A publication of the

Dermatology Foundation

Progress in Dermatology

Editor: Alan N. Moshell, M.D.

VOL. 36 December, 2002 NO. 4

Electrical Stimulation of Wound Healing

Joseph C. Ojingwa, M.D., Ph. D. and R. Rivkah Isseroff, M.D.

Department of Dermatology School of Medicine University of California, Davis

INTRODUCTION

We generally do not think of skin as an electrically - responsive tissue. Yet, the skin generates an electric current upon wounding, and increasing evidence implicates endogenous electric fields as important mediators of the repair process. For decades, investigators have attempted to enhance skin wound healing by applying various forms of electrical stimulation (ES). This concept of therapeutic ES is not new and is in current use for other clinical indications including neuromuscular rehabilitation, pain control, and bone healing. This review will take an evidence-based approach to evaluating both the clinical and basic research that provides strength of evidence for the use of ES to accelerate or improve cutaneous wound healing.

ELECTRICAL STIMULATION FOR WOUND HEALING

ES, or electrotherapy, is defined as the application of electric current from electrodes placed directly within a wound or on skin in close proximity to it. Its use in skin wound healing is not new: the use of electrostatically charged gold leaf to enhance the healing of small pox lesions is noted about 300 years ago[1], and rediscovered more recently in the 1960's[2, 3]. The use of ES for the treatment of diseases in general was abandoned early in the last century because of concerns regarding the efficacy of this therapy. ES faded from the medical practice after the Flexner Commission report[4] in 1910 suggested that ES was not scientifically based. It was not until the past three decades that renewed interest in this technique has emerged. As the number of successful studies being published increases, the use of ES for the treatment of soft tissue injuries is slowly becoming more widely accepted. ES has very recently been approved for Medicare coverage by the Centers for Medicare and Medicaid Services (CMS)[5] for the treatment of stasis, arterial, pressure and diabetic ulcers that have not responded to standard wound therapy. Thus, the use of this modality by dermatologists may increase, and understanding the underpinnings of its efficacy is important to its effective therapeutic use.

Electrical Stimulation Modalities

Three basic treatment regimens are commonly used today, direct current (DC), pulsed current (PC), and alternating current (AC) (Figure 1). The advantages and disadvantages of each are briefly described to facilitate comparison of the reported results using these modalities.

Direct Current (DC)

Electric current that is continuous and unidirectional in flow (from cathode to anode) is defined as direct current. This form of current is also sometimes referred to as galvanic current. The duration of the current may vary from 1 second to longer times. If the flow of current is unidirectional but less than 1 second, it is no longer a DC current but referred to as pulsed current. Continuous DC is pulseless, thus has no waveform (Figure 1A) and no reversal of polarity unless it is reversed manually.

The passage of electric current through tissue produces electrothermal, electrochemical or electrophysical effects. The electrothermal effect is described by Joule's Law which states that heat production is proportional to the square of the total current, the resistance, and the time for which the current flows. Normal skin presents high resistance, thus thermal damage may ensue from continuous DC stimulation. When using DC to treat wounds, to avoid thermal damage both the amplitude and treatment time must be minimized.

The production of this issue of *Progress in Dermatology* has been underwritten by Galderma Laboratories, L.P.

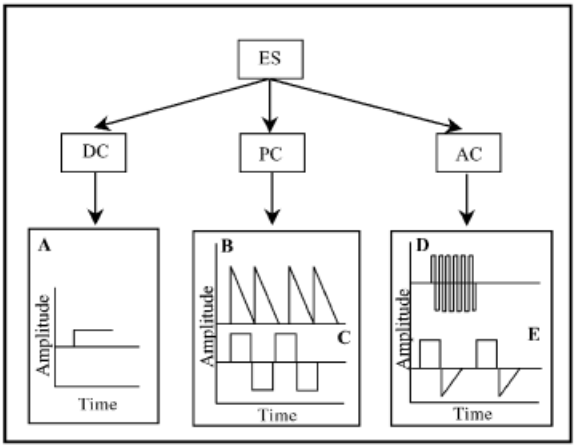

Figure 1: Electric Stimulation Modalities. ES: electrical stimulation
DC: direct current, PC: pulsed current, AC: alternating current. Panel A: Continuous DC, Panel B: Twin-spike Monophasic (also called High Voltage Pulsed Current, HVPC), Panel C: Rectangular Symmetrical Biphasic (also called Low Voltage Pulsed Current, LVPC), Panel D: Biphasic Symmetrical (also used for TENS), Panel E: Balanced Asymmetrical Biphasic

DC causes an electrochemical reaction in tissue as well. Positively charged sodium ions migrate toward the negatively charged pole (cathode), combining with water to yield the base sodium hydroxide. At the anode (positive pole), there is formation of hydrochloric acid due to the redistribution of chlorine. These resultant changes in pH may induce chemical burns or blisters. Shortening treatment time, polarity reversal, or decreasing current amplitude can minimize this hazard.

Pulsed Current (PC)

A mechanism to reduce the electrothermal and electrochemical hazards of DC current application is to utilize pulsed current (PC), defined as a unidirectional or bidirectional flow of charged particles for a short duration of time. In the successful protocols, each pulse tends to last for a milli or microsecond followed by a relatively long interpulse interval at which current amplitude is zero. Most PC protocols do not exceed 20 mA of total current and are thus very safe to use.

Numerous, and sometimes confusing, names have been assigned to PC (e.g. interrupted square, trapezoidal, triangular, sawtooth, spike) because of the different shapes the waveforms exhibit. One of the ways of eliminating the confusion is to describe the pulses according to three basic parameters of the waveforms: amplitude, duration, and frequency. This can be further simplified by grouping in two common delivery configurations: either monophasic or biphasic.

A monophasic pulse is a brief duration of unidirectional flow of charged particles. An example of a monophasic PC is the commonly used high voltage pulsed current (HVPC). The waveform of HVPC is a monophasic spike delivered in pairs (twin peaked, Figure 1B). Because each peak or spike has very short pulse duration (2 to 50 msec), a high voltage (100 to 500V) is needed in order to produce currents in the 1mA range. The amplitude and pulse rate often selected for wound healing is usually between 80 to 200V and 50 to 120 pulses per second (pps) respectively, minimizing the electrochemical changes under the delivering electrodes in skin[6].

Biphasic pulse is one that deviates from baseline (zeroline) first in one direction and then in the opposite direction. The biphasic waveform can be delivered in a number of protocols, and an example is demonstrated in Figure 1C. One biphasic protocol that has been used successfully in some clinical trials is the low voltage pulsed current (LVPC).

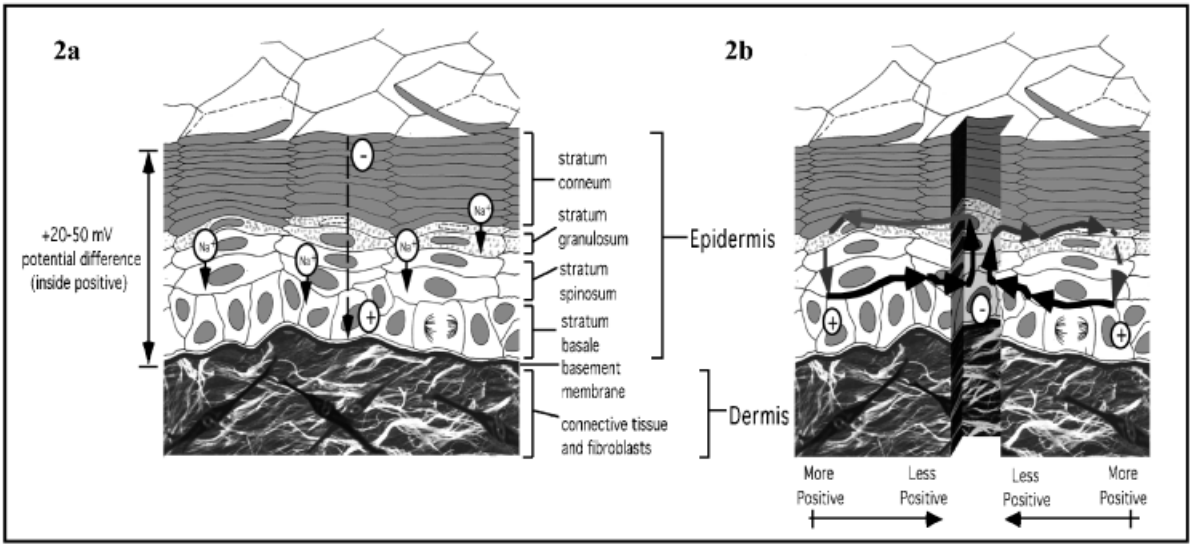

Figure 2. Generation of skin wound electric fields.
Unbroken skin maintains a "skin battery", derived by apical-basal transport of Na^+, and generation of a transepithelial potential (2a). When wounded, the potential drives current flow through the newly formed low resistance pathway (2b), generating an electric field whose negative vector points toward the wound center at the lower portion of the epidermis.

