CHAPTER 1

INTRODUCTION

1.1 Structure of the Skin [1,2]

The skin is one of the most important organs of the body. It is also called the **integument**. Its surface is as large as the body itself, an area in average-sized adults of roughly 1.6 to 1.9 m^2 (17 to 20 ft^2). Its thickness varies from slightly less than 0.05 cm (1/50 inch) to slighty more than 0.3 cm (1/8 inch). Skin functions are crucial to survival and are very diverse. They include such different functions as protection, temperature regulation and sensations.

The skin is a thin, relatively flat organ classified as a membrane - the *cutaneous membrane* composed of two main layers: an outer, thinner layer called the *epidermis* and an inner, thicker layer named the *dermis*. Under the dermis lies a layer of connective tissue called *subcutaneous tissue* or *superficial fascia*.

1.1.1 Epidermis

The outer layer or *epidermis* has a surface of horny, nonliving cells that form the body's protective envelope. These cells are constantly being shed and replaced by new ones which are made in the lower or inner layer of the epidermis. There are no nerves or blood vessels in the epidermis, injuries restricted to this layer cause no bleeding or pain. The epidermis is divided into five layers [2-4]:

(a) *Stratum germinativum*

This is the layer of epithelial cells that lies on the basement membrane. The growth of the epidermis takes place by multiplication of the cells of the germinative layer. The cells previously formed are pushed upwards towards the surface. In their upward progress, these cells undergo a chemical transformation with the soft protomic cells becoming converted into the flat scales which are constantly being rubbed off the surface of the skin. The pigment in the skin is found in greatest amount in the cells of the *stratum germinativum*. No blood vessels pass into the epidermis but fine nerve fibers lie between the cells of the inner layers.

(b) *Stratum spinosum*

This is a multilayer group of spindle-shaped cells that has been pushed outwards towards the surface by newly forming cells in the *stratum germinativum.* The cells of this *stratum* are living and metabolically active.

(c) *Stratum granulosum*

This is a thin layer where the cells of the outer surface of the *stratum spinosum* acquire granules of *keratohyalin* which are seen in microscopic sections as dense masses in the cytoplasm. The cells are still living.

(d) Stratum lucidum

This is a thin layer in thick areas of the epidermis, such as those of the palms and soles. As the name implies, it stains lightly. The internal cellular structure has largely disappeared. This layer is not present in thin skin; therefore, it is not seen in Figure 1.1.

(e) Stratum corneum

This is composed of many layers of dried, dead, and flattened epithelial cells called *cornified cells* and is converted to a water-repellent protein called *keratin*. The outer layers of the *stratum corneum* gradually scale away from the skin and new layers are continually formed from beneath.

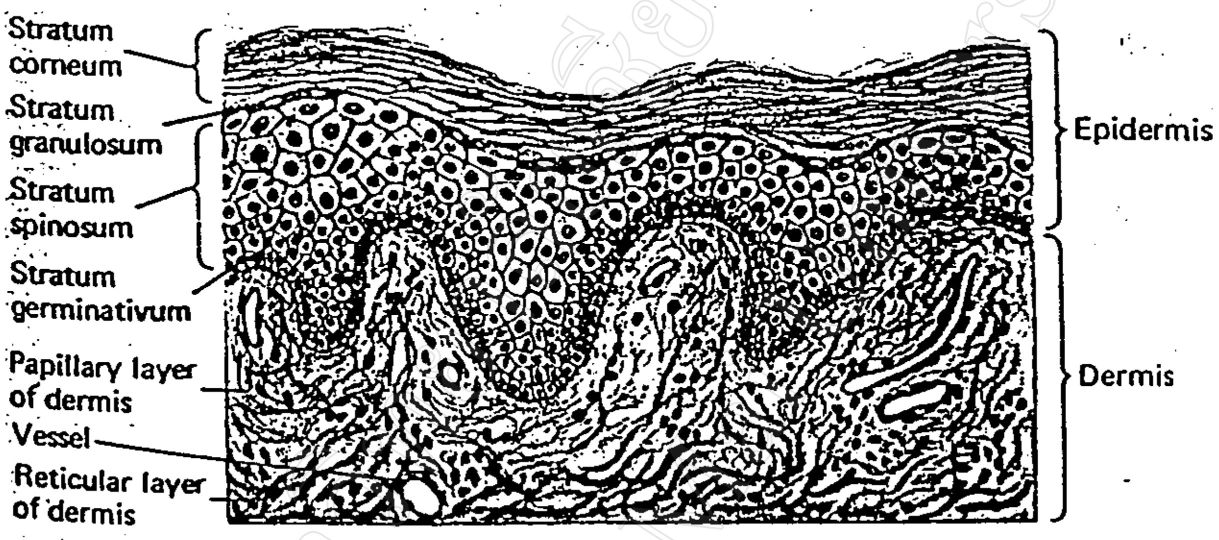


Figure 1.1 : A sectional view of typical skin [3].

