World J. Surg. 14, 819–824, 1990

World Journal of Surgery

Progress in Burn Treatment and the Use of Artificial Skin

Ronald G. Tompkins, M.D., Sc.D., and John F. Burke, M.D.

Surgical and Trauma Services, Massachusetts General Hospital, Department of Surgery, Harvard Medical School, Boston, Massachusetts, U.S.A.

Recently improved survival from thermal injuries has been demonstrated both in children and adults. This increase in burn injury survival rates is the result of multiple changes in treatment; probably the most important changes are, first, a more aggressive management of the wound with prompt excision of devitalized tissues and immediate closure of the wound, and, second, a better understanding and management of metabolic, immunologic, and nutritional aspects of the injuried patient. Artificial skin is a very important additional treatment modality that has more recently become available and promises to contribute significantly to improvements in wound management and survival rates by its ability to physiologically close a burn wound immediately after its excision.

The consequences of thermal injury with the greatest contribution to the mortality rate are the immunometabolic and bacterial sequelae of a large, open wound. These effects of the open wound are magnified by other factors including depletion of the patient's host resistance by the injury and by malnutrition. The combination of all these factors results in a life-threatening infection originating in the burn wound itself. Systemic antibiotics, topical wound therapy, and gentle wound debridement representing traditional burn therapy do not eliminate the sequelae of open wounds and their consequences. A more realistic approach is the rapid excision of devitalized tissue and closure of the wound immediately following excision. This approach requires rigorous protection of the wound from cross-infection and attention to nutritional requirements to avoid total caloric or protein malnutrition. Physiological closure of the wound is as important as excision because although excision removes the dead and bacteria-containing tissues and may eliminate systemic toxic effects produced by these tissues, the metabolic and bacteriologic problems of an open wound persist.

Prompt excision and immediate wound closure are methods that may be easily employed in the small and moderate-sized burns (<50% body surface area) because sufficient donor skin is available for wound closure. In large or massive burns (≥50% body surface area), however, wound closure using physiologically acceptable materials is far more difficult because of an inadequate supply of available donor skin as autografts and a limited time interval before allografts are rejected by the host in the absence of immune suppression. When these transplants are rejected, open wounds (and all their attendent problems) are again created. Because immediate wound closure in large and massive thermal injuries is a major problem, artificial skin was developed to obtain physiologic wound closure immediately after injury.

Supported in part by the National Institutes of Health grants GM 21700 and GM T32-07035.

Reprint requests: Ronald G. Tompkins, M.D., Sc.D., Trauma Services, Bigelow 13, Massachusetts General Hospital, Boston, Massachusetts 02114, U.S.A.

Progress in Burn Treatment

Prompt Excision and Immediate Wound Closure

Significant improvements in the treatment of thermally-injured patients has occurred over the past 10–15 years leading to significant improvements in the expected survival rates in adults [1, 2] and particularly in children [3, 4]. In children, average mortality has declined from 9% to 1% or 2.5% of admissions [4]. Infants less than 1 year of age survive as well as other children and young adults. Dramatic improvement in survival has occurred in patients with large or massive injuries (≥50% body surface area) as shown in Fig. 1 [4]. Since 1979, mortality from thermal injury in children involving less than 70% body surface area area has been essentially eliminated and survival rates for children with greater than 80% body surface area injury is now substantial (78%).

In adults, the improvement in survival rates are less dramatic than in children but are nonetheless significant as seen in Table 1 [2]; survival rates from major injuries in adults are confounded by the influences of coexistent aging processes. In adults, mortality has declined from 24% to 7% of adult admissions over the time period of 1974 to 1984 [2]. In adults, younger patients (<40 years old) have greater expectations of surviving large and massive thermal injuries (≥50% body surface area) and older patients (≥60 years of age) are more likely to survive small and moderate-sized burns. Even in adults, the expected survival from massive burns (≥70% body surface area) has doubled from 24% to 48% [5].

