Chapter 2

Literature Review

2.1 Burn

2.1.1 Definition and Causes of Burns

Burn is a distinct category of trauma, which is the dissipation of the epidermis, muscles, vessel, and nerve by its severity. Causes of burn include: scalds–hot liquids or steam, open-flame, hot metal contact, chemical, electrical or radiation. Burn is quickly followed by severe pain, inflammation and blistering. If the burn is deepen and the patient is in unhealthy condition, malignant ulcer can resulted.

2.1.2 Classification of Burns

Classification of burn is based on the depth of tissue damage. All burns irrespective of their sources may be classified into three degrees:

First-degree (also called superficial) burns damage only the epidermis. Tissue damage is minimal. The skin will heal without intervention. The most common causes are overexposure to sunlight and brief scalding. It is not included in calculations for burn size.

Second-degree burns include the epidermis and some portion of the dermis. There are two separate types: superficial partial-thickness burns or deep partial-thickness burns.

Superficial partial-thickness burns heal within three weeks. There is usually only a change in the skin color, or pigmentation.

Deep partial-thickness burns require longer than three weeks to heal. They might heal by itself but may need special care from a doctor to heal better and faster. A skin graft is usually recommended for deep second degree burns.

Third degree burns destroy the full thickness of the epidermis and dermis. They do not heal by themselves. Most deep partial-thickness burns and third degree burns are best treated with early excision and immediate skin grafting.

2.1.3 Determination of Severity of Burns

Severity of burns is related to the surface area and depth of the burn, age, the location of the burn wound, and the severity of associated injuries (if any). The total body surface area for burnt case is accurately determined by using the chart of Lund and Browder (Table 1.1). Alternatively, a quick

assessment may be made in the adult using Wallance's "Rule of Nines" that is related to total body surface area. Percentage distribution are: anterior trunk 18%, posterior trunk 18%, each arm 9%, each leg 18%, head 9%, and genitalia area 1%. Percentage of total body surface area of burn is calculated from percentage in each part of body and added them together. This is used to identify the level of burn patient.

Minor burn, means the severity of burn depending on these following characteristics of burn. Adult patients who have second degree burn and the extent of burn is less than 15%TBSA. Children patients age 1 – 15, who have second degree burn and the extent of burn is less than 10%TBSA. In addition, minor burn also means third degree burn wound with the extent of burn less than 2%TBSA.

Moderate burn, means the severities of burn depending on these following characteristics of burn. Adult patients who have second degree burn and the extent of burn is 15 – 25%TBSA. Children patients age 1 – 15, who have second degree burn and the extent of burn is 10 – 20%TBSA. Besides, moderate burn also means third degree burn wound with the extent of burn less than 15%TBSA.

Major burn, means the severity of burn depending on these following characteristics of burn. In adult and children between 1 – 15 years of age, the severity of burn is second degree burn if the extent of burn is more than 25%TBSA. Besides, major burn also means third degree burn wound with the extent of burn more than 15%TBSA. Wound sites from major burn can include hands, face, eyes, ears, feet or perineum. Patients with major burn generally received their injuries from inhalation injury, electrical injury, burn injury complicated by other major trauma and poor-risk patients with burn.

Table 1.1: The Lund and Browder chart. This chart permits fairly accurate assessment of the extent of body surface involvement.

	Relative Percentage of Areas Affected by Growth					
	Age in Years					
	0	1	5	10	15	Adult
A – ½ of head	9 ½	8 ½	6 ½	5 ½	4 ½	3 ½
B – ½ of one thigh	2 ¾	3 ¼	4	4 ¼	4 ¼	4 ¾
C – ½ of one leg	2 ½	2 ½	2 ¾	3	3 ¼	3 ½

2.1.4 Burn Wound Management

The management of burnt wound can be devided into two categories. One is for the acute phase, and the other is for the late phase. Several methods of treatment can be used for the acute phase, such as simple dressing, excision and skin graft etc, with their own respective merits.

Skin graft is an operation where a doctor attached donor skin to a place on the body that has been burnt. It can be used as coverage for wound on the body, and is classified into, autografts, allograft, skin substitute, and cell culture.

Autograft is a preferred treatment for certain types of burn wound. Removal of patient's own skin from donor site for grafting accompanies morbidity, pain, scarring and is sometimes insufficient. Skin from donor site has to be at least the same size as burn site, in order to reduced any changes of contracture after the wound is partially heal. The most preferred donor site is at the thigh (or other available donor site with healthy skin). Doctor will usually choose the donor site with most available largest area in healthy skin area for skin grafting.