1.1.2 Dermis

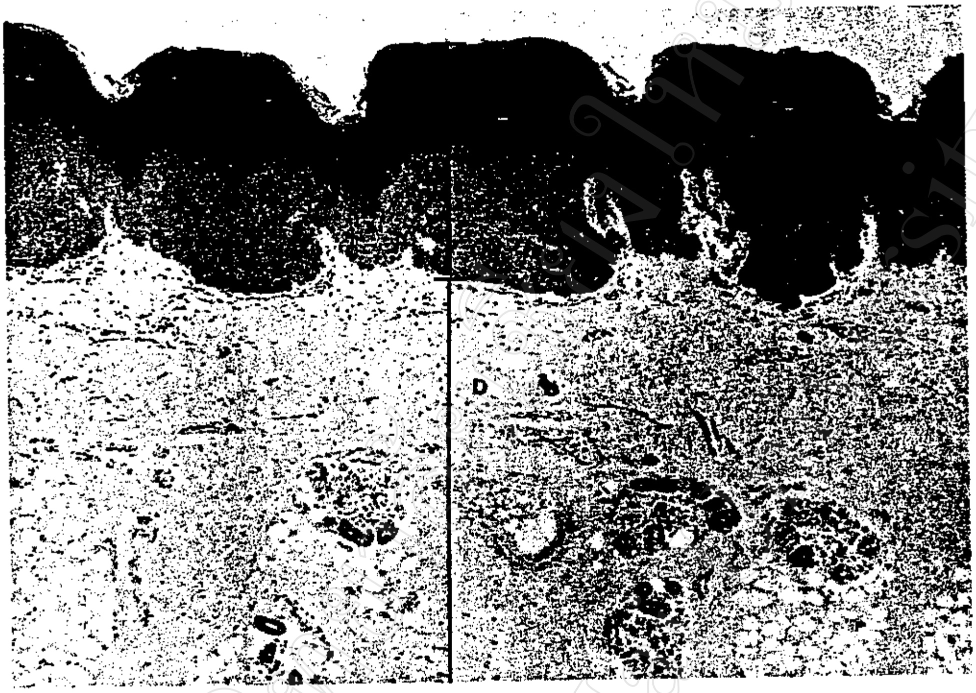
The *dermis* is a semidense layer of connective tissue that lies underneath the epidermis. It is a much thicker layer and much tougher than the epidermis. It contains blood vessels, nerves, and connective tissue. The sweat glands are located in the dermis and they collect fluid containing water, salt, and waste products from the blood. This fluid is then sent through tiny canals that end in pores on the skin's surface. The dermis is divided into two layers.

(a) Papillary (or superficial) layer

The *Papillary layer* is fairly cellular and contains finer fibers. This layer is increased by protrusions in the form of small conical elevations called *papillae.* The papillae consist of small bundles of fibrillated tissue, the fibrils being arranged parallel to the long axis of the papillae. Within this tissue is a loop of capillaries while some papillae, especially those of the palmar surfaces of the hands and fingers, contain *tactile corpuscles*, which are numerous where the sense of touch is acute.

(b) Reticular (or deeper) layer

The *reticular layer* consists of a *reticulum* (network) of fibers. Most of the fibers are collagenous fibers which impart toughness to the skin. Elastic fibers are also present in the reticular layer. These make the skin stretchable and elastic (able to rebound). These bands interlace and the tiny spaces left by their interlacement are occuied by adipose tissue and sweat glands. The reticular layer is attached to the parts beneath by a subcutaneous layer of aerolar connective tissue which, except in a few places, contains fat. In some parts, as on the front of the neck, the connection is loose and movable ; in other parts, as on the palmar surfaces of the hands and the soles of the feet, the connection is close and firm. In youth, the skin is both extensile and elastic, so that it can be stretched and wrinkled and return to its normal condition of smoothness. As age advances, the elasticity is lessened and the wrinkles tend to become permanent.



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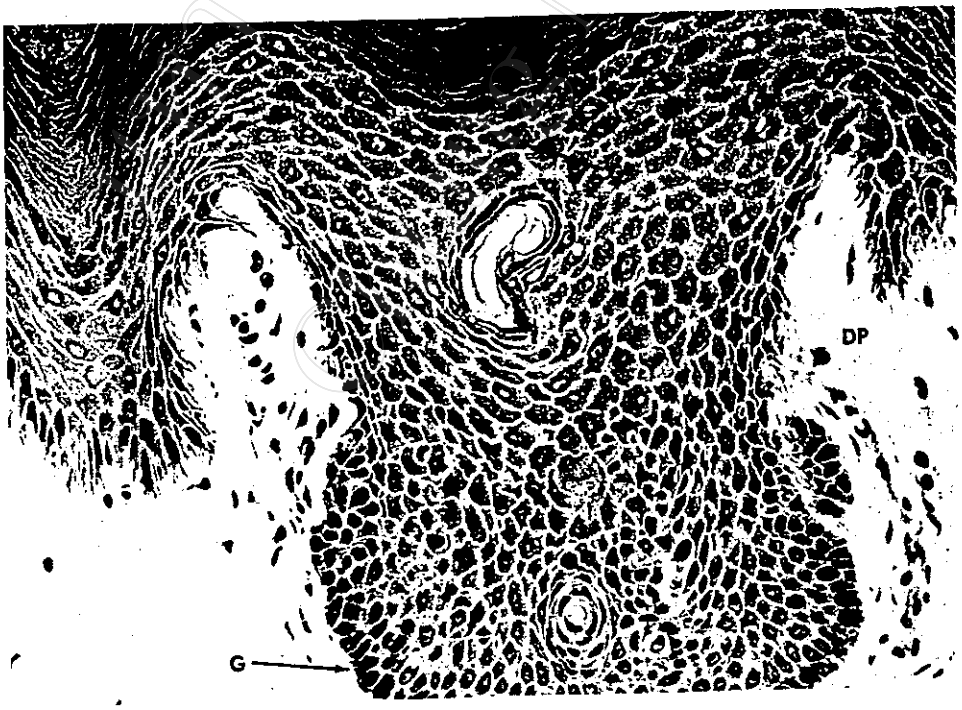

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Figure 1.2 : Micrographs of skin. **(1)** Low-power (x90) view showing the epidermis (E) and the dermis (D) underlying it. **(2)** High-power (x450) view illustrating the junction between the epidermis and the dermis. Note the dermal papillae (DP) protecting upwards into the epidermis. In the *stratum germinativum* (G), cells divide and move outwards. Dark-staining granules in the *stratum granulosum* (GR) indicate the first keratinization of these