the majority of displaced fractures of the upper extremity in children and adults.

MATERIALS AND METHODS

The aforementioned technique was used in 148 adult patients with displaced radius fractures and 96 children with upper extremity fractures. The technique was first used by Dr. Seymour Zimbler and the senior author in 1969. It has required little refinement since that time. New developments in tourniquets and tourniquet inflation systems have been instituted.

Prior to administration of the anesthetic, a detailed history is elicited. Patient education is vital regarding the specifics of the procedure as well as being able to communicate tourniquet discomfort to the orthopaedic surgeon. Soft roll padding is placed around the upper arm and a single or double tourniquet is used. A new low pressure double cuff and battery-powered portable pressure pump system (Zimmer - A.T.S.tm 1500 Tourniquet System) is used currently, replacing the previous use of a pretested blood pressure cuff acting as the tourniquet. From operating room experience of the senior author, generally patients with large arms require special consideration to ensure adequate pressure is being applied. The originally designed double tourniquet has two rather small bladders that inflate to occlude the vessels. This design works well on average size or smaller arms. On larger arms two of the single tourniquets placed side by side or a system with wide double cuffs is recommended. The vessels can be occluded more gently, more reliably, and with less pressure using wider cuffs.

Thirty-five milliliters of 0.5% lidocaine without epinephrine is drawn into a syringe and labeled. With the cuff in place but not inflated, a twenty-five or twenty-three gauge scalp vein needle is inserted carefully into a vein on the dorsum of the hand. The veins can be distended using a standard venipuncture tourniquet, gently applied around the mid-forearm proximal to the fracture. The needle is gently secured with tape. The patient is placed in a supine position and the arm is elevated. Both tourniquets are rapidly inflated to 280 mm/Hg. Inflation of both tourniquets simultaneously doubles the length of vessel compression. A single wide cuff which compresses the majority of the brachium may be substituted if no double cuff is available.

To better localize the medication to the fracture site, the venipuncture tourniquet is placed around the forearm just proximal to the fracture. Lidocaine 0.5% (without epinephrine) is slowly injected through the scalp vein needle. During the intravascular injection, the forearm becomes blotchy with multiple areas of pale hypovascularity. This is followed by slow diffusion of these areas and development of a dusky purple appearance (cutis marmorata)[15]. Swelling or weal formation about the injection site suggests extravascular injection. If this occurs, the injection is stopped, the tourniquets are deflated, and a new intravenous site is chosen.

Only 35cc of lidocaine is needed in a full size adult and the dose can be appropriately reduced for smaller patients and children (2.45 mg/kg). Some report that doses as low

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Figure 1. The patient volunteered to have this picture taken during her anesthesia and fracture reduction. She is laying comfortably during this post sugar tong casted final manipulation of the fracture.

as 1.0 to 1.5 mg/kg can be used with dilution of the lidocaine to 0.25%[2,5]. Pain relief at the fracture site occurs rapidly but complete anesthesia is not achieved for five to seven minutes. This time can be used to organize the casting materials and alert the radiology department of the eminent arrival of the patient. The arm can be held in finger traps as seen in Figure 1. Weight can be placed over the inflated tourniquets. At 15 minutes post-lidocaine injection, the more distal of the two tourniquets can be let down to allow lidocaine migration under the distal cuff. The proximal cuff is generally well tolerated for approximately 20 minutes. If additional time is required, the distal cuff can be reinflated with proximal cuff deflation. This usually affords approximately 15 more minutes of anesthesia.

The author has used a sugar tong cast made of plaster or synthetic materials as shown in Figure 1. The elastic wrap is placed directly onto the casting material and becomes adherent to the casting material. This prevents inadvertent loosening of the cast in the ensuing weeks. The cast is molded and appropriate correction forces are applied while the cast hardens. Once the cast has become rigid, the patient can be mobilized to the radiology suite or portable x-rays can be obtained. There is enough anesthetic time available should a repeat reduction be required.

Release of the tourniquet is performed sequentially by deflating to zero followed by immediate inflation to 280 mm/Hg. The tourniquet is permanently deflated and removed from the upper extremity after three minutes[2]. This allows a gradual release of any remaining non-bound lidocaine metabolites into the system. The patient is observed for an additional 15 minutes.

DISCUSSION

The physician treating fractures in the upper extremity has many options to reduce pain while manipulating and casting the extremity. General anesthesia affords complete patient relaxation and comfort. It remains the entity of choice for specific fracture patterns, e.g. supracondylar pediatric elbow fracture, however, it is not recommended for routine fracture reductions. Scalene or axillary block anesthesia affords excellent relief, but these blocks are less predictable and more uncomfortable for the patient[12].

Ketamine works well as an anesthetic agent and is particularly useful in children with burns who require frequent dressing changes. Ketamine reduces the gag reflex and can depress respiration. It is not recommended for use in adults because of the occurrence of severe unpleasant dreams[8]. Nitrous oxide cannot be given in high enough concentrations to be an effective and safe anesthetic[10]. Hennrikus et al described its use in combination with a hematoma block, noting improved patient tolerance of the reduction maneuver. Of concern, however, is the reduction of the gag reflex noted and the importance of fully monitoring these patients.

Manipulation of the fracture following sedation with narcotic agents is commonly used. This requires close monitoring of the patient prior to and following reduction. After the fracture has been stabilized, with the significant reduction in pain, respiratory depression has been described[9].

Hematoma blocks are common and easy to administer. However, we feel that the pain relief offered by intravenous lidocaine is much greater than that of a hematoma block. Additionally, hematoma blocks are not as predictable in the subacute setting.

The success rate of intravenous regional anesthesia approaches 100%[12]. The reported incidence of adverse side effects is low. There is the possibility of a systemic reaction to the local anesthetic agent when it is released into the circulation[12]. The patient should be questioned during the injection of the anesthetic to determine the presence of early warning signs of toxicity such as circumoral numbness and tinnitus[4]. Lidocaine toxicity is generally considered to be 500 mg for the adult or approximately

7.0 mg/kg. In children the toxic dose is given as 5.0 mg/kg, yet metabolism of lidocaine in children is at the adult levels by age six months[16]. The dose given in these fracture patients is 2.45 mg/kg.

The chief complication of lidocaine toxicity is convulsions. The aim of treatment is to stop the seizure and treat any respiratory or cardiovascular depression before cerebral hypoxia occurs[4]. Thiopental (50-100 mg.) or diazepam (5-10 mg.) can be used in incremental intravenous doses to rapidly abort a convulsive episode[4].

The authors have never had a patient experience a seizure or display any other evidence of toxicity from the lidocaine. Using good equipment and double checking before releasing and changing tourniquets is the best prevention of inadvertent cuff release. The recommended minimum time to cuff release is 20 minutes[6]. Fatalities using this technique with lidocaine have not been reported. There have been seven reported fatalities using intravenous bupivicaine[12].

Lidocaine without preservative in a single use vial is recommended. The preservative is toxic when used intradural or intrathecal. However this should have little risk given intravenously, intra-muscularly, or subcutaneously (personal communication with Robert Thompson, Director of Clinical Pharmacology at the University of New Mexico, February 23, 1995), though inflammation of vein or phlebitis has been reported[15]. Lidocaine solutions containing epinephrine are contraindicated and have caused multifocal premature ventricular contractions, and hemodynamic changes in the laboratory[14].

Patients with a known hypersensivity to lidocaine or with a history of certain cardiac diseases may not be candidates for intravenous anesthesia[12]. Untreated heart block is a relative contraindication, because sudden release of lidocaine into the systemic circulation may convert a partial heart block into a complete block or asystole[12]. Sickle cell disease or trait and cellulitis are also contraindications to this procedure[12]. It should be noted that asymptomatic bradycardia has been described following cuff release[12]. It is a transient event with no sequelae to the patient.

SUMMARY

The use of small dose intravenous lidocaine without exsanguination for upper extremity fractures in children and adults is described. A twenty-plus year experience with this technique in the outpatient setting has shown it to be effective and safe. Attention to detail is essential and inadvertent tourniquet release must be avoided.

ACKNOWLEDGEMENTS

Thanks to Seymour Zimbler, M.D., Chief of Orthopaedic Surgery at the Beth Israel Hospital in Boston, Massachusetts. He introduced this technique to the senior author. Also thanks go to Jennifer Clark, who helped in the preparation of this manuscript.

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SPONTANEOUS RUPTURE OF ULNAR-SIDED DIGITAL FLEXOR TENDONS: DON'T FORGET THE HAMATE

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Randolph J. Ferlic, M.D.
William F. Engber, M.D.

INTRODUCTION

Spontaneous rupture of a digital flexor tendon due to an abnormality of the carpus is uncommon. We have recently encountered two patients who presented with the sudden inability to flex the interphalangeal joints of the little finger due to pathology of the hamate bone. The purpose of this paper is to review their management with an emphasis on the association of hamate pathology with attritional rupture of ulnar sided digital flexor tendons.

CASE REPORTS

Case #1

A sixty-seven year old, right-hand dominant male presented to the Hand Service complaining of hypothenar pain and an inability to flex his right little finger. Seven weeks earlier he was attempting to clean snow from his running snowblower with a piece of wood when the wood was forcefully impacted against the palmar aspect of his hand. He noted immediate pain and swelling in the hypothenar region but was able to grasp objects without difficulty. His symptoms gradually improved until three weeks later when he noted the inability to flex his little finger. He denies any further trauma to the hand or digit, prior hand injury, or history of inflammatory arthritis or steroid injection. At the time of presentation, he was unable to actively flex both the proximal and distal interphalangeal joints of his fifth digit (Fig. 1). Physical examination revealed tenderness in the hypothenar and palmar regions of the hand. Routine roentgenograms were unremarkable, but a carpal tunnel view revealed a fractured hook of the hamate (Fig. 2). The preliminary diagnosis was attritional rupture of the fifth digit flexor tendons and surgical exploration was recommended.

At operation, proliferative tenosynovitis was encountered throughout the carpal canal. The flexor digitorum profundus and superficialis tendons of the little finger were completely disrupted and frayed adjacent to an irregular ununited fracture of the hook of the hamate. The entire flexor digitorum superficialis and approximately one-third of the profundus of the ring finger was also frayed. The hook of the hamate was excised and the base smoothed. The distal remnant of the little finger profundus tendon was then transferred to the ring finger profundus via a Pulvertaft weave technique. The hand was immobilized for two weeks followed by active and passive physiotherapy. Three months postoperatively pulp-to-palm distance of the little finger was five mm (Fig. 3).

Case #2

A seventy year old, steroid-dependent asthmatic male presented with a four week history of an inability to flex his right fifth digit. He complained of difficulty grasping objects, particularly a golf club. He could not recall any traumatic incident and denied any history of digital, palmar or forearm pain. Physical examination confirmed the lack of active flexion of the proximal and distal interphalangeal joints of the little finger. Radiographs, including a carpal tunnel review, were normal.

