




Artificial Skin

Introduction

- ▶ Our skin is a major organ of the body that acts as a barrier to pathogens and trauma.
 - ▶ Skin defects caused by burns, venous and diabetic ulcers, or acute injury occasionally induce life-threatening situations.
 - ▶ Thus, the need for a functional and cost-effective permanent skin substitute for burn victims has always been garnered.
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U.S. Burn Statistics

- ▶ Approximately 2.4 million burn injuries are reported per year in the United States.
- ▶ Medical professionals treat approximately 650,000 of the injuries; 75,000 are hospitalized. Of those hospitalized, 20,000 have major burns involving at least 25% of their total body surface.
- ▶ Between 8,000 and 12,000 of patients with burns die, and approximately one million will sustain substantial or permanent disabilities resulting from their burn injury.
- ▶ Patients with major burns exceeding 60% of their total body surface area often do not survive since too much of the organ has been destroyed and cannot be permanently replaced.

Hospital Costs

- ▶ Burns are one of the most expensive catastrophic injuries to treat. For example, a burn of 30% of total body area can cost as much as \$200,000 in initial hospitalization costs and physicians fees.
- ▶ The cost of waiting for your own skin to grow can be more painful than the burn itself!

Background

- ▶ Although attempts to cover wounds and treat severe
 - burns is cited as far back as 1500 B.C., it has only been in the past few centuries that a significant number of solutions have emerged.
- ▶ The bulk of these solutions involve using skin grafts
 - from humans (allografts) or animals (xenografts), or using membranes fabricated from natural or synthetic polymers.

Background

- ▶ **The best material for wound closure is the patient's own skin; however autografting has several disadvantages (Schulz, 2000):**
 - The donor site is a new wound.
 - Scarring and pigmentation changes occur.
 - Dermis is not replaced.
 - Donor site is a potential site for infection.
 - Donor site is not unlimited.
 - Extensive burns makes it impossible.

Cadaver Skin: Allograft as a Temporary Skin Substitute

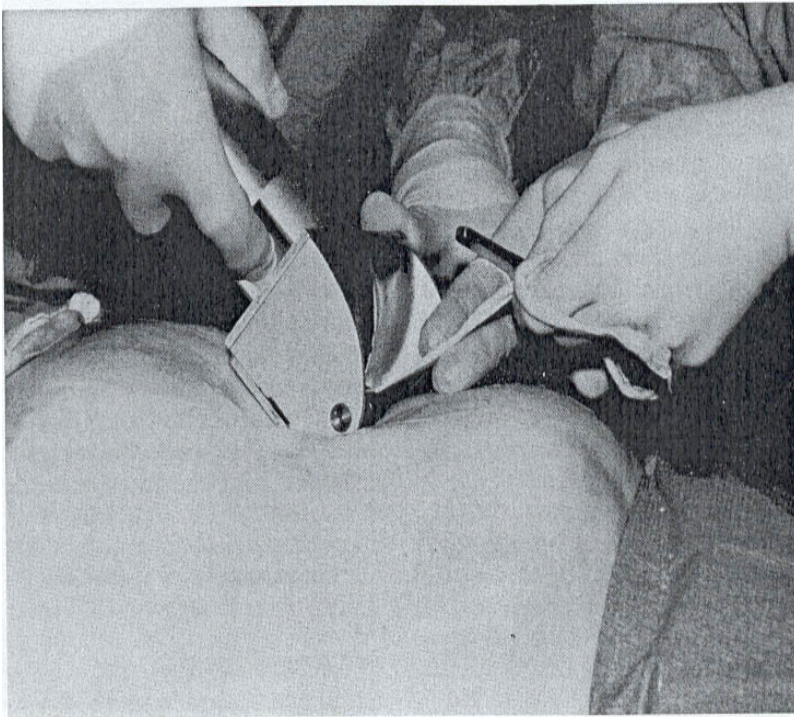


Fig. 9-5 Cadaver skin being removed with a dermatome.

- ▶ The annual national requirement for cadaver skin is estimated to be only 3000 m².
- ▶ Yet only 14% to 19% of human skin needed is being recovered.

Xenografts

- ▶ Xenografts, particularly porcine skin grafts, are commercially available and are an effective means of short-term wound closure (Yannas, 1980).
- ▶ A Xenograft is normally removed on the third or fourth day of use before extensive adhesion onto the wound bed sets in, thereby necessitating its traumatic excision prior to drying and sloughing off (Yannas, 1980)

Synthetic Polymers

- ▶ The use of synthetic polymers has not so far led to the solution of the problem of a skin substitute.
- ▶ A high incidence of infection and a relatively low capacity for inducing vascularisation and epithelialisation are frequently reported.
- ▶ However, useful insights into the requirements for a satisfactory skin replacement have been discovered through the use of synthetic polymers.