These improvements in survival may not be attributed to any single factor but are probably the results of many changes in therapy over the years [6, 7]. These include: (a) improved resuscitation techniques, (b) new methods in anesthesia man-

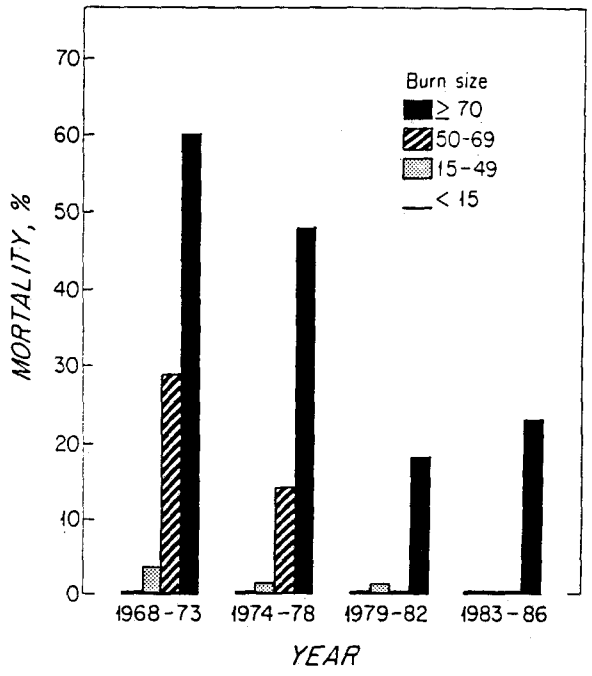

Fig. 1. Mortality rates for 1,674 children admitted to the Shriners Burns Institute (Boston unit) versus time by burn size. Mortality has markedly declined in the massive burn size group (≥ 70% body surface area) and has essentially been eliminated in moderate and large burn sizes (15–69% body surface area) during the most recent time period. Reprinted with permission [4].

agement and respiratory care, (c) better understanding and attention to metabolic and nutritional requirements, and (d) improved infection control methods such as patient isolation, topical antimicrobials, and systemic antibiotic therapies. The individual contribution of the treatment method of prompt eschar excision and immediate wound closure is not exactly known because large, prospective, randomized clinical trials in patients with large thermal injuries have not been conducted. Multiple smaller prospective trials and retrospective studies have been carried out at the University of Washington [8, 9], University of California [10], and the Shriners Burns Institutes of Galveston [3] and Boston [11, 12]. These studies demonstrate that prompt excision does shorten hospital stay. Although an improvement in survival may be controversial, these trials demonstrate a diminished morbidity as evidenced by a decreased incidence of septic complications and a decrease in catabolism and immunological deficiences [13]. In addition, several centers have reported improvements in long-term function and cosmesis leading to a decreased incidence of reconstructive procedures [9, 13].

With this demonstrably increased likelihood of survival, after injury, it is becoming more important to focus attention on improving the quality of life by improving the long-term functional and cosmetic results. We feel strongly that the initial phase of acute burn care should accomplish both a definitive functional and cosmetic repair of the injury in addition to a physiological closure of the burn wound. Although wound closure represents a life-saving measure in itself, immediate wound closure should begin the functional and cosmetic repair and not leave this important aspect of care to secondary operations. This can be accomplished during acute hospitalization by multiple efforts including: (a) proper planning of donor sites and saving some donor regions for covering the face or hands when practical, (b) using nonmeshed grafts for closing all excised areas of less than 20% body surface area, (c) excising areas strongly dependent on cosmesis and/or function as early as possible once the acute threat to survival has been resolved, and (d) perhaps most importantly, excising wounds as early as possible after injury in an effort to prevent the establishment of inflammation and increased scar formation which is the inevitable consequence of the long-standing open wound.

Progress in Artificial Skin

Requirements

An approach to skin replacement was taken by Burke and Yannas that incorporates a combination of biological and mechanical aspects [14–19]. A composite open lattice membrane was selected whose fibers were composed of collagen and chondroitin 6-sulfate [a glycosaminoglycan (GAG)]. This membrane is mechanical in origin, but after implantation, the membrane becomes incorporated into the patient via cellular invasion of the lattice by cells from the wound itself. This latter property is important because purely mechanical skin replacements are doomed to failure as a result of the bacteriologically unprotected surface location of skin substitutes. This constant exposure to the environment results in bacterial colonization within the implant and at the interface of the implant and the host tissue. Since host antibacterial defenses are usually defective at the prosthesis-tissue interface (for poorly understood reasons), failure from sepsis is inevitable. In order to avoid failure from sepsis, it was, therefore, necessary to use prosthetic materials that were transformed from an implanted membrane that was purely mechanical to a biologic replacement tissue that closely resembled normal dermis and participated in normal antibacterial processes. During this transformation, from a purely mechanical to a purely biologic skin replacement, the implanted mechanical membrane must be completely biodegraded and leave a tissue replacement that consists solely of host tissues.

