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# VII. Wound and Fracture Healing

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## Electrical Stimulation for Augmentation of Wound Healing

**Scott R. Crowgey, M.D., and Steven M. Sharpe**
Veterans Administration Research and Development, Decatur, GA 30033
**Sponsor:** *VA Rehabilitation Research and Development Service*

**Purpose**—This project will attempt to identify aspects of the wound healing process that may be augmented by the exogenous influence of electromagnetic fields. A theoretical analysis of the possible effects of electromagnetic fields on wound healing will include analyses of the interaction of electromagnetic fields with cellular structures and of the deposition of heat in damaged tissue via exogenously applied energy fields. This analysis will then be used as a basis for developing a plan for future investigations into the potential application of electrical stimulation for the augmentation of wound healing.

The initial research will involve a review of the literature to identify aspects of wound healing that could be influenced by electrical stimulation. Efforts will then be directed toward developing mathematical models of the possible electrical interaction of electromagnetic fields with cells and cell structures to determine how these interactions could be optimized to improve wound healing. It is anticipated that the literature will not contain all the information necessary to develop these models. Any gaps in necessary information and data will be filled, if practical, using tissue phantom modeling materials, blood, and possibly even primitive tissue culture exposed to a variety of known electromagnetic environments, using easily constructed exposure chambers.

## Development of a Mathematical Model of Fracture Healing in Long Bones

**Gary Beaupre, Ph.D., and Dennis Carter, Ph.D.**
Rehabilitation Research and Development Center, Veterans Administration Medical Center, Palo Alto, CA 94304
**Sponsor:** *VA Rehabilitation Research and Development Service*

**Purpose**—When a long bone is fractured, its mechanical properties change significantly as the bone heals. However there is very little quantitative information on how mechanical stresses influence the healing process and on how the mechanical properties of the fracture site change as the bone regenerates back to its original shape and structure.

Much attention has been given to the development of fixation devices for fractured long bones, and many different mathematical models have been used to evaluate the stress states and deformations caused by the application of these devices. The mechanical properties assumed at the fracture site influence the results of these analyses. The development of a mathematical model to quantify how a bone heals in the presence of different stress states and how the mechanical properties change accordingly will offer insights into the fracture healing process for both normal and pathological healing situations. A better understanding of fracture biomechanics will provide guidelines in the design of treatment modalities for fractures and fracture nonunions.

To date, there have been numerous histological and morphological studies on the healing process of fractured bones. The healing process has been categorized into four basic phases: 1) initial reformation of the vascular system with formation of soft callus tissue; 2) formation of cartilaginous callus; 3) formation of bone tissue; and 4) remodeling of bone tissue. These sequential phases stabilize and progressively stiffen and strengthen the healing bone.

Some data are available on the mechanical properties of the tissues involved, but no models exist that can describe or predict this healing process. Our hypothesis is that the transition from the initial phases of fractured bone to its original structure, in particular from the cartilaginous stage to the formation of bone tissue, is influenced by the local state of stress and strain within the tissues participating in the healing process. As healing proceeds, the material and structural properties of the fracture are changed, resulting in a progressive increase in the structural integrity of the bone.

**Progress**—The finite element method is being used to create a mathematical model of a fractured long bone. The idealized bone is based upon the midshaft geometry of the human femur. The appropriate loading and boundary conditions are obtained from previous studies using: 1) load-sensing implants and prostheses; 2) *in vitro* experiments; and 3) static and dynamic mathematical models of lower limb forces. An iterative mathematical procedure that triggers the transformation of cartilage into bone will be used. This procedure will permit the temporal and geometric pattern of healing to be both predicted and followed.

In this study two- and three-dimensional nonlinear finite element models of an idealized fractured bone are being developed. Initial fracture callus geometry was determined from previous studies. Preliminary studies suggest that the local strain energy density is a likely candidate for the controlling mechanism that triggers the transformation from cartilage into bone.

## Bioelectricity in Fracture Healing

**John F. Connolly, M.D.; Dennis A. Chakkalakal, Ph.D.; Louis Lippiello, Ph.D.**
Veterans Administration Medical Center, Omaha, NE 68105, and the University of Nebraska Medical Center, Omaha 68131
**Sponsor:** *VA Rehabilitation Research and Development Service*

**Purpose**—To investigate the role of bioelectricity in fracture healing, two research projects are under way: "Electrical Osteogenesis: Mechanisms and Causes of Failure," and "Scientific Basis for a New Protocol in External Fixation of Fractures." The basic knowledge of bioelectricity's role derived from these studies will be used to identify electrical signals that will be most effective in promoting healing in fractures that are difficult to heal. In patients with an osteoporotic condition, external fixation is preferred over internal fixation. However, external fixation has a tendency to delay fracture healing. Therefore, we are attempting to identify electrical signals that may be applied to prevent such a delay.

**Progress**—We are developing objective methods for measuring the rate of return of mechanical rigidity, bone blood flow, and skin-surface electrical activity toward normal in fracture healing in dogs so that these can eventually be used in humans for diagnosis of problem fractures, for choice of the optimum method of treatment, and for prognosis of all fractures.

