

# Growth Factor and Human Skin-Equivalent Products

When used by an experienced wound-care team, the new biologic wound-care products can reduce the resolution time of some venous leg ulcers and diabetic foot ulcers by 50%.

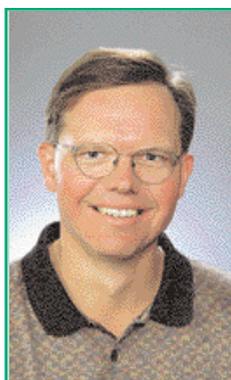
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The purpose of this article is to discuss the standard care of venous and diabetic ulcers, and to explain why some patients' lesions exhibit protracted healing times. This article also will review the composition,

method of application, possible mechanism of action, cost of treatment and the results of clinical investigations regarding three new wound-care products: Apligraf™, Regranex™ and Dermagraft™. Finally, the article will outline which patients would benefit the most from these new biologic products.



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## **Epidemiology of Venous Leg and Diabetic Ulcers**

Venous leg ulcers are chronic wounds associated with long-standing venous hypertension. Venous lesions are present in 1% to 2% of the total population. While they are not a cause of limb loss, venous ulcers can be a source of life-threatening cellulitis. The most frustrating aspect of venous ulcer management (besides

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the protracted healing rate) is the fact that 43% of venous ulcers recur.<sup>1</sup>

Diabetic foot ulcers occur in 3% of diabetics. The ulcers develop as a result of many factors, the most important being the triad of peripheral neuropathy, local trauma and ischemia. Diabetic foot ulcer patients account for more hospital days (average length of stay is 23 days) than all the other diabetic complications combined. Despite comprehensive measures by health-care workers, 7% of these patients will require some degree of lower extremity amputation.<sup>2</sup>

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### **The Basis of Venous Ulcer Therapy**

In venous disease, the hemodynamic abnormalities must be corrected (*i.e.*, early surgical intervention in patients with superficial or perforator vein incompetence) and ambulatory hemodynamic support (*i.e.*, compressive therapy) must be provided before local wound-care modalities can be successful.<sup>1</sup>

Compressive bandaging to reduce or eliminate edema, and a moist wound environment to debride the chronic tissue and aid in the development of granulation tissue, are prerequisites for epidermal repair. The different compressive systems include Profore™, "duke boot" or Surepress™ (long-stretch systems) and Comprilan™ and Circaid™ (short-stretch or no-stretch systems). None of the dozens of different topical dressing products have been found to be superior to compressive therapy.<sup>3</sup>

### **The Basis of Diabetic Foot Ulcer Therapy**

The standard treatment regime for diabetic foot ulcers includes:

- 1. Management of concomitant medical problems** (*e.g.*, blood sugar control, hypothyroidism, anemia);
- 2. Revascularization of ischemic regions.** Objective tests are essential (*e.g.*, ankle brachial indexes with Doppler-determined toe pressures or transcutaneous oxygen assessment);
- 3. Pressure relief.** Pressure relief is the mainstay of treatment for neuropathic, but adequately perfused, foot lesions. Relief can be accomplished by using a total contact cast or an air-cast walking brace with a total contact insert. Any ulcerogenic bony prominences must be excised, and, in some cases, the achilles tendon must be lengthened to decrease abnormal biomechanical forefoot loading.
- 4. Aggressive treatment of infections.** Infections tend to spread quickly, and often are associated with underlying osteomyelitis.
- 5. Routine sharp debridement of the wound** is important for complete removal of callus, fibrin and necrotic tissue, and accelerates wound healing.<sup>2</sup>

### **Growth Factors and Wound Healing**

Knowledge of growth factors and wound-healing science is expanding daily. Basically, there are two types of wounds: acute or chronic. The acute (*i.e.*, surgical or traumatic) wound in healthy individuals heals quickly without complications, and requires only local wound care. Chronic wounds occur in the compromised patient, and take much longer to heal, with frequent recurrences. In the case of chronic wounds, medical and supportive treatment, as well as local wound care, is necessary for a successful outcome.

Table 1

## Suggested Inclusion and Exclusion Criteria for the Use of Growth Factor and Human Skin-Equivalent Wound Products

### ► Inclusion Criteria

1. Neuropathic, diabetic foot ulcers or venous leg ulcers showing no appreciable improvement after four to six weeks of standard therapy by an established wound-care program.
2. Adequate limb perfusion must be present and documented using objective tests (*e.g.*, transcutaneous oxygen testing, Doppler-determined ankle-brachial indexes with toe pressures).
3. The patient is willing to comply with the requirements of continued off-loading therapy (total contact casting or air-cast walking boot and custom inserts) for diabetic foot ulcers and compressive therapy (*e.g.*, Profore™) for venous lesions.
4. The physician using these products must be trained in their application and in the patient selection protocol.

