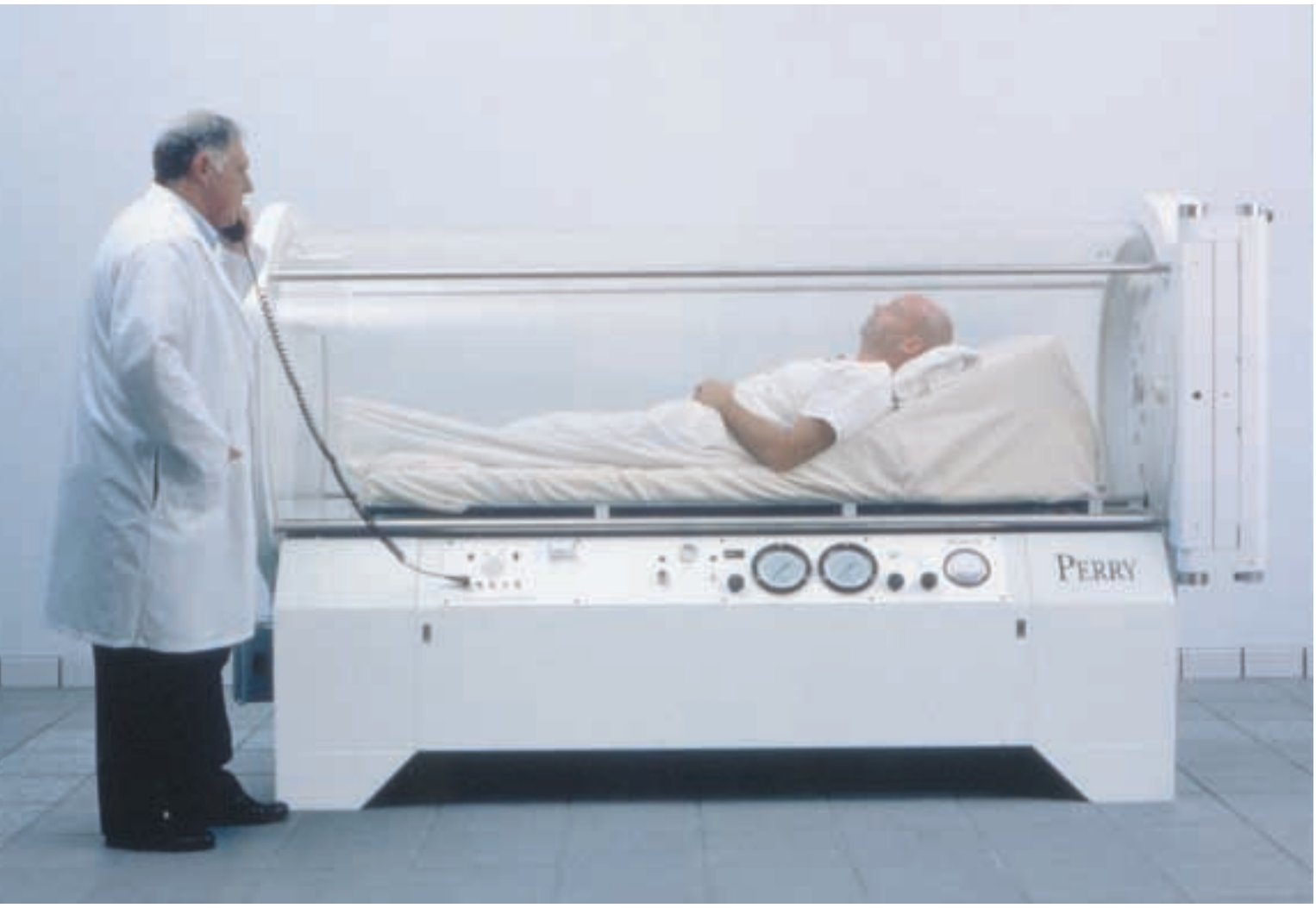

Despite enormous advances in technology, the non-healing wound remains a challenge for all health care professionals. In the last analysis, successful treatment is determined by meticulous debridement and frequent dressing changes. Ischemia, chronic passive congestion, infection, malnutrition, immunodeficiency, old age, cigarette smoking, and coagulopathies are but a few of the factors that contribute to poor wound healing. Advances in microvascular and reconstructive surgery, as well as the use of growth factors and biologic dressings, have added new dimensions to wound therapy. The use of hyperbaric oxygen has gained wider acceptance as have specialized wound centers that emphasize a multidisciplinary approach.

