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# Reduced Wound Contraction After Grafting of Full-Thickness Burns with a Collagen and Chondroitin-6-Sulfate (GAG) Dermal Skin Substitute and Coverage with Biobrane

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Full-thickness burns destroy both the epidermal and dermal tissues of the skin. This study evaluates a collagen and chondroitin-6-sulfate dermal skin substitute (graft) that was applied to excised full-thickness burns and covered with Biobrane.

Experimental conditions included: (a) no burn, subcutaneous implantation of the graft; (b) burn, excision, graft, coverage with Biobrane and bandages; (c) burn, excision, no graft, coverage with Biobrane and bandages; (d) burn only. Forty-one days post-surgery, subcutaneous implantation ( $N = 3$ ) of the graft caused no detectable contraction or necrosis of the overlying skin, whereas all burn wounds contracted. Measurements of wounds (percentage of original wound size) showed statistically significant differences between the following treatments; (a) graft plus Biobrane ( $N = 10$ ), 34%; (b) no graft plus Biobrane ( $N = 9$ ), 25%; (c) untreated burns ( $N = 6$ ), 16%.

Semi-quantitative evaluation of time to healing indicated by spontaneous detachment of Biobrane from wounds showed that grafted, excised wounds healed in an average of 2.7 weeks, while ungrafted, excised wounds required an average of 4.3 weeks to heal. Histological appearance of healed wounds after grafting and coverage with Biobrane resembles undamaged skin without epidermal adnexal structures.

Excision of full-thickness burn eschar, followed by grafting with a collagen and chondroitin-6-sulfate dermal skin substitute and coverage with Biobrane provides reduced wound contraction within a six-week period of observation compared to non-excised wounds. Both more rapid and more complete wound healing took place compared to excised wounds that were not grafted.

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Severe burn injuries can cause extensive full-thickness skin loss and are accompanied by immunosuppression<sup>1</sup> that contributes to more than 10,000 fatalities and 100,000 hospitalizations each year.<sup>2</sup> Effective treatment of these injuries must ultimately replace the damaged skin by wound closure with stable tissue while restoring normal immune function.

Current treatment for permanent closure of full-thickness burn injuries includes early and complete excision of burn eschar<sup>3</sup> followed ultimately by application of meshed split-thickness autograft.<sup>4</sup> However, cases of large body surface area (BSA) burns often lack sufficient donor sites to supply needed grafts and multiple rehar-

vesting of donor sites is performed to permanently close the excised wounds.

These practices inflict additional injury to the patient, require multiple surgical operations, extend hospitalization, and can yield suboptimal functional and cosmetic results. Progress toward improved treatment of full-thickness burn injuries should provide clinical advantages, such as reduced amounts of donated tissue needed to complete grafting procedures, reduced numbers of surgeries required for grafting, shortened hospitalization time, and superior functional and cosmetic results from grafting.

By definition, full-thickness burns destroy both dermal and epidermal components of the skin. Models of full-thickness skin substitutes have employed:

- collagen-glycosaminoglycan (GAG) dermal membranes combined with thin epidermal autografts or epidermal cell suspensions,<sup>5,6</sup>
- collagen gels contracted by fibroblasts together with allogeneic cultures of epidermal keratinocytes,<sup>7</sup>
- epidermal suction blisters over allogeneic dermis,<sup>8</sup>

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- cultures of autologous epidermal keratinocytes over de-epidermized allogeneic dermis,<sup>9</sup> or
- combination of cultures of autologous epidermal keratinocytes with a collagen and chondroitin-6-sulfate (GAG) dermal skin substitutes.<sup>10</sup>

Materials used to accomplish permanent wound closure must meet the same requirements for clinical efficacy as materials used as skin substitutes and wound dressings.<sup>11</sup> Beneficial properties required for materials used in dermal skin replacements include flexibility, correct moisture flux, hemocompatibility, eventual degradation of the grafted material, minimal immunogenicity and inflammation, promotion of connective tissue regeneration, control of infection and fluid loss, and reduced scarring and contracture<sup>12</sup> compared to conventional autografting techniques. These properties have been incorporated into the dermal skin substitute reported in the present study. In addition, methods have been established for deliberate regulation of the pore size of the collagen-GAG material used in this study.<sup>13</sup> The methods provide very high reproducibility of structural pore size and contribute to its ability to function as a substrate for culture of normal human epidermal keratinocytes on its surface.<sup>10</sup>

