Clinics in Dermatology (2005) **23**, 376–387

Clinics in Dermatology

Allogenic skin in the treatment of burns

Andrew Burd, MD*, Tor Chiu, BM, BCh, MA

Division of Plastic and Reconstructive Surgery, Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong

Abstract Allogenic skin has had a major role in acute burns care for over 100 years. The principle source of allogenic skin is from cadavers. Allogenic skin provides the gold standard for temporary skin substitutes. The main drawbacks to its wider use are availability and disease transmission. The major obstacle to prolonged use is its immunogenicity. As more effective means are developed to ensure the supply and safety of allogenic skin and novel ways of circumventing the immunologic problems are developed, it is possible that allogenic skin may find a new role as a permanent skin replacement in future burns care.

Introduction

The history of allogenic skin transplantation and the development of the modern science of immunology are closely linked.[1] These aspects have already been discussed in previous papers. The history of skin grafting evolved through the 1800s. In 1869, Reverdin,[2] working in la Charite in Paris, treated an avulsion injury with a skin autograft and reported the use of a skin allograft the following year.[3] Meanwhile in England, Lawson,[4] an ophthalmologist used full-thickness autografts to repair eyelids. Pollock[5] first used skin grafts in burn wounds. In the United States, Girdner[6] employed cadaveric allograft skin, taken from a suicide victim, to treat a patient with a severe burn from a lightning injury and reported an immediate take of 75%. Brown popularized the use of allograft skin with his experiences in the Second World War when he used the ready supply of allogenic skin as a "dressing".[7,8]

The mechanism of autogenic skin graft "take" has been the focus of much research interest for many years. From this, enquiry into the nature of allogenic skin take has developed, including vascularization. In turn, this has led to significant advances in the understanding of the biologic processes of immunology. Medewar and Gibson, observing the behavior of viable allograft, described the stages of rejection and particularly the second set reaction. Rappaport, working with another plastic surgeon, Converse, received the Noble Prize for his investigation and elaboration of the HLA system.[9]

In this paper we propose to briefly describe the burn injury together with the processes of burn wound healing. We then review the strategies of management of burns, which aim to optimize the outcome with regard to available resource allocation and stress the role of allogenic skin in the immediate and the reconstructive phases of treatment. We then describe the available sources of allogenic skin and some of the medicolegal aspects related to allogenic skin use. Finally, we look at the evolving nature of allogenic skin usage and look at potential applications for allogenic skin in future burns care.

* Corresponding author. Tel: +852 2632 2639; fax: +852 2648 1891.
E-mail address: andrewburd@cuhk.edu.hk (A. Burd).

0738-081X/$ – see front matter
doi:10.1016/j.clindermatol.2004.07.019

Definition of a burn

A burn is an injury caused by a pathologic flux of energy within a tissue resulting in a disruption of functional integrity. The source of the energy may be thermal, chemical, electrical, or radiation. The spectrum of burn injury ranges from an inconsequential superficial burn to the fatal destruction of the entire body surface. What is remarkable is that, with the advances in the understanding of the pathophysiology of the burn injury and the more aggressive approach to management, the prospect of surviving a complex major burn is better now than ever before.[10]

Pathophysiology

The pathophysiologic reaction to a burn injury is complex and varies with the cause. In thermal injuries, the changes in the burn wound are mainly caused by the direct effects of heat, but superimposed on these are changes associated with an acute inflammatory process. It is these latter changes that account for the widespread and devastating effects of major burns on the entire homeostatic functions of the body.[11]

The local response to a sudden increase in body surface temperature is the dilatation of blood vessels in an attempt to dissipate heat. A further increase in tissue temperature triggers an inflammatory response. The mediators of this response are peptides and other low-molecular-weight substances that regulate the cellular function and microenvironment of the tissues. The key cells in the postburn inflammatory response are the polymorphonuclear leukocyte, mast cell, and endothelial cell. These cell types together with platelets represent the prime target sites responsible for the mediation, progression, and resolution of the inflammatory response. A very simplified account of this process is given here as more detailed accounts are given elsewhere.[12,13] Activation of complement and coagulation cascades with the release of histamine from mast cells results in a short phase of vasodilatation and plasma protein leakage from postcapillary venules resulting in local edema formation. Intracellular proteases released because of cell damage activate kallikrein, which is responsible for transforming kininogen to kinin. Kinins have several effects, including vasodilatation, pain stimulation, and leukocyte migration. A delayed phase of leukocyte and platelet margination then results in the release of prostaglandins, prostacyclins, thromboxanes, leukotrienes, and lipoxins, which is accompanied by a substantial increase in microvascular permeability and changes in vasomotor control. The prolonged posttraumatic phase of vasodilatation and antiplatelet aggregation is regulated through endothelial cells via 2 different mediators, prostaglandin I_2 and nitric oxide. Hypercoagulability of the lymph and the plasma has been observed 2 to 3 hours after injury and correlates with the finding of increased levels of kinins in lymph. Disseminated intravascular coagulation may also accompany a severe burn.

As the tissues are infiltrated by leukocytes, the efficient elimination and destruction of injured tissue is effected. Neurotransmitters are also involved, especially substance P, which evokes vasodilatation, plasma protein leakage, and calcitonin gene-related peptide, which is a potent vasodilator.

Histopathology

An accurate determination of the depth of injury is an important consideration when formulating a management plan for a patient with burn.[14,15] The depth of injury is classified by descriptive terminology. The skin may be either partially or completely destroyed. If partially destroyed, this may be superficial, intermediate, or deep (Fig. 1). Most burn injury, however, will contain areas of varying depth of tissue damage. Theoretically, wound biopsy with histopathologic examination would seem to be a very precise method for determining the depth. Biopsies will leave permanent scars in partial-thickness wounds, they are expensive to process and take time to process. Furthermore, the burn wound is a dynamic entity and it may take up to a week for a stable state to be achieved.