We used both internally fixed and externally fixed long-bone fracture models (radius and tibia) in dogs that heal normally and those that are delayed to carry out our studies according to the following two themes:

A) Characterize these long-bone fracture models through biomechanical, physico-chemical, vascular, histomorphometric, and biochemical measurements so that we can understand details of the differences between a normally healing fracture and a delayed-healing one.

B) Investigate roles of electrical activity that occur in living systems naturally following injury and of externally applied electricity in altering the various features of these fractures revealed from the above study.

**Preliminary Results**—From the studies under theme A, we obtained the following results: 1) a method for determining an index of rigidity of the fractured bone; 2) a method for measuring the return of the venous flow in bone toward normal; 3) a predictable relationship between the patterns (with respect to time) of the reestablishment of blood flow and mechanical properties; and 4) the relationships between biomechanical and biochemical features and also between biomechanical features and calcification in fractures.

From the second set of studies, theme B, the results were as follows: 1) There are two naturally occurring "batteries" in dogs—one associated with the epidermis of skin and the other with the endosteum of bone—that become activated in response to an injury involving both bone and the surrounding tissues. 2) Skin-surface measurements of electrical voltage and current reveal different patterns associated with normal and delayed-healing fractures within the first 3 to 4 weeks after the injury. 3) Two different DC signals (1 microampere and 7 microamperes) applied during the first week after fracture seem to stimulate cell proliferative activity that leads to a significant acceleration of bone formation at the fracture site at 7 weeks after injury; two different cell populations or two different mechanisms may be involved in this response. 4) Comparison of five different electrical signals similar to those used clinically in fracture healing, as applied in long bones in dogs, demonstrate widely different features (amplitude, frequency, etc.), even though they have comparable clinical efficiency.

Our studies under theme B also suggest that none of these signals may be the most effective one for fracture healing. We expect that the knowledge about the influence of specific electrical parameters on the various features of fracture healing gained from our studies will be a useful contribution to the development of more reliable procedures for electrical therapy and prognosis in fracture healing.

## Stimulation of Repair of Cortical Bone Transplants by Implantation of Piezoelectric Materials: A Development Study

**G. V. B. Cochran, M.D., M.Sc.D.**
Orthopaedic Engineering and Research Center, Helen Hayes Hospital, W. Haverstraw, NY 10993, and Surgical Research Service, Castle Point Veterans Administration Medical Center, New York 12511
**Sponsor:** *VA Rehabilitation Research and Development Service; New York State Department of Health*

**Purpose**—Stimulation of bone healing by microampere electric currents now is a recognized form of clinical treatment. For this purpose, various devices are available that aim to improve the healing of bone in problem cases, particularly for individuals with delayed nonunion. Typically, the stimulatory current is provided by a battery-powered device that delivers current to bone via electrodes or by an external electromagnetic device that induces currents in bone. Our purpose is to develop a novel approach to electrical stimulation of bone healing that employs microampere currents generated during physiological loading by a piezoelectric material that is incorporated as part of an internal fixation plate. Because piezoelectric materials produce an electrical charge under mechanical loading, we are thus developing an implant that not only will stabilize bone but also will act as a self-generating electrical stimulation device that requires no separate power source.

**Progress**—To date we have designed and tested several versions of the "piezo plate." Initial tests showed that piezoelectric materials placed on the plate (so as to be in direct contact with bone) were not effective, probably because charge density over the surface was too low. Accordingly, we developed a device in which the piezoelectric material is sealed within the plate and all the charge developed is collected and delivered to bone via electrodes. During the past year we concentrated on electronic and mechanical design considerations necessary to create a version that could be used for trials in large animals as a precursor to fabricating an initial model for clinical use.

**Preliminary Results**—Our animal tests so far have concentrated on the electrical output of prototype plates under functional conditions. These tests demonstrated that even on intact bone (such as in a late stage of fracture healing), the deformation produced by limited weightbearing is adequate to produce electric currents in the range known to stimulate osteogenesis, after necessary rectification and processing by miniature circuitry. Furthermore, we showed that an implanted plate can be activated by external, low-power ultrasound to generate currents in an optimal stimulatory range. These developments hold promise for reducing the incidence of nonunion in problem fractures and may have potential for enhancing fixation of joint replacement prostheses.

**Future Plans**—The next phase of our study, "Testing of Design Parameters for a Prototype Piezoelectric Internal Fixation Plate," has been approved and involves testing the effects of the plate on bone healing in sheep.

## Stress Analysis of Internal Fracture Fixation of Long Bones

**Gary Beaupre, Ph.D., and Dennis Carter, Ph.D.**
Rehabilitation Research and Development Center, Veterans Administration Medical Center, Palo Alto, CA 94304
**Sponsor:** *VA Rehabilitation Research and Development Service*

**Purpose**—Internal fixation of fractured long bones using metal plates is a standard procedure for treating fractures that would be unstable if treated conservatively (e.g., splinted or casted). A possible complication resulting from internal fixation is refracture of the bone after the plate is removed. Some clinical studies have shown refracture rates to be as high as 20 to 25 percent.

Internal fixation is used on the long bones of both the lower (femur and tibia) and upper (humerus, ulna, and radius) extremities. Although exact figures for the number of fractures treated with internal fixation are not known, the popularity of this treatment mode is steadily increasing, particularly for treating forearm fractures where full range-of-motion in pronation and supination may be jeopardized with conservative treatment.