Replacement of the dermal component of skin is equally important, if not more important, than replacement of the epidermis because it is the dermis that provides mechanical integrity and stability to the skin and that eliminates the host's inflammatory response. It is well known that dermis does not regenerate its normal anatomy during usual wound healing without a template (a collagen-GAG matrix with a 3-dimensional structure resembling that of normal dermis). We have observed, however, that if the fibroblasts synthesizing new connective tissue in a healing open wound could be induced to reproduce the 3-dimensional structure of dermis and not the 3-dimensional structure of scar, a tissue would be produced that acted like dermis and not like scar, i.e., a "neodermis" [20]. The mechanical open fibrous membrane described above is made with its fiber structure resembling dermis and, when transplanted in an excised wound, this membrane acts as a template to provide 3-dimensional anatomic information to incoming fibroblasts. Newly synthesized connective tissue matrix is laid down on the slowly-degrading scaffolding of the

Table 1. Survival statistics in categories by age and burn size.

Burn size (% body surface area)	Age (yr)	Massachusetts General Hospital 1974–1977	Massachusetts General Hospital 1979–1984	Curreri et al. [27] 1979	Feller et al. [28] 1976	Bull [29] 1971
20	20	98	99	95	95	95
	40	97	99	95	95	90
	60	89	95	80	65	80
40	20	90	96	85	85	80
	40	83	93	80	70	70
	60	55	75	40	18	30
60	20	70	86	60	50	50
	40	56	76	50	30	30
	60	23	44	7	0	0

Adapted from Reference 2 with permission.

implanted membrane and provides a replacement tissue resembling the 3-dimensional structure of dermis rather than scar. In the absence of this template, dermis is replaced by scar and wound closure is simply the result of scar contracture. Wound closure by scar contracture is probably the result of evolutionary processes. These processes have resulted in survival from what would otherwise be a lethal injury; however, a more ideal solution to the problem of tissue replacement is that of regeneration of the normal anatomy in the absence of an inflammatory reaction and avoidance of scar formation.

This dermal template may also be provided by transplantation of skin from other individuals as with allografts; however, current methods of transplantation require immunosuppression to allow acceptance of this foreign tissue and to avoid immunological rejection. Although immune suppression in patients with potentially lethal injuries may be successful [21, 22], this approach is not an ideal solution to the problem because immune suppression potentially exposes patients to an even greater risk of bacterial invasion and sepsis.

Replacement of lost skin initially with the mechanical dermal template was necessary because regeneration of local tissues is a very slow process and does not provide survival value in these potentially lethal injuries as rapidly as is necessary. Following a major cutaneous injury, 2 major and immediate threats to survival are bacterial invasion and massive fluid losses; these consequences of the open wound must be addressed early after injury. Although regeneration of local tissues may be the best long-term solution to achieve skin integrity and optimal function, clinical wound closure must be achieved shortly after injury and well before regeneration is possible to insure survival. In this regard, until basic science techniques to promote rapid tissue regeneration are available, the use of artificial skin to provide an immediate, physiological wound closure with the subsequent development of a "neodermis"appears to be the only practical and clinically successful solution to the problem of wound closure in the absence of sufficient host skin.

Skin replacement materials must have many additional properties. The skin replacement must allow cellular migration (e.g., endothelial cells and fibroblasts) into the membrane and promote the formation of new connective tissue elements within the membrane. The material should be biodegradable such that the membrane will be completely replaced by regenerated host tissues. Although the membrane may be man-made and nonviable, it must have mechanical properties similar to the tissue that it replaces. Finally, the initial mechanical prosthesis must eventually evolve in its final mature stages to become viable tissue that participates in the constant biological processes of tissue remodeling, wound healing, bacterial defense, and, if required, tissue growth. And, above all, the tissue substitute should be immunologically acceptable to the host and should not initiate the process of immunological rejection which results in the short-term loss of the grafted substitute and, in the long-term, contributes to scar formation.