Wound Healing in the 21st Century

Victor A Hanson, md, facs

Stem cells have been used in experimental animals to replace damaged tissues. Currently their use has been approved only for bone marrow rescue of patients receiving high-dose chemotherapy.

Genetic manipulation of cellular mechanisms to reverse pathologic conditions will likely characterize wound healing in the 21st century. Although the human genome has been mapped, a better understanding of how the gene functions will be necessary before significant advances can be realized. But significant progress is being made. Recently, researchers identified the gene in Candida responsible for its biofilm coating. Inhibition of this gene with loss of its biofilm would render it harmless.

ntroduction

Minimally invasive surgery has taught us that multiple small wounds heal faster than one large one, and the patient's energy levels return to normal sooner. The mantra of our digital age is "smaller and faster is better!" However, a historical review of wound management tells a very different story.

Ambrose Pare was a French military surgeon practicing in the mid-16th century. He is often quoted as saying, "I treat the wound, but God heals it." He earned a reputation for a "kinder, gentler" approach to wound management and had some notable successes. The standard of care in his day was a hot iron and boiling oil. Regrettably his wisdom was lost in time because in the mid-19th century Civil War surgeons managed most wounds of the extremities by amputation. Although ether and chloroform had been discovered, unfortunately Lister had not as yet advanced his germ theory of disease. In field hospitals, it was not uncommon to leave knives and saws on tables in the open air, and rarely did surgeons wash their hands or change their aprons between cases. Thus most wounds became infected and the mortality of amputation was 50%.

Factors in wound healing

One thing that has not changed during the past five centuries is the four phases of wound healing: coagulation, inflammation, proliferation, and maturation. These stages are usually seamless but, should one phase be defective, a non-healing, chronic wound may result.

Our knowledge of the factors that influence each phase has increased tremendously, as has our understanding of molecular biology, especially since the recent mapping of the human genome. For example, we now use growth factors to accelerate wound healing.[2,3,4,5] However, despite advances in new technology, successful healing of the chronic wound still requires meticulous debridement and frequent dressing changes, and it is unlikely that compassion will become a mismatch any time soon.[6]

Malnutrition, advanced age, chemotherapy, HIV, and cortisone-suppressed inflammation are associated with poor wound healing. While the British Navy in the 18th century did not know the critical role Vitamin C played in the proliferative phase of wound healing, thanks to James Lind (1716-1794), they were able to prevent deaths from scurvy with citrus fruits. Physiologic tissue levels of pO_2 and lysyl oxidase are necessary for the formation and polymerization of collagen. Deficits of either will delay the maturation phase and decrease wound tensile strength.[7,8]

For years clinicians have said, "If the wound is wet, make it dry. If it is dry, make it wet!" However, recent studies comparing saline wet to dry dressings, with hydrocolloid dressings have demonstrated the fallacy of this time-honored practice.[9,10,11] Today most health care professionals favor a moist wound environment for optimal healing, especially for the three most prevalent chronic wounds: the diabetic foot ulcer, the venous stasis ulcer, and the bed sore. Although these wounds have a complicated etiology, low-tissue oxygen tension is a common denominator.[7,8]

The diabetic foot ulcer

Perhaps no chronic wound has as many factors responsible for non-healing as the diabetic foot ulcer.[12,13,14,15,16,17] Roughly 7% of our population has or will have diabetes and 11 % of those will develop foot ulcers.[18,19,20,21,22] Perhaps the single most important factor responsible for the foot ulcer is neuropathy.[17] The latter is responsible for the development of the hammer toe and claw foot deformities that predispose patients to ulcerations over the metatarsal phalangeal joints of the foot.

Without sensation, the victim of a diabetic foot ulcer may have little incentive to seek medical attention. The loss of nerve function is known to interfere with the inflammatory response and thus contributes to delayed wound healing. Elevated blood sugars diminish the ability of leucocytes to kill bacteria. A study published in 1991 demonstrated that 48% of chronic diabetic foot ulcers have clinically unrecognized osteomyelitis.[23,24]

The presence of 10^5 bacteria per gram of tissue is associated with poor wound healing.[25,26,27]

Thus an unrecognized chronic infection is another mechanism that delays wound closure. Appropriate antibiotic therapy will stimulate wound healing very much like a growth factor.

In 20% of chronic diabetic foot ulcers arteriosclerosis is responsible for diminished tissue perfusion and lowered oxygen tension.[28,29] Successful revascularization will determine whether or not the ulcer heals.