Safety, clinical effectiveness, predictability and availability are among the fundamental requirements for permanent skin substitutes. Separate evaluation in vivo of materials used to produce skin substitutes in vitro (cultured cells, dermal replacements) or ex vivo (allogeneic dermis) is necessary to confirm whether the individual components of composite grafts meet these basic requirements. The present study demonstrates that grafting of a collagen-GAG dermal skin substitute to excised full-thickness burns reduces wound contraction when compared to burn wounds that were excised but not grafted and to burns that were not excised. Burns that were excised and grafted healed more quickly than excised burns that were not grafted. Excised and grafted burns also promoted regeneration of connective tissue — “neodermis”<sup>11</sup> — in the skin. The repaired connective tissue has the histological appearance of undamaged dermis without epidermal adnexal structures.

## Methods and Materials

**Graft preparation.** Dermal skin substitutes (grafts) were prepared from bovine collagen (Eastern Regional Research Center, US Department of Agriculture, Philadelphia, PA) and chondroitin-6-sulfate (“GAG”; sodium salt, Type C, Sigma Chemical, St. Louis).<sup>14</sup> Collagen was dispersed and GAG dissolved in 0.05M acetic acid; a co-precipitate was formed by dropwise addition of GAG to collagen while stirring in a refrigerated blender; the co-precipitate was frozen. Frozen co-precipitate was lyophilized and treated in a vacuum oven (105°C, 0.001 torr) for 24 hrs. The dried material was cut into 1.5 × 3.0 cm pieces, rehydrated in 0.05M acetic acid for 24 hours, cross-linked in 0.25% glutaraldehyde for 24 hours, washed extensively in purified water (Millipore Milli-Q, 18 megaohm-cm resistivity), and stored in 70% isopro-

panol prior to grafting. Immediately before application, grafts were washed with several changes of purified water followed by several changes of isotonic saline solution. Gross appearance of the collagen-GAG dermal skin substitute is shown in Fig 1A; its histological appearance is shown in Fig 1B.



Fig 1A

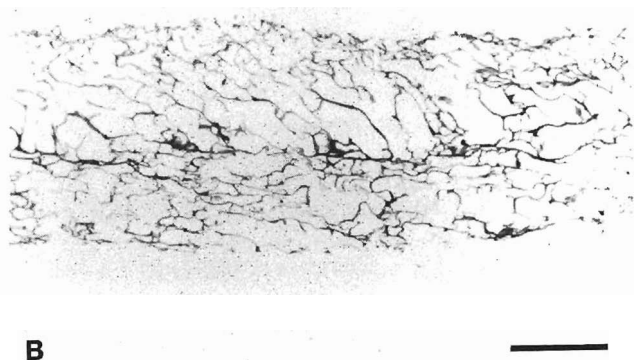


Fig 1B

**Fig 1.** Dermal skin substitute. **A.** Gross appearance of the collagen and chondroitin-6-sulfate membrane used as a graft in this study. Material is a biological plastic whose structural and biochemical compositions can be modified according to the procedures by which it is prepared. **B.** Photomicrograph of the transverse aspect of the dermal skin substitute used as a graft. Material has a sponge-like structure that allows ingrowth of connective tissues from the woundbed. Scale bar = 1 mm.

**Burned mouse model.** CF-1 mice (female four to eight weeks old, 20 to 25 grams) were shaved and depilated on the dorsal side, anesthetized with methoxyflurane vapor for three minutes and then received an approximate 15 to 20% BSA (1.5 × 3.0 cm) full-thickness burn by exposing a demarcated area of the depilated dorsum to steam for six seconds.<sup>15-17</sup> Immediately following burn and/or surgery, 1 cc of saline was injected intraperitoneally and morphine was injected subcutaneously at a dose of 15 mg/kg.

After 48 hours, eschar was excised through the panniculus carnosus and a dermal skin substitute (1.5 × 3.0 cm) was grafted onto the wound with six stent-type sutures. Grafts were covered with Biobrane (Woodroof Laborato-

ries, Santa Ana, CA), dressed with cotton gauze and wrapped with elastic adhesive bandages (Elastic, Johnson and Johnson Products, New Brunswick, NJ). Dressings were changed and measurements of wound size were made at six, 13, 20, 27, 34, and 41 days post-surgery.