Allograft (Homograft or human skin or human cadaver skin) is a tissue graft from a donor of the same species to a genetically dissimilar body or a graft from a genetically different entity. Allograft has been a good second choice for closure of burn wound whenever a sufficient amount of skin autograft is not available. These kinds of grafts provide only a temporary covering, which will be rejected by the recipient body within a few weeks.

Skin substitutes are used to treat burn patients whenever autograft is not available and when only temporary covering is needed. Many different

products are available, including synthetic, biological and biosynthetic skin substitutes, such as OpSite, cadaver skin, pigskin, amniotic membrance, allograft, biobrane, and tegaderm.

Cell culture is one way of treatment in burn patients when normal skin is a limiting factor (from massive burn). This is the permanent skin substitute for the epidermal reconstruction and replacement of skin in burn patient. Large number of sheets can be grown from a small piece of patient's normal skin. All these procedures are performed under sterile conditions.

Some of these methods may have side effect that compromises the outcome: graft retraction may occur with this graft. Success of skin grafts depends on sufficient immobilization and early intervention for hematoma, seroma, or infection.

2.2 The Development in Skin-Cells Culturing Research

2.2.1 Development in the International Level

Cells culturing started in 1952 when Billingham & Reynolds successfully used Trypsin enzyme to separate a living epidermis. Later in 1970, Rheinwald & Green also triumphantly cultured keratinocyte in a serum media. The results of their works enable a much broader laboratory study on skin-cells biology.

In 1980, Nicholas E. O'Connor & John Mullikin from Brigham and Woman Hospital pioneered the first use of Autologous human Epithelium to cover the burnt. After that, in 1984, O'Connor & Green from Shriner Burns Institute successfully used cultured keratinocytes graft on patient with approximately 95% loss of total body surface area (95% TBSA). Keratinocytes were cultured by obtaining a small sample of healthy, unburned human Epithelial cell, cultured the cells in the laboratory for approximately 2 – 3 weeks until the desire size was reached, then transferred the skin graft sheet to the burnt site of the patients. The transplanted skin graft sheet went through a process call Epithelialization, developing into a complete epidermis, within 7 days.

During the past 10 years, Green's skin-cells culturing method has been used in order to skin grafts patients with skin loss and solves the problem of insufficient skin for grafting causes by acute accidental burnt or chronic diabetic, leg ulcers, venous ulcers and other kinds of illness. Human Keratinocytes culturing method has been improved continuously, with its commercialized forms now available in specialized store.

Doherty and Austin (1986) described the clinical experience with two boys who suffered partial-and full-thickness burns over more than 95% of their bodies. The total percentage of wound coverage provided by the cultured Epidermal cells was 49% and 54% of the boys' bodies. Within 15 months post-burn, both boys were discharged from the hospital and are now recovered from their burn condition.

In 1989, Xia et al. succeeded in establishing a tissue culture system for human Sebaceous glands. However, their results fluctuated significantly depending on the condition of the donor skin, such as gender, age and race.

In the last decade, human keratinocyte culture technique has expanded among countries such as U.S.A., Europe and Canada. By 1992, it had been used to graft more than 240 patients in the United States. During the survey made in 1995, 20% and 15% of the Canadian and American centers used Cultured Epidermal Autograft (CEA) respectively.

Cultured Epithelial Autolografts have been commercially available since 1998. The advantages of this technique include the ability to provide large areas of permanent wound coverage with autologous cells and regeneration of dermis. Although, the use of this technique requires patient's skin biopsy specimen and 2 – 3 weeks delay for cultivation.

At Burn Center, Indiana University School of Medicine, they have utilized the Allodermis technique as a substrate for Cultured Epithelial Autograft (CEA) as advocated by Cuono et al. To date, 23 patients with an average TBSA of 55% (46.5% - 3rd degree) have been treated utilizing this protocol. CEA take was appropriately 89% by day 10 with an average final take of 78%. The trunk and legs had the highest take rates.

During the past 2 – 3 years, some countries, especially the U.S.A., were attempting to generate dermis equivalent from Fibroblast, Collagen and synthetic biomaterial substance, in order to reinforce and increase the shelf life of the product.

Cultured Composite Autograft (CCA) are composed of Autologous Keratinocytes and Fibroblasts, which are obtained from a patient biopsy. The cultured sheets total growth process ranges from 16 to 18 days. CCA provide permanent wound coverage and are indicated for patients suffering from deep dermal and/or full-thickness skin injuries such as massive burns. The structure has several advantages including; large, thick, durable grafts, easy application and an 80% take. (Sherman Oakes Burn Center, US. 1995)

Advantages of Cultured Epithelial Autografts include reduced pain and infection, healthy granulation tissue growth, general well being and no premalignant change.