In the most superficial injuries, only the upper epidermis shows changes. Nuclei appear either pyknotic and possess a perinuclear halo or, with greater damage, stain only faintly eosinophilic or not at all. In superficial partial-thickness burns, subepidermal blisters are often seen. There is necrosis of the epidermis together with the coagulation of collagen in the papillary dermis. As the burn becomes progressively deeper, a good indicator of the depth of irreversible damage

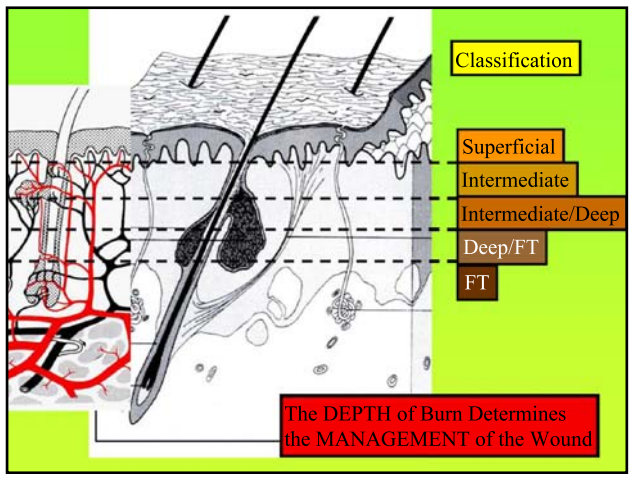

Fig. 1 A diagrammatic representation of skin relating the depth of burn to the blood supply to the skin. This classification is clinical and is a pragmatic attempt to rationalize the burn wound management.

to the collagen is apparent in the appendageal structures where there is generally a fairly sharp demarcation between heat-coagulated and relatively normal epithelium. With full-thickness burns there will be complete dermal necrosis with loss of all appendageal structures and coagulation necrosis may extend into the subcutaneous fat and underlying muscles. The depth of burn determines the capacity of the wound to heal.

Burn wound management

A number of factors influence the management of the burn wound:

1. the extent in % body surface area involved—affecting logistics;
2. the depth of the burn—affecting surgical strategy;
3. the resources available;
4. the expertise available;
5. the preburn condition of the patient.

Burns wound healing, regeneration, and repair

Regeneration is the capacity of a tissue to renew itself so that the end result is indistinguishable from the preinjured tissue.[16] Regeneration is a feature seen in superficial partial-thickness burns. The injury involves the loss of epidermis and basement membrane and the papillary dermis. There may be a highly exudative and painful wound.

The exudative phase persists for several days and as it decreases, the nature of the exudates changes. The viscosity and relative protein content increase and eventually a fibrin layer seals the wound. In the meantime, the basal keratinocytes at the margin of the wound begin to undergo mitosis. In the normal resting state, only approximately 12% of basal keratinocytes are proliferating at any time giving the skin a tremendous reserve capacity.[17] Re-epithelialization begins not just at the wound margin but also from the appendageal structures. The rate of keratinocyte proliferation and migration is extremely high and when the exposed dermal surface is re-covered, contact inhibition abruptly stops migration and redirects the cells to stratification. A superficial partial-thickness burn will heal with a stratified squamous epithelial in a matter of days. Disturbance in normal pigment expression can occur even with no scarring. In people with darker pigmentation, areas of absent pigment, can have major social and psychologic sequelae.

As the burn becomes deeper, the nature of the wound changes (Fig. 2). With an intermediate partial-thickness burn the epidermis is destroyed as with the superficial partial-thickness burn, but there is more dermal damage. The damage to the dermis involves an irreversible denaturation of the collagen. The inert collagen has to be removed for re-epithelialization to take place. Removal involves an autolytic process with enzymatic degradation and phagocytosis. This is augmented by an inflammatory response. Healing takes longer. As the depth of burn increases through the thickness of the dermis the phenomenon of inflammation plays an even more important role in the healing process. Typically, inflammation initiates a cascade of events with polymorphonuclear leukocytes being attracted to the wound site. Their principle role is proteolysis and phagocytosis of debris. They signal to macrophages which, when activated, enter the wound site to undertake a more detailed assessment of the damage and through a cytokine-mediated signaling process will recruit fibroblasts to begin the process of replacing the damaged collagen. Fibroblasts involved in wound healing have the capacity to produce abundant amounts of collagen but have lost the capacity to place and organize it in a highly structured way. The end result of dermal repair is the deposition of disorganized collagen, which is physically apparent as scar tissue. Scarring represents a very complex biologic phenomenon and hypertrophic and keloid scars represent clinical descriptions of a heterogeneous group of disorders with various etiologies and pathologic mechanism which result in the production of a disorganized connective tissue. The duration of the phase of wound closure, that is, re-epithelialization and the incidence of adverse scarring increases as the depth of burn increases.

Scarring is the major cause of long-term morbidity after a burn and can result in physical disability when function is

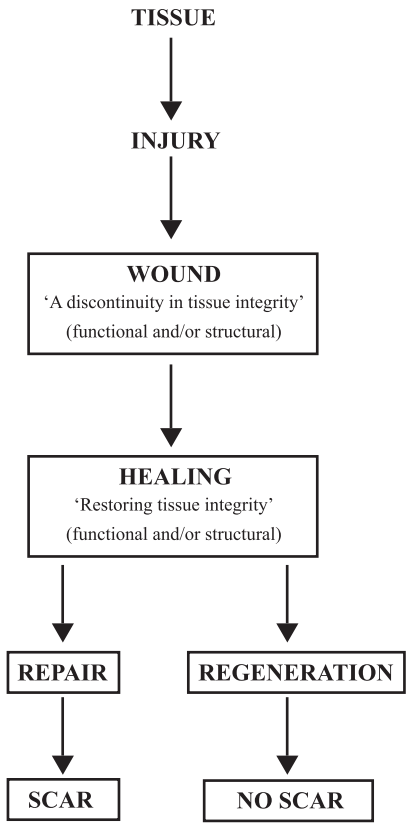

Fig. 2 The ideal to pursue is to achieve tissue regeneration after injury.

impaired and psychologic and social isolation when deformity distorts features particularly on the face and other regions of high esthetic impact.