After observation, animals were sacrificed and repaired tissues were prepared for histological examination. Experimental controls included (a) no burn, subcutaneous implantation of the dermal replacement (three animals); (b) burn, excision, no graft, coverage with Biobrane and dressings (nine animals); and (c) burn only (six animals).

**Data collection and interpretation.** Direct measurements were made of wound length and width at anterior, medial, and posterior edges of uninjured skin to identify a total of eight points as the wound perimeter.<sup>18</sup> Wound size was calculated as the area within the perimeter defined by the points. At the time intervals shown above, wound area measurements were recorded and notations were made for each animal to note whether the Biobrane dressing had spontaneously detached from the wound. At each time interval, wound size for each animal is expressed as a fraction of the original wound size, multiplied by 100, and plotted as percentage of original wound size.

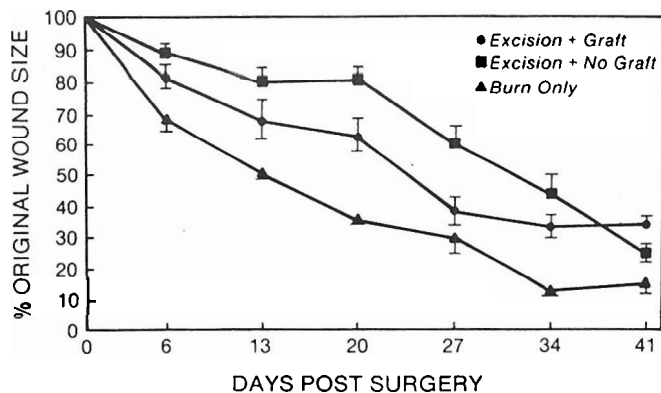
Semi-quantitative evaluation of wound healing in excised burns was made by determining the time in weeks to spontaneous detachment of the Biobrane dressing from the wound of each animal.

Data for each experimental condition were analyzed as the mean  $\pm$  standard error of the mean (SEM) and submitted to pairwise comparison by Student's T test. P values derived from the T test are expressed at the lowest calculated limits. Statistical significance was assumed at  $p < 0.05$ .

## Results

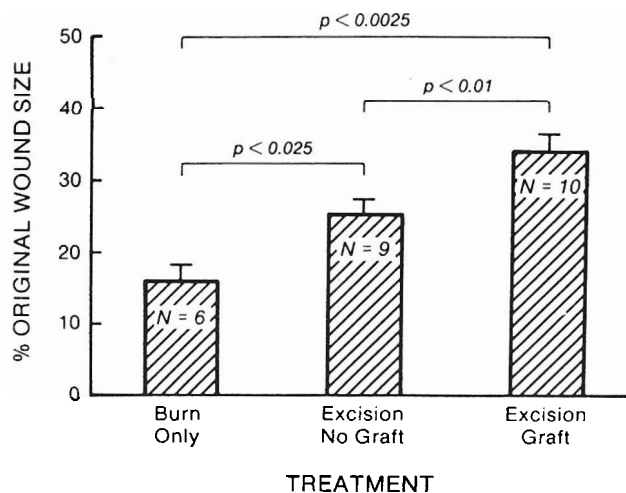
Animals included in the study had no apparent secondary complications or infections during the period of observation. Animals were weighed before treatment and at each dressing change. During the first week post-surgery, a slight weight loss was observed, but general recovery of the animals was reflected by steady gain of weight thereafter.

**Wound size vs. time.** Determination of wound size vs. time for conditions in which animals received burns is shown in Fig 2. All burns contracted, whether or not excised. Untreated burns contracted most rapidly and to the greatest degree ( $p < 0.0005$ , compared to subcutaneous implantation). Wound size of untreated burns had stabilized between five to six weeks of observation. Burns that were excised and covered with Biobrane, whether grafted or not grafted, contracted more slowly than non-excised burns. Burns that were excised and not grafted contracted most slowly and wound contraction had not stabilized by the end of the observation period. Wound size of grafted burns had stabilized by four to five weeks post-surgery.