### ► Exclusion Criteria

1. Wounds with clinical evidence of infection or suspected osteomyelitis.
2. Ulcers complicated by exposed tendon, joint or bone, or a sinus tract.

\* I acknowledge the input of Dr. Keith Bowering, Edmonton, Alberta.

For a wound to heal, reparative cells (*e.g.*, platelets, neutrophils, macrophages, fibroblasts) must be attracted to the site of the injury (chemotaxis). Cells must then proliferate and divide (mitogenesis), a new blood supply must be created (angiogenesis), and a collagen matrix must be formed (wound remodeling). This process occurs smoothly and promptly in the acute wound setting.

In the chronic wound, however, the inflammatory stimuli remain (*i.e.*, an untreated metabolic condition, repetitive trauma to a neuropathic injury, infection, local hypoxia, patient malnutrition). This produces a critical imbalance between the wound levels of proteolytic enzymes and its

endogenous inhibitors, resulting in massive tissue turn-over and failed wound closure (Figure 1).<sup>4</sup>

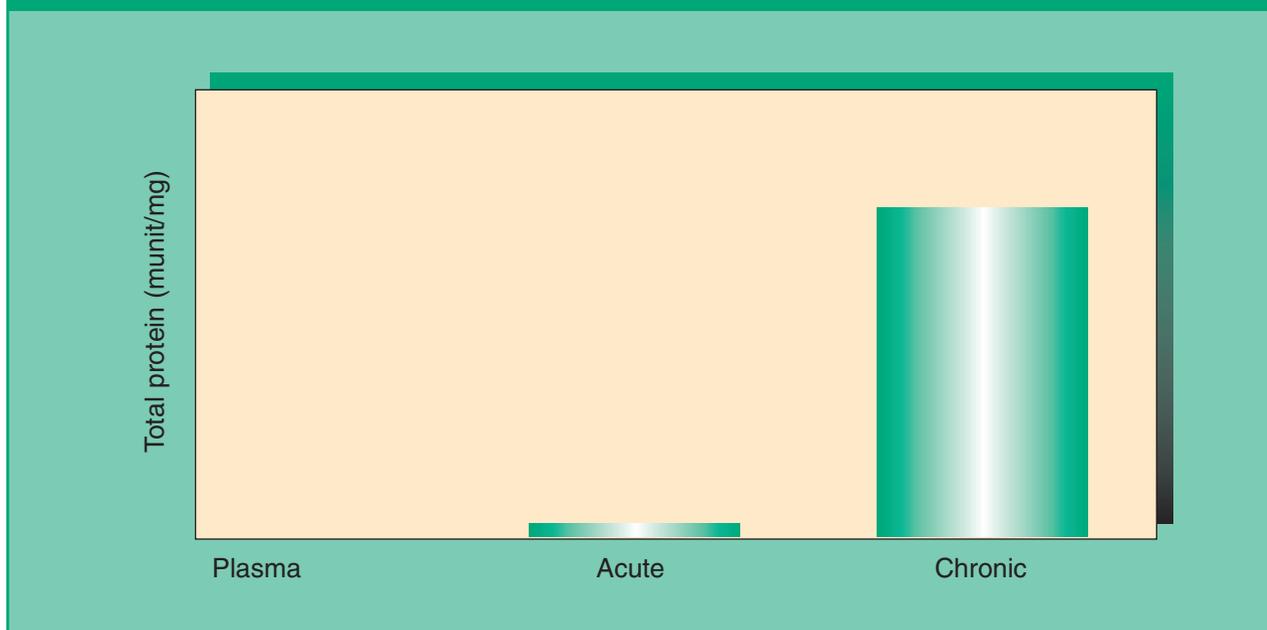
In the chronic wound, one can observe:

1. Impaired chemotaxis of the inflammatory cells into the site of injury;<sup>5-7</sup>
2. Deficiency in growth factors;<sup>8,9</sup>
3. Collagen and GAG matrix protein abnormalities;<sup>10,11</sup> and
4. Deficiencies in re-epithelialization of venous ulcers.<sup>12,13</sup>

Between 45% to 52% of patients with lower extremity ulcers experience a protracted healing course (*i.e.*, more than six months to wound closure), even when they are cared for by an experienced wound-care team. The need for adjunctive

Figure 1

### Chronic Wound: Elastase Activity Level



treatment modalities (*i.e.*, growth factor and human skin equivalent products), therefore, has been postulated.