Alternating Current (AC)

AC is defined as a current that changes the direction of flow with reference to the zero baseline at least once every second. The typical AC is symmetrical (although asymmetric waveforms have also been used) and can be delivered in various waveforms (Figure 1D & E). The transcutaneous electrical nerve stimulation (TENS) devices currently available use a type of AC. Current is usually delivered at 15 to 20 mA with a pulse duration of 150 μsec. Some successful studies using AC for wound healing have been reported in the literature (see Table 4).

THEORETICAL AND SCIENTIFIC BASIS FOR USE OF ES

Evidence for electric fields in wounds

The existence of ionic currents exiting injured tissues has been known for some time: it was first demonstrated by Matteucci in 1830[7]. Dubois-Reymond[8], founder of the science of bioelectricity, was the first to experimentally demonstrate in 1843 the existence of wound currents. He measured approximately 1mA of current from a wound in human skin. Other, more recent studies have confirmed this finding: for example, currents of up to 10 mA/cm^2 have been measured with the vibrating probe technique exiting amputated finger tips in children[9]. Transepithelial potentials between 20-50mV, inside positive, have been recorded in human skin, maintained by a "skin battery"[10], presumably generated by inward transport of sodium ions through the membrane Na^+/K^+ ATPase pumps[11]. In intact human skin, current flow is limited by very high resistance stratum corneum. When a wound disturbs the epidermal integrity, there is a net flow of current through the low resistance wound pathway and the resultant generation of a lateral electric field within or beneath the adjacent epidermis. The negative pole of this field vector therefore points towards the wound from all neighboring regions (Figure 2).

Numerous studies[11-14] have shown that there is a "current of injury" when amphibian skin is wounded, and have provided other compelling evidence for a role of endogenous electric fields in wound healing in the newt[15, 16]. When wound electric fields are nullified either pharmacologically or electrically, the rate of wound re-epithelialization is significantly reduced. Jaffe and Vanable[17] have suggested that since a moist environment is required for current flow, this may account for the more rapid healing noted in wounds that are occluded with film dressings. Together, there is a significant scientific literature to support the notion that endogenous electric fields form immediately upon wounding of skin and play a role in the wound healing process.

Galvanotaxis

One mechanism by which the electric fields may participate in wound healing is by directing cell migration and, as such, enhancing wound healing. The concept of directional migration in an electric field, or galvanotaxis, is not a new one. Many cell types have been noted to exhibit this response (reviewed by Nuccitelli[18] and Robinson[14]). Of importance in skin wound healing is the recent work demonstrating that the migration of human skin-derived keratinocytes is also guided by electric fields, notably fields of the same magnitude as those found in mammalian wounds[19, 20]. Application of an electric field across a wound made in vitro to a confluent sheet of cultured keratinocytes enhances the migration of the cathodally facing cells (Figure 3). Thus, wound- generated electric fields may contribute to wound healing by guiding keratinocyte migration and enhancing re-epithelialization. Endothelial cells also respond to electric field with a directional migratory response[21], and the wound-generated electric field may, likewise, direct dermal angiogenesis required for wound repair.

The mechanism by which cells respond to an electric field with directional migration is the subject of ongoing investigations. Electric field-induced lateral electrophoresis and redistribution of proteins within the plasma membrane is one proposed mechanism. For example, the EGF receptor rapidly lateralizes on the cathodal side of keratinocytes exposed to dc electric fields[22]. Other possible targets include membrane channels and resul-

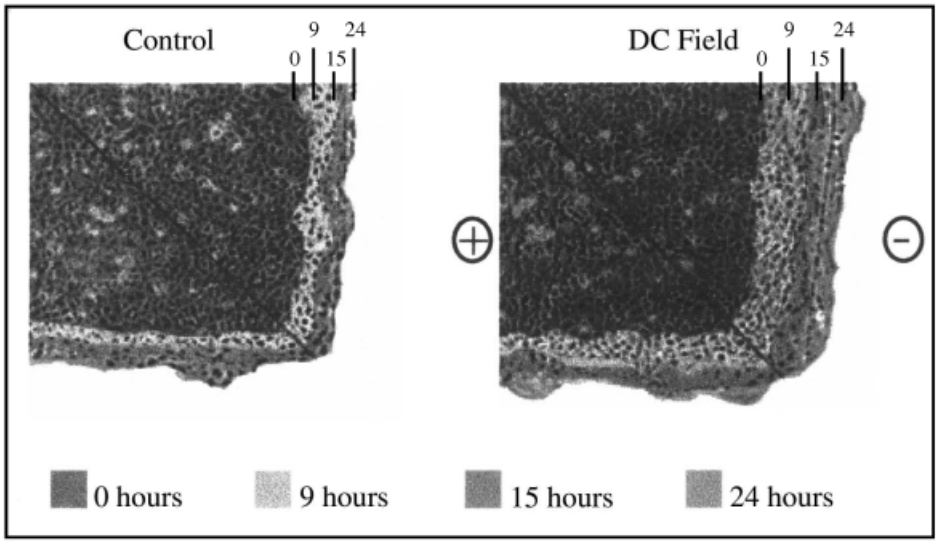

Figure 3. Electric fields enhance wound healing in vitro. Confluent cultures of neonatal human keratinocytes were "wounded" by cutting through the culture with a scalpel (cut edge is indicated by the marker for time 0). One culture dish was exposed to an applied DC electric field of 100 mV/mm (lower culture, labeled Field; + and - indicate anodal and cathodal poles of the applied field), and one culture was not exposed to an electric field (upper culture, labeled Control). Both cultures were returned to the incubator and maintained in tissue culture medium at 37° C. At 9, 15, and 24 hours after the initial wounding, the cultures were removed from the incubator and the wounded edge digitally imaged. Images were overlain with respect to the time 0 edge and pseudo-colored for ease of visualization. Increased outgrowth from the cathodally-facing edge can be seen in the Field-exposed culture.

tant changes in ion fluxes[23], changes in the organization of the actin cytoskeleton[24-29] in the distribution of adhesive structures, such as integrins[30], or local activation of protein kinases[31, 32]. Intensive investigation in this area continues.

In vitro cellular effects of ES

DC effects on cell migration, i.e. galvanotaxis, have been well documented, as noted above. Pulsed DC protocols, which limit the potential for cellular damage, have also demonstrated potentially beneficial cellular effects. An increase in protein synthesis and thymidine incorporation into DNA has been observed by Bourguignon and Bourguignon[33, 34] in cultured human fibroblasts treated with high voltage pulsed current (HVPC) in the range of 50-200V and pulse rates of 60-125 pps. Voltages intensities greater than 250V inhibited both protein and DNA synthesis. This same treatment protocol upregulates insulin receptors on fibroblast membrane[33]. The rationale for low voltage pulsed current (LVPC) protocol in clinical wound healing studies may also derive from work by Petty and colleagues[35] who have demonstrated that electric fields with periods of 20-s match endogenous cellular metabolic oscillations in NADP, and thus may contribute to a metabolic effect. Using AC (10 pps, approximately 40 mV/m) Cheng and Goldman[36] noted that fibroblasts exposed to the field demonstrated increases in ^{3}H-thymine incorporation. Of particular significance in this study, is the experimental protocol, in which fibroblasts were incorporated into a 3-dimensional collagen matrix prior to electric field exposure, thus, providing a better model of the dermal wound environment. Oscillating electric fields of very low periodicity (1pps, 2V/cm) can also effect cell function. Cho et al.[37] documented numerous morphologic changes accompanied by alterations in migratory speed and directedness of migration in macrophages exposed to these fields. Evidence cited from the above studies demonstrate that electric fields, delivered to cells in multiple varieties of waveforms, have numerous biologic cellular effects and thus may contribute to the wound healing process.