Development

The development of artificial skin primarily involved design of a membrane that prevented bacterial invasion and passively regulated the physiologically normal escape of moisture from the wound bed. Although these were the essential design goals, many other characteristics of skin including both physical and biological properties were necessarily incorporated into the design [14, 15, 23–25].

The current artificial skin is a bilayer, polymeric membrane comprising an upper layer of silicone and a lower layer of highly porous cross-linked collagen-chondroitin 6-sulfate matrix [14, 15]. This polymeric bilayer represents a stage 1 membrane which may be applied to a clean, freshly excised wound bed and provide physiological wound closure. After 2 weeks and up to 12 weeks, the upper silicone layer is peeled away and a very thin (<0.003 inch thickness) epidermal autograft is placed on this "neodermis." The neodermis represents the collagen-chondroitin 6-sulfate matrix that has become incorporated into the wound bed and allowed migration of endothelial cells and fibroblasts into the matrix. New extracellular substances (glycosaminoglycans and collagen) have been synthesized in the neodermis and the artificial collagen has begun to be biodegraded. Successful "take" of thin epidermal grafts on this membrane has been uniformly excellent. Stage 2 membrane, which remains in an early developmental form, represents the collagen-chondroitin 6-sulfate matrix that has been seeded with autologous epidermal cells before the dermal template is placed on the wound. Stage 2 membrane, therefore, contains all the necessary elements (dermal and epidermal) for skin regeneration.

Physical Properties. Reproduction of physical properties of skin was important in the developmental phases of stage 1

membrane. Some important features include: (a) fluid flux, (b) pore structure, (c) impermeability to bacteria, and (d) handling properties such as wetting, rigidity, suturing characteristics, and peel strength. An extremely important physical property of the artificial skin was to achieve an optimal rate at which moisture travels from the wound bed through the membrane. The normal human physiological rate of moisture flux is 0.5 mg/cm^2 per hour [23]. A rate significantly higher than this physiological rate leads to dehydration of both the wound bed and the artificial skin. Dehydration results in a loss of "wetting" of the wound bed (ability to form an air-free and intimate interface between membrane and wound in all areas). In other words, wrinkles form and sepsis and graft loss ensues. On the other hand, if the moisture flux is significantly lower than the normal rate, then water accumulates at the graft-host interface and edema formation undermines the attachment of the artificial skin to the wound bed.

Other physical properties had strong biological implications such as the average pore size (average distance between collagen-chondroitin 6-sulfate bundles in the lattice structure of the dermal template). It became apparent that migration of the host cellular elements (e.g., endothelial cells and fibroblasts) into the dermal template depended on the chemical composition of the matrix and also its physical dimensions. Initial attempts at skin replacements with an average pore size of 10 μm were unsuccessful, whereas artificial skin with an average pore size of 50 μm allowed prompt access of cells to the matrix. Control over the resultant average pore size was achieved by proper conditions of coprecipitation of the collagen-chondroitin 6-sulfate matrix. Similarly, wetting was an extremely important feature because air pockets or dead spaces that were inadvertently created at the membrane-wound interface led to local sites of bacterial proliferation and local sepsis. It was, therefore, necessary to design a membrane which wet efficiently; in other words, the membrane intimately contacted the wound bed and displaced air from the membrane-wound interface as it spread over the wound bed. The mechanical property governing this interaction is surface energy; proper design required conditions in which the surface energy of the membrane-wound interaction was lower than a membrane-air interaction. Once the surfaces were in apposition and attached, proper design considerations required that the forces required to dislodge this attachment (such as peeling forces) should be greater than that usually encountered with dressing changes and the limited active and passive postoperative activities. Balancing these design considerations for pliability was the property of rigidity that was required in order for the artificial skin to hold sutures. These and other design considerations were necessarily incorporated into the artificial skin [23–25].

Biological Properties. The biological properties that were important included: (a) low or absent level of antigenicity and minimal or absent host inflammatory response, (b) cellular interaction with the host that allowed not only migration but attachment of fibroblasts and secretion of new connective tissue matrix within the dermal template, (c) biodegradation at a controlled rate into nontoxic metabolic products, and (d) absence of scar formation [23–25].

