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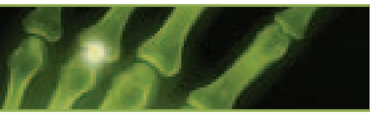


Orthopedic Update

Current Trends in Orthopedic Surgery

Vol. 2, No. 2, 2008

INSIDE THIS ISSUE

Advances in Bone Regeneration

Improved Healing, Osteoporosis Diagnosis, Fracture Repair, Outcomes of War-Related Injuries

Recent orthopedic discoveries have led to advances in understanding mechanisms of bone regeneration and are rapidly being translated into clinical applications that improve musculoskeletal patient care across a spectrum of bone disorders.

At Mayo Clinic, a tradition of multidisciplinary collaborative research has created highly productive lines of inquiry related to bone regeneration. Recent highlights include

- Exploration of the molecular mechanisms such as signaling pathways of bone growth and resorption
- Design of bone-regenerating scaffolding to cue bone growth
- Design of an automated imaging system to calculate bone strength
- Development of bone and nerve regeneration techniques to treat war-wounded patients

Waves of Innovation

Michael J. Yaszemski, MD, PhD, head of Mayo Clinic's Tissue Engineering and Biomaterials Laboratory at Mayo Clinic in Rochester, Minnesota, views advances in bone regeneration as waves of innovation occurring on multiple fronts. The Tissue Engineering Laboratory's biomaterials area provides synthesis, characterization, processing, and tissue-engineering application of novel polymeric and composite biomaterials. These biomaterials are used as drug delivery vehicles or temporary scaffolds in 3 main areas: bone, cartilage, and nerve tissue engineering (Figure 1).

"We are able to use more strategies for restoring structural and mechanical function of bone than ever before, which means providing more patients with excellent outcomes than ever before," Dr Yaszemski explains. "Bone usually heals itself pretty well—but there are times it doesn't do this. When that happens, we need to integrate biology and engineering to coax the bone to heal, which is why the multidisciplinary team is so important."

For example, a complex tumor resection for bone cancer involving the pelvis may require removal of bone that leaves a gap of 7 inches. "That big gap won't fill with bone. A large defect may not follow the usual rules of healing and leaves a part of the skeleton structurally

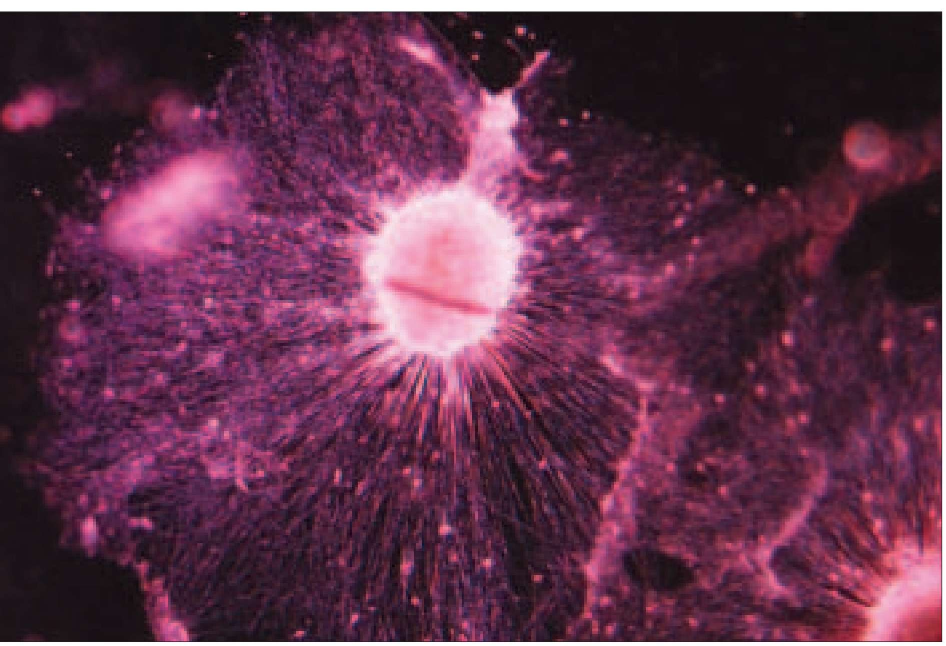


Figure 1. *Dorsal Root Ganglion Explant.* *Polymeric biomaterials developed in Mayo Clinic Tissue Engineering and Biomaterials Laboratories are used as drug delivery vehicles or temporary scaffolds in 3 main areas: bone, cartilage, and nerve tissue engineering. Here a positively charged OPF hydrogel culture supports a rat embryo dorsal root ganglion explant containing neurons, Schwann cells, and supporting cells.*

incompetent,” Dr Yaszemski explains. In these patients, surgeons restore the structural function with an allograft, usually from a cadaver. “But this dead bone takes longer to fill the defect and is not as robust as the patient’s own bone.”