Animal studies

Animal studies using a variety of wound models and ES protocols have, with few exceptions, reported an enhancement in some aspects of wound healing (Table 1). Notable is the improvement in tensile strength observed in wounds treated with DC, usually with the negative electrode placed over or within the wound site[38-42]. Other studies demonstrate concomitant increases in the number of fibroblasts within the wound, and an increase in collagen production[42-45]. As other ES protocols have become popular, they too have been assessed in animal models. The pulsed HVPC and LVPC protocols, have also demonstrated a positive effect on wound healing, primarily increasing the rate of wound closure. Overall, the studies using continuous DC demonstrated increased wound tensile strength while those with HVPC did not. Certain cautions should be used when extrapolating animal studies to humans. For example, pig dermis is considerably thicker than human dermis and as such the difference could create a different skin resistance thus interfering with current flow. The studies are not directly comparable to one another, given the variety in animal models, wounds, ES protocols and electrodes used. In addition, most of the animal wound studies are not models for chronic non-healing wounds. These caveats aside, one can nevertheless conclude that the animal studies provide evidence to support the efficacy of ES in wound healing, although it is not quite clear which ES protocol is superior.

Antibacterial Effects of ES

When a wound is infected, its healing is delayed. There is evidence from both in vitro and in vivo studies suggesting that ES have bacteriostatic and bactericidal effects on microorganisms known to colonize dermal wounds. The growth of Escherichia coli B in culture medium is inhibited with treatment of DC 1.0 - 140 mA, but not AC protocols[46]. The effect is most notable at the cathode. Likewise, DC treatment has been noted to decrease the growth rate of Staphylococcus aureus[47] in vitro. Since the magnitude of the effect varies with the type of electrodes used, toxicity from electrolytic products cannot be ruled out in these studies. In full thickness rabbit skin wounds experimentally infected with Pseudomonas aeruginosa, cathodal DC stimulation with 1mA significantly decreased bacterial count[48], providing in vivo confirmation of the in vitro results. HPVC has also been examined for its ability to curtail bacterial growth. Growth of the common wound bacteria Staphylococcus aureus, E. coli, and Pseudomonas aeruginosa is inhibited by HPVC, with a linear relationship between inhibition and duration of exposure of HVPC and the voltage (150-300V)[49]. In an attempt to identify the mechanism by which HVPC kills bacterial in vitro, Szuminisky and colleagues[50] delivered HVPC at 500V into culture media containing 4 different species of bacteria that commonly colonize wounds, S. aureus, E. coli, Klebsiella and P. aeruginosa. Both direct and indirect (production of antimicrobial factor in the medium exposed to ES) bactericidal effects were observed, both at the positive and negative poles. Although there was no local increase in temperature during the application of the current, the investigators were unable to determine whether the inhibitory effect was due to direct action of the current on the organism, or the pH changes observed. It should be noted that voltages used in this study are higher than those used in clinical settings. Thus further investigation is needed to clarify the role of ES in infection control in wound healing.

In summary, the research literature provides evidence that ES has inhibitory effects on common pathogens that colonize dermal wounds. In vitro studies have shown that antibacterial effects are more likely to occur with non-noxious μA DC applied to wound pathogens via the cathode whereas the voltage required for antibacterial effect with HVPC would be intolerable for patients (250 to 500V). Antibacterial effects of other ES protocols are lacking. The mechanisms by which ES inhibits these organisms are unknown and remain controversial.

CLINICAL SCIENCE RESEARCH

Forty years after the first reported clinical use, ES is still not a first line clinical modality for treating skin wounds. The lack of knowledge regarding the mechanism as well as lack of carefully controlled studies seems to be major arguments to dissuade its use. In spite of the evidence showing beneficial effects of ES, lack of standardization across treatment protocols has made it

virtually impossible to compare reported studies. Nevertheless, a number of successful randomized controlled studies have been published in the last decade substantiating the use of ES for healing of chronic wounds. These studies are important in providing information to clinicians and their patients who seek adjunctive therapies for hard-to-heal wounds, as well as to third party payers who base reimbursement for services on evidence-based clinical studies. This section will address human studies designed to test the clinical efficacy of the three most common types of ES: DC, PC or AC. One recent meta-analysis of published studies concluded that ES induces substantial improvement in the healing of chronic wounds[51]. However, another critical review[52] concluded that larger, randomized control studies with sufficient power are needed before a definitive pronouncement regarding the efficacy of this modality can be made. These studies are summarized in the text below and listed in Table 2.

Direct Current Studies

The first successful report of DC application on human wounds is the very often-quoted case report by Assimacopoulos in 1968[53] (Table 2). This is a very limited report of three patients with chronic leg ulcers due to venous insufficiency, which healed after six weeks of application of 50 to 100 μA direct current, with cathodal stimulation. Other simultaneous interventions, such as systemic antibiotic treatment, preclude assessment of the contribution of ES to the healing process. Two larger patient series were reported later, wherein 83[54] and 76[55], patients with ulcers of various etiologies were treated with DC ES, and their rate of healing was found to be improved over the patient's historical healing rates. These protocols included initial application of the cathodal electrode to the wound for a 3-day duration followed by anodal electrode placement, with polarity reversed every 3 days. Although the in vitro studies noted earlier might provide some rationale for either anodal or cathodal stimulation of the wound, it appears that the choice of protocol parameters in these studies is arbitrary. Recognizing the limitations of non-controlled studies, Carley and Wainapel[56] designed a randomized clinical trial based on this DC protocol. In this study, 30 patients with chronic skin ulcers located either below the knee or in the sacral area were paired according to age, diagnosis, location and wound size. One member of the pair was randomly assigned to an experimental group which received DC therapy, 300 μA and 500 μA, in addition to standard wound care; the control member received only standard wound care. Results of this study showed a 1.5 to 2.5 times increased healing rate for the treated group as compared to the control group evident at 3, 4 and 5 weeks after onset of therapy. However, weaknesses in the design of the study, with the absence of exclusion and inclusion criteria, and lack of detail regarding the "standard of care" applied to wounds of presumably different etiology, undermine the validity of the conclusions drawn from this study.

Pulsed Current Studies

Clinical studies that use PC devices can be categorized into two groups: low voltage PC (LVPC) and high voltage PC (HVPC) (see Figure 1). Clinical studies of PC are summarized in Table 3

Low Voltage PC studies

Since 1991, 4 randomized, double blind, multi-center studies evaluating LVPC treatment for chronic wounds have been published[57-60]. These studies enrolled larger numbers of patients, ranging from 47 to 74, primarily with decubitus ulcers of stage II, III, or IV. In each protocol the control group received sham ES with an inactive device, and documented standard care. Three studies, Feedar et al[57], Mulder,[59], and Gentzkow et al[58] used similar treatment protocols of approximately 30 mA, 64-128 pps applied 30 minutes twice daily to the wounds. The fourth study by Wood et al[60] applied much lower currents (300-600 μA at 0.88 pps) three times a week for unreported treatment periods. The outcome measured in each study was the change in the percentage of the initial ulcer area, defined by the product of the width X length of the wound. All four studies demonstrate statistically significant reductions in the areas of the ES treated wounds.

Despite the rigor of the studies, these too have come under recent criticism. For example, Sheffet et al[52] have pointed out assignment bias and resultant differences between the control and treatment groups in Gentzkow's study. Margolis[61] noted that the reported 3% healing rate for the control decubitus ulcers in Wood's study was lower than expected using standard moist saline dressings. These shortcomings notwithstanding, the preponderance of the evidence does support a role for this ES protocol in enhancing chronic wound closure, at least in stage II-IV decubitus ulcers.

High Voltage PC

Fewer randomized controlled trials of HVPC have been performed, and these have evaluated limited numbers of patients, with mixed ulcer diagnoses, which weaken the study design and outcome analysis. One, by Kloth and Feeder[62], evaluated 16 patients with chronic ulcers of various etiologies treated with 45 minutes of HVPC, 100 to 175V at 105 pps, 5 days per week. The polarity of the stimulating electrodes was reversed when the rate of ulcer healing plateaued. Ulcers of both treatment and control (sham treated) groups received standard wound care. The ulcers of the treatment group healed over a mean period of 7.3 weeks at a rate of 45% per week. A concern of this study is that the patients in the control group had a mean increase in wound size on average of 11% per week, varying significantly from the reported healing rates for ulcers with standard care[63]. A subsequent study by Griffin et al[64], in a single-blind randomized controlled trial, demonstrated similar acceleration of healing when they assessed the efficacy of HVPC on 17 spinal cord-injured men with stage II, III and IV decubitus ulcers. The treatment protocol in this study was HVPC of 200V intensity at 100 pps with the cathodal electrode applied directly to the wound for 1 hour a day for 20 days. The control group was sham treated, and both groups received standard wound care in addition to the HVPC or sham HVPC. Despite this relatively short treatment protocol, the HVPC-treated patients with stage IV ulcers showed a 67% decrease in wound surface area by the 20th day of treatment compared to 15% decrease for the control group. Given the small sample size, the findings just achieved statistical significance. The third randomized controlled study of patients with chronic dermal ulcers treated with HVPC was performed by Gogia et al[65]. Twelve patients with

stage III ulcers of mixed etiologies on the leg or foot received either standard wound or standard wound care in addition to HVPC of 250V at 100 pps with the cathodal electrode placed directly over the wound daily for 20 minutes a day, 5 days a week for 4 weeks. Treatments began with the negative electrode placed over the wound for 4 days, then polarity reversed for the final 16 treatments, citing some of the earlier animal work to support the choice of these reversal parameters. Although the study reports a 37.4% of HVPC-treated lesions had healed compared to 27.2% for control lesion, these findings did not reach statistical significance given the small number of subjects.