Refracture rates for the radius and ulna of 10 to 20 percent can be directly interpreted in terms of longer healing times with an associated loss of human productivity and increased medical costs for reoperations and prolonged physician treatment.

Although both vascular damage and mechanical stress shielding have been implicated as contributing factors leading to refracture, no studies have assessed mechanical stress shielding using realistic mathematical models. All studies to date have assumed that no motion or slip occurs between the plate and the bone. However, numerous *in vitro* tests have shown that slipping between plate and bone occurs to a significant degree. By utilizing a nonlinear, mathematical model that permits slipping between plate and bone, we will be able to determine accurately the extent to which stress shielding is responsible for bone refracture.

We hypothesize that refracture after plate removal is caused by a combination of vascular damage and mechanical stress shielding. The importance of stress shielding has been overemphasized in all previous mathematical models because earlier studies have not incorporated realistic interface conditions. By including realistic interface conditions, we may arrive at a significantly different assessment of the amount of stress shielding. This in turn may have significant impact on future plate design and on current plate application techniques.

**Progress**—Using a nonlinear finite element model, we are capable of simulating slipping motion between the internal fixation plate and the fractured bone. Coulomb-friction contact elements are used to model the interface between the plate and bone and between the underside of the screw heads and the plate. Screw tightness, friction coefficients, plate material, and plate-bone conformity will be studied parametrically.

An idealized plated bone model has been developed and analyzed for five possible *in vivo* loading conditions. The degree of mechanical stress shielding is shown to be intimately related to how tightly the screws are applied. Loose screws produce minimal stress shielding; tighter screws produce more stress shielding. Estimates of screw tightness at plate explantation combined with the results of the present study suggest that previous predictions of stress shielding may be grossly in error.

## Quantifying Fracture Healing by Impulse Transfer Functions

**R. E. Jones, M.D.; M. G. Strauss, Ph.D.; R. W. Bucholz, M.D.; K. L. Lawrence, Ph.D.**
Veterans Administration Medical Center, Dallas, TX 75216; University of Texas at Arlington, Arlington, TX 76019; University of Texas Health Science Center at Dallas, Dallas TX 75235
**Sponsor:** *VA Rehabilitation and Research Development Service*

**Purpose**—The need for a technique to quantify fracture healing and the role it would play in redefining clinical union, identifying delayed unions, and optimizing rehabilitation programs for accelerated fracture healing is well recognized in the orthopaedic community. Currently, only two tests to assess fracture healing are available—the roentgenogram and manual manipulation. Both are qualitative. Over the past 4 years, we have sought to develop a technique to quantify fracture healing in long bones via natural frequency analysis.

**Progress**—The natural frequencies of a structure are the frequencies at which the structure will vibrate with large amplitudes compared to other frequencies. Previous research has shown how the natural frequencies of the *in vitro* tibia change as the depth of a cross-sectional cut increases. The effects of the fracture location, callus size, and calcification process on the natural frequencies *in vivo,* and the relation of callus strength are being studied.

In the clinic, 26 patients with tibia fractures were followed. For the 24 normally healing patients, a correlation of R = 0.74 existed between the days postinjury and the normalized natural frequency. Two patients developed delayed unions and demonstrated different healing curves compared to the normally healing patients.

In order to establish the correlation between the natural frequencies and the strength of the union, a dog model was established, and experiments were performed. Twenty-one male mongrel dogs underwent unilateral radial osteotomies. The forelimb was placed in a padded plastic spoon splint for 6 weeks postsurgery. Starting at 2 weeks postsurgery and at weekly intervals, each dog was placed in an elevated total body harness so that its limbs would hang clear of any surface; resonance testing was then performed on the radii of the unconscious dog. The impact transfer functions of both radii were obtained by impacting an instrumented hammer at the proximal lateral radius while an accelerometer was held against the anterolateral radius. Similar to the human study, the transfer function was obtained using a Fourier transform. After the designated healing time for a dog had been reached, the dog was euthanized, and both forelimbs were promptly removed. A 10-cm section from each radius was removed. The fracture site was at the midlength. Each section was subjected to torsional failure.

**Preliminary Results**—The results of the torsional tests from 20 dogs showed an increase in torsional strength with increased time until approximately 100 days postosteotomy, at which time the torsional strength of the callus was twice the torsional strength of the intact radius. With the data from only 4 dogs analyzed, a trend appeared. As time progressed, the fracture radius natural frequency squared divided by the normal radius natural frequency squared, also increased. The linear regression lines for the torsional strength versus time and that of the natural frequency versus time are very similar in slope. This implies that it would be possible to follow the course of healing in long bone fractures noninvasively by this technique and to identify abnormal deviations from the normal healing pattern sooner than present techniques allow. Clinical union may be quantitatively assessed *in vivo*. This method could also be used to determine what affects the rate of healing and to tailor an optimal rehabilitation scheme to accelerate fracture healing.