#### When to Consider Using Biologic and Human Skin-Equivalent Wound Products

Approximately 48% to 55% of venous leg and diabetic foot ulcers will heal in less than five to six months without any complications. The remaining 45% to 52% of patients, however, are at risk of developing limb-threatening cellulitis, or require an amputation because of the markedly protracted wound-resolution course. Clinically, it is prudent to attempt to identify these high-risk patients as soon as possible, so that referral to a recognized wound-care team can be made without delay. Suggested guidelines for the use of growth factor and human skin-equivalent products are outlined in Table 1.

#### Choosing the Correct Growth Factor or Human Skin-Equivalent Product

Apligraf<sup>TM</sup> currently is available for the treatment of refractory venous leg ulcers, while Regranex<sup>TM</sup> and Dermagraft<sup>TM</sup> are available for the treatment of refractory diabetic foot ulcers.

*Apligraf<sup>TM</sup>* is a bi-layered manufactured living skin equivalent, with an epidermis of layers of human keratinocytes, stratum corneum, and a dermis of Type 1 bovine collagen with human living fibroblasts (Figure 2).

Apligraf<sup>TM</sup> consists of normal skin's functional building blocks in a non-rejectable form (*i.e.*, keratinocytes and fibroblasts do not express HLA Class II antigen or the co-stimulatory molecule B-7 and CD 40).<sup>14</sup> Apligraf<sup>TM</sup> may be effective in wound healing as a "graft take" (depending on the wound-bed preparation), or by secondary intent where the epidermal cells, dermal fibrob-

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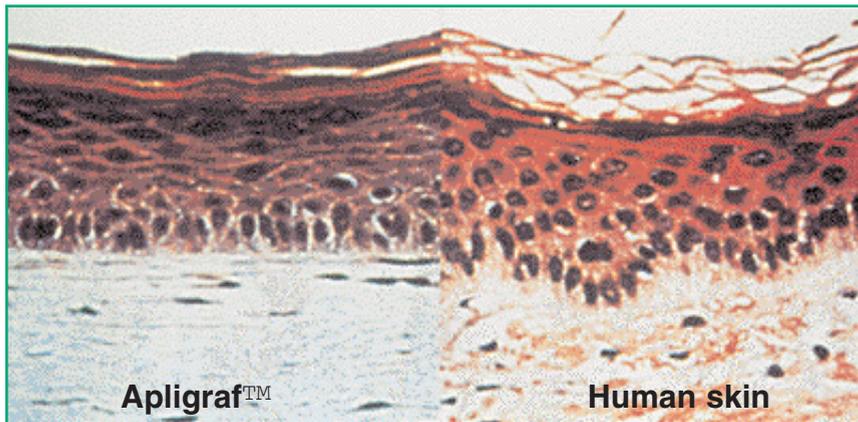


Figure 2. Histology section comparing Apligraf™ with human skin

lasts and extra-cellular matrix interact with the wound base and produce a host of complimentary growth factors and cytokines (Table 2). Apligraf™ has been found to accelerate the healing of venous lesions that are larger than 1,000 mm<sup>2</sup>, deeper than full thickness, and more than six months old.<sup>15</sup>

Apligraf™ is applied using sterile technique. First, a fenestrated piece of Apligraf™ is placed (with the dermal layer facing down) on a freshly debrided wound base (Figure 3). Secondly, this preparation is bolstered in place by an immobilizing wrap (Figure 4). Finally, the Profore™ com-



Figure 3. Application of Apligraf™ to the wound



Figure 4. Dressings following Apligraf™ application

pression system is applied. Patients are encouraged to limit their level of walking and standing for the next week. Patients must return to the clinic one week after the initial treatment with Apligraf™ for re-examination of the synthetic graft site. Caution must be used so that the graft site is not overtly disturbed when reapplying the compression dressing. Compression dressing must be reapplied each week

until wound resolution is achieved. Indications for the application of a second sheet of Apligraf™ are still being reviewed.

A 6.5 cm<sup>2</sup> sheet of Apligraf™ costs \$950. Funding may be available on a case-by-case basis from the Worker's Compensation Boards, Department of Veterans' Affairs and some insurance companies.

**Regranex™** is available as an adjunctive treatment for diabetic foot ulcers. Regranex™ is a topically applied gel, consisting of recombinant human platelet-derived growth factor (PDGF-BB).