Surgical exploration revealed prominent tenosynovitis predominantly involving the ulnar sided contents of the carpal tunnel. The profundus and superficialis tendons of the fifth digit were ruptured and the ring finger was frayed four cm adjacent to a roughened irregular hamulus. The tendons appeared to have been sequentially eroded by this abnormal surface during digital range of motion. Excision of the hook of the hamate was performed and the little finger profundus tendon was transferred to that of the ring finger. Following two weeks of splint immobilization, active and passive physiotherapy was initiated. Six weeks postoperatively, pulp-to-palm distance of the little finger was four mm. At six months postoperatively, the patient continues to do well and is without complaints.

DISCUSSION

The hamulus or hook of the hamate can be palpated 1.5 to 3.0 centimeters distal to the pisiform along a line projected from the pisiform to the index metacarpal head. The hook can also be located at the intersection of Kaplan's cardinal line (from the first web space parallel to the proximal transverse palmar crease) with a longitudinal line extending proximally from the ulnar border of the ring finger. The hook represents the most distal ulnar border of the carpal tunnel. The radial surface provides a pulley for the flexor digitorum profundi of the ring and small

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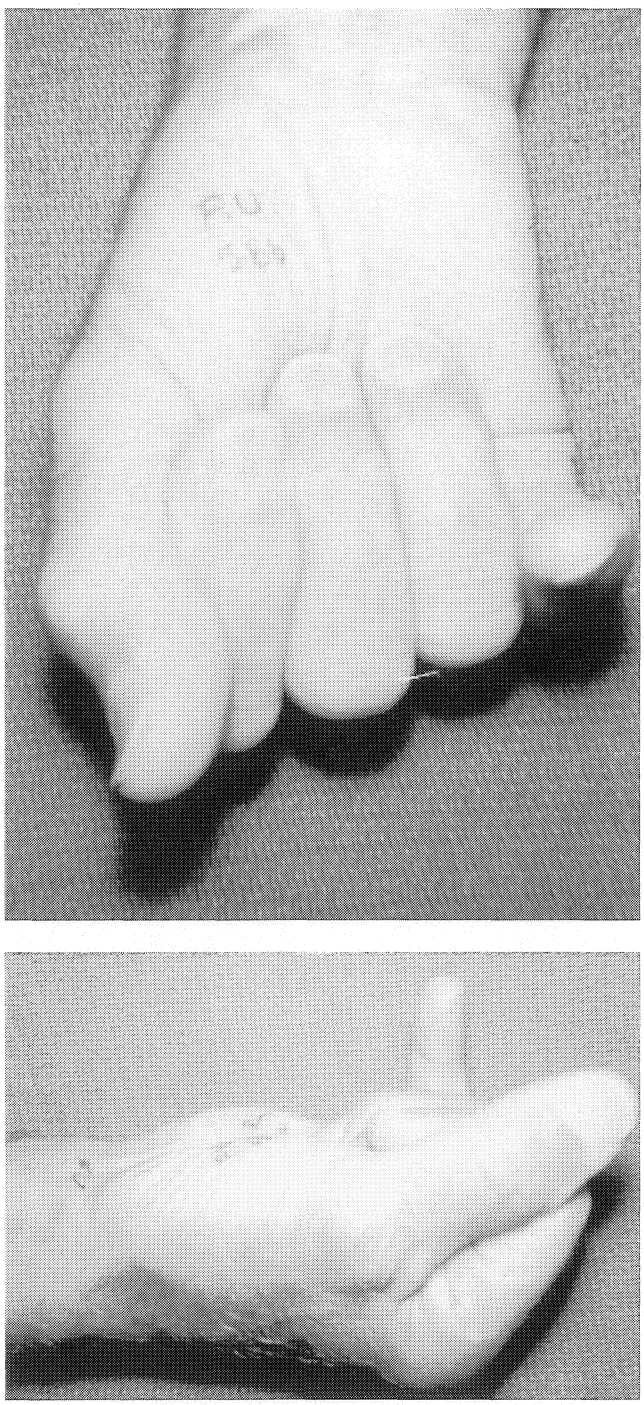

Figure 1. Anteroposterior (1A) and lateral (1B) views of the hand demonstrating the lack of proximal and distal interphalangeal joint flexion.

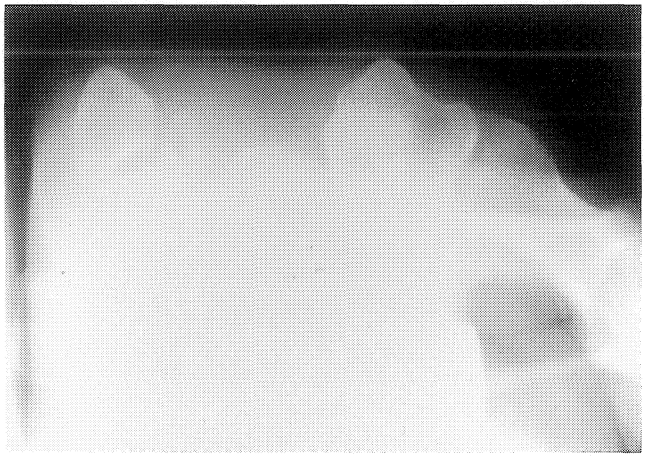

Figure 2. Carpal tunnel view roentgenogram revealing a fracture of the hook of the hamate.

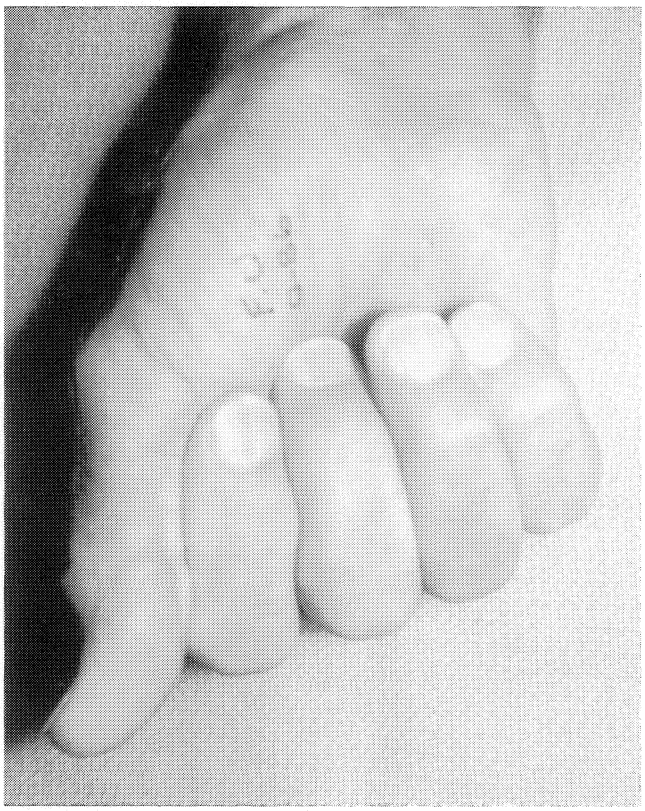

Figure 3. Active range of motion at three month follow-up.

fingers during the ulnar deviation of the power grip[1]. In addition, the flexor digitorum superficialis tendons of the little and ring fingers course around the base of the hook also placing them at risk for attritional injury.

The most common reason for attritional wear and rupture of ulnar-sided finger flexor tendons appears to be an ununited fracture of the hamulus[2-9]. However, tendon rupture secondary to an osseous projection from the hook has also been described[8]. The proposed etiology of such tendon ruptures is chronic repetitive wear and fraying against rough bone. Previous reports, however, have included patients who had been injected into the hypoth-

enar region for presumed tendonitis. Thus, some authors believe that tendons rupture in such instances because of inadvertent intratendinous injection with secondary weakening of their structural integrity. Both of our patients clearly had irregular bony surfaces on the hook of the hamate and evidence of fraying of the adjacent profundus tendon supporting an attritional etiology. Neither patient had a history of steroid injection, but our second patient was a steroid-dependent asthmatic. This association between systemic steroids and spontaneous tendon rupture has not been previously reported to our knowledge. Theoretically systemic steroids may have weakened the digital flexor tendons of this patient making them more susceptible to rupture in the presence of irregular osseous surfaces.

Both of our patients' treatment included complete excision of the hamulus. The literature supports such an approach for symptomatic hook of the hamate nonunion with low complication rates, predictable pain relief, and return to activities including professional sports[9,10]. However, excision of an asymptomatic hamulus nonunion is controversial. Proponents believe that excision of the hook in such a situation is easier than treating the complications of flexor tendon attenuation and rupture[2,5,6]. The role of complete excision for osseous projections alone is also controversial. Okuhara described a case involving rupture of both little finger flexor tendons that was successfully treated by resection of the bony projection and tendon grafting[8]. We believe that completely excising the hamulus is preferable, because simply attempting to excise or smooth an irregular bony process may inadvertently leave adjacent irregular surfaces capable of causing continued fraying and tendon rerupture.

Management of the flexor tendon injury itself is based upon intraoperative findings. Treatment options include direct repair, tendon transfer, grafting or tenodesis. Direct repair is usually not feasible due to fraying, and tendon grafting can be technically challenging particularly when attempting appropriate graft tension. The preferred treatment for rupture of both the superficialis and profundus tendons of the little finger is transfer of the little finger profundus to the ring finger profundus.

When a patient presents with an apparent "spontaneous" rupture of a little or ring finger flexor tendon, the hamate must be assessed for nonunion or osseous projections. A careful history and physical examination should be combined with appropriate roentgenographic studies. We have found the carpal tunnel view particularly helpful but polytomography is sometimes necessary to clearly delineate the hamulus. We believe that complete excision of the hamulus is the treatment of choice for both nonunion and bony projections causing attritional tendon rupture.

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A STRESS FRACTURE OF THE SCAPULAR BODY IN A CHILD

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Georges El-Khoury, M.D.§
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While any bone is subject to stress fractures, locations in the lower extremity are typical. The calcaneal body, metatarsal shafts, femoral shaft or neck, and tibial or fibular shaft are common locations in military recruits, long distance runners, and ballet dancers[7]. Stress fractures of the upper extremity are far less frequent. Different patterns occur in children due to the softness of the immature skeleton. Again, fractures of the lower extremity predominate, with fractures of the proximal third of the tibia and distal half of the fibula most common, although isolated cases involving the femoral shaft and neck are reported[3, 5, 6, 8, 15]. Only a few cases of stress fractures involving the scapula exist in the literature, none of which involve a child[1, 2, 4, 13].