Thus, the HVPC studies each seem to have some shortcomings in study design, which limit the interpretation of the findings. Although the currently reported work is certainly intriguing, more studies with larger sample sizes and rigorous study design are needed, to be able to reach a firm conclusion regarding the utility of HVPC in wound healing.

Alternating Current (AC) Studies

AC has been applied to chronic wounds in two types of protocols: symmetric square -wave, most commonly delivered using a portable TENS device, or asymmetric biphasic pulsed wave. As opposed to DC or PC stimulators, AC stimulation is generally delivered by electrodes adjacent to the wound rather than directly overlying it.

TENS

Initial case report[66] and uncontrolled case series[67, 68] treating patients with TENS applied to nerves in the vicinity of the wounds suggested this approach might be beneficial. The etiologies of the treated ulcers were varied, but included neurotrophic lesions, with the rationale that the neural stimulation provided by TENS would enhance healing. One interesting study by Kaada and Emru[69] used TENS therapy to treat 32 patients with longstanding lower leg ulcers secondary to leprosy. Patients received trains of 5 pulses (25 mA at 100 pps, 0.1 to 0.2 millisecond duration) for 30 minutes sessions, twice daily for 5 to 6 days per week. Twelve weeks post-treatment, 59% of the patients healed completely. All those who completed therapy healed completely with a mean healing time of 5.2 weeks. All the above TENS studies were uncontrolled studies, and all used different treatment regimens, making conclusions difficult to draw.

Thus far there has been only one randomized controlled study of the effect of TENS on wound healing. Lundeberg et al[70] studied 64 diabetic patients with stasis ulcers. The patients received either TENS therapy (treatment parameters not given) for 20-minutes, twice daily for 12 weeks or sham treatment. The polarity was changed after each session. All patients received standard wound care, which was a compression dressing. After 12 weeks, 42% of the treated group healed compared to 15% of the control, with statistical significance. This study does support a role of TENS stimulation in the treatment of ulcers in diabetic patients.

Biphasic Pulsed

Asymmetric biphasic pulsed waveforms have been used in some wound healing studies, presumably because the asymmetry of the waveform allows the polarity of one pole to predominate. One case series[71] and one non-randomized control trial[72] have suggested that this modality may be useful in enhancing healing in a wide array of chronic ulcers. However, only one randomized controlled trial has evaluated the efficacy of this modality.

Baker et al[73] evaluated the effects of two stimulation waveforms on healing rates in patients with diabetic ulcers. Patients received stimulation with either an asymmetric biphasic or symmetric biphasic square-wave pulse both at 50 pps, at unreported amplitudes. A third group received a sham ES. All patients in the study received standard wound care. In this study, treatment with asymmetric biphasic ES showed a statistically significant 60% increase in the healing rate, as compared to controls. This study suggests that the asymmetric biphasic wavelength may be more advantageous in ulcers in diabetic patients. The rationale for this is not entirely clear.

It appears that most of the studies on the efficacy of AC stimulation for wound healing evaluated patients with decubitus ulcers, so no inferences may be comfortably extended to other types of non-healing wounds. The double-blind randomized controlled study by Lundeberg et al[70] is particularly strong, and its results do support a role for AC therapy in decubitus ulcers. Its efficacy in other chronic wounds remains to be evaluated.

STRENGTH OF EVIDENCE RATING FOR ES

In 1994, the Agency for Health Care Policy and Research (AHCPR, now known as the Agency for Healthcare Research and Quality) convened a panel of experts who subsequently published a guideline for the treatment of pressure ulcers[74]. The panel recommended that clinicians "consider a course of treatment with electrotherapy for stage III and IV pressure ulcers that have proved unresponsive to conventional therapy. Electrical stimulation may also be useful for recalcitrant stage II ulcers." In the 1994 AHCPR document, the strength of evidence rating assigned to ES was "B" based on the following rating scale:

A : Results of two or more randomized controlled clinical trials (RCT) on chronic wounds in human provide support.

B : Results of two or more controlled clinical trials on chronic wounds in humans or when appropriate results of two or more controlled trials in an animal model provide indirect support.

C : This rating require one or more of the following: 1) results of one controlled trial; 2) results of at least two case series/descriptive studies on chronic wounds in humans; or 3) expert opinion.

Another comprehensive review of the modality has been recently undertaken in the UK by the National Coordinating Centre for Health Technology Assessment. Although sixteen randomized controlled trials were included in their review many were excluded because of the previously noted flaws in their design. Their conclusion, published in 2001[75], was that "there may be some benefit associated with electrotherapy in the healing of chronic wounds," but that the evidence was generally insufficient to unequivocally conclude that ES is beneficial for the treatment of chronic wounds.

Of particular interest to practitioners in the United States, however, is the Centers for Medicare and Medicaid Services (CMS, formerly known as HCFA) July 2002 decision on coverage of ES for chronic wounds[5]. The decision was based on a comprehensive review that began in 1995, with in-depth analysis of all published clinical trials, and input from the American Physical Therapy Association, an outside technology assessment firm (Emergency Care Research Institute, whose 313 page 1996 comprehensive report is available on-line[76]), the Association for the Advancement of Wound Care, reports from the Agency for Health Care Policy and Research, and the Medical and Surgical Procedures panel of the Medicare Coverage Advisory Committee (MCAC). The panel concluded that there was adequate evidence to draw the conclusion that ES is an effective adjunctive therapy for chronic non-healing wounds. Their decision was to allow coverage for ES in chronic wounds that do not respond to standard care. Interestingly, the panel specifically did not single out any one type of ES delivery system, thus allowing this to the discretion of the practitioner. This decision has the potential to radically change our approach to wound care, by providing national coverage for ES as a second-line of treatment for a large group of patients with venous stasis, diabetic, arterial, or pressure ulcers. To be able to use this new therapeutic tool to the patient's full advantage, the dermatologic community will need to develop treatment protocols that allow for continued assessment of the efficacy of this novel modality.

PRECAUTIONS

Adverse effects of ES are rarely reported, and consist of anecdotal reports of skin irritation or tingling sensation that is perceived under the electrodes in occasional cases. Skin irritation is more likely to be reported when continuous DC or monophasic PC with long pulse duration is used. Pain may be experienced in patients with severe peripheral vascular occlusive disease.

Contraindications

The following conditions are considered to be contraindications for the use of ES to for wound healing.

Presence of Cancer

It has been recommended that ES not be used in patients who have concurrent malignancies The concept expressed is that ES may cause mitogenic activity or proliferation of the malignant cells[77].

Osteomyelitis

Patients with active osteomyelitis have been precluded from the use of ES. Stimulation of tissue repair may facilitate premature closure of the wound leading to the covering of the area of osteomyelitis[77]. This may also result in abscess formation.

Implanted electrical devices

Electrical implants and cardiac pacemaker functions may be disrupted by ES. Use of ES device (TENS) by Resmussen and associates[78] to patients with different cardiac pacemakers was found to be safe.

Topical substances with metallic ions

Topical substances containing metallic ions used for wound treatment (e.g. povidone-iodine, zinc, silver sulfadiazine etc.) should be cleaned thoroughly before application of ES[79]. Heavy metal ions are known to be toxic when absorbed percutaneously. Direct current has the ability through the process of iontophoresis to transfer these heavy metal ions into the systemic circulation. Thorough cleaning is therefore mandatory before the use of ES.

Overlying Vital Organs and Nerves

ES is contraindicated in the upper chest and anterior neck. These areas of the body are very sensitive to any stimulation because of the presence of certain vital organs (carotid sinus, phrenic nerve, parasympathetic nerve and ganglia and the heart)[79].