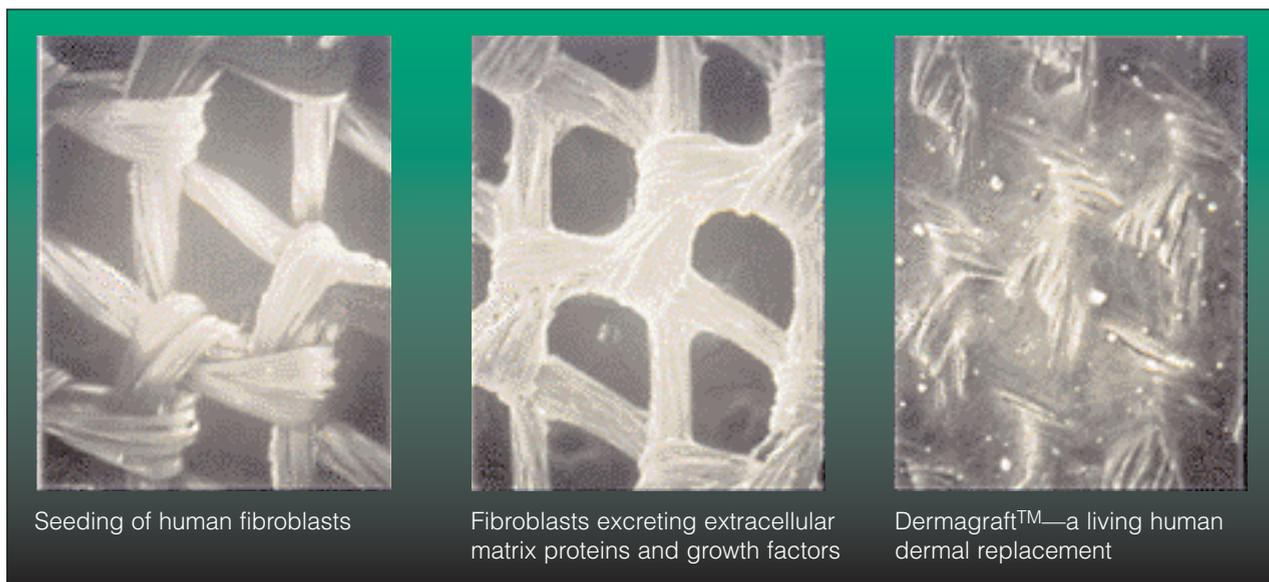


Figure 5. Growth of Dermagraft™

PDGF-BB is the first growth factor released when the skin is injured, and is present at every stage of normal wound healing. Regranex™ appears to enhance the expression of the transforming growth factor beta (TGF-beta). This enhancement accelerates collagen synthesis. By increasing the activation of inflammatory cells, PDGF-BB also may have an indirect effect of chemotaxis and angiogenesis. Collagenase activity also is stimulated, facilitating wound remodeling.<sup>16</sup>

A 1998 interim report from the Canadian Diabetic Foot Ulcer Trial showed that Regranex™, when used with standard treatment protocols, can accelerate the healing of selected diabetic foot ulcers by producing wound closure at two to three months *versus* five months with standard treatment alone.<sup>17</sup>

During treatment, the patient removes a tube of Regranex™ from the refrigerator each day, cleans the wound with normal saline, and applies a thin film of Regranex™ to cover the wound base. The patient then reapplies a non-stick padded dressing, followed by the mandatory air-cast walking boot

and total contact insert. The patient must return to the clinic every one to two weeks for sharp wound debridement and monitoring.

A 15 g tube of Regranex™ costs \$600, and most patients require two to three tubes during a treatment course.

**Dermagraft™** is a allogenic human neonatal dermal fibroblast culture that is grown on a degradable scaffold (Figure 5). Researchers believe that Dermagraft™ promotes wound healing because, firstly, its bioabsorbable mesh acts as a temporary wound cover, and, secondly, the implanted fibroblasts secrete complementary growth factors (*i.e.*, vascular endothelial growth factor [VEGF], keratinocyte growth factor [KGF], insulin growth factor-1 [IGF-1]). VEGF is mitogenic to endothelial cells, promoting angiogenesis. KGF enhances keratinocyte migration and epithelialization, while IGF-1 stimulates collagen synthesis. Dermagraft™ also is thought to have an indirect positive effect on the inflammatory phase of healing and mediator PDGF-A.<sup>18</sup>

