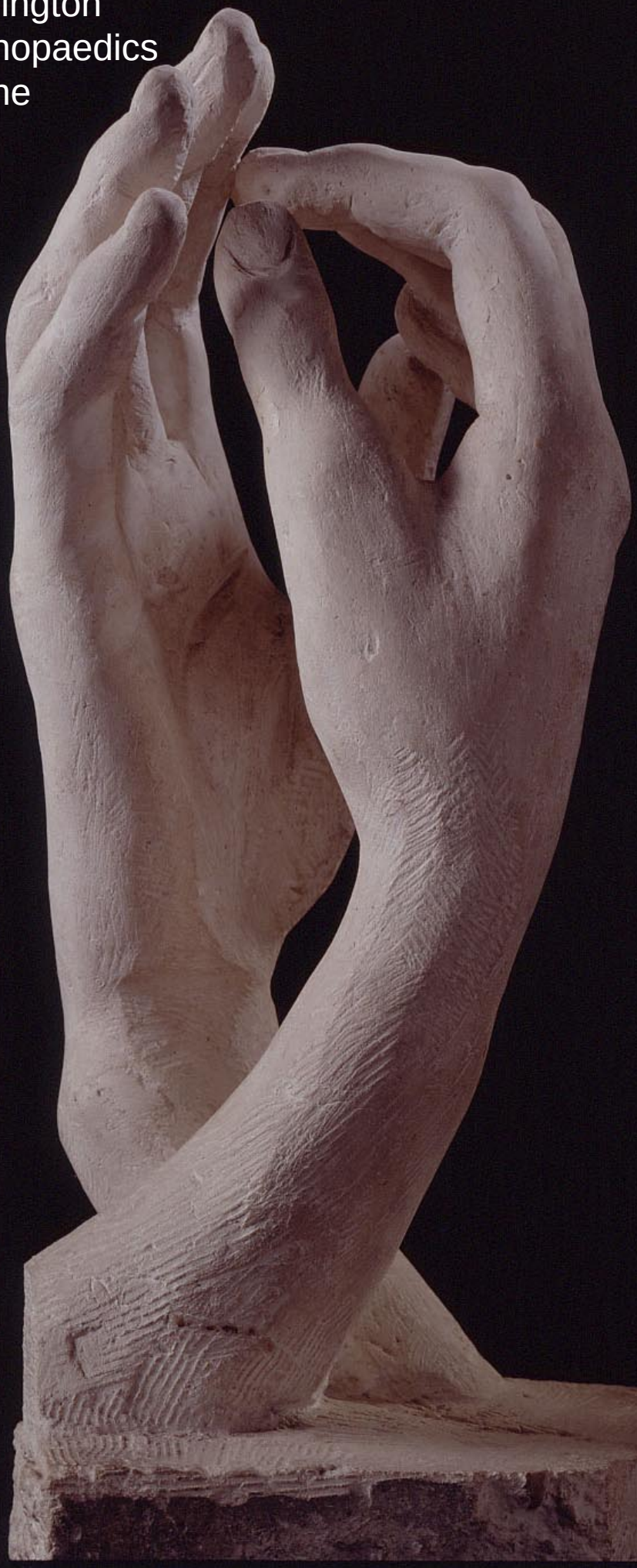
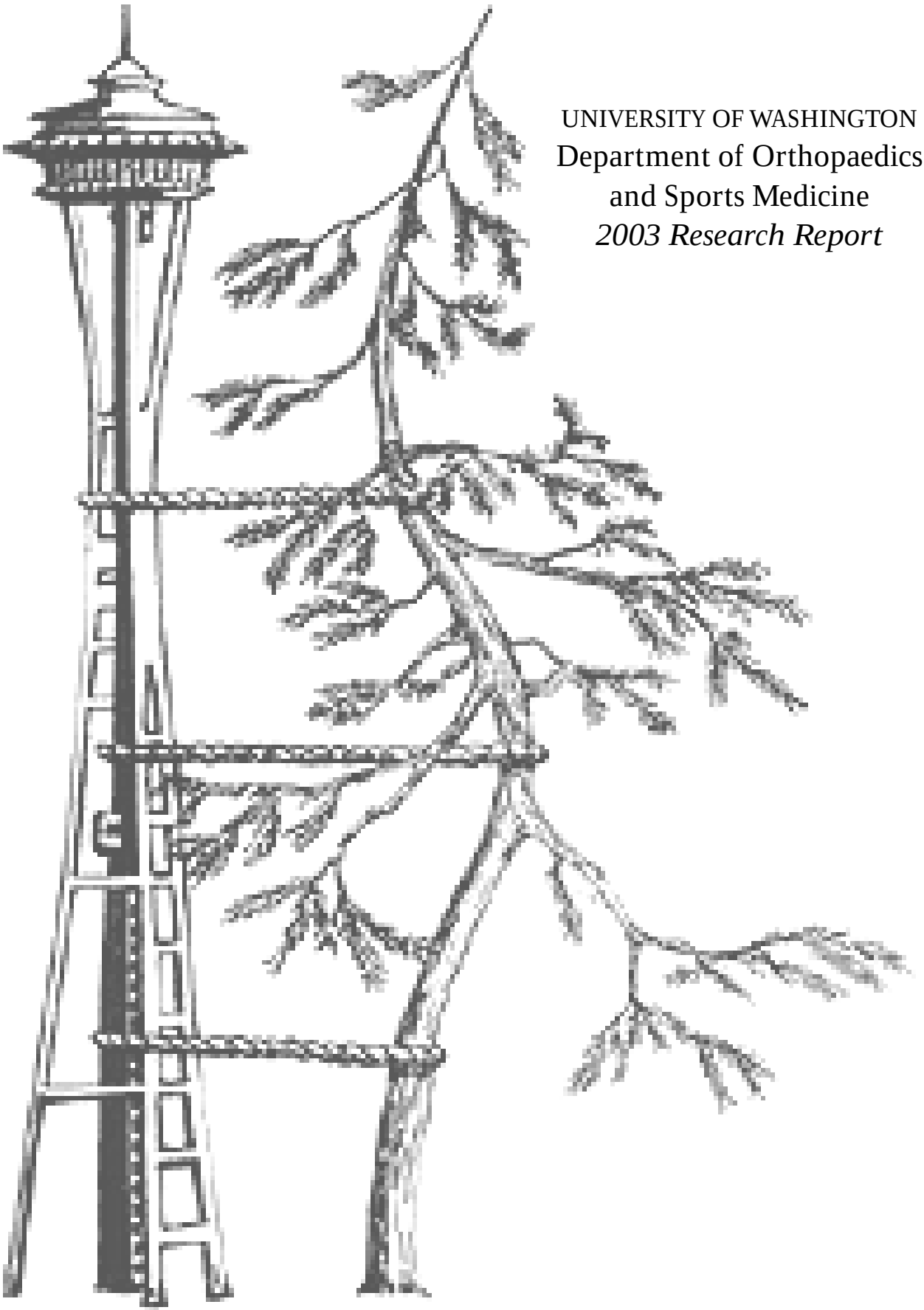
University of Washington
Department of Orthopaedics
and Sports Medicine



2003 Research Report



UNIVERSITY OF WASHINGTON

Department of Orthopaedics and Sports Medicine

2003 Research Report

UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Department of Orthopaedics and Sports Medicine
University of Washington
Seattle, WA 98195

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Cover Illustration: "La Cathédrale" by Auguste Rodin
S. 1001, pierre, 69 x 29.5 x 31.8 cm
Photograph: Eric and Petra Hesmerg
Musee Rodin

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Foreword

This year's edition of the Department of Orthopaedics and Sports Medicine Research Report is dedicated to our outstanding hand program and to the newly established UW Medicine Hand Institute at Roosevelt. It is fitting to include an article from our clinical faculty member, Paul Brand. Orthopaedic surgeons get to know Dr. Brand through his classic articles on the hand. Paul Brand was born in 1914 in the mountains of India, where his parents were missionaries. He went to London, England, for his education and had his medical and surgical training at London University. In 1946 Paul and his wife, Margaret, who is also a doctor, went to India, where Paul taught surgery at the Christian Medical College and Hospital in Vellore. Dr. Brand became the first surgeon in the world to use reconstructive surgery to correct the deformities from leprosy in the hands and feet. He was elected Huntarian Professor of the Royal College of Surgeons of England in 1952. In 1961 he was honored by Queen Elizabeth with appointment as "Commander of the Order of the British Empire." He was also the recipient of the Distinguished Service Award from the Department of Health and Human Services, United States Public Health Service. But, his early mastery of hand biomechanics is only part of the story. Outside orthopaedics he is known for his spiritual appreciation for the human body expressed in books such as *Fearfully and Wonderfully Made*, and *Pain: The Gift Nobody Wants*. I suspect you will enjoy his article in this report, and if so, you may enjoy these books and some of his other articles, such as "Low Moments in My Surgical Career" and "The Pursuit of Happiness." He is truly a renaissance man.

In searching for the cover art to honor our hand program, I discovered this 1908 sculpture at the Musee Auguste Rodin, 77, Rue de Varenne in Paris, called *La Cathédrale*. Like Brand, Rodin was awed by the human form – you know some of his other works that celebrate the body, such as *The Thinker*, *The Kiss*, *The Age of Bronze*, and perhaps *Man with a Broken Nose*. Rodin was born in 1840 and died in 1917 when Dr. Brand was three years old. *La Cathédrale* is composed of two upraised right hands coming together to evoke the spiritual space of ancient cathedrals.

The U.W. hand program is led by three orthopaedic hand surgeons, Chris Allan, Doug Hanel and Tom Trumble and two plastic surgeons, Nick Vedder and Arshad Muzaffar. This team includes the first full-time hand surgeons at the University of Washington. The members of this team are prolific in their teaching, their research, their publications and their clinical care. To learn more about "How D'ya Sew an Amputated Finger Back On?," "Amazing Operation Gives Boy Two New Thumbs," "Single-Portal Endoscopic Carpal Tunnel Release Compared with Open Release," "Man's Hand Reattached after Daring Rescue at Sea," and to discover the identity of the winner of the Bovill Award for the best paper of the year given at the Orthopedic Trauma Association annual meeting, please see http://www.orthop.washington.edu/hand_wrist. The last time we had hands on our Research Report Cover was in 1994. You can download this PDF at http://www.orthop.washington.edu/dept. Can you identify the artist before looking at the answer on the copyright page?

In this year's report you will meet our three new faculty members, help us welcome our new residents and celebrate the graduation of our chief residents. You will also get a chance to experience some of the breadth and depth of our research program. We have selected some basic science articles on the cell and molecular biology of cartilage and sarcomas. Other articles show the importance of rest in building bone and the ability of amputated digits to regenerate. Several articles concern the foot, ranging from the relation of foot position to injury, and treatment of big toe deformities, to the value of special footwear for individuals with diabetes. You can also learn of the impairment of bone healing by smoking and the value of special blood pressure measurements to avoid amputation after knee dislocation. Our faculty and residents have presented

Dr. Paul Brand

answers to other questions, such as "How do folks do when the head is dislocated from the neck?"; "How can you predict the result of a shoulder replacement?"; "Does the source of funding affect the outcome of research?"; "Is Synvisc better than cortisone for knee arthritis?"; "How can fractures of the scaphoid be stabilized?"; "How do older people fare with fractures of the hip socket?"; "Does rowing cause back pain?"; and "When do medical students learn about bones and joints?" While this is only a sample, it presents quite a variety.

We are a bigger and stronger Department now than ever before. Our excellence is the result of (1) the many superior staff, residents, students and faculty that work in the Department, (2) the patients that trust us to restore their comfort and function, and (3) those generous individuals and groups that give us the financial support to carry on our work. With your help we will continue to pursue new and better ways to help people stay 'fit for life!'

Best wishes,

F. A. Matsen III

Frederick A. Matsen III, M.D.
Residency Alumnus, 1975

Neuropathology By Sunrise

PAUL BRAND, M.D.

It was about fifty-five years ago. I was working at the Christian Medical College at Vellore in south India. I had completed my own residency training in London during the years of what we called 'the Blitz.' London was being bombed every night and we young surgeons were faced with large numbers of cases of severe trauma. Our patients had been dug up from under fallen houses and suffered from crushed limbs and from wounds caused by broken glass. I had become very experienced at analyzing the exact causes of paralysis of the hand and also the legs. I had become experienced at using many types of tendon transfer operations to restore balance to the limbs of patients who had come in with paralysis of any one or more of the motor nerves in the limbs. I had also worked in the Orthopaedic unit of a Children's Hospital where I had been responsible for treating many cases of poliomyelitis, which was common in London in those days.

Thus on starting orthopaedic surgery in India I was on the lookout for cases of polio and of severe trauma because in that area at least I was more competent than anybody else.

It wasn't long before I noticed that outside the gates of the hospital there were usually numbers of beggars who displayed deformities of the hands and feet and of their faces. Several of these beggars had deformities of the hand that looked like polio cases that I had seen in London and many others had severe wounds which were being displayed without dressings in order to excite the pity of passersby who would then put some money in the hat or bowl of these beggars.

I was shocked to see so many deformities and so many wounds outside the hospital and I expressed my feelings to one of the older Indian doctors as he came through the gate. I said, "Why do we allow these wounded, paralyzed patients to stay outside the hospital and collect money by begging? Surely we should take them into the hospital and we could find the cause of their problems and operate to treat them!"

The Indian doctor smiled at me and said, "It's very obvious that you are new to this part of the world, and you don't realize that all these beggars are lepers and it is leprosy that has caused the paralysis and deformities and wounds that don't heal. Another thing you don't know is that if we allowed any of these leprosy patients to come into the hospital, all of the other patients would run away. In fact, many of the staff would leave the hospital rather than be required to be in close contact with these lepers. You won't find any general hospital in India that would ever admit a leprosy patient if they wanted to stay in business."

When I continued asking questions about leprosy and saying that we surely ought to be able to make a special ward where we could study the exact cause and correctability of the paralyses, the older doctor laughed at me and said that if I really wanted to examine leprosy patients, I would have to go to a leper colony. He said that many missions had set up crude centers where lepers could be fed and looked after. No other patients will go there. He went on to say, "But don't get any ideas about operating on these hands and feet. You can see from the wounds and the ulcers that lepers have non-healing flesh. If you try to operate you will simply make a new wound that also will never heal. Don't forget they have non-healing flesh."

I went on making inquiries from other doctors who were experienced in India and it soon became clear that there was no future in trying to study leprosy in our hospital at Vellore. I made inquiries and found there was a leprosy colony about eighty miles from us and it was run by a Scottish mission society. The doctor in charge, a Dr. Cochrane, had had many years of experience caring for lepers. So I made a habit of driving down to the leprosarium and talking to Dr. Cochrane who tried to teach me from his own experience all the main features of leprosy. Dr. Cochrane's background was dermatology and since many of the manifestations of leprosy involve swellings and wounds at the surface of the body, dermatology was a useful background to have.

There was no cure for leprosy in those days. There was a drug called Dapsone which was under trial and which seemed to be effective in arresting the progress of the disease, but in most cases the germ of leprosy, microbacterium leprae, soon became immune to Dapsone and would result in a recurrence of the disease.

One thing I learned from Dr. Cochrane was that superficial sensory nerves became paralyzed in leprosy and it resulted in the patient being unable to feel either light touch or pain. Dr. Cochrane also agreed that he wouldn't want to operate on a leprosy patient because he was afraid that the operation wound would not heal.

It was in that leprosarium that I began to study the pattern of paralysis and I learned that the most common muscles to become paralyzed were the intrinsic muscles of the hand, particularly those that were supplied by the ulnar nerve. Median nerve paralysis also occurred in the intrinsic muscles, especially those supplying the thumb. I found that the motor branches of the radial nerve were very rarely paralyzed and I found no cases of paralysis of the median nerve muscles in the forearm. They were very rarely paralyzed, whereas the ulna nerve muscles in the forearm were very frequently paralyzed.

Dr. Cochrane couldn't tell me why or in what way various muscles were paralyzed in leprosy, although he knew that the big muscles in the thigh and in the upper arm did not seem to suffer paralysis.

I was getting more and more fascinated by this strange disease and determined that somehow we would find a way to operate, using muscles that were not going to get paralyzed to replace those which were already paralyzed.

The one thing that I had to discover before starting to operate was to find out what was the cause of paralysis and why some nerves seemed so much more prone to be paralyzed, although surely the whole body had the same bacteria. Why did they cause paralysis to some

muscles and not to others?

It was obviously essential for me to get an autopsy of somebody who had suffered leprosy in a severe form and study all the nerves.

Here I had a problem. I couldn't have an autopsy at the medical college because there were no leprosy patients there, and in any case, it was very difficult to get permission for autopsy in India, where the average family demanded that they take their family member home to die, or at least within a few hours to take the body to be cremated or buried within 24 hours of death, because in that hot climate a dead body would rapidly decay and become offensive.

I communicated with several leprosy colonies and asked them to inform me quickly if they had a patient who was dying and who did not have an urgent family insistence about the disposal of the body. After quite a long time I finally got a message from a leprosy colony saying that a patient had just died and that the family wanted to take the body at about sunrise the next day, but in the meantime they had no objection to my performing an autopsy, so long as it was finished by about dawn.

I could get away from my work only in the evening and had problems finding the way. I took with me an assistant surgeon and a pathology technician with a box of little bottles of formalin so that we could take specimens from nerves or other tissues and keep them for histological study later.

It was after midnight when we finally found the leprosy colony and met the guard at the gate who knew we were coming and who had two hurricane lanterns. He said that he would take us to the hut where the body was lying and would leave one hurricane lantern with us and take the other one back with him. We hadn't expected to have a formal laboratory to work in, but we were a little shocked to find that we had to go through the leprosy colony and out the back gate and then walk a distance over sand dunes, almost to the beach. There we found a mud-walled hut with a thatched roof, no electricity and just a wooden table on which the corpse of this elderly, deformed patient was lying. The guard hung the hurricane lantern from the bamboo rafters overhead. It gave enough light so we could see to walk around the room, but it was of no help for a careful dissection. Fortunately, we had brought with us two pen-sized flashlights. We found that if we held the flashlights in our mouths we could do a dissection in the small circle of light that the flashlight illuminated. The guard left us there in this weird situation and pulled the heavy wooden door shut behind him, commenting that we should leave it shut, otherwise the jackals might come in, attracted by the smell.

My assistant doctor worked on the right hand side, exposing all the nerves in the right arm and the right leg, while I worked on the left-hand side, exposing the nerves in the left arm and the left leg. Starting at the shoulder I patiently exposed the median nerve, the radial nerve and the ulnar nerve. I kept the nerves in continuity, whereas my assistant on the other side cut across the nerves, taking specimens at different measured levels above and below the elbow and giving the specimens to our technician for preservation.

I shall never forget that strange, dark, isolated hut, nor shall I forget the details of the pathology as it appeared in the nerves during my dissection. Starting at the level of the shoulder and working my way down the ulner nerve I was able to follow little branches and twigs from the nerves and all the time the only light I had was a circle of about six to eight inches wide. The nerve looked quite normal to me as I worked my way from the axilla towards the elbow, and then gradually as I got nearer to the elbow, the nerve seemed to be swollen. Then as the nerve went behind the medial epicondyle of the humerus the nerve became very swollen and looked obviously diseased. When I dissected below the elbow, moving towards the wrist, the ulnar nerve suddenly began to change and by the time it was two or three centimeters below the elbow the nerve again seemed to be quite normal, neither swollen nor inflamed. It remained the same way until it was within a few centimeters of the wrist. There the nerve began to be swollen again and as it crossed the wrist and into the palm, each little nerve branch to the various fingers were swollen and appeared diseased.

Then I worked on the median nerve and again found that it seemed to be normal at the level of the axilla and then as it passed down to the elbow it remained normal. It was normal as it crossed the elbow and it was normal as we moved down the forearm until we got quite close to the wrist and now it began to be swollen and diseased and swollen again as it broke into the branches supplying the abductor pollicis brevis.

And so we went on, carefully, slowly, little by little. The room began to be uncomfortably stuffy and the body itself began to develop an offensive odor. We moved down to the legs and began to expose a normal looking sciatic nerve and femoral nerve. We saw some changes in the nerves around the knee and especially around the neck of the fibula and so as we approached the ankle some of the nerves became swollen and diseased and others seemed to be normal in appearance. But nothing that we saw gave us any clue as to <u>why</u> certain bits of nerves were swollen and certain bits of the same nerve looked normal. The same nerve might have an area of disease followed by an area that looked normal, followed by another area of disease, but…..WHY? We hoped that perhaps the histology would explain this to us.

Finally, after we had spent perhaps four or five hours on the careful, meticulous dissection and when the room was getting intolerably warm and stuffy, we began to see the light of sunrise around the cracks of the door. We looked at each other and said, "Now is the time to get a little bit of rest and then we can go back and sew up all the incisions." We felt as if we were largely defeated because we really had no way to tell why some parts of the nerves seemed to be diseased and other parts absolutely normal, but we couldn't stand to be in that room any longer. We pushed the room open and went out onto a sand dune and we looked out towards the sea and now the sunrise began to be bright and beautiful. The path of the sunrise light came across from the horizon as a bright, shining path across the sea to where we were.

We took great deep breaths of the fresh air of that dawn and we shook ourselves to get rid of the sense of confinement that we had been experiencing for so many hours in that hut. Then we turned back to the hut, having left the door wide open and we saw that the sunrise, now brilliant with light, was shining straight through the

door and onto the body and all its open incisions. The way the body was lying on the table exposed the whole of the left side to the sun's rays. To the right side, where all the specimens had been taken, was still mostly shade.

As I stood at the entrance to that hut and looked at all the nerves that I had been exposing and had previously only seen six inches at a time, I suddenly experienced the most amazing sensation of revelation. Now for the first time I could see the whole length of the nerves. It became amazingly clear that wherever a nerve came to lie close under the skin, it was always swollen, and where it came very close it looked diseased and totally abnormal. It was also clear that wherever any nerve was lying deep in the arm, and especially where it was lying under a muscle, it looked absolutely normal. Thus the ulna nerve, where it crossed the elbow behind the epicondyle, was obviously diseased and swollen, but moving further down the forearm the ulna nerve took a dive and lay deep to the flexor carpi radialis muscle and deep to some of the fibers of profundus - there it looked absolutely normal. Then towards the wrist, as the fibers of the flexor carpi ulnaris and the profundus thinned out and gave place to tendons, there the ulna nerve became closer to the skin and there again it began to be swollen. The twigs of nerve in the palm of the hand and at the side of each finger were all swollen and abnormal.

I cried out. I almost shouted, "We've got our answer!" Nerves near the skin are paralyzed, nerves deep to muscles are safe.

The median nerve did not come near the surface of the skin where it was crossing the elbow joint; it remained deep to upper arm muscles and to the origins of the flexor muscles for the wrist and fingers.

We went back into our little room and looked back at our dissections, seeing them for the first time as whole nerves, rather than little segments of nerves. We took photographs and then we quickly stitched up the incisions just about in time for the family to come and take the body away.

Back at the medical school I spent time in the library trying to find any other example of nerve paralysis that was dependant on depth under the skin.

I found an account from Australia where a similar mycobacterium, the m. ulcerans which affects cattle was found to grow in an incubator only if the temperature was set at about seven degrees Celsius below body temperature. They had been trying to grow the microbacterium but had failed. One day, some agar plates of mycobacterium ulcerans had been put into the incubator at ordinary body temperature, but by a mistake, the incubator was set at about thirty degrees Celsius. The next day they found the mycobacterium ulcerans had grown beautifully in the agar plate at the cooler temperature.

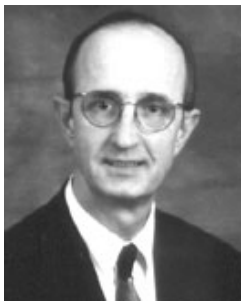
This completed our study because it was obvious that microbacterium leprae seems to thrive and do all its damage in tissues that are cool, and do not rise much above thirty degrees Celsius. Although it has still not proved possible to grow the microbacterium leprae, this must be due to some other factor, but it is true that in the body only those parts of the body that are below normal body temperature are damaged by leprosy.

We were very happy to identify this factor which had never been identified before, and which has proved to be an explanation for features that characterize leprosy but do not characterize most other mycobacterial diseases like tuberculosis. For example, tuberculosis can damage deep bones and joints and causes tuberculomas in the brain, as well as skin, whereas leprosy never grows deep in the body or brain. Leprosy affects the eyes, but only in the cornea and anterior chamber, which are cool, and never affects the retina which is much warmer.

We were able to map the arms and legs for surgical purposes, knowing that deeply placed nerves supply muscles which do not ever become paralyzed and which can be used for tendon transfer, whereas nerves which are superficial supply muscles which are very liable to become paralyzed and are therefore not appropriate to be used for tendon transfers.

I don't know how long it would have taken us to work out the pattern of paralysis in leprosy or the relationship of m. leprae to temperature, if it had not been for that exciting moment when the SUNRISE illuminated so effectively and so much more efficiently than a whole five hours of flashlight images that never allowed us to see all the nerves in continuity.

UW Medicine Hand Institute



(Top to Bottom) Drs. Trumble, Hanel, Allan, Vedder, and Muzaffar.

Dear Colleagues,

The hand surgery faculty in the Department of Orthopaedic Surgery and Sports Medicine and the Division of Plastic Surgery in the Department of Surgery are pleased to announce that Paul Ramsey, M.D., Dean of University of Washington School of Medicine, approved our application for a Hand Surgery Institute on May 7, 2003. The Hand Surgery Institute formalizes the incredible cooperation between Orthopaedic Surgery and Plastic Surgery. We have four faculty in Orthopaedic Surgery:

Thomas Trumble, M.D.
Douglas Hanel, M.D.
Christopher Allan, M.D.
John Sack, M.D.

And two faculty in Plastic Surgery:

Nicholas Vedder, M.D.
Arshad Muzaffar, M.D.

They provide 24 hour on call coverage for University of Washington Medical Center, Harborview Medical Center, Children's Hospital Medical Center and the Veterans Administration Medical Center. Our hand team is the only group available to manage severe amputation and limb threatening injuries for the five state region of Washington, Montana, Alaska, and Idaho and Wyoming on a full time basis. We perform care for nearly all the major hand and upper extremity injuries in this five state region.

Together we administer an accredited hand fellowship, and we train three fellows in hand surgery every year who have their primary boards in either plastic or orthopaedic surgery. The fellows are selected through the National Resident Matching Program. During our last accreditation review this spring we won top honors for our academic program. We also provide the clinical and didactic education for both the orthopaedic and plastic surgery residents. In addition to the clinical program, our residents and fellows take part in clinical, biomechanical, and microsurgery research programs as you can tell from this research report.

As a cooperative effort we manage hand surgery clinics at all four medical centers in the University of Washington as well as an office in Bellevue at the Eastside Specialty Center. Our distinguished team includes three full professors with numerous grants and awards for research. Because of our clinical productivity, the University of Washington Medical Center has sponsored a hand surgery center in the Roosevelt II building complete with dedicated out patient operating rooms, clinic and office space, hand therapy, advanced diagnostic imaging with magnetic resonance imaging, computerized tomography and arthrography. Our combined clinical productivity has resulted in over 10,000 office visits per year and nearly 4,000 surgeries. As the first full time hand surgeon at the University of Washington, I look on in wonder and awe at the tremendous growth of our hand team that the formation of the Hand Institute celebrates. The timing of this research report highlighting the hand surgery service is another brilliant bit of planning by our Chairman in Orthopaedic Surgery, Frederick A. Matsen III, M.D. He is also the chairman with the vision to recruit full time hand surgery faculty and crystallize the the role of hand surgery at the University of Washington.

Sincerely,

Thomas Trumble

Thomas Trumble, M.D.

Visiting Lecturers

John J. Callaghan, M.D.

This year at our annual LeCocq Lecture on January 23rd and 24th, we were honored to have Dr. John J. Callaghan as our 2003 LeCocq Lecturer. Dr. Callaghan is a Professor of Orthopedic Surgery at the University of Iowa and is the Lawrence and Marilyn Dorr Chair in Hip Reconstruction and Research. He is active in a number of professional societies and is currently serving as the Chairman of the Anatomy and Imaging Committee for the American Academy of Orthopaedic Surgeons and Program Chairman for the Association of Arthritic Hip and Knee Surgery. He also serves as an Associate Editor for the Journal of Bone and Joint Surgery and the Journal of Arthroplasty as well as a consultant reviewer for the Journal of Biomechanics, American Journal of Sports Medicine, and Clinical Orthopaedics and Related Research. Dr. Callaghan is well known for his expertise in knee and hip joint reconstruction. His publications, awards, and grants in this area are numerous. The faculty, residents, and community physicians were treated to 3 innovating lectures from Dr. Callaghan during the 2 days: "Choices and Compromises in Hip and Knee Surgery," "Why Did We Leave Charnley Total Hip Replacement?," and "Mobile Bearing Knee Replacement: Are We Going Forward, Backwards, or Sideways?"

Joshua J. Jacobs, M.D.