Burn wounds vary widely, so does treatment, and there are few universal standards. The most widely accepted surgical principles are that superficial partial-thickness wounds do not require surgery and all-thickness wounds do require surgery.

Goals of burns treatment

The goals of burns treatment can be succinctly stated as survival of the patient with rapid healing of the wound, with minimal scarring and abnormal pigmentation. This treatment should be cost-effective and user-friendly. The outcome of treatment should be the restoration, as near as possible, to the preburn quality of life in terms of health and psychologic well-being. There will of course be patients in whom an enhanced quality of life should be aimed for in, for example, patients with self-inflicted burns due to psychologic or social pressures.

Strategies of management

The following section describes the present strategies of management in our Burns Unit and reflects an evolving philosophy of burns care which are guided by the factors mentioned in Burn wound management section. The most important consideration is that after a burn the protective functions[18] of the skin are lost and the burn wound needs immediate and appropriate topical treatment. An overview of burn wound treatments is shown in Table 1. This table outlines the 2 major options in treating the burn wound with biologic or nonbiologic dressings.[19] The properties of the ideal dressing have been summarized in Table 2. This short list enumerates the ideal properties, but as yet there is no single dressing that combines these properties, and certainly, no such product that is also readily available and easy to use.[20-22] Table 3 lists some of the properties of human allograft skin which render it such a valuable skin substitute in the burn wound. Nevertheless, these favorable properties have to be considered in the context of the availability of allogenic skin and its preparation before application. The role of skin banking and the safety and performance of skin allografts have been the subjects of a previous paper. Suffice to say that allografts can be viable or nonviable and the nonviable allografts can be processed with glycerolization, lyophilization, or irradiation. Viable allografts can be used fresh or cryopreserved in liquid nitrogen.[23-26]

There are 2 skin banks in Hong Kong run by the 2 university hospitals. The skin bank in Queen Mary Hospital stores viable allograft in liquid nitrogen. The skin bank at the Prince of Wales Hospital gamma-irradiates the cadaver skin and subsequently stores it in liquid nitrogen. The use of cadaver skin in Hong Kong is limited because of the low number of donors in the Chinese community. The prevailing cultural belief is that the body should not be disturbed after death and less than 30 cadavers are harvested each year by the Prince of Wales Hospital team.

Classification of depth

The classification of burn depth is descriptive as mentioned above. The clinical assessment of burn depth is open to a wide variation in accuracy. Pape, reporting an audit of the use of laser Doppler imaging, correlated clinical and laser Doppler imaging assessments with histology. The accuracy of the laser Doppler imaging was 97% compared with 60% to 80% for established clinical methods in a study of intermediate-depth burns.[27] Serial laser Doppler imaging studies also confirm the dynamic nature of the burn wound, particularly scalds, confirming that the depth of burn is not dictated solely by functions of the injury.

The working assessment of burn depth is made based not only on the clinical appearance but also on the history of the injury and the first aid given. By this means it is possible to make a broad classification of 3 principle categories of burn: the superficial partial-thickness burn, the full-thickness burn,

Table 1 Topical treatment strategies for acute burns care

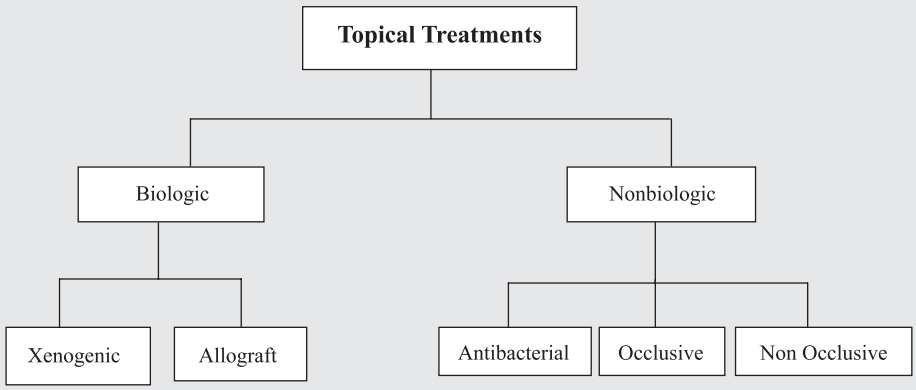

Table 2 Properties of the ideal burns dressing, the 4 P's

Ideal burns dressing properties
Protects
Proteolytic
Promotes healing
Pain relieving

and others. It is this third category that is most challenging in terms of management. The goals of treatment for the patient with burns are intimately associated with the goals of treatment of the burn wound. The overall goal is to promote survival with the minimum of scarring. Scarring, however, is a complex phenomenon and is the outcome of natural healing of a dermal injury; therefore, the apparently paradoxical objective in burn wound management is to prevent natural wound healing. The pathophysiology of the burn injury and the pathology of wound healing have been described. It follows then that one of the primary goals in burn wound management is to suppress inflammation in the healing wound.

Superficial partial-thickness burn

In the superficial partial-thickness wound, inflammation is not a problem. The wound heals by epidermal regeneration and a multiplicity of dressings, biologic and non-biologic, are available to dress such wounds (Fig. 3).