Differentiation between healing stress fractures, myositis ossificans and bone tumors is difficult on isolated radiographs. Unfortunately, histologic specimens of a healing stress fracture can also be misinterpreted as a bone forming tumor, and therefore biopsies are best delayed until the possibility of a stress fracture can be clinically excluded. In fact, a case of misdiagnosis of osteosarcoma based on a biopsy of a stress fracture of a rib (honeymoon fracture) was reported[9]. When stress fractures occur in unusual locations, concern regarding the nature of the lesion is greater. In this report, we discuss a case of a stress fracture of the body of the scapula in a child.

CASE REPORT

D.W., a healthy seven year old boy, presented to his pediatrician with a one week history of pain and swelling over the body of the left scapula with pain on range of motion of the left shoulder. The boy had a history of a minor fall on his shoulder while playing approximately a week prior to the onset of the pain. He had no history of repetitive use of the left upper extremity. He had no systemic symptoms or other relevant medical problems.

Radiographs on initial presentation showed a lytic region extending from the lateral border across the body of the scapula with surrounding sclerosis and profuse periosteal reaction (Figure 1). A CT scan was obtained due to concern that this might represent a tumor. This showed a linear lucency with surrounding sclerosis, and was interpreted as a stress fracture although bone forming tumors could not be ruled out. (Figure 2)

It was elected to follow the lesion over two weeks to confirm the diagnosis of stress fracture. The boy was instructed to rest the upper extremity in the interim. On his return in two weeks, repeat radiographs showed clear evidence of callus formation and fracture consolidation. (Figure 3) Repeated radiographic exams showed continued resolution of the fracture. Three months following initial presentation radiographs showed complete healing and remodeling. (Figure 4) No further problems developed.

DISCUSSION

Stress or fatigue fractures occur when bone is subjected to repeated loading at a frequency exceeding the ability of the bone to repair itself. Although these factures can progress to complete fractures with displacement through the fracture site, patients usually present prior to this with complaints of pain without any obvious trauma. In some patients, the source of the repetitive loading is clear, although this is not always the case. Plain films are negative early in the course of healing with a linear sclerosis appearing in stress fractures of cancellous bone during repair. In diaphyseal bone, the fracture appears as a linear cortical lucency with surrounding periosteal reaction. Bone scans or CT provide a more sensative means of making the diagnosis when plain films fail to show the lesion[10].

Stress fractures of the upper extremity are much less frequent than those of the lower extremity. There are only a few prior reports of stress fractures involving the scapula. Boyer described a fracture of the coracoid process following repeated loading due to trapshooting[1]. Dennis et al. discussed three cases of stress fractures of the acromion process following superior migration of the humeral head due to large rotator cuff tears[4]. Veluvolu et al. described a case of an avulsion fracture of the supraspinatus due to repeated jogging while holding weights in the hands[13]. Brower et al. discussed a case of an assembly line worker with an avulsion of the teres minor due to repetitive use of the arm in an overhead position at work[2].

Stress fractures in children can be difficult to diagnose on initial appearance. A detailed history of what activities elicit the pain may be lacking. Children show a much more

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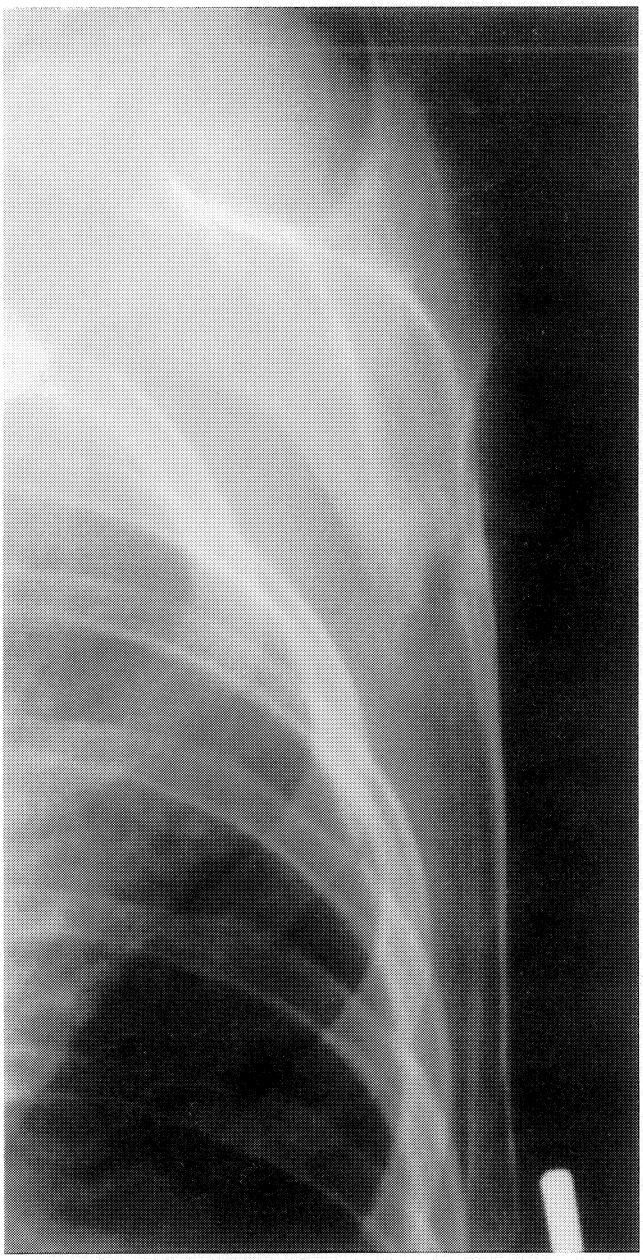

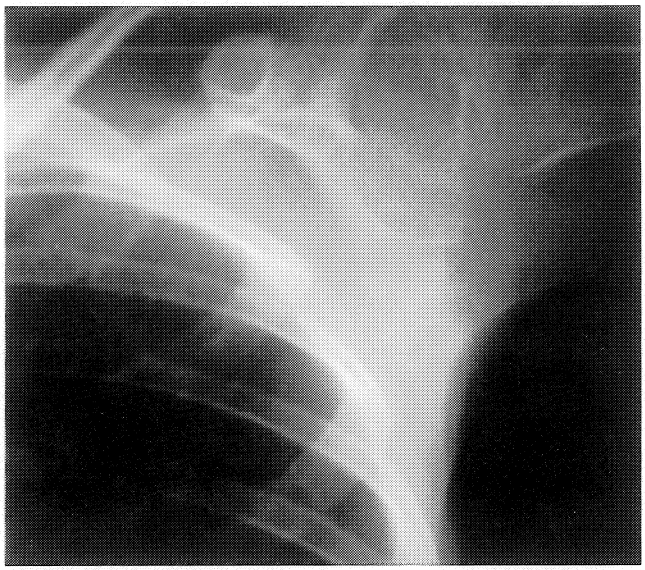

Figure 1a,b. Radiographs made two weeks after the onset of pain in the left shoulder of a seven year old boy. Abundant periosteal reaction around a central lytic region is apparent.

abundant periosteal reaction than adults, and the radiographic appearance may suggest Ewing's or osteogenic sarcoma, osteoid osteoma or osteomyelitis. The concern over the possibility of tumor or infection when these lesions occur in children has been discussed[5, 6, 7, 14]. Proceeding with a biopsy based on the initial appearance of the lesion may subject the child to an unnecessary surgical procedure and slow resolution of the fracture. Delaying treatment by several weeks in order to observe the course of the lesion is warranted when the diagnosis is uncertain.

The case presented describes a young child with persistent pain in the scapular region. Although he reported a fall to this region prior to the onset of pain, it was of insufficient energy to cause an acute fracture of the scapular body, which usually is associated with high energy injuries[10,11,12]. In addition, the presence of periosteal reaction on radiographs one week following the fall indicates a process which must have predated the described fall. Given the clinical history and radiographic behavior of the lesion, it must be considered a stress fracture. This case illustrates the need to consider this diagnosis even when such lesions appear in unlikely locations.

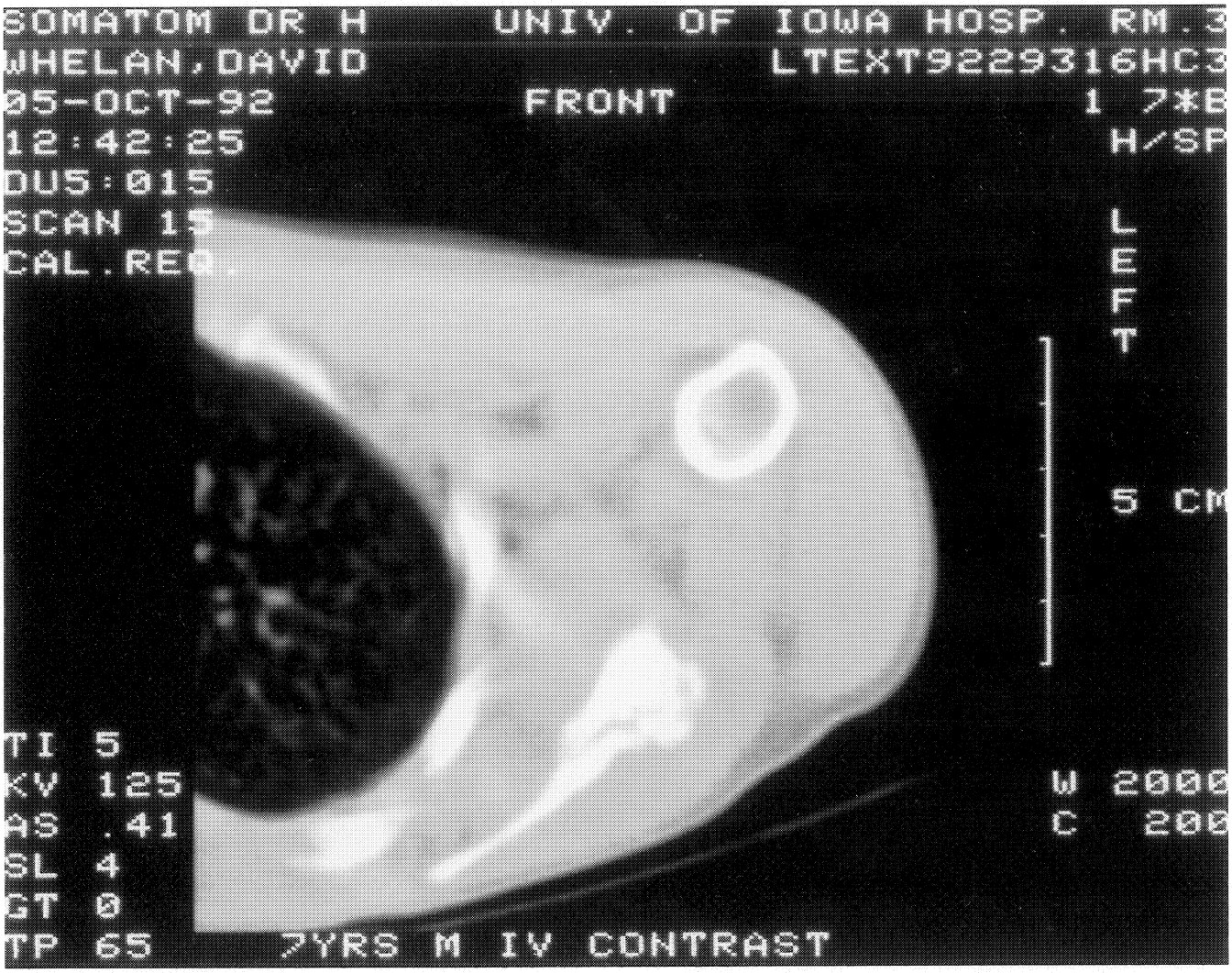

Figure 2. CT appearance of the lesion at two weeks. A linear lucency suggestive of stress fracture is apparent.