This year at our annual Residents' Research Days on May 29th and 30th, we were honored to have Dr. Joshua J. Jacobs as our OREF Hark Lecturer. Dr. Jacobs is the Crown Family Professor and Associate Chairman for Academic Programs in the Department of Orthopaedic Surgery at Rush Medical Center, Chicago. He also serves as the Director of the Section of Biomaterials and the Director of the Orthopaedic Residency Program. He is active in a number of professional societies and is currently a member of the Hip Society and is Chairman of the Council on Research and Scientific Affairs of the American Academy of Orthopaedic Surgeons. Dr. Jacobs is well known for his expertise in the field of Biomaterials. His major research focus is on the biocompatibility of permanent orthopaedic implants, particularly joint replacement devices. During the 2 days of lectures, the faculty, residents, and community physicians were treated to 3 lectures from Dr. Jacobs: "The Basic Science of Periprosthetic Osteolysis," "Systemic Implications of Total Joint Replacement," and "Corrosion of Metallic Orthopaedic Implants." In addition to Dr. Jacobs' lectures, the R3s and the R4s presented the progress of their research, while the R5s presented the completion of their research projects.

Back Pain in Former Intercollegiate Rowers: A Long-Term Follow-Up Study

CAROL C. TEITZ, M.D., JOHN W. O'KANE, M.D., AND BONNIE K. LIND, M.S.

In a previous analysis, we found that the prevalence of back pain during intercollegiate rowing was 32 percent. When college rowers develop back pain, often they and their parents ask, "Is this back pain likely to be a life-long problem?" The current outcome analysis was undertaken to answer this question by determining whether the back pain associated with intercollegiate rowing resolves or persists, the variables that might predict resolution or persistence, and the severity of current back pain. In addition, the lifetime prevalence of back pain in rowers who had no back pain during college was compared to that in the general population.

Meta-analyses of back pain in the general population report lifetime prevalence rates ranging widely from 11-84% and point prevalence rates from 5.6 to 33 %. The inclusion criteria for "lifetime" back pain in these studies varies from "have you ever had low back pain" to "have you ever had low back pain daily for at least 2 weeks?" Waxman et al completed a two-phase population-based questionnaire study of low back pain over a 3-year period. Fifty-nine percent of 1455 adults aged 25-64 had experienced at least one episode of low back pain that lasted more than one day. The likelihood of having pain increased significantly with age. Hellsing and Bryngelsson studied 6626 men nearly 40 years of age who had been examined for the first time at the age of 18 during examinations for military service. The prevalence of low back pain increased from 38% to 74% during the 20-year period. A significantly increased risk for frequent pain problems at follow-up exam was found in those subjects whose earlier back pain had caused absence from work or reduced activity levels.

METHODS

Surveys were sent to 4680 former intercollegiate rowing athletes who had graduated between 1978 and 1998 from 5 schools with strong rowing programs. 2165 surveys were returned (46%). Resolution or persistence of back pain was examined in three different ways. Subjects were asked whether they had ever had back pain since college ("any"), if so, whether it had been continuous since college, and regardless of whether or not it had been continuous, whether they had back pain at the time of completing the survey ("current"). In addition, we examined the association of continuing to row after college with current back pain. To determine the potential effect of the severity of college back pain on subsequent back pain, we analyzed the prevalence of any, continuous, and current back pain in relation to time loss from college rowing and ending the collegiate rowing career. To assess the severity of back pain subsequent to college, we asked the subjects to rate their current pain and the worst pain they had had on a scale of 1-10 with 1 being hardly noticeable. We also asked whether work had been missed because of back pain. For comparisons to previous back-pain literature, we considered a positive response to the question "Subsequent to college, have you ever had back pain lasting more than one week?" as "lifetime prevalence." We consider current back pain as "point prevalence."

Picture 1: Intercollegiate rowers.

RESULTS

Resolution or persistence

790 of 1561 subjects (51.4%) answered that they had back pain lasting at least one week at some point since college (lifetime prevalence). The time from college graduation to completion of the survey ranged from 0-20 years with a mean and median of 13 years. Subsequent back pain was twice as likely in subjects who had back pain in college than in those who had not had back pain during college (78.9% vs. 37.9%). 479 subjects (32.4%) had back pain at the time of completing the survey (point prevalence). Those who had back pain in college were almost three times as likely to have current back pain as those who had not had back pain during college (57.7% vs. 20.2%). Ninety-eight subjects reported back pain that had been continuous since college (19.8%). Of 1561 subjects, 662 were female and 897 were male. (Two subjects did not report their sex). Sex was not a significant predictive variable for the persistence of back pain by any of the three measures. Among rowers who had back pain in college, age was a significant variable only in the lifetime

prevalence of back pain (p=0.01). Among rowers who were asymptomatic in college, age was significantly associated with prevalence of current pain as well as with the lifetime prevalence of back pain (p<0.001) (Figure 1).

Predictive variables

502 subjects reported that they were still rowing at the time of the survey. Based on whether or not they had pain in college, there was no significant difference between the proportions of subjects who continued to row. 337 of 1046 subjects with no back pain during college rowing were still rowing (32.2%) and 165 of 515 subjects with college back pain (32%) were still rowing. Current pain was noted in 32.1% of those still rowing and in 32.5% of those who were no longer rowing. There was also no association between the current prevalence of back pain and the intensity of after-college rowing (defined as competitive, recreational, or sporadic)(p=0.4).

Subjects who missed more than one week of practice or competition while in college were more likely to have subsequent and current back pain than those with less time loss (p<0.01). Rowers who ended their college rowing careers because of back pain were more likely to have subsequent episodic, continuous, and current back pain (p<0.002) (Figure 2).

Severity of post-college back pain

The mean severity rating for all rowers whether or not they had pain in college was 3.5±1.9. Those with college pain reported a similar average severity of their current pain to those with no college pain (3.6 vs. 3.5, p = 0.55). The mean severity rating of worst back pain since college for all rowers whether or not they had pain in college was 6.4±2.2. Those with college pain reported a significantly higher average rating of their worst pain than those with no college pain (6.9 vs. 6.3, p < 0.002).

Of 790 subjects reporting back pain since college, 195 (26.2%) reported missing work because of back pain. The percentage of subjects missing work due to back pain was not related to the presence or absence of college back pain (26.1% vs. 26.4%). Among those who missed work because of back pain, those with physical jobs were no more likely to miss work than those with sedentary jobs (65.8% vs. 67%).

Discussion

Bending and rotating the spine increases the risk of low back pain. Although rowing involves similar motions, the lifetime prevalence rates of low back pain in former rowers are not significantly different from those in the general population. Rowers who develop back pain in college have more subsequent back pain than rowers who did not have back pain in college (78.9% vs. 37.9%) confirming Biering-Sorensen's finding that a previous episode of low back pain is a strong predictor of future episodes. Nevertheless, even in rowers who had back pain in college, this lifetime prevalence rate is similar to rates of 74% reported by Hellsing and Bryngelsson in their subjects who had back pain as 18 year olds. Moreover, only 51% of all rowers had ever had back pain since college, similar to the 59% lifetime prevalence rate noted in subjects of

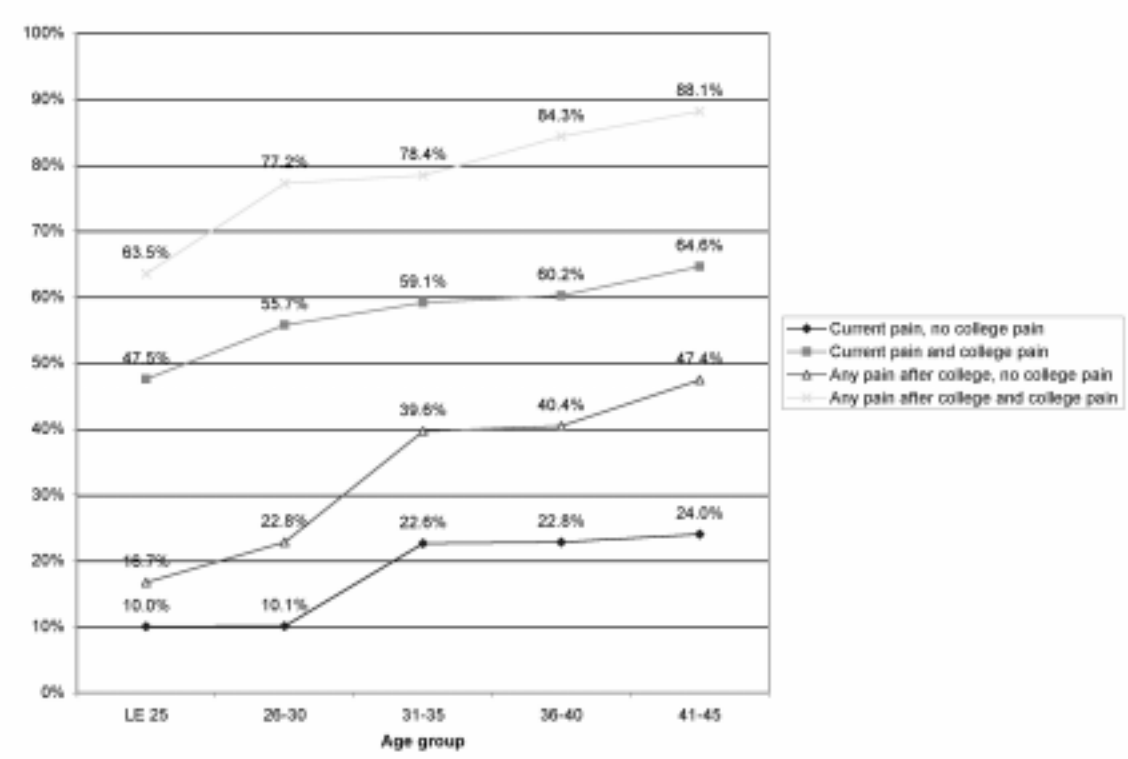


Figure 1: Lifetime and point prevalence of back pain as a function of age.

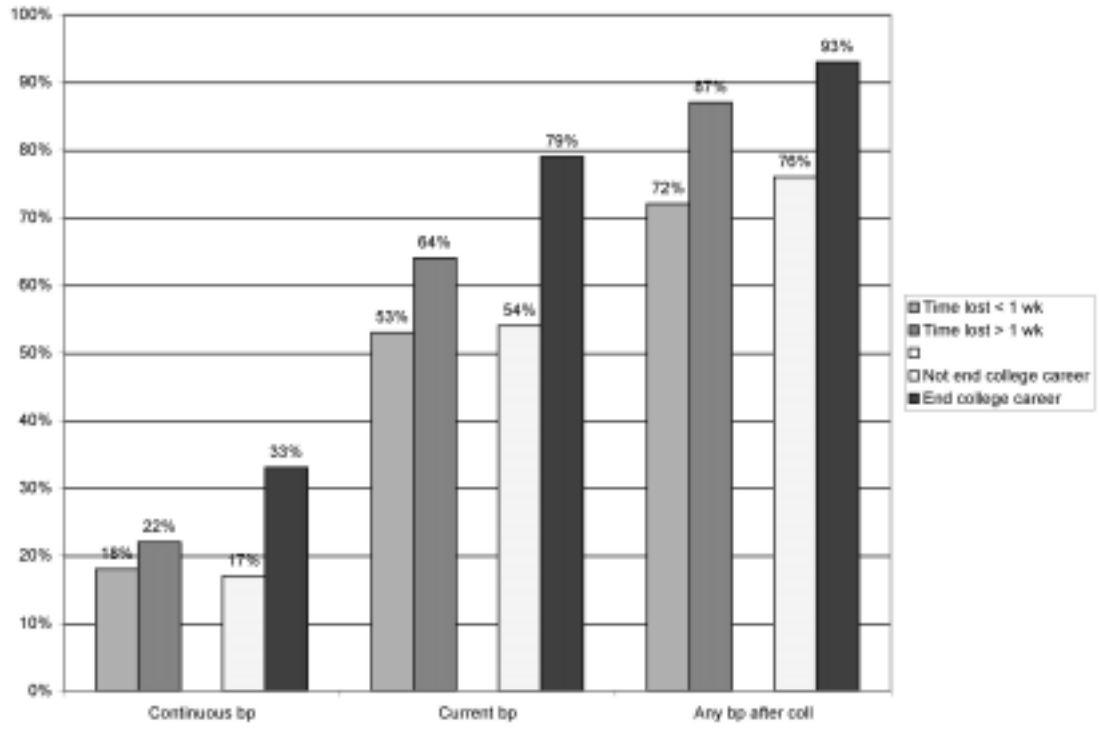


Figure 2: Prevalence of subsequent back pain as a function of time loss in college.

similar ages in two other population-based studies and in the range of the oft quoted 60-80% of the general population that will experience one episode of acute back pain at some point in life. When looked at by decade, the higher lifetime prevalence of back pain in older rowers is likely due to the older rowers having more "exposure" time to develop back pain than the younger rowers. This correlation of age and lifetime prevalence of back pain was also found in other studies. Furthermore, the increase in back pain prevalence in our subjects from 32% at college age to 84.3% at age 40 is similar to that in Hellsing and Bryngelsson's study of subjects at age 18 (38%) and 40(74%).

Continuous back pain has not been reported previously. Therefore, we cannot compare findings in other studies with the prevalence of continuous back pain in our subjects who began having back pain in college.

Our point prevalence rate of 32.4% is at the upper end of the prevalence range previously reported (12-33%). This relatively high prevalence rate may represent a bias on the part of respondents in that rowers with back pain at the time the survey instrument arrived might be more likely to participate in our study. Nevertheless, if this bias exists in our study, then the lifetime prevalence rates noted above would be potentially even lower than those in the general population.

An additional factor that might contribute to our relatively high point prevalence rate is continuing to row subsequent to college. Based on our previous study, we expect at least a 32% prevalence of low back pain in actively competitive rowers. Although the current rowers are not all rowing competitively, they have the additional risk factor of age. Nevertheless, the overall prevalence of back pain in our subjects who are still rowing is 32.1%, essentially unchanged from the prevalence of back pain during college rowing.

Rowers with greater time loss from college rowing and those ending their college rowing careers because of back pain had a higher likelihood of subsequent back pain than rowers with less time loss who were able to continue rowing in college.

The mean severity of current back pain in our subjects was 3.5±1.9 on a scale of 1-10 with 1 being hardly noticeable. Hillman et al reported a mean severity score of 6.24. They also noted that 26.5% of their subjects reported pain in the mild (grade 1-4) category, 40.8% in the moderate (grade 5-7) category, and 32.6% in the severe category (grade 8-10). Our subjects with current pain compare favorably. 75.6% report mild, 19% moderate, and only 5.4% severe pain. Twenty six percent of our subjects missed work because of back pain. This rate is similar to the 22.5% found by Biering-Sorensen in a general population and the 26% found in the 15 highest-risk major industries by Guo et al. In our study, among those who missed work because of back pain, those with physical jobs were no more likely to miss work than those with sedentary jobs.

Conclusion

Rowers who develop back pain during competitive college rowing are no more likely than the general population to have episodic back pain

subsequent to college or to miss work because of back pain. Also they report less severe pain than subjects in previous population-based studies. Moreover, rowers who do not develop back pain in college have significantly lower rates of back pain as they age than the general population. If one can complete a college rowing career without back pain, one's prognosis for back pain later in life is better than that in the general population.

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Acknowledgements

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Corticosteroid Versus Synvisc (Hylan GF-20) Injections for Knee Osteoarthritis: A Prospective, Randomized Trial, and Results of a Retrospective Study Evaluating Adverse Reactions to Repeated Courses of Synvisc

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Both corticosteroid and hyaluronic acid injections are widely used to palliate the symptoms of knee osteoarthritis; however, little research has been done that compares the two interventions. The present report tests the hypothesis that there are no significant differences between hylan GF-20 (Synvisc) and the corticosteroid betamethasone sodium phosphate / betamethasone acetate (Celestone-Soluspan, admixed with lidocaine and marcaine) in terms of pain relief or improvement in function, as determined by validated scoring instruments.

This report also summarizes the results of a separate retrospective study that used a contemporaneous control group to evaluate the likelihood of painful adverse reactions to repeated courses of Synvisc compared to patients treated with a single course of that product.

METHODS

The prospective trial enrolled 100 patients with knee osteoarthritis (Table 1), who were randomized to receive either intra-articular Synvisc or Celestone-Soluspan (CS), and who were followed for six months. Patients with end-stage ("bone-on-bone") arthrosis visible on weight-bearing radiographs (Figure 1) were excluded from the study, as prior work has shown Synvisc to be much less effective in this patient population. Synvisc patients received one course of 3 weekly injections. CS patients received one injection at study enrollment, and could request one more injection any time during the study. An independent, blinded evaluator assessed patients with the WOMAC index, the Modified Knee Society Score (KSS), and the visual-analog pain scale (VAS).

The retrospective study on repeated treatments with Synvisc involved auditing the records of all patients at the study site who received more than one course of treatment with hylan GF-20 (N=19 patients), and comparing the number of painful local reactions they experienced to that of a group of patients who received only one course of treatment during the same 15-

Treatment	Age (years)	Weight (lbs.)	BMI*	Gender (% female)	NSAID Use (% using)
Corticosteroid N=50 patients	64 (40-83)	86 (40-143)	29.3 (17-58)	56	56
Synvisc N=50 patients	66 (39-79)	86 (48-141)	28.8 (21-51)	52	64
p-value	0.97	0.96	0.82	0.69	0.41

Table 1: Prospective study: Baseline demographic and clinical parameters. Values presented as median (range) except where noted. *BMI=Body Mass Index.

	Single-Course Group N=42	Multiple-Course Group N=19	p-value
Mean Age, years (range)	64.4 (range, 39-79)	61.0 (range, 38-77)	0.13
Gender	21 female (50%)	12 female (63.2%)	0.34
Severe DJD	15 (35.7%)	6 (31.6%)	0.75
Mean BMI (range)	30.9 (range, 21.2-51.0)	30.9 (range, 23.0-41.1)	0.73
Bilateral Injections	15 (35.7%)	6 (31.6%)	0.75

Table 2: Retrospective study: Baseline demographics and clinical parameters.

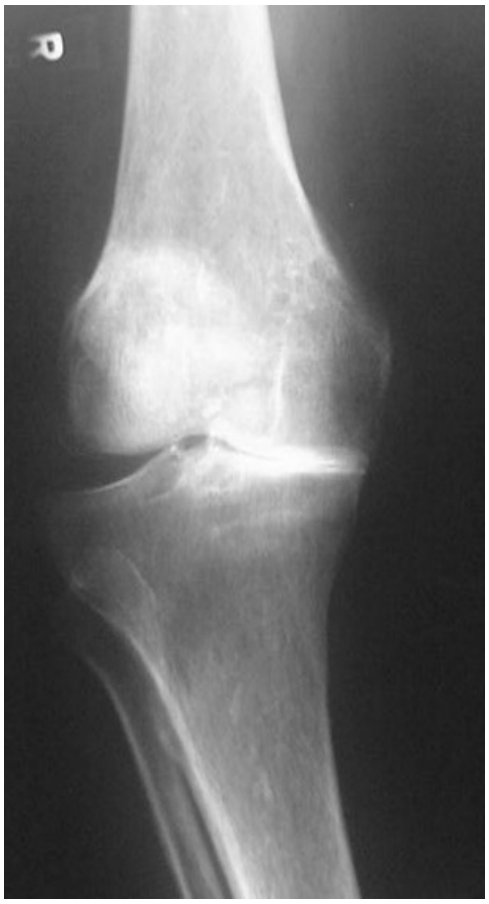

Figure 1: Anteroposterior (AP) radiograph of a knee, obtained with weight bearing, which demonstrates end-stage ("bone-on-bone") arthrosis of the medial compartment. Such patients were excluded from the present report, as prior work has found Synvisc to be much less effective in the presence of disease of this severity.

month period at the same center (N=42 patients, Table 2). An acute local reaction to hylan GF-20 was defined as acute onset of pain and swelling in the knee, that occurred in temporal proximity (within 72 hours) of a hylan GF-20 injection, in the absence of another cause such as acute trauma. Painless effusions that were noted on routine follow-up were not considered to be adverse reactions. In all cases, the acute local reactions were rather severe and not difficult to distinguish from patients' typical arthritic effusions and baseline arthritic pain levels. All patients noted severe pain and limitation of activity, and all underwent aspiration and corticosteroid injection with prompt amelioration of symptoms. The single-course group was prospectively enrolled and followed, as part of the prospective randomized trial mentioned above. The two groups were compared with respect to several demographic and clinical parameters, in order to make certain that no factors other than the additional course(s) of Synvisc could account for any observed differences in the rates of painful local reactions.

All injections in both studies were performed using the identical superolateral injection technique by the same two fellowship-trained orthopaedic knee surgeons. All patients who received intra-articular corticosteroid injections were documented to have had immediate relief of symptoms, which tended to validate the efficacy of those investigators' needle placement. All patient evaluations in both studies were performed by the same trained study nurse, without the involvement of the treating surgeons.

Results

In the prospective, randomized trial, both CS and Synvisc patients demonstrated improvements from baseline WOMAC scores (55 to 40 points, $p<0.01$; and 54 to 44 points, $p<0.01$, respectively). Scores on the KSS did not show statistically significant improvement for CS patients or Synvisc patients (58 to 70 points, $p=0.06$; and 58 to 68, $p=0.15$, respectively). VAS scores improved for Synvisc patients, but not for CS patients (70 to 52 mm, $p<0.01$; vs. 64 to 52 mm, $p=0.28$). However, there were no significant differences in WOMAC, KSS, or VAS results between the two treatment groups, despite 80 percent power to detect clinically relevant differences (Table 3). Women demonstrated a statistically significant improvement in only one of the six possible outcomes/treatment combinations (the WOMAC scale for female Synvisc patients), while men demonstrated significant improvements in five of six (all measures except the KSS for male Synvisc patients). The gender-related differences could not be explained by differences in age or disease severity.

Painful local reactions to hylan GF-20 occurred significantly more often in patients who had received more than one course of treatment (4 of 19 patients, 21.1 percent), than in patients who received only a single course of treatment (one of 42 patients, 2.4 percent; $p=0.029$). All of the reactions were severe enough to cause the patient to seek care on an unscheduled basis. Following corticosteroid injection, the reaction abated without apparent sequelae. With the numbers available, no significant differences were detected between the multiple-course and single-course groups in terms of age, gender, body-mass index, disease severity or bilaterality of disease (Table 4).

Conclusions

The prospective randomized trial detected no differences in pain or function between intra-articular injections with Synvisc or CS at six months' follow-up. The difference in pharmacy cost between the two treatments is over 100-fold, with a corticosteroid injection costing about $5, and a course of Synvisc costing nearly $600. To our knowledge, this is the first trial to compare CS and any viscosupplement that was not funded by the manufacturer of the hyaluronic

Treatment	Time Point	WOMAC	KSS	VAS
Corticosteroid	Before treatment	55	58	64
	3 months	42	72	52
	6 months	40	70	52
p-value*		<0.01*	0.06	0.28
Synvisc	Before treatment	54	58	70
	3 months	41	69	45
	6 months	44	68	52
p-value*		<0.01*	0.15	<0.01*

Table 3: Prospective study: Changes in median outcomes scores over time. *p-values refer to changes over time within each treatment group, based on the Friedman Test; p-values <0.05 were considered statistically significant. N.B. No significant differences were detected between treatment groups by any of the three outcomes instruments at either follow-up interval, using the Mann-Whitney test (p=0.29-0.61 at 3 months and p=0.69-0.98 at 6 months).

acid product in question. This study is also the largest prospective randomized trial comparing any hyaluronic acid product to any corticosteroid, the first study of this type to use validated disease-specific outcomes instruments such as the WOMAC index or the KSS, and the first comparative trial to evaluate Synvisc, the most widely used intra-articular hyaluronic acid product in the United States, against a corticosteroid. Women demonstrated significantly less response to treatment than did men for both CS and Synvisc on all three outcome scales. Such significant gender-related differences warrant further investigation.

Results from the retrospective study suggest it may be reasonable to counsel patients who have been treated with a course of hylan GF-20, and who desire an additional course of treatment, that the likelihood of a painful acute local reaction to the medication appears to be increased.

Given the additional pain and potential risk associated with the three-injection course of Synvisc, and given the approximately 100-fold difference in pharmacy cost at our institution, the authors do not consider Synvisc a first-line treatment for OA patients considering intra-articular knee injections for palliation of symptoms. Further study of the frequency of acute local reactions following repeated courses of hylan GF-20, and inquiry into the mechanisms of those reactions, are warranted.

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	Severe DJD	Gender	Bilateral Injections	Age	BMI	Time to reaction
Severe-Course Group (1 of 42 patients*)						
Patient 1	No	M	Yes (reaction unilateral)	49	26.2	<6 hours of 1st injection
Multiple-Course Group (4 of 19 patients*)						
Patient 1	Yes	M	Yes (reaction unilateral)	62	24.4	<6 hours of 1st injection, 3rd course
Patient 2	Yes	F	No	58	37.2	<24 hours of 1st injection, 2nd course
Patient 3	No	F	No**	52	23.0	36 hours after 2nd injection, 2nd course
Patient 4	No	F	No**	60	25.7	<24 hours of 3rd injection, 2nd course

Table 4: Retrospective study: Characteristics of patients with acute local reactions. *Frequency of reaction: 2.4% (single-course group) versus 21.1% (multiple-course group); p=0.029. **Patient had bilateral injections done at the first course of treatment, and unilateral injections done at the second course of treatment.

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The Association Between Smoking and Nonunion of Long Bone Fractures

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Failure of fracture union is an uncommon occurrence. The diagnosis is made primarily by clinical and radiographic assessments. Delayed union suggests a slowed pace of fracture repair outside that which is expected for the injury. Nonunion represents complete absence of progression of healing that is predicted to persist indefinitely. The designation of delayed or nonunion is not based on absolute time criteria, but represents a time continuum individualized for each patient's injury. Increased local fracture comminution and instability, bone loss, soft tissue disruption, and/or open wounds characterize high-energy fractures. These features, among other variables, are particularly associated with altered fracture healing.

The detrimental effect of cigarette smoking on fracture repair is controversial, and the relative risk of subsequent fracture delayed or nonunion is unknown. Clinically, increased rates of pseudarthrosis after spinal fusions, and an increased time to union after fracture of the tibia have been reported. Recently, however, authors have been unable to demonstrate an association between smoking and fracture union. The purpose of this report is to define the risk of altered long bone fracture healing requiring operative intervention in tobacco smokers.

MATERIALS AND METHODS

A retrospective case-control study design was employed using a trauma database at an urban level-1 University trauma center. Patients were excluded if they were skeletally immature, had insufficient follow-up, or had their initial fracture stabilization performed at an outside institution. Between 1995 and 2000 inclusive, 197 operatively managed long bone delayed and nonunions were identified. Over the same time period, 197 control patients with healed long bone fractures were identified. The cases and controls were matched on age (within 5 years), and fracture pattern using the AO/OTA Fracture Classification System. Patient records were reviewed to obtain demographic data, fracture specific data, and associated injuries. Cigarette smoking behavior was obtained from the hospital and trauma registries, and from a review of emergency room, social work, clinic, and hospital discharge reports. Patients were categorized either as smokers or nonsmokers and no attempt was made to quantify the amount or numbers of cigarettes smoked over any time interval. The Injury Severity Score (ISS) is a validated measure of the degree of systemic injury. Each patient's ISS was recorded and used as a surrogate for the magnitude of associated polytrauma. Open fractures were defined as those fractures that communicated with an open wound to the outside environment.

Statistical analysis consisted of performing an overall odds ratio to estimate the relative risk of fracture nonunion in smokers versus nonsmokers. The presence of polytrauma, and open fractures are independently known to be potential confounding factors. Comparison of ISS between cases and controls was performed using the t-test. The rate of occurrence of open fractures between cases and controls was assessed using the Chi-square test. Stratum-specific odds ratios were obtained for cases and controls with open fractures, and an adjusted odds ratio using the Mantel-Haenszel method was then performed.

RESULTS

One hundred and ninety-seven long bone delayed/nonunion fracture cases were identified and consisted of 2 clavicles, 19 humerii, 17 radii/ulnae, 61 femurs, and 98 tibias. Cases were then matched by age and the AO/OTA Fracture Classification to 197 healed control fractures. The total study population, therefore, consisted of 394 total fractures. The mean age of the entire group was 38.3 years.

The mean ISS for the cases and controls was 14.2 and 13.8, respectively ($p=0.6327$). One hundred and three open fractures occurred in the cases (52.3%) as compared with 69 open fractures (35.0%) in the control group. This difference was statistically significant using the Chi-square test ($p=0.001$).

Ninety-nine of 197 cases versus 74 of 197 controls were identified as smokers. Calculation of the overall odds ratio demonstrated that smokers were 70% more likely to develop a delayed/nonunion than nonsmokers (OR, 1.7; 95% CI=1.12-2.51). Because a statistically significant number of cases had sustained open fractures as compared to the control group, stratum-specific odds ratios were performed for cases and controls according to the presence or absence of an open fracture. The evaluation of only closed fractures established that smokers were 96% more likely to develop a delayed/nonunion than nonsmokers (OR, 1.96; 95% CI=1.14-3.37). However, no statistically significant increased risk of delayed/nonunion could be shown in smokers versus nonsmokers with open fractures (OR, 1.41; 95% CI=0.76-2.62), suggesting that this variable was not a significant confounder. The Mantl-Haenszel adjusted odds ratio accounting for the presence of an open fracture confirmed a 70% increased likelihood of delayed/nonunion in smokers as compared to nonsmokers (OR, 1.7; 95% CI=1.13-2.55).