To have a long-lasting positive effect in the patient’s skeleton, the bone must heal. Jennifer J. Westendorf, PhD, a molecular biologist in the Department of Orthopedic Surgery, studies signaling molecules that cue and direct bone healing. “Once bone gets the signal to regenerate, the natural growth mechanism takes over. Working as a team, we can create conditions that optimize bone regeneration,” explains Dr Westendorf.

Cell Signaling to Increase Bone

Managing osteoporosis by stimulating new bone formation and improving the healing of fractures are related problems that Dr Westendorf’s research team is addressing. The team focuses on understanding the complex interactions of key proteins, signaling pathways, and cell types involved in bone tissue remodeling dynamics.

“Osteoclast-mediated bone resorption and bone replacement through osteoblast-mediated bone formation are tightly coupled. The compounds we’re looking at in vivo as possible therapeutic agents alter the balance of osteoblasts and osteoclasts,” says Dr Westendorf. “They suggest that the development of agents that target more than 1 cell type could have important implications for clinical treatment of osteoporosis. These same signaling pathways might also be modulated to accelerate healing of fractures and to treat the 5% to 10% of fractures that fail to heal satisfactorily.”

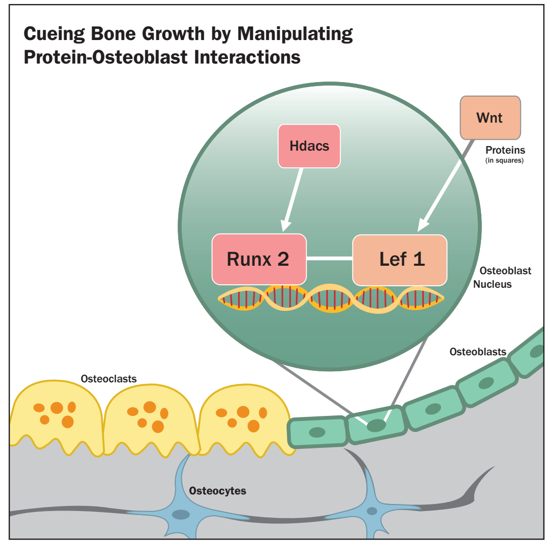
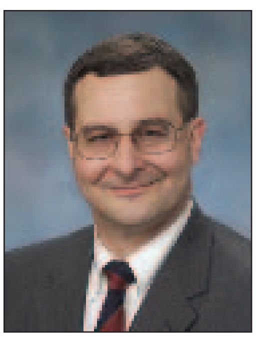
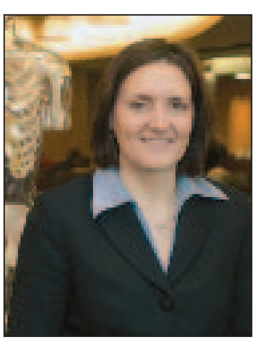


Figure 2. ***Cueing Bone Growth.*** *Unraveling the interactions of molecular players (the proteins Runx2, Hdacs, Lef1, and Wnt) and their roles in bone formation through osteoblasts plays a central role in orthopedic research at Mayo Clinic. Recent research by Dr Westendorf and her colleagues suggests modulating multiple pathways and targeting both osteoblasts may be a promising new strategy for developing a drug to increase bone mass in osteoporosis and to improve fracture healing.*



Michael J. Yaszemski, MD, PhD



Jennifer J. Westendorf, PhD

Bone Regeneration Scaffolding

Connective tissue cells are contact dependent. For bone cells to make bone, they have to encounter a surface and secrete material that becomes mineralized and then ossifies into bone. By implanting a scaffold, bone regeneration is prompted by mimicking conditions in nature that favor bone growth. The scaffold creates the necessary contact points that cue cells to grow (Figure 2).