Figure 3. At four weeks, further consolidation of the fracture callus is apparent.

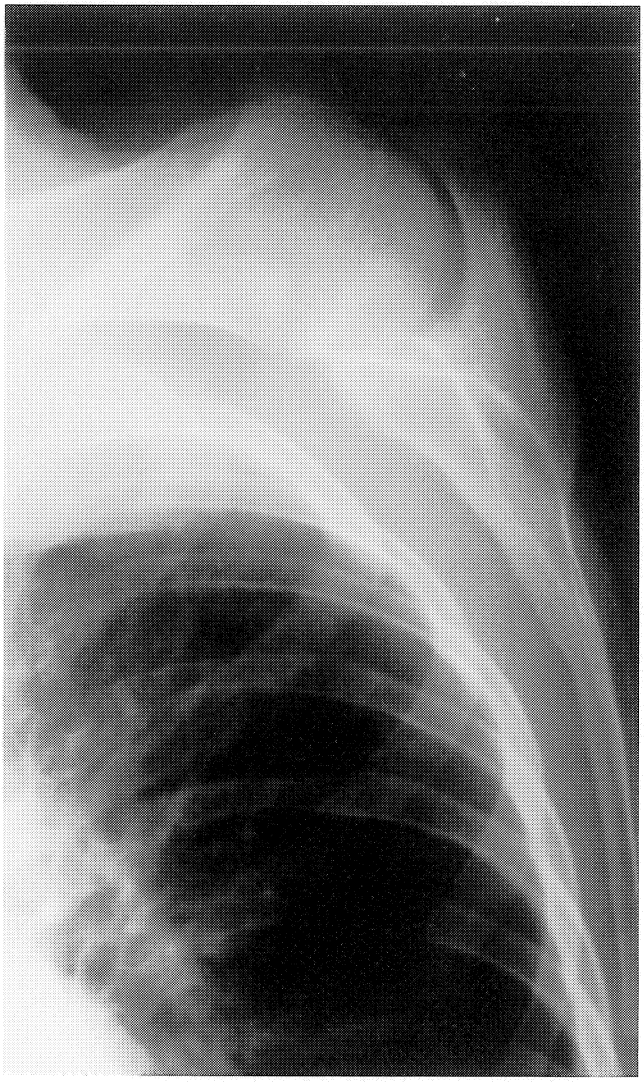

Figure 4. By three months, complete resolution and remodeling of the fracture had occurred.

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REMINISCENCE OF FELLOWSHIP
Steindler's First Fellow

Leo J. Miltner, M.D.

I was given the first fellowship in Orthopaedic Surgery under Dr. Steindler in 1925. During my senior year in medical school I was the lone intern at Mercy Hospital in Iowa City. During that time I assisted many different surgeons, especially Dr. Steindler who had 20 or more private patients at Mercy Hospital. I was privileged to know and admire him while assisting with casting and taking patient histories.

After a year of internship in 1924 at Holy Cross Hospital in Salt Lake City, I wrote Dr. Steindler and inquired about a residency. He replied that Dean Seashore, Head of the Graduate College, had awarded him a fellowship in Orthopaedic Surgery at the salary of $100 a month, and that he would like me to accept the position. I was honored that Dr. Steindler chose me for that first fellowship position.

In the beginning of the first year of the fellowship, Dr. Steindler gave me various directions. I spent half of my time doing statistical work for the operative procedures of the Department for the past many years. I made statistical analyses and charts which would later be included in Dr. Steindler's books and writings. I was assisted by residents and by Mrs. Clapp, wife of the Department of Music Chairman. Many evenings we would analyze as many as 75 records regarding a special operation of Dr. Steindler's and make statistical charts accordingly.

Another part of the fellowship involved research work with rabbits and dogs. For that purpose we bought and established a dog kennel in the slough just north of the old Children's Hospital. A man by the name of Young managed the dog kennels. We established a dog laboratory for operative procedures in the basement of Children's Hospital. There we did experimental work to find substances which would enhance tendon sheath grafting, tendon anastomoses, and tendon fixation. At that time, tendon transfer work was popular. Leo Mayor from New York City was a leader in this area and visited Dr. Steindler regularly.

I had learned to cut blocks of tissue and make histologic slides while an intern at Mercy Hospital. As Dr. Steindler's fellow, I did this every Sunday morning so the slides would be ready for a seminar to review the previous week's cases.

My fellowship experience was very special and quite different from that of the ordinary resident or intern. In many instances it included being first assistant to Dr. Steindler during his operative procedures at Mercy Hospital. He would drive his old Essex car to the Children's Hospital to pick me up in the morning and we would drive over to Mercy at 7:00 a.m. Usually he would finish his surgery around 9:00 a.m.

Another assignment during my course at Iowa was reviewing the old X-ray plates. Many of them were in glass. The glass was discarded, but among the thousands of X-rays plates, I selected ones that were especially good for teaching purposes. The X-rays often showed up better on glass than on other types of standard film. These were saved for Dr. Steindler's review and use in making slides for his collection.

Another of my major projects during the fellowship was studying focal infections in arthritis. For this purpose the Orthopaedic Department rented a special house in Iowa City to keep as many as a dozen arthritic patients at a time. They were rotated to eventually study all focal infections in 100 different arthritic patients. The patients were referred to all the departments at the University notably, ENT, Dental, GI, GU, and Gynecology. The reports from the studies of these referrals were formulated into a synopsis. The results were read before the Committee of Professors and showed, among other points, that ENT infections seemed to relate to the activity of the arthritis.

During my third and fourth years under Dr. Steindler I did a considerable amount of teaching. For two years I taught the senior class of medical students the subject of Orthopaedic Surgery. Dr. Steindler came in every so often to give a short lecture, but basically I was in charge of the teaching. Also, I was designated to teach the graduate college of ladies who were teaching Physical Education and working for major degrees. I lectured to them in their Kinesiology course, and they would observe orthopaedic surgery.

The last year and a half I assisted Dr. Steindler in his office taking histories on his private patients and doing the usual chores.

One of my interests was selection of residents and interns. Dr. Steindler didn't enjoy selecting the men. He gave this responsibility to his secretary, Mrs. Hicks and me. Many of the applicants which were beginning to apply in large numbers had long pedigrees. It was our practice to judge them by photographs and the character of their background and training.

In the Spring of 1929, Dr. Steindler learned of a job opening at the Peking Union Medical College in Peking, China. They needed an Orthopaedic Surgeon to head their division. Dean Houghton, Dean of the Iowa Medical School, had previously been director of the Medical School

in Peking. Dr. Steindler recommended me to Dean Houghton, and I was given the appointment.

During my time at Iowa I became acquainted with a number of notable men in Orthopaedic Surgery who were guests of Dr. Steindler and the Department. These included Dr. Orr of Lincoln, Nebraska, Dr. Mel Henderson, Chief of Orthopaedics at the Mayo Clinic, Dr. Leo Mayor of New York City, and many other leaders. All of them had the greatest respect for Dr. Steindler.

All in all, my fellowship at the University of Iowa was truly a wonderful learning experience under the guidance of a great leader and man. Dr. Steindler was a truly cultured and educated gentleman in every respect. I feel lucky in having the good fortune to have worked with him for five years.

THE FATES OF ILLUSTRIOUS BONES

Richard L. Jacobs, M.D.

Most high schoolers of my era had major prurient interest in Boccaccio's *Decameron* and its oft-amorous adventures. Like the rest, I devoured the *Decameron* and, without even knowing it, expanded my adolescent horizons with classic literature. Franz von Suppe even wrote the opera "Boccaccio" along the same lines. They didn't carry the libretto of that in the high school library, but Rex Brown claimed that he had seen it!

You can therefore understand perfectly what happened years later. I was browsing through a soon-to-be demolished bookstore in Boston and purchased a copy of Boccaccio's *The Fates Of Illustrious Men* (Decasibus Virorum Illustrium). I found he could write about something else! In penance for my youthful folly, I read and enjoyed the book. Because some of the famous bones I am going to write about came from Florence, I have stolen and revised his title! It is only fair; you can look in any book of quotations and find that he was the first to use that famous saying, "Better is the enemy of good!"

Any right-thinking orthopedist should have an interest in anything pertaining to bones, so this will be a discourse on some of the famous bones I have seen or heard of thus far in my career.

Most schoolchildren know the unhappy story of Abraham Lincoln and John Wilkes Booth. The story is that Booth sought refuge in the Garrett barn, where he was shot and killed by Sergeant Boston Corbett. Boston Corbett was a religious fanatic and self-castrated eunuch. Some claim that Booth actually shot himself as he died of a pistol shot, as Corbett didn't have a pistol at the time of the shooting! Drs. Barnes and Woodward performed the autopsy on Booth, removing the cervical spine. They found that the mid-cervical vertebrae and spinal cord had been demolished by a pistol ball. The spinal segment was sent to the Army Medical Museum for preservation, while the body was buried in the yard of the Washington Arsenal Penitentiary. Because of renovations in the arsenal, the body was dug up two years later, placed in a gun box and stored in a warehouse until 1869. Because of the lack of a cervical spine, the head lay separated from the body. Friends passed the head back and forth in the process of identification to reconfirm the identity, and the body was laid to rest in an unmarked grave in Baltimore's Green Mount Cemetery[15]. Old Abe fared no better himself. Years after his interment, grave-robbers tried to steal his body from the cemetery in Springfield, Illinois. The malefactors were thwarted, but contemporary newspaper reports vividly describe the state of his remains, wearing white gloves, face perfectly recognizable but with a thin layer of scattered green mold. His eternal rest was insured the second time; they put a giant mass of structural steel over him and then poured concrete over the whole area.