DEVICES

At present, not a single ES device has been approved or received premarket approval (PMA) by the Food and Drug Administration (FDA) for wound healing. PMA requires extensive clinical trials to show safety and effectiveness of the device. Therefore, use of any ES device at this time is considered "Off Label", for which there is sanction as part of the practice of medicine[80]. Indeed, the CMS decision to allow use of ES for chronic wounds notes specifically that while currently no devices are approved by the FDA for delivering ES to cutaneous wounds, "lack of approval for this particular indication, does not preclude physicians and other health care providers from providing this therapy as an off-label use[5]." Noting these caveats, Table 5 lists devices that have been used off-label for ES therapy. Respective manufacturers were contacted, and those who provided data are presented in the table. Devices such as Neuromuscular Electrical Stimulator (NMES) have specific FDA applications which include: (a) increase local blood circulation, (b) reducing edema, (c) preventing retardation of muscle atrophy and (d) strengthening muscle and preventing postoperative venous thrombosis. Pain Management Devices such as TENS have specific FDA-approved applications, which include (a) relief of both acute and chronic pain, (b) increase in local and distal blood circulation and (c) relief of postoperative pain.

Safety of Devices

Extensive safety studies on ES devices for wound healing have not been performed. To date, there have been no adverse reactions or complications reported in any DC studies of wound healing. In PC studies, there have been 7 cases of uncomfortable tingling, 1 case of skin irritation and 1 case of excessive bleeding at the ulcer site reported in 2 studies[57, 59]. AC studies of wound healing have reported no complications or any adverse reactions. More rigorous investigation for possible adverse effects, as required by FDA for approval, needs to be undertaken.

SUMMARY AND IMPLICATIONS FOR CLINICAL PRACTICE

The use of ES is currently attracting interest because of its potential to improve and accelerate wound healing. In vitro and in vivo studies have shown that ES can increase both DNA and collagen synthesis, direct epithe-

lial, fibroblast, and endothelial cell migration into wound sites, inhibit the growth of some wound pathogens and increase tensile strength of the wound scar. Animal studies of ES, with rare exception, demonstrate the beneficial effect of ES on various aspects of wound healing. Clinical reports are heavily dominated by case reports and case series, which are suggestive, but not definitive studies. A number of randomized controlled trials have demonstrated efficacy of ES for healing of chronic wounds, with the strongest evidence supporting its use for pressure ulcers, but inconsistencies in the protocols used by the different investigators make it difficult to choose one ES regimen over another. The recent decision of the Centers for Medicare and Medicaid

Table 1. Effects of ES on Wound Healing in Animal Studies

Author (Reference #)	Animal	Wound	ES Type	Result
Assimacopoulos [39]	Rabbit	Incisional	DC, 50-100 μA	Increase tensile strength
Konikoff [38]	Rabbit	Full-Thickness excisional	DC, 20 μA	Increase tensile strength
Bigelow et al. [40]	Dot	Incisional	DC, 6-12 μA	Increase tensile strength
Taskan et al. [42]	Rat	Incisional	DC, 300 μA	Increase fibroblast number and wound tensile strength
Smith et al. [41]	Mice	Incisional	DC, 10-20 mA	Increase in tensile strength
Dunn et al. [45]	Guinea pig	Full-Thickness excisional collagen sponge implant	DC, 20-100 μA	Increase fibroblast ingrowth and collage alignment
Cruz et al. [46]	Pig	Burn	HVPC, 175V, 60pps	Increase wound contraction and number of fibroblasts
Castillo et al. [43]	Rat	Burn	Biphasic PC, 40 μA, 67 pps	Increase collagen density
Carey and Lepley [81]	Rabbit	Incisional	DC, 200-300 μA	At positive electrode, increase PMN and lymphocytes
Wu et al. [82]	Rabbit	Incisional	DC, 40-400 μA	No increase in tensile strength over control
Alvarez et al. [83]	Pig	Partial-Thickness excisional	DC, 50-300 μA	Improves epithelialization of superficial skin
Brown and Gogia [84]	Rabbit	Incisional	HVPC, 30-60V, 80 pps	No significant improvement in wound healing
Brown et al. [85]	Rabbit	Incisional	HVPC, 30-60V, 80 pps	Enhance wound closure. No increase in tensile strength over control.
Brown et al [86]	Rabbit	Full-Thickness incisional	HVPC, 30-60V, 80 pps	Increase rate of wound closure. No increase in tensile strength over control
Byl et al. [87]	Pigs	Incisional	LVPC, 100 μA, 60V, 1 pps	Increase subcutaneous oxygen
Reger et al.[88]	Pig	Experimental pressure ulcer	AC, 7-10mA, 40 pps DC, 600 μA	Both AC and DC showed reduced healing time . DC reduced the wound area more rapidly than AC but AC reduced wound volume more rapidly than DC
Thawer et al. [89]	Mice	Full-Thickness excisional	LVPC, 12.5V, 200pps	Increase rate of wound closure

Table 2. Direct Current Clinical Studies of Wound Healing

Author (Reference #)	Stimulus Type	Dosage Applied/Polarity	Study Type	Wound Type	Treatment Group	Number of Patients or Lesions	% Patients or Lesions Healed/Time	Other Reported Outcomes
Assimacopoulos [53]	DC	50-100 μA/cathode	Case report	Venous	DC	3	100/6weeks	Not available
Wolcott et al.[54]	DC	200-800 μA 2 hours 2 times/day for 16 weeks; switch polarity/cathode	Case series	Mixed	DC	75	40/16wk	Healing rate/wk: Paraplegic = 9.3% Peripheral arterio-sclerotic = 14.4% Venous stasis = 14.4% Others = 100%
			"Embedded" RCT	Mixed		Contralateral lesions		Healing rate/wk
					DC	8	75 /15.4wk	27.0%
					Control	8	0/15.4wk	5.0%
Gault and Gatens [55]	DC	Regimen similar to Wolcott et al., except polarity revered only once	Case series	Mixed	DC	100	48/4.7wk	Healing rate/wk: 28.4%
			"Embedded" RCT	Mixed	DC	6	50/4wk	Healing rate/wk: 30.0%
					Control	6	-33/4wk	14.7%
Carley & Wainapel [56]	DC	300-700 μA 2 hours 2 times/day. Otherwise regimen similar to Wolcott et al.	RCT	Not Specified	DC	15	Not reported	Healing rate/wk: 18%
					Control	15		9%
Katelaris et al. [90]	DC	20 μA /cathode	Comparative controlled	Venous	DC + povidone Povidone DC + saline Saline	4 11 5 4	Not reported	Healing time (M days) 85.3 49.2 45.9 46.1

RCT = Randomized Controlled Trial; DC = Direct Current; wk = week; M = Mean

Services to allow reimbursement for ES treatment of chronic ulcers means that the dermatologic practitioner will likely become more familiar with this novel treatment approach, and that wound care centers will include this option for recalcitrant ulcers. While no ES devices dedicated to wound healing are currently available, the large size of the potential market for such devices predicts that these devices will rapidly be offered. As the number of successful randomized controlled trials increases, the use of ES as an adjuvant therapy for wound healing will very likely become more widely accepted by physicians and wound care providers.

Table 3. Pulsed Current Clinical Studies of Wound Healing.

Author (Reference #)	Current Type	Dosage Applied/Polarity	Study Type	Wound Type	Treatment Group	Number of Patients or Lesions	% Patients or Lesions Healed/Time	Other Reported Outcomes
Feedar et al. [57]	LVPC	35 mA @ 128 pps (rectangular pulses of 29.2 mA and 132 µs duration) for 30-minutes sessions BID; cathode initially; 7 days/wk	Double-blind RCT	Mixed	LVPC Control (Sham)	26 24	0/4 wk 0/4 wk	Healing rate/wk: 14% 8.25%
Mulder [58]	LVPC	30, 35, or 40 mA @ 128 pps for 30-minute BID/ Cathode	Double-blind RCT	Mixed	LVPC Control (Sham)	26 24	Not reported	Healing rate/wk 36% 13%
Gentzkow et al. [59]	LVPC	Regimen similar to Feedar et al.(1991)	Double-blind RCT	Decubitus (Stage III/IV)	LVPC Control (Sham)	21 19	50/4 wk 23/4 wk	Healing rate/wk (%) 12.5 5.8
Wood et al. [60]	LVPC	300 µA followed by 600 µA @ 0.8 pps/ Cathode	Double-blind RCT	Decubitus (Stage II/III)	LVPC Control (Sham)	43 31	56.1/8 wk 4.0/8 wk	Decrease in wound size (≥80%) 73% 13%
Kloth and Feedar [62]	HVPC	100V @ 105 pps, 45-minute/day x 5 days/wk/ Anode	Single- blind RCT	Decubitus (Stage IV)	HVPC Control (Sham) Crossover	9 7 3	100/7.3 wks 0 /17 wks	Healing rate/wk 45% 11.6% 38%
Griffin et al. [64]	HVPC	200V @ 100 pps for 1-hr/day x 20 days/ Cathode	Single-blind RCT	Decubitus (Stage II-IV)	HVPC Control (Sham)	8 8	37.5/20 days 22.2/20 days	After 20 days Stage II ulcer healing: 2/2 HVPC vs 2/2 Sham Stage III ulcer healing: 1/5 HVPC vs 0/6 Sham Stage IV ulcer healing: None for HVPC or Sham
Gogia et al. [65]	HVPC	250V @ 100 pps for 20 minute/day x 20days/ Cathode	RCT	Mixed	HVPC Whirlpool	6 6	Not reported	At day 20 Rate of Healing: 34.7 % 27.2 %

LVPC = Low Voltage Pulsed Current; HVPC = High Voltage Pulsed Current; RCT = Randomized Controlled Trial

Table 4. Alternating Current Clinical Studies of Wound Healing.