## Altered Collagen and Wound Metabolism in Non-Healing Diabetic Ulcers

**Roger E. Pecoraro, M.D.; John Olerud, M.D.; Mary Ann Riederer-Henderson, Ph.D.; Ernest Burgess, M.D.; Frederick A. Matsen III, M.D.; Craig Wyss, Ph.D.**
Seattle Veterans Administration Medical Center, Seattle, WA 98108
**Sponsor:** *VA Rehabilitation Research and Development Service*

**Purpose**—This project was designed to test the hypothesis that potentially correctable metabolic abnormalities may interact with ischemia, neuropathy, and infection to obstruct healing of diabetic ulcers. Subjects include diabetic and nondiabetic patients admitted to the Seattle VAMC Amputation Service who may require lower extremity amputation as a result of diabetes and/or vascular disease. We will test whether recent poor glycemic control, abnormal ascorbic acid metabolism, altered zinc availability to injured tissue, and increased nonenzymatic glycosylation of dermal collagen are associated with and potentially responsible for failure of wound healing that leads to amputation in diabetic individuals.

The objective of these cumulative investigations is to identify metabolic abnormalities that are potentially correctable and that may contribute to limb loss and wound failure in diabetic individuals.

**Progress**—Glycemic control in diabetic patients is being documented by measurements of fasting plasma glucose and glycosylated hemoglobin. Ascorbic acid levels are determined in samples of plasma from all patients and in leukocytes and dermal tissue from selected patients, measured by high-performance liquid chromatography. Zinc levels are being measured in samples of plasma, leukocyte, and wound tissue by atomic absorption spectrophotometry. Collagen fractions are extracted from skin and wound tissue specimens from amputated limbs for subsequent measurement of the extent of glycosylation of collagen. Nutritional status is being evaluated by a laboratory panel of nutritional indicators. Vascular status of diabetic and nondiabetic amputation subjects is being documented by standardized measurements of limb transcutaneous oxygen tension ($TcPO_2$) and segmental doppler blood pressures.

To date, we have studied 79 diabetic individuals who have been candidates for or who have actually received limb amputations. A total of 49 nondiabetic amputees, all with peripheral vascular disease, were enrolled. In addition, many of the biochemical and vascular measurements were standardized in 10 healthy nonsmoking elderly males without diabetes or vascular impairment. Vascular and plasma metabolic measurements have been made in 150 control diabetic individuals admitted to the same hospital but who have not had amputations or lower extremity ulcers.

**Preliminary Results**—Both diabetic and nondiabetic amputation patients have shown significant deficiencies in plasma zinc and ascorbic acid levels. Preliminary analysis of tissue extracts suggests that ascorbic acid is concentrated in dermal tissues at sites of cutaneous ulceration. Further studies are in progress to determine if tissue concentrations of ascorbate and zinc in these patients are suboptimal for adequate wound healing. Experimental iatrogenic microwounds have been inflicted on the limbs of a volunteer subgroup of patients 7 days before amputation; histologic evaluations of those tissues, in progress, will provide a semi-quantitative independent index of cutaneous wound healing to correlate with the metabolic parameters.

We confirmed the observation that many patients with diabetes, unlike nondiabetics requiring amputation resulting from advanced peripheral arterial disease, often fail to heal limb ulcers despite adequate cutaneous oxygen diffusion.

## Morphological and Clinical Studies of Microwounds in Ischemic Human Tissue

**John Olerud, M.D.**
School of Medicine, University of Washington, Seattle, WA 98195
**Sponsor:** *VA Rehabilitation Research and Development Service*

**Purpose**—The purpose of this project is to study in a systematic fashion morphological and clinical features of small standardized wounds created on the lower extremities of normal elderly subjects and patients with severe peripheral vascular disease (PVD) necessitating amputation.

**Progress**—We developed a standard human wound model for evaluating 12 morphological events of repair. The events include presence of scab, epidermal migration, epidermal closure, epidermal hyperplasia, amount of stratum corneum, stratum granulosum, fibrin neutrophiles, monocytes, fibroblasts, collagen, and capillaries. Wounds from 18 diabetics, 13 patients with PVD, and 11 normal subjects were fully processed and evaluated. The results were entered on a computer database, and preliminary data analysis was done. Additionally, we developed a timetable of immunohistochemical events of healing in elderly normal subjects using 10 antibodies relevant to the repair process (filaggrin, keratin, *Ulex europeus* I, laminen, type IV collagen, type I collagen, type III collagen, vimentin, thrombospondin, and factor VIII). This wound model and timetable will be used for comparative studies of normal subjects and patients with PVD and DM.

## Transcutaneous Oxygen Tension as Predictor of Wound Healing

**Frederick A. Matsen III, M.D.; Ernest M. Burgess, M.D.; Craig R. Wyss, Ph.D.; Richard M. Harrington, M.S.**
Limb Viability Laboratory, University of Washington, Department of Orthopaedics, Seattle, WA 98195
**Sponsor:** *VA Rehabilitation Research and Development Service*

**Purpose**—Transcutaneous oxygen tension is the surface oxygen tension measured with a small heated sensor sealed to the surface of the skin. Cutaneous heating induces local hyperaemia in the skin under the sensor and allows measurement of the potential for oxygen delivery in relation to metabolic needs. The oxygen that diffuses through to the surface of the skin is that delivered in excess of local metabolic needs. This year our group published reports on the relation between transcutaneous oxygen tension measurements ($TcPO_2$), ankle systolic blood pressure measurements (ABP), and the clinical outcome of both vascular surgery and amputation surgery.