Within the next 5 years, Drs Yaszemski and Westendorf hope to refine the bone regeneration scaffolding for clinical use with humans. They are working to expand the scaffold function for human therapy as a drug delivery vehicle, in addition to a mechanical support to initiate bone growth. Results from animal studies testing incorporation of bone morphogenic protein 2 (BMP2) into various bone tissue–engineered composites are encouraging in terms of bone growth and sustained bioactivity.

“Once the scaffolding is available, clinicians can embed it with drugs or signaling molecules to guide growth and influence treatment,” Dr Yaszemski says. For example, in patients with cancer, scaffolds can be used both to fill critical-sized defects so holes caused by aggressive resections close and to deliver chemotherapeutic agents to fight residual cancer cells. If infection is a threat, the scaffolding can be loaded with antibiotics for sustained release. The Mayo team envisions creating a scaffold that automatically recognizes and responds to skeletal contact and then delivers the necessary molecules to optimize therapy.

Automatically Calculating Bone Strength

Another bone regeneration project analyzes the degree of mineralization of bones, as quantified by CT scans, in order to calculate load-bearing strength of the vertebrae. Dr Yaszemski is collaborating with Mayo Clinic imaging specialists to automate an existing algorithm to provide rapid results. “For this process to be useful for patients, it has to be automated—it’s too time-consuming now,” says Dr Yaszemski. “When we achieve this, we’ll have a useful tool to quantitatively assess the strength of bones.”

The tool would calculate vertebral load-bearing capacity. Rapid results could be helpful for diagnosis of osteoporosis, for assessing its progression in a series of time measurements, or to determine the effectiveness of a particular treatment when strength is calculated at baseline and after treatment through sequential imaging studies. Explains Dr Westendorf: "If a patient has a hole in a bone, Mayo clinicians can work together to fix it. For example, we can make a polymer and fill it with cells and modify the cells for maximum benefit—then analyze our work with this imaging program to see how effective the treatment has been."

Combined with Mayo's epidemiologic database of CT scans containing bone strength information, data from its new program to calculate bone strength may be used to help set quantitative norms for bone strength.

Dr Yaszemski envisions this tool helping to identify patients at risk of developing osteoporosis—and treating them before the condition is problematic. "We prefer to prevent rather than treat, and we may be able to do that with this tool by identifying patients early on, before they develop insufficiency fractures, and then treating them to prevent osteoporosis," he says.

Biodegradable Scaffolding for War-Related Injuries

The Armed Forces Institute of Regenerative Medicine (AFIRM) consortium was created and funded by the US Army Medical Research and Materiel Command, in conjunction with the Office of Naval Research and the National Institutes of Health. In the new consortium, to which Mayo Clinic orthopedics belongs, AFIRM will use regenerative medicine techniques to help develop new products and therapies to repair battlefield injuries. This innovative approach uses cell therapy, including stem cells, tissue and biomedical engineering, and transplants.

Mayo Clinic's involvement focuses on bone and nerve regeneration and is led by Dr Yaszemski, who also is a brigadier general in the US Air Force Reserve. He has cared for patients in Iraq, as deputy commander of the Air Force Theater Hospital in Balad. "The opportunity to collaborate at this level to meet the medical and surgical needs of our injured service members is a privilege, and we are proud to contribute in whatever way we can," Dr Yaszemski says.

Mayo Clinic's biodegradable scaffolding has a promising application in AFIRM efforts for improving healing of peripheral nerve injuries. Dr Yaszemski explains: "We've designed the scaffold with a channel down the middle for loading with Schwann cells and for adding signaling molecules that diffuse outward to modulate growth. It provides an efficient, durable solution for regenerating bone tissue." Because the scaffolding is composed of natural body materials, it eventually converts to ordinary metabolic products over time and does not require complex aftercare.

Rapid Intraoperative Diagnostic Test for Prosthetic Joint Infection

Arlen D. Hanssen, MD, and Robin Patel, MD

Prosthetic joint infections are one of the most persistent and serious challenges to successful outcomes of prosthetic implantation procedures. Prosthetic joint infections are difficult to diagnose and the inaccuracy of the traditional tissue-sampling method to detect infection has been a concern for more than a decade.