In the 1970s, diabetic foot registries were started in the United Kingdom and at the Emory School of Medicine. These clinics were dedicated to the multidisciplinary approach to the diabetic foot ulcer and were responsible for a 50% reduction in the amputation rate.[30,31,32] No doubt this team approach served as a model for today's wound-care centers.

The bed sore

Pressures in skin overlying bony prominences approach 90 mm Hg, and capillary flow stops at 30 mm Hg pressure; therefore, the skin overlying the elbows, the sacrum, hips, and heels is prone to pressure hypoxia. Sensory deficits from organic brain syndromes, spinal cord injury, and peripheral neuropathy prevent the bed-sore victim from changing positions in response to local discomfort. The moisture from feces and urine macerates hypoxic skin resulting in a chronic infected ulcer.

The venous stasis ulcer

In the stasis ulcer, chronic passive congestion associated with venous insufficiency results in hypoxia. As mentioned above, the latter is associated with poor collagen synthesis and is aggravated by edema. Compression dressings and elevation are effective treatment for the stasis ulcer.

Improving wound healing

It is important to identify and eliminate factors that delay wound healing, such as protein calorie malnutrition, smoking, hypertension, renal failure, and poorly controlled diabetes. Using the gut to correct malnutrition is preferable to total parenteral nutrition, since the former route eliminates systemic immune response syndrome.[33]

Improving lung function with pulmonary bronchodilators, physiotherapy, nasal oxygen, antibiotics, and reversal of congestive heart failure will improve tissue pO_2 and thus promote wound healing. Hyperbaric oxygen corrects low-tissue oxygen tension in many chronic ulcers and, with the availability of spacious hyperbaric pressure chambers, claustrophobia is no longer a deterrent (Figure 1). People can move about and watch movies and television while their tissue oxygen tensions reach levels of 1400 mm Hg (normal is 97 mm Hg). (Figure 2)

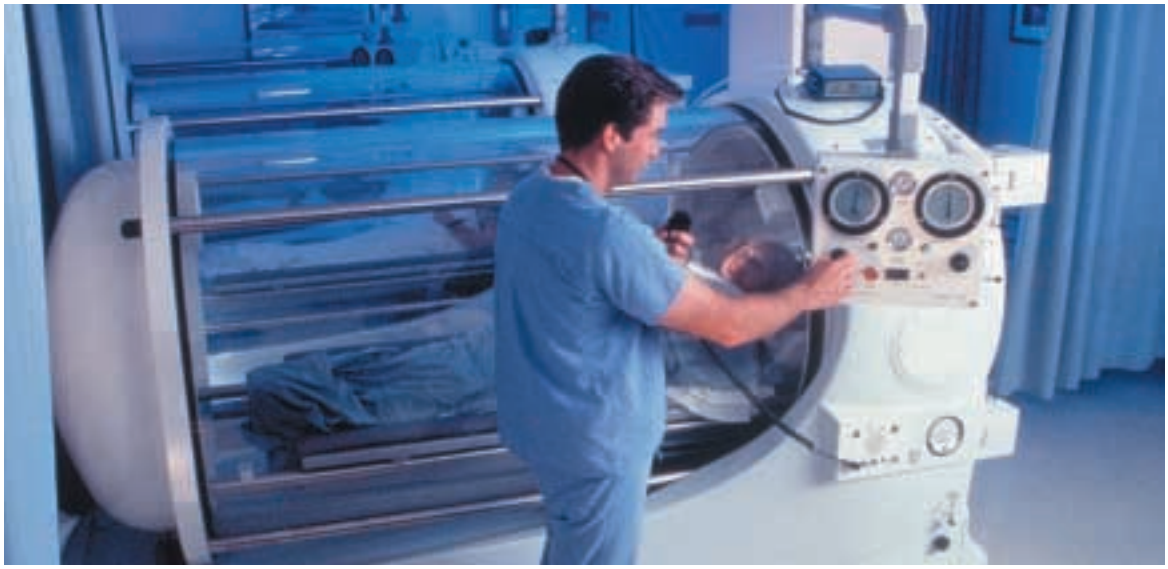

FIGURE 1

Hyperbaric oxygen therapy delivers high concentrations of oxygen to injured areas systemically through an enclosed pressurized chamber.

Growth factors and stems cells may be the "new wave" in wound care technology. Currently Regranex™ is the only FDA-approved growth factor for the treatment of diabetic foot ulcers. Fortunately, the recombinant DNA techniques used to manufacture Regranex™ have eliminated the risk of HIV and hepatitis.