**Preliminary Results**—Both $TcPO_2$ and ABP were measured before and after 53 vascular procedures performed to relieve limb-threatening ischemia. In the patients without diabetes, those with post-surgical ABP greater than 75 mmHg or $TcPO_2$ greater than 20 mmHg showed resolution of the clinical symptoms within 60 days after surgery. All patients falling below these levels underwent subsequent limb amputation.

Diabetic patients had different results, with many having high ABP in conjunction with low $TcPO_2$. This was attributed to a high incidence of calcific medial stenosis leading to elevated ABP measurements. The clinical outcome of vascular surgery on diabetic patients was uncorrelated with the postsurgical ABP and poorly correlated with postsurgical $TcPO_2$. Those with postsurgical $TcPO_2$ below 20 mmHg all had unfavorable outcomes, but many with higher values also sustained slow healing of ulcers, persistence of rest pain, and/or limb amputation.

In the study of 284 amputation surgeries, $TcPO_2$ and ABP were measured within the 2 weeks before surgery. The amputations were performed at levels selected by clinical criteria only. The surgery was classified a success if the amputation wound eventually closed and healed, even if it required a long period and/or local debridement. For both diabetic and nondiabetic patients undergoing either foot or below-the-knee amputation, there is a significantly increasing risk of amputation failure as presurgical $TcPO_2$ values decrease. Thirty percent of surgeries on limbs with measurements in the range 11 to 20 mmHg failed; more than 60 percent failed on limbs with measurements less than 10 mmHg. For above-the-knee amputations, presurgical $TcPO_2$ had no predictive value in the surgical outcome.

Presurgical ABP appeared to have predictive value only for patients without diabetes. Among diabetic patients, calcific medial stenosis appears to interfere with ABP measurements. Even among nondiabetic patients, there were a large number (greater than 50 percent) with undetectable pulses but sufficient limb blood supply to heal an amputation.

We conclude that presurgical $TcPO_2$ measurements are useful as an addition to or replacement for ABP in evaluating the outcome of vascular and amputation surgery.

## Enhancement of Ulcerated Tissue Healing by Electrical Stimulation

**L. Vodovnik, D.Sc.; A. Stefanovska, Dipl.Eng.; R. Turk, M.D.; H. Benko, P.T.; M. Malezic, Dipl.Eng.; V. Kosorok, M.D.**
Electrical Engineering, E. Kardelj University; University Rehabilitation Institute; Jozef Stefan Institute, 61000 Ljubljana, Yugoslavia

**Sponsor:** *National Institute for Handicapped Research, Washington, DC; Slovene Research Community, Ljubljana, Yugoslavia*

**Progress**—Pulsed or DC electrical currents have been successfully applied in healing indolent wounds. In our preliminary experiments, dual-channel stimulation was applied to spinal-cord-injured patients with decubitus ulcers, to postamputation wounds, and to ulcus cruris. After encouraging results on 30 patients, a study was started on 10 spinal-cord-injured patients with decubitus ulcers, which had developed over a period of several months. Stimulation was started 1 week after admission to the Rehabilitation Institute. Two channels of biphasic stimulation with tetanizing currents were applied through four electrodes across the wound. The stimulation parameters were a frequency of 40 Hz and a pulse width of 250 microseconds. The amplitude (up to 50 mA) was adjusted to achieve minimal muscle contraction when feasible. Stimulation was applied twice daily for 20 minutes. Once weekly the volume of the wound was measured by approximate measurements of surface and depth, the wound was photographed, and wound tissue samples from the center, the periphery, and from eventual pockets were taken for bacterial tests.

The size of all wounds decreased after stimulation. The initial healing rate ($cm^3$/day) depends on the initial wound volume ($cm^3$). The healing rate per 1 $cm^3$ initial wound volume ranged between 0.01 and 0.02 per day. Thus, an initial wound of 200 $cm^3$ started to heal with a rate of about 2 to 4 $cm^3$/day, the rate decreasing exponentially with time. The time constant of healing is thus between 50 and 100 days. Bacterial tests had previously produced no consistent relation between the healing process and changes in the types of bacteria.

## Acceleration of Fracture Healing Electrical Fields

**Carl T. Brighton**
University of Pennsylvania, Philadelphia, PA 19104
**Sponsor:** *National Institutes of Health*

**Purpose**—The object of the proposed research is to continue investigating the effects of applied electrical fields on the acceleration of fracture healing in laboratory animals. The proposed research was designed: 1) to determine the optimum parameters of applied (exogenous) electricity for accelerating fracture healing; 2) to determine the role of stress-generated (endogenous) electricity in fracture healing; and 3) to determine the mechanism of electrically induced osteogenesis at the cell level.

Methods to be used include the comparison of the osteogenic response of *in vitro* fetal rat tibia and *in vivo* healing rabbit fibula to constant DC, various pulsed unidirectional electric fields, and various electromagnetic fields. Osteogenesis and bone healing will be evaluated by incorporation of tritiated thymidine, Ca45, and 35SO4 as well as by maximum resistance to bending as determined by an Instron Testing Machine. Stress-generated potentials will be measured in fracture calluses. Origin of stress-generated potentials will be evaluated by altering collagen in tendon biochemically. The mechanism of action of electrically induced osteogenesis will be sought by determining: 1) $PO_2$ and pH changes in the vicinity of a cathode; 2) changes in surface of cell membrane; 3) mitochondria release of calcium; 4) cellular proliferation and migration; and 5) collagen and proteoglycan biosynthesis and processing.