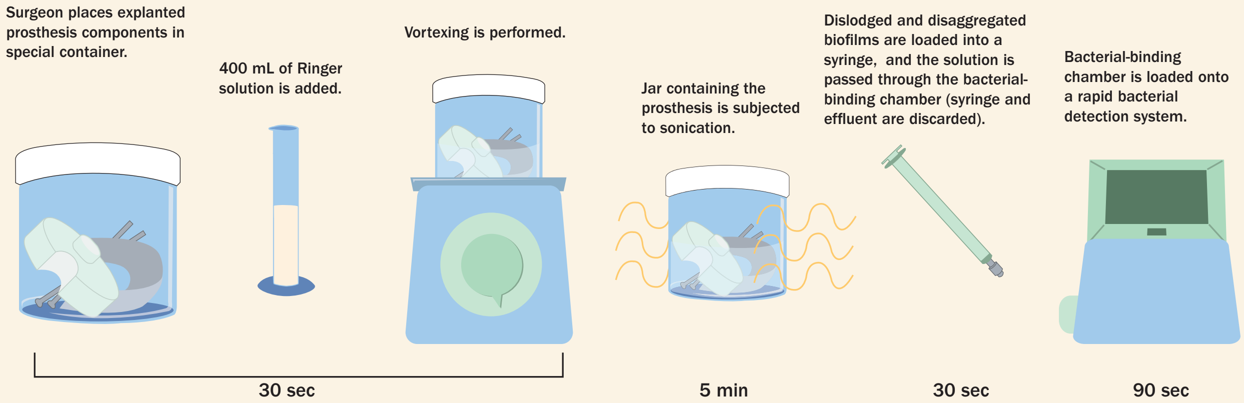
Superior Sensitivity, Rapid Results

In 2007, a report published in the *New England Journal of Medicine* from a multidisciplinary Mayo Clinic orthopedic surgery–infectious disease team, using an innovative diagnostic method called sonication, demonstrated improved sensitivity for detecting the presence of microbes associated with infected hip and knee implants—78.5% compared with 60.8% for conventional tissue culture. The team is further improving sonication by adding technology for rapid bacterial detection. The goal is to enable a surgeon to detect live bacteria within 5 to 10 minutes to speed and clarify the diagnosis of prosthetic joint infection at the time of surgery (Figure 1, see page 4).

"The consequences of inaccurate diagnosis of prosthetic joint infection for patients are often extreme," explains Mayo Clinic orthopedic surgeon Arlen D. Hanssen, MD. "Undiagnosed prosthetic joint infection can cause morbidity and mortality. Patients face the trauma and risk of an unnecessary component resection in the case of false-positives. We need to improve on this situation to improve patients' quality of life."

"The success of sonication was a key first step in helping us get better control of prosthetic joint infections—we've been using it at Mayo Clinic since March 2007," adds Robin Patel, MD,

Figure 1. *Rapid Intraoperative Diagnostic Test for Prosthetic Joint Infection*



Total time to diagnosis of infection: 7.5 minutes

a microbiologist at Mayo Clinic in Rochester. "Now, we're taking the important next step to improve the usefulness of sonication by adding rapid bacterial detection to this technique. Getting results quickly, in less than 10 minutes, will be a great benefit. We'll produce high-quality information in a critical time frame so the surgeon can use it to the patient's best advantage."

About Sonication

Using sonication, the team obtains microbial samples from explanted hip and knee prostheses using sound waves to dislodge and disaggregate microbes contained in surface biofilms into a solution surrounding the prostheses. The sonicate fluid is then cultured. In addition to improved sensitivity, the sonication method captures greater numbers of organisms and detects more polymicrobial infections than conventional methods. Team members emphasize the need for performing both aerobic and anaerobic cultures—11% of positive cultures were obtained only on anaerobic plates and 5% of positive cultures only on aerobic plates.

The Mayo Clinic investigators focused on microbes existing in the biofilm state. "Our approach was this: If the bacteria are in the biofilms on the prosthetic surface, we need to look at biofilms. We are able to get the microbes off without damaging them—a key point," says Dr Patel. "We need living infectious agents for evidence of infection, and the sonication process we developed gives us live organisms."