DISCUSSION

The impact of cigarette smoking on surgical procedures on the spine have been well documented and include a negative clinical impact in terms of outcomes, union rates, and clinical recovery after both cervical and lumbar arthrodesis procedures.

The effect of smoking on fracture union has been controversial, and conflicting reports have been published. Recently, Adams et al., compared 140

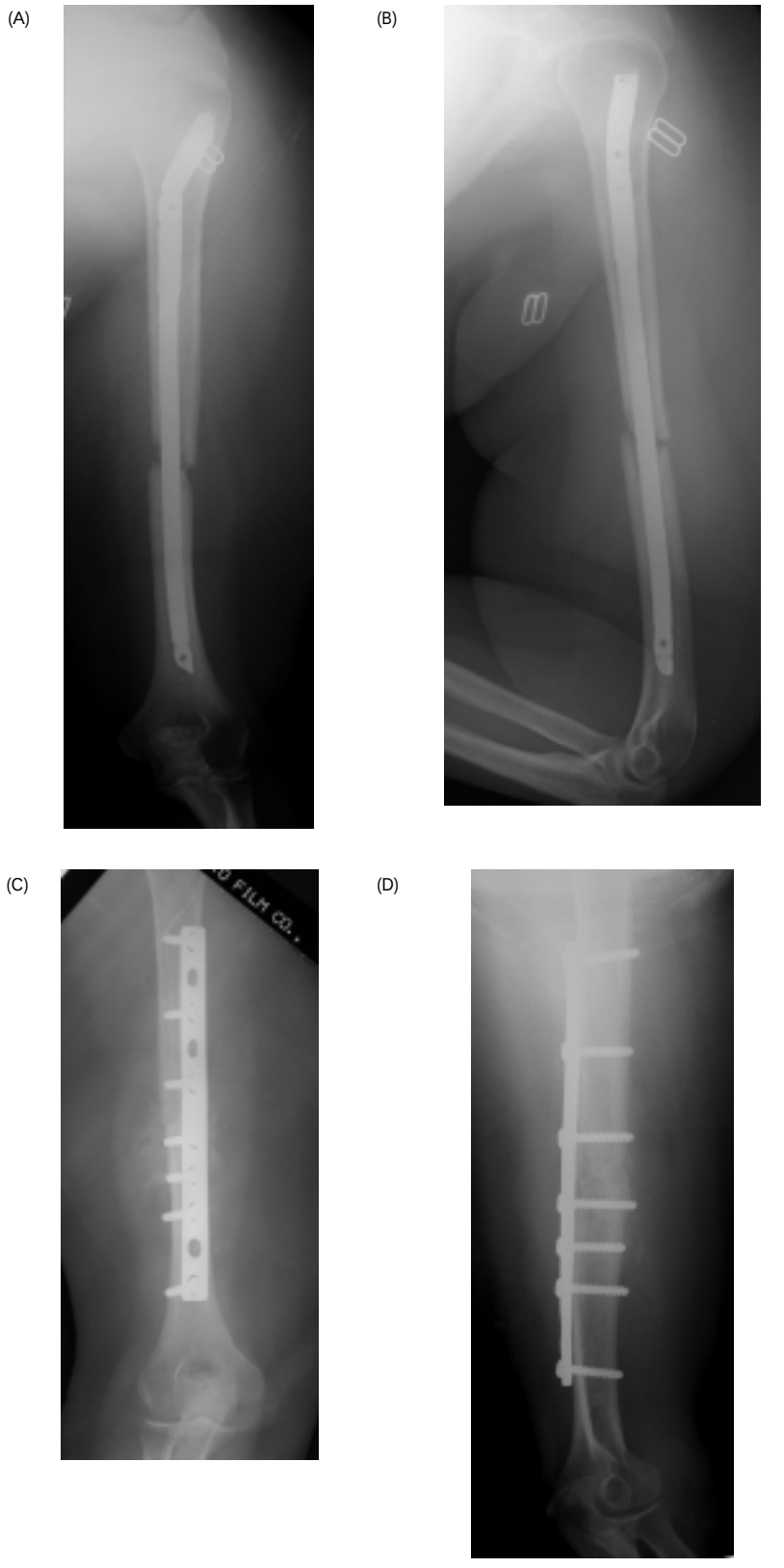

Figure 1: A and B: Five months post medullary nailing, these anteroposterior and lateral images demonstrate an atrophic nonunion of a mid-diaphyseal humeral shaft fracture. C and D: Treatment consisted of removal of the previously placed medullary implant, plate fixation, autograft bone grafting, and smoking cessation measures.

smokers with 133 nonsmokers with open tibia fractures. Despite the increased rates of flap failure and surgical procedures for nonunion in smokers, they were unable to establish a relationship between smoking and nonunion with statistical significance. Giannoudis was also unable to demonstrate an association between union rates and smoking in a comparison of 32 femoral diaphyseal nonunions and 67 healed control patients.

The goal of the present study was to determine the relative risk of long bone fracture delayed and nonunion in smokers as compared to nonsmokers. A retrospective case-control methodology was employed, with cases and controls matched by age and fracture pattern using the AO/OTA Fracture Classification System. This alpha-numeric radiographic fracture classification system is the standard system supported in the orthopaedic literature and codes each fracture according to a consistent segment within each bone. Each patient's fracture can then be subtyped and grouped according to the degree of comminution and orientation of major fracture planes. Thus, this classification system not only allows for the consistent direct grouping of fractures based on their radiographic appearance, but also indirectly pools fractures according to the injurious mechanism, severity, and prognosis. Matching of fracture types based on this classification was performed to eliminate discordant fracture patterns with dissimilar union rates. The definition of delayed union or nonunion was at the attending surgeon's discretion. We chose, however, to include only those patients with delayed/nonunion that were managed *operatively* as the endpoint for selecting cases. We felt that this most consistently defined the presence of the condition being examined, and similarly, identified those cases that were felt to have clinical relevance. Because our institution is a referral center for acute injuries and complex post-traumatic reconstructive problems, cases and controls were required to have had their initial and definitive acute fracture stabilizations performed at our institution to minimize bias related to their initial care.

Our data suggests that cigarette smokers are 70% more likely to have an acute long bone fracture result in delayed/nonunion as compared to nonsmokers. A statistically significant rate of open fractures was found in the cases as compared to the controls. Because the presence of an open fracture is an independent risk factor for delayed/nonunion, stratum-specific odds ratios were performed. This demonstrated that smokers with closed fractures were 96% more likely to proceed to delayed/nonunion than nonsmokers with closed fractures. An increased risk of delayed/nonunion in smokers with open fractures, however, was not demonstrated (OR, 1.41; 95% CI=0.76-2.62), suggesting that smoking and open injuries may not have a cumulative effect. Given that the presence of an open fracture was not a confounding variable, the Mantel-Haenszel adjusted odds ratio (OR, 1.7; 95% CI=1.13-2.55), is similar to the overall odds ratio.

This study has demonstrated a near two-fold risk of delayed/nonunion of acute closed long bone fractures in patients who smoke. Smoking should be considered a substantial biologic risk factor for altered fracture healing and patients should be counseled as such. The dose-response relationship, and the effect of smoking cessation in the acutely injured scenario are areas for further research.

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The Value of the Ankle-Brachial Index for Diagnosing Arterial Injury Following Knee Dislocation: A Prospective Study

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Vascular injury associated with knee dislocation is a common and potentially limb threatening complication. A greater than eight-hour delay in revascularization can lead to above knee amputation. Controversy remains as to the optimal method of diagnosing possible vascular injury. While routine arteriography has long been advocated, recently some authors have questioned the need to perform arteriography on all patients. These authors suggest that 'hard' findings on physical examination (active hemorrhage, expanding hematoma, absent pulse, distal ischemia or bruit) are effective evidence for identifying arterial injury. They criticize routine arteriography for the delay it causes in revascularization, its potential complications and for its high cost.

Critics of physical examination alone cite the potential for missed diagnosis leading to devastating vascular compromise. A recent meta-analysis of the accuracy of the pulse examination in patients with knee dislocation concluded that an abnormal pedal pulse is not sensitive enough to detect a surgical vascular injury, and these authors recommended the "liberal use of angiography".

At Harborview Medical Center, our urban level-1 trauma center, the Ankle-Brachial Index (ABI) has long been used to diagnose or rule out arterial injury in both blunt and penetrating extremity trauma. However, no published series has described the efficacy of the ABI in a pure population of patients with knee dislocation.

We present a consecutive series of patients with knee dislocation evaluated by both ABI and physical examination to assess the reliability of these methods for identifying arterial injury.

MATERIALS AND METHODS

Fifty-one patients ranging in age from 15 to 74 years with 52 knee dislocations admitted to Harborview Medical Center over a 40-month period (October 1998 - February 2002) were enrolled in a standardized treatment protocol. Systolic blood pressures for all four extremities were obtained with a Doppler probe and standardized blood pressure cuff. In the lower extremity the systolic pressure was measured at the posterior tibial and dorsalis pedis arteries. To calculate the ankle-brachial index, the highest measured arterial pressure in the ankle or foot was divided by the higher of the brachial arterial pressures from both upper extremities.

By palpation, pulses were determined to be either normal, diminished (compared to the contralateral limb), or absent. Hypotensive patients were resuscitated in the Emergency Department (ED) prior to assessing ABI's, pulses, or clinical signs of perfusion. In all cases, an assessment of vascular status was documented within one hour of arrival to the ED. For those patients who presented frankly dislocated (n=18), vascular evaluation was made after closed reduction. Patients were excluded from this study if they presented to our institution more than 24 hours from injury (n=7), if they had a vascular injury treated at an outside institution prior to transfer to ours (n=5), or if they had bilateral upper extremity injuries precluding adequate brachial pressure measurements (n=1). This left a total of 38 patients with 38 knee dislocations available for study evaluation.

Nineteen patients were involved in motor vehicle accidents, eleven were pedestrians struck by automobiles, two were injured in industrial accidents, three fell from a significant height, two were injured during athletics, and one morbidly obese patient sustained a dislocation stepping from bed.

Those patients with an ABI ≥ 0.90 were immobilized and admitted for serial examinations, delayed arterial duplex examination and eventual ligament reconstruction. Patients with an ABI < 0.90 underwent either emergent arteriography (Figure 1) in a radiology suite adjacent to ED, or underwent immediate surgical exploration. Three patients with non-dopplerable pedal pulses in the injured limb were considered to have an ABI of 0.0. All patients were seen in follow-up at two weeks and six weeks, then three, six and twelve months from injury or last surgery, and then annually when possible.

RESULTS

Eleven patients had ABIs < 0.90 (range 0.0 - 0.74) in the limb ipsilateral to the knee dislocation (Figure 2). ABIs for the contralateral limb ranged from 0.92 - 1.2 (average 1.05). Two patients with expansile knee hematomas underwent emergent exploration and revascularization with reverse saphenous vein grafting (RSVG) for a transected popliteal artery. These patients did not undergo preoperative arteriography. The nine remaining underwent emergent arteriography and were found to have arterial injury requiring surgical intervention. Their arterial injuries included 6 popliteal artery occlusions, one popliteal artery transection, one common femoral artery thrombosis with peroneal artery thrombosis, and one superficial femoral artery (SFA) high-grade chronic stenosis with an intimal flap that altered the popliteal artery flow. All underwent surgical revascularization and RSVG. One patient also required angioplasty of his SFA stenosis. Follow-up for these patients averaged twelve months (range 8-24 months) and at their most recent follow-up, ten of eleven patients had no complication of revascularization. One patient airlifted from a remote location arrived in the ED sixteen hours after injury. This patient had an ABI of 0.25 and a popliteal artery occlusion apparent on arteriogram. Despite emergent revascularization and multiple fasciotomies, this patient developed progressive necrosis of all four leg compartments and ultimately required above knee amputation.

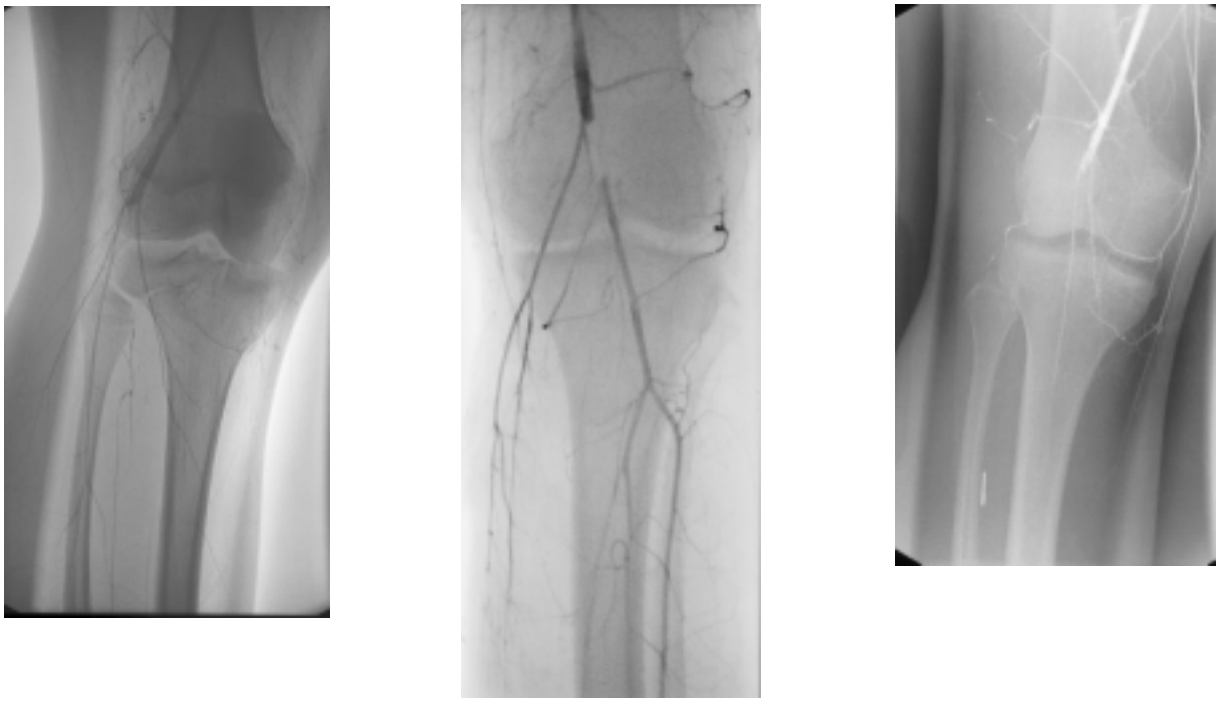

Figure 1: Arteriograms in a patient with an ABI of 0.25 demonstrating complete popliteal artery occlusion.

For this series of patients with knee dislocations, an ABI of < 0.90 indicated surgical arterial injury in 100%. Similarly, the sensitivity, specificity and PPV of an ABI < 0.90 was 100%.

Twenty-seven patients had ABI's ≥ 0.90 in the injured limb (range 0.90 - 1.46 - see Figure 2). ABI's for the contralateral limb ranged from 0.92 - 1.46 (average 1.08). None had evidence of vascular injury detectable by daily serial clinical examination and/or arterial duplex ultrasonography. Clinical follow-up in this group averaged 19 months (range 4-36 months). No patient in this group had signs of delayed vascular compromise. In this study population, the negative predictive value of an ABI > 0.90 was 100%.

Of eleven patients with vascular injury and ABI < 0.90, one had normal palpable pulses (matching the contralateral limb), and an ABI of 0.74. This patient had arteriographic finding of a chronic SFA 90% stenotic lesion and a popliteal artery flow limiting intimal flap. Ten patients in this group had diminished (n=1) or absent (n=9) pulses. Of 27 patients with ABI > 0.90, three had decreased (n=2) or absent (n=1) pulses, and 24 had normal pulses. The sensitivity, specificity and PPV for an abnormal pulse examination in determining arterial injury were therefore 91%, 89% and 77% respectively. The NPV of a normal (symmetric) pulse examination was 96%.

Discussion

The utility of the Ankle-Brachial Index in assessing chronic arterial insufficiency is well established. Its role in assessing acute arterial injury is also supported for both penetrating and blunt upper and lower extremity trauma.

Our data suggest that the ABI is extremely useful as a non-invasive screening tool for assessing acute vascular injury in the patient with knee dislocation. In our series, the ABI had a greater sensitivity, specificity and positive predictive value (all 100 %) than our clinical pulse evaluation. Had we relied only on clinical presentation, three patients would have undergone an unnecessary arteriogram. More importantly, one patient with normal pulses but acute arterial injury would have been excluded altogether from arteriographic study.

Our data also supports the role of preoperative arteriography in patients with ABI scores < 0.90. Though evidence reveals that the popliteal artery is the most likely site of vascular injury, in two of our study patients, other than popliteal artery injury occurred. One patient with multiple injuries including a bowel injury, scalp laceration and ipsilateral thigh degloving injury had a common femoral artery occlusion with ipsilateral peroneal artery thrombosis. His ABI score was 0.0. A second patient with a subarachnoid hemorrhage and knee dislocation following MCA had both a chronic high-grade SFA stenosis and an acute popliteal artery injury. His ABI score was 0.74. Given our current diagnostic tools, only arteriography, whether done in the ED or at the time of surgery would enable rapid identification of these anatomical variations.

Conclusion

Our data support the conclusion that routine arteriography is not necessary to accurately diagnose a vascular injury. Though the proponents of physical examination alone provide promising clinical results, our study indicates that the ABI should be

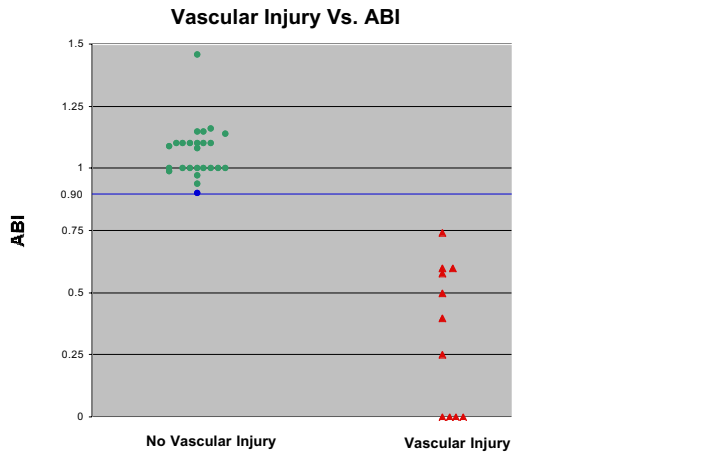

Figure 2: Graphic representation of the ABI in those patients with vascular injury all below 0.90 (range 0.0 - 0.74), and those without vascular injury, all above 0.90 (range 0.92- 1.46).

included as an integral part of the examination process. The ABI was initially developed as a means to minimize the rate of negative arteriography, to avoid arteriography that failed to alter overall management, to minimize potential complications, to avoid treatment delays and to lower costs. Our results suggest that the ABI effectively accomplishes all these goals in the patient with knee dislocation. The ABI is neither time consuming, invasive, costly, nor is it associated with complications. We feel strongly that the ABI should be considered not a separate procedure, but an extension of the physical examination in patients with a knee dislocation.

ACKNOWLEDGEMENT

The authors wish to thank Sarah Holt, M.S., for her assistance in the statistical analysis of the data presented.

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When Do Medical Students Learn Musculoskeletal Medicine?

GREGORY A. SCHMALE, M.D.

A recent study revealed that 80% of incoming residents across a variety of medical fields failed to demonstrate basic competency in musculoskeletal medicine on a 25-question exam whose content was supported by Orthopaedic Program Chairs and Medicine Department Chairs across the country. It is unclear whether the failure of these new residents was a result of curricular inadequacies at the pre-clinical level or deficiencies in clinical experiences.

BACKGROUND

The University of Washington trains approximately 180 students per year. The major pre-clinical experience in musculoskeletal medicine takes place during winter quarter of the second year. This course, entitled the Musculoskeletal System, lasts 8 weeks and includes approximately 40 total hours of contact time. Of this, 16 hours are spent in the gross lab doing dissection, 4 hours are spent in small group physical exam, and 20 hours are spent in anatomy and clinical correlation lectures. During this same quarter of second year, 25 hours are spent in a problem-based curriculum with an emphasis on orthopaedic issues, and additional 2 hours are spent learning physical exam skills in an introductory clinical medicine course. Clinical rotations in Orthopaedics are elective, routinely lasting four weeks, though all students are required to complete a four-week rotation in Rehabilitation Medicine.

The caliber of University of Washington students is high. The mean Part I and Part II National Board scores for the medical school are above the national average, and the pass rate for the exam is also above average. Over the past five years, University of Washington students have averaged 0.2-0.3 standard deviations above the national mean on the musculoskeletal sub-test.

METHODS

Surveys of second-, third-, and fourth-year medical students at the University of Washington were administered to evaluate the effectiveness of the curriculum in teaching key concepts in musculoskeletal medicine. Second-year students were surveyed twice, before and after their primary introductory course in the musculoskeletal system. The survey instrument was a two-form, web-based, anonymous questionnaire, each consisting of 12 of 24 short-answer questions on musculoskeletal medicine, previously validated at the University of Pennsylvania. This report contains data from one year's survey of a second year class, pre- and post-course, a third year and a fourth year class.

RESULTS

Survey results revealed marked improvement in understanding of basic musculoskeletal medicine in second-year students as a result of the pre-clinical course, with the mean score improving from 19% to 60% correct (pre-test standard deviation of 12, post test standard deviation of 20) (Figure 1). Yet, only 20 of 74 (27%) second year

Picture 1: Second year medical students practice physical examination of the knee during their musculoskeletal system course.

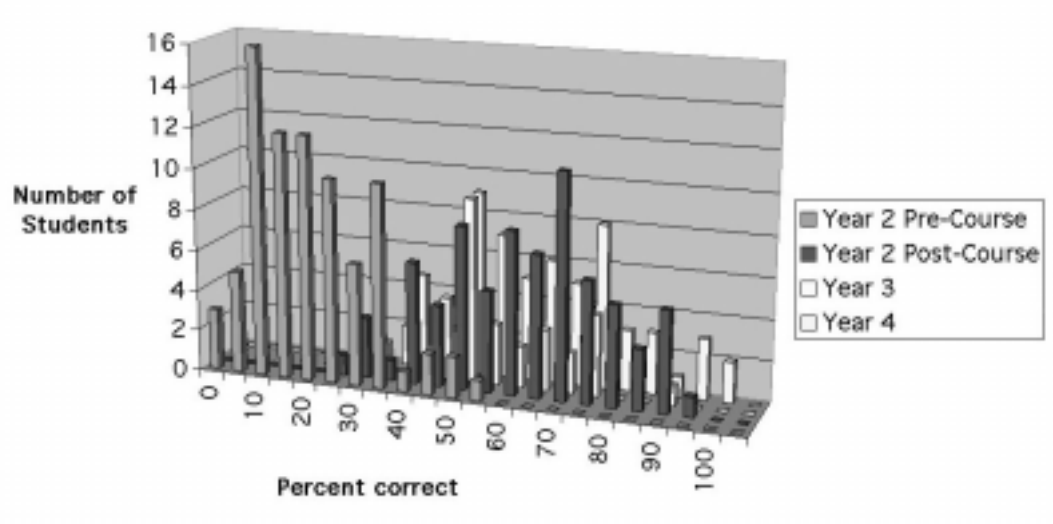

Figure 1: Histogram of student scores by year in medical school.

students post-course demonstrated competency, deemed as a score greater than or equal to 70%. Likewise, only five of 34 third-year students (15%) and 20 of 59 fourth-year students (34%) demonstrated competency (Table 1). Though less than 50% participation was achieved for each survey, these results support prior reports of the high incidence of inadequate preparation of medical students in musculoskeletal medicine.

No differences were found when comparing types of questions - anatomic vs. clinical - by year. An item analysis revealed the lowest frequencies of correct answers were on questions related to disc disease and low back pain, across all years of students.

Discussion and Conclusion

These results call into question the appropriateness of our pre-clinical curriculum in musculoskeletal medicine. Comparison of questions to curriculum for the second year introductory course has revealed that each topic represented by the 24 survey questions is represented by direct instruction in the curriculum. It may be the case that without routine clinical reinforcement of the issues first raised in the musculoskeletal introductory course, learning will not reliably occur. The routine use of standardized multiple choice tests as a measure of competency may also disguise a higher level of misunderstanding than suggested by scores on these standardized examinations.

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	Number of Students	Score			Number Passing	Percent Passing
		(mean)	(std dev)	(range)		Score > 70%
Second Year Pre-Course	79	19%	12	0-54	0	0
Second Year Post-Course	74	60%	17	23-91	20/74	27%
Third Year	34	53%	13	29-90	5/34	15%
Fourth Year	59	62%	17	27-100	20/59	34%

Table 1: Study groups.

RNA Interference Suppresses Expression of EWS/FLI-1 in Ewing's Sarcoma Cells

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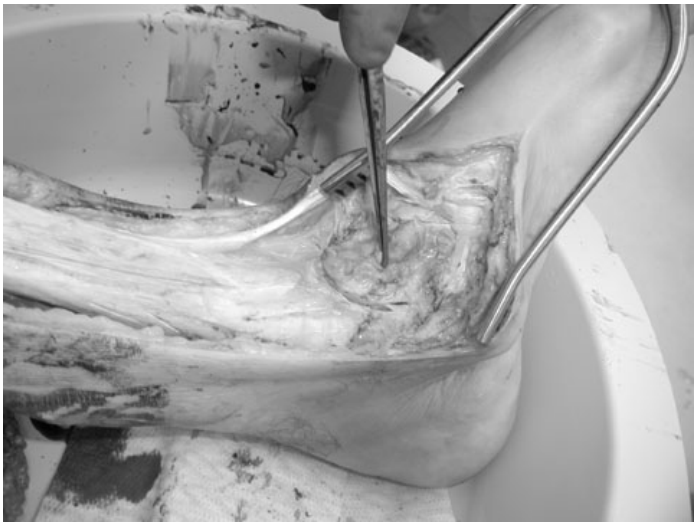
Despite progress in treatment, Ewing's sarcoma remains an often fatal skeletal cancer of adolescents. In over 90% cases of Ewing's sarcoma and the related peripheral primitive neuroectodermal tumors (PNET), a highly specific and recurrent t(11;22) balanced chromosomal translocation results in the fusion of a portion of the gene EWS on chromosome 22 to a portion of the chromosome 11-derived gene FLI-1. This translocation is believed to be the fundamental genetic defect that causes Ewing's sarcoma. The resultant EWS/FLI-1 fusion protein causes abnormal gene expression (transcription and splicing). Despite the discovery of the fusion protein over 10 years ago the treatment of Ewing's sarcoma remains a combination of surgery, chemotherapy and radiotherapy. Most importantly, even with current treatment regimens a significant number of children and young adults will develop untreatable pulmonary metastases.



Picture 1: Gross example of Ewing's sarcoma tumor, seen at end of tweezers.

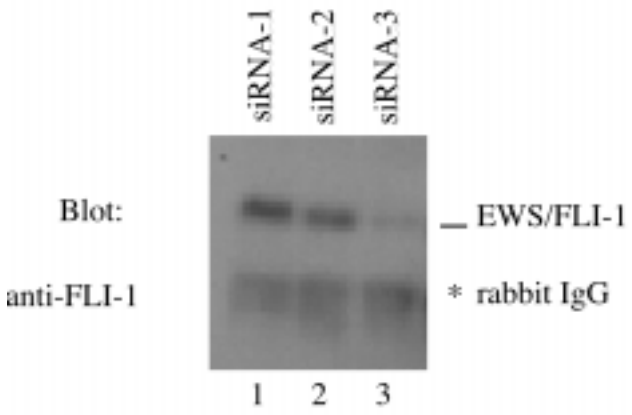


Figure 1: Western blot of SK-ES cells treated with double-stranded small interfering RNAs targeting EWS/Fli-1 mRNA. EWS/Fli-1 protein was detected with anti-Fli-1 antibody. siRNA-2 is small interfering RNA EFT11 (negative control), siRNA-2 is small interfering RNA targeted against the EWS/Fli-1 breakpoint, and siRNA-3 is small interfering RNA Fli1-1282 targeted against the 3' end of EWSS/Fli-1. As shown in lane 3, siRNA Fli1-1282 results in a nearly complete absence of expression of EWS/Fli-1 protein. There was no detecable normal ("wild type") Fli-1 protein detected in the control or experimental cells. The row labeled "rabbit IgG" refers to the antibody used to concentrate the EWS/Fli-1 fusion protein.