## Biomechanics of Metastatic Defects in Bone

**Wilson C. Hayes**
Beth Israel Hospital, Boston, MA 02215
**Sponsor:** *National Institutes of Health*

**Purpose**—Advances in the palliative treatment of patients with established metastatic malignancies have not only prolonged patient survival but have also increased the incidence of bony metastases and subsequent pathological fractures. Thus, prevention and effective treatment of fractures associated with metastatic defects in bone have become increasingly important aspects of the care of cancer patients. Unfortunately, there are currently available only the crudest of clinical guidelines for assessing the increased fracture risk associated with metastatic lesions in bone. Therefore, the appropriate time for prophylactic stabilization of impending fractures is not known. This investigation will be directed in the long term to the development of comprehensive biomechanical guidelines for the orthopaedic assessment and treatment of metastatic defects in long bones, the proximal femur, and the spine.

A four-phase staged approach will be used. In Task I, we will conduct retrospective radiographic reviews of patients exhibiting metastatic lesions in those regions and will determine the most frequent sites and approximate shapes of the lesions. As part of this task, we will also develop improved diagnostic imaging procedures for the description of lesion geometries. In Task II, we will determine *in vitro* the strength reductions associated with simulated defects in long bones, the proximal femur, and the spine. In Task III, we will use finite element modeling of defects in these regions to provide a theoretical framework for interpreting the experimental results and assessing the sensitivity of the fracture risk predictors to individual patient variations. In Task IV, we will combine these findings by developing structural predictors of fracture risk for individual patients with particular lesions. Biomechanical guidelines appropriate for each skeletal region will be developed and tested retrospectively in clinical populations. These guidelines should represent a significant improvement in the orthopaedic care of patients with metastatic defects in bone.

## Management of Burn Injuries

**J. H. Evans, Ph.D.; J. M. Courtney, Ph.D.; J. D. S. Gaylor, Ph.D.**
Bioengineering Unit, Regional Burns Unit, and Plastic and Oral Surgery Unit, University of Strathclyde, G4 ONS Glasgow, Scotland
**Sponsor:** *Dow Corning Corporation*

**Purpose**—Work continues on providing a broad-based better understanding of the burn wound and hypertrophic scar and on improving the management of burned patients. Currently, research is directed to assessing burn depth, determining mass and energy loss from the burn wound, developing synthetic dressings, *in vitro* expansion of autologous epithelium, and the treatment of hypertrophic scars with silicone gel and pressure garments.

**Progress**—A thermographic technique, employing a low-cost and convenient pyroelectric Vidicon camera, is based on previous work using an animal model along with a mechanically scanned detector.

Laboratory and clinical investigations are being conducted on novel burn dressings and on candidate materials including silicone-based materials and hydro-gels. Consideration is being given to mechanical strength and conformability, mass and energy flux, bacterial control, and drug release. Electromagnetic enhancement of the rate of expansion of epithelium is being studied *in vitro* to provide a clinically acceptable source of autologous skin for the management of the severely and extensively burned patient.

**Preliminary Results**—A substantial trial has demonstrated that a silicone gel dressing can make a significant contribution to the rate of resolution of hypertrophic scars. On many sites, particularly the face and hands, it is more manageable and better tolerated than is therapy based on pressure. No significant complications have been observed in a trial of 150 patients.

## Quantitative Evaluation of Nerve Repair

**Vincent R. Hentz, M.D.; Joseph Rosen, M.D.; John Wikswo, Ph.D.; Kenneth Cummins, Ph.D.; Gordon Abraham, M.S.**
Rehabilitation Research and Development Center, Veterans Administration Medical Center, Palo Alto, CA 94304
**Sponsor:** *VA Rehabilitation Research and Development Service*

**Purpose**—The treatment of peripheral nerve injuries rarely results in recovery of function adequately approaching that before the injury. In dealing with these injuries, the physician faces two major problems. First, the lack of objective methods for assessing the extent of peripheral nerve injury or the extent of regeneration in previously injured nerve compels physicians to rely on subjective criteria in making clinical decisions regarding the management of these injuries. Second, present methods of peripheral nerve repair, even those employing modern microsurgical techniques, rarely result in regeneration sufficient for full functional recovery. A number of adjuncts to traditional repair methods offer the promise of increased or directed regeneration, but the effectiveness of these new approaches needs to be assessed objectively.

The development of a simple method for evaluating the extent of a nerve injury will help the physician make objective decisions regarding the timing and type of care of the injured nerve. The use of the appropriate modality for the treatment of nerve injuries will enhance and speed the regenerative process and will lead to fuller recovery of function.

Purely mechanical (suture) methods of reapproximating peripheral nerves result in very limited functional axonal regeneration. It is thought that this is due primarily to scar formation at the repair site, which prevents proximal axons from crossing the repair site and establishing functional connections. We have been studying sutureless repair methods that use biodegradable wraps that provide total circumferential alignment of the nerve, block scar invasion at the repair site, and improve the milieux for axonal regeneration. The preliminary results of our early investigation indicate that none of the purely mechanical alignment techniques hold any significant advantages to regeneration. Regeneration is being assessed using electrophysiological methods that estimate the number and velocity distribution (DCV) of axons both proximal and distal to the repair site. The analysis methods presently used require involved mathematical computation and must be performed off line. Such evaluation methods are currently inappropriate for clinical use by physicians.