Intermediate partial-thickness burn

The challenge starts with the burn that involves the dermis and causes some fixed staining in the wound from blood

Table 3 Properties of allogenic skin which make it the present gold standard for temporary wound coverage

1. The intact stratum corneum provides a barrier function which
   a. limits desiccation of the wound.
   b. limits evaporative water loss.
   c. reduces bacterial contamination.
   d. protects underlying viable tissue.
   e. limits exudative tissue fluid loss.
2. The biomechanical properties of the dermal component allows
   a. effective draping of wound.
   b. permits movement of joints.
3. The biochemical properties of the skin cause
   a. in the partial-thickness burn
      i. reduced pain
      ii. enhanced healing
      iii. decreased scar
   b. in full-thickness excised wounds
      i. promotes angiogenesis on the wound bed which aids subsequent autograft take.

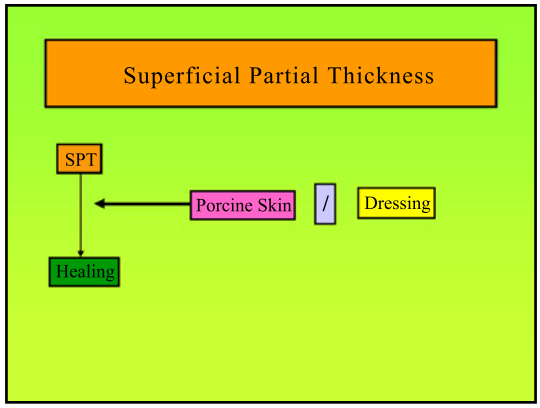

Fig. 3 Allogenic skin would be an ideal dressing for the superficial partial-thickness burn but the large number of such burns with the ready availability of alternative treatment strategies does not justify such use.

extravasation (Fig. 4). Such patients are frequently children who have sustained scalds. A clinical observational study comprised 6 children aged between 11 and 18 months who had scalds clinically assessed to be deep dermal. These children comprised a pilot cohort for a cost/benefit study proposed by the senior author (AB) while working in the UK. With full parental consent these children were taken to the operating room for an examination under anesthesia. After complete cleansing and removal of any blistering skin, the depth of burn was again assessed. The parameters used to assess burn depth were clinical based on the history of burn injury taking account of the temperature of the scalding agent, the duration of contact, and the nature and timing of the first aid applied. Features in the examination of particular note were the presence of fixed staining of the dermis and a subjective tension in the tissues denoting significant edema deep to the burned skin. A test shave was performed with a Watson knife if there was doubt. Having established the depth of burn being either intermediate or deep partial thickness, and the extent of the burn being greater than 10% body surface area but less than 30% body surface area, the clean

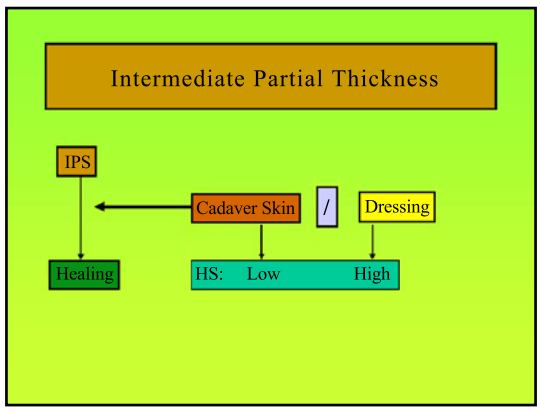

Fig. 4 Allogenic skin has a definite role as a dressing in the intermediate partial-thickness burn.

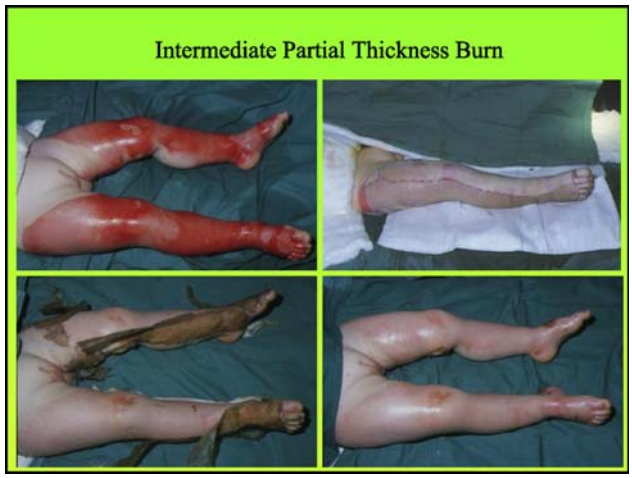

Fig. 5 A series of clinical pictures showing a child with a scald injury and fixed dermal staining (top left). The wound has been cleaned and cadaver skin applied directly to it (top right). Two weeks later the cadaver skin desiccated and peeled off (bottom left). The underlying burn was healed, and subsequently, no hypertrophic scarring developed (bottom right).

burn wound was covered with glycerolized cadaver skin. The skin was meshed but not expanded before application and was fixed in place by histoacrylate glue. The cadaver skin was covered with nonadherent gauze, dressing gauze, and crepe. Patients were discharged after 48 hours and readmitted at 1 week for a dressing inspection. As these were all infants, dressing changes were performed under mask general anesthesia. If the cadaver skin was still attached to the burn tissue, the patient was redressed for a further week and again readmitted for a second operative change of dressing.

All 6 children treated with glycerolized cadaver burn applied over unshaved burn proceeded to heal within 2 weeks. In 2 out of 6 cases the cadaver skin had separated by 1 week but in the other 4 cases the complete separation took 2 weeks. The illustration shows the sequence with the clearly dried cadaver skin peeling off. None of the 6 cases proceeded to develop hypertrophic scarring (Fig. 5).