The Anatomy of Human Skin

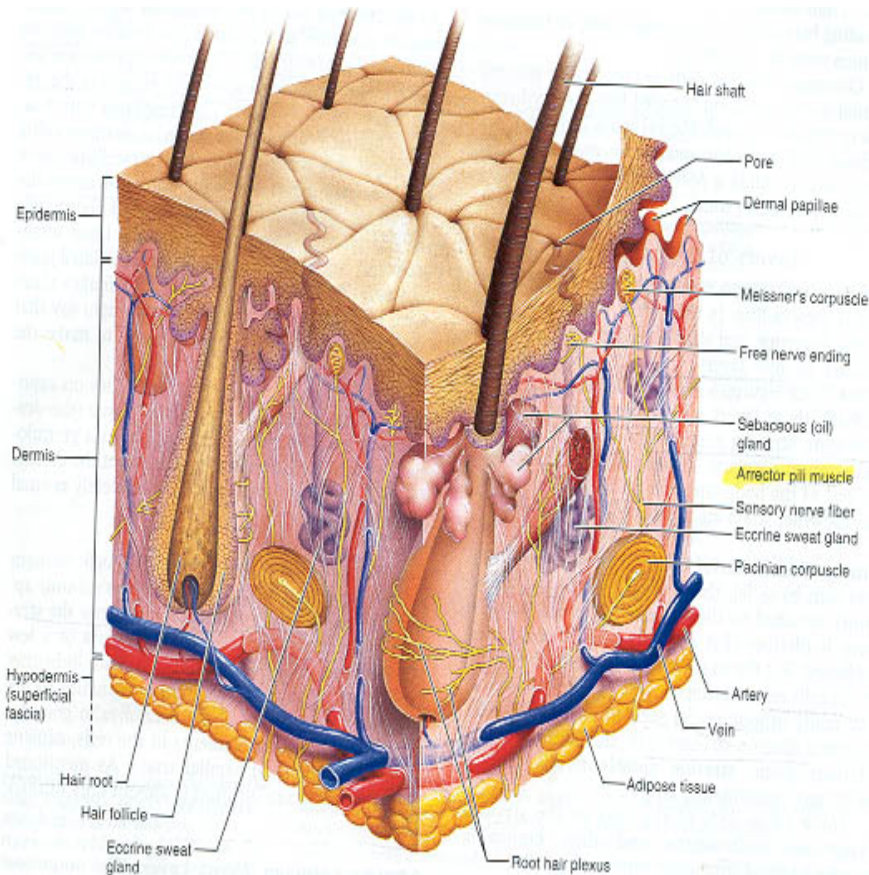


FIGURE 5.3 Skin structure. Three-dimensional view of the skin and underlying subcutaneous tissue. The epidermal and dermal layers have been pulled apart at the right corner to reveal the dermal papillae.

- ▶ **Epidermis (5 layers)**
Keratinocytes provide protective properties.
Melanocytes provide pigmentation.
Langerhans' cells help immune system.
Merkel cells provide sensory receptors.
- ▶ **Dermis (2 layers)**
Collagen, glycoaminoglycans, elastine, ect.
Fibroblasts are principal cellular constituent.
Vascular structures, nerves, skin appendages.
- ▶ **Hypodermis (fatty layer)**
Adipose tissue plus connective tissue.
Anchors skin to underlying tissues.
Shock absorber and insulator.

Eight Functions of Human Skin

1. **Protect underlying tissues from injury: mechanical, heat, cold, biological.**
2. **Prevent excess water loss.**
3. **Act as a temperature regulator.**
4. **Serve as a reservoir for food and water: adipose tissue**
5. **Assist in the process of excretion: H₂O, Salt, Urea, Lactic Acid.**
6. **Serve as a sense organ for cutaneous senses: pain, heat, cold, pressure, touch.**
7. **Prevent entrance of foreign bodies: microorganisms.**
8. **Serve as a seat of origin for Vitamin D.**