This project is based on two fundamental hypotheses. First, we feel that nerve function following injury, or axon regeneration following repair, can be reliably, quickly, and safely evaluated by electrophysiological methods that estimate the number and health of the axons crossing a focal lesion or repair site. For this tool to be generally applicable, it must be appropriate for both noninvasive and invasive (intraoperative) studies. Second, to enhance nerve regeneration in any significant and reliable fashion, modern mechanical repair methods will have to be coupled with other modalities that intrinsically influence the rate and/or direction of axonal regeneration (tropic factors), that improve the axonal environment at the repair site (pseudoperineurial barriers), or that decrease the effect of scar formation.

**Progress**—We are currently developing a simple technique for characterizing nerve function and regeneration at the repair site. This method estimates the number of axons that cross a focal lesion (or repair site) and their distribution of added conduction delays. This approach requires considerably less computation than DCV analysis. We are also investigating the possibility of using magnetic recording and/or stimulating techniques for intraoperative evaluation of exposed nerve bundles. By employing magnetic coupling for recording, the practical problems of mechanical nerve damage, stimulus artifact, and operating-room ground loops will be minimized. The resulting signals, which reflect longitudinal current in the axons, can be analyzed by any of our methods of nerve evaluation. Initial experiments on magnetic measurement of action currents from rat sciatic nerve, performed in cooperation with John Wikswo, Ph.D., of Vanderbilt University, have been quite promising. Innovations by Dr. Wikswo permit measurements at room temperature using inexpensive equipment.

**Preliminary Results**—During this project we have compared the use of a biocompatible, biodegradable "pseudoperineurial barrier" to standard microsutures in several primate nerve repair and nerve graft models. In spite of intraoperative technical problems with the first-generation pseudoperineurial barrier, the initial results from postoperative electrophysiologic assessments of the number of axons having regenerated across the repair site indicate that the barrier does as well as or better than standard suture repair methods.

There is mounting evidence that an autoimmune reaction follows destruction of the perineurial blood-nerve barrier during nerve injury. We have studied the effects of an immunosuppressive agent, Cyclosporin-A, in decreasing the initial inflammatory response associated with nerve injury in a rat model. Preliminary histologic results indicate a significant diminution of inflammatory cells about the repair site. Early electrophysiological studies indicate some enhancement of regeneration. In contrast, studies of the effects of the ability of electromagnetic fields to enhance regeneration have not produced significant results.

Encouraging results have been obtained using simulated data to test the model for characterizing focal conduction delays that occur at the site of nerve injury or repair. The programs will soon be adapted to run on portable evoked potential equipment, and human intraoperative assessments of nerve injuries will soon follow.

Several modifications in the neuromagnetic system have allowed the acquisition of reliable data from primates and rats. These data indicate that the neuromagnetically derived waveforms can be processed exactly like the electronically recorded counterparts. The development of an openable clip-on toroid will permit human studies to begin soon.

## Nerve Coupler—Sutureless Peripheral Nerve Repair at the Fascicular Level

**Joseph Rosen, M.D.**
Rehabilitation Research and Development Center, Veterans Administration Medical Center, Palo Alto, CA 94304
**Sponsor:** *VA Rehabilitation Research and Development Service*

**Purpose**—Current methods of peripheral nerve repair often result in unsatisfactory restoraton of function of nerves. Factors at the repair site that can contribute to these poor results include: 1) poor alignment of the repair site by suture methods; 2) ingrowth of surrounding scar tissue that blocks the repair site; and 3) outgrowth of nerve tissue from the repair site into surrounding tissue with consequent neuroma formation.

The importance of our study lies in its potential for improving the current state of peripheral nerve repair. Peripheral nerve damage associated with trauma to bones, tendons, and other structures occurs in approximately 30 percent of extremity trauma. Nerve injuries prevent successful rehabilitation more than any other form of trauma. Motor dysfunction, loss of tactile discrimination, sympathetic dystrophy, and postregenerative pain can greatly impair self-care and other tasks of daily life, leading to long-term disability. Improved nerve repair would theoretically improve veterans' quality of life following nerve repair.

Present methods of peripheral nerve repair by suture are based on an anatomical approach that attempts to reestablish continuity of the multiple layers of nervous tissue. In suture repair, either the epineurial or perineurial layers of connective tissue are reconnected by sutures to promote healing of the nerve. In suture repair, the discrete tissue layers are obliterated by scar tissue at the repair site. An alternative to this anatomical approach is a cellular approach involving the construction of an artificial perineurium. The perineurial layer divides the nerve into two distinct cellular environments. The intrafascicular Schwann cells, axons, and endoneurial fibroblasts compose the nerve's regenerating unit. The cellular components of the extrafascicular environment are responsible for the fibrous reaction to injury.

In a number of previous papers, the investigator has developed and described tubes that reconstruct the perineurium. This sutureless method of nerve repair (fascicular tubulization) allows the nerve to reestablish the perineurium naturally. Histology and electrophysiology have shown collagen tubes to be an effective repair method in rat monofascicular and cat multifascicular models. Bioresorbable polyglycolic acid (PGA) tubes were shown to be successful in the rat monofascicular model by qualitative and quantitative histology. No prior methods of nerve repair have used this fascicular tubulization technique.