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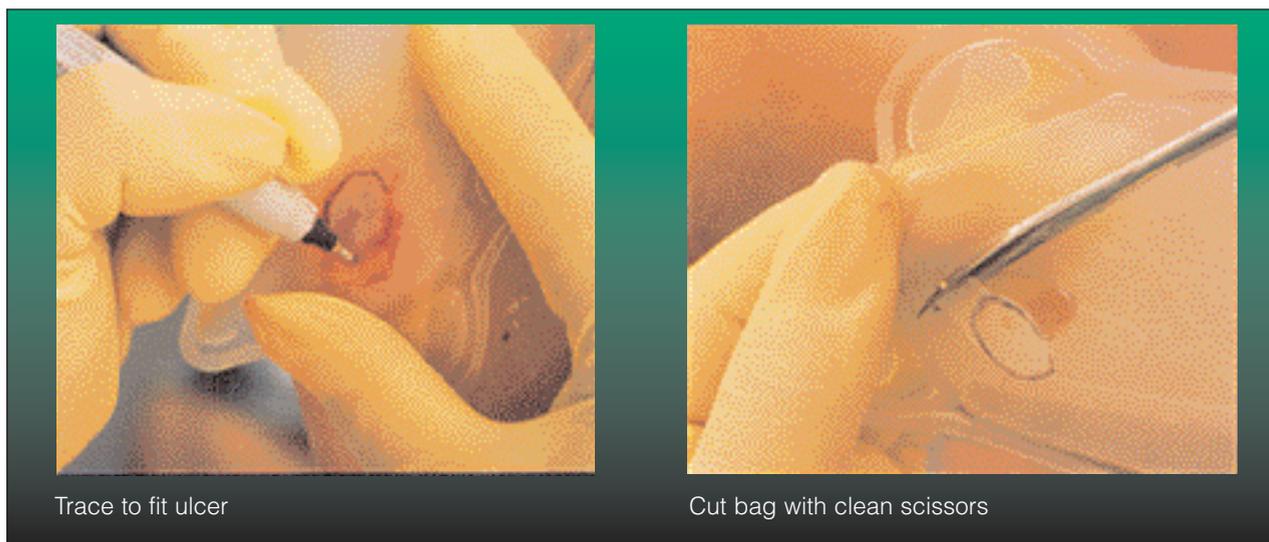


Figure 6a. Tracing and cutting Dermagraft™

Preliminary investigations suggests that Dermagraft™ has a positive impact on the healing of diabetic foot ulcers. The results of a large multi-centered United States trial are anticipated in September 1999.<sup>19-21</sup>

Dermagraft™ comes in a cryopreserved state, so it must be thawed and rinsed with normal saline before it can be cut and implanted on freshly debrided ulcer bases (Figure 6). A non-adherent dressing should then cover the graft site, followed by a bolster wrap to immobilize the area. The patient's air-cast walking boot with total contact insert is reapplied, and its mandatory use is reinforced to the patient. The dressing can be left in place for one week (unless soiled). After one week, the patient is required to return to the clinic to have the procedure repeated. Dermagraft™ may be applied each week for a maximum of 10 weeks.

Ten sheets of Dermagraft™ cost \$4,800, but each sheet can be shared by more than one patient, provided that strict measures are employed to prevent cross-contamination.



Figure 6b. Implanting Dermagraft™

### **Conclusion**

The new biologic wound-care products are not a "magic bullet" to heal refractory wounds. When used by an experienced wound-care team, however, the resolution time of venous leg ulcers and diabetic foot ulcers can be reduced by 50%. The following points concerning use of the current biologic wound-care products should be remembered.

- Present standard-care protocols are effective in 55% of patients with lower extremity ulcers.

- Chronic lesions are the physician's domain, since it is essential to look at the patient as a whole.
- The sooner a refractory lesion is identified and treated, fewer patient complications will occur and the treatment approach will be more cost-effective.
- Patients must have at least four to six weeks of standard wound therapy provided by an established wound-care team without appreciable improvement in ulcer size before they can be considered for biologic or human skin-equivalent therapy.
- Wounds that are compromised by inadequate circulation, infection, exposed tendon, joint or bone, sinus tracts or underlying osteomyelitis are not candidates for growth factor or human skin-equivalent therapy.
- The new biologic wound-care products should be used only by physicians trained in the application of these products and patient selection criteria. A National Biologic Wound Registry ideally should be formed to track the outcomes of these patients. This information then could be presented to the provincial health authorities to solicit support for growth factor/human skin-equivalent wound programs.

As biologic wound-care products grow more and more sophisticated in the coming years, the medical and economic focus on these products will intensify.

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