Following on from this pilot study and other reported studies this strategy was implemented while in the UK. It was not possible to justify such routine use in Hong Kong where the availability of cadaver skin is less plentiful. Nevertheless, the concept of occlusive biologic dressings and/or adherent nonbiologic dressings is being evaluated. The biologic dressing is porcine skin, the nonbiologic dressing is Aquacell hydrofiber product manufactured by Convatec. The results are preliminary but both appear to be better than alternative strategies of daily dressings with silver sulfadizine cream on the one hand or shaving and grafting on the other.

Intermediate to deep partial-thickness burns

As the burn injury increases in depth so does the amount of dead tissue that has to be autolyzed before healing can occur. As autolysis is a time-related process it follows that the more autolysis that has to occur the longer it takes for healing to occur and the worse the scarring that results. Nevertheless, although there are significant dermal remnants with appendageal structures there is the capacity for re-epithelialization to take place. These then are the key points to support a modification of the "no–graft" strategy which is to debride the burn before applying the dressing. The debridement is undertaken surgically in the operating room by tangential shaving and the wound is then dressed. Fig. 6 shows the strategy with the possibility of applying medicated dressings to the debrided wound. This is the least satisfactory of the options. The use of biologic dressings is better with porcine skin being acceptable and allogenic cadaver skin being best. Again, the availability of resources dictates the management in the individual cases. Another approach for this type of burn is indicated in the figure and is based on the practice is Dr Fiona Wood's unit in Perth, Australia. Patients admitted with burns will have a skin biopsy taken under local anesthetic as part of the admission procedures. This biopsy is then taken to the laboratory to initiate keratinocyte cultures. A few days after the patient is taken to the operating room and the burn wound is debrided, an ultrathin autograft mesh is applied with cultured cells sprayed onto the interstices.

This account of the management of the intermediate to deep partial-thickness burn does indicate that the reality in contemporary burns care is that much of the treatment is derived from a compromise between empiricism and pragmatism and is not truly based on controlled clinical trials.

The deep partial-thickness/full-thickness burn

The strategy for managing this type of burn is depicted in Fig. 7. The depth of burn is determined in the operating room on a result of "test shaves." There may be areas of

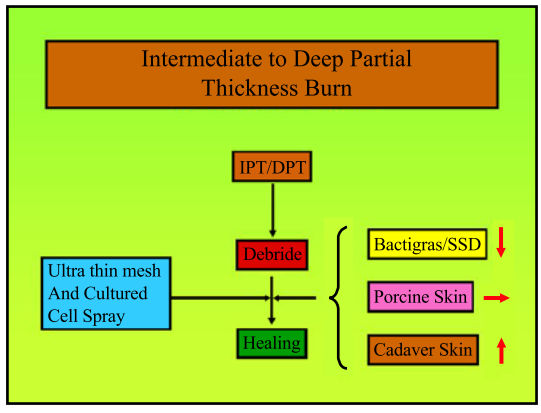

Fig. 6 As the burn depth increases, the role of surgery increase. After debriding the burn tissue the wound can be dressed with a variety of materials. Allogenic skin is the best in comfort, conformability, and durability.

surviving deep dermis but other areas where there is destruction of dermis completely with involvement of some underlying fat. The burn is not so deep as to warrant a fascial excision and the bed that is left after shaving will consist primarily of dermal remnants and adipose tissue. The methods used to cover this type of wound will depend on the extent of the wound. Sheet autograft is ideal for the smaller wounds. Meshed autograft is acceptable for larger wounds when the mesh ratio is 1:1:5 or 1:3. Nevertheless, once the ratio becomes greater the viability of the graft bed within the interstices of the mesh is a concern. The major threat to viability is desiccation of the tissues. In this situation, allograft skin provides a protective, biologic dressing for the autograft. This method of overlying the autograft with allograft is called the "sandwich" technique (Fig. 8). Alexander[28] classically described a meshed allograft overlay; it is better, however, in the authors' experience to use fenestrated or closed meshed allograft on the outer layer of the sandwich. Again, another variation of the sandwich technique is to use cultured keratinocyte spray as well as meshed autograft and apply the allograft over both. The allograft acts on a temporary dressing and does not revascularize. It maintains a moist protective environment, which supports re-epithelialization. As the migrating keratinocytes spread to cover the interstices of the meshed autograft they begin to differentiate and stratify. Eventually, the wound is covered with stratum corneum derived from the autograft and the allograft is displaced.

Full-thickness burns

With a burn that is unquestionably of full thickness, the removal is by excision. Tangential shaving is generally not appropriate. The depth of excision will depend upon a number of factors including the extent of the burn, the site of the burn, and the age and general health of the patient.

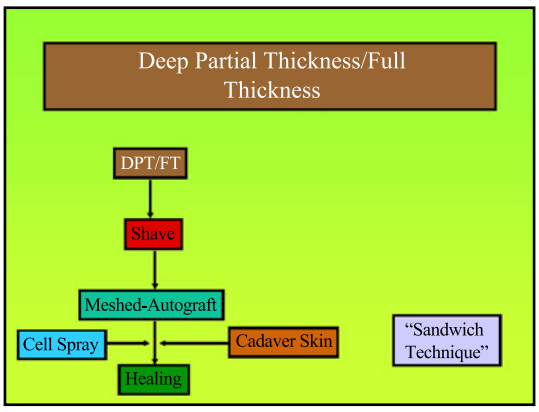

Fig. 7 With the application of meshed autograft, allogenic skin can again be used as a dressing to protect the wound in the healing phase.