The results of peripheral nerve repair may be improved by developing a better method to approximate the transected ends of a nerve. The development of a device that couples the ends of the nerve together without sutures might improve on the poor results of suture repair. The "nerve coupler" will precisely approximate the ends of a transected nerve fascicle. This will improve the alignment at the repair site. The device will also act as a barrier to the ingrowth of scar tissue from outside the perineurium. It will serve to block the outgrowth of intrafascicular nerve tissue into the extrafascicular space.

**Progress**—The first objective of this pilot study was to determine a satisfactory design and material for the nerve coupler. Prototype plexiglass couplers and bioresorbable polyglycolic acid (PGA) couplers were studied in the monofascicular rat peroneal nerve. These 1- to 3-month short-term studies were designed to determine how effectively the coupler maintained the integrity at the repair site during regeneration. These studies also compared coupler repair with controlled perineurial suture repairs. Gross and microscopic reactions to coupler materials were evaluated. Repair site organization was assessed by histology. The results of this pilot study will be used to modify the design of the nerve coupler.

**Preliminary Results**—Trials of plexiglass couplers in two animals demonstrated simple application of the coupler and excellent nerve alignment on gross visual examination. Histological evaluation showed excellent alignment and minimal cellular reaction at the coupler repair site. Studies of 1, 2, and 3 months' duration using PGA couplers again showed simple application of the coupler and excellent gross alignment at the sutureless repair site. Microscopic evaluations of 1- to 3-month animals revealed fair to excellent organization at the coupler repair site and minimal to moderate reaction to coupler material.

**Future Plans**—Our next goal is to obtain VAMC RAG funding to continue our studies of the nerve coupler in the rat peroneal nerve. We would like to perform long-term studies to evaluate repairs using quantitative histology and electrophysiology. We would also like to evaluate new designs and new materials for the coupler in future studies.

## Evaluation of Tubular Internal Fixation Plate for Fracture Management

**Savio L-Y. Woo; Richard Coutts, M.D.; David Amiel, Dip.Ing.; Steven Garfin, M.D.; Wayne Akeson, M.D.**
Veterans Administration Medical Center, La Jolla, CA 92103 and University of California, San Diego, CA 92103
**Sponsor:** *VA Rehabilitation Research and Development Service*

**Purpose**—The overall objective of this project is to determine whether significant advantages can be obtained from internal fixation of diaphyseal fractures using plates with improved design. Specifically, our goal is to test the newly developed design criteria. That is, moderate bending and torsional plate rigidities are needed for early immobilization to achieve fracture healing without bone shortening and/or angulation, and low plate axial rigidity is desirable to minimize stress (strain) shielding of the underlying bone during the postunion remodeling process. A new plate with a tubular cross-section is made of stainless steel filled with polyethylene. This plate has the aforementioned desired rigidity characteristics and will be used in a canine unilateral midshaft femoral osteotomy mode. A traditional solid stainless steel plate of identical external geometry will be used in a separate series of animals with similar osteotomy. In addition, it is also our goal to test whether such a low axial rigidity plate can prove to be advantageous to the recovery of full structural properties of the underlying bone following plate removal.

**Progress**—At present, the evaluation of the bone lying beneath both the traditional solid stainless steel (control) and the new tubular (experimental) plates is being performed using X-ray, geometric measurements, histomorphometric measurements, and biochemical techniques. Specifically, a comparison is being made between the actual physical properties of bone and the structural and mechanical properties obtained by biomechanical bending and by axial and torsional testing.

**Preliminary Results**—Histomorphometric data have shown that on the average, bone porosity is higher for the control solid stainless steel plate, whereas there is an increase in new bone growth and less porosity for bone lying beneath the experimental hollow plate. This information correlates well with the bioengineering tests performed. With further comparison and study of these test results, we hope to provide more insight into the problem of localized osteopenia that occurs with the use of internal fixation plate systems.

## Biomechanical Considerations of Metal and Composite Materials for Bone Fracture Fixation Plates

**Savio L-Y. Woo ; Wayne H. Akeson; Richard D. Coutts**
University of California, San Diego and San Diego Veterans Administration Medical Center, La Jolla, CA 92103
**Sponsor:** *VA Rehabilitation Research and Development Service*

**Progress**—This study, together with others, refutes the necessity of extremely high plate bending and torsional rigidities (absolute immobilization of the fractured bone ends) for union. Plates with significantly less rigidities, and applied without "compression", were able to achieve equivalent and better bone healing with the aid of callus formation. The results of this series of experiments confirm that osteonal bone union is slow and mechanically inferior to callus union.

The design criteria developed by our laboratory—that is, moderate bending and torsional rigidities (to provide adequate but not "rigid" fixation of fractured bone for formation of periosteal callus and for union) together with the low plate axial rigidity (to allow the healed bone to share a larger portion of the physiological stresses to reduce the instances of stress-protection osteopenia)—may be an ideal compromise between investigators who advocate rigid internal fixation systems and those who advocate flexible ones. A tubular cross-sectional stainless steel plate may be an optimal design for such a less rigid fixation plate system. Other materials and designs following these guidelines also should be pursued.