Disadvantages of Cultured Epithelial Autografts include blister formation, low shear resistance, Parakeratosis, Dyskeratosis, scar contracture and high cost.

The benefits of Cultured Epithelial Autografts are that it can be used as a biological skin for severe burn treatment, has a Fibroblasts characteristic and also effective for chronic ulcer, since it contain TGF (alpha) Polypeptide growth factor that aids in the proliferation of cells in chronic ulcer.

2.2.2 Development in Thailand

The Biomaterial laboratory research team has done a survey, regarding the present condition of skin grafts and skin substitute materials usage in 140 hospitals in Thailand.[1] Hospitals are categorized into 39 private and 101 public hospitals. Of all these public hospitals, 83 are provincial hospitals serving the 12 counties over the whole country of Thailand, 5 run by The Ministry of Public Health, 5 belong to The University Bureau, 3 belong to The Ministry of Defense, 1 under The Ministry of Interior, 3 belong to The Bangkok Metropolitan Authority, and 1 own by an independent association. All these hospitals have more than 500 patient beds, surgery department and their own operating room. Survey finding shows that during the past 1 year, there was no case of skin graft culturing in Thailand. The percentage of permanent method use for treatment of burnt and scalded patients is 100% use of the patient own skin (autograft) in hospital. The other temporary methods include, 15.4% use of placenta (amnion), 15.4% use of donor skin (allograft), and 12.8% use of skin substitute, such as, Duoderm, Opsite, Tegaderm, Lyoform, etc, and another 56.4% answered no to all of the above methods. Eighty-two point five percent of the people who answered the questionnaire knew and heard about the skin graft culturing done in the laboratory in order to permanently grafted onto the patient, and 88.1% of the people who answered the questionnaire showed interest in using cultured skin graft for patients treatment.

A group of surgeon in Thailand has tried to culture human keratinocyte, but was not successful in detaching the keratinocyte sheet for application, due to shrinkage of the sheet. The group also has problems in research budget and the feasibility of the application of this technique in Thailand. Finally, they decided to settle on the operation of skin bank, using cryopreservation technique for allograft, instead.

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[1] Unpublished Survey Report by the team of BIOTEC researchers including Nares Damrongchai, Ph.D., Ms. Dokor Sompong and Ms. Watcharin Meerod with some help from the author of this thesis.

A project by the Biomaterial laboratory, BIOTEC adapted modification of Green's method and successfully use human keratinocyte from baby foreskin and normal adult skin to cultured a complete, nonshrinking, partial differentiated keratinocyte sheet. At the moment, they are moving to the clinical trial stage at the Siriraj and Chulalongkorn Hospitals. Until now, more and more interest is picking up in the area of skin graft culturing, but no clinical result has been available from any group yet.

2.3 Cost Estimation from Provider Side

Creese and Parker (1994) in their study classified cost by inputs into two categories of resource: capital costs and recurrent costs. Capital cost is the cost of the acquisition of goods and services that ususally last for more than one year, such as building, and equipment. While recurrent costs do not last for more than one year, such as material supply, operational cost, and health personnel salary, their civil servant medical benefit and child tuition reimbursement. Hence, provider costs can estimate by calculate capital cost and recurrent cost.

Suvimon Pavananunt (1994) studied the total provider cost of heart transplantation from the day of operation to the day of discharge. The cost was classified by input, as recurrent cost and capital cost. The recurrent cost components are personnel cost, drug cost, and supply cost. The impotant implication from this study is that the hospital incurs most of cost for heart transplantation, while cost recovery is a minor part of the total.

Krisana Pornputtichai (1997) studied the provider cost of bone marrow transplantation in hamatologic disorders from the day of admission to the day of discharge and follow up for six months. The costs were classified by inputs, to be capital cost and recurrent cost. The recurrent cost, which classified into two components: the personnel cost and the material cost. The material cost was drug cost, and blood cost. The implication of this study was how the hospital would cope with the high cost of catastrophic illness among hematologic disorders.

Gore DC (1997) studied outcome and cost analysis for outpatient skin grafting. The purpose of this study is to assess patient outcome and cost for managing operative burn injuries without hospitalization. Hospitalized patients and outpatients were similar in age and extent of burn; however those hospitalized underwent skin grafting sooner after injurry. Inpatients also had a significantly larger area skin-grafted. Graft take was very good in each group. Cost as indexed by patient charge was substantially less for

outpatients ($2,397±$222) than for inpatients ($17,220±$410). These results demonstrate a significant cost reduction with nonhospitalized operative care of burn injuries without any overt detriment in outcome thus endorsing outpatient skin grafting when amenable, and also illustrates that delaying operative intervention reduces the burn area required for grafting.