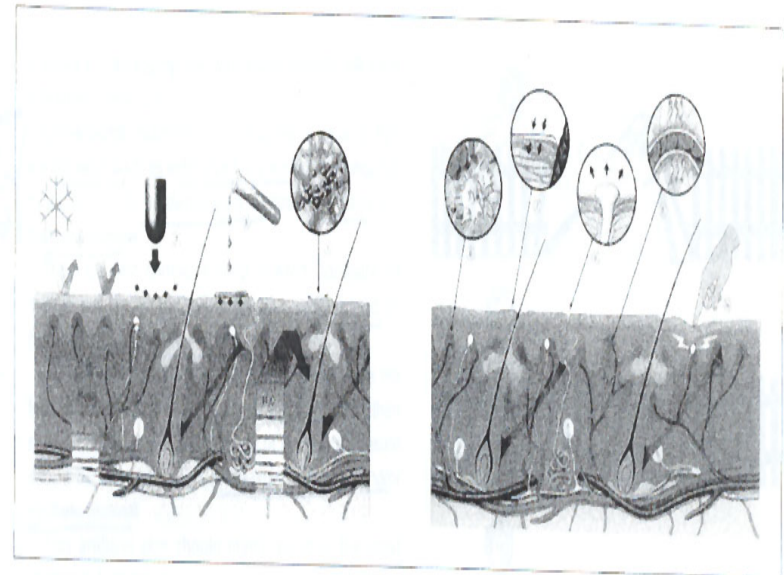


Fig. 2 - Functions of the skin

Phases of Wound Healing

1. Vascular Response
2. Blood coagulation
3. Inflammation
4. Formation of new tissue
5. Epithelialisation
6. Contraction & Remodeling

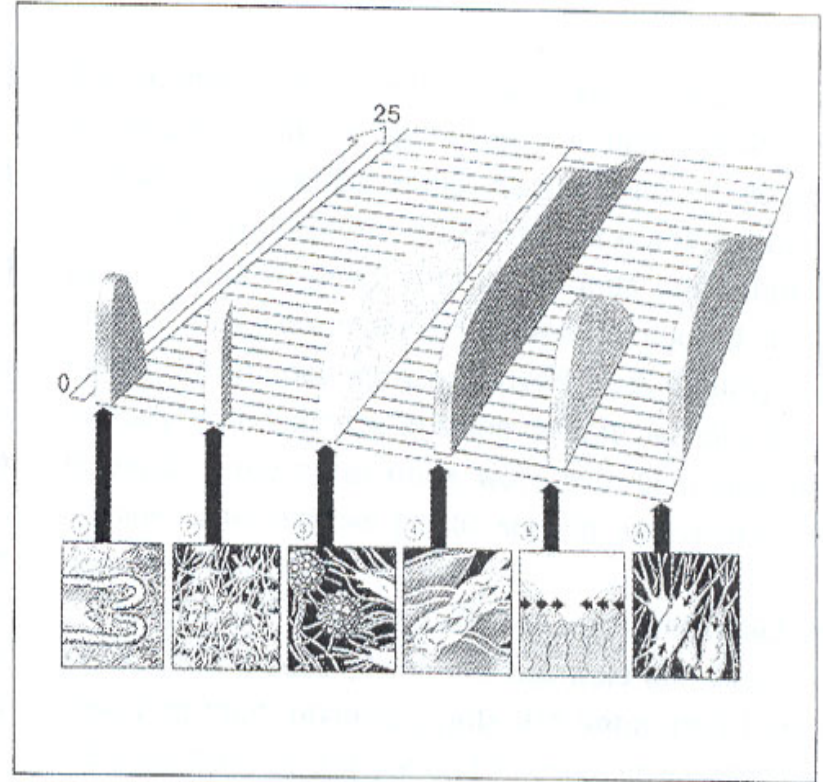


Fig. 4 - Phases of wound healing:
1 Vascular response; 2 Blood coagulation; 3 Inflammation;
4 Formation of new tissue (granulation and neo-angiogenesis);
5 Epithelialisation; 6 Contraction and remodelling.

Given the structural, functional, and wound healing constraints, what are the minimum design requirements for a viable artificial skin substitute?



General Design Properties

▶ Essential Design Properties

- "The dermal replacement should provide both the information necessary to control the inflammatory and contractile processes and also the information necessary to evoke ordered recreation of autologous tissue in the form of a neoderms" (Schulz, 2000).
- "The initial replacement material should provide immediate physiologic wound closure and be eliminated once it has provided sufficient information for reconstitution of neoderms" (Schulz).

