First National Workshop on Treatment Modalities for Healing Chronic Wounds

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This workshop – held at the Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa on 21 February 2001 – brought together, for the first time in Israel, more than 500 physicians, nurses, scientists and representatives of the biotechnological industry to discuss the recent advances in chronic wound healing. The workshop served to both highlight the multidisciplinary character of wound healing and promote its importance in medicine. The objectives of this workshop were not only to share the latest developments in the field of wound healing but also to provide useful information for clinical practice. The members of the scientific committee comprised Dr. Y. Har-Shai (chairman), Prof. H. Bitterman, Prof. A. Eldad and Dr. A. Orenstein. The companies that supported this workshop were Convatec–Philtel, Chemitec, Polyheal, Janssen-Cilag, Johnson & Johnson Medical Israel, Coloplast, Dexon, Genmedix, and ProMedico.

The workshop began with a presentation by Dr. R. Almog (Carmel Medical Center, Haifa) on the epidemiology of chronic wounds. Chronic wounds are a heterogeneous group of lesions with various etiologies. Pressure sores and leg ulcers are the most common types of chronic wounds, constituting approximately 70–80% of all such wounds in western countries. Point prevalence of leg ulcers in the general population has been found to be between 1.1 and 6.3 per 1,000 in different studies, and lifetime prevalence at ages 65+ reaches 3.6%. Approximately 80% of all cases occur at age 65 and over, and the age-standardized ratio between males and females is 1:1.4. The ulcers are recurrent in 60–70% of the cases and in 40–50% they last more than one year. Venous insufficiency is the most common cause of leg ulcers. Venous insufficiency, arterial insufficiency and diabetes combined are responsible for 80–90% of leg ulcers. Venous ulcers appear at a younger age, have a higher rate of recurrence, are larger, and 95% of them involve the gaiter area. The annual incidence of leg ulcers in diabetic patients is 1–3%. Fifty percent of lower extremity amputations in the United States are performed in diabetic patients and 85% of them are preceded by diabetic leg ulcer. The fatality rate among diabetic patients with leg ulcers is twice that among other diabetic patients. A list of preventive measures for diabetic patients was also presented.

Dr. A. Baruchin (Barzilai Medical Center, Ashkelon) presented an overview of the history of wound healing, which included the treatment of wounds in wars and warfare and the development of surgery. While the methods used to treat wounds and injuries seem at first glance to be numerous and varied, they are all simple variations of three fundamental measures: faith healing, hygienic therapy, and drug cures. Faith healing attempts to remove morbid states by influencing the mind. Hygienic therapy is founded on the recognition that the body tends to cure itself and that people do recover from injury. Its measures of treatment are thus designed to supply the conditions for recovery, to assist the body to cure itself, and to minimize the effects of the trauma. Such treatment includes rest, immobilization, bathing, fresh air, sunlight and diet; but it also includes hyperalimentation, fluid resuscitation, and anti-toxins. The third means of treatment, the utilization of drugs, is a relic of poison lore. As medicaments, drugs may be used for different purposes: as an antidote or to treat a specific injury. In various stages of civilization at various times, each of the three methods of treating injuries has had periods of ascendancy. With the accumulation of scientific knowledge in the last part of the nineteenth century, and still today, hygienic therapy has again become predominant, while drug treatment has been relegated to a subordinate position.

Dr. M. Kulikovsky (Linn Medical Center, Haifa) discussed the advantages of occlusive or moisture-retentive dressings. Moisture optimizes the environment for wound healing, enabling improved collagen synthesis by fibroblasts, improved cell migration and angiogenesis, better granulation tissue formation, and painless debridement, resulting in lower rates of bacterial infection and pain and improved cosmetic results. In recent years, manufacturers have begun to develop a new generation of dressings that are often referred to as "occlusive." In fact, some are totally occlusive, while others are actually semi-permeable (to oxygen, water vapor, and CO_2). The latter type of dressing, referred to as "moisture-

retentive," meets the criteria of the ideal dressing, i.e., it removes excess exudate but maintains a humid wound bed, allows autolytic debridement and gaseous exchange, keeps growth factors in the wound, provides thermal isolation, protects against secondary infection, and permits "atraumatic" dressing changes. Thus, the beneficial effect of the "moisture-retentive" dressings may be due in part to the constant contact between the wound and the various mitogenic factors, including platelet-derived growth factor (PDGF) and PDGF-like peptides. While medical professionals know that moisture sustains life, they are often reluctant to apply this principle to the healing of wounds due to fear of infection and maceration; yet retrospective studies demonstrate that hydrocolloid dressings are associated with the lowest clinical infection rate (1.3%) compared to that of foam (2.4%) and gauze (7.1%) dressings. Among the explanations for this low infection rate are the material's relative impermeability to exogenous bacteria, the ability of viable neutrophils in the wound fluid to destroy bacteria and of natural substances in the accumulated fluid to inhibit bacterial growth, and the reduction in necrotic tissue in the occluded wound.