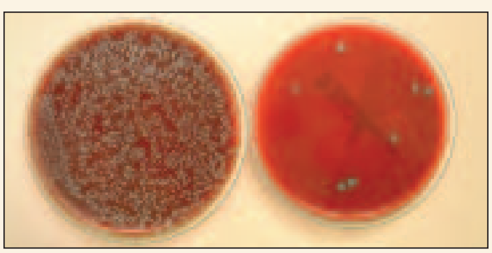
The Mayo team also is expanding the test's application beyond hips and knees to other devices and implants, because the data suggest this technology has broad applicability. This new diagnostic test is the subject of a pending patent owned by Mayo Clinic.

Coupled with surgical experience and other clinical methods for assessing infected prosthetic joints (such as leukocyte count, erythrocyte sedimentation rate, and serum C-reactive protein), the greater sensitivity and high specificity of sonicate fluid testing have the potential to increase the accuracy of diagnosing a prosthetic joint infection.

"Combining the sonication process with rapid detection technology will allow the surgeon to make a better decision in the operating room about whether an infection is present

Continued on page 8

Figure 2. ***Sonicate vs Tissue Sample Microbial Yield***

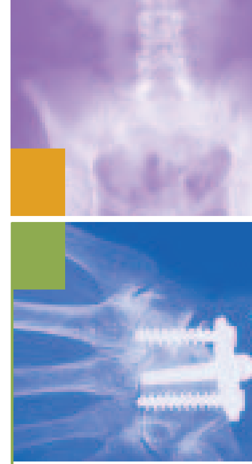


Sonicate fluid *yields more microbes in terms of colony-forming units and numbers of species.*

Results: *Confident diagnosis, improved treatment; increased likelihood of optimal patient outcomes.*

Tissue samples *yield fewer microbes, both in terms of colony-forming units and species present.*

Results: *Diagnostic imprecision, risk of unnecessary or delayed surgery; suboptimal patient outcomes.*



Short-Term Recovery Is Faster With Mini Posterior Incision Total Hip Arthroplasty Than a 2-Incision Approach

Over the past 5 years, there is increasing interest in the claim that the 2-incision total hip arthroplasty technique results in a faster short-term recovery compared with other methods. However, comparative studies of similar patient groups managed with the same advanced multimodal anesthetic and rehabilitation protocols have been lacking.

A Mayo Clinic orthopedic research team designed a prospective, randomized study to evaluate this claim. The results were published in the May 2008 issue of *Journal of Bone and Joint Surgery (American)** and provide the first rigorous data set comparing patient groups and rehabilitation protocols. The findings were surprising. Contrary to the claim, the study concluded that the mini posterior incision is the management technique with a faster recovery from total hip arthroplasty.

Methods

Between November 2004 and January 2006, the Mayo Clinic orthopedic team randomly assigned 72 patients undergoing total hip arthroplasty to the 2-incision technique group (n=36, 20 men, 16 women; mean age, 67 years; mean body mass index, 28.7) and the mini posterior incision group (n=36, 20 men, 16 women; mean age, 66 years; mean body mass index, 30.2). All received the same uncemented acetabular and femoral component designs and participated in the same comprehensive perioperative pain management program and rapid rehabilitation protocol.

Results

Data show that

- The patients in the 2-incision group recovered more slowly than did those in the mini posterior incision group as measured by mean time to discontinue use of a walker or crutches, to discontinue all walking aids, and to return to normal daily activities.
- The clinical outcome, measured on the basis of SF-12 scores, was similar at 2 months and 1 year postoperatively.
- The 2-incision total hip arthroplasty was a more complex surgical procedure, with a longer mean operative time (95 vs 72 minutes). The rate of complications (2.8%) was the same in the 2 groups.

* Pagnano MW, Trousdale RT, Meneghini RM, Hanssen AD. Slower recovery after two-incision than mini-posterior-incision total hip arthroplasty: a randomized clinical trial. *J Bone Joint Surg Am*. 2008 May;90(5):1000-6.