General Design Properties

- It should protect the wound by providing a barrier to the outside (Beele, 2002)
- It should control water evaporation and protein and electrolyte loss (Beele)
- It should limit excessive heat loss (Beele)
- It should decrease pain and allow early mobilization (Beele)
- It should provide an environment for accelerated wound healing (Beele)
- The risk of infection must be taken into account (Beele)

More General Design Properties

▶ Physical Characteristics

- It should be easy to manipulate the product, i.e. easy to place and dress the skin substitute effectively (Beele)
- It should improve the cosmetic appearance of the scar (Beele)

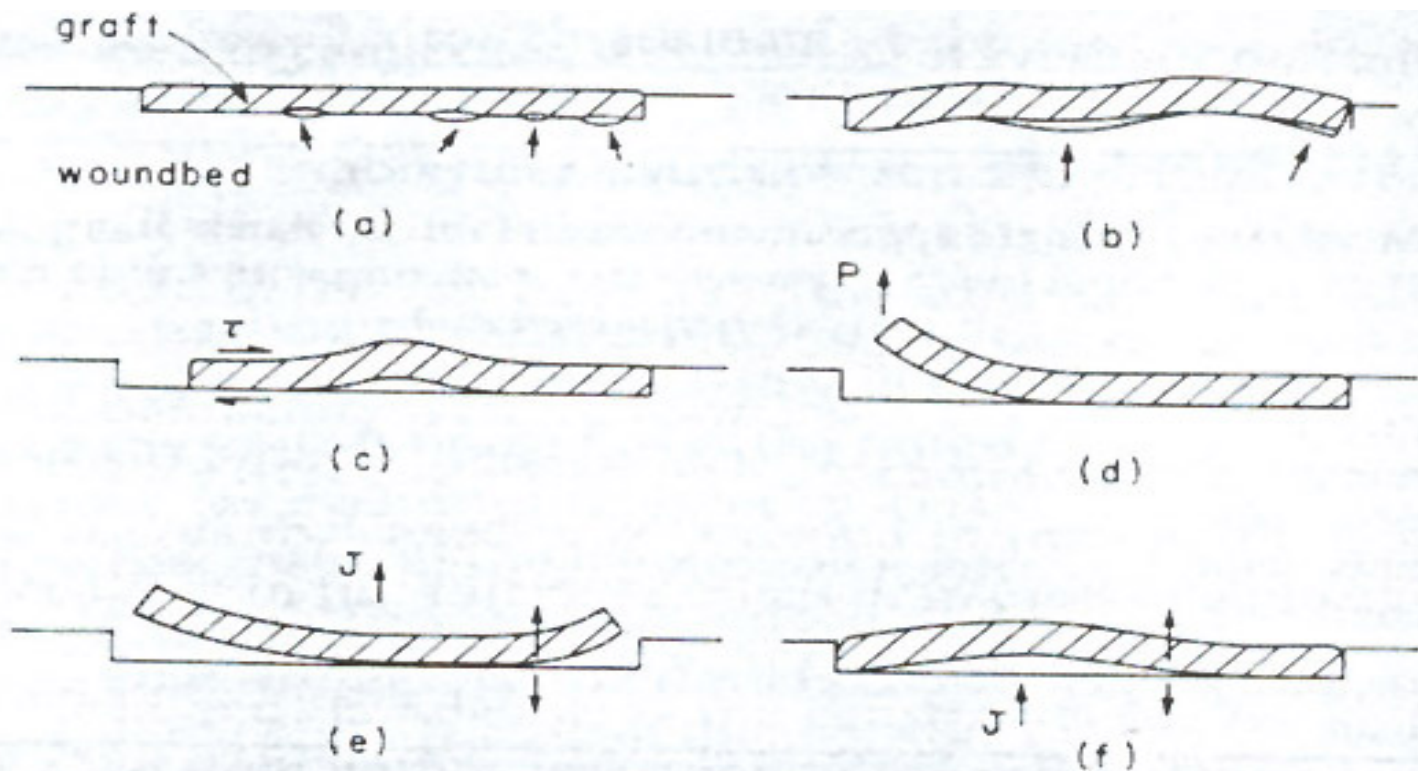
▶ Availability

- It should be readily available off the shelf and custom made.

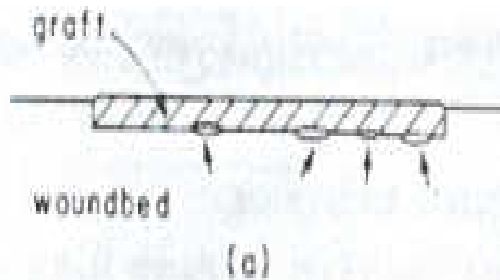
▶ Cost

- Cost should not preclude the use of the device.