Dr. Y. Ramon (Rambam-Elisha Medical Centers, Haifa) presented the indications for hyperbaric oxygen therapy (HBOT) for non-healing wounds. The purpose of HBOT, which administers oxygen via the respiratory tract at a pressure higher than atmospheric, is to normalize or obtain high tissue oxygen pressure. The HBOT induced increase in dissolved oxygen content in blood plasma (from 0.3 to 4.4 vol% at 2.0 ATA) correlates with an increase in tissue O_2 pressure (from 45–90 to 800–1,100 mmHg). This elevation in oxygen tension induces significant positive changes in the wound repair process by directly enhancing fibroblast replication, collagen synthesis, cross-linking, and rapid capillary growth. At the cellular level, HBOT increases leukocyte bactericidal activity and has a direct effect on anaerobic organisms. It also stimulates up-regulation of PDGF receptor sites in the wound. Controlled clinical experience has demonstrated that HBOT can be an effective adjunctive therapy for carefully selected chronic problem wounds such as diabetic feet, compromised amputation sites, non-healing traumatic wounds, post-irradiation wounds, and vascular insufficiency ulcers. Measuring transcutaneous oxygen pressure ($TcPO_2$) may help identify appropriate candidates for therapy and determine when host competency has been achieved. Dr. Ramon concluded that patients with baseline dermal hypoxia, determined by transcutaneous oxymetry mapping, and the physiologic capacity to respond to a centrally delivered oxygen challenge may benefit from HBOT administered in addition to appropriate wound care. Once dermal hypoxia has been resolved, it is likely that the maximal benefit from HBOT has been achieved.

Dr. N. Kalderon (Bnai-Zion Medical Center, Haifa) reported his experience of more than 3 years using topical ozone and oxygen treatment for long-enduring leg ulcers. Dr. Kalderon's study included 103 patients whose leg ulcers, lasting a mean of 8.5 months, were due to diabetes mellitus, venous or arterial insufficiency, or a combination thereof. Twenty-one of these patients had been candidates for limb amputation at a different institution. Local treatment consisted of conventional topical wound care with adjuvant treatment of ozone and oxygen delivered topically onto the wounds three times a week, employing a newly designed microclimate chamber. Healing was assessed by serial digital photography, computerized plannimetry, and quantitative bacterial counts of the affected wounds. No side effects were observed. The mean number of treatments was 28.5 per patient. In 78/103 patients (including 18 of those who were previously candidates for amputation) spontaneous healing was noted or skin grafting was applied to the well-granulated wounds. Heavy bacterial colonization was eradicated within 24–48 hours. Although in 25 of the 103 patients no amelioration was observed due to delayed disloughing of the eschar, the bacteriostatic effects of ozone on the wound's flora was significant. In addition, 5/19 patients underwent below the knee amputation. In view of the beneficial effects of topical ozone treatment, it was recommended to further extend the study to a larger group of patients and to compare the results of this study with the ozone's effects on a controlled group of patients.

Dr. A. Orenstein (Sheba Medical Center, Tel-Hashomer) described the application of macrophages for the treatment of chronic wounds. Macrophages are versatile cells found in every tissue in the body, which perform a number of diverse cellular functions enabling them to kill invading microorganisms as well as to produce growth factors involved in wound healing. The common precursor to these wound-healing macrophages are monocytes, whose differentiation into a macrophage of specific phenotype and function is determined by conditions in the local microenvironment. Its phagocytic abilities, antigen-presenting capacity and diverse secretory potential place the macrophage in the center of the wound-healing process. This biologically complex sequence of events involves cellular and molecular processes such as inflammation, cell migration, angiogenesis, fibroblast proliferation, collagen synthesis and deposition, and re-epithelization. The macrophage has a key function in almost every stage of the process, serving as the coordinator of the process by producing cytokines and growth factors such as IL-1, IL-6, PDGF BB, TGF-α, TFF-γ1, VEGF, FGF, IGF-1, MDGF and TNF. Previous studies showed that wound repair was enhanced in old mice by local injection of macrophages derived from young mice. Once a method was developed for preparation of human activated macrophages from a blood unit in a closed sterile system, these cells were successfully used for the treatment of human decubital ulcers in both elderly and paraplegic patients.