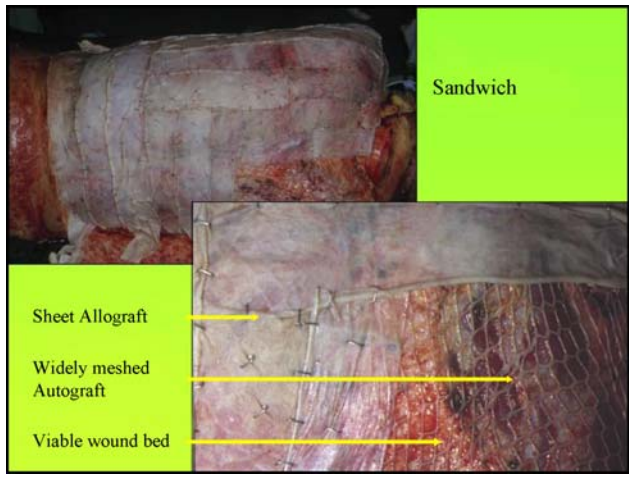

Fig. 8 This clinical picture shows the application of 1:4 meshed autograft overlain with sheet allograft. Although it is claimed that this technique is suitable for 1:6 and 1:9 meshed autograft, such "flimsy" skin can be difficult to handle and results in prolonged healing times.

As the burn size becomes more extensive there is a greater tendency to use a fascial excision as there is lower blood loss when tissues are removed at this level. Such an excision does however cause a very significant deformity particularly if the chest of a female patient is burnt. "Excision" is best carried out with the unipolar diathermy set on coagulation mode. If body-contouring adipose tissue is left, the plane of separation is best done at the level of the superficial fascia. The tissues are put under tension and a feathering action of the needle point diathermy sweeps through the connective tissue matrix. The aim is to produce as little trauma to the fat cells as possible. With a very extensive deep burn, removal just superficial to the deep fascia may be preferred. Surgery at this level is much quicker. Again, the tissues are put under tension and the plan of excision is through the loose areolar tissue between the fascial layer and the adipose layer. After excision at this level, there is some fatty tissue left, which although not providing a significant contouring effect, does allow for some protective mobility of the subsequent grafts in distinction to grafts applied directly to a fascial bed.

Once the bed has been prepared the question of cover arises (Fig. 9). It is after the excision of extensive full-thickness burns that allograft skin finds yet another role in the acute burn and this is to act as temporary cover. The role of temporary cover of allograft skin in burns does have some history attached to it and 2 aspects will be discussed in detail later, the Cuono technique and immunosuppression of viable allograft recipients.

Considering the diagrammatic strategy again, if a full-thickness skin defect can be closed with meshed autograft and allograft as in the sandwich technique, that is fine. With a more extensive burn, the cadaver skin may be applied briefly to the excised wound bed before the application of a dermal regeneration template or left for a longer time while

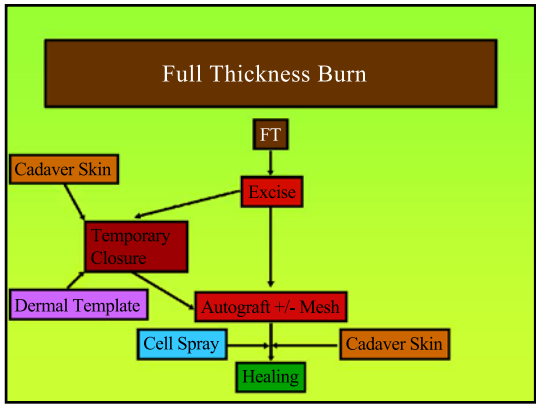

Fig. 9 In the full-thickness burn allogenic skin may find a role in temporary wound closure. In this situation viable allogenic skin can be used from both cadaver and living donors. In this situation the allogenic skin can be considered a temporary transplant.

awaiting healing of donor sites to allow secondary cropping and autografting.[29]

Overview

It is obvious from the overview in Fig. 10 that cadaver skin (allograft) has a number of distinct roles to play in the routine management of different types of burns. The strategies described here are just that, descriptive and not prescriptive. They are based on the availability of resources, and without doubt, if more allogenic skin was available it would, in our practice, be used more. For the reasons already alluded to in Table 3, it is an excellent skin substitute in the patient with burn.

Cuono technique

A number of other applications deserve mention. In the early 1980s the survival of patients with more and more extensive burns was being achieved principally through the possibility of being able to cover the excised burn wound with autogenous cells. This was a consequence of the clinical application of autologous keratinocyte culture. In Boston, Rheinwald and Green[30] were refining the laboratory techniques to produce sheets of autologous keratinocytes; Burke and Yannis[31] independently were working on a dermal regeneration template; Bell et al[32] were looking at composite in vitro bilayer skin reconstruction. Meanwhile in Yale, Cuono et al[33] had monitored the techniques of cell culture but was concerned about the dermal replacement. In 1987 he published his paper describing the use of allogenic