**Fig 2.** Wound size vs. time. Comparison of wound sizes (mean  $\pm$  SEM) at six, 13, 20, 27, 34, and 41 days post-treatment with: burn excision, graft, Biobrane ( $\bullet$ ); burn, excision, no graft, Biobrane ( $\blacksquare$ ); burn only, no excision ( $\blacktriangle$ ). All wounds contract vigorously. Excised wounds covered with Biobrane show delayed contraction compared to non-excised burns. Wound size at day 41 had stabilized in grafted, excised burns ( $\bullet$ ) and in non-excised burns ( $\blacktriangle$ ), but not in excised, ungrafted burns ( $\blacksquare$ ).

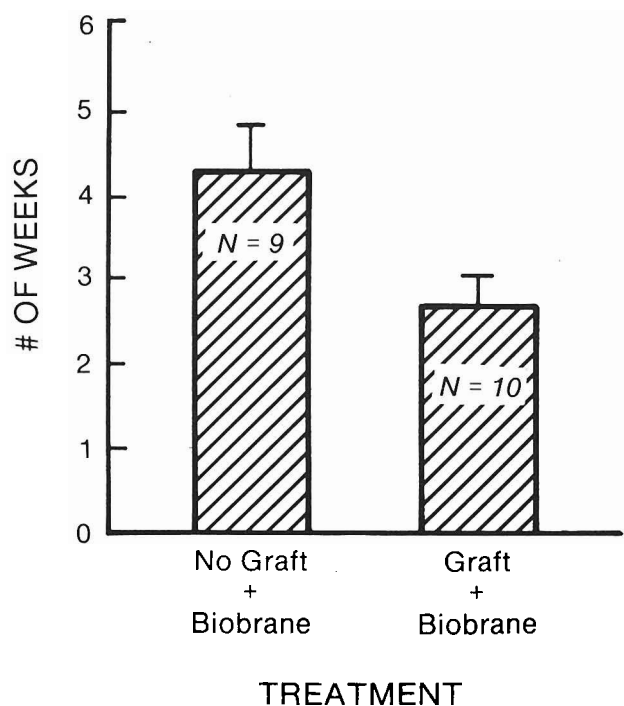
**Wound size at day 41.** Differences of wound size among the tested conditions at 41 days post-treatment are shown in Fig 3. Wounds healed after a treatment of burn only had contracted to  $16.15\% \pm 2.24$ . Excision of burn eschar without grafting resulted in a wound size of  $25.38\% \pm 2.16$ . Grafting with collagen-GAG dermal substitutes resulted in a wound size of  $34.11\% \pm 1.94$ . Statistical significance (P values) among pairs of treatments at 41 days post-treatment is also shown in Fig 3; burn only vs. excision and no graft,  $p < 0.025$ ; excision and graft vs. excision and no graft,  $p < 0.01$ ; burn only vs. excision and graft,  $p < 0.0025$ . Pairwise comparison of each condition to each other condition demonstrates statistical significance of all treatment conditions at acceptable levels of confidence.



**Fig 3.** Wound size at post-surgical day 41. Comparison of percentage of original wound size (mean  $\pm$  SEM) after treatments as indicated: (left) burn only,  $16.15\% \pm 2.24$ ; (center) excision, no graft,  $25.38\% \pm 2.16$ ; (right) excision, graft,  $34.11\% \pm 1.94$ . P values of pairwise comparison of the treatments demonstrates statistical significance ( $P < 0.05$ ) between each pair of conditions.

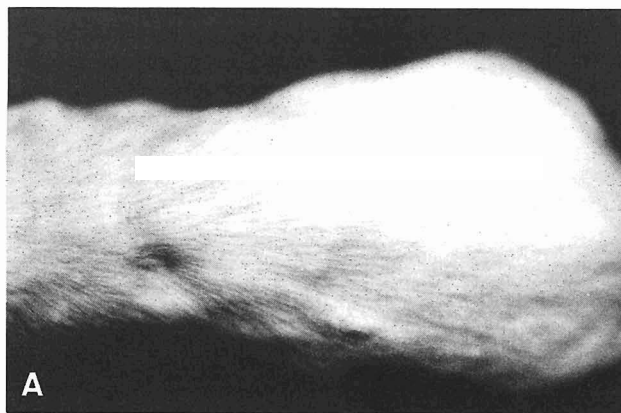
**Time to wound closure.** Wound dressings adhere initially to the wound bed or to newly applied grafts by interaction with coagulum from the treated wound. Re-epithelialization of the wound results in the release of the coagulum and of the adhered dressing. Therefore, spontaneous detachment of the dressing, Biobrane, from the treated wound was used in this study as a semi-quantitative index of wound closure by re-epithelialization.