Recent advances in tumor biology have led to an effective molecularly targeted treatment, the Bcr-Abl kinase inhibitor imatinib mesylate (Glivec), for chronic myelogenous leukemia and gastrointestinal stromal tumors. Similar translocations are frequently present in musculoskeletal sarcomas and as such, offer an attractive rationale for targeted molecular therapies. Several studies have reported on the use of antisense ribonucleic acid (RNA) technology to modulate the growth of Ewing's cells in culture and in mice by targeting the messenger RNA (mRNA) that encodes the chimeric protein EWS/FLI-1. In essence, antisense RNA binds to and inactivates the complementary strand of mRNA, leading to a specific reduction in EWS/FLI-1 mRNA and protein. RNA interference (RNAi) is a recently described endogenous biological process that like antisense RNA destroys specifically targeted messenger RNAs. RNAi using double stranded "small interfering" RNA (siRNA) is a more robust process than antisense RNA in that lower concentrations of RNA are required, suppression of the targeted message is more complete, and the requirements to identify a specific susceptible region of the targeted mRNA are less stringent. The double stranded RNA effects sequence specific gene suppression of targeted mRNA of identical sequence. EWS/FLI-1 messenger RNA possesses

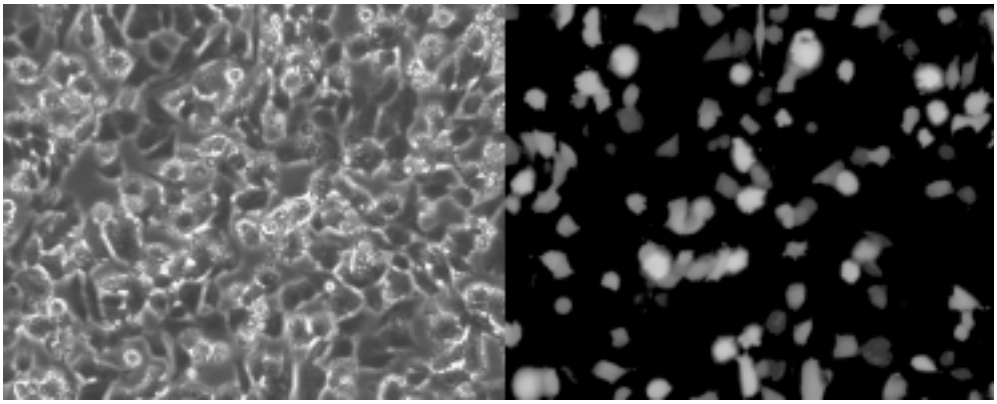


Figure 2: Transfection efficiency of SK-ES cells with electroporation. Light microscopy (magnification 100X) of SK-ES cells on left half of image with the same field illuminated with fluorescence microscopy on right side. Ther SK-ES cells have taken up green fluorescent protein (GFP) DNA after electroporation. Expressed GFP appears green when exposed to fluorescent light. Transfection efficiency, or the percentage of cells that express GFP is approximately 50 percent.

a unique genetic sequence in the region of the fusion (breakpoint). This specific target makes EWS/FLI-1 an attractive target for RNA interference. Previous studies with antisense technology have demonstrated that targeting EWS/FLI-1 can revert malignant Ewing's cells to a more normal phenotype, even shrinking tumors in a mouse model. Here we describe our initial attempts to "knock-down" expression of EWS/FLI-1 in the widely studied SK-ES (Sloan Kettering - Ewing's Sarcoma) Ewing's sarcoma cell line.

Results

The antisense and sense strands of the siRNA targeted against the junction of EWS and FLI-1 and the the 3-prime end of FLI-1 mRNA were chemically synthesized. SK-ES cells were grown to confluence in a 15 cm plate. The cells were trypsinized and resuspended in sterile saline with various double-stranded siRNAs at a concentration of 200 nM. A standard process referred to as electroporation (literally, shocking the cell membrane) was used to facilitate the passage of the siRNA through the cell membrane. A random sequence of double-stranded siRNA was used as a negative control (EFT11). The cells were incubated for an additional 36 hours in McCoy's tissue culture medium and then were harvested for Western blotting. Western blotting permits the separation and quantitation of proteins of different sizes by the speed through which they travel through a polyacrylamide gel. The proteins in the gel were transferred to a nylon membrane and EWS/FLI-1 was detected with a commercially available monoclonal anti-FLI-1 antibody.

As demonstrated in Figure 1, Lane 3, there was a dramatic reduction in expression of the EWS/FLI-1 fusion protein associated with the double stranded siRNA (FLI-1 1282) targeting the 3' end of the fusion protein. Surprisingly, the siRNA (EFT21, Lane 2) that specifically targeted the fusion breakpoint did not appreciably affect expression of EWS/FLI-1. The negative control (EFT11, lane 1) did not affect expression, nor did combinations of siRNAs result in additional repression of expression (Lanes 4-6).

One subset of SK-ES cells was electroporated under identical conditions as for the siRNA with DNA encoding green fluorescent protein (GFP). Green fluorescent protein is synthesized only by cells that have taken up the DNA and is readily detectable with a fluorescent microscope. This yields what is referred to as transfection efficiency, or the percentage of cells that have successfully taken up the GFP DNA and are synthesizing GFP. As seen in Figure 2, the transfection efficiency was approximately 50%.

Discussion

These results suggest that it is possible to specifically suppress expression of EWS/FLI-1 chimeric mRNA and protein with double stranded siRNA. The newly discovered process of RNA interference is a potent method to specifically target individual proteins. The sequence of DNA at the breakpoint of EWS/FLI-1 is found nowhere else in the human genome and thus represents the ideal target for siRNA. It is estimated that there is about a 50% likelihood that any given 21-base sequence is susceptible to RNA interference thus we are now developing addition siRNAs targeted against the breakpoint. As seen in Figure 1, Ewing's cells do not synthesize detectable quantities of FLI-1 protein. Thus the 3' end of EWS/FLI-1, while shared with the normal FLI-1 protein, still may be a legitimate target for RNA interference. We are now evaluating the effects of our siRNA consructs on the growth and phenotype of Ewing's cells in vitro. At least in the earlier stages of the disease, Ewing's sarcoma cells likely require continued expression of EWS/FLI-1 RNA and protein to maintain a cancerous phenotype. As techniques for viral delivery of siRNA improve to permit long-term stable expression of specific siRNAs, RNA interference might one day be used in a multimodality treatment strategy that includes gene therapy.

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Central Screw Placement in Simulated Scaphoid Waist Fractures: A Biomechanical Study

WREN V. MCCALLISTER, M.D., JEFF KNIGHT, B.S., ROBERT KALIAPPAN, M.D., AND THOMAS E. TRUMBLE, M.D.

The internal fixation of scaphoid fractures remains a challenging task. Use of the Herbert screw for the internal fixation of acute fractures of the scaphoid waist gained popularity after its introduction in 1984.

It has been shown that the technical aspects of screw insertion are important in the clinical outcome of acute fractures of the scaphoid waist. In addition, higher rates of central placement in the proximal fragment of the scaphoid have been reported when using cannulated screws. In this study, we investigate a model of internal fixation for scaphoid waist fractures using the Herbert-Whipple cannulated screw. Biomechanical properties of this fixation are evaluated, under single load to failure conditions, in centrally aligned versus eccentrically aligned screws. Thus, we test our hypothesis that there exists an optimal positional placement for screws used in the internal fixation of acute fractures of the scaphoid waist, centrally located within the proximal fragment of the scaphoid.

MATERIALS AND METHODS

Each of eleven bilateral pairs of scaphoids from fresh cadaveric wrists was used in this study. The density of each scaphoid was determined according to Archimedes' principle.

One scaphoid in each pair had central screw placement and the other eccentric. A smooth transverse osteotomy was made at the narrowest aspect of the scaphoid waist using a custom manufactured jig and the osteotomy fixed using standard technique for Herbert-Whipple cannulated screws. This resulted in all specimens having the same length of thread contact area and a reproducible eccentric position with respect to the central axis of the scaphoid. Screw placement was confirmed with orthogonal radiographs and central positional placement was defined as a screw position within the central one-third of the proximal fragment of the scaphoid on both the antero-posterior and lateral radiographs (see Figures 1 and 2).

For mechanical testing, the proximal fragment of each fixed specimen was potted in polymethylmethacrylate and oriented at a 45-degree angle to the horizontal plane to mimic its normal attitude in a wrist held in the neutral position. This enabled delivery of a dorsal-to-volar cantilever load via pneumatically driven plunger, which represents the primary physiologic load encountered by the scaphoid (see Figure 3). A constant load was applied twice, first the load was increased until two millimeters of displacement was recorded, then the load was returned to zero and increased again to record load at failure and mechanism of failure. Stiffness was calculated using the load and displacement measurements.

STATISTICAL METHODS

Statistical analysis was performed using software to calculate the Wilcoxon signed rank non-parametric analysis to compare the specimen's stiffness and strength. Power analysis resulted in a computed sample size of 7.84. To provide an extra margin of safety, we have elected to use eleven matched pairs of scaphoids.

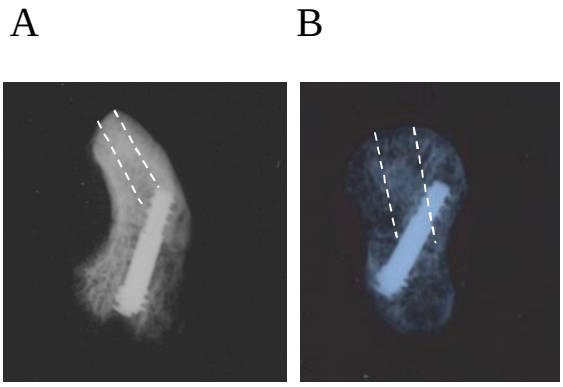

Figure 1: Central screw position. Antero-posterior (A) and lateral (B) radiographs showing central placement within the central one-third of the proximal pole of the scaphoid.

RESULTS

When measured according to Archimedes' principle, the mean density (standard deviation) for left scaphoids was 1.67 grams per cubic centimeter (.84), while right scaphoids had a mean density of 1.98 grams per cubic centimeter (1.03). There was no significant difference between the density of the right and left scaphoids within each matched pair. Tables 1 and 2 show the data for biomechanical testing.

For all specimens, the mode of failure was screw migration and fracture at the screw-bone interface with dorsal wedge opening. In no case was there either fracture at less than two millimeters of displacement or fracture of the polymethylmethacrylate. Upon retrieval of all screws after failure, there was no evidence that any of the screws sustained a plastic bending deformity.

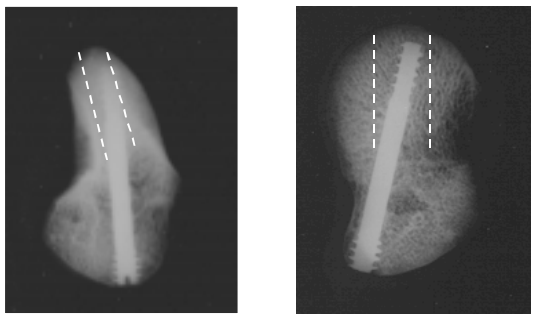

Figure 2: Eccentric screw position. Antero-posterior (A) and lateral (B) radiographs showing eccentric placement with respect to the central one-third of the proximal pole of the scaphoid.

DISCUSSION

Our hypothesis was that central screw position in the proximal fragment of the scaphoid would offer biomechanical advantage when compared to eccentric positioning. There are no directly comparable studies available for comparison. We selected a transverse osteotomy model for this study because it resembles the originally reported fracture by Herbert and Fisher and is an accepted model in previously published investigations. It is for this fracture type that internal fixation is advocated in the acute setting when displaced or unstable and for those with non-displaced fractures who desire a quicker return to function.

Technical aspects of screw insertion are critical to the success of internal fixation when treating acute fractures of the scaphoid waist. Accurate placement of non-cannulated screws in the proximal fragment of the scaphoid is difficult and the use of a cannulated system improves accuracy of placement.

Biomechanical testing has demonstrated that cannulated screws are superior to the non-cannulated Herbert screw in their ability to generate compressive forces across the fracture and resist cyclical bending loads.

Central placement of the screw in the proximal fragment of the scaphoid, using either cannulated or Herbert screws, is associated with significantly decreased times to union. In addition, there is evidence that post-operative range of motion is correlated with the degree of scaphoid alignment achieved by internal fixation.

The results of our investigation suggest that when screws are positioned in the central portion of the proximal fragment of the scaphoid, significantly greater force is required to generate fracture displacement when compared to screws that are eccentrically positioned (see Tables 1 and 2).

Limitations of this study include the use of cadaveric specimens, use of a linear osteotomy, and lack of measurement under cyclical loading conditions. In addition, this study is subject to the usual limitations that apply to biomechanical investigations when attempting to extrapolate to the clinical setting including the impact of the local tissue environment and forces realized in vivo.

The advent of the Herbert screw greatly improved the internal fixation of scaphoid fractures. The introduction of cannulated screws demands that the surgeon make an informed decision regarding their use. Current experimental evidence supports improved compressive forces and better resistance to cyclical bending loads when using cannulated screws. In addition, improved post-operative alignment and range of motion are associated with central placement of the screw in the proximal fragment of the scaphoid and using cannulated screws results in a higher rate of central placement. These data, in combination with the results of this study, suggest that central screw placement in the proximal fragment of the scaphoid offers both clinical and biomechanical advantages. Clinical efforts and

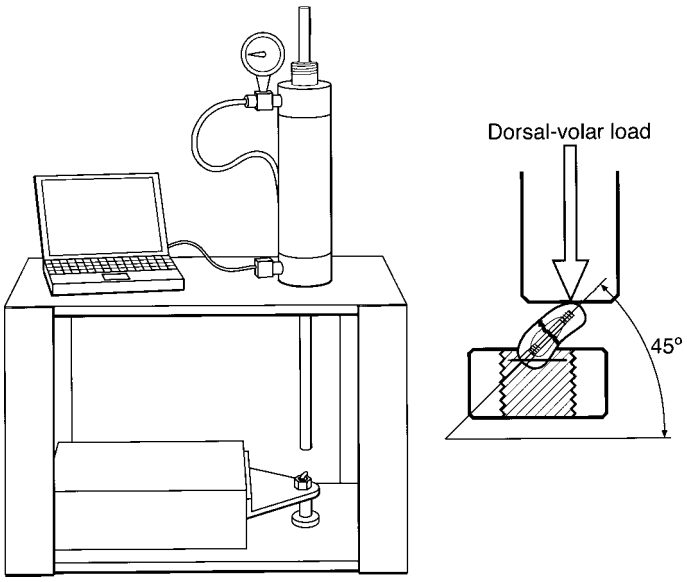

Figure 3: Schematic depicting the potted scaphoid specimen and testing apparatus for delivery of dorsal-to-volar cantilever bending load.

Parameter	Screw Position Central	Eccentric
Stiffness (N/mm)	12.7 ± 4.47	8.88 ± 3.44
Load at 2mm displacement (N)	126 ± 74.9	59.1 ± 47.8
Load at failure (N)	712 ± 412	513 ± 354

Table 1: Results of biomechanical testing (n=11).

Parameter	Screw Position % Central > Eccentric	Significance
Stiffness	43%*	$p < .01$
Load at 2 mm displacement	113%	$p < .01$
Load at failure	39%	$p > .05$

Table 2: Comparing biomechanical properties of central versus eccentric screw placement in the proximal pole of the scaphoid. *Central screw position resulted in 43% greater stiffness when compared to the eccentric screw position.

techniques that facilitate screw placement in the central portion of the proximal fragment of the scaphoid should be encouraged when undertaking the open reduction and internal fixation of acute fractures of the scaphoid waist.

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Surgical Intervention for the Clawed Hallux Deformity

FADY N. ELIAS, B.S., WILLIAM R. LEDOUX, PH.D., TRACY J. YUEN, B.S., SOREN L. OLSON, B.S., RANDAL P. CHING, PH.D., AND BRUCE J. SANGEORZAN, M.D.

The term clawed hallux refers to a specific deformity of the great toe. It is clinically defined as the extension of the first metatarsophalangeal joint (MTPJ) combined with flexion of the interphalangeal joint (IPJ) (Figure 1). It causes 2 clinical problems; an increased pressure beneath the first metatarsal head and deformity that causes the toe to rub on the shoe, either of which may lead to the development of an ulcer (Figure 2). This imbalance is presumed to be a result of a functional "overpull" (a disproportionate load) of one or more of the three extrinsic muscles of the first ray: the peroneus longus (PL), extensor hallucis longus (EHL), and flexor hallucis longus (FHL). This deformity has been reported in several patient populations including those with cerebral palsy, SCI, head injury, and diabetes mellitus (Figure 1). Only one surgical procedure is described for treatment of the clawed hallux and it is blind to the deforming force. The purpose of our research was to assess the effectiveness of different surgical interventions (the modified Jones procedure and the flexor hallucis longus transfer) in correcting both the deformity and its mechanical consequences. We examined the angular changes at the MTPJ and IPJ as well as the plantar pressures beneath the first metatarsal and the distal hallux.

METHODS

Six fresh-frozen cadaver feet (84 years of age, SD 3.5 years) were obtained for this IRB-approved study. The tibia and fibula of each foot were sectioned 12 cm proximal to the ankle and the extrinsic tendons were dissected free to the superior extensor retinaculum. The feet were randomly selected for either the modified Jones procedure (EHL transfer into the dorsal first metatarsal) or transfer of the FHL into the proximal phalanx. These two procedures address different etiologies.

In the modified Jones procedure, the IPJ of the great toe was exposed through an L-shaped incision on the medial side of the foot. The tendon of the EHL was dissected and cut transversely 1cm proximal to the IP joint. The synovial sheath around the EHL was excised. A transverse hole 3 mm was drilled on the inferomedial aspect of the first metatarsal neck and continued along the long axis of the bone until the dorsolateral aspect of the neck. The tendon was passed through the hole and sutured to itself and the periosteum for reinforcement.

For the FHL transfer, a medial incision was made over the MTPJ and carried distally to the IPJ. The FHL tendon was exposed under the proximal phalanx. The incision was carried distally to expose the FHL attachment at the distal phalanx. The tendon was cut at its most distal attachment to the distal phalanx. The synovial sheath of the FHL was excised. A 3 mm transverse hole was made through the base of the proximal phalanx. The tendon was passed through the hole and sutured to itself and the periosteum.

The specimens were tested pre- and post-surgical intervention in a loading frame capable of statically simulating different phases of the gait cycle. The position of the bones of interest was measured using the Fastrak electromagnetic motion analysis system; sensors were fastened to carbon fiber rods that were rigidly attached to talus, 1st metatarsal, proximal phalanx and distal phalanx. The Pedar insole pressure measurement system was used to measure the plantar pressure. Plastic tendon clamps were attached to the free tendons of the extrinsic musculature and the loading protocol developed by Olson et al was used to simulate overpull of the PL, FHL, and EHL. Paired t-tests were conducted to determine statistical significance between pre-operative and post-operative conditions. Due to small sample, differences between surgical procedures were not statistically analyzed.

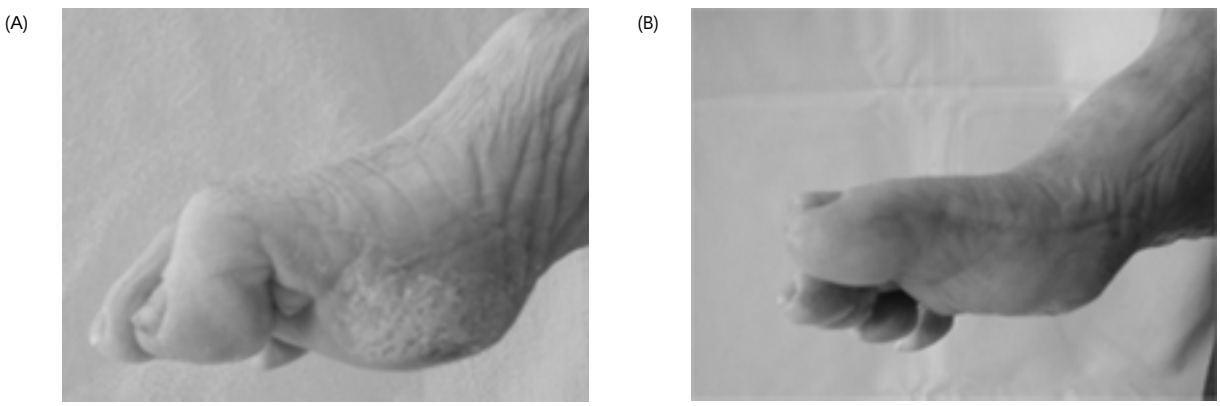

Figure 1: A medial/lateral photograph of a clawed hallux patient (a) pre- and (b) post-op (6 weeks).

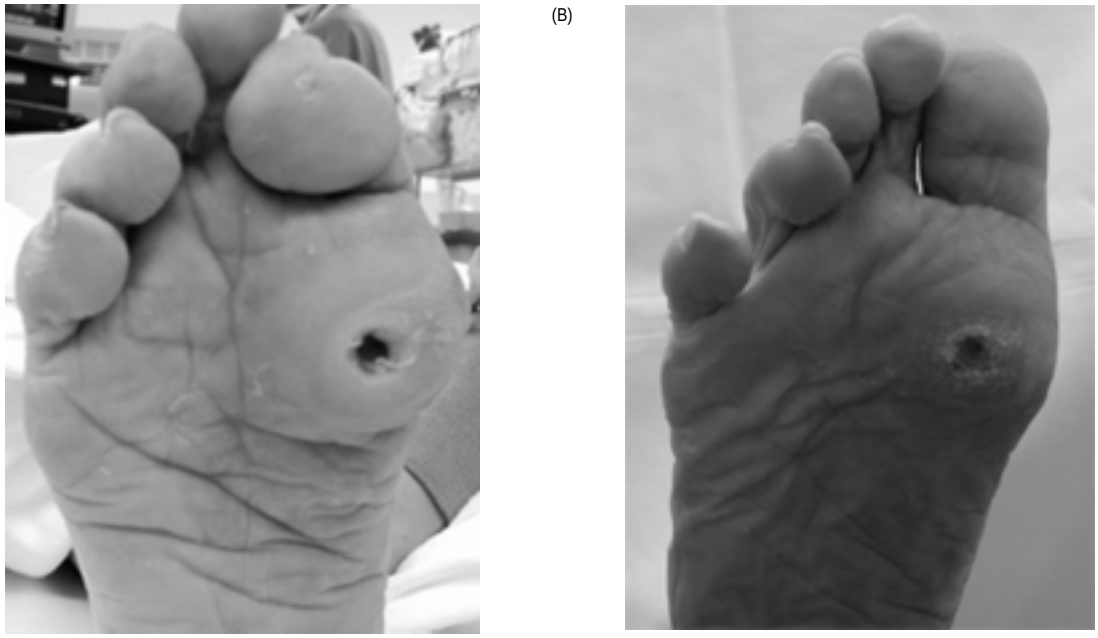

Figure 2: A plantar ulcer under the first metatarsal head of the same clawed hallux patient (a) pre- and (b) post-op (6 weeks).

Results

Both surgical procedures were successful at straightening the toe, both at the IPJ and MPJ. A significant reduction was found in the average MTPJ angles when comparing pre-surgical vs. post-surgical data (Figure 3a) with the overpull of PL (0.59˚ ± 0.25˚ vs. 0.17˚ ± 0.34˚, p = 0.0118), FHL (3.11˚ ± 1.47˚ vs. 0.22˚ ± 0.47˚, p=.0114), and EHL (3.73˚ ± 1.87˚ vs. 0.48˚ ± 1.30˚, p = 0.0103). A significant reduction was also found post-surgically with the average IPJ angles (Figure 3b) when the PL (0.22˚ ± 0.23˚ vs. 0.13˚ ± 0.21˚, p = 0.0144) and FHL (10.33˚ ± 6.05˚ vs. 1.70˚ ± 2.35˚, p = 0.0363) were overpulled. Although the average IPJ angle was reduced with the overpull of the EHL post-surgically (8.26˚ ± 6.13˚ vs. 1.39˚ ± 2.47˚, p = 0.0819), this reduction was not statistically significant. Surgery also resulted in an observed reduction of plantar pressure beneath the 1st metatarsal (Figure 4a), but only the PL overpull was significant (8.83 N/cm^2 ± 5.21 N/cm^2 vs. 4.25 N/cm^2 ± 5.84 N/cm^2, p = 0.0438). The only trend with the hallux pressure (Figure 4b) was a decrease in post-surgical pressure with the FHL overpull, but the difference was not significant. Surgical procedures are successful at correcting the deformity and at reducing the pressure beneath the metatarsal. Not surprisingly the degree to which the changes occurred depend upon which of the muscles was causing the problem.

Discussion

Our laboratory has demonstrated that a disproportionate load applied to the first ray extrinsic muscles creates a clawed hallux. To measure the effectiveness of surgical correction, the modified Jones procedure and the FHL transfer were performed on 6 randomly assigned feet. A reduction in the angular changes at the MTP and IP joints were observed with both interventions as well as a reduction in the plantar pressure beneath the first metatarsal. Both procedures corrected the deformity.

Aberrant pressure beneath the first metatarsal has been associated with diabetic foot ulcers. Thus optimal plantar pressure reduction is an important surgical outcome. The trend of the means suggests that the FHL transfer reduces first metatarsal pressure more than the modified Jones, but the data suggest that the FHL transfer does not decrease hallux plantar pressure as well as the modified Jones (data not shown).

Limitations of this study include the inability of simulating post-surgical healing; we did, however, examine the feet after testing and found no surgical failures with regard to tendon slippage. Another limitation associated with this study is the inability to model a normally dynamic and chronic disorder with the use of static cadaver feet obtained from advanced age specimens.

The peroneus longus has been shown to both stabilize and plantar flex the first metatarsal; it is also the primary muscle involved in increasing the plantar pressure under the first metatarsal. Therefore, future surgical treatment should take this into account. Our future investigations will allow us to quantitatively assess which surgical intervention is best at alleviating the clawed hallux as measured by the reduction of angular changes at the MTP and IP joints as well as significantly reducing plantar pressure under the first metatarsal. In addition, this study provides some guidance for selecting a surgical procedure that best fits the clinical problem.

Acknowledgements

Department of Veterans Affairs A0806C and The Medical Student Research and Training Program at the University of Washington

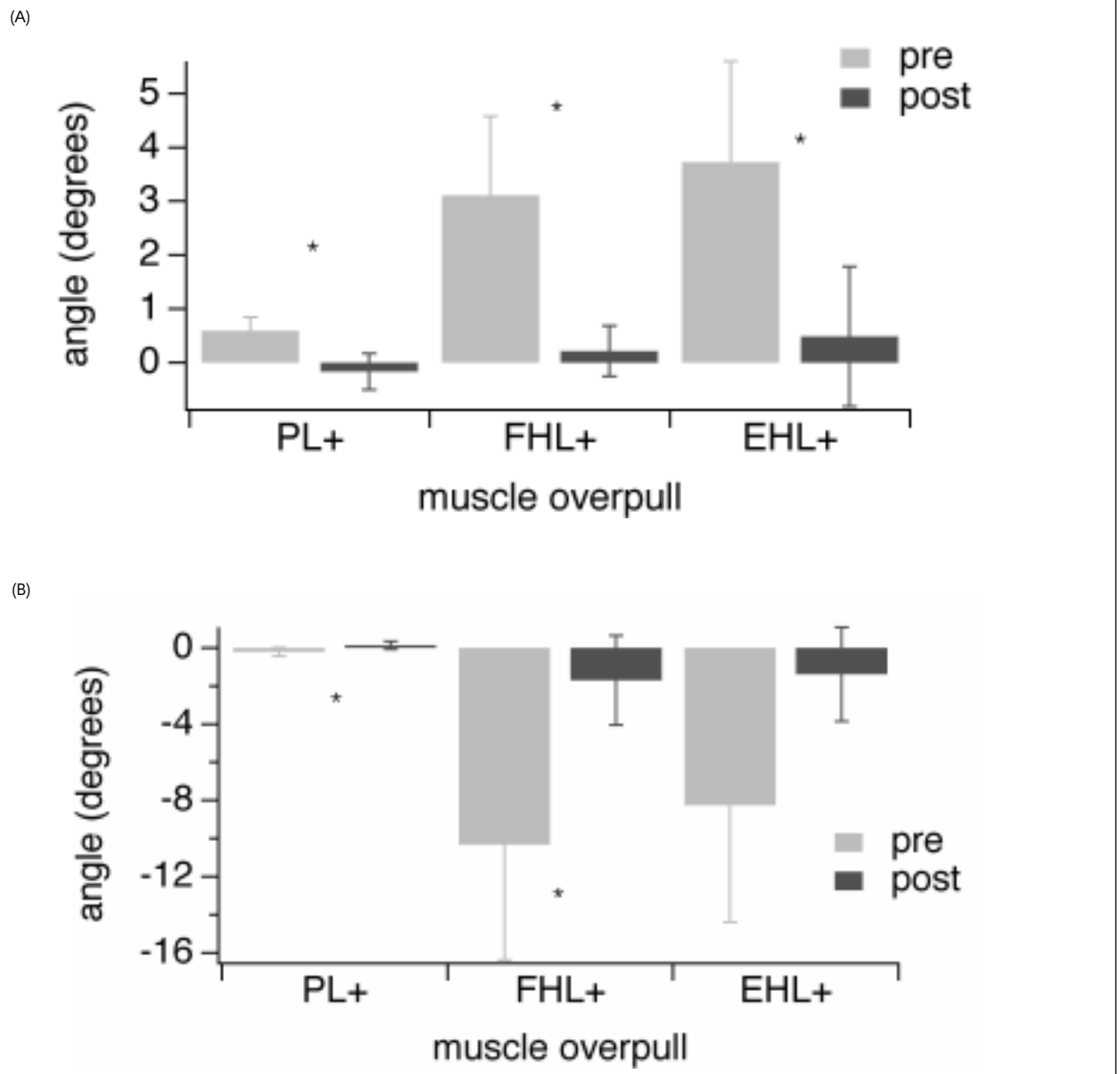

Figure 3: (a) Average MTPJ angle (+/- SD) for pre- and post-surgical data. (b) Average IPJ angle (+/- SD) for pre- and post-surgical data. An asterisk (*) denotes a statistically significant difference.