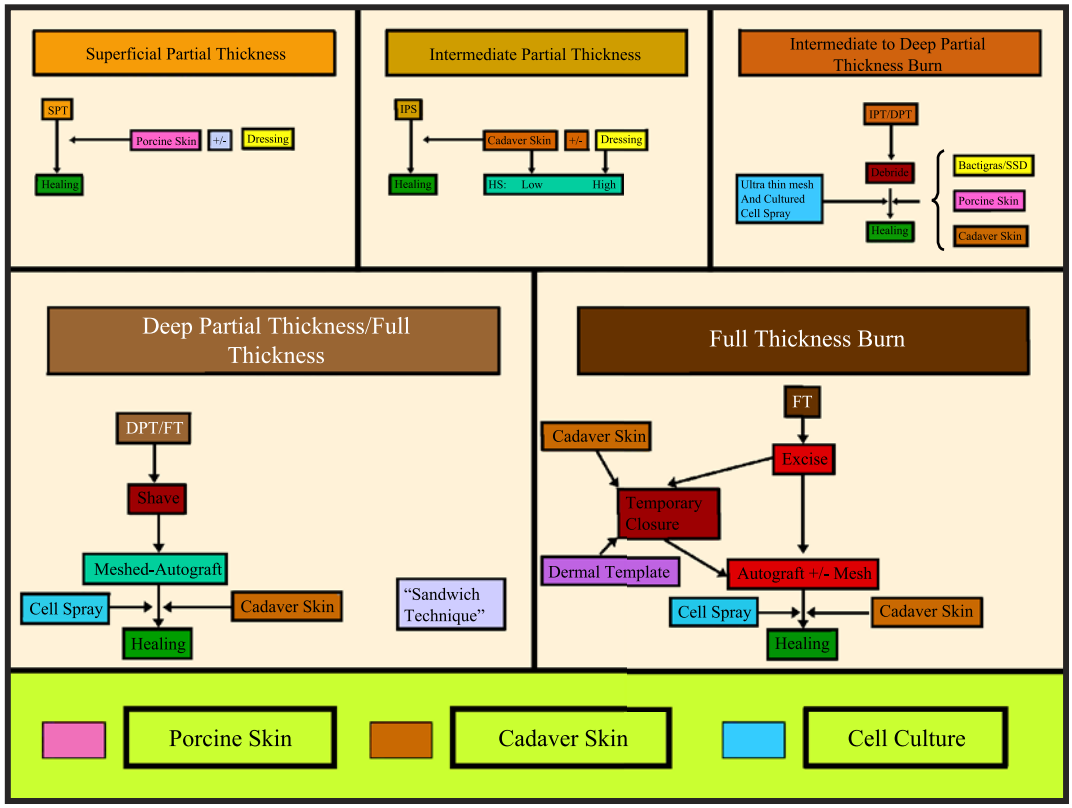

Fig. 10 This overview depicts a management strategy for acute burns care that relies on 3 biologic dressings: porcine skin, cadaver (allogenic skin), and autologous cell culture. Such a strategy is based more on pragmatism and empiricism. The variability of the burn wound and ethical considerations make the development of an evidence-based approach to acute burn wound care a difficult, but not insurmountable, challenge that has yet to be faced.

skin to resurface the excised burn wound.[34] The immunosuppression associated with the burn wound and the reduced immunoreactivity of the allograft allowed for a vascular incorporation of the viable allograft. Once autogenic keratinocyte cultures were ready the patient was returned to the operating room, whose allogenic epidermis was removed by either dermabrasion or tangential shaving.[35] The autogenic keratinocyte cultures were then applied. This technique became known as the Cuono technique and has inspired further investigation with acellular allodermis.

Allodermis

Alloderm is a commercial product derived from donated human tissue that is processed in a 3-step manner to produce an acellular but biologic matrix. The first step is to separate the epidermis and dermis while retaining the basement membrane. The next step is to remove the dermal cells with low-molecular-weight detergents while stabilizing the matrix from autolysis by inhibition of metalloproteinases. The third stage is a protected freeze-drying process, which maintains matrix organization and stability. Before clinical application the matrix is rehydrated and applied to a full-thickness defect. The matrix becomes revascularized and over the course of several months the allogenic components become replaced with autologous collagen and proteoglycans. The dermal bed has to be covered with either ultrathin autografts or cultured skin and favorable cosmetic and functional outcomes after its use in hand and foot burns have been published.[36,37]

Immunosuppression

The possibility of using allogenic skin and immunosuppression has been explored clinically and experimentally. An extensive burn injury is in itself immunosuppressive; nevertheless, the extreme antigenicity of skin inevitably results in the rejection of allograft. As in other allotransplants, attempts have been made to prolong the allograft acceptance by pharmacologically induced immunosuppression.

The agents most frequently used are cyclosporin and cyclosporin A. Black et al[38] reported on the use of cyclosporin-induced long-term allograft survival in 1987. This experimental work on rat models was further evaluated in the early 1990s.[39] An interesting observation in this later study was that the immunosuppressive effect of the burn injury was quickly reversed after early excision and grafting. This emphasizes the need for additional immunosuppression if burn wound cover with allograft alone is to be attempted.

The outcome of attempts to immunosuppress patients with large burns and allografts have on the whole been disappointing. While there are occasional reports of prolonged survival these are rare and more often the experience has been that patients succumb to sepsis possibly related to the immunosuppression.[40]

Medicolegal implications

The nature of the allograft in terms of its regulatory definition can have significant medicolegal consequences. This is illustrated by the events in Hong Kong which have been previously described.[41] Briefly, after an arson attack in the Immigration Tower in August 2000, the skin banks in Hong Kong were faced with an immediate shortage of supplies. As a result, glycerolized allogenic skin was ordered from the Euro Skin Bank. This raised problems with the Human Organ Transplant Board and related to the Human Organ Transplant Ordinance (HOTO).

The Human Organ Transplant Ordinance

In 1993, a local newspaper in Hong Kong ran a story suggesting that Hong Kong residents had transplants in the People's Republic of China using organs procured there. There were rumors that this process was facilitated by Hong Kong doctors and the Hong Kong Medical Association adopted guidelines against the practice of buying and selling human organs for purposes of transplant. Continuing controversy led to the Human Organ Transplant Bill, modeled on the English Human Organ Transplants Act of 1989. The Bill became operational on April 1, 1998. It prohibits commercial dealing of organs and restricts the transplanting of organs between unrelated persons.[42]

The practice of buying and selling human organs is both morally and ethically repugnant. As such, the HOTO is essential to protect against such practices. At the same time, however, it is important that such an ordinance is both precise in its terminology and practical in its application. In both respects, the current ordinance is lacking but medical terminology and understanding are equally imprecise on these issues.