I always thought the customs of bereavement and death were different but interesting. My father was a Congregational minister. When I was ten years old, one member of his congregation died. They had an auction to dispose of his effects. Flush with profits from my Des Moines Register paper route, I attended. My treasures were two. The first was an elegant cherrywood folding lapdesk which I still have. The second, and more important, was a book *John Paul Jones Commemoration* (Government Printing Office, 1907). It seems that someone remembered that they hadn't seen John Paul for a long time; they knew he was dead, but knew no details. This early Naval hero of the battle of the Serapis and the Bonne Homme Richard, died forgotten in France on 20 July 1792. The French realized that we might someday want to reclaim him, so they placed him in a double lead casket with the body packed in straw. Alcohol was introduced through a tap hole to preserve him. He was buried in a later abandoned graveyard in Paris. The book details how our government finally located the cemetery and excavated him. He was later buried with a ceremony at the Naval Academy at Annapolis in 1907, 115 years after his death. The book documents the whole process pictorially, and is fascinating. The mummified gentleman himself is seen (Figure 1). I will guarantee you that every kid in my neighborhood saw the pictures before I was done! For several months, it was a mad dash from streetlight to streetlight as I delivered my newspapers early in the morning. One instinctively knew that he couldn't be in Fort Dodge, but there was no harm in taking every precaution! I still have the book after 55 years.

Unusual things did happen in Fort Dodge. We had a park on the west side of town. At the entrance were two sagging plaster pillars. On them was stencilled the exciting news EXPOSITION PARK, HOME OF THE CARDIFF GIANT! A big variety park had been there years before. A swimming pool and a roller rink were left. Everything else, including the giant, was gone. In the late 1800's people were a little less sophisticated than they are today. Two upstate New York con-artists named William Newell and George Hull sought their fortunes. They came to Fort

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Figure 1 John Paul Jones, much, much later!

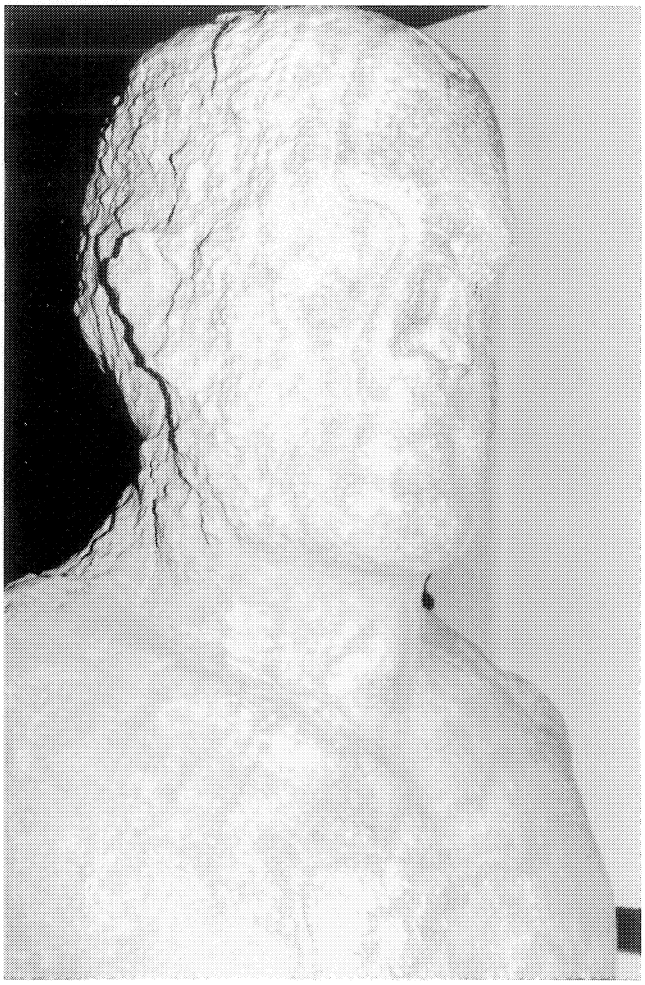

Figure 2 The Cardiff Giant

Dodge's famous gypsum mines (the world's largest deposit—even larger than the mines near Paris that originated "plaster of Paris") and purchased a large block of gypsum at the Cardiff Mines. They shipped it to Chicago where two sculptors, Fred Mohrmann and Henry Salle, carved a giant man. They gave him "pores" by pounding upon him with multiple needles embedded in a block of wood. They aged the whole sculpture with brief immersion in sulphuric acid. The sculpture was then transported to a farm near Cardiff, New York and buried. They then arranged for this "petrified man" to be "accidentally" discovered. Interest was worldwide and they made a fortune taking it on exhibition. The gullible P.T. Barnum tried to buy the giant but after failing, he found another petrified man and made a fortune exhibiting it. The hoax was eventually discovered and interest waned. Gardener Cowles, the Des Moines publisher, eventually purchased and kept the giant man for decades. After long negotiations, he was sold to the Farmer's Museum in Cooperstown, New York where he remains to this day. I took this picture of the giant during a recent visit to the museum (Figure 2)[33].

A recent report on the activities of the forensic pathologist, Bill Maples, completely captured my imagination. Rumor always had it that the 12th president of the United States, Zachary Taylor, had been poisoned by arsenic. Maples obtained permission to exhume the body and 150 years later, a saw cut through the lead casket and the lid was opened. There was the president, with a thick shock of black hair and a bow-tie under his chin! Maples cut away the clothing and took tissue samples. Analysis of the tissue at the Oak Ridge laboratories did not confirm poisoning. In another case, he confirmed and authenticated the bones of Francisco Pizarro, Spanish conqueror of Peru, from a crypt in the Cathedral of the Plaza de Aramis in Lima.[12]

Then there was General Dan Sickles, who lost his leg during the Civil War and donated it to the Armed Forces Institute of Pathology where it can still be seen. He had already been involved in a major scandal as he murderously confronted his wife and her lover, Phillip Key (son of Francis Scott Key of Star Spangled Banner fame). Key died and Sickles' presidential ambitions were dashed. The names change, but the story is repeated often enough![18]

The Arctic explorer Robert Peary brought six Inuit Indians with him to New York City. Four died and after prolonged negotiations, their skeletons were finally shipped back to Greenland in 1993.[16]

If you have ever read and enjoyed Edgar Lee Masters' *Spoon River Anthology*, you know how interesting graveyards can be. In Albany's County Cemetery is the grave of a young boy over which stands the carved statue of a boy with a bumblebee on the bridge of his nose. Years ago he died of anaphylactic shock after being stung. You can literally feel the parents' grief. Also in Albany's Graceland Cemetery is a small stone that reads "Parcella Post-an infant whose unknown parents sent the little body by mail to an Albany undertaker. November 20, 1922".

Another regional treasure is the Green-Wood cemetery in Brooklyn, New York.[20] At the turn of the last century, the social elite of New York were buried there. You can spend a quiet afternoon "visiting" with such as Henry Ward Beecher (remember the doggerel verse "Thus did the hen reward Beecher"?) and his Mrs. Horace Greeley (go West, young man!), Samuel F.B. Morse (artist and only incidentally elaborator of the Morse code), Currier and Ives (remember the wonderful Christmas prints?), Duncan Phyfe (master furniture artisan), and the infamous "Boss" Tweed. Also located there are the remains of Lola Montez who was the mistress of King Ludwig of Bavaria at the height of her professional career.

In medical school, Franklin Top told us about Typhoid Mary when we took Public Health courses. Her true name was Mary Mallon. A beautiful raven-haired Irish lass, she was one of the first proven vectors of the disease as we began to realize that the germ theory made sense. She worked as a household servant and cook in the late 1800's near New York City. It was calculated that she was responsible for the death of three and the infection of 53 more before quarantined. She died in 1938, and was buried in St. Raymond's cemetery in the Bronx.

Simon Schama has done it again in his book *Dead Certainties*[32]. It is set in Boston 150 years ago and tells how Professor Webster of the Harvard chemistry department paid his debt to Dr. Parkman. Blunt trauma to the head killed Parkman and his body was dismembered. The parts were concealed beneath the floor of the chemistry building, but the professor's secret was discovered. Now you know why the undergraduates at Harvard accord their chemistry professors the utmost respect! Endless jokes still abound 15 decades later, and the story appears in many true crime anthologies.

Dead and Buried in New England[23] is a small travel guide giving information about the burial sites of 306 noteworthy Yankees. You will find the location of the remains of such wildly disparate characters as Paul Revere, Increase and Cotton Mather, Sacco and Vanzetti, Mother Goose and Hugh Lofting (Doctor Dolittle author!). My favorite is the tomb of Roger Williams in Providence, Rhode Island. The founder of Rhode Island, he died in 1683 and was first buried in an apple orchard. He was moved in 1860 to his present resting spot. The roots of an apple tree had consumed most of the organic matter in their path. The tomb contained a braid of hair, nails and some bits of decayed wood from his casket. The roots had taken the shape of his body as they consumed it. A chemistry professor took the opportunity to write a book entitled *Who Ate Roger Williams?*

James Murfin has written about the fate of some of our famous patriots[27]. General Joseph Warren was the first American general to die in the revolution and was also a prominent Massachusetts physician (ask any proper Bostonian!). He was originally buried on the battlefield at Bunker Hill for ten months until the British left. Paul Revere had made two artifical teeth for him, and by this means Revere identified him when he was dug up. You can now see his grave in the Old Granary burying ground. Ethan Allen of the "Green Mountain Boys" was probably "resurrected" and dissected by medical students. General "Mad Anthony" Wayne was buried in a fort near Lake Erie in 1799. When he was dug up 10 years later, his body was perfectly preserved. Frontiersmen were practical, and there was the problem of transporting his remains home. So they "boned" him, removing all soft tissue from the body. They buried the skin in the original grave, and took the bones home to be buried in St. David's church courtyard in Radnor, Pennslyvania where they remain to this day!

Another of my favorite books includes a chapter entitled "Some Assembly Required"[36]. The body of an Oklahoma badman, shot after an aborted train robbery, spent the next 65 years as a prop at the Laugh In the Dark Funhouse in Long Beach, California before someone realized it was a real human being! If you are a sometimes sailor, you may even have seen him. I was often there on shore leave, but can't honestly say that I remember him! Another chapter tells how the skull of the Swedish mystic, Emmanuel Swedenborg, was stolen three times after his burial in 1772. His present skull almost surely isn't the one he was wearing when he died! It also tells how the remains of Father Junipero Serra, founder of the Franciscan missions were identified over 200 years after his death.

Since I previously mentioned Barnum, consider the case of John Ringling of Ringling Brothers, Barnum and Bailey Circus[4]. Because of a combination of litigation and familial disinterest, the bodies of both Ringling and his wife Mabel remain unburied over 50 years after their deaths! It seems that Henry Ringling North was trying to rectify the situation at the time the book was written.

Skidmore College is only a short drive from Albany, and I hope eventually to meet one of the English professors named Regina M. Janes.[1] Her academic subspecialty lies in decapitation. She delivered the Moseley Faculty Research Lecture in 1990 with the title "Beheadings In Progress". She can tell you who did it to whom and when; obviously a formidable and interesting lady! As you will see elsewhere in this paper, the literature is replete with many interesting variations on this theme.