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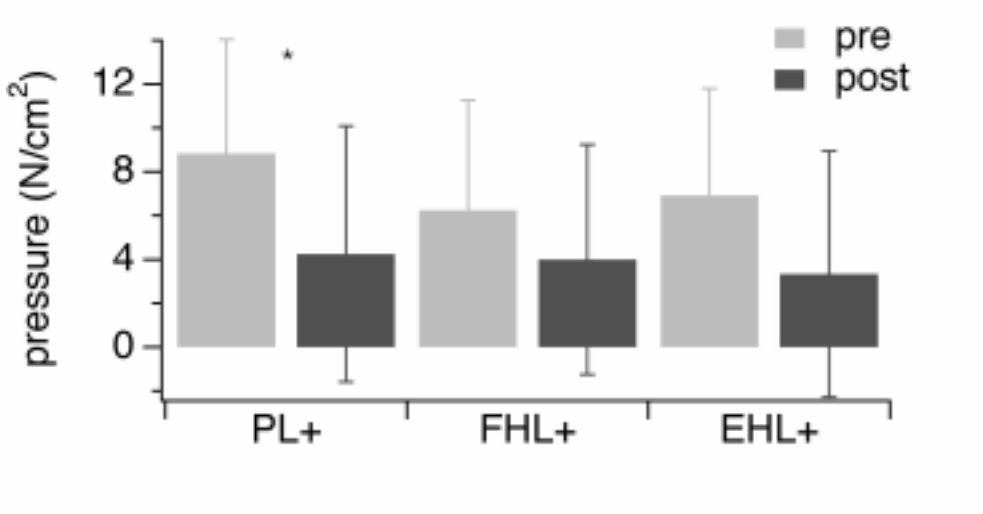

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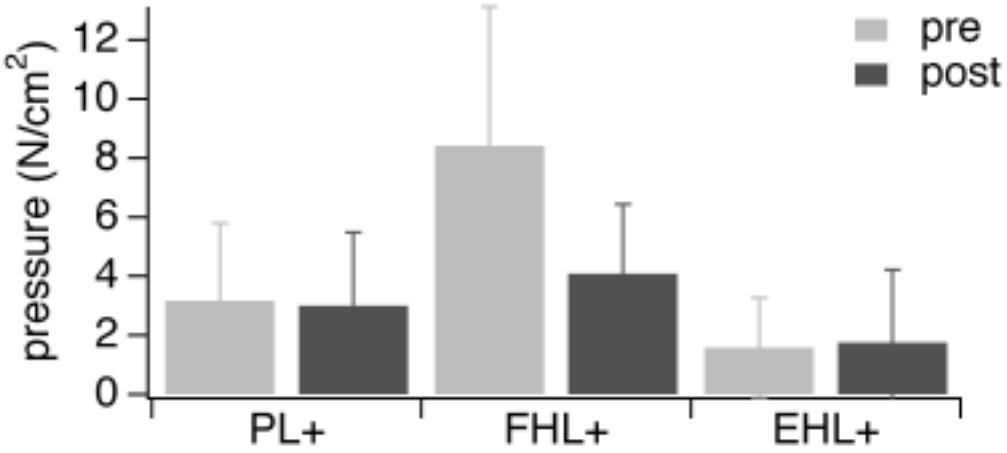

Figure 4: (a) Average first metatarsal pressure (+/- SD) for pre- and post-surgical data. (b) Average hallux pressure (+/- SD) for pre- and post-surgical data. An asterisk (*) denotes a statistically significant difference.

Association Between Funding Source and Study Outcome in Orthopaedic Research

SETH S. LEOPOLD, M.D., WINSTON J. WARME, M.D., E. FRITZ BRAUNLICH, M.D., AND SUSAN SHOTT, PH.D.

Numerous external factors have been associated with study outcome in non-surgical specialty journals. Studies have suggested that funding from the pharmaceutical industry, publication from certain countries, attitudes of the editors of the journal in question, and relationship with the tobacco or alcohol industries all may be associated with positive outcomes in the published medical literature. To our knowledge, the potential associations between such external factors and study outcomes in orthopaedics has not been reported.

Orthopaedic journals are placing a greater emphasis on meta-analysis and evidence-based medicine. Both of these clinically-relevant avenues of inquiry depend upon the absence of systematic biases and external factors in the submission and selection of articles for publication. For example, if there is a bias towards the publication of positive results over negative ones in clinical trials, meta-analyses will systematically overestimate the success rates of treatments investigated.

The present report tests the hypotheses that funding source, country of origin, and presence of a co-author with training in epidemiology or statistics are related to the likelihood of a published orthopaedic study arriving at a positive conclusion.

METHODS

Material for the study consisted of articles published over a 1-year period during 1999-2000 in the American Edition of The Journal of Bone and Joint Surgery (JBJS), The American Journal of Sports Medicine (AJSM), and The Journal of Arthroplasty (JA).

All articles reviewed were reproduced and redacted such that the authors' names, departmental and institutional affiliations, academic degrees, and funding disclosures were obscured from view during the review process.

A pool of three orthopaedic reviewers analyzed the articles according to predetermined criteria. Two reviewers provided the primary evaluation of each article, and a third reviewer provided the deciding vote in cases when the two initial reviewers did not agree.

The reviewers also collected descriptive data on all articles analyzed, including presence or absence of a control group, use of randomization, study design (prospective, retrospective, other), and statement of a testable hypothesis.

The reviewers then classified each study into one of two groups, with respect to study outcome: (1) Positive/Favorable/Significant Difference Noted; (2) Negative/Unfavorable/No Significant Difference/Other. The reviewers applied strict, standardized criteria to the articles to make the determination of outcome, which have been published and validated elsewhere. Briefly, a positive study is one that emphasizes a beneficial result obtained by the studied variable. If no beneficial result was emphasized (or if the study was not designed to detect a beneficial result), a positive result is defined as a study that detects a statistically significant difference of a principal study endpoint, regardless of direction. To minimize the likelihood that any bias toward positive outcomes would be overstated, studies that did not clearly meet criteria as positive studies were counted in the negative group.

Three potential predictors of the likelihood of a positive outcome were investigated: funding source, country of origin of the study, and presence of a coauthor with particular expertise in statistics or epidemiology. Reviewers were blinded to these variables throughout the review process.

RESULTS

A total of 315 studies were reviewed from the three journals. Only 3.5% of published studies were randomized, 10.5% clearly stated an experimental hypothesis, and 21.0% were prospective. About half of the studies reviewed (50.5%) included an experimental control of some type; in principle, most or all of those studies could have articulated a hypothesis.

A majority of the studies that could be evaluated for outcome reached a positive conclusion (66.4%). Clinical studies (studies involving human subjects) were not significantly different from basic science studies with respect to the likelihood of arriving at a positive outcome ($p > 0.4$).

The receipt of commercial funding was the only variable analyzed that was found to be significantly associated with a positive outcome. Of studies that received any funding from industry sources, 78.9% concluded with a positive outcome, compared with only 63.3% of studies that received no such funding ($p = 0.025$; Table 1).

Country of origin and presence of a statistician as a co-investigator were not significantly associated with positive outcome in this analysis ($p=0.25$, and $p=0.94$, respectively).

Agreement generally was good between the two primary reviewers

"The human intellect…is more moved and excited by affirmatives than by negatives."

Sir Francis Bacon (1561-1626)
Renaissance author, philosopher, and father of inductive reasoning.

during the blinded evaluation phase of the study. In only 0.6% of studies reviewed (two of 315 studies) did the two primary reviewers disagree on one or more study end points; in those cases, the third reviewer served as the adjudicator.

Discussion

The present report found that published studies receiving funding from commercial parties were significantly more likely to present a positive conclusion than studies that were either self-funded or funded through non-profit sources. Other variables, such as the involvement of a statistician with the research, or the country of origin of the study, were not found to be significantly related to outcome.

The fact that industry-funded research published in orthopaedic journals was more likely to conclude with a positive message about the implants or pharmaceuticals evaluated does not necessarily imply that those studies are flawed, or that the investigators have been corrupted. Pharmaceutical companies perform considerable in-house research, presumably guiding them towards more promising medications, which they then investigate in collaboration with university- and community-based investigators, perhaps increasing the likelihood that their public collaborations will result in positive studies. Sizeable grants from commercial interests also may allow the inclusion of more patients, perhaps decreasing the likelihood of Type-II statistical error from insufficient sample size, again tending to increase the likelihood of studies concluding positively.

On the other hand, there is evidence that other factors may have an impact. Grants from commercial interests often are accompanied by contracts that include restrictive covenants, effectively giving the corporate sponsor the right to prevent publication of the results, if those results are deemed detrimental to the goals of that sponsor. These "gag clauses" have delayed or prevented publication of numerous studies, and have resulted in threats of expensive legal action against investigators and institutions attempting to publish despite those contracts. There are numerous examples of commercially-funded trials that have been halted by the sponsor before completion, when it became evident that the results being generated would be financially unfavorable to the sponsoring corporate interest. Although it is widely agreed that this practice is unethical, it appears to be common. Psychosocial or economic influences affecting the investigator have also been suggested as contributing to the disproportionately positive outcomes observed in commercially-funded trials.

The present report also found that a large majority of studies (66.4%) published in three widely-read orthopaedic journals over a one-year period concluded with positive outcomes. However, in order to know with certainty that the preponderance of positive studies observed in the present report indeed represents a bias, there would need to be an assessment of both published and unpublished manuscripts. This would allow the determination of whether there is an increased conditional probability of publication for manuscripts that report positive outcomes over those that report negative ones. Evaluation of this "denominator" was beyond the scope of the present report. There is, however, strong evidence from other work that the high proportion of positive studies observed in analyses like the present report may represent a bias, and not a mere coincidence or a natural by-product of the research process.

Positive-outcome bias is harmful for several reasons. First, even the most careful reader cannot detect its presence by reading individual articles. Positive outcome bias can only be suspected when a large number of studies are evaluated, as was done in the present report. Second, and more importantly, the effect of publication bias in journals is magnified when clinical trials are selected for inclusion in meta-analyses and clinical reviews. If the published literature consists disproportionately of positive studies, the resultant meta-analyses will demonstrate a substantial upward bias in the overall estimates of treatment effects.

If other investigators confirm the findings of the present study, and if some of the influences and less-than-ethical behaviors of commercial parties documented in non-surgical specialty journals are prevalent in orthopaedics, then provision of financial disclosures alongside published articles may not be sufficient. In that circumstance, it might be worth considering adjusting the peer-review process to provide disclosure of potential conflicts of interest to reviewers when manuscripts are reviewed, rather than merely disclosing such relationships to readers at the time of publication.

Outcome	Whole Cohort	Industry-Funded	Statistician Involved	Country	
				USA	Other
Positive N (percent)	200 (63.5)	45 (78.9)*	29 (65.9)	120 (65.9)	59 (63.4)
Negative N (percent)	101 (32.1)	12 (21.1)	15 (34.1)	62 (34.1)	34 (36.6)

Table 1: Comparison of Positive and Negative Studies, by Study Variables. *$p < 0.025$ compared with studies that received no commercial funding; no other variables showed statistical significance at the $p < 0.05$ level.

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Augmenting Skeletal Integrity at Senescence via "Restful" Physical Activity

SUNDAR SRINIVASAN, PH.D., STEVEN C. AGANS, B.S., KATY KING, B.S., NICHOLAS Y. MOY, B.S., SANDRA L. POLIACHIK, PH.D., AND TED S. GROSS, PH.D.

Age and menopause related bone loss markedly compromise skeletal integrity. The accompanying incidence of skeletal fractures substantially increase health care expenditures, erode quality of life and raise levels of morbidity. Physical exercise, an attractive lifestyle choice for many, holds promise as a non-invasive, non-pharmacologic intervention against age-related bone loss. However, the mild and moderate types of exercise most successfully implemented in the elderly have proved ineffective in enhancing bone mass. The ineffectiveness of mild and moderate loading is consistent with the age related degradation in bone mechanotransduction (i.e., in the ability to perceive, initiate and sustain an osteogenic response). Interestingly, we recently observed in both young and adult animals that insertion of a 10-s unloaded rest interval between load cycles transformed low-magnitude, repetitive loading incapable of influencing bone cell populations into regimens that substantially enhanced osteoblastic activation (nearly 6-fold) and bone formation (over 4-fold). Given the surprising osteogenic potency of this unique stimulus, we hypothesized that rest-inserted loading could potentially overcome age-related deficits in mechanotransduction function. Here, we test our hypothesis by examining whether insertion of rest between load cycles enhances bone formation in the aged skeleton.

METHODS

Aged female C57BL/6 mice (21 Months, n=30) underwent mechanical loading utilizing the non-invasive murine tibia model. The right tibiae were subject to a 1-Hz waveform and received 50 load cycles/day over 2-weeks with animals being randomly assigned to one of three protocols: i) repetitive low-magnitude loading (low), ii) repetitive high-magnitude loading (high), iii) rest-inserted low-magnitude loading wherein a 10-s unloaded rest interval was inserted between each load cycle (low - 10s rest). The low- and high magnitude protocols were calibrated to induce 1200 με and 2400 με at the tibia mid-shaft. Animals were allowed normal cage activity between loading protocols. Calcein was administered on days 3 and 12 and

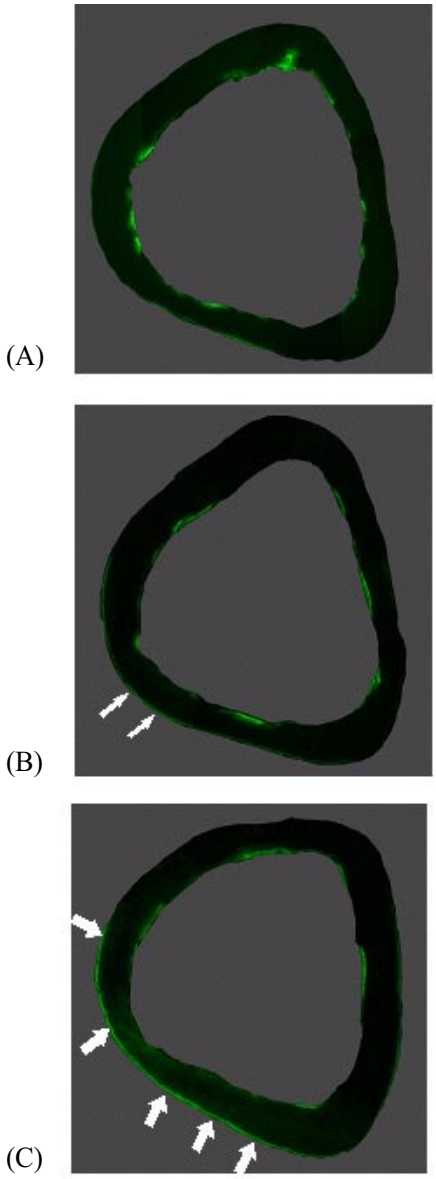

Figure 1: Composite fluorescent images of mid-shaft cross-sections from control tibia (A) and tibiae exposed to low-magnitude (B) and low-magnitude rest-inserted loading (C). While low-magnitude loading only minimally influenced periosteal bone formation compared to controls, insertion of 10-s rest between low-magnitude cycles substantially enhanced bone formation (C).

animals sacrificed on day 15. Upon sacrifice, the right (experimental) and left (intact contralateral control) tibiae were disarticulated and dissected of soft tissue. Mid-shaft cross sections (100 μm) were obtained and bone formation assessed via measures of dynamic histomorphometry.

Results

Consistent with the response of the senescent skeleton to mild types of activity, exposure of the aged murine tibia to 50 cycles/d of low-magnitude loading (low, 1200 με) did not significantly enhance periosteal bone formation rates compared to pooled contralateral controls (0.05 ± 0.03 vs 0.03 ± 0.01 $\mu m^3/\mu m^2/d$, p= 0.12, Figure 1). In contrast, both high-magnitude loading (high, 2400 με, 0.12 ± 0.02 $\mu m^3/\mu m^2/d$, p= 0.03), and low-magnitude rest-inserted loading (0.13 ± 0.03 $\mu m^3/\mu m^2/d$, p= 0.01) significantly enhanced periosteal bone formation (Figure 1 and Figure 2).

Discussion

Similar to previous reports, low-magnitude mechanical loading (low, comparable in magnitude to that encountered during mild functional activity) was not sufficient to significantly enhance periosteal bone formation in the aged skeleton. Increasing strain magnitudes by 2-fold (high, similar in magnitude to that attained during strenuous activities) was required to induce significant bone formation. However, implementation of this approach (i.e., high-magnitude loading) is of limited feasibility as the elderly are unable to consistently comply with strenuous types of loading events capable of building bone mass. As an alternate strategy, we found that inserting a 10-s rest interval between load cycles transformed a non-stimulatory low-magnitude regimen into a potent osteogenic stimulus in the aged skeleton.

In terms of mechanisms underlying the observed responses, the benefit of rest-inserted loading in the aged skeleton is surprising (particularly, the potency of low-magnitude rest-inserted loading). This is especially so considering the limited availability of osteoprogenitor cells and the increased propensity for fully differentiated osteoblasts in aged bone tissue to undergo apoptosis. Within this context, while rest-inserted loading transforms a subtle stimulus and enables sustained activation of the aged periosteum, the rest interval may also provide a critical non-stimulatory window that facilitates improved osteoblast survival. Given the ease of implementation of this novel stimulus (inserting an unloaded rest interval between load cycles), our future investigations of underlying mechanisms and optimization of this concept, including exploitation of synergy with select growth factors, should allow consideration of low-magnitude, rest-inserted exercise regimens for building bone mass and augmenting skeletal integrity in the frail elderly.

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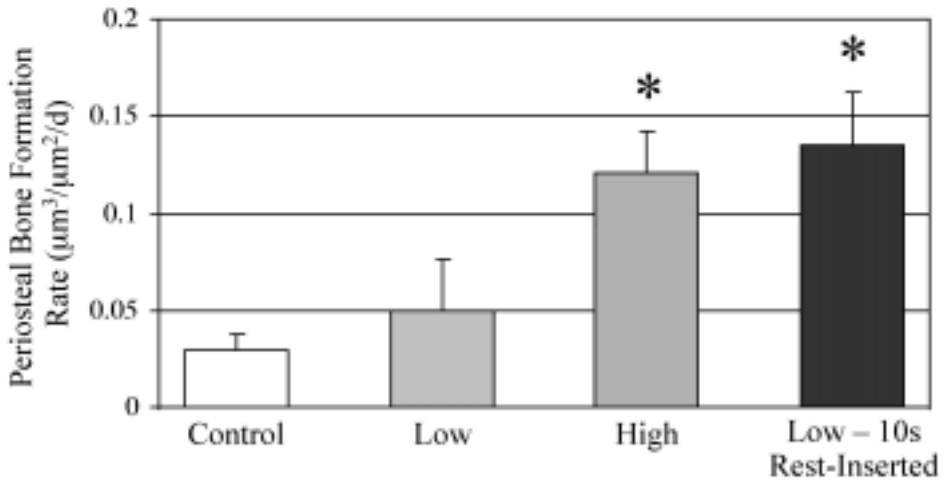

Figure 2: When 'standard' or repetitive loading protocols were utilized, the aged skeleton required high-loading magnitudes (High) in order to initiate significant (*) bone formation (i.e., low magnitude loading was not osteogenic). Instead, insertion of a 10-s rest between low-magnitude load cycles (Low-10s Rest) was potently osteogenic in the senescent skeleton and significantly increased bone formation over 4-fold compared to controls.

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Regrowth of Amputated Rabbit Digit Tips

CHRISTOPHER H. ALLAN, M.D., TRACI BARTHEL, M.D., AND BRIAN P. RUBIN, M.D., PH.D.

In certain instances, higher vertebrates including man respond to injury with regeneration of functional tissues rather than with the production of scar. Digit tip amputation is one such instance. The cellular and molecular events involved in this phenomenon are not well understood. The most common animal model of this process is presently the mouse, whose small size makes certain types of study technically challenging. In this study, digit tip amputations were performed on the middle digit of the left forepaw of ten New Zealand White rabbits. Amputation of the distal phalanx immediately distal to the distal interphalangeal (DIP) joint was performed under 3.5x loupe magnification. Eight weeks later the digits were removed for study. Regrowth of multiple tissue types (bone, nail, epithelium, subcutaneous tissue) was seen in all cases where the plane of amputation passed distal to the DIP joint, suggesting that the rabbit may be useful in the study of this phenomenon, particularly for work where the small size of the mouse digit makes the manipulation of regrowing tissues difficult.

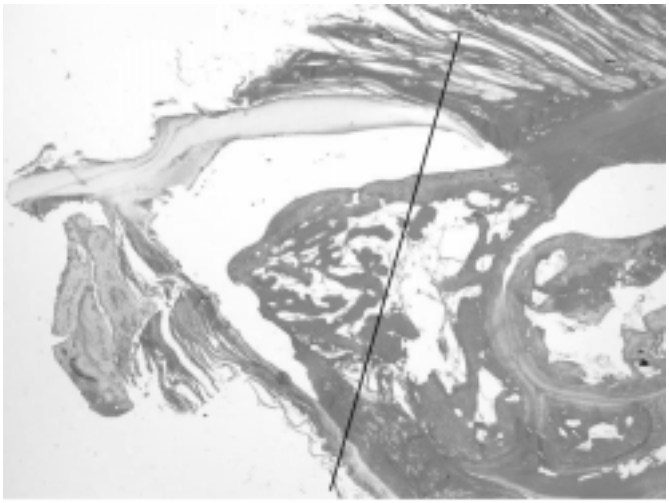

Figure 1a: Amputated and regrowing digit tip, 8 weeks; line = plane of amputation.

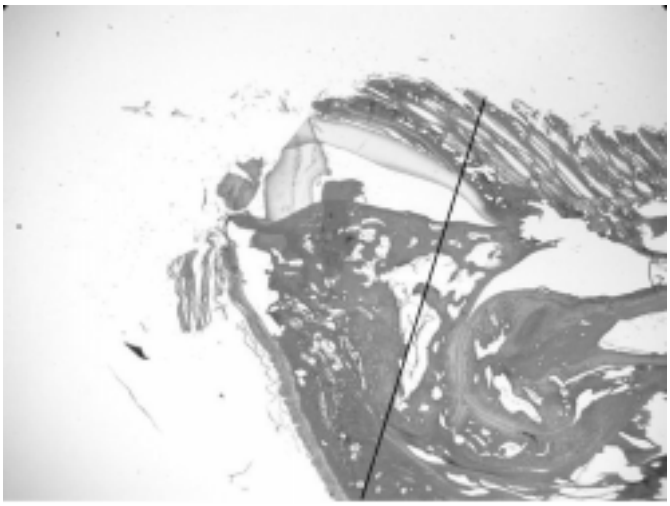

Figure 1b: Second specimen; note preparation artifact with nail overlying distal tip.

INTRODUCTION

The observation that children can regrow amputated fingertips has interested many researchers since this was first noted in the 1970s. Our group works in the field of hand trauma surgery and is highly motivated to develop improved treatments for our severely injured patients. We have wished to learn more about the cellular and molecular processes involved in digit tip regrowth, believing that this information alone or combined with tissue-engineering techniques may help us improve present treatment options.

Finding work with mouse digit tips quite technically challenging due to their small size, we decided to assess the response to digit tip amputation in a larger animal.

MATERIALS AND METHODS

Methods

Ten immature New Zealand White rabbits were anesthetized and the middle digit of the left forepaw amputated in a region distal to the distal interphalangeal joint. Amputated digit tips were preserved to document level of amputation. The amputation site was dressed and animals given pain medication. Daily dressing changes were performed and dressings discontinued when the wound was dry. Eight weeks after surgery the operated digit was removed from the left forepaw for histological evaluation. At the same time, the contralateral (right forepaw) middle digit was removed for comparison.

Histology

Amputated digit tips (Day 0) and operated digits (eight weeks) as well as control digits (eight weeks) were treated in formalin and decalcified for twenty-four hours, then embedded in paraffin for sectioning. Specimens were stained with hematoxylin and eosin and sectioned for standard light

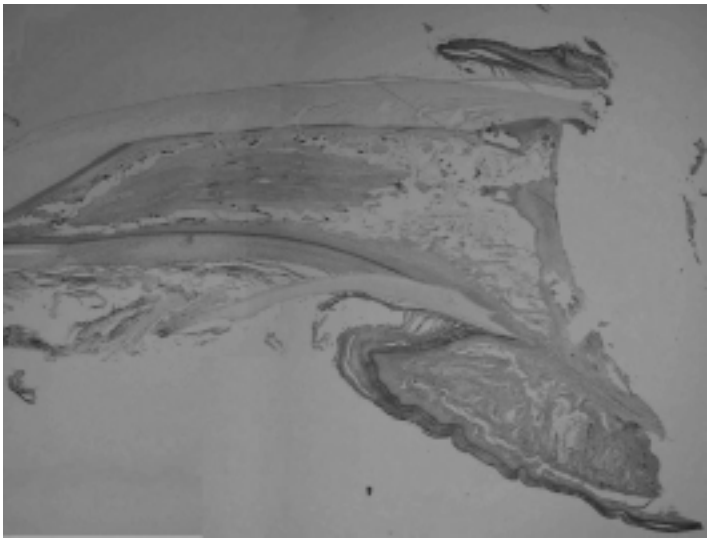

Figure 2: Amputated rabbit digit tip; plane of amputation distal to DIP joint.

microscopy. Day zero amputated digit tips were compared with eight week specimens to confirm level of amputation and to evaluate the response to tip amputation.

Results

Of the ten specimens evaluated, four passed through the DIP joint, rather than distal to it. In these cases no regrowth of digit tip tissues was seen, and the wound healed with a stump. In the remaining six cases where the plane of amputation appeared to pass distal to the DIP joint and through the base of the proximal phalanx, regrowth of the digit tip to varying degrees was seen (Figure 1a and b), with the formation of several tissue types including bone, nail, epidermis, dermis, and subcutaneous tissue, and without evidence of scarring. The tissues regrew incompletely, as compared with the extent of the tissue removed at the time of amputation (Figure 2) and as shown in an image of a normal rabbit digit DIP joint without tip amputation (Figure 3).

Discussion

Millions of persons are affected by traumatic limb loss and severe extremity injury. In 1996, (National Health Interview Survey), there were 1,285,000 amputees in the US alone. Present treatments include reattachment, repair, revision amputation, use of a prosthesis, transplantation, and various reconstructive procedures. It is extremely rare for any of these treatment options to restore normal function, and several have potentially severe side effects.

The features of the regenerative response to injury are the same as those required for successful tissue engineering: cells, scaffolds and signaling molecules are all involved. We plan to identify cells and signaling pathways involved in this regrowth. We may either stimulate enhanced regeneration in situ or better engineer replacement tissues for patients with severe limb injuries, since the cells and signaling molecules involved in regenerative healing form new and functional tissue so successfully.

Evaluation of healing at different time periods and in animals of different ages should provide interesting information. More stringent analysis of the healing tip is needed, as one of our priorities is to identify the first population of cells to appear after wounding. These cells may be stem-cell-like in function, and therefore useful in enhancing in-situ regeneration and tissue engineering strategies.

Summary

At eight weeks after tip amputation through the digit just distal to the DIP joint, the rabbit digit tip demonstrates regrowth of multiple tissue types including bone, epithelium, subcutaneous tissue, and nail, with no evidence for scar tissue formation. These findings are consistent with tissue regeneration. The rabbit digit tip amputation may represent a useful model of this phenomenon of tissue regeneration in higher vertebrates.

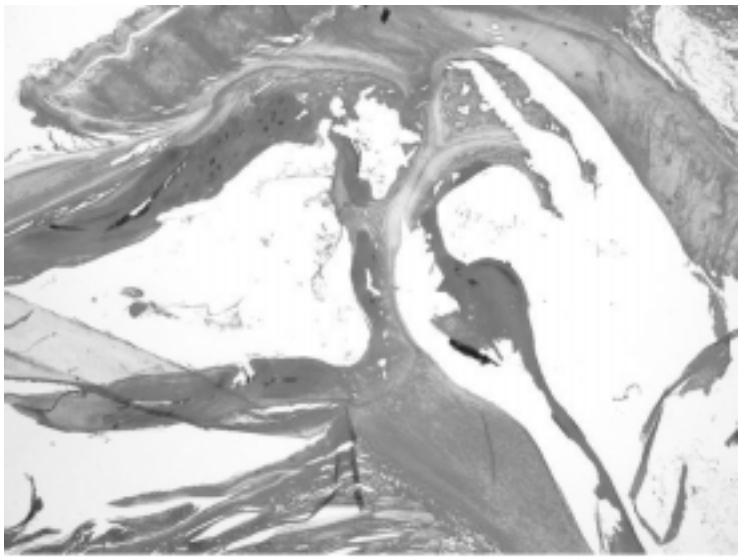

Figure 3: Rabbit digit DIP joint, no amputation: note volume of bone of distal phalanx compared with regrowing specimens.