Biodegradation, antigenicity, porosity, and mechanical strength of the composite were optimized using a collagen-GAG coprecipitate as the dermal template. Bovine collagen (primarily type 1) was selected because of its low level of antigenicity, relatively well-understood physical properties, and stability after a very high degree of purification. Coprecipitation of the collagen with GAG allowed inhibition of collagenase degradation without increasing the rigidity or brittleness of the matrix. Collagenase is the primary enzyme that is active in biodegrading the collagen matrix in vivo. In addition, collagen-GAG membranes have a higher modulus of elasticity (tensile strength) and higher energy of fracture than collagen alone. Additional stability can be achieved by formaldehyde or glutaraldehyde cross-linking; however, such covalent cross-linking leads to a brittleness in the heavily treated fibers. Addition of GAG to collagen together with mild covalent cross-linking with glutaraldehyde, therefore, allowed not only control of the rate of biodegradation of the dermal template but also control over the mechanical behavior of the matrix. The additional feature of porosity which was described earlier as being important in cellular migration into the matrix is easily controlled with adjustment of collagen to GAG ratios in the coprecipitates. Chondroitin 6-sulfate, of the glycosaminoglycans evaluated, demonstrated an optimal inhibition of collagenase and acceptable tensile properties. A final but important consideration was that degradation products of the collagen-GAG dermal template were nontoxic.

Stage 1 artificial skin is a 2-layer composite membrane that is similar to dermis and epidermis in its appearance. The dermal portion is a coprecipitate of bovine collagen and chondroitin 6-sulfate. The average pore size is 50 $\pm$ 20 μm (mean $\pm$ SD). This dermal template coprecipitate is sterilized by a cross-linking step by heating the freeze-dried matrix to 105°C and immersing the coprecipitate into a glutaraldehyde solution [14]. The temporary epidermal portion is a conventional medical grade silicone membrane (100 μm thickness) which controls the water flux to 1–10 mg/cm^2 per hour. This silicone is aseptically applied as a liquid monomer onto the dermal template; bonding between the silicone and collagen-GAG occurs as curing takes place. The bilayer is stored in polyethylene bags either in 70% isopropyl alcohol or in a freeze-dried form. The freeze-dried membranes may be maintained indefinitely and then be available for use within minutes.

Clinical Results

Treatment with artificial skin has been suggested to demonstrate survival value in children [15] and in adults, the experience is smaller but shows an adjusted odds of dying of 0.52 [5]. In other words, in adults, the likelihood of dying was reduced to half the likelihood of dying without artificial skin treatment. It was estimated, based on this experience [5], that an estimated 160 adult patients will be necessary to show statistical significance in the treatment of artificial skin. As artificial skin becomes more readily available and clinical experience with its use increases, the survival value of artificial skin may become more apparent.

From the clinical experience now available, we see that immediate wound closure with artificial skin is now possible and that the dermal template becomes incorporated into the patient's tissues without the host's immune rejection reaction [14–16, 19, 20]. Inflammation has not been seen; no extensive

foreign body reactions or inflammatory infiltrates have been observed either at the interface of the dermal template and the wound bed or within the dermal template itself. Synthesis of a neovasculature and new extracellular matrix within the dermal template has been observed. Using serial biopsy examinations, small tufts of young connective tissue may be observed at the lower margins of the dermal template in the very early phases after placement. Endothelial-lined vessels may be seen within the neodermis by 1 week and, by 14 days, a cellular infiltrate of new connective tissue may be easily seen extending to the upper two-thirds of the neodermis. Later biopsies demonstrate resorption of the original dermal template, replacement of the template with normal dermal architecture, and an absence of solidly-packed collagen bundles that are characteristic of scar. These histological findings are confirmed clinically by the elastic nature of the healed wound without noticeable wound contracture.

Complications associated with the use of artificial skin have been minor in nature and involve loss of the grafted artificial skin by hematoma formation, wrinkling, and focal sepsis. The incidence of these complications has been quite low [5, 15, 19, 26]. Hematoma, wrinkles, and focal sepsis have usually involved only a small proportion of the artificial skin segment and have been treated by local measures. Subsequent "take" of epidermal autografts in these regions has been normal.