Comparison between grafted and ungrafted wounds of the average post-surgical time in weeks to spontaneous detachment of the Biobrane dressing is shown in Fig 4. Biobrane detached from grafted excised burns in an average time of 2.7 weeks and from ungrafted excised burns in an average of 4.3 weeks.



**Fig 4.** Time to wound closure. Average post-surgical time in weeks to spontaneous detachment of Biobrane from excised wounds: no graft plus Biobrane (left), 4.3 weeks; graft plus Biobrane (right), 2.7 weeks. Detachment of Biobrane represents closure of the wound due to re-epithelialization.

**External appearance at day 41.** External appearance of animals 41 days after treatment is shown in Fig 5. Subcutaneous implantation of the collagen-GAG grafts results in no appreciable change of the overlying skin, except that it is slightly raised even at 41 days post-surgery (Fig 5A). Grafted wounds exhibit a smooth surface, are pink in color, and are soft to the touch (Fig 5B). Ungrafted wounds are raised, rough, and pink to red in color. Animals that received burn only develop a narrow, reddened, and contracted scar at day 41 (not shown).



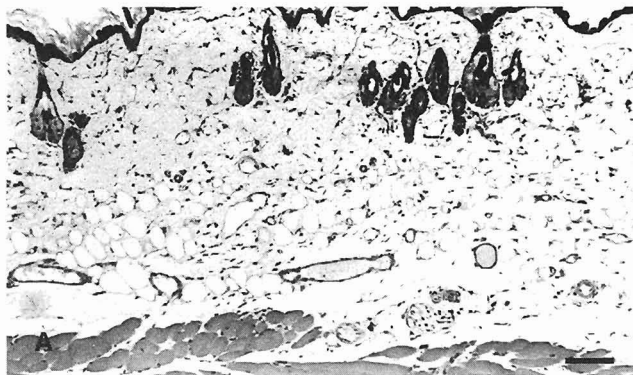
**Fig 5A**



**Fig 5B**

**Fig 5.** External appearance at post-surgical day 41. **A.** Subcutaneous implantation of graft shows no necrosis or contraction of overlying skin. **B.** Excision and graft, healed wound is smooth, flat, soft, pink, and pliable.

**Histologies at day 41.** Histological examination of healed burns is shown in Fig 6. Subcutaneous implantation of collagen-GAG grafts produces no evidence of inflammatory infiltrate, encapsulation or necrosis of tissue adjacent to the implanted graft. Skin over the implant (Fig 6A) exhibits normal histological organization including preservation of hair follicles, sebaceous glands, and piloerector muscles. The epidermis consists of about two to three cell layers. Excised burns repaired by grafting with a collagen-GAG dermal substitute are



**Fig 6A**

shown in Fig 6B. Grafted wounds result in complete restoration of the dermal and epidermal components of the skin. Healed connective tissue of the wound is characterized well by the term "neo-dermis."<sup>12</sup>

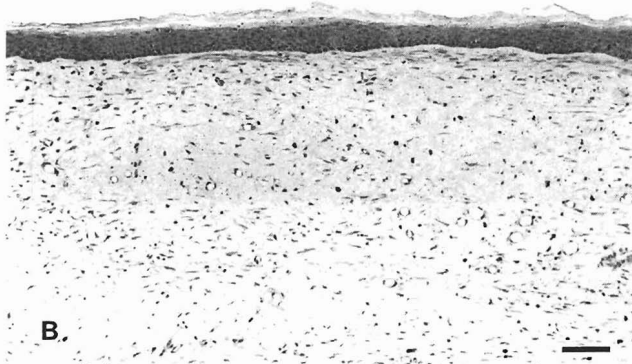


Fig 6B

No evidence of inflammatory infiltrate is seen and the tissue density — including vascular supply, distribution of fibroblasts and extracellular matrix — is uniform across the width of the wound. Blood vessels are observed within only a few cell diameters of the dermal-epidermal junction. The epidermis, which has healed from the wound margins, is uniformly about six to eight cells in thickness and somewhat hypertrophic compared to undamaged epidermis. Epidermal adnexi (hair follicles, sweat and sebaceous glands) are absent, but histiotypic stratification, differentiation, and desquamation are present.