Try a tour of the cemetaries of New York City[9]. Like the earlier mentioned work on New England, this book gives over 350 biographies of famous grave sites in the New York area. Scott Joplin is at St. Michael's and Billy Holliday's spirit is probably still singing the blues at St. Raymond's Cemetery. Go to Flushing Cemetery for a visit with Bernard Baruch and Louis Armstrong. You can visit Woodlawn Cemetery and Fiorello LaGuardia (remember the Little Flower and come away with a big smile!). You can plan out your own agenda and see things that would never occur to the average tourist.

Like me, you will probably be happy to learn that a French chemical company has recently funded the restoration of the crypt of St. Mark's in Venice. Below sea level, it flooded and had been walled up since 1580. It has now been restored to pristine waterproof glory by chemical technology, and church authorities are strongly considering return of the relics of St. Mark to the crypt. This bit of information is one of the advantages of my years of membership in the American Chemical Society![8] I am just as partial to Padua. I once had the fancy to go to the monastery there and saw reliquiries containing the tongue and radius of St. Anthony.

I consider network news a part of my continuing education and was gratified to watch NBC news on 31 Jan. 1995. Archeologists in Siwa, Egypt, claim to have uncovered the burial place of Alexander the Great; he died in 323 B.C. I then watched the 11 o'clock news and no more mention of it! No mention of it since then, either. Poor sense of proportion, I would say.

When in Florence, Italy, I visted the Church of the Cross. As you enter the main doors, you see the tombs of famous men including Dante Alegherii, Michaelangelo, Machiavelli and Gallileo! Dante must have been entombed there as recently as the 20th century. In life, he was exiled from Florence for political reasons, under threat of death. He died years later in Ravenna and was buried there. He

Figure 3 Machiavelli's tomb

was not safe, even in death. Eight years after he died, Cardinal Bertrand du Poyet became involved. The good Cardinal had already ordered Dante's book *De Monarchia* to be burned in public. He now wanted his bones also burned "to the eternal shame and extinction of his memory". Poyet did not prevail, and the remains were preserved. As recently as 1902, Federn stated that the Florentines had unsuccessfully entreated for return of the remains but gave up in the 1860's. They must have eventually succeeded. My memories of Dante are keen for this reason; when I was finishing grade school, we had to start giving book reports. My older brother Robert (grew up to be an English professor) had sage advice for me. "Pick a ponderous book which you think the teacher won't have read!" I went into the dusty furthermost reaches of the Fort Dodge Public Library and came up with an old edition of Dante's "Inferno", illustrated by Gustave Dore. I read it and wrote the report though the teacher didn't believe I had read it.

The tomb of Nicolo Machiavelli inspired another reverie (Figure 3). I remembered Western Civilization and George Mosse, one of the most delightful professors I had in my undergraduate days at Iowa (he made history come alive, and he swore in the heat of professorial exposition-a trick I later emulated). Machiavelli's *The Prince* was one of the first books on political science. "A man who wants to be completely virtuous will come to grief among those of lesser virtue!"

In recent years much of the original documentation of Galileo Galilei's trials has been released by the Vatican for scholarly research (Figure 4). Historians appear to be rewriting history in light of the information.[31]

Another great book[38] discusses an archeological dig beneath St. Peter's Basilica in Rome. They have found what they think are the skeletal remains of St. Peter, and the book shows the bones. There can be no absolute proof, but there is strong evidence. Imagine, telling folks you have seen the bones of St. Peter!

The fate of the bones of a famous explorer is uncertain, but grim. You have probably heard of the Verrazzano Straits Bridge in New York. It is named after Giovanni da Verrazzano. Paolo Giovio's nephew, Guilio Giovo states that (Verrazanno) "with six of his men . . . disembarked on a deserted island which seemed covered with tall trees. They were taken by cruel people who suddenly attacked them. They were killed, laid on the ground, cut into pieces

Figure 4 Galileo's tomb

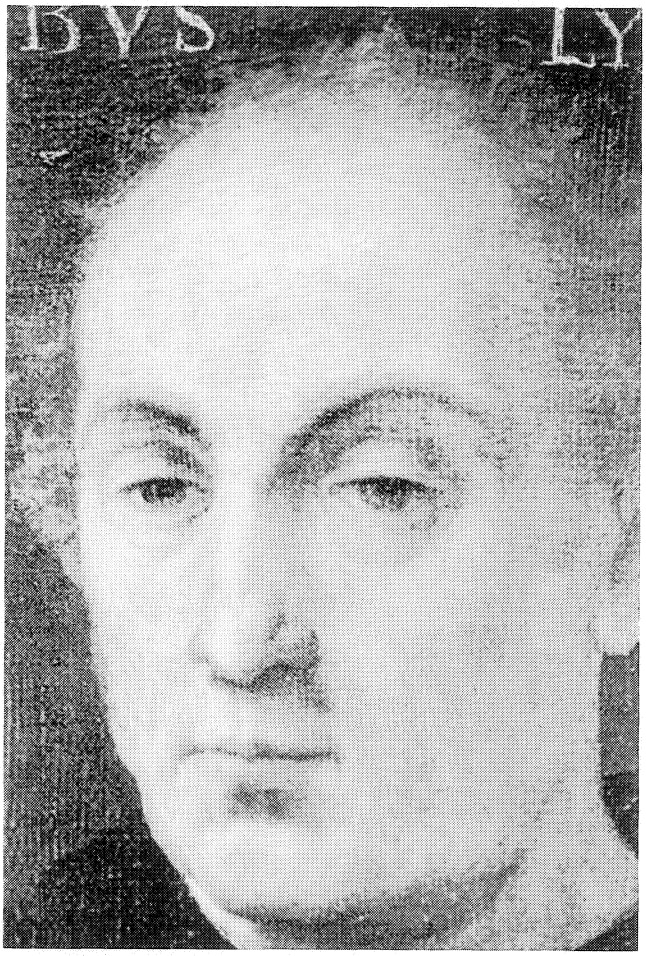

Figure 5 Columbus

and eaten down to the smallest bone by those people. Such a sad death had the seeker of new lands!" We must assume that Verrazzano is still there on some unknown island in the West Indies. Just remember that the next time you drive over the bridge![39]

I once visited Christopher Columbus' birthplace in Genoa (Figure 5). Ferdinand and Isabella financed his voyage to the new world. What you may not know is the phenomenal post-mortem wanderings of this soul. He died in 1506 and was buried in Valladolid, Spain. His son, Don Diego, transferred the remains to the monastery of Las Cuevas in Seville in 1509. After Don Diego himself died in 1526, his widow had the remains of both men interred at the Cathedral at Santo Domingo, Espanola in 1541. In 1795, Espanola was lost, and they removed what they thought were Columbus' remains to Havana Cathedral in Cuba. Well, in 1877, the cathedral at Santa Domingo was being renovated and a lead box with inscriptions almost surely proving it contained the remains of Columbus was found and reinterred. In 1898, the Spaniards removed what they claimed were the remains of Columbus from Havana to the cathedral in Seville. Most historians think that they actually have Don Diego's remains, not his father's. Do you think that is the end of the story? Wrong! In time for the 400th anniversary of Columbus' discovery of the New World, they built a concrete museum in the shape of a cross and removed his remains from the cathedral to this new building. Columbus is probably still in Santa Domingo, and his travels (travails?) may continue![19]

It is claimed that the famous violinist Paganini sold his soul to the devil to get ahead. No mortal human could play that well. The effects and new kinds of bowing he introduced remained beyond belief, and were thought beyond the capacity of any good Christian. They called him the "spawn of the devil" but all came to hear him play. He laughed all the way to the bank. Later physicians surmised that he suffered from Marfan's syndrome, but Ehler's—Danlos may be closer to the truth. The ultimate fate of Paganini could be the devil in action. When he died in Nice in 1840, he refused the last rites of the church. The Bishop denied permission for burial, so his body was left in his apartment for two months. Paganini was then stored in the cellar for a year. He was next stored in a leper house at Villefranche. His next stop was a concrete vat at an unused olive oil factory before he was moved to an estate in Cap Ferrat. Four years after his death, his body was buried for the first time on his estate at Polecevera. A year after that, they dug him up and moved him to Villa Gaione near Parma. He was again disinterred and his famous bones moved to Parma in 1876, 36 years after his death, for a fitting Christian burial. Was he done? No! In 1893, the Czech violinist Ondricek had the corpse disinterred for his idle perusal. It wasn't reburied until 1896, three years later. The features of the face were said to still be recognizable, but the lower body was reduced to a skeleton.[13]

Another arcane little book[25] details the death of Ivan the Terrible in 1584 and the opening of his tomb in 1953 by the Soviets. The detailed description of the remains concludes that he had severe arthritis. He likely drank to excess to alleviate the pain, hence his history of drunkeness. Another chapter includes an actual photograph of Oliver Cromwell's head. After he was beheaded, the trophy was impaled on an iron spiked pole for exhibition. The spike is still embedded!

I recently found Herodotus' *History of the Greek and Persian Wars*. It held a clipping from Time Magazine, 17 Jan. 1972 showing pictures of a recent Soviet archeologic dig near Ordzhonikidze, Southern Ukraine. They found the intact royal tomb of the Scythian tribesmen. The article included pictures of the skeletal remains of a princess, covered with gold plaques and ornaments. She had chronic osteomyelitis of the left femur with a deformed knee joint.

In Sir Richard Burton's translation of *Arabian Nights,* I shall never forget his encyclopedic listing of the hundreds of Arabic terms for concealed but highly esteemed parts of the human anatomy! He was supposedly the first infidel (in disguise) to see the sacred black stone embedded in the wall of the Kaaba at Mecca. He was an adventurer in the truest sense. His recent biography[5] enthralls. If you have the will, you can visit his tomb outside of London. His body lies in an Arab tent fashioned of marble and copper. He may have lost out to Speke in the search for the source of the Nile (you may have seen the dramatization on the Public Television Network). He will never lose in any way in my imagination!

Remember when the end was near for Jesus. He had disrupted the second Temple in Jerusalem. He overturned the tables of the moneychangers, derided the sale of sacrificial animals and the privileges of the Temple priests. Caiaphas, the high priest of the Temple, probably forced the hand of Pontius Pilate into the crucifiction. Now, archeologists have made a sensational find. In Christ's time, the wealthy were put into a stone sarcophagus ("flesh-eater", literally) at death. They stayed there for six or seven years until only the bones were left. The bones were then removed (readying the sarcophagus for the next body) and placed into small engraved stone boxes called ossuaries. The ossuaries were then placed in a grouping around the sarcophagus. The archeologists think they have found the ossuary of Caiaphas, and you can see it in an article in the *Biblical Archeology Review*! The Ministry of Religious Affairs of Israel has since reburied it on the Mount of Olives. (Did you know that Gethsemane literally means "olive press"?).