Author (Reference #)	Current Type	Dosage Applied/Polarity	Study Type	Wound Type	Treatment Group	Number of Patients or Lesions	% Patients or Lesions Healed/Time	Other Reported Outcomes
Kaada [68]	TENS	Constant square-wave pulses of 15-30 mA @ 100 pps; 30-40minutes, 3 times/day	Case report	Mixed	TENS	10	70/ 22 wks	None reported
Barron et al. [69]	TENS	Modified biphasic square-wave: 600 µA, 50V @ 0.5 pps, 3 sessions, 3 times/day x 3 wks	Case series	Decubitus	TENS	6	33/ 3 wks	Significant difference between means of initial lesion size and final reported sizes
Kaada & Emru [69]	TENS	30, 35, or 40 mA @ 128 pps for 30-minute, 2 times/day/Cathode	Double-blind RCT	Lepromatous Lesions	TENS	32	59/ 12 wks	Mean healing time = 5.2 wks
Lundeberg et al. [70]	TENS	AC (square-wave pulses) of 1 ms pulse width @ 80 pps. Current sufficient to produce paresthesia- 20-minute, 2 times/day	Double-blind RCT	Diabetic ulcers	TENS Control (Sham)	32 32	42/12 wks 15/12 wks	Percentage of ulcers healed at: 2wks = 0% TENS vs 4% Sham 4wks = 12% TENS vs 7% Sham 8wks = 25%TENS vs 11%Sham 12wks = 42% TENS vs 15% Sham
Karba et al. [71]	Biphasic AC	Biphasic AC current of 15 –20 mA; 0.25 ms pulse duration @ 40 pps, 1-hr /day	Case series	Mixed	Vascular Decubitus Posttraumatic	82 14 17	95% of all wound healed (unspecified time)	Vascular lesions = 90% healed by 10 wks Decubitus lesions = 100% healed by 5.5 wks
Stefanovska et al. [72]	Biphasic AC	Biphasic AC current of 15-25 mA @ 40 pps; 2 hr /day	RCT	Decubitus	AC DC Control	82 18 50	Not reported	Normalized healing rate/day 5.43 AC, 3.11 DC 2.21 Contr.
Baker et al. [73]	Biphasic AC	A: Asymmetric biphasic current: below motor response, 50 pps, 100-µs pulse duration. B: Symmetric biphasic current: below motor response, 50 pps, 300-µsec pulse duration. C: Micro current: 1mA, 1 pulse, 10-µsec pulse duration	RCT	Diabetic ulcers	A B C Control	29 24 20 19	Not reported	Healing rate/wk A: 27% B: 16% C: 17% Control: 17%

AC = Alternating Current; RCT = Randomized Controlled Trial; TENS = Transcutaneous Electrical Nerve Stimulation

Table 5. Device Specifications of Electrical Stimulators[1]

Manufacturer	Model	Type of Unit	Waveforms	Amperage	Voltage, Volts	Delivery Mode	Frequency Range, Hz	Intended Application
Avra Tronics[91]	Galvanator 770	PC	Monophasic	N/A	0- 500	Pulsed	4-80	Neuromuscular stimulation
Chattanooga[92]	Intelect Legend	HVPC, NMES	Monophasic	0-2500 mA peak	0-500	Pulsed, interrupted	1-120	Neuromuscular stimulation
Dynawave[93]	Dynawave Model 12	Microcurrent NMES	Monophasic	Microamp	0-500	Pulsed, interrupted	1-105	Neuromuscular stimulation
Electro-Medical, Inc[94]	Electro-Acuscope 85	TENS	Biphasic	25-600 microamp	N/A	Pulsed	0.5-320	Pain management
Electro Therapeutic Devices [95]	Accu-O-Matic	TENS, microcurrent	Monophasic Biphasic	20-600 microamp	55 peak	Pulsed	0.8-320	Pain management
Empi [96]	Eclipse+	TENS	Biphasic	0-60 mA	N/A	Pulsed	2-125	Pain management
Rehabilicare[97]	GV II	PC	Monophasic	0-700 mA	0-350	Pulsed, interrupted	1-100	Neuromuscular stimulation
Neuro Care Inc[98]	NC 1000	NMES	Biphasic	0.1-2.0mA	20-440	Pulsed	47	Neuromuscular stimulation, Soft tissue injuries, Decubitus ulcers stage IV, Diabetic Neuropathy
Staodyn [99]	Dermapulse	PC	Monophasic	0-42 mA	N/A	Pulsed	64, 128	Wound management
Universal Technology Systems, Inc.[100]	PGS-3000	PC, NMES	Monophasic	N/A	0-330	Pulsed	1-100	Neuromuscular stimulation

[1] Adapted from reference 76.Health Technology Assessment Information Service. Electrical Stimulation for the Treatment of Chronic Wounds.ECRI: Emergency Care Research Institute,Plymouth Meeting, PA,1-313, 1996 http://www.cms.gov/coverage/download/8b3-ii4.pdf
PC: Pulsed Current, HVPC: High Voltage Pulsed Current, NMES: neuromuscular electrical stimulator, TENS: Transcutaneous electrical nerve stimulator.

Acknowledgements

The authors acknowledge with gratitude Dr. Luther Kloth who gave us the benefit of his thoughts and generously contributed information and suggestions for the writing of this review, and Dr. Richard Nuccitelli who introduced the authors to this area of research and has been an active research partner in the galvanotaxis studies. Some of the work reported in this review was supported in part by NIH grant AR44518. RRI has been a previous recipient of a research support from the Dermatology Foundation.

References

1. Robertson WGA. Digby's receipts. Ann Med History 1925;7:216-219.
2. Kanof NM. Gold leaf in the treatment of cutaneous ulcers. J Invest Dermatol 1964;43:441-442.
3. Wolf M, Wheeler PC, Wolcott LE. Gold-leaf treatment of ischemic skin ulcers. JAMA 1966;196:693-696.
4. Flexner A. Medical education in the United States and Canada: a report to the Carnegie Foundation for the Advancement of Teaching.Carnegie Foundation for the Advancement of Teaching,New York, NY,346, 1910.
5. Centers for Medicare and Medicaid Services. Electrostimulation for wounds: decision memorandum (#CAG-00068N).Centers for Medicare and Medicaid Services,2002 http://cms.hhs.gov/coverage/8b3-ii3.asp#P256-48704.
6. Newton RA, Karselis TC. Skin pH following high voltage pulsed galvanic stimulation. Phys Ther 1983;63:1593-6.
7. Matteucci C. On the influence of electricity on animal purrefaction. Edinburgh: William Blackwood; London: T. Cadell; 1830:230-31.
8. Dubois-Reymond E. Vorlaufiger abrids einer untersuchung uber den sogenanten froschstrom und die elecomotorischen fische. Ann Phys U Chem 1843;58:1.
9. Ilingworth CM, Barker AT. Measurement of electrical currents emerging during the regeneration of amputated fingertips in children. Clin Phys Physiol Meas 1980;1:87-89.
10. Barker AT, Jaffe LF, Vanable JW, Jr. The glabrous epidermis of cavies contains a powerful battery. Am J Physiol 1982;242:R358-66.
11. McGinnis ME, Vanable JW, Jr. Voltage gradients in newt limb stumps. Prog Clin Biol Res 1986;210:231-8.
12. Rajnicek AM, Stump RF, Robinson KR. An endogenous sodium current may mediate wound healing in Xenopus neurulae. Dev Biol 1988;128:290-9.
13. Stump RF, Robinson KR. Xenopus neural crest cell migration in an applied electrical field. J Cell Biol 1983;97:1226-33.
14. Robinson KR. The responses of cells to electrical fields: a review. J Cell Biol 1985;101:2023-7.
15. Sta Iglesia DD, Cragoe EJ, Jr., Vanable JW, Jr. Electric field strength and epithelization in the newt (Notophthalmus viridescens). J Exp Zool 1996;274:56-62.
16. Chiang MC, Cragoe EJ, Jr., Vanable JW, Jr. Intrinsic electric fields promote epithelization of wounds in the newt, Notophthalmus viridescens. Dev Biol 1991;146:377-85.
17. Jaffe LF, Vanable JW, Jr. Electric fields and wound healing. Clin Dermatol 1984;2:34-44.
18. Nuccitelli R. Physiological electric fields can influence cell motility growth, and polarity. Adv Cell Biol 1988;2:213-33.
19. Nishimura KY, Isseroff RR, Nuccitelli R. Human keratinocytes migrate to the negative pole in direct current electric fields comparable to those measured in mammalian wounds. J Cell Sci 1996;109:199-207.
20. Sheridan DM, Isseroff RR, Nuccitelli R. Imposition of a physiologic DC electric field alters the migratory response of human keratinocytes on extracellular matrix molecules. J Invest Dermatol 1996;106:642-6.
21. Li X, Kolega J. Effects of direct current electric fields on cell migration and actin filament distribution in bovine vascular endothelial cells. J Vasc Res 2002;39:391-404.