Excised burns that were not grafted (Fig 6C) are sometimes not completely re-epithelialized by 41 days post-surgery. In this example, remodeling of the connective tissue beneath the dried coagulum and migrating epithelium continues at day 41. Blood vessels seem to be of larger diameter and to occur at higher frequency than in grafted wounds, although vessel diameters were not quantitated in this study. Increased number and size of blood vessels could account for the generally more red-

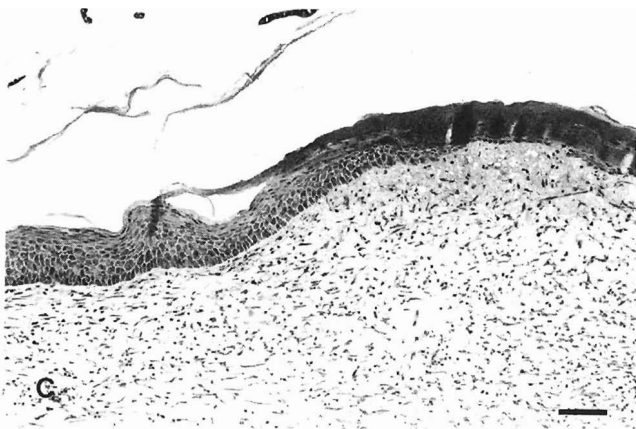


Fig 6C

dened color of the healed, ungrafted wounds. The epidermis is hypertrophic but of less uniform thickness than in grafted wounds; its convoluted external surface accounts in part for the rough appearance seen on gross examination.

Histological appearance of wounds that have healed after a treatment of burn only is shown in Fig 6D. Compared to surrounding undamaged tissue, the repaired wound site generally is raised, more narrow in width than excised wounds, and exhibits a hypertrophic epidermis similar to healed, excised wounds. Regenerated connective tissue is comparable to both grafted and ungrafted wounds in distribution of fibroblasts and connective tissue matrix. However, similar to ungrafted excised wounds, the reddened color of healed non-excised burn may be accounted for by the apparently greater number and size of blood vessels than in grafted excised burns.

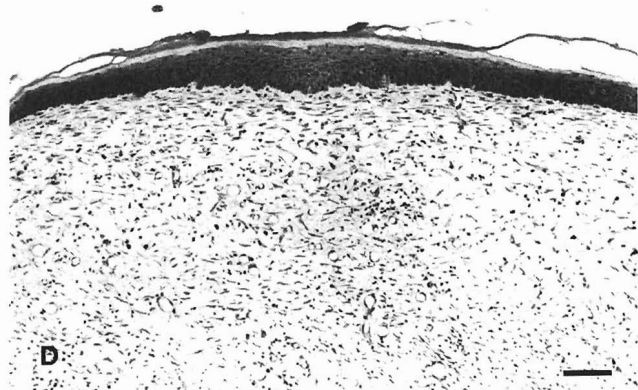


Fig 6D

**Fig 6.** Histologies at post-surgical day 41. A. Subcutaneous implantation of graft shows no necrosis of overlying skin and no encapsulation of implanted graft. B. Healed wounds after excision of eschar and application of the collagen-GAG graft plus Biobrane. Surface is flat (co-linear with the undamaged skin of the wound margin) and epidermis is fully stratified and differentiated but lacks adnexal structures. Regenerated dermis has no inflammatory infiltrate and resembles undamaged dermis. C. Incompletely healed wound after excision of eschar and application Biobrane without graft. Epidermal keratinocytes migrate over healing dermis and under dried exudate. Irregular thickness and external contour of the hypertrophic epidermis accounts partially for the rough surface of ungrafted excised burns. D. Non-excised burns heal to produce raised tissue with hypertrophic epidermis and dermis that contains a high frequency of large diameter vascular vessels. Scale bar = 1 mm.

## Discussion

For decades, conventional treatment of full-thickness skin loss injuries has been application of meshed split-thickness autograft. Although this practice is very effective, cases of very large total body surface area (TBSA) skin loss from burns often lack sufficient donor sites to complete the grafting process before secondary complications, usually sepsis, result in mortality.

Split-thickness meshed autografts provide some dermis and a source of epidermis that can be expanded by less than 10-fold to close excised full-thickness skin loss injuries. Consequently, with large TBSA burns, multiple reharvesting of donor sites is performed, which requires repeated surgeries, additional trauma to the patient, and extended hospitalization. For these reasons, development of a substitute for autograft represents a major advance in the treatment of full-thickness burns.