The future

Perhaps the most exciting recent experimental development in wound healing has been the use of stem cells that originate in the bone marrow and have the potential to differentiate into other cell types, tissues, and possibly organs. (See "Stem Cell Research: Medical Panacea or Moral Nightmare" in the July 2001 issue.) Their current approved use is to rescue the bone marrow in patients receiving high-dose chemotherapy. More to the point, reports in the literature describe successful animal experiments using stem cells to repair damaged spinal cords, secrete insulin, and replace tendon, bone, and damaged myocardium.[34,35] Although the role of stem cells in wound healing is still experimental, if successful in humans, their potential would be unlimited.

It is important to identify and eliminate factors that delay wound healing, such as protein calorie malnutrition, smoking, hypertension, renal failure, and poorly controlled diabetes.

In 1953, Watson and Crick described the mechanisms by which the double helix of DNA codes for a protein and passes genetic information to succeeding generations during cell division. This marked the beginning of molecular biology that reached its apotheosis with the mapping of the human genome. The latter accomplishment notwithstanding, very little is known about the mechanisms of DNA expression. Recently the gene responsible for the biofilm coating of Candida was discovered. Inhibition of this gene blocks the formation of its biofilm and converts the yeast from a lethal pathogen to a harmless flora.[36] The genetic manipulation of cellular mechanisms to correct a pathological condition will probably be the wave of the future.

Artificial skin consisting of neonate epithelium and intestinal submucosal cells have been approved by the FDA for application to the chronic wound.[37,38] This skin is effective but expensive. Further studies will be needed to evaluate which combinations of growth factors, artificial skin, and hyperbaric oxygen work best and are the most cost effective. Certainly, the future of wound healing in the 21st century appears bright and exciting.

About the author

Victor A Hanson, MD, FACS, is in private general surgical practice in Atlanta, Georgia. He completed medical school, an internship, and residency training in general surgery at the University of Pennsylvania. Hanson has been a Naval flight surgeon, and worked in the departments of surgery for Upstate Medical Center in Syracuse, New York, and Thomas Jefferson University in Philadelphia, Pennsylvania. He presented a session on wound healing at AST's annual national conference in Atlanta in May.

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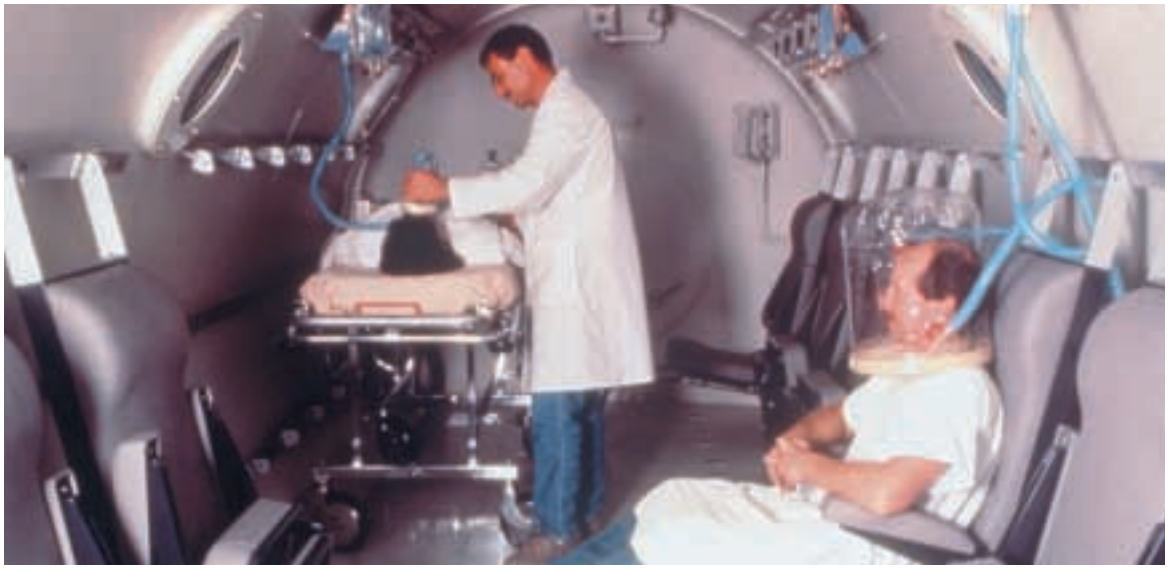

FIGURE 2

Larger hyperbaric chambers reduce the problem of claustrophobia for some patients.

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Images courtesy of Perry Baromedical Corporation, Riviera Beach, FL, 800-741-4376