ACKNOWLEDGEMENTS

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Diagnosis and Treatment of Craniocervical Dissociation: A Series of 17 Consecutive Survivors Over Seven Years

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Acute traumatic osseoligamentous instability at the craniocervical junction is usually fatal. However, improved patient retrieval and emergent management techniques have increased patient survival to hospital. Delays in diagnosis are thought to have potentially devastating consequences. Causes of missed diagnosis are manifold, and include low clinical suspicion, presence of multiple life threatening injuries, and difficulty visualizing relationships at the craniocervical junction on conventional radiographs. Our goal was to evaluate potentially correctable causes of delayed diagnosis of CCD while comprehensively evaluating a series of patients treated with posterior instrumented occipitocervical fusion.

MATERIALS AND METHODS

A retrospective study was conducted of 17 consecutive survivors of CCD at Harborview Medical Center (HMC) between 1994 and 2002. Data collected from spine and trauma registries, medical records and spinal imaging studies were retrospectively reviewed to identify (i) the timing and manner of diagnosis; (ii) the effect of delayed diagnosis on neurologic function; (iii) the diagnostic reliability of the lateral cervical spine radiograph (C-spine lateral); (iv) surgical and non-surgical complications, and (v) neurologic outcome. A delay in diagnosis was defined as the failure to identify or suspect CCD upon completion of the ATLS-mediated spinal evaluation, typically defined as completion of a lateral plain radiograph and CT scan of the cervical spine.

Two patients (12%) had normal sensorimotor function of the extremities, and 15 patients (88%) had spinal cord injuries (SCI) (2 complete, 13 incomplete). All patients had associated injuries.

A lateral cervical spine radiograph was obtained as part of the initial trauma evaluation. CT scans of the head and cervical spine were obtained in all patients. Radiographic screening of the craniocervical junction was done using Harris' lines, Wackenheim's line, and Powers' ratio. Nine patients were seen at other hospitals first and may have been initially treated according to a different algorithm.

Once CCD was identified or suspected, provisional stabilization was secured through manual reduction and HALO application under fluoroscopic guidance (Figure 1). MRI of the cervical spine was obtained to determine the extent of ligamentous disruption and SCI. Patients with MRI findings of craniocervical osseo-ligamentous injury who had grossly preserved alignment (< 2mm displacement) and whose craniocervical stability remained unclear were evaluated with traction tests (Figure 2).

Definitive management of CCD entailed rigid occipitocervical segmental instrumentation and arthrodesis with structural bone graft secured to the occiput and cervical spine (Figure 3). Postoperative immobilization was achieved with a brace or HALO. Postoperative CT scans assessed alignment and hardware placement. Healing was confirmed 3 months postoperatively with upright flexion-extension lateral radiographs. Clinical follow-up was provided through the Northwest Regional Spinal Cord Injury System.

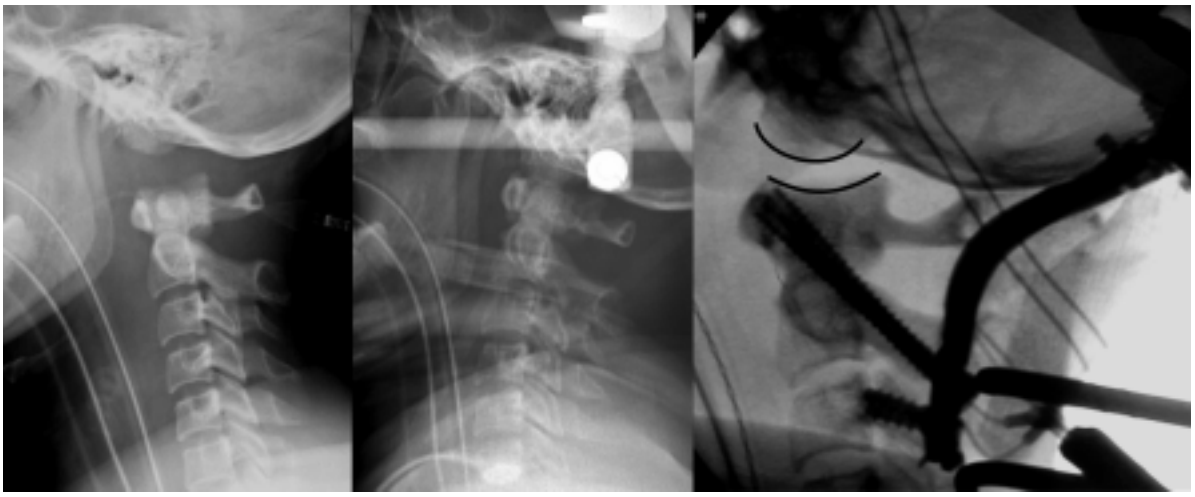

Figure 1: Widely displaced Stage 3 CCD. From left to right: C-spine lateral x-rays after injury, after provisional closed reduction with a HALO, and after internal fixation in a 35 year-old woman who sustained a highly displaced stage 3 CCD when she was struck by a motor vehicle. Even with open reduction, the atlanto-occipital articulation remained distracted and anteriorly translated (black lines).

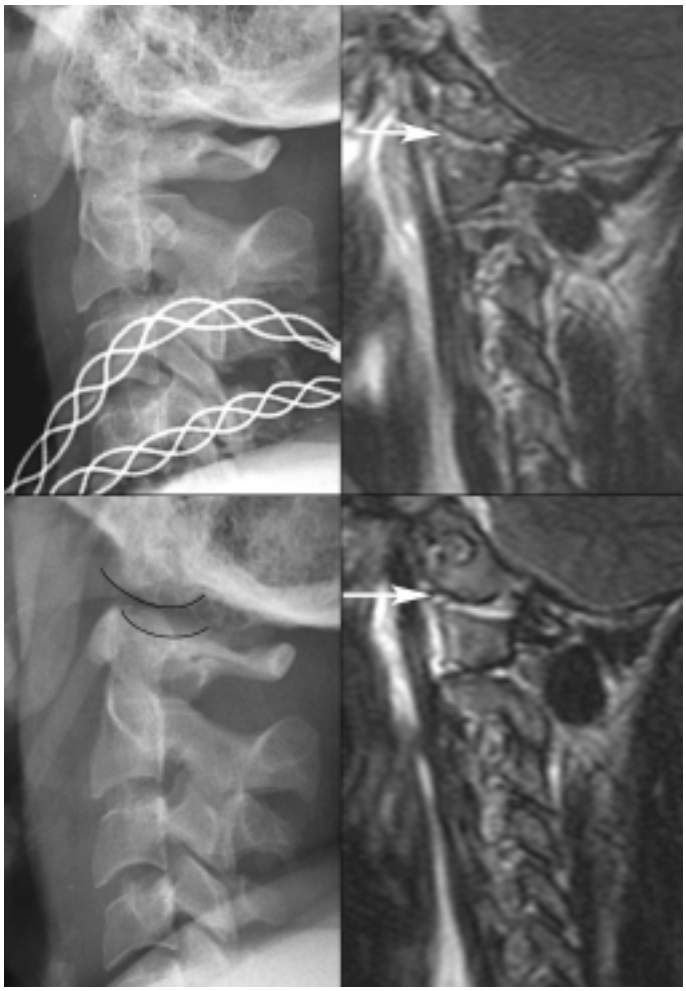

Figure 2: Mildly displaced Stage 2 CCD. Clockwise from top left: C-spine lateral, sagittal MRI through left atlanto-occipital joint, sagittal MRI through right atlanto-occipital joint, and traction C-spine lateral in a 39 year-old woman who sustained a mildly displaced stage 2 CCD with a basion-dens relationship within 2 mm of normal and only mild, unilateral right-sided loss of atlanto-occipital congruence (white arrows). The traction radiograph was used to distinguish this as a highly unstable stage 2 injury (black lines) requiring internal fixation, rather than a stage 1 injury in which closed treatment would have sufficed.

RESULTS

Diagnosis

Four of 17 patients (23%) were diagnosed with CCD during initial trauma evaluation. Two of these injuries (12%) were detected on the initial C-spine lateral and the other 2 were diagnosed on the cervical spine CT scan. None of these 4 patients worsened neurologically before surgery.

Thirteen of 17 patients (76%) had a delay in diagnosis, which averaged 2 days in length (range 1 to 15 days). Five of these 13 patients (38%) had worsening of their neurologic condition before CCD was clinically recognized.

Operative stabilization was undertaken in all patients. Average follow-up was 15 months (range 6 to 45 months).

One patient had postoperative worsening of sensorimotor function caused by a malreduction that resulted in hydrocephalus and cerebellar infarction, presumably from vertebrobasilar insufficiency. He underwent urgent occipitocervical realignment, decompression and stabilization, and placement of a ventriculoperitoneal shunt. At 16-month follow-up, the quadriplegia had resolved, with a mildly broad-based gait as his only sign of neurologic dysfunction.

No patient had occipitocervical pseudarthrosis or hardware failure.

One (6%) superficial wound infection required antibiotics and local wound care. One (6%) patient who had repair of a traumatic dural tear required a lumbar subarachnoid drain to resolve CSF wound drainage.

The average ASIA motor score improved from 50 preoperatively to 79 at follow-up. Eleven of 13 (85%) patients with incomplete SCI improved by one ASIA grade. Neither of the two patients without SCI worsened neurologically. One of the two patients with complete SCI improved from a high cervical to a T5 level. The second patient, who presented with wide craniocervical displacement (Figure 1) remained ventilator-dependent with a motor score of zero 16 months postoperatively. She was the only patient without motor improvement.

The average Basion-Dens Interval (BDI) improved from 16 to 10 mm, and average Basion-Axial Interval (BAI) decreased from 10 mm to 8 mm.

DISCUSSION

Autopsy studies have ascribed up to 90% of traumatic fatalities to injuries of the upper cervical spine. Bucholz estimated a survival chance of 0.65 to 1% for patients with CCD based on a prospective morgue study. However, dramatic improvements in the emergent management of trauma victims appear to have improved survival. The burden of appropriately anticipating, identifying and treating survivors is thus shifting to the clinician.

Previously recognized difficulties in diagnosing craniocervical instability were highlighted in this series. The highly unstable nature of these injuries was either entirely unrecognized or drastically underappreciated in over three-fourths of our patients. This problem can be attributed to misleading clinical and radiographic features, and the lack of a systematic approach to evaluating the craniocervical junction. Most patients had cognitive impairment due to loss of consciousness (13 patients, 76%) or a closed head injury with intracranial hemorrhage (13 patients, 76%), which contributed to diagnostic difficulties. Since the trauma C-spine lateral remains key in the initial evaluation of a patient with suspected cervical spine

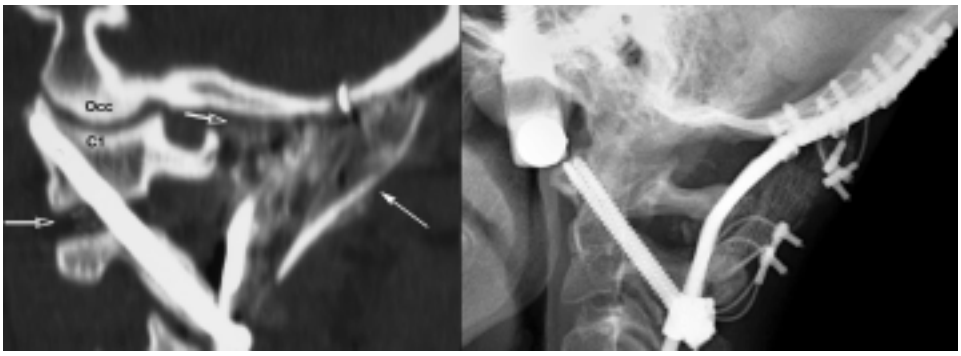

Figure 3: Operative Technique. Postoperative sagittal CT (left) and lateral C-spine x-ray (right) illustrating congruent reduction of atlanto-occipital and atlanto-axial joints and arthrodesis using segmental occipitocervical instrumentation, C1-2 transarticular screws, structural bone graft with suboccipital and C2-sublaminar fixation (solid arrow) and autologous cancellous bone graft in the C1-2 joints and at the craniocervical junction (open arrows).

trauma the most alarming finding of this study is how infrequently craniocervical instability was suspected on standard radiographic evaluation (2/17 patients, 12%). Retrospective review of these x-rays showed both the BDI and BAI to be within normal parameters in only 1 patient.

Even a short delay in diagnosis and treatment carried potential life-threatening consequences. Five of 13 (38%) undetected injuries were recognized after a decline in neurologic function, which occurred even with cervical collar immobilization and full spine precautions, highlighting the inadequacy of standard bracing in stabilizing CCD.

Other pitfalls in the radiographic diagnosis of craniocervical instability can be attributed to associated fractures of the upper cervical spine . This tended to lead to insufficient immobilization for craniocervical stability and a loss of urgency in further evaluating the craniocervical junction. In the current study, ligamentous avulsion fractures occurred in 9 patients (53%), with more than one fracture type seen in 6 patients (35%). The frequency with which avulsion fractures were identified suggests that their presence should heighten suspicion for CCD and trigger early follow-up investigation of ligamentous integrity with MRI.

Traynelis has identified three occipitocervical injury patterns based on direction of displacement. However, directional criteria, may be misleading since complete ligamentous disruption renders the position of the head arbitrary. Furthermore, this classification does not address injury severity or spontaneously repositioned injuries. Based on our clinical experience, we propose a 3-stage classification system with therapeutic implications. A Stage 1 injury is a stable minimally- or non-displaced craniocervical injury with preservation of sufficient ligamentous integrity for nonoperative treatment. Stage 2 represents a spontaneously reduced bilateral craniocervical disruption with minimal displacement (BAI/BDI < 2 mm beyond normal) in which a traction test confirms complete loss of craniocervical stability, requiring internal fixation. Stage 3 represents a highly unstable injury defined by gross craniocervical malalignment (BAI/BDI > 2mm beyond acceptable limits), also requiring internal fixation. The term "craniocervical dissociation" is reserved for Stage 2 and 3 injuries, where ligamentous instability is complete.

Increased awareness is important for prompt diagnosis and stabilization of craniocervical instability. Thirteen of 17 survivors had a delay in diagnosis either at our institution or the transferring hospital. A disciplined, systematic approach to the evaluation of screening cervical spine imaging studies offers the potential to identify most injuries. In addition to its therapeutic implications, a classification system that includes a category for spontaneously reduced yet highly unstable injuries may heighten awareness that even a life-threatening injury such as CCD may present with a misleadingly subtle radiographic appearance. Delayed diagnosis places the patient at risk for neurologic worsening. With timely diagnosis and internal occipitocervical fixation, even patients with severe neurologic deficits may experience a great deal of functional improvement.

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Acetabular Fractures in Senior Patients

ALYSANDRA SCHWARZ, M.D. AND M.L. CHIP ROUTT, JR., M.D.

Each year, the number of persons living past the age of 65 years increases. It is estimated that by the year 2020, the population of individuals older than 65 years will climb to 52 million from its current level of 30 million. Similarly and not surprisingly, the incidence of acetabular fractures in this age group is also increasing.

Different opinions exist regarding the optimal treatment for senior patients with acetabular fractures. Treatment remains a controversial issue since these patients have more comorbid medical conditions which increase their risk of complications. These medical comorbidities cause some authors to propose conservative treatment of acetabular fractures, usually consisting of bed rest with or without skeletal traction. The complications of prolonged bed rest include skin breakdown, urinary infections, pulmonary problems, among others. Closed management of displaced acetabular fractures results in articular malunion with resultant arthritis. Hip arthroplasty in patients with acetabular malunion is associated with increased rates of acetabular component loosening. In order to avoid such problems, surgical treatment is advocated by some authors in an attempt to provide accurate fracture reduction and stable fixation. Unfortunately for these patients, osteopenia allows more extensive articular impaction injuries and similarly complicates stable fracture fixation. Certain surgical modifications such as cable fixation, allograft cortical bone supplementation, or bone cement augmentation have been described to address the problem of poor bone quality in senior patients with acetabular fractures. Few authors advocate acute total hip arthroplasty in these patients as treatment for the acetabular fracture. Hip arthroplasty in such situations is associated with predictable complications such as acetabular component loosening and postoperative dislocation. Acute hip arthroplasty requires restoration of the acetabular fracture osseous anatomy prior to implantation of the component which further prolongs the surgical procedure.

We evaluated our senior patients with displaced acetabular fractures treated operatively using routine surgical techniques and implants. We report the epidemiology of this form of acetabular fracture treatment in patients over the age of 65, with special attention to hospital course and perioperative complications.

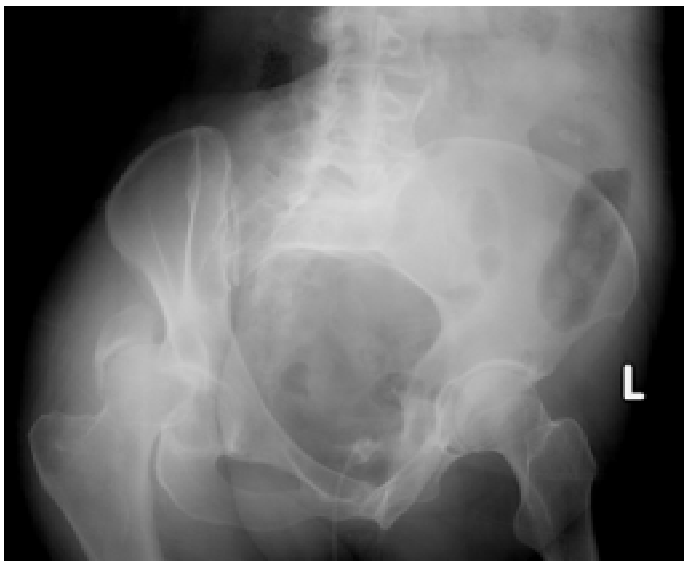

Figure 1A: This 72 year old female was injured in an automobile accident. She sustained a fracture-dislocation of her right hip. The obturator-oblique pelvic radiograph demonstrates the posterior wall acetabular fracture pattern.

MATERIALS AND METHODS

Between January 1, 1996 and December 31, 1999, we treated 352 patients with displaced acetabular fractures operatively using conventional techniques of open reduction and internal fixation. Only 27 (7.67%) of these patients were 65 years of age or older. The average age of these 27 senior patients was 76.3 years, ranging from 65 to 89 years. There were 18 male and 9 female patients. Fifteen fractures were left-sided and 12 were right-sided injuries. The average time from injury until surgery was 3.8 days (range 1 to 8 days). The mechanisms of injury included falls in 14 patients, motor vehicle accidents in 11 patients, and sports injuries in 2 others. Fourteen of the 27 senior patients had associated injuries, while 13 had isolated acetabular fractures. Eight patients had fracture-dislocations which required manipulative reductions acutely in the emergency department. All of the patients were placed in skeletal traction prior to surgery.

Each patient was fully evaluated by the geriatric medicine and/or general surgery consultants prior to surgery. All patients were screened for venous thromboses using duplex ultrasound evaluations. The patients were treated perioperatively with thromboembolic stockings, sequential compressive devices, and subcutaneous heparin.

Radiographic evaluations included anteroposterior pelvic and Judet oblique acetabular plain radiographs, and pelvic computed tomography preoperatively for all patients. Two patients were noted to have pelvic ring involvement in addition to their acetabular fractures. The femoral head and acetabular dome were carefully evaluated for impaction injuries using the preoperative pelvic imaging studies. The fractures were then classified

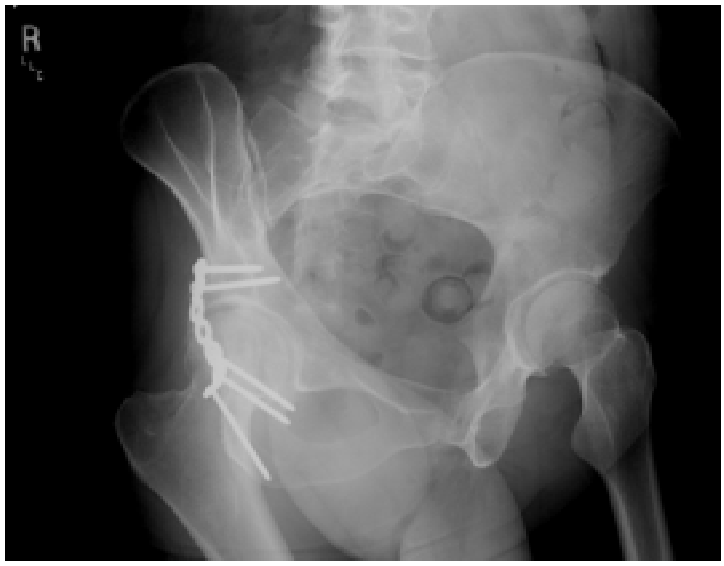

Figure 1B: This pelvic computed tomography (CT) axial image of her acetabular dome reveals the posterior displacement, fracture comminution and osteochondral impaction components.

according to Letournel based on the imaging studies. There were 10 patients with elementary fracture patterns: 5 posterior wall and 5 anterior column fractures. Seventeen patients had associated fracture patterns: 9 associated both column, 3 anterior column with associated posterior hemitransverse, 3 T-type, 1 transverse with associated posterior wall, and 1 posterior column with associated posterior wall.

Operative treatment included open reduction with internal fixation, and percutaneous fixations. All 27 patients were positioned on a radiolucent operating table and received intravenous antibiotic prophylaxis. Twenty-five patients had significantly displaced acetabular fractures mandating open reduction and internal fixation. An ilioinguinal anterior surgical exposure was chosen for 15 patients: 8 with associated both column, 5 with anterior column, and 2 with anterior column with associated posterior hemitransverse fractures. A lateral Kocher Langenbeck surgical exposure was selected for 6 patients: 5 posterior wall, and 1 posterior column with associated posterior wall fractures. A prone Kocher-Langenbeck approach was used in 4 patients: 3 T-type, and 1 transverse with associated posterior wall fractures .

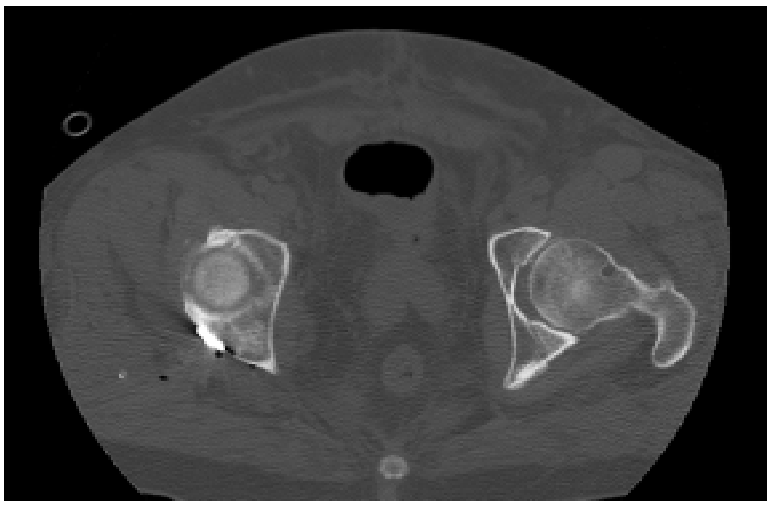

Figure 1C: The postoperative pelvic CT scan shows the fracture reduction and implant location. The osteochondral impaction fragment has been elevated and its defect filled with cancellous bone graft.

Standard fixation techniques were used for all 27 patients. Twenty-three patients were treated with open reduction and internal fixation using at least one reconstruction plate, with an average of 1.5 plates per patient. Two other patients underwent open reduction and internal fixation using lag screws only. Two patients had minimally displaced acetabular fractures which demonstrated instability on examination of the hip using fluoroscopic imaging. These two patients had closed reduction and percutaneous fixation of their acetabular fractures using cannulated 7mm cancellous screws only. One patient had an associated both column fracture, and the other patient had an anterior column with associated posterior hemitransverse fracture.

Seven patients had impaction fractures of the femoral head. Six patients had acetabular dome impaction injuries. Three of the five posterior wall fractures had associated marginal impaction injuries. Three of the six patients with dome impaction required cancellous allograft bone grafting, and all three patients with marginal impaction underwent autogenous bone grafting from the greater trochanter.

Postoperative duplex scans were obtained on all patients immediately after surgery and at one week intervals until discharge.

RESULTS

Twenty-one patients had significant associated medical conditions at presentation.

Eight patients had a prior operation at the proposed site for acetabular fixation. The previous surgical site was incorporated into the acetabular exposure in seven patients. One patient's surgical plan was changed due to the preexisting surgical incision.

The average estimated blood loss for the patients treated with open reduction and internal fixation was 817 cc. Eight of the 25 patients treated with open reduction received cell saver blood, with the average amount

returned being 422 cc. Six of the 25 patients treated with open reduction received intraoperative blood transfusions, with an average of 2.3 units transfused. The two patients with percutaneous fixation had minimal blood loss.

Twenty patients (74%) developed 42 documented complications (210%). Only seven patients (26%) had an uncomplicated hospital course.

Multisystem organ failure accounted for the only postoperative death. Ten patients were admitted to the intensive care unit immediately following surgery, one patient was transferred to the ICU on the first postoperative day, one patient was admitted to a cardiac monitoring ward, and the other fifteen patients were admitted directly to a routine orthopedic hospital ward. Sixteen patients underwent an additional 30 invasive diagnostic or therapeutic procedures while hospitalized.

Fourteen patients (51.9%) had diagnosed deep venous thromboses (DVT). Two DVTs were noted preoperatively, and treated with a vena caval filter. Twelve patients had documented DVTs postoperatively yet prior to hospital discharge. Three of these patients required placement of an inferior vena caval filter due to medical conditions which prohibited the use of systemic anticoagulation. No complications resulted from the vena caval filters. The other nine patients had routine systemic anticoagulation. There were no diagnosed incidents of gastrointestinal bleeding as a result of therapeutic anticoagulation in these patients. There was a single wound hematoma which required evacuation two weeks postoperatively.

Cardiopulmonary complications occurred in 14 patients (51.9%). Five patients developed pneumonia. Another patient developed a symptomatic pulmonary embolus confirmed by a ventilation perfusion lung scan. Six patients required intubation and mechanical ventilation while hospitalized, one requiring conversion to a tracheostomy prior to discharge. Respiratory depression resulted from excessive narcotic sedation and required chemical reversal in one patient. Another patient had congestive heart failure postoperatively.

Neurological complications resulted in seven patients (25.9%). Five patients had transient altered mental status. Two patients suffered cerebrovascular accidents. Only one patient suffered delerium tremens secondary to alcohol withdrawal. There was one postoperative sciatic nerve palsy.

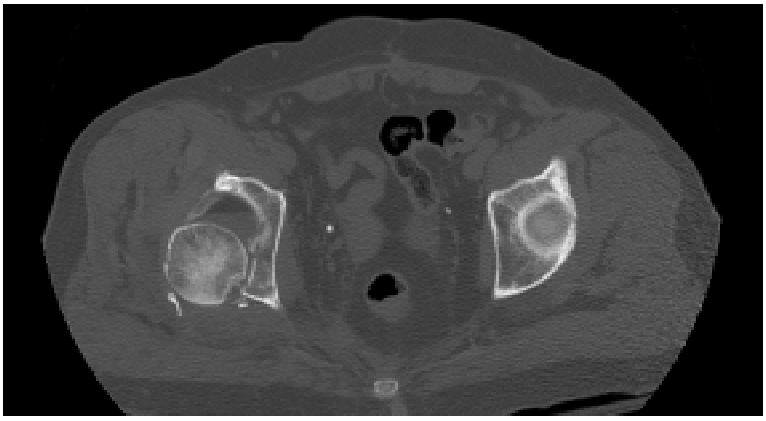

Figure 1D: She was asymptomatic at her one year follow up evaluation. The oblique acetabular radiographs confirm uneventful healing without arthritis or ectopic bone formation. The osteochondral fragment did not collapse.

Gastrointestinal complications were limited to postoperative symptomatic ileus in only two patients. Two patients developed bacteremia without known etiology. Only one urinary tract infection was identified.

Unusual complications included postoperative blindness in one patient, great toe embolus in one patient, and subdiaphragmatic placement of a chest tube in one patient. Another patient had thrombocytopenia requiring transfusion, while one patient developed acute renal failure requiring hemodialysis. One patient died from multisystem organ failure.

The average duration of hospitalization was 15.3 days (range 5 to 42 days). Twenty three patients were independent with activities of daily living prior to injury. Of these, 16 were discharged to a skilled nursing facility, 4 were transferred to inpatient rehabilitation, 2 were discharged home, and one expired. Two patients resided in assisted living quarters prior to admission. Of these, one returned to the same location and the other was admitted to a skilled nursing facility. Both patients who were residing in a skilled nursing facility prior to surgery were readmitted to the same facility.

SUMMARY

Displaced and unstable acetabular fractures in senior patients are difficult to manage effectively for a variety of reasons. Poor bone quality complicates the surgeon's attempts to achieve stable internal fixation. The patient's medical comorbidities complicate their treatment. Spencer (1989) reported on the conservative treatment of 25 patients over the age of 65 with acetabular fractures. He found a 30% rate of unacceptable functional result. He noted that fractures had late displacement, despite sustained treatment with traction. He defined poor prognostic indicators as osteoporosis, femoral head fractures, delayed diagnosis, inadequate radiographs, inappropriate traction, and early weight bearing. Some surgeons believe that if conservative treatment does not lead to an acceptable outcome, the elderly patient may be a candidate for a delayed total hip arthroplasty. Unfortunately, the osseous deformity of the malreduced acetabulum makes these reconstructive procedures more difficult. Clinical outcomes after delayed arthroplasty are inferior to those for degenerative conditions. Romness and Lewallen (1990) found the loosening rates of acetabular components after post traumatic reconstructions are four to five times greater than in surgeries performed for routine hip arthroplasty.