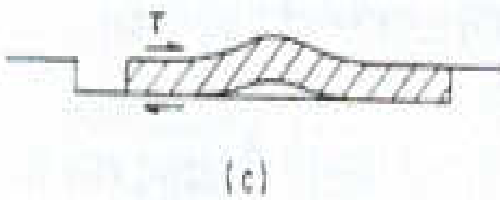
Schematic Representation of Specific Mechanical Problems that Should Not Arise (Yannas, 1985).



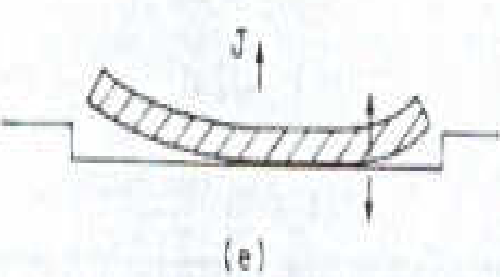
Specific Physiochemical and Mechanical Problems to Overcome (Yannas, 1985).



a) Skin graft does not displace air pockets efficiently from graft-woundbed interface.

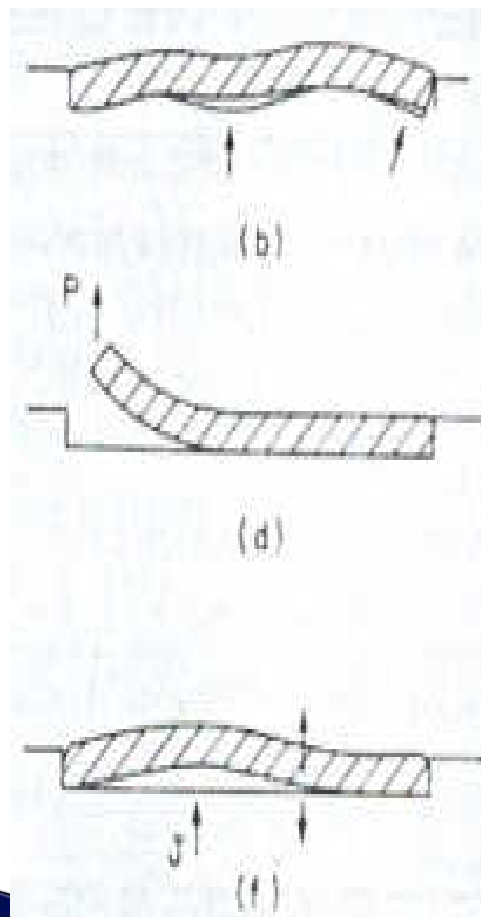


c) Shear stress causes buckling of graft, rupture of graft woundbed bond and formation of air pockets.



e) Excessively high moisture flux rate through graft causes dehydration and development of shrinkage stresses at edges and peeling.

Specific Physiochemical and Mechanical Problems to Overcome (Yannas, 1985).



- b) Flexural rigidity of graft is excessive; graft does not deform sufficiently under its own weight to make contact with depressions in wounded surface, thus air pockets form.
- d) Peeling force lifts graft away from wounded.
- f) Very low moisture flux causes fluid accumulation at graft-wounded interface and peeling.

Literary Review Up to 1990's (Beele, 2002)

Antiquity: Indian description of using autologous soft tissue flaps.

Greeks used dressings for skin wounds.

Renaissance: Amboise–Pare provide wound healing foundation.

1850's: Reverdin and Thiersch use autologous skin grafts.

1914: Kreibich was the first person to cultivate keratinocytes in vitro.

1948: Medawar autotransplanted keratinocytes.

1960's: Yannas and Burke begin their work using materials science and mechanics.

1975: Rheinwald & Green describe a technique to cultivate human keratinocytes.

1980's: Yannas and Burke describe a bilaminate collagen–glycosaminoglycan matrix with a silicon surface. After take of the matrix. The silicon surface is removed and can be replaced with autologous cultured epidermal cells.










1981: Bell constructs the first living skin equivalent with collagen fibroblast gel with keratinocytes cultured on top of contracted gel.

1983: Helton used cultured allografts in burn patients

1985: Boyce and Ham introduce an alternative culturing method.

1989: Possible to cryo–preserve keratinocyte sheets.