The Human Organ Transplant Board were contacted with full details of the importation of the cadaver skin from the Euro Skin Bank and its subsequent use. Their position was stated as follows: "The Board agrees that the ordinary dictionary definition of 'transplant' applies to the Human Organ Transplant Ordinance (Cap 465) (HOTO), that is, the transfer of an organ from one person to another during a grafting or transplant operation, regardless of permanence. Therefore, the application of glycerolized cadaver skin, the so-called 'temporary life saving measure' is a transplant operation which falls within the ambit of the HOTO even though it does not involve permanent skin replacement. If cadaver skin is imported for the purpose of performing such 'temporary life saving measure', section 7 of the HOTO will apply, that is, it must be accompanied by a certificate

containing the required information with an acceptable signatory and the certificate must be submitted to the Board before the procedure commences. In addition, section 6 of the HOTO must be complied with by submitting Form 2 upon the transplant of organ in Hong Kong or Form 3 as to the final disposal of an organ imported but not transplanted to the Board within 30 days after these procedures are conducted. A person who fails to comply with such requirements may be guilty of an offence and is liable upon conviction to a fine at level 5 and to imprisonment for 3 months."

The requirements of the ordinance

The ordinance defines an *organ* as "any part of the human body consisting of a structured arrangement of tissues which, if wholly removed, cannot be regenerated by the body, and includes part of an organ." The list of human organs subject to the provision of the ordinance includes the skin. It is noted that the list may be updated from time to time taking into account state-of-the-art technology in transplant surgery.

The import of human organs is covered in considerable detail by the ordinance. Any person importing an organ for the purpose of transplant in Hong Kong must:

1. apply for an Import License from the Port Health Office of the Department of Health, and
2. ensure that the organ is accompanied by a Certificate, signed by a person in the country of origin who is acceptable to the Board, and by the required supporting documents.

The Certificate for the import of human organs for transplant requires the following declarations to be signed by either the medical practitioner who removed the organ in the country of origin or the Medical Director of the Institute/ Hospital that provided the organ.

This is to certify that

(1) In obtaining the organ, all applicable laws of _____, the country of origin, were complied with;
(2) The source of the organ, as far as can be ascertained, is not infected with any disease that could be transmitted to the recipient of the organ through transplanting;
(3) The organ was removed in a hospital in which the government of the country of origin has authorized organs to be removed for transplanting;
(4) As far as can be ascertained, no person in the country of origin has made/received or intends to make/receive a payment for supplying the organ; and information on the donor is provided below:
    a) Name
    b) Age
    c) Sex
    d) Date of removal of organ
    e) Where the donor is deceased
        i) Time and date of death
        ii) Cause of death (if known)

This form was sent to the Medical Director of the Euro Skin Bank for completion. The form was returned partially completed with the following statement.

> In compliance with European tissue banking regulations, details of all skin donors are kept on file at the Euro Skin Bank. However, the Dutch laws on personal privacy prevent us from disclosing these details to third parties. Quality certificates, attesting to the viral and bacteriologic safety of the batch were sent with the order.
>
> For your information, the Euro Skin Bank is a non-profit division of the Dutch Burns Foundation, which is a national charity. Glycerol-preserved allografts are non-viable and were developed as a temporary biological dressing for the treatment of burns and other conditions involving skin loss. In the Netherlands, the product is classified as a pharmaceutical product and is prepared under the auspices of J Prins, PhD, pharmacist.
>
> Allograft procurement and processing comply with the guidelines of both the American and the European Tissue Bank Societies. The product has been passed by the regulatory bodies of all European countries.
>
> I trust that the above information will reassure you of the legitimacy of the glycerol-preserved allografts which are provided by the Euro Skin Bank. If you have further comments or queries, I will be happy to respond.

The outcome of discussions between the legal and regulatory authorities is that an agreement has been reached that it is not reasonable to make a request that would breach the privacy laws of another country. It is thus acceptable to order human cadaver skin from the Euro Skin Bank without complete access to all the donor details. Such requests, however, must have prior approval from the Human Organ Transplant Board.

The future

While considerable research effects are directed toward the development of skin substitutes, another line of research is toward modifying the immunologic problems related to the rejection of the allograft. There are several reports describing the co-application of auto- and allogenic tissue in an attempt to develop a form of tissue chimerism.[43,44] In these experimental studies, allodermal matrix was incorporated although the adnexal structures were lost. The ever growing interest in stem cell research opens up new possibilities where recipient stem cells could be incorporated

into allogenic skin. Nevertheless, it is the epidermis with the Langerhans' cells that is the most antigenic. Mixed keratinocyte cultures are being investigated as a way of reducing antigenicity. There is, however, another approach using stem cell chimerism to modify graft rejection.[45] This has been described in solid organ transplants, principally the kidney. The principle is not to reduce the intrinsic antigenicity of the donor organ but increase the immune tolerance of the recipient. This is achieved by priming the thymus of the recipient with donor tissue by some days before the transplant. Later the thymus is injected with the chimeric stem cells from donor and recipient bone marrow. After the transplantation of the kidney the recipient does not generate an immune response such that prolonged survival of the organ is possible with no additional pharmacologic immunosuppression of the recipient.[46] These clinical findings raise the possibility of extending the use of allogenic skin in patients with burns. Such a strategy is not without problems as the skin is intensely antigenic and there are always concerns regarding disease transmission with allogenic tissue transplant. Nevertheless, this strategy needs to be explored as it could open up the possibility of treating patients with extensive burns with more rapid wound cover than presently possible and would be particularly applicable for resource-limited health care environments.

Conclusions

Allogenic skin has played a major role in burns care for over 100 years. This role has evolved to a certain degree but its primary function as a temporary skin cover remains. The separation of allodermis from the allo-epidermis has opened up the role for permanent dermal replacement. It is, however, in immunology that the answers will be found to immune modulation such that allogenic skin may one day become a permanent form of skin replacement in the patient with burns.

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