Treating Osteoarthritis of the Elbow by Arthroscopic Osteophyte Resection and Capsulectomy

Arthroscopic osteophyte debridement and capsulectomy is an emerging technique to treat primary arthritis of the elbow joint. A recently published Mayo Clinic retrospective review identified 41 patients with primary osteoarthritis in 42 elbows who underwent this minimally invasive procedure by the same surgeon. The report,"Osteoarthritis of the elbow: results of arthroscopic osteophyte resection and capsulectomy,"was published in the *Journal of Shoulder and Elbow Surgery*.*

Results

Preoperative elbow motion, pain, and Mayo Elbow Performance Index scores were compared with those at the latest follow-up. At an average follow-up of 176.3 weeks, significant improvements occurred in

- flexion (117.3° to 131.6°; P<.001)
- extension (21.4° to 8.4°; P<.001)
- supination (70.7° to 78.6°; P=.006)
- Mayo Elbow Performance Index scores (81% good to excellent results; P<.001)
- decreased pain (P<.001)
- infrequent complications (heterotopic ossification, ulnar dysesthesias)

Conclusion

This minimally invasive and safe procedure effectively addresses the pathologic processes associated with arthritis of the elbow Arthroscopic surgery offers excellent visualization and access to all areas of the joint. However, it is a technically demanding operation that is best performed by experienced arthroscopic surgeons. Of special concern is the potential for neurovascular injury.

* Adams JE, Wolff LH 3rd, Merten SM, Steinmann SP. Osteoarthritis of the elbow: results of arthroscopic osteophyte resection and capsulectomy. *J Shoulder Elbow Surg.* 2008 Jan-Feb;17(1):126-31.

To learn more about Mayo Clinic's ongoing orthopedic research visit mayoresearch.mayo.edu/mayo/research/ortho/index.cfm

Walking in Step

Motion Analysis Laboratory Assists Orthopedic Surgeons to Improve Patient Care

Human gait is an intricate interaction of neurologic signals, muscle function, joint motion, and limb alignment. Gait is so complex that it cannot be accurately assessed for underlying neuromusculoskeletal abnormalities with the unaided human eye (Figure).

The Mayo Clinic Motion Analysis Laboratory is one of the oldest and most advanced centers dedicated to overcoming the limits of the unaided visual examination of gait for the purpose of improving patients' mobility. Typical patients who benefit from a motion analysis study are those experiencing altered neuromuscular function, musculoskeletal degeneration, or problems with balance. The motion analysis assessment aids both diagnosis and evaluation of treatment modalities.

Deconstructing Gait

Motion Analysis Laboratory specialists integrate sophisticated technologies to understand gait and musculoskeletal pathology. They work closely with Mayo Clinic orthopedic surgeons. Together, they deconstruct pathologic gait abnormalities to arrive at an understanding of the underlying orthopedic problems to be corrected.

Traditional observation of a patient walking or palpation of joints yields insufficient information on which to base a surgical treatment strategy. Gait analysis distinguishes the components that contribute to abnormal gait, thus allowing surgeons to precisely target anatomic structures to be corrected and determine the degree of correction needed. It also provides important information about limb alignment and rotation that affect function.

Gait analysis is especially helpful with pediatric patients, such as those with cerebral palsy, who, in the past, often faced serial surgical procedures to lengthen or transfer various muscles. By obtaining a full picture of the patient's condition, Mayo Clinic's orthopedic surgeons can perform complex bilateral surgery in a single event, thereby avoiding multiple procedures and increased risk (see Case Study).

"In the past, there was a repeated pattern, often referred to as the 'birthday syndrome'—the patient would require another surgical procedure every year," explains Anthony A. Stans, MD, a pediatric orthopedic surgeon at Mayo Clinic in Rochester. "First, the Achilles tendon might need lengthening. Then the next year the hamstrings would be tight; the next year the hip flexors would be operated on, and so on. Motion analysis helps us accurately assess the dynamic factors so that we can correct all the problems in a single-event, multilevel surgery, sometimes with 2 surgical teams working bilaterally at the same time. Our goal is to try to avoid the birthday syndrome."

Kenton R. Kaufman, PhD, PE, directs the Mayo Clinic Motion Analysis Laboratory. He studied with the founders of the field of motion analysis, which was an extension of early 20th-century German research on the effects of backpack loading on soldiers' locomotion. Dr Kaufman views the laboratory's clinical contributions this way: "Dynamic assessment of the person in motion is our key advantage. Traditional imaging tools used to evaluate musculoskeletal problems (such as x-rays, CT scans, and MRI) are static; the patient is either standing or lying down.