Types of Skin Substitutes

Trade Name	Schematic Representation	Layers
Blobrane™ (Dow Hickam/Bertek Pharmaceuticals, Sugar Land, TX).		<ol style="list-style-type: none"> 1. Silicone 2. Nylon Mesh 3. Collagen
Transcyte® (Advanced Tissue Sciences, Inc. La Jolla, California, USA)		<ol style="list-style-type: none"> 1. Silicone 2. Nylon Mesh 3. Collagen seeded with neonatal fibroblasts
Apligraf® (Organogenesis Inc, Canton, MA and Novartis Pharmaceuticals Corporation, East Hanover, NJ)		<ol style="list-style-type: none"> 1. Neonatal keratinocytes 2. Collagen seeded with neonatal fibroblasts
Dermagraft® (Advanced Tissue Sciences, Inc. La Jolla, California, USA)		<ol style="list-style-type: none"> 1. Polyglycolic acid (Dexon™) or polyglactin-910 (Vicryl™) seeded with neonatal fibroblasts
Integra® (Integra Life Science Corporation, Plainsboro, New Jersey)		<ol style="list-style-type: none"> 1. Silicone 2. Collagen and glycosaminoglycan
Alloderm® (LifeCell, Woodlands, Texas.)		<ol style="list-style-type: none"> 1. Acellular de-epithelialised cadaver dermis
Epice1™ (Genzyme tissue repair corporation, Cambridge, MA.)		<ol style="list-style-type: none"> 1. Cultured autologous keratinocytes
Laserskin™ (Fidia Advanced Biopolymers, Italy) also marketed as Vivoderm™ by ER Squibb & sons Inc,		<ol style="list-style-type: none"> 1. Cultured autologous keratinocytes 2. Hyaluronic acid with laser perforations
Cadaveric allograft (from not for profit skin banks)		<ul style="list-style-type: none"> • cryopreserved in order to retain viability • lyophilised • glycerolised

Product	Advantages	Disadvantages
Biobrane	Can be easily peeled off; good for donor sites and superficial partial-thickness burns within 6 hrs; shortens time in hospital; low cost	Temporary coverage
Transcyte	Readily available; easier to remove than allograft; good for partial-thickness burns; stimulates epithelialisation; less scarring; improves healing rate.	Temporary coverage; cost 16 times more than Biobrane
Apligraf	Immediate availability; 1 step procedure; easy to handle; primary role is treatment of chronic ulcers; hastens healing in deep and chronic wounds; improves cosmetic and functional outcomes	Temporary coverage; limited viability; most expensive
Dermagraft	Readily available; living dermal structure; used for chronic lesions, foot ulcers.	Temporary coverage; only 1 main application

Product

Advantages

Disadvantages

Integra

Immediate permanent wound coverage; allows ultra-thin split-thickness skin autografts; most widely accepted for burn patients; allows migration of patient's own endothelial cells and fibroblasts; studies over 10 years now; cosmetically better than using just autograft; greater elasticity; avoids risk of infection

Complete wound excision; 2 step procedure; susceptible to infection; relatively expensive compared to cadaveric allografts; learning curve is steep.

Alloderm

Immediate permanent wound coverage; good for being a template for dermal regeneration; good take rates; reduces scarring; allows 1 step grafting of an ultra thin split skin graft

Allograft supply; little barrier function; no virus screening; 2 step procedure; most expensive

Epicel

Covers large areas; permanent; immediate permanent wound coverage; minimal risk of disease transmission

3 - 5 wks to produce 1.8 m² from 2 cm²; fragile; expensive because of quality control; spontaneous blistering; susceptible to infection and contractures;

Laserskin

Delivers keratinocytes to the wound in an upside-down manner

Expensive

Observations from designing dermal replacements

- ▶ The thicker the dermal layer of a split-thickness skin graft, the less the graft contracts.
- ▶ Partial-thickness wounds with superficial dermal loss heal with less hypertrophic scarring.
- ▶ Full-thickness skin grafts contract minimally.
- ▶ The length of illness in burn cases is essentially restricted to the length of time the burn wound is open.
- ▶ Full-thickness dermal injuries heal by contraction and hypertonic scarring, producing subepithelial scar tissue that is nothing like the original dermis.

Further Research

- ▶ The actual biological elements and events being critically tested in mechanical studies are only guessed at, and analysis can rarely go beyond the science of mechanics.
- ▶ There are promising possibilities:
 - ✓ Pulsed ultrasound techniques may soon provide accurate imaging of skin structures as well as measurements of blood flow in the skin.
 - ✓ The multifrequency shear wave method may be able to resolve mechanical properties of the epidermal tissues discretely.

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