Neolithic bones found in a dig in northern Syria showed common and understandable skeletal abnormalities related to daily activities. The one that interested me most was the repeated finding of severe degenerative arthritis in the first metatarsophalangeal joint of females of the era. It seems that they had to kneel, leaning forward, to grind grain between stones. With the joint in stressed hyperextension, you can appreciate the pain they must have experienced! Think of the fame you could have experienced had there been such a thing as an orthopedist in that day, and if you were that orthopedist.

In *The Mummy's Tale,*[10] Natsef-Amun was a priest and scribe at the temple at Karnak in Egypt over a millennium before Christ's time. His mummy was found and taken to England in 1828. An autopsy was done by the standards of the time. The autopsy was repeated in our era. This book details and shows illustrations of the findings. He was either strangled or hanged, and certainly had parasites including filiariasis and Guinea worms. They finish with a forensic reconstruction of the soft tissue of the head. You can see just what he looked like.

Archeologists recently uncovered 430 new tombs near the Great Pyramid on the Giza Plateau in Egypt. These are probably the final resting places of the artisans and overseers who built the tomb. They are a treasure trove of artifacts of the common man of the era. An inscription on the tomb of Sheduu says "I have been a good man all of my life and have never hurt anyone. If you disturb my tomb, you will be eaten by an alligator, a hippopotamus and other animals!" Later, someone else added "You will also be bitten by the scorpion on land and the snake in water!"[22]

If your interest remains with mummies, pyramids and the like, read E.A.Wallis[37]. You can literally learn how to do it yourself. If not preserving a favorite relative, there are directions to preserve a bull, antelope, cat, crocodile, shrew, ibis, hawk, frog, scorpion, beetle, snake or fish. I remember with affection my early childhood visits to the Oriental Institute in Chicago where you could do a fluoroscopic examination of a mummy! And then think upon Sir Winston Churchill's famous advice to a friend concerning the coming funeral of his mother-in-law. "By all means, have her embalmed, cremated and buried! One must be sure!"

Tycho Brahe was a famous Danish astronomer of the sixteenth century. As an impetuous young man, he fought a duel. He didn't come away with the usual cherished Germanic dueling scar. His nose was cut off! What was said to be a gold and silver prosthesis was fashioned. His tomb in Prague was restored at the 300th anniversary of his death in 1901, and the grave was opened. No prosthesis was found, but the skull around the nasal region was stained with copper oxide, probably the end result of corrosion of the prosthesis.[14]

Whatever happened to Jan Ignace Paderewski? The famed concert pianist sought refuge in the United States at the start of World War II, but he died in New York City on 27 June 1941. A huge parade and requiem mass were held to send him off in style. Franklin Roosevelt saw to it that his remains were placed in the memorial sepulcher to the Spanish American War dead in Arlington National Cemetery "until Poland shall be free". An identifying tablet was placed by President Kennedy in 1963. His remains were reinterred in St. John's Cathedral in Warsaw on 5 July 1992, 51 years after his death! At the request of his sister, his heart was removed and will remain in a crypt at the Shrine of Our Lady of Czestochowa in Doylestown, Pennsylvania.[2]

Gustave Flaubert's descriptions of people, times and places were exquisite in detail. Never will I forget Emma Bovary engaged in the most endearing and basic of human exercises. At Flaubert's interment, the gravediggers had miscalculated. His coffin was too long for the modest hole they had excavated. It wasn't discovered until they had

already started lowering the casket. The ropes slipped and the casket fell, wedging head-first into the grave. Try as they might, they couldn't remove it. Emile Zola, who was there, cried "enough, enough!" and the funeral party left the graveside. The necessary corrections were done after their departure. You might say that he really didn't want to go![35]

Father Damien founded the famous leper colony at Molokai in the Hawaiian Islands in 1873. On his death he was buried in Belgium. When Pope Paul II beatified him, he was exhumed and a portion of his remains taken to the Molokai church to be buried in a ceremony celebrating his sainthood.

An article in *Scientific American* shows pictures of the skull of a patient who suffered from Paget's disease[6]. The skull is grossly thickened and enlarged. It goes on to tell the story of Egil, an Icelandic hero of the tenth century A.D.. Egil had a similar deformity with an unusual, menacing skull that was known to be able to withstand the blow of an ax in battle. The author is looking forward to the opportunity of unearthing the remains of Egil from the old churchyard at Mosfell (the third time in 1,000 years).

In Greenland, there are mummies buried fully dressed in freezing temperatures over 500 years ago. Their preservation really amounted to freeze-drying. The roentgenograms in one case revealed non-union of a fractured clavicle. Another had scoliosis with a primary lumbar curve. The cache of bodies was accidentally found by two hunters in 1972. The pictures of their native dress are immediate in their appeal.[17]

A huge aboriginal burying ground was found near Lake Victoria in New South Wales. The ground may contain the remains of 10,000 skeletons and is the largest ever discovered of a hunter-gatherer society. Whole new ideas of the size of early settlements is emerging.[29]

The Russian royal family during the second decade of this century was executed by a squad of Bolshevik gunmen and their bodies discarded in a place unknown to the rest of the world until now! There was always question about whether a young daughter, Anastasia and a son, Alexei, survived. With the change in the political situation in Russia, the truth is finally coming out, accompanied by a flood of newspaper articles and an excellent well-documented book.[30] Geli Ryabov, a respected Russian author first let out the news in 1989. He claimed to have found the skeletal remains of the family, and published a memorable picture of the skull of Tsar Nicholas. Dr. William Maples, head of an American forensic team, explored the site in 1991 and noted that bones appropriate for Anastasia and Alexei were not found! Computer modeling of the skulls identified the Tsar and Tsarina. DNA fingerprinting further confirmed the identification when matched with blood from living royals, including Prince Phillip of England. Anna Anderson claimed to be Anastasia but matching with a lock of her hair disproved her claim. Radzinsky's book gives a wealth of detail that makes the whole era come alive again. A mocking headline and story[3] just about sums it up. Entitled "We're really, really sorry!", it states that the remains are to be buried in the St. Petersburg cathedral in a ceremony planned for March, 1995 (more than 75 years from the time of their execution). Nicholas' brother Gregory has already been reburied. He was exhumed as another source of DNA for comparison testing!

In Vienna, you can visit the Capuchin Church and see the crypts of 146 Hapsburg emperors, empresses and princes in zinc caskets. In 1919, the last Emperor and Empress of the Austria-Hungary empire fled into Swiss exile as World War I ended (with them on the wrong side!). He later died and was buried in Switzerland. She lived on in a Swiss home for the elderly. When she died in 1989, her heart was cut out and buried beside her husband (a royal tradition). Her body was returned to Vienna and buried in the family crypt. Zita had come home. It is said she schemed to the end to return her husband, and later her son, Otto, to the throne. It came to nothing, but they did have a huge state funeral for her, a melancholy echo of things and times past![28]

Frederick the Great was one of the icons of German nationalism. He died in 1786 and had asked to be buried in the garden of his palace, San Souci. His heirs knew that this was not enough and had him buried in Potsdam's gothic Garrison Church. There he stayed until 1943. Adolph Hitler had him removed to a salt mine to protect his remains from Allied air raids. This was the right decision, because the church was destroyed by a bomb as World War II ended. The allies reinterred him in the Hohenzollern castle near Stuttgart where he remained until 1991, 48 years later. Helmut Kohl, the German chancellor, then had the remains buried at San Souci, which is where Frederick had wanted to be in the first place! This was his fourth interment.

Before I conclude with more English recollections, think of the ill-starred Franklin expedition searching for a Northwest Passage in the Canadian Arctic. They all perished, probably from a combination of scurvy, exposure and lead poisoning from the soldered seams of their canned-goods containers. An expedition from the University of Alberta dug up the frozen remains of Petty Officer John Torrington from the tundra 138 years after his death. Twenty years old at the time of his death, he was perfectly preserved. Those present said it was as if he were looking out from the tomb as the world was looking in at him! The Smithsonian Magazine had an article showing a picture of him in his tomb. With his lips retracted, teeth showing, he certainly did look chilly!

As the author Thomas Hardy's body was being prepared for cremation, a cat stole his heart! The remains were buried in Westminster Abbey. They eventually found the remains of his heart, but that had to settle for separate burial in Stinson, England.

John Wyclif accepted nothing but the Bible as authority on the Christian religion. Expelled from Oxford in 1382 after his doctrines were condemned by the London synod, he died in 1384. I recently learned that he was posthumously honored for his advocacy of religious reform by having his remains dug up and burned at the stake 44 years after his death.

Imagine the day Lord Byron returned to the Sandwich Islands (our Hawaii), returning the bodies of King Liholiho and his queen. They had died in England of measles. He brought them back for burial in the temple of Ku. This is the exact same location where the natives killed and ate the famous explorer, Captain Cook. You can visit their tomb and look for spare parts of Captain Cook as well (the natives returned part of his cleaned bones to the English, but the inventory was by no means complete!)[11] His lament might be like Ronald Reagans's in King's Row, "Where's the rest of me?"

Another book[26] includes photographs of the American giant, the Irish giant and the Sicilian dwarf from the collection of John Hunter. Also included is news of Lord Byron. When he died in 1824, he was buried in the family vault in Nottingham. When the church was remodeled in 1938, Canon Barber took the opportunity to open the casket. Witnesses claimed the body was well preserved and recognizable. He supposedly had a clubfoot. In the casket, they found that the foot had been amputated after death and lay separately. Neither foot was clubbed, and the deformity had been from a contracted Achilles tendon. No one knew why the foot had been amputated. They conclude with a quotation from John Hunter; "Never perform an operation on another person which, under similar circumstances, you would not have performed on yourself."