Letournel defined osteopenia of the innominate bone the most important contraindication to operative

treatment, yet he treated 103 acetabular fractures in patients over the age of 60 with open reduction and internal fixation. Advantages of a reconstructed acetabulum include possible restoration of function, preservation of native joint, and, if future arthroplasty is required, more normal osseous anatomy for implant placement. Potential disadvantages are encountered if conversion to a total hip arthroplasty is required and include the presence of scar tissue and an increased infection rate.

In our series, 27 senior patients with acetabular fractures were treated operatively and, 74% of these patients had a complicated clinical course. Twenty of our patients had a 210% complication rate.

Conclusion

The surgical treatment of displaced acetabular fractures is especially challenging in senior patients. Those with medical comorbidities have increased postoperative complication rates. Senior patients and their family members should be aware of such associated risk prior to operative intervention.

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Preoperative Factors Associated with Greater Improvement Following Humeral Hemiarthroplasty

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Hemiarthroplasty has been shown to be effective in improving the comfort and function of shoulders in which the humeral joint surface has been lost, specifically in patients with primary glenohumeral arthritis, secondary degenerative joint disease, avascular necrosis of the humeral head, and those with combined loss of the glenohumeral joint surface and rotator cuff. However, the published reports indicate large variability in the effectiveness of this procedure. For example, in two recent series of hemiarthroplasties, the rate of unsatisfactory results were 25% (Sanchez-Sotelo, 2001) and 47% (Sperling, 1998). The factors contributing to the variability in effectiveness of hemiarthroplasty have not been well studied.

The authors suggest that preoperative decision-making by patients and their surgeons could be better informed if the factors associated with the effectiveness of the procedure were identified. The purpose of this study was to test the hypothesis that the effectiveness of humeral hemiarthroplasty is significantly related to factors that can be identified before surgery.

METHODS

Excluding procedures for the management of acute fractures and non-unions, the senior author performed eighty-six primary hemiarthroplasties between January 1, 1990 and October 1, 1999. Each of these patients was invited to participate in follow-up study using follow-up self-assessment questionnaires. This report concerns the seventy-one shoulders in sixty-eight patients who provided follow-up data at least 24 months after their surgery.

The preoperative characteristics of each shoulder were characterized including: (1) patient age, (2) patient gender, (3) diagnosis (primary degenerative joint disease, secondary degenerative joint disease, avascular necrosis, post-traumatic arthritis, cuff tear arthropathy, rheumatoid arthritis, and capsulorrhaphy arthropathy), (4) the integrity of the rotator cuff, (5) the presence of prior surgery, (6) a standardized shoulder function questionnaire, and (7) general health status as assessed by the SF-36.

The preoperative radiographic appearance of the glenoid on standardized anteroposterior and axillary views was characterized based on methods previously described, but modified to use plain films rather than computerized tomographic scans. The classification was initially conducted independently by three of the authors who were asked to classify each shoulder as uneroded, superiorly eroded, posteriorly eroded, medially eroded, or anteriorly eroded according to the dominant direction of the erosion. All three of the authors agreed in 86% of the cases. One disagreed in 11% and all three disagreed in 3% of the cases. The disagreement in these 14% was resolved by discussion among the three reviewers so that each shoulder could be included in the statistical analysis.

RESULTS

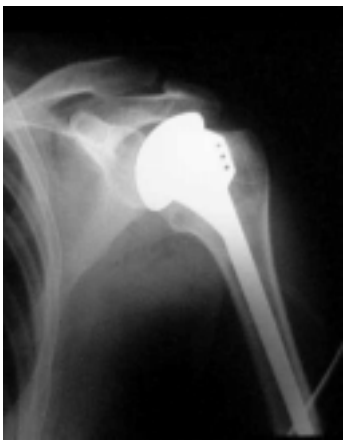
Patients undergoing hemiarthroplasty had significant improvements overall in shoulder function with the average number of shoulder functions performable increasing from 3.3 to 5.9 ($p < .00000003$) with an average improvement of 2.6 ± 3.6. The improvement in total number of functions was not significantly correlated with age ($R2 = 0.04$).

Ten of the twelve individual shoulder functions also were significantly improved for the entire study population: (1) arm comfortable at side ($p < .001$), (2) sleep comfortably ($p < .001$), (3) tuck in shirt ($p < .001$), (4) hand behind head ($p < .01$), (5) one pound to shoulder height ($p < .001$), (6) eight pounds onto a shelf ($p < .001$), (7) carry 20 pounds ($p < 0.05$), (8) toss a softball underhand ($p < .01$), (9) throw overhand ($p < .05$), and (10) wash back ($p < .001$). The ability to place a coin on the shelf ($p < .07$) and to do usual work ($p < .11$) were not significantly improved.

The SF-36 comfort score for the entire study population improved from 31 to 52 ($p < .001$). The remaining scores did not improve significantly.

The pre- and postoperative shoulder function and SF-36 pain scores were compared for each of the seven diagnoses (see Table 1). The diagnosis had a significant effect on the effectiveness of the procedure (ANOVA $p < .01$). Hemiarthroplasty was most effective in improving the function and comfort in shoulders with avascular necrosis and posttraumatic arthritis. It was effective with secondary degenerative joint disease and primary degenerative joint disease. It may have been effective in rheumatoid arthritis, but the improvement was not significant with the number of patients in this study. It was least effective in cuff tear arthropathy and capsulorrhaphy arthropathy; these effects were not significant.

The effectiveness of



Picture 1: X-ray of humeral prosthesis.

Diagnosis	# Shoulders	Preop SST	Postop SST	Significance (p)	Preop Comfort	Postop Comfort	Significance (p)
Post-Traumatic Arthritis (PT)	7	1.7	6.8	.041	26.7	51.9	.26
Avascular Necrosis (AVN)	11	3.9	9.1	.00004	27.8	61.1	.0004
Cuff Tear Arthropathy (CTA)	23	3.1	4.6	.09	33	54.4	.027
Degenerative Joint Disease (DJD)	8	3.3	5.4	.02	26.3	37.4	.005
Secondary Degenerative Joint Disease (SDJD)	12	3.9	6.2	.03	30.5	63.2	.007
Capsulorrhaphy Arthropathy (CA)	3	3.7	4.7	.09	25.9	38.9	.55
Rheumatoid Arthritis (RA)	7	3	5	.23	42.2	53.3	.26

Table 1: Changes in function an comfort for different diagnoses.

Characteristic	# Shoulders	Preop SST	Postop SST	Significance of Change (p)	Significance of group (p)
Female Gender	40	2.6	5.1	.0002	NS
Male Gender	31	4.1	6.7	.0001	
Cuff Intact[1]	34	3.2	6.4	.00002	.26
Cuff Tear	27	3.0	5.2	.0019	
Uneroded Glenoid Bone[2]	16	3.3	8.4	.0001	.001
Eroded Glenoid Bone	40	3.0	4.7	.0017	
Previous Surgery[3]	16	3.4	4.0	.3783	.015
No Previous Surgery	43	2.9	6.6	.0000001	

Table 2: Differences between patients in shoulder function pre- and postoperatively looking at previous surgery, cuff tear, and glenoid surface. (1) Preoperative radiographs were not available on 15 shoulders; (2) Data on cuff integrity was not available on 10 patients; (3) Data on previous surgery was not available on 12 patients.

hemiarthroplasty in improving the number of functions performable and the SF-36 comfort score was also correlated with patient gender, cuff integrity, lack of radiographic evidence of glenoid bone erosion, and previous surgery. These results are illustrated in Table 2. Shoulders with radiographically uneroded glenoid bone and those without previous surgery demonstrated the greatest gains in shoulder function. Shoulders with superior erosion demonstrated the least improvement, but with the numbers in this study, this result was not significantly different than other patterns of glenoid erosion.

Rotator cuff status did not have a significant effect on the effectiveness of shoulder arthroplasty in improving overall function in this study, but the power of this conclusion was low (.21). However, the effect of cuff integrity was significant on the improvement of patients' ability to place a coin on a shelf at shoulder level (p .009), to lift a pound to the level of the shoulder (p .02), and to lift eight pounds to the level of the shoulder (p .01).

Discussion

The results of this study support the hypothesis that identifiable preoperative characteristics are statistically associated with greater effectiveness in improving shoulder comfort and function after hemiarthroplasty. Previous surgery, a radiographically eroded glenoid, and diagnoses such as rheumatoid arthritis and capsulorrhaphy arthropathy were associated with less effectiveness. Defects in the rotator cuff were associated with less improvement in the ability to lift different weights to shoulder level.

Little has been published regarding the relationship of preoperative characteristics to the effectiveness of shoulder hemiarthroplasty. Kay et al found better results in patients with avascular necrosis compared to those with sequela of trauma (1988). While there was pain relief on both categories, there was a better postoperative range of motion for avascular necrosis. Levine discovered that 86% of patients with concentric glenoids achieved satisfactory results following hemiarthroplasty, whereas only 63% of patients with non-concentric glenoids achieved the same result (1997). These results are consistent with our observation that a diagnosis of avascular necrosis and a radiographic appearance of uneroded glenoid bone are associated with greater effectiveness.

Conclusion

This study confirmed that the effectiveness of hemiarthroplasty is statistically associated with characteristics of the shoulder that can be determined before surgery. These associations may be of use in preoperative decision making by surgeons and patients considering shoulder hemiarthroplasty.

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The Effect of Foot Position on Mechanism of Fracture in Automobile Frontal Collisions

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Lower limb injuries are second only to head trauma as the primary consequence of motor vehicle accidents and may be the most frequent cause of permanent disability. In a frontal crash, a common mechanism of foot injury involves the occupant's knee pocketing against the dashboard due to his or her continued forward motion as the vehicle decelerates. This effectively locks the tibia in position momentarily. Force applied to the foot from either the floorboard deforming into the footwell space, and/or the load against the foot from the occupant's own weight and deceleration can result in significant foot injuries. An example, from our CIREN (Crash Injury Research and Engineering Network, National Highway Traffic Safety Administration) crash investigation data, is shown in Figure 1. In this example, the floorpan remained intact, yet a calcaneus fracture was sustained by the driver.

Understanding the basic mechanisms and the magnitude of forces required to cause injury is a first step to modifying vehicle structures to prevent these injuries. A driver with his/her foot on the brake during the crash may experience forced dorsiflexion, or dorsiflexion combined with either inversion or eversion, along with the compressive load applied to the foot during the collision. We found that when impact forces are applied to the foot in these different positions, the force required to create injury with the foot everted and dorsiflexed was 40% lower than with the foot dorsiflexed. From field studies we found a number of cases with no footwell intrusion but significant foot injuries, as shown in Figure 1, implying that mechanisms other than trapping the foot against the crushed floorpan may be causing foot injuries. These observations, along with epidemiological data, demonstrate that the brake pedal, specifically how it aligns the foot during a frontal collision with the driver braking, is a source of foot injuries. New technologies, such as "drive by wire", that is without mechanical linkages, will allow placement of driving controls, including the brake pedal, in positions which could reduce the potential for foot injury.

Figure 1: Example crash from CIREN data showing (upper) the frontal collison of the vehicle, (middle) lack of any significant intrusion into the footwell area, (lower) the resulting calcaneus fracture.

METHODS

Field studies

The motor vehicle crash information included in this study was collected from our CIREN Center. Each crash site had scaled documentation of the roadway, traffic controls, road surface type, conditions, and road grade at both pre- and post- impact locations. A scaled drawing with impact and final resting positions was completed to assist in calculation of the speed and force at impact. Exterior inspections of the vehicle were performed, a damage crush profile was collected and entered into crash analysis software (Win SMASH, U.S. Dept of Transportation) to calculate the change in velocity (Delta V) of the vehicle during impact and the energy dissipated during the crash event. An inspection of the interior of the vehicle from which the injured person had been removed was performed to determine points of contact and restraint system use. This inspection also included assessing intrusion into the passenger compartment especially the toe pan and side panels forward of the A pillar or kick panel. With Institutional Review Board approval, the injuries were assessed by examining the patient's medical records and imaging studies.

Biomechanical studies

The IRB approved cadaveric protocol utilized 15 pairs of fresh frozen feet, with the tibia of each specimen sectioned about 20 cm above the ankle. The soft tissues around the foot and ankle remained intact. Each specimen was potted and mounted, with about

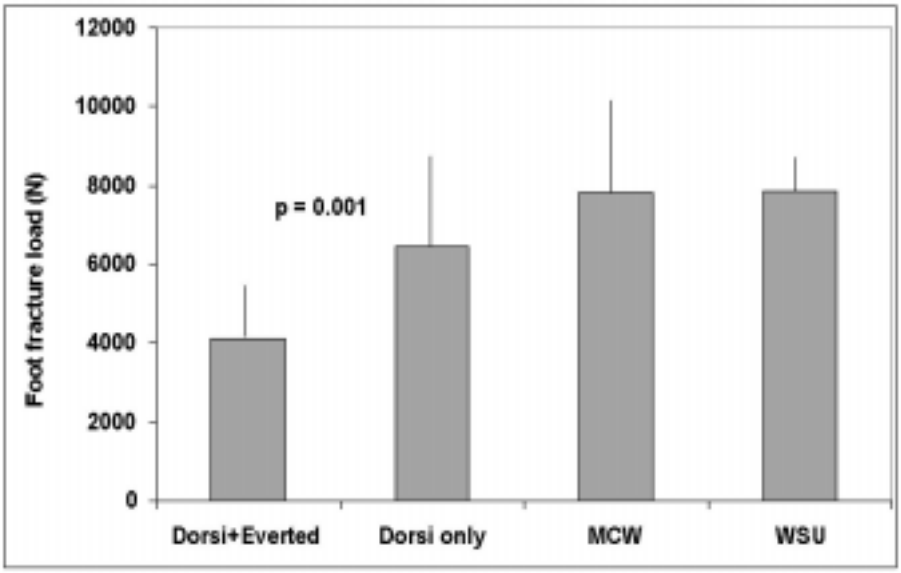

Figure 2: Peak load to failure of the dorsiflexed and everted foot (dorsi+everted), the foot dorsiflexed only (dorsi only) and data from two other studies where the specimens were loaded only in dorsiflexion (MCW - Medical College of Wisconsin, WSU - Wayne State University).

10cm of tibial shaft exposed, into an impact apparatus. This consisted of a frame with a high capacity uniaxial load cell. Attached to the load cell was a cylinder into which the potted specimen was placed such that impact force was transmitted through the foot to the cylinder and the load cell. The Achilles tendon was inserted into an electrical cable trap, connected to a pneumatic cylinder, and loaded with a tensile force of 1100N. High speed video was taken of each specimen during loading. The impactor consisted of a 4 bar pendulum and an impact surface which contacted the plantar surface of the foot. The impact surface of the pendulum was an aluminum plate which could be angled either to 20° of dorsiflexion, or 20° of dorsiflexion combined with 30° of eversion as the compressive load was applied. Impact force was generated by raising the 110kg impactor to a height of 38 cm and releasing it. Post impact, specimens were radiographed and dissected to determine the injury produced. A paired t test was used to assess differences in peak load between the two groups of paired specimens.

Results

Field studies

In a total of 17 frontal crashes selected from the Harborview CIREN data, an example of which is shown in Figure 1, significant tibial shaft, ankle or foot injuries were reported. The mean principal direction of force (PDOF) was 0.6° or just about head-on, with a mean speed change (delta V) of 52 kph (32.1 mph) resulting in a mean toe pan intrusion of 15.1 cm. Almost all victims were drivers (16 of 17) and 10 were female. The majority were belted, with 4 restrained by both airbags and lap/shoulder belts, 4 only had lap/shoulder belts, one was restrained by an airbag and a shoulder belt, and 8 had only a deployed airbag for protection. The majority (13 of 17) injured their right lower extremity. Fibula fracture occurred in 8 cases, calcaneus fracture in 3 cases, malleolus fracture in 3 cases, and talus fracture in 4 cases. Ten had additional lower extremity or pelvic injuries.

Biomechanical testing

Based on results from 9 of the 15 paired specimens, Figure 2, the mean load to failure for feet that were loaded in compression with dorsiflexion was 6468N, (sd = 2435N). When feet were loaded in dorsiflexion and eversion, the mean load was 4107N, (sd = 1630N), which was significantly lower ($p = 0.001$). There were notable differences in the types of fractures sustained in the two groups. With the foot dorsiflexed, only one malleolar fracture was noted. In contrast, with eversion and dorsiflexion, 5 malleolar fractures resulted. In the example of Figure 3, a calcaneus fracture resulted from a foot loaded in dorsiflexion. In the sequence, the gap between the posterior facet of the talus and its articulation with the calcaneus decreases, then the talar facet acts as a fulcrum with the compressive load applied anterior to it and the Achilles load posterior. This creates 3 point bending and a crack opens, not at the point of contact with the talar facet, but on the opposite (plantar) side. The crack rapidly progresses and the calcaneus fractures into two components. With the foot everted under load, the load path is medial to the longitudinal axis of the tibia causing the foot to continue to evert and fracturing the malleolus as it dislocates.

Conclusion

The results of testing showed that there was a difference in the mean load to failure of specimens forced into eversion along with dorsiflexion when subjected to axial compression, compared with feet positioned just in dorsiflexion. There were differences in the types of fractures created with considerably more malleolar fractures in specimens which were everted as well as dorsiflexed. The load paths appeared different as well with the compressive load being offset to the tibial shaft with the foot everted.

These observations along with

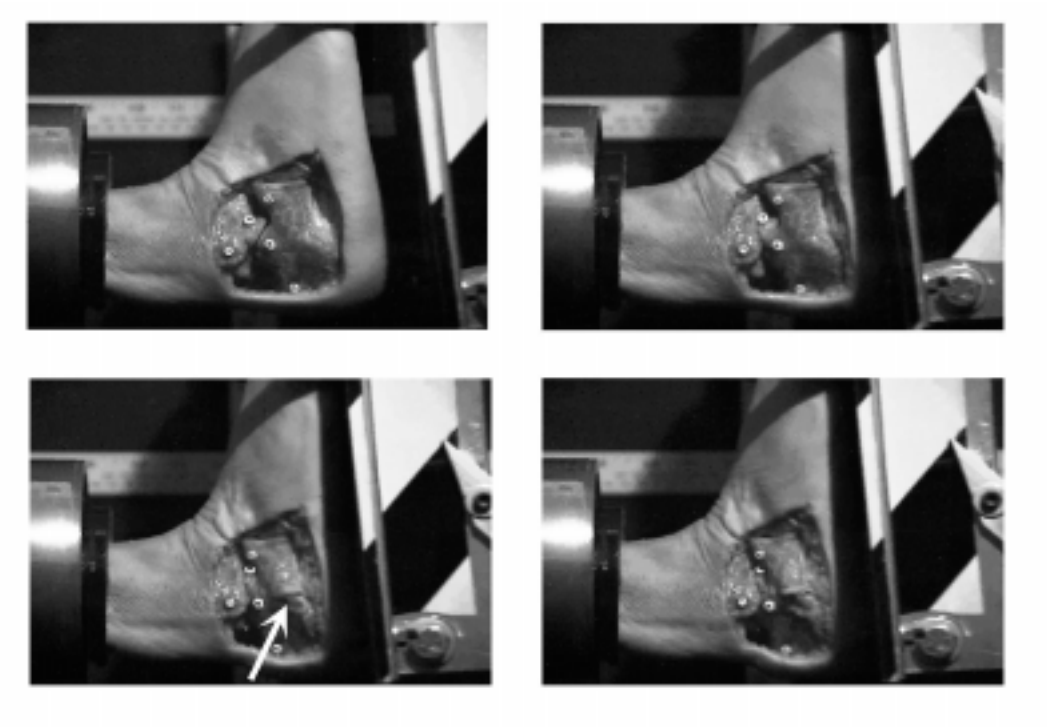

Figure 3: (upper left) dorsiflexed specimen before impact, (upper right) initial contact, (lower left) with loss of joint space crack forms on plantar surface of calcaneus (arrow), (lower left) calcaneus fractured.

epidemiological data, not presented here, showing that drivers who were braking at the time of the crash were much more likely to sustain foot fracture, indicates that the brake pedal, even in vehicles where the floor pan does not intrude, can be a mechanism of injury. New designs, such as a yielding brake pedal, devised by one auto manufacturer, may reduce the injury potential to the foot in frontal crashes.

ACKNOWLEDGEMENT

This study was supported by CIREN (Crash Injury Research and Engineering Network, National Highway Traffic Safety Administration).

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Effect of Therapeutic Footwear on Foot Reulceration in Patients with Diabetes: A Randomized Controlled Trial

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Many people with diabetes experience foot ulcerations, and subsequently lower-limb amputations. Footwear has been implicated as a primary cause of foot ulcers, yet research is limited on the efficacy of shoe and insert combinations to prevent reulceration. Our main objective was to determine whether extra-depth and extra-width therapeutic shoes used with two different types of inserts reduce reulceration in diabetic individuals with a history of a previous foot ulceration. A secondary objective was to evaluate the pivotal events leading to lower limb amputation in these patients.

DESIGN, SETTING, AND PARTICIPANTS

This study was a randomized clinical trial of 400 diabetes patients with history of foot ulcer in two Washington State health care organizations. Study eligibility criteria were diagnosed diabetes; ages 45-84; males from either the Veterans Administration or Group Health Cooperative (GHC) and women from GHC (as there were very few female veterans who could meet the eligibility criteria); history of a full thickness foot lesion, paronychia or a foot infection requiring antibiotic treatment; no foot deformities requiring a custom shoe; shoe size 8-12 for men and shoe size 7-10 for women (sizes were limited to contain manufacturing costs); ability to walk one block and climb one flight of stairs per day (to insure the footwear would be worn); and willingness to consent to randomization and study footwear provisions. Exclusion criteria were a prior lower extremity amputation of more than one digit; a lesion either unhealed or healed for less than 1 month; requirement of boots, custom shoes, or non-traditional footwear for daily activities; a history of or active Charcot foot deformity; non-ambulatory status; or a terminal illness that would make two year survival unlikely.

Subjects were enrolled between August 1997 and December 1998 and followed closely for 2 years. Data collected at regular intervals documented physical, foot, and diabetes characteristics; footwear use; foot lesions; and ulcers.

Pivotal Events for 84 Ulcer Episodes	Number By Group					
Shoe related Ulcers	Group 1 N = 121	Group 2 N = 119	Group 3 N = 160	Percent of Total	Total	% Insensate
Study shoe	7	2	0	10.7	9	100
Non study shoe	5	0	19	28.6	24	88
Non Shoe related Ulcers						
External trauma	8	10	8	30.9	26	96
Self care	2	4	0	7.1	6	83
Critical ischemia	0	3	1	4.8	4	75
Paronychia	3	1	1	6.0	5	40
Decubitus	0	1	5	7.1	6	67
Other	0	1	3	4.8	4	75
Total Episodes	25	22	37	100	84	86

Table 1: Pivotal Events and Foot Insensitivity for Ulcer Episodes in the Clinical Trial of Footwear, from JAMA - 2002;287:2552-58.

INTERVENTIONS

Participants were randomly assigned one of three study arms. Group 1 received 3 pairs of therapeutic shoes and 3 pairs of customized medium-density cork inserts with a neoprene closed-cell cover (n = 121). Group 2 received 3 pairs of therapeutic shoes and 3 pairs of prefabricated, tapered polyurethane inserts with a brushed nylon cover (n = 119). Group 3 did not receive therapeutic shoes or inserts, and were instructed to wear their usual footwear (controls; n = 160).

OUTCOME MEASURES

The main outcome measure was foot reulceration, compared among the 3 groups. A secondary outcome was lower limb amputation.

RESULTS

Two-year cumulative reulceration incidence across the 3 groups was low in all three groups: 15% in the study shoe plus custom customized medium-density cork inserts group, 14% in the study shoe plus prefabricated, polyurethane insert group, and 17% in controls. These rates, for all three groups, were much less than we predicted using previously published data that indicated reulceration rates of 30 to 50% in similar high risk diabetic individuals.

In the intent-to-treat analysis, we were unable to show a significantly lower risk of reulceration in patients assigned to therapeutic shoes compared with controls (risk ratio [RR] for the cork-insert group, 0.88; 95% confidence interval [CI], 0.51-1.52 and RR the for prefabricated-insert group, 0.85; 95% CI, 0.48-1.48). All ulcer episodes in patients assigned to therapeutic shoes and 88% wearing

Patients	Average Age	Sex	Pivotal Event	Description of Pivotal Event	Co-Morbidity	AmputationLevel
1.	51	M	Shoe related	Fissure and infection on large callus located lat. to 5^{th} metatarsal head.	DM, CHF, IHD	R 5^{th} ray
2.	74	M	Non shoe related, minor environmental trauma	Patient's foot ran into bed at night. Cut on lateral side of heel.	DM, CHF, IHD, Lung CA, Prior LL bypass	R Transfemoral
3.	69	M	Non shoe related, minor environmental trauma	Caregiver at nursing home stepped on patient's foot. Wound on dorsum 3^{rd} toe.	DM, CHF, HTN, COPD, CLF	R Transfemoral
4.	76	M	Non shoe related, minor environmental trauma	Patient bumped his lateral foot against wall.	DM, IHD, Quintuple heart bypass, Bilateral LL bypass, AAA repair	R Transtibial
5.	56	M	Non shoe related, minor environmental trauma	Minor trauma, patient bumped his toe while vacuuming barefoot.	DM	L Transtibial
6.	61	M	Non shoe related, minor environmental trauma	Patient's foot bumped into cart leading to traumatic wound 2^{nd} toe.	DM, CRF requiring dialysis	R distal 2^{nd} toe
7.	66	F	Non shoe related, minor environmental trauma	Bumped 5^{th} toe against furniture.	DM	L 5^{th} toe
8.	69	M	Critical ischemia	No history of trauma. "Spontaneous" appearance of necrotic area on dorsum of foot.	DM, CHF, HTN, COPD requiring O2, Prostate metastatic CA	R Transfemoral
9.	68	M	Critical ischemia	No history of trauma. "Spontaneous" appearance of necrotic area on great toe.	DM, HTN	L Hindfoot
10.	71	M	Self-care trauma	Accidentally cut lateral border of toe nail with his scissors.	DM, bilateral carotids endarterectomy, TIA, HTN, CHF, IHD	R hallux
11.	50	M	Decubitus	Decubitus ulcer lateral malleolus after prolonged bedrest.	DM, Repaired ruptured AAA, COPD, chronic pancreatitis, Prior LL bypass	L Transfemoral

Table 2: Description of Pivotal Events Leading to Lower Limb Amputation, from: Smith DG, et al, Accepted by Foot and Ankle International. M: male; F: female; PAD: peripheral arterial disease; DM: diabetes mellitus; CHF: chronic heart failure; IHD: ischemic heart disease; HTN: hypertension; COPD: chronic obstructive pulmonary disease; CLF: chronic liver failure; AAA: abdominal aortic aneurysm; TIA: transient ischemic attack; CRF: chronic renal failure; PY: pack-year; $TcPO_2$: transcutaneous oxygen pressure.

nonstudy shoes did occur in patients with foot insensitivity.

Table 1 shows the two pivotal events that contributed most to ulcer episodes were shoes 39% (10.7% due to study shoes and 28.6% due to nonstudy shoes), and external trauma 31%. Insensate patients comprised the majority of patients reporting ulcers: 100% insensate among ulcers reported to have occurred in study shoes; 88% in non-study shoes; and 96% attributed to external trauma.

Amputation was not the primary study endpoint as few were expected. During the two-year follow-up, eleven participants underwent lower limb amputation. Incidence of amputation was 13.8 per 1000 persons-year. Analysis of the pivotal events is detailed in Table 2. This revealed: six amputations directly related to minor external trauma, two due to progression of vascular disease with dry gangrene, one due to decubitus ulcer, one due to self-care injury, and only one due to a footwear related ulcer. The amputation levels were: four transfemoral, two transtibial, one hindfoot, one fifth ray, and three at the toe level.

CONCLUSION

This study of persons without severe foot deformity does not provide evidence to support widespread dispensing of therapeutic shoes and inserts to diabetic patients with a history of foot ulcer. Study shoes and custom cork or preformed polyurethane inserts conferred no significant ulcer reduction compared with control footwear. This study does suggest that careful attention to foot care by health care professionals may be more important than therapeutic footwear. The study does not negate the possibility that special footwear is beneficial in persons with diabetes who do not receive such close attention to foot care by their health care providers or in individuals with severe foot deformities.

This prospective study also showed that amputations in high risk patients with diabetes were mostly related to household accidents, and only infrequently related to footwear. Progression of severe vascular disease was a major factor that lead to higher anatomic level of amputation. Strategies to reduce external trauma unrelated to shoes appear indicated.

The highest risk patients, those who are insensate, have proven once again they are the most vulnerable to complications. Limited health care resources might be better utilized to develop a comprehensive approach to care for these individuals. These patients and their providers should jointly explore individualized strategies to decrease the events that give rise to foot ulcers and to amputations.