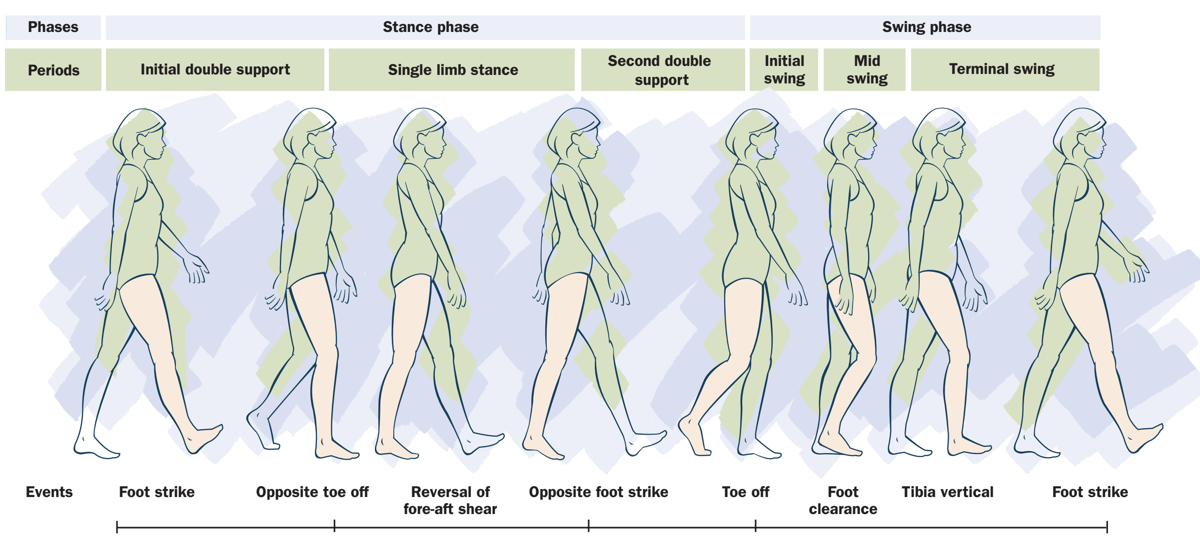


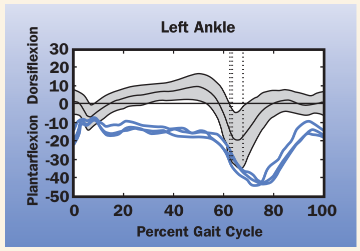
Figure. ***The Gait Cycle.*** *This intricate cycle of neurologic signals, muscle function, joint motion, and limb alignment is so complex that it cannot be accurately assessed for underlying neuromusculoskeletal abnormalities with the unaided human eye.*

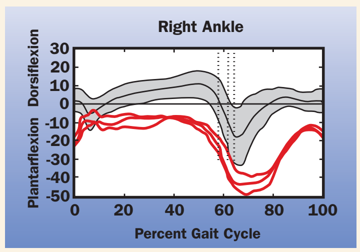
Gait Analysis Aids Treatment of Cerebral Palsy–Related Spastic Diplegia

Before Strayer Surgery (Lengthening the Fascia of the Gastrocnemius Muscle)

Presentation: A 6-year-old girl was evaluated for gait analysis because she was walking up on her toes on both left and right sides. The toe walking was due to a severe limitation in ankle movement and is a common problem for children with spastic cerebral palsy.

Gait Analysis Method: The gait study was performed with the child walking barefoot. Each foot was considered individually. The record of her ankle movement shows the left side in blue and the right side in red. In these graphs, the horizontal axis represents a full gait cycle from foot contact through stance and swing to ipsilateral foot contact. The average ankle movement is shown as a solid line and the shaded gray areas represent ± 2 standard deviations for ankle movement measured from subjects with no impairments. Three trials are shown in each graph averaged together to allow comparison with studies performed on another occasion.





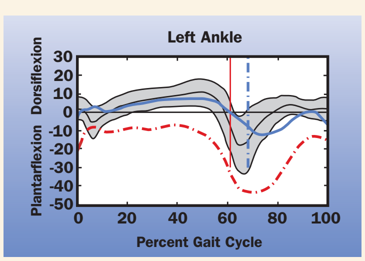
Interpretation of Data: The graphs of the child's ankle movement show that

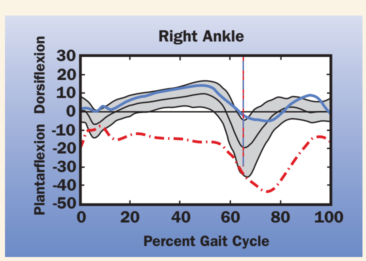
1. She walks with her ankles in plantarflexion throughout the entire gait cycle. In contrast, individuals with unimpaired movement patterns allow the ankle to go into dorsoflexion during stance.
2. Based on her dynamic movement pattern, she is a candidate for surgical intervention to correct the plantarflexion contractures.