The author, Shelley, drowned in 1822 as his ship sank off of Livorno. Trewlawny was present at his cremation. All of the body was consumed save for some bone fragments, the skull and jawbone. His entire heart remained and Trewlawny burned his hands as he snatched it from the furnace. Did he have calcific pericarditis?[7]

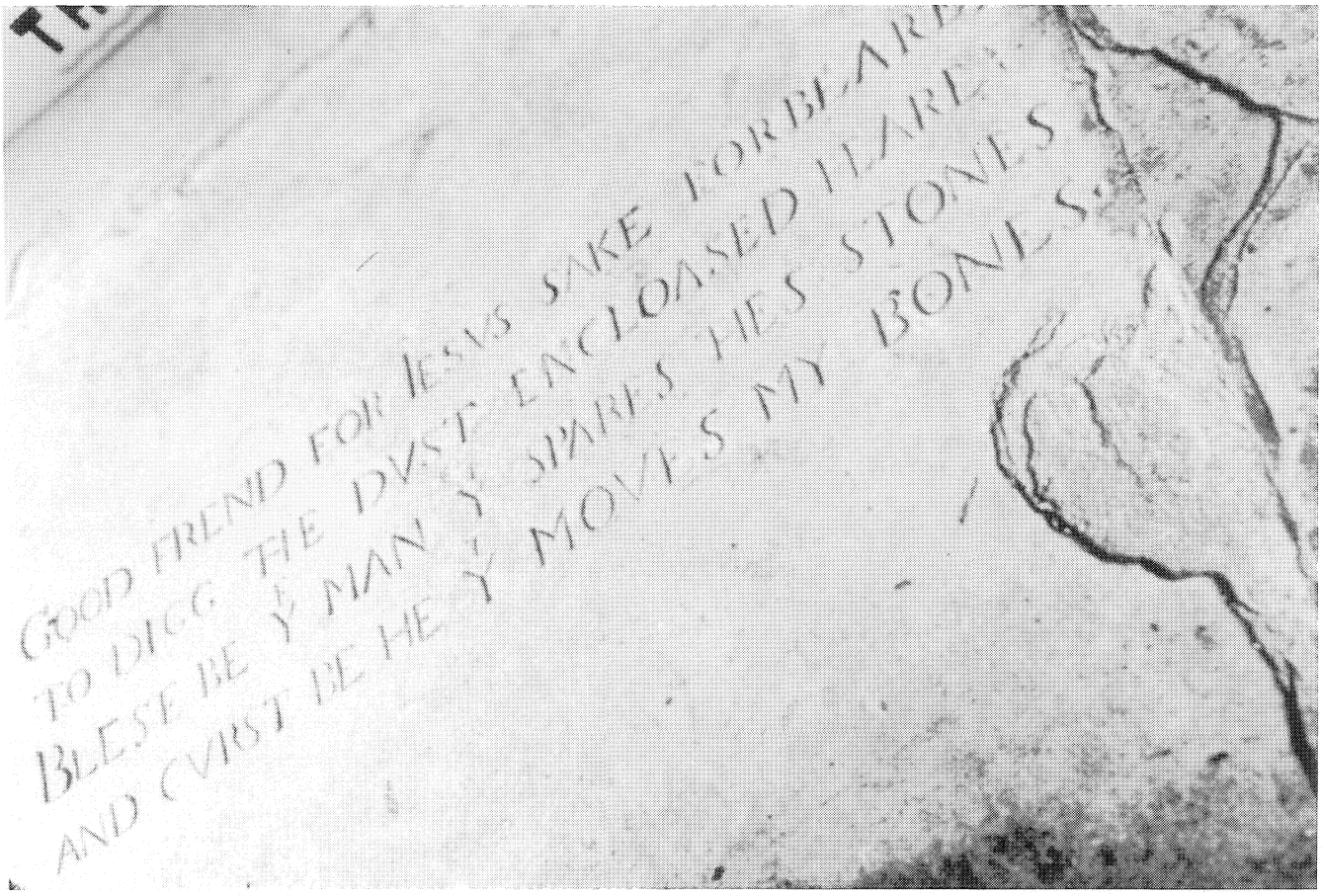

Figure 6 Shakespeare's tomb

William Shakespeare is buried in the sanctuary of Holy Trinity Church in Stratford. Over his grave (Figure 6) reads the stone "Good friend for Jesus sake forbeare to digg the dust encloased heare; blese be ye man y spares thes stones and curst be he y moves my bones". Scholars of questionable heritage and lesser rectitude have occasionally suggested that his works were written by Sir Francis Bacon or others. As I recall, one actually claimed evidence to this effect was buried with Shakespeare in his tomb. He tried, to no effect, to get permisson to disinter him for this purpose.

The young Edward became King of England in about 970 A.D., but his doom was already sealed by his treacherous mother, Queen Elfrieda. She had ambitions for her younger son, Ethelred. She invited the new King Edward for a visit at Corfe Castle but had him waylaid and murdered as he approached the portals. He was dragged, lifeless, by his horse after the assault. He went down in history as Edward the Martyr. Over 900 years later in 1931, the English archeologist J. Wilson Clariidge was exploring the ruins of the Abbey Church at Shaftesbury, England. He found a lead casket containing bones afflicted with multiple fresh fractures with no sign of healing. Based on all available information and engravings on the casket, the forensic pathologist Thomas E.A. Stowell, in conjunction with the British Museum, authenticated the bones as those of Edward. The bones still languish in a bank vault. A legal decision must be reached as to their fate!

What of Edward's successor Ethelred? (Figure 7) A delightful book by Elizabeth Longford[21] tells all. As a hapless infant, Ethelred urinated in the baptismal font as he was being consecrated to God. From this omen, St. Dunstan predicted a dire future for the English people in the time of Ethelred. King Ethelred was completely ineffectual as a ruler. He paid off successive waves of invading Danes and finally fled to France in 1013 A.D. Because of this, he went down in history captioned as "Ethelred the Unready"!

By whatever the standard, the death of Ethelred's son, Edmund Ironside, was bizarre. The treacherous Edric closely studied the habits of Ironside and one night concealed himself in the pit of the royal privy. Edmund came that night, as usual, to relieve himself. At that instant, Edric placed the tip of his dagger at the anal verge and thrust upward. The dagger was left impaled in the bowels of the dying king. Edric then went to Canute and hailed him as the new king. Canute rewarded him by decapitation and placed his head on a pole on the highest point in the tower of London.

This business of beheading could be called a common thread for much of royalty. Consider the fate of the Duke of Monmouth. He was beheaded in disgrace in 1685. His loving family had him disinterred at a more opportune time. His head was sewn back on and a portrait of him painted for his ancestors to cherish!

Figure 7 Ethelred. He really does look unready!

Charles I of England was slow to develop as a child; he did not walk until the age of three. As a monarch, he experienced increasing civil disobedience and was finally overthrown by Oliver Cromwell and the Roundheads. They beheaded him in 1649, and he was buried in St. George's Chapel. In 1813, 164 years after his death, his tomb was accidentally opened. His plain leaden casket, exposed, was opened to satisfy curiosity. Unshrouded, the form of much of the soft tissue was intact. The delicate tissue of his eyeballs collapsed even as the body was being viewed. The body of the fourth cervical vertebra had been cleanly transected by the headsman's axe (all this in an account by Sir Henry Halford, the King's physician in 1813). The body was then embalmed and the head neatly stitched back in place. It was then reinterred in the vault along with the bodies of Henry VIII and Jane Seymour. Workmen covertly removed one of Charles' vertebrae and fashioned it into a salt cellar. One of his metacarpals was also taken to make a knife handle! The thieves were found out years later. With typical English style and ceremony,

these relics were placed in a separate little casket and reinterred with his body in 1888 by the instruction of Queen Victoria. They opened a small hole in the ceiling of the vault, and lowered the little casket on silken cords until it rested on the top of Charles' casket.

In all, then, I decried the whole process of funerals and interment when I was younger. As you can see, I have developed a lively interest in the whole process now! Years later, I would wander through our family cemetaries in the backwoods of Missouri and hear distant voices, see distant visions as I viewed the stones of my ancestors. Lines would come back from the *Spoon River Anthology*, "They are all sleeping, sleeping on the hill-------"

In conclusion, this edition is dedicated to Don Kettlekamp. I've known Don for many years and went to medical school with his younger brother Dick. Don was a menace as a high school wrestler in our state of Iowa. He went on to become nationally ranked when he enrolled at Cornell. He, Dick Hauser and Lowell Lange were a regular killer's row! A few years back, I caught Don completely unaware as I introduced him at a meeting. I said that one cannot completely understand terror until standing on the opposite side of a wrestling mat facing Don in purple tights! As I said that, he had a grin from ear to ear. Although I think we are both getting a few years older, he will always be a dear friend.

Editors' note: This article is adapted from a presentation given by Dr. Jacobs at a past University of Iowa Orthopaedic Alumni meeting dinner.

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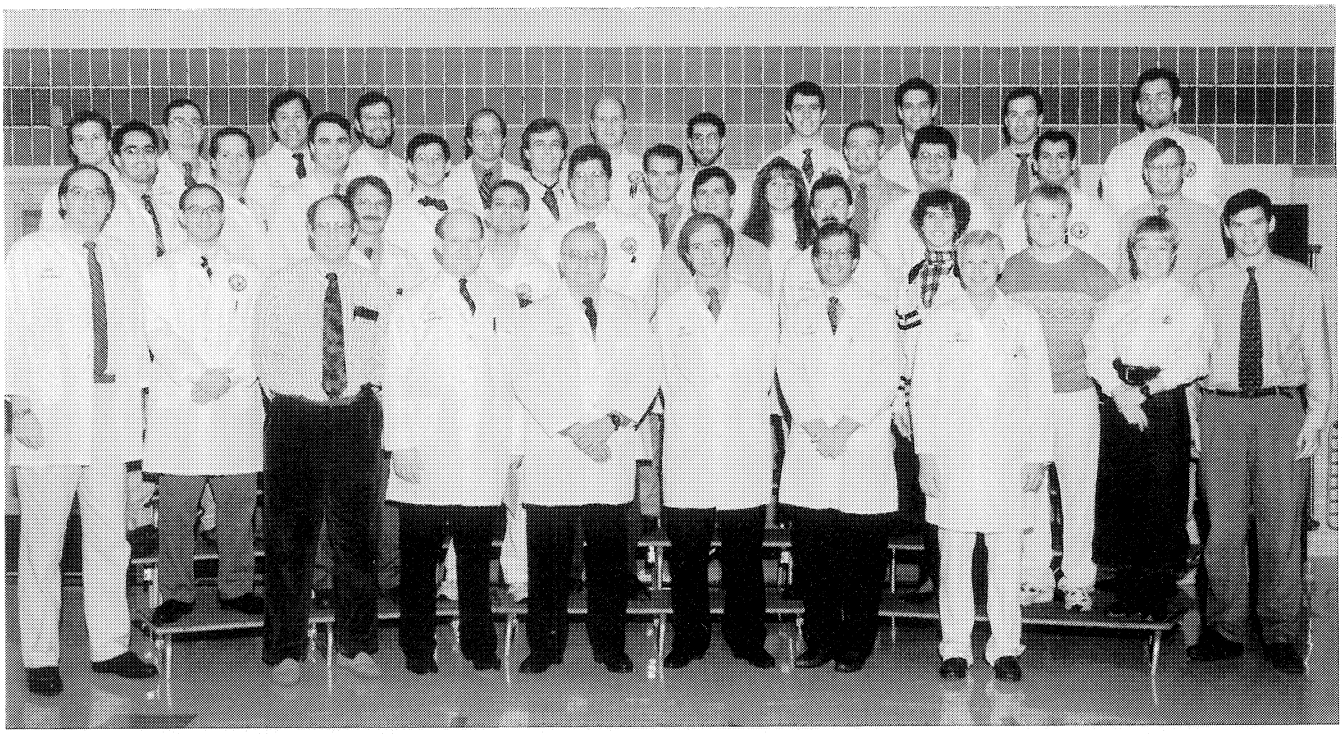

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