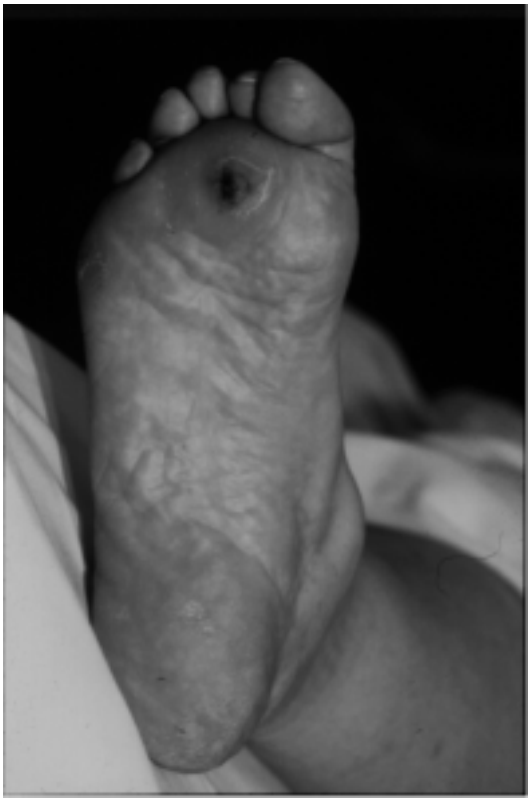

Figure 1:Superficial diabetic ulceration into the dermis located under the right 2nd metatarsal head.

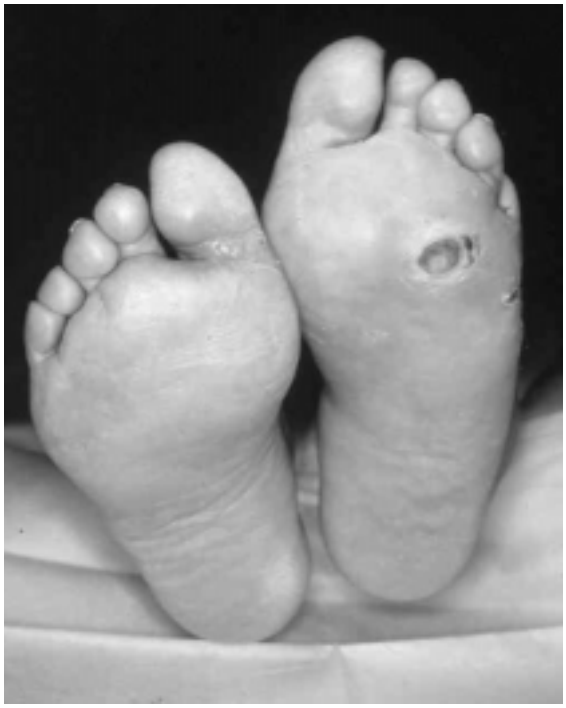

Figure 2: Deep diabetic ulceration through the dermis into the subcutancous tissue located under the 4th metatarsal head.

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COL11A2 Collagen Gene Transcription is Differentially Regulated by EWS/ERG Sarcoma Fusion Protein and Wild-Type ERG

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Cancers arise when genetic changes, such as chromosomal translocations and point mutations, enable cells to escape the control mechanisms that usually serve to limit cell division to periods of growth or normal replenishment of cells. A better understanding of the specific pathways that lead from a genetic change to a cancerous cell may yield targets for molecular treatments. In addition, by studying the aberrant processes of tumor cells one can often gain a window of insight into normal cellular processes.

Ewing's sarcoma is a highly aggressive bone and soft tissue tumor that occurs in adolescents and is of unknown tissue origin. Most Ewing's sarcomas exhibit a specific t(11;22) chromosomal translocation that results in the fusion of EWS to the ETS-family member Fli-1. In a subset of patients, a specific t(21;22) chromosomal translocation involving the Ewing's sarcoma gene (EWS) and the ETS-related gene (ERG) generates instead an EWS/ERG fusion gene. In the resultant hybrid EWS/ERG fusion protein, a portion of the ETS family protein ERG is replaced by a piece of the RNA-binding protein EWS.

CADO-ES1 is an established human Ewing's sarcoma cell line that can differentiate into neural and mesenchymal cell lineages. Because expression of mouse Col11a2 has been linked to neural and mesenchymal cell phenotypes, we analyzed this cell line for expression of the COL11A2 collagen gene. We confirmed that CADO-ES1 cells express both COL11A2 mRNA and EWS/ERG fusion protein. Since the ERG transcription factor is known to participate in cartilage differentiation from mesenchyme (chondrogenesis), a marker of which is the activation of COL11A2, we investigated whether ERG and/or EWS/ERG participate in regulating COL11A2 expression.

RESULTS

We characterized the COL11A2 promoter and tested the ability of both wild-type (normal) ERG and the EWS/ERG sarcoma fusion protein to stimulate the COL11A2 promoter using a luciferase assay. Various proteins (transcription factors) interact with the promoter region of genes to regulate gene expression. Luciferase is the protein that enables fireflies to glow. The gene for luciferase can be introduced into living cells under the control of the COL11A2 promoter and luciferase expression can then be quantified using a luminometer, thus giving an indication of how efficient EWS and EWS/ERG are at promoting synthesis of COL11A2 protein. We found that expression of EWS/ERG, but not wild-type ERG, activated the COL11A2 promoter (Figure 1) and this activation required not only the N-terminal region of EWS but also an intact DNA-binding domain from ERG.

Electrophoretic mobility shift assay (EMSA) is used to detect whether a specific protein binds to the regulatory (promotor) sequence that controls expression of a specific gene. In essence, the bound protein slows down the migration of the regulatory gene sequence through a gel. The complex is then detected by a specific anti-protein antibody and the distance traveled through the gel can be visualized. Using the COL11A2 promoter sequence, EMSA showed involvement of EWS/ERG and ERG in the formation of DNA-protein complexes.

Based upon our previous studies of sarcoma fusion proteins, we were interested in whether both EWS/ERG and wild-type ERG would bind to RNA polymerase II (Pol II). This was tested using western blotting and immunoprecipitation with antibodies specifically targeting RNA Pol II and EWS/ERG or ERG. Interestingly, EWS/ERG but not wild-type ERG would bind RNA Pol II.

Finally, we have previously published our discovery of an ERG-associated histone methyltransferase with a SET domain that we named

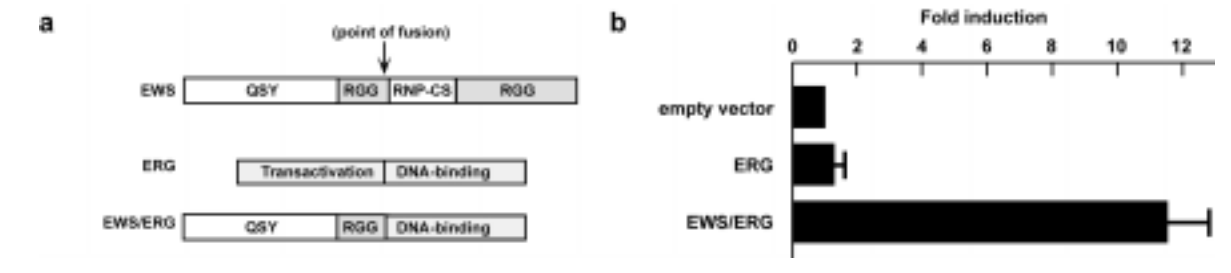

Figure 1: Differential effects of ERG and EWS/ERG on the COL11A2 promoter. a) Schematic of EWS, ERG, and EWS/ERG. In the EWS/ERG fusion protein the transactivation domain of ERG is replaced by the N-terminal domain of EWS. b) Effect of ERG and EWS/ERG expression constructs on the activity of wild-type COL11A2 promoter in NIH3T3 cells. EWS/ERG but not ERG activates the COL11A2 promoter thus resulting in a greater induction of luciferase expression as measured by the luminometer (horizontal axis).

ESET. Histones are proteins that control the physical structure and thus ultimately the expression of genes in chromosomes. Histone methyltransferases in turn bind other proteins such as histone deacetylases that together determine the conformation of histones and thus regulate the physical accessibility of transcription factors to gene promoters. Histone deacetylases in fact inhibit gene transcription. We hypothesized that a histone methyltransferase (such as ESET) bound to both ERG and histone deacetylase may in part account for the inability of ERG to activate the COL11A2 promoter. To evaluate this possibility we treated CADO-ES1 cells with the histone deacetylase inhibitor trichostatin A. This in fact enabled ERG to activate the COL11A2 promoter therefore abolishing the differential effects of EWS/ERG and ERG (Figure 2).

Discussion

Our findings indicate that ERG and the sarcoma fusion protein EWS/ERG differentially regulate expression of the COL11A2 gene. Even though both wild-type ERG and the EWS/ERG fusion protein share the same DNA-binding domain and are expected to bind to the same promoter sequence, the human COL11A2 promoter construct is transactivated by EWS/ERG, but not by ERG. Our results together with a recent report on induction of the Id2 gene by EWS-ETS, reveal that an EWS fusion protein is able to activate an authentic promoter that is not activated by its wild-type counterpart. Furthermore, electrophoretic mobility shift assay confirms the interaction of EWS/ERG and/or ERG with the COL11A2 promoter. Thus, activation of COL11A2 is at least partially mediated by the interaction between the COL11A2 promoter and the DNA binding domain of EWS/ERG.

In this study we also investigated why EWS/ERG, but not ERG, activates COL11A2. Our study points to at least two potential mechanisms. First, since inhibition of histone deacetylase significantly enhanced the effects of ERG on COL11A2 promoter activity, transactivation by ERG appears to be epigenetically (a change in the pattern of gene expression without a change in the DNA sequence) suppressed. Second, as evidenced by immunoprecipitation experiments, EWS/ERG fusion protein recruits RNA Pol II in vivo whereas wild-type ERG does not. By fusing the N-terminus of EWS to the DNA-binding domain of ERG, the EWS/ERG oncogenic protein is able to recruit RNA Pol II directly to the site of transcription and this could serve to bypass suppression by histone deacetylase complexes. These findings therefore provide new insights into the mechanisms underlying collagen gene expression in general, and COL11A2 expression in particular.

In addition to transcriptional deregulation, EWS sarcoma fusion proteins are reported to interfere with basic cellular processes such as RNA splicing. Unlike wild-type EWS protein, the C-terminal domains of EWS fusion products are unable to recruit certain factors that regulate spilicing of RNA, which may partly explain the abnormal splicing patterns and abnormal protein expression in Ewing's sarcoma cells. The finding that EWS/ERG binds RNA Pol II also suggests a coupled mechanism for stimulated gene expression and altered RNA splicing. Since gene transcription and RNA splicing are physically linked via RNA Pol II and its associated proteins, EWS/ERG has the potential to deregulate gene activation, epigenetic gene repression, and RNA-splicing. All of these processes are integral to cell growth and differentiation.

While the cell of origin (benign counterpart) of Ewing's sarcoma remains unknown, the expression of COL11A2 in CADO-ES1 cells supports a neural/mesenchymal origin. Interestingly, the regulatory elements of the COL11A2 active in CADO-ES1 cells differ from those active in cells of cartilage and neural tissues. It is likely that other genes with promoter properties in common with COL11A2 are also differentially regulated by EWS/ERG and ERG, and the implications we believe are therefore fundamental to an understanding of Ewing's tumor pathobiology.

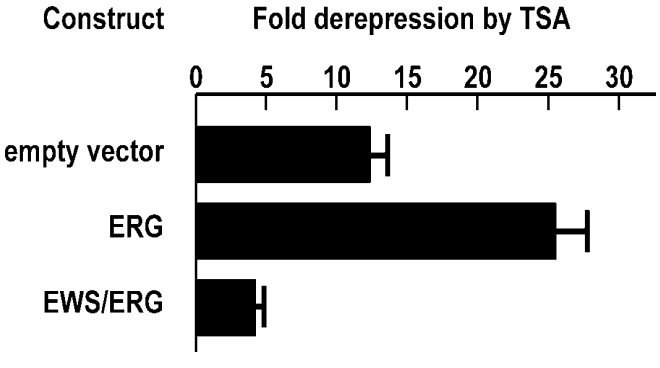

Figure 2: Derepression of ERG after treatment with Trichostatin A (TSA). NIH3T3 cells were co-transfected with the wild-type COL11A2 promoter and ERG or EWS/ERG expression plasmid. Transfected cells were assayed for luciferase 18 hours after treatment with TSA and compared with untreated cells. Luciferase activities relative to the untreated cells are shown as fold of derepression (stimulation). ERG is able to activate the COL11A2 promoter after treatment with the histone deacetylase inhibitor TSA.

Acknowledgements

The authors thank Ken Kodama for the CADO-ES1 cells. This work is supported by a VA Merit Review Award (to H.A.C.), the Orthopaedic Research and Education Foundation (to H.A.C.), and by NIH grants 1R01CA90941 (to L.Y.), 5R01AR37318 and 5R37AR36794 (to D.R.E.).

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Cross-Linking of Collagens II, IX and XI in Chondrocyte Cultures As a Monitor of Normal Matrix Assembly

RUSSELL J. FERNANDES, PH.D. AND DAVID R. EYRE, PH.D.

Cartilage contains three tissue-specific collagens, types II, IX and XI. In the extracellular matrix all three co-polymerize to form a fibrillar framework that is stabilized by inter-molecular covalent cross-links. Trivalent hydroxypyridinoline (HP) cross-links between the amino- (N) and carboxy- (C) telopeptides of type II collagen molecules and the helical region of adjacent type II collagen molecules are the most prevalent. Pyridinoline and divalent cross-links also bond type IX collagen molecules to the N- and C- telopeptides of type II collagen. Type XI collagen is linked to the N- and C- telopeptides of type II collagen by divalent ketoamine cross-links. This co-polymeric fibrillar network is the basis of the tensile strength of cartilage.

In vivo, chondrocytes synthesize and deposit collagen molecules in the cartilage matrix. *In vitro*, chondrocytes are difficult to culture as they dedifferentiate and synthesize matrix molecules not characteristic of cartilage (e.g. type I collagen). Over the past decade, a better understanding of chondrocyte biology has led to improved cell culture techniques and a new field of research, cartilage tissue engineering. Under suitable culture conditions chondrocytes can be induced to synthesize and form a matrix based on type II collagen. To what degree the fibrillar matrix is normal, in terms of the coassembly of the minor collagens (types IX and XI) is not well characterized.

This study investigated the ability of chondrocytes, cultured under different conditions, to assemble collagen types II, IX and XI into the co-polymeric cross-linked network that typifies cartilage matrix *in vivo.*

METHODS

Antibodies

The monoclonal antibody 1C10 recognizes an epitope near the C-terminus of the helix (CB9,7) of type II collagen chains. The monoclonal antibody 10F2 recognizes a cleavage-site (neoepitope) in a sequence in the C-telopeptide cross-linking domain of type II collagen. This antibody detects the C-telopeptides of type II collagen (even as short fragments) if cross-linked to collagen chains.

Cell Culture

Chondrocytes were cultured under conditions that would favor the differentiated phenotype. The Swarm rat chondrosarcoma chondrocyte cell line RCS-LTC, was maintained as a high density monolayer culture in DMEM with BCS and ascorbate for a period of 2 weeks. Human fetal epiphyseal chondrocytes were maintained as high density pellet cultures in the presence of FBS and ascorbate for 3 weeks. Chondrocytes from adult human talus cartilage were maintained in high density micromass cultures in DMEM containing ascorbate, with or without 100ng/ml human recombinant FGF-18 for a period of 5 weeks. Alginate recovered chondrocyte (ARC) engineered tissue, using human adult articular chondrocytes (2 and 4 weeks post alginate culture), was a gift from Koichi Masuda, M.D. (Department of Orthopaedics, Rush Presbyterian St. Luke's Medical Center, Chicago).

Collagen extraction

The collagen network laid down by the cultured cells was depolymerized using pepsin. Pepsin cleaves in the telopeptide domains of type II collagen and in the non-collagenous domains of the minor collagens, type XI and IX, but leaves the triple helical domains intact. The short stubs of cleaved telopeptides remain cross-linked to the triple-helical sites to which they were attached in the matrix and the antibody 10F2 detects the α1(II) C-telopeptide wherever it is cross-linked to collagen chains or chain fragments (Figure 1).

RESULTS

The Swarm rat chondrosarcoma cell line RCS-LTC synthesizes and deposits collagen types II, IX and XI in the extracellular matrix. As seen in Figure 2, lane 1, the antibody 10F2 reacted with the α1(II) collagen chain as expected for a cross-linked type II collagen polymer. (C-telopeptide of type II collagen cross-linked to α1(II) collagen chains). The antibody also reacted with α1(XI) collagen chains implying this chain was cross-linked to the C-telopeptide of type II collagen. A third immunoreactive band is seen only after reduction with DTT. This band from its properties is the α3(IX) collagen chain cross-linked to a C-telopeptide of type II collagen. As shown in Figure 1 these cross-linking sites have all been reported to occur in normal articular

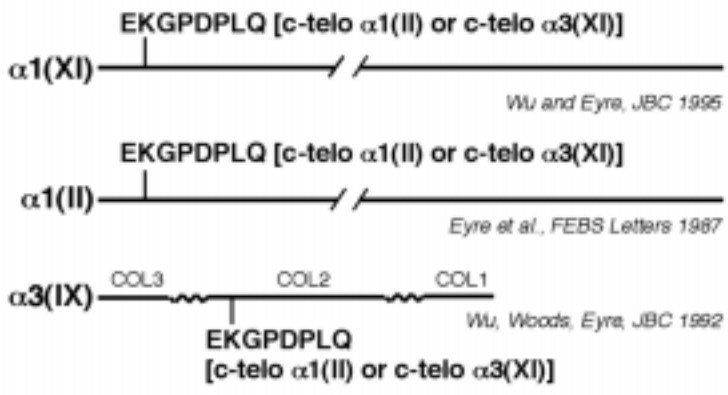

Figure 1: C-telopeptides of type II collagen are cross-linked to chains of type XI, II and IX in normal cartilage.

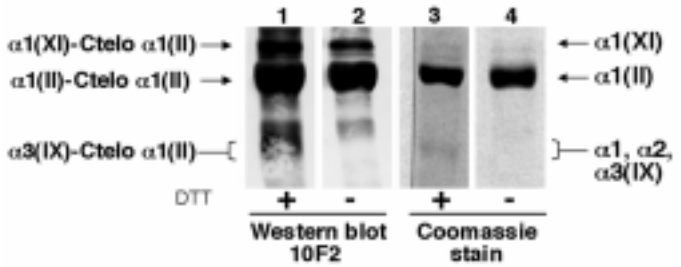

Figure 2: The collagen heteropolymer formed in RCS-LTC chondrocyte monolayers.

cartilage.

The fetal human chondrocytes elaborated an extensive extracellular matrix containing type II collagen. The antibody 1C10 detected the α1(II) and the β1(II) chains of type II collagen (Figure 3). The antibody 10F2 reacted with the α1(II) chain indicating a cross-linked collagen network within a week in culture. 10F2 also reacted with the α1(XI) chain after 2 weeks in culture, showing that type XI collagen was copolymerized and cross-linked to C-telopeptides of type II collagen.

FGF-18 is a trophic factor for mature chondrocytes. Cultured in micromass, the human adult chondrocytes elaborated a matrix less copious than that of fetal chondrocytes. The antibody 1C10 was able to detect type II collagen in the matrix of both FGF-18 treated and untreated chondrocytes indicating a differentiated phenotype (Figure 4). The antibody 10F2 showed a slightly stronger reaction with the α1(II) chains in FGF-18 treated cultures than in control. The α1(XI) collagen chains were faintly immunoreactive. The results indicate that a copolymeric collagen type II/XI network had formed.

When cultured by the alginate recovered chondrocyte method, the extracellular matrix of the engineered tissue contained type II collagen as detected by antibody 1C10 (Figure 5). The antibody 10F2 reacted strongly with the α1(II) collagen chains showing that the type II collagen was polymerized and cross-linked. The α1(XI) collagen chains were also immunoreactive showing the presence of a type XI-type II collagen co-polymer.

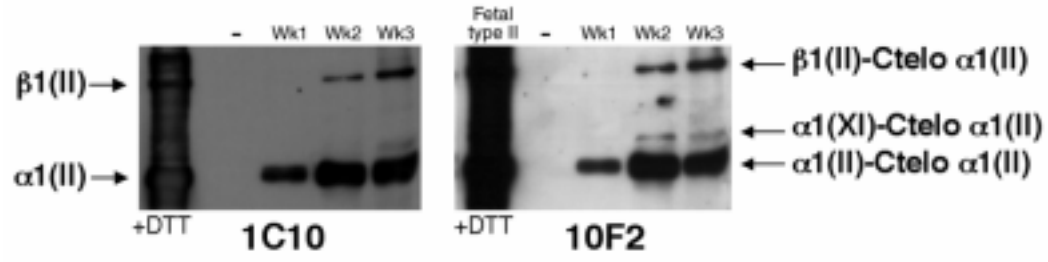

Figure 3: The collagen network formed in human fetal chondrocyte pellet cultures.

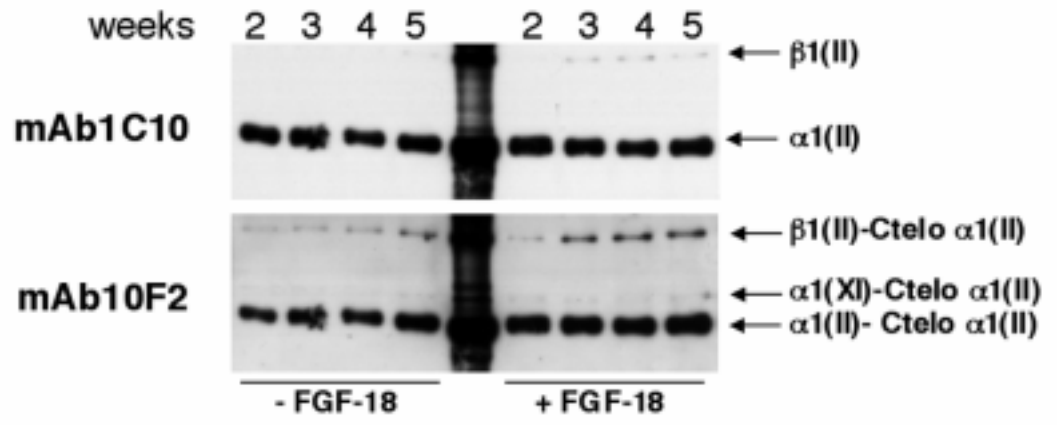

Figure 4: Collagen from human adult chondrocyte micromass culture.

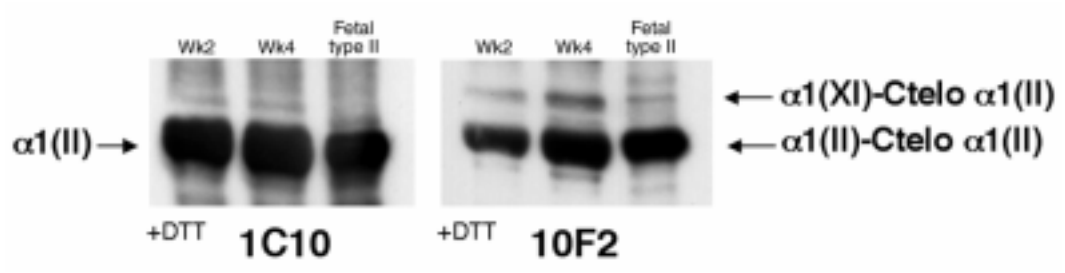

Figure 5: Demonstration of the collagen heteropolymer in tissue engineered from human adult chondrocytes.

Conclusion

Under appropriate culture conditions we can demonstrate that human and rat chondrocytes remain differentiated and form a fibrillar matrix of the collagen II, IX, XI heteropolymer characteristic of hyaline cartilage.

Since it is clear that each of the minor collagens is essential in regulating the organization of the network (e.g. fibril diameters modulated by type XI), fingerprinting the pattern of inter-type cross-linking provides a screen for normal matrix assembly. This could be useful in assessing the quality of cartilage in disease and when produced as a healing response or by tissue engineering methods.

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Graduating Residents
Class of 2003

Ben DuBois, M.D.: Ben will return to the University of Washington Department of Orthopaedics as a shoulder and elbow fellow in our Advanced Clinical Experience program.

Guy Schmidt, M.D.: Following his residency he will be doing a sports medicine fellowship at The Rosenberg/ Cooley Clinic in Utah. Afterwards, he hopes to return to Montana.

Brian Shafer, M.D.: Next year Brian will be doing a sports medicine fellowship with James Tibone at the University of Southern California Center for Athletic Medicine, in Los Angeles, afterwards he might return to Arizona where he is from.

Andrew Howlett, M.D.: Andrew will return next year as our Trauma Fellow at Harborview Medical Center. The following year he will join our Sarcoma Service as the fellow under Dr. Ernest Conrad.

Emma Woodhouse, M.D.: Emma will be an ACE next year in our Advanced Clinical Experience program with our shoulder and elbow service.

Incoming Residents

Jamie Antoine: Jamie attended Union College in Schenectady, New York where he received a B.S. in Biology. He received his medical degree from Albany Medical College. He is currently completing his surgical internship at the University of Washington. His interests outside of medicine include ice hockey, weight training and basketball.

Mary R.A. Cunningham: Mary attended George Mason University in Fairfax, Virginia where she received a B.S. in Biology. She received her medical degree from the University of Virginia. She is completing her surgical internship at the University of Washington. Personal interests include traveling, backpacking, hiking, and gardening.

Joseph Lynch: Joe received a B.A. in Environmental Science and Public Policy from Harvard. In addition, he completed four years of course work at MIT studying Military Science as required by the Navy ROTC program. He received his medical degree from Oregon Health Sciences University. Interests outside of medicine include skiing and mountain biking.

Jeremiah Clinton: Jeremiah attended Montana State University in Bozeman, Montana where he received a B.S. in Biomedical Science. He earned his M.D. from the University of Washington. He is finishing his surgical internship at the University of Washington. His interests include alpine skiing, rock climbing and woodworking.

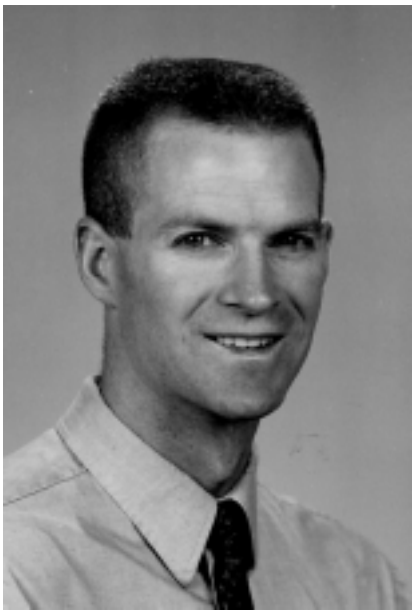
Evan Ellis: Evan received his B.A. in Psychology from Johns Hopkins University. He earned his medical degree from the University of Michigan. He is currently completing his internship at the University of Washington. Outside of medicine he enjoys basketball, golf, volleyball, and jogging.

Allison MacLennan: Allison attended the University of Michigan where she received a B.S. in Biology. She also received her medical degree from the University of Michigan. She is currently completing her surgical internship at the University of Washington. Personal interests include music, both singing and playing the viola, dance, films, and jogging.

2003 Department of Orthopaedics
New Faculty

Dheera Ananthakrishnan, M.D.

Dr. Ananthakrishnan completed her undergraduate work in Mechanical Engineering at Massachusetts Institute of Technology in 1990, followed by a masters degree in Bioengineering from the University of Washington. She then attended medical school at the Albany Medical College in New York, earning her degree in 1996. Her internship and residency were completed at the University of Illinois in Chicago in 2001. She has just finished a two-year spinal deformity fellowship under Dr. David Bradford at the University of California San Francisco. She joins our faculty as a spine surgeon based at the University of Washington Medical Center.



Richard J. Bransford, M.D.

Although born in Omaha, Nebraska, Richard is fluent in Kiswahili and French after being raised in Kijabe, Kenya. While living in Kenya, he attended a boarding school for five hundred missionary children where Richard became involved in sports, especially basketball, volleyball and soccer. During this time he spent summers observing his father in the operating room. Richard left Africa to attend college in the United States where he received his undergraduate B.S. degree in Biology from Westmont College in 1992. He graduated summa cum laude as well as Valedictorian of his graduating college class. In 1995 he was awarded the MAP-Reader's Digest International fellowship which was a sponsorship to continue his work at a mission hospital in Indonesia. He proceeded to earn his M.D. degree at Vanderbilt University School of Medicine in 1996. He completed his residency at the University of Washington, where, afterwards, he was a fellow in the spine service's Advanced Clinical Experience program. He has just completed a pediatric fellowship in Australia and now joins our faculty as a spine surgeon practicing at the University of Washington and the local VA hospital.

Lisa A. Taitsman, M.D., M.P.H.

Dr. Taitsman received both her undergraduate and medical degrees from Brown University. She then earned her Masters in Public Health from Harvard School of Public Health. She served as a surgery intern at Beth Israel Medical Center and then completed her residency in Boston in the Harvard Combined Orthopaedic Residency Program. After acting as chief resident at Massachusetts General Hospital, she completed a trauma fellowship at Harborview Medical Center/ University of Washington. Dr. Taitsman has remained at Harborview where she joins the orthopaedic trauma faculty.

RESEARCH GRANTS

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National Institutes of Health (NIH)

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Ted S. Gross, Ph.D.

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APRIL 2002 THROUGH MARCH 2003

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