In summary, artificial skin has been successful in its early clinical experience. Artificial skin, an off-the-shelf material, now makes it feasible to achieve immediate and permanent wound closure even in massively burned patients without immunosuppression and rejection. Long-term results demonstrate that artificial skin is incorporated into the tissues, is biodegraded, and eventually replaced by dermis with normal architecture not resembling scar. Likewise, these long-term results appear to demonstrate an elasticity and durability of artificial skin that more closely resembles normal skin than autograft, although it is too soon to assess a reduction in scar formation and eventual wound contracture. Early results are extremely encouraging but await careful, detailed studies on survival and eventual cosmetic and functional results.

The basic treatment method of prompt excision and immediate wound closure accompanied by metabolic and immunologic support have markedly improved the expected survival following extensive burn injuries. The development of artificial skin, although its use is not extensive enough thus far to provide solid evidence, promises an ability to physiologically and cosmetically close the most extensive burn wounds immediately after injury. This ability will lead to further increases in survival rates as well as lead to improvements in both functional and cosmetic outcomes following extensive burn injury.

Résumé

On a démontré récemment l'amélioration du taux de survie après lésions thermiques à la fois chez les enfants et chez les adultes. Cette augmentation des taux de survie dans les lésions par brûlures est due aux nombreuses améliorations du traitement. Les changements les plus importants sont probablement d'abord une attitude plus agressive de la lésion avec excision immédiate du tissu dévitalisé et fermeture rapide de la lésion, puis compréhension et traitement meilleurs des aspects métaboliques, immunologiques et nutritionnels du patient. La greffe de peau est un adjuvant trés important qui s'est améliorée depuis peu de temps. Elle laisse entrevoir des progrès significatifs dans le traitement de la lésion et le taux de survie grâce à ses possibilités de fermeture physiologique d'une brûlure juste après l'excision.

Resumen

Recientemente se ha registrado una mayor supervivencia en pacientes con quemaduras, tanto en adultos como en niños. Tal incremento en las tasas de sobrevida es el resultado de múltiples modificaciones en el tratamiento de las quemaduras. Probablemente las modificaciones más importantes son, en primer lugar, un tratamiento más agresivo de la herida, con remoción precoz del tejido desvitalizado y la cobertura inmediata, y, en segundo lugar, una mejor comprensión y manejo de los aspectos metabólicos, inmunológicos, y nutricionales del paciente quemado. La piel artificial representa una muy importante modalidad terapéutica adicional que recientemente ha llegado a estar disponible y que promete ser un avance significativo en el manejo de la quemadura para el logro de mejores tasas de sobrevida, gracias a su capacidad de lograr el cierre fisiológico de la herida por quemadura inmediatamente después de realizada la resección.

References

1. Demling, R.H.: Improved survival after massive burns. J. Trauma *23*:179, 1983
2. Tompkins, R.G., Burke, J.F., Schoenfeld, D.A., Bondoc, C.C., Quinby, W.C., Behringer, G.C., Ackroyd, F.W.: Prompt eschar excision: A treatment system contributing to reduced burn mortality. Ann. Surg. *204*:272, 1986
3. Herndon, D.N., Gore, D., Cole, M., Desai, M.H., Linares, H., Abston, S., Rutan, T., van Osten, T., Barrow, R.E.: Determinants of mortality in pediatric patients with greater than 70% full thickness total body surface area thermal injury treated by early total excision and grafting. J. Trauma *27*:208, 1987
4. Tompkins, R.G., Remensnyder, J.P., Burke, J.F., Tompkins, D.M., Hilton, J.F., Schoenfeld, D.A., Behringer, G.C., Bondoc, C.C., Briggs, S.E., Quinby, W.C.: Significant reductions in mortality for children with burn injuries through the use of prompt eschar excision. Ann. Surg. *208*:577, 1988
5. Tompkins, R.G., Hilton, J.F., Burke, J.F.: Increased survival after massive thermal injuries in adults: A preliminary report using artificial skin. Crit. Care Med. *17*:734, 1989
6. Tompkins, R.G., Burke, J.F.: Burn therapy 1985: Acute management. Int. Care Med. *12*:289, 1986
7. Demling, R.H.: Burns. N. Engl. J. Med. *313*:1389, 1985
8. Gray, D., Pine, R.W., Harnar, T.J., Marvin, J.A., Engrav, L.H., Heimbach, D.M.: Early excision versus conventional therapy in patients with 20 to 40 percent burns. Am. J. Surg. *144*:76, 1982
9. Engrav, L.H., Heimbach, D.M., Reus, J.L., Harnar, T.J., Marvin, J.A.: Early excision and grafting vs. nonoperative treatment of burns of indetermined depth: A randomized prospective study. J. Trauma *23*:1001, 1983
10. Demling, R.H.: Effect of early burn excision and grafting of burns. J. Trauma *24*:830, 1984
11. Burke, J.F., Bondoc, C.C., Quinby, W.C.: Primary burn excision and immediate grafting: A method shortening illness. J. Trauma *14*:389, 1974
12. Burke, J.F., Quinby, W.C., Bondoc, C.C.: Primary excision and prompt grafting as routine therapy for the treatment of thermal burns in children. Surg. Clin. North Am. *56*:477, 1976
13. Heimbach, D.M.: Early burn excision and grafting. Surg. Clin. North Am. *67*:93, 1987