22. Fang KS, Ionides E, Oster G, Nuccitelli R, Isseroff RR. Epidermal growth factor receptor relocalization and kinase activity are necessary for directional migration of keratinocytes in DC electric fields. J Cell Sci 1999;112:1967-78.

23. Bedlack RS, Jr., Wei M, Loew LM. Localized membrane depolarizations and localized calcium influx during electric field-guided neurite growth. Neuron 1992;9:393-403.

24. Soong HK, Parkinson WC, Sulik GL, Bafna S. Effects of electric fields on cytoskeleton of corneal stromal fibroblasts. Curr Eye Res 1990;9:893-901.

25. Soong HK, Parkinson WC, Bafna S, Sulik GL, Huang SC. Movements of cultured corneal epithelial cells and stromal fibroblasts in electric fields. Invest Ophthalmol Vis Sci 1990;31:2278-82.

26. Onuma EK, Hui SW. Electric field-directed cell shape changes, displacement, and cytoskeletal reorganization are calcium dependent. J Cell Biol 1988;106:2067-75.

27. Onuma EK, Hui SW. A calcium requirement for electric field-induced cell shape changes and preferential orientation. Cell Calcium 1985;6:281-92.

28. Onuma EK, Hui SW. The effects of calcium on electric field-induced cell shape changes and preferential orientation. Prog Clin Biol Res 1986;210:319-27.

29. Luther PW, Peng HB, Lin JJ. Changes in cell shape and actin distribution induced by constant electric fields. Nature 1983;303:61-4.

30. Brown MJ, Loew LM. Graded fibronectin receptor aggregation in migrating cells. Cell Motil Cytoskeleton 1996;34:185-93.

31. Baker LP, Peng HB. Tyrosine phosphorylation and acetylcholine receptor cluster formation in cultured Xenopus muscle cells. J Cell Biol 1993;120:185-95.

32. Peng HB, Baker LP, Dai Z. A role of tyrosine phosphorylation in the formation of acetylcholine receptor clusters induced by electric fields in cultured Xenopus muscle cells. J Cell Biol 1993;120:197-204.

33. Bourguignon GJ, Jy W, Bourguignon LY. Electric stimulation of human fibroblasts causes an increase in Ca2+ influx and the exposure of additional insulin receptors. J Cell Physiol 1989;140:379-85.

34. Bourguignon GJ, Bourguignon LY. Electric stimulation of protein and DNA synthesis in human fibroblasts. Faseb J 1987;1:398-402.

35. Rosenspire AJ, Kindzelskii AL, Petty HR. Interferon-gamma and sinusoidal electric fields signal by modulating NAD(P)H oscillations in polarized neutrophils. Biophys J 2000;79:3001-8.

36. Cheng K, Goldman RJ. Electric fields and proliferation in a dermal wound model: cell cycle kinetics. Bioelectromagnetics 1998;19:68-74.

37. Cho MR, Thatte HS, Lee RC, Golan DE. Integrin-dependent human macrophage migration induced by oscillatory electrical stimulation. Ann Biomed Eng 2000;28:234-43.

38. Konikoff JJ. Electrical promotion of soft tissue repairs. Ann Biomed Eng 1976;4:1-5.

39. Assimacopoulos D. Wound healing promotion by the use of negative electric current. Am Surg 1968;34:423-31.

40. Bigelow J. Effect of electrical stimulation on canine skin and percutaneous direct electric current on healing wounds. In: Brighton C, Black, J., Pollack, S.R., ed. Skin Interface Healing and Electrical Properties of of Bone and Cartilage. New York, NY: Grune and Stratton; 1979.

41. Smith J, Romansky N, Vomero J, Davis RH. The effect of electrical stimulation on wound healing in diabetic mice. J Am Podiatry Assoc 1984;74:71-5.

42. Taskan I, Ozyazgan I, Tercan M, Kardas HY, Balkanli S, Saraymen R, Zorlu U, Ozugul Y. A comparative study of the effect of ultrasound and electrostimulation on wound healing in rats. Plast Reconstr Surg 1997;100:966-72.

43. Castillo E, Sumano H, Fortoul TI, Zepeda A. The influence of pulsed electrical stimulation on the wound healing of burned rat skin. Arch Med Res 1995;26:185-9.

44. Cruz NI, Bayron FE, Suarez AJ. Accelerated healing of full-thickness burns by the use of high-voltage pulsed galvanic stimulation in the pig. Ann Plast Surg 1989;23:49-55.

45. Dunn MG, Doillon CJ, Berg RA, Olson RM, Silver FH. Wound healing using a collagen matrix: effect of DC electrical stimulation. J Biomed Mater Res 1988;22:191-206.

46. Rowley BA. Electrical current effects on E. coli growth rates. Proc Soc Exp Biol Med 1972;139:929-34.

47. Barranco SD, Spadaro JA, Berger TJ, Becker RO. In vitro effect of weak direct current on Staphylococcus aureus. Clin Orthop 1974;100:250-5.

48. Rowley BA, McKenna JM, Chase GR, Wolcott LE. The influence of electrical current on an infecting microorganism in wounds. Ann N Y Acad Sci 1974;238:543-51.

49. Kincaid CB, Lavoie KH. Inhibition of bacterial growth in vitro following stimulation with high voltage, monophasic, pulsed current. Phys Ther 1989;69:651-5.

50. Szuminsky NJ, Albers AC, Unger P, Eddy JG. Effect of narrow, pulsed high voltages on bacterial viability. Phys Ther 1994;74:660-7.

51. Gardner SE, Frantz RA, Schmidt FL. Effect of electrical stimulation on chronic wound healing: a meta-analysis. Wound Repair Regen 1999;7:495-503.

52. Sheffet A, Cytryn AS, Louria DB. Applying electric and electromagnetic energy as adjuvant treatment for pressure ulcers: a critical review. Ostomy Wound Manage 2000;46:28-33, 36-40, 42-4.

53. Assimacopoulos D. Low intensity negative electric current in the treatment of ulcers of the leg due to chronic venous insufficiency. Preliminary report of three cases. Am J Surg 1968;115:683-7.

54. Wolcott LE, Wheeler PC, Hardwicke HM, Rowley BA. Accelerated healing of skin ulcer by electrotherapy: preliminary clinical results. South Med J 1969;62:795-801.

55. Gault WR, Gatens PF, Jr. Use of low intensity direct current in management of ischemic skin ulcers. Phys Ther 1976;56:265-9.

56. Carley PJ, Wainapel SF. Electrotherapy for acceleration of wound healing: low intensity direct current. Arch Phys Med Rehabil 1985;66:443-6.

57. Feedar JA, Kloth LC, Gentzkow GD. Chronic dermal ulcer healing enhanced with monophasic pulsed electrical stimulation. Phys Ther 1991;71:639-49.

58. Gentzkow GD, Pollack SV, Kloth LC, Stubbs HA. Improved healing of pressure ulcers using Dermapulse, a new electrical stimualtion device. Wounds 1991;3:158-170.