Materials used as permanent skin substitutes must meet the same criteria as temporary skin substitutes and wound dressings. Namely, these materials must be safe, effective, predictable, and available. Standardized procedures should be used for preparation, for evaluation of consistency of composition, and for sterilization. De-epidermized dermis has been used therapeutically<sup>8,9,19</sup> and as a model of skin reconstructed in vitro,<sup>20</sup> but consistency of composition of these ex vivo tissue derivatives is variable at best. They also carry the risk of transmission of disease and their availability is subject to limitation of supply from tissue banks.

Conversely, preparations in vitro of dermal skin substitutes by reproducible procedures have been developed<sup>7,12,13,21</sup> that allow uniform structural and biochemical composition of implanted materials to enhance predictability of results in vivo. These deliberately prepared implants are truly plastic materials and can be modified structurally (to optimize their physical properties for specific applications) and biochemically (for controlled release drug delivery or promotion of tissue regeneration with decreased scarring). Furthermore, collagen-GAG dermal substitutes may be stored in the dry state for extended periods of time, which allows its accumulation and maximizes availability. This study also demonstrates a beneficial effect of collagen-GAG dermal skin substitutes on reduced wound contraction.

Although several models for skin replacement have been described,<sup>5,7,8,22</sup> there is a lack of quantitative analysis of the materials in vivo regarding their effects on wound contraction as an index of wound repair. Use of any kind of skin substitute may be limited dramatically if the final outcome leads ultimately to loss of function from scarring or to a cosmetic result that does not compare favorably with conventional autograft. To become the conventional treatment for full-thickness burns, skin substitutes must provide both short- and long-term improvements in wound repair compared to autograft. The present study begins to provide the quantitative data needed to substantiate qualitative improvements.

Low immunogenicity of collagen-based implants may be expected to increase the probability of acceptance onto the woundbed. In this study, subcutaneous implantation of the collagen-GAG dermal skin substitute resulted in lack of encapsulation or fibrosis and absence of inflammatory infiltrate. Absence of the implant by histological examination of surrounding tissue after 41 days implies its resorbance. Rate of resorbance is a function both of the mass per unit volume of the implant and of the degree of cross-linking with glutaraldehyde (in this example). Although rate of resorbance may have an important

impact on the qualities of the tissue that regenerates around the implant, no studies have yet been performed to determine this rate.

Relatively large amounts of wound contraction were observed in all conditions in which burns were administered. However, the panniculus carnosus of mice contributes to more aggressive wound contraction than occurs in humans.<sup>23</sup> In addition, grafts used in this study did not contain an epithelial component; regenerated epidermis migrated over the healing wound from the wound margins. Nonetheless, results of gross appearance and histological examination indicate that this graft can promote the regeneration of connective tissue from the woundbed and also support the reestablishment of a fully stratified epidermis from the wound perimeter. Reepithelialization during healing can contribute to wound contraction;<sup>21</sup> therefore, replacement of the epidermal component of the skin during the grafting process may further reduce wound contraction by reducing the need for epithelial wound closure from the wound perimeter.

Contraction of ungrafted wounds had not stabilized by the end of the 41-day observation period. Application of Biobrane to full-thickness skin defects has been shown to delay wound contraction in rats,<sup>25</sup> but this delay only extends the time of contraction and does not reduce the total amount of contraction. Therefore, ungrafted excised burns that are covered with Biobrane may be expected to continue to contract to the same final wound size as non-excised burns. In comparison, grafted wounds had stabilized in size by day 27 to 34. Based on these premises, the relative size of ungrafted wounds would be expected to decrease compared to grafted, excised burns with longer periods of observation than were used in this study.

## Conclusion

A dermal skin substitute that can be deliberately formulated, prepared, sterilized, and stored has been shown to reduce contraction of excised full-thickness burns compared to ungrafted excised burns and to non-excised burns in a murine model over a 41-day period of observation. Subcutaneous implantation of the graft was not immunogenic and resulted in its resorption.

The dermal substitute promoted the regeneration of connective tissue from the woundbed and supported the re-establishment of a fully stratified and differentiated epidermis without adnexal structures. Dermal skin substitutes of bovine collagen and chondroitin-6-sulfate meet many of the criteria as part of an alternative to skin autograft in treatment of skin loss injuries.

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