14. Yannas, I.V., Burke, J.F., Orgill, D.P., Skrabut, E.M.: Wound tissue can utilize a polymeric template to synthesize a functional extension of skin. Science *215*:174, 1982
15. Burke, J.F., Yannas, I.V., Quinby, W.C., Bondoc, C.C., Jung, W.K.: Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. Ann. Surg. *194*:413, 1981
16. Burke, J.F.: Observations on the development of an artificial skin: Presidential address, 1982 American Burn Association Meeting. J. Trauma *23*:543, 1983
17. Tompkins, R.G., Burke, J.F.: Update on artificial skin. Adv. Trauma *3*:183, 1989.
18. Jaksic, T., Burke, J.F.: The use of "artificial skin" for burns. Ann. Rev. Med. *38*:107, 1987
19. Goodenough, R.D., Molnar, J.A., Burke, J.F.: Closure of burn wounds using an artificial skin. Surg. Rounds *Nov.*:16, 1982.
20. Burke, J.F.: The effects of the configuration of an artificial extracellular matrix on the development of a functional dermis. In The Role of Extracellular Matrix in Development, New York, Alan R. Liss, Inc., 1984, pp. 351–355
21. Burke, J.F., May, J.W., Albright, N., Quinby, W.C., Russell, P.S.: Temporary skin transplantation and immunosuppression for extensive burns. N. Engl. J. Med. *290*:269, 1974
22. Burke, J.F., Quinby, W.C., Bondoc, C.C., Cosimi, A.B., Russell, P.S., Szyfelbein, S.K.: Immunosuppression and temporary skin transplantation in the treatment of massive third degree burns. Ann. Surg. *182*:183, 1975
23. Yannas, I.V., Burke, J.F.: Design of an artificial skin. I. Basic design principles. J. Biomed. Mater. Res. *14*:65, 1980
24. Yannas, I.V., Burke, J.F., Gordon, P.L., Huang, C., Rubenstein, R.H.: Design of an artificial skin. II. Control of chemical composition. J. Biomed. Mater. Res. *14*:107, 1980
25. Yannas, I.V., Burke, J.F., Warpehoski, M.: Design principles and preliminary clinical performance of an artificial skin. In Advances in Chemistry Series, No. 199, Biomaterials: Interfacial Phenomena and Applications, S.L. Cooper, N.A. Peppas, editors, Washington, American Chemistry Society, 1982, pp. 475–481
26. Heimbach, D., Luterman, A., Burke, J.F., Cram, A., Herndon, D., Hunt, J., Jordan, M., McManus, W., Solem, L., Warden, G., Zawacki, B.: Artificial dermis for major burns: A multicenter randomized clinical trial. Ann. Surg. *208*:313, 1988
27. Curreri, P.W., Luterman, A., Braun, D.W., Shires, G.T.: Burn injury analysis of survival and hospitalization time for 937 patients. Ann. Surg. *192*:472, 1980
28. Feller, I., Flora, J.D., Bawal, R.: Baseline results of therapy for burned patients. J. Am. Med. Assoc. *236*:1943, 1976
29. Bull, J.P.: Revised analysis of mortality due to burns. Lancet *2*:1133, 1971