59. Mulder GD. Treatment of open-skin wounds with electric stimulation. Arch Phys Med Rehabil 1991;72:375-7.

60. Wood JM, Evans PE, 3rd, Schallreuter KU, Jacobson WE, Sufit R, Newman J, White C, Jacobson M. A multicenter study on the use of pulsed low-intensity direct current for healing chronic stage II and stage III decubitus ulcers. Arch Dermatol 1993;129:999-1009.

61. Margolis DJ. Utility of direct current in decubitus ulcers. Arch Dermatol 1994;130:660-1.

62. Kloth LC, Feedar JA. Acceleration of wound healing with high voltage, monophasic, pulsed current. Phys Ther 1988;68:503-8.

63. Alm A, Hornmark AM, Fall PA, Linder L, Bergstrand B, Ehrnebo M, Madsen SM, Setterberg G. Care of pressure sores: a controlled study of the use of a hydrocolloid dressing compared with wet saline gauze compresses. Acta Derm Venereol Suppl 1989;149:1-10.

64. Griffin JW, Tooms RE, Mendius RA, Clifft JK, Vander Zwaag R, el-Zeky F. Efficacy of high voltage pulsed current for healing of pressure ulcers in patients with spinal cord injury. Phys Ther 1991;71:433-42; discussion 442-4.

65. Gogia PP, Marquez RR, Minerbo GM. Effects of high voltage galvanic stimulation on wound healing. Ostomy Wound Manage 1992;38:29-35.

66. Westerhof W, Bos JD. Trigeminal trophic syndrome: a successful treatment with transcutaneous electrical stimulation. Br J Dermatol 1983;108:601-4.

67. Barron JJ, Jacobson WE, Tidd G. Treatment of decubitus ulcers. A new approach. Minn Med 1985;68:103-6.

68. Kaada B. Promoted healing of chronic ulceration by transcutaneous nerve stimulation (TNS). Vasa 1983;12:262-9.

69. Kaada B, Emru M. Promoted healing of leprous ulcers by transcutaneous nerve stimulation. Acupunct Electrother Res 1988;13:165-76.

70. Lundeberg TC, Eriksson SV, Malm M. Electrical nerve stimulation improves healing of diabetic ulcers. Ann Plast Surg 1992;29:328-31.

71. Karba R, Vodovnik, L. Promoted healing of chronic wounds due to electrical stimulation. Wounds 1991;3:16-23.

72. Stefanovska A, Vodovnik L, Benko H, Turk R. Treatment of chronic wounds by means of electric and electromagnetic fields. Part 2. Value of FES parameters for pressure sore treatment. Med Biol Eng Comput 1993;31:213-20.

73. Baker LL, Chambers R, DeMuth SK, Villar F. Effects of electrical stimulation on wound healing in patients with diabetic ulcers. Diabetes Care 1997;20:405-12.

74. Agency for Health Care Policy and Research. Treatment of Pressure Ulcers.U.S. Department of Health and Human Services, Public Health Service,Rockville, MD,AHPCPR Publication no. 95-0652, p 1-154, 1994 http://hstat.nlm.nih.gov/hq/Hquest/db/46/screen/DocTitle/odas/1/s/63378.

75. Cullen N, Nelson EA, Flemming K, Sheldon T. Systematic reviews of wound care manangement: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy. Health Technology Assessment 2001;5:145-221.

76. Health Technology Assessment Information Service. Electrical Stimulation for the Treatment of Chronic Wounds.ECRI: Emergency Care Research Institute, Plymouth Meeting, PA,1-313, 1996 http://www.cms.gov/coverage/download/8b3-ii4.pdf.

77. Kloth L, McCulloch JM, Feedar JA. Wound healing: alternatives in managment. Contemporary perspsectives in rehabilitation. 5 vol. Philadelphia, PA: F. A. Davis; 1990.

78. Rasmussen MJ, Hayes DL, Vlietstra RE, Thorsteinsson G. Can transcutaneous electrical nervestimulation be safely used in patients with permanent cardiac pacemakers? Mayo Clin Proc1988;63:443-5.

79. Sussman C. B, N.N. Electrical stimulation for wound healing. In: Sussman CB, ed. Wound care: Acollaborative practice manual for physical therapists and nurses. Gaithersburg, MD: Aspen Publishers, Inc.; 1998:357-388.

80. Federal Food, Drug, and Cosmetic Act. Federal Register. 21CFR 1998: http://www.fda.gov/opacom/laws/fdcact/fdcactg.htm.

81. Carey LC, Lepley D. Effect of continuous direct electric current on healing wounds. Surg Forum1962;13:13-35.

82. Wu KT, Go N, Dennis C, Enquist I, Sawyer PN. Effects of electric currents and interfacial potentials onwound healing. J Surg Res 1967;7:122-8.

83. Alvarez OM, Mertz PM, Smerbeck RV, Eaglstein WH. The healing of superficial skin wounds isstimulated by external electrical current. J Invest Dermatol 1983;81:144-8.

84. Brown M, Gogia PP. Effects of high voltage stimulation on cutaneous wound healing in rabbits. PhysTher 1987;67:662-7.

85. Brown M, McDonnell MK, Menton DN. Electrical stimulation effects on cutaneous wound healing in rabbits. A follow-up study. Phys Ther 1988;68:955-60.

86. Brown M, McDonnell MK, Menton DN. Polarity effects on wound healing using electric stimulation in rabbits. Arch Phys Med Rehabil 1989;70:624-7.

87. Byl NN, McKenzie AL, West JM, Whitney JD, Hunt TK, Hopf HW, Scheuenstuhl H. Pulsed microamperage stimulation: a controlled study of healing of surgically induced wounds in Yucatan pigs. Phys Ther 1994;74:201-13; discussion 213-8.

88. Reger SI, Hyodo A, Negami S, Kambic HE, Sahgal V. Experimental wound healing with electrical stimulation. Artif Organs 1999;23:460-2.

89. Thawer HA, Houghton PE, Kloth LC, Butryn A. Effects of electrical stimulation on wound closure in mice with experimental diabetes mellitus. Wounds-a Compendium of Clinical Research and Practice 2000;12:159-162,164-169.

90. Katelaris PM, Fletcher JP, Little JM, McEntyre RJ, Jeffcoate KW. Electrical stimulation in the treatment of chronic venous ulceration. Aust N Z J Surg 1987;57:605-7.

91. AVRA Tronics. Model 770 GALVANATOR: a physical therapy stimulator instrument for pulsed galvanic stimulation of muscles and localized tissues (promotional material). AVRA Tronics, Greenvale, NY.

92. Chattenooga Group Inc. Intelect Legend Series User Manual. Chattenooga Group, Inc., Hixson, TN,1-42, 2000 http://www.chattgroup.com/.

93. DynaWave Corporation. The DynaWave Model 12 high voltage electrical stimulator therapy device: (promotional material). DynaWave Corporation, Geneva, IL, 2002 http://my.inil.com/~dynawave/dw12.htm.

94. Biomedical Design Instruments Inc. ELECTRO-ACUSCOPE 85P- Biomedical Design Instruments, Inc. (promotional material). Biomedical Design Instruments, Inc., Burbank, CA,2002 http://www.designmed.com/ 85p.htm.

95. Electro-Therapeutic Devices Inc. The Healing Touch, Accum-O-Matic, SP series; An effective, non-invasive micro-current stimulator (promotional material). Electro-Therapeutic Devices Inc., Markham, Ontario, Canada,2000 http://www.etd-acupuncture.com/ accu_o_matic.html.

96. EMPI Inc. Eclipse+.Product overview (promotional material). EMPI Inc., St. Paul, MN, 2000 http://www.empi.com/b/b2_1.htm.

97. Rehabilicare Inc. GV II product data sheet. Rehabilicare Inc., St. Paul, MN,1999 http://www.rehabilicare.com/all_products.html#gvii.

98. Neuro Care Inc. Neuro Care, Inc. Product Catalog. Neuro Care Inc, Salem, OR,1996 http://www.neurocare.com/products.html.

99. Statodyne Inc. Dermapulse for accelerated healing (promotional material). Statodyne Inc., Longmont, CO,1-4, 1994 http://informagen.com/Resource_Informagen/Full/9/1939.php.

100. Universal Technology Systems Inc. Therapy through new technology: introducing the PGS -3000 Portable Pulsed Galvanic Stimulator (promotional material). Universal Technology Systems Inc., Jacksonville, FL,1-2, 1994 http://www.kinexmedical.com/pulsed.html.