Prof. A. Eldad (Hadassah Medical Center, Jerusalem) addressed the current state of artificial skin and skin substi-

tutes as a treatment for chronic skin ulcers. An ideal skin substitute is permanent, stable, off the shelf, and inexpensive. Unfortunately, the wound conditions in chronic skin ulcers do not allow a favorable response to the currently available, artificial, biological or synthetic skin substitutes, as these require a viable and clean wound bed with reasonable perfusion. Skin homografts serve as the gold standard for skin substitutes, available as fresh, cryopreserved, lyophilized or irradiated grafts. Homografts are the only skin substitutes known to "clean" infected wounds, i.e., they reduce bacterial counts in wound biopsies. However, while they are being "taken" by the wound they actually delay wound healing, as all homografts are eventually rejected. In addition, they carry the risk of infectious disease transmission, and fresh or frozen homografts are not always available. Xenografts, mainly pig skin, are inexpensive and available but are not vascularized and serve mainly as biological dressings that need to be replaced every 3–4 days as they tend to get infected. Autologous keratinocytes can be produced in a tissue culture laboratory in the hospital or bought from a commercial company. These are live growth factors producing epidermal grafts that can be tailored to match any size needed, but they are very expensive and do not resist wound contamination. If accepted, they are not durable and need prolonged protection. Other available biological, synthetic or semi-synthetic skin substitutes such as Alloderm, TransCyte, GammaGraft, and Integra, are quite costly and do not usually tolerate wound contamination or compromised blood supply to the wound. Artificial skin substitutes may be the preferred wound treatment of the future, however their current status does not make them a reliable modality for the treatment of skin ulcers.

Dr. L. Gilead (Hadassah Medical Center, Jerusalem) presented the use of medical maggots for microsurgical biological debridement of chronic ulcers. Dr. Gilead briefly reviewed the history of this treatment, from the eighteenth century to the present. In Israel the use of maggots for treatment of chronic wounds was initiated in 1996. Maggots, the larvae of the green bottle fly *Lucilia sericata*, are cultured in the laboratory under strict sterile conditions. This type of maggot was selected mainly because of its ability to affect necrotic tissue in the wound without damaging the living surrounding tissue. The maggots produce an abundance of proteolytic enzymes and antibacterial substances in addition to lanolin and other granulation tissue growth-enhancing materials. Their minute initial size (2–3 mm) and mobility enable them to penetrate all necrotic areas of the wound, where their products and movement induce degradation and clearance of the necrotic debris. To date, 203 wounds – mostly leg ulcers (176) of various etiologies and pressure sores in 123 patients – have been treated with maggots. Within a relatively short treatment period, as compared to any other modality, this treatment achieved a significant debridement and sterilization of the ulcer bed, enabling further treatment toward complete wound healing. Complete debridement was achieved in 78% of the wounds, significant debridement in 17.8% of the wounds, partial debridement in 2.6%, and the treatment failed in only 1.6% of the wounds. The side effects were pain in 20–25% of the patients, which was most often controlled with analgesics, and a few cases of psychological problems of a very mild nature. The maggots have proven to be an invaluable tool in the treatment of hard-to-heal chronic wounds, as they are easy to use, relatively cheap and enormously effective.

Dr. A. Shoufani (HaEmek Medical Center, Afula) introduced the vacuum-assisted closure (VAC) technique for wound control and treatment. This system is based on the application of controlled, sub-atmospheric pressure to the wound by means of a special vacuum machine. The application of equal pressure to the wound is ensured by the use of polyurethane ether foam of 400–600 m pore size. Thus, the technique converts the wound from an open to a controlled closed wound. All necrotic tissue must be debrided. The wound is dressed with antibiotic-impregnated tulle (Sufra-tulle, Vaseline gauze). The sterile foam is trimmed to match the appropriate size and geometry of the wound. A non-collapsible evacuation tube is then attached to the foam and the surface of the foam is covered with an adhesive drape to create an airtight seal. The tube is connected to a pump machine that controls the vacuum pressure and can activate continuous or intermittent pressure, as necessary. It is recommended to start with a continuous pressure of 50–125 mmHg and continue with intermittent pressure, applying a constant negative pressure value from the second change of dressing, which is changed every 3 days. The VAC system can be used to treat wounds of various types, including chronic wounds (pressure, stasis, diabetic ulcers), sub-acute wounds (infected dehisced wounds, orthopedic wounds), and acute wounds (traumatic, avulsed, gunshot wounds), as a primary technique to achieve closure or as an adjunct method to prepare the wound for surgery. The mechanisms of action of the VAC are removal of excess fluids from the interstitial space and decrease of mechanical pressure on the microvasculature and lymphatic systems, and improving blood perfusion as well as oxygen and nutrient delivery to the wound. The technique's positive effects, documented in animal and clinical studies, include angiogenesis, increased blood flow to the wound, and higher rates of granulation tissue formation and bacterial clearance from the wound.