After Surgery

1-Year Follow-up: After bilateral Strayer gastrocnemius lengthening surgery, the child was seen for another gait analysis. The original analysis is shown in red and the follow-up study appears in blue.

Conclusion: The graphs show improvement on both sides to normal movement patterns.





Kenton R. Kaufman, PhD, PE, and Anthony A. Stans, MD

These imaging modalities only tell us about the patient's underlying musculoskeletal structure. In contrast, the modalities of the Motion Analysis Laboratory tell us how a person is using his or her structure to move; in other words, we can assess dynamic function. This capacity is unique, and it enables us to sort out the compensations from the problems so we can treat the patient's problems properly and efficiently."

Collaborative Care for Cerebral Palsy

Supported by advances in motion analysis, the trend in the field of orthopedic surgery toward single-event, multilevel surgical procedures for select patients is evolving rapidly at advanced musculoskeletal centers. Pediatric patients with cerebral palsy are among those who benefit most from these advances. Motion analysis is especially helpful for stratifying the subset of patients who have difficulty walking and whose locomotion might be improved by surgery—yet for whom surgery also poses a serious risk to their ability to walk.

Says Dr Stans: "The old saying that 'There is no problem you can't make worse by surgery' is especially true for patients with cerebral palsy, because cerebral palsy is an injury to the brain. As orthopedic surgeons, we are, in effect, trying to treat the disease at a site distant from its origin. A gait analysis study obtained in the Motion Analysis Laboratory is really beneficial in these patients because it helps us get a detailed picture of the intersections of neurology and muscle function in patients who are just at the threshold of ambulation. We want to minimize risks to the patient, such as overlengthening a tight Achilles tendon or making a muscle too weak. We are trying to improve function and quality of life for these patients and minimize the risk of reducing their ability to ambulate."

Mayo Clinic Orthopedic Update

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Daniel J. Berry, MD
Arlen D. Hanssen, MD
Michael J. Stuart, MD

Rapid Intraoperative Diagnostic Test for Prosthetic Joint Infection *(continued from page 4)*

or not, although we still will not know which organisms are present with rapid testing. But we will know that microbes are there—and that they are alive and infectious—and we can make the correct treatment decision," explains Dr Hanssen.

Legacy of Fighting Orthopedic Infections

The evolution of Mayo Clinic's new method into a rapid intraoperative diagnostic test for prosthetic joint infection is a direct outgrowth of nearly 3 decades of multidisciplinary collaboration at Mayo Clinic to prevent and control musculoskeletal infections.

Expertise in infectious diseases is so critical to Mayo Clinic orthopedic surgery outcomes that, since the 1980s, Mayo Clinic orthopedists and infectious diseases specialists have had joint appointments in the Department of Orthopedic Surgery and the Division of Infectious Diseases. These interactions have led to the formalization of the clinical service known as the Orthopedic Infectious Diseases Consulting Group.

To assure that this legacy of leadership in musculoskeletal infection is maintained, the Mayo School of Graduate Medical Education offers its infectious disease fellows a specialized rotation in orthopedic infectious disease. In this rotation, fellows conduct research and participate in outpatient and inpatient care to experience the full spectrum of collaborative, multidisciplinary medicine in the context of musculoskeletal infections. In addition, the Mayo School of Graduate Medical Education has started a new 1-year fellowship program in orthopedic infectious diseases for advanced training.

The 18th Annual Mayo Clinic Symposium on Sports Medicine

November 14-15, 2008, Rochester, Minnesota

The 18th annual Mayo Clinic Symposium on Sports Medicine, offered through the Mayo School of Continuing Medical Education, will be held in Rochester, Minnesota, on November 14-15, 2008.

For more information or to register, phone 800-323-2688 or 507-284-2509; fax 507-284-0532; or visit www.mayo.edu/cme/sports.

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