In 1997, RA Hopper and colleague had surveyed the pattern of use, cost and availability of skin substitute in the United States and Canadian adult burn centers and found that:

The British Columbia Tissue Bank and LOEX are the only facilities in Canada providing Cultured Epithelial Allograft (CEA) to Canadian burn centers. CEA was supplied by the British Columbia Tissue Bank at $1,500 per flask (10 by 20 cm. sheet). This price was designed to cover only the cost of supplies.

LOEX has also supplied CEA to units in Montreal, Quebec and Halifax, Nova Scotia and more recently to a hospital in Ottawa. An initial processing fee of $2,700 followed by $5.50 to $6.25 per cm^2 of graft is designed to cover the laboratory's processing expenses on a nonprofit basis.

CEA is available commercially from Genzyme Corporation (Massachusetts) at US$435 per 25 cm^2 flask. Additional costs include biopsy analysis of US$500 and a variable transportation cost of approximately US$2,000.

Human cadaver skin (allograft) will be the best and the golden standard for temporary dressing of burn wound. The Firefighter's Burn Unit Skin Bank provided fresh and frozen cadaver skin to the two provincial burn units: Manitoba and Toronto. The provincial units are charged $25 per piece of skin ranging from 5 by 10 cm. to 10 by 30 cm. The cost per unit for The Nova Scotia Firefighter's Burn Treatment Society Skin Bank is approximately $100 per 6 by 30 cm. carrier. Human cadaver skin is also available to Canadian units from American sources. Two estimates given are US$150 per quarter square foot (7.5 by 30 cm.) for the New York Firefighters Lifelink and US$450 for a 6 by 30 cm. carrier from a source in Seattle, Washington.

Pigskin (xenograft) has gained acceptance as a temporary dressing alternative to allograft due to its lower cost and greater availability. All pigskin was purchased from private industry. Price varied depending on the form, dimension and quantity purchased. Frozen, sterile, perforated pig skin costs around US$65 for an 8 by 61 cm. roll, whereas the perforated shelf-stored form of the same dimensions costs US$73.85.

For allodermal graft, the present cost is US$2.60 per cm^2 and with transportation cost, via air express, will be around US$30.

Biobrane is a temporary skin substitute made of silicone bonded to nylon mesh. Retail cost of a 13 by 13 cm. sheet of Biobrane is approximately $28.

Cost of synthetic dressings such as, Opsite, Duoderm and Tegaderm varies with size and make, from $1.88 for a 10 by 14 cm. sheet to $2.65 for a 10 by 10 cm. sheet.

Table 2: Approximate Cost of Various Skin Substitutes for Coverage of 10% Total Body Surface Area Wound*

Skin Substitutes	Sources	Price (CDN$)•	Price (US$)•
Human Cadaver Skin	-Firefighter's Burn Unit Skin Bank$^{\delta}$	270	197.08
	-Nova Scotia's Firefighter's Burn Treatment Society Skin Bank$^{\delta}$	1,000	729.93
	-New York Firefighter's Skin Bank	1,660	1,211.68
Pigskin	-Brennen Medical Inc., Minnesota Frozen, sterile	260	189.78
	-EZ-Derm	340	248.18
Cultured Epithelial Allograft	-Vancouver Skin Bank$^{\delta}$	13,500	9,854.01
	-Laboratoire des Grands Brules$^{\delta}$	11,000	8,029.20
	-Genzyme Corporation, Massachusetts	44,800	32,700.73
Alloderm	Lifecell Corporation, Texas	6,700	4,890.51
Lifeskin	Culture Technology Inc, California	29,200	21,313.87
Biobrane	Dow B. Hickam, Texas	310	226.28
Duoderm	Bristol-Myers Squibb Inc.	46	33.58
Opsite	Smith and Nephew Inc.	40	29.20
Tegaderm	3M Canada Inc.	26	18.98

* Calculated from the estimated total body surface area of 1.88 m2 for a man of height 178 cm. and weight 70 kg.

• Prices as of autumn 1995, with conversion ratio of US$ 1.00 = CDN$ 1.37 where applicable, which does not take into consideration the discounts offered due to hospital contacts, quantity purchased, etc. Additional costs such as, transportation, biopsy processing or additional dressing are not included.

δ Availability depends on local demand, and transfers are done on a nonprofit basis.