Dr. B. Yaffe (Sheba Medical Center, Tel-Hashomer) elaborated on the role of free flaps in the management of difficult wounds. Delayed healing can be the outcome of deficient vascularity, peripheral or central neuropathy, immune deficiency, severe infection, or loss of a large amount of tissue. The etiology may be the cause of the injury (for example, cold injury or irradiation), the patient's general condition, the anatomical site of injury, or the patient's habits or medication. Principles of treatment include establishing and eliminating the prob-

able causes of delayed healing, thoroughly debriding the wound, improving blood supply, treating the infection, and covering the wound. The final step is to try to prevent recurrence. Although in many instances free tissue transfer is the only possible way to close these wounds, it should be remembered that surgery is the last step in the wound-management ladder and that all the steps are equally important.

Dr. C. Zinman (Rambam Medical Center, Haifa) analyzed the surgical treatment of the diabetic foot. In diabetes, tissue loss from infection, chronic ulceration and ischemia are the most frequent reasons for amputation. A pre-operative clinical examination includes the patient's tissue quality, level of tissue necrosis from infection, nutrition, immune status, and functional abilities. Pre-operative screening tests for perfusion pressures and oxygen diffusion should also be conducted. To determine whether to save the foot, the following factors should be considered: the condition of the soft tissue envelope, correctable deformities and contractures, and sensation. The surgical amputation level is a result of the interaction between the ideal biological and functional levels. Most often the goal is to salvage part of the foot, since patients with partial foot amputations require less energy to ambulate than patients with below- or above-the-knee amputations. Occasionally, the most distal amputation is not the wisest, and better functioning can be achieved with the higher level amputation, as in the case of non-ambulatory patients, patients with spasticity, or patients with severe contractures. For non-ambulatory patients, the goals are not only to obtain wound healing, but to minimize complications and improve sitting balance, transfers and nursing care. Surgical principles include early excision of all necrotic and infected tissue; maximal skin preservation; and excision of tendons, nerves, volar plates and capsular tissue. Primary wound closure can be considered when minimal necrosis or purulence is present, with good skin edge vascularity and a clean wound. Normal bone or tissue may need to be excised to achieve an optimal amputation level. Dr. Zinman also discussed indications and treatment for partial calcanectomy, osteomyelitis of the metatarsals and lesser metatarsal heads, as well as the etiology of the neuropathic ulcer and its differentiation from the ischemic ulcer.

Prof. R. Shafir (Sourasky Medical Center, Tel Aviv) reported on Polyheal's first product, "Poly 1," which is a water-based suspension of non-biodegradable synthetic, electrically charged and chemically inert microspheres capable of promoting wound healing without the further addition of other therapeutic substances. These microspheres act by providing additional surface area for cell attachment and activating cells involved in the wound-healing process. Applying Poly 1 on a rat embryonal myoblast cell culture resulted in enhanced creatine phosphokinase activity. Studies of rat wounds showed enhanced collagen production and wound closure as compared to control groups. The current configuration of the product is an aqueous suspension comprising the synthetic microspheres and the buffer in a plastic container for single use. It is applied to the wound by wetting its whole surface, followed by a simple gauze dressing for coverage. The product was studied for toxicity and side effects on animals, with no adverse reactions reported. A human safety study is currently underway on healthy volunteers in a U.S. hospital. Polyheal was tested for safety and efficacy in two uncontrolled pilot clinical trials in which the product was applied to 24 patients with recalcitrant chronic wounds (leg and foot ulcers and one irradiation wound) and a history of unsuccessful wound healing treatments. Twice-daily they received "Poly 1" treatment and dressing regimen for periods ranging from 7 to 46 days. During the treatment period, approximately 65% of the wounds either completely closed or became graftable, approximately 25% improved significantly, and approximately 10% did not change. "Poly 1" was found to be safe and biocompatible. In all cases, no adverse events, side effects or complications were encountered. Furthermore, over 80% of the patients reported a pain relief effect following the application of "Poly 1." At this stage, Polyheal Ltd. plans to test its products in additional clinical trials to treat indications such as burns and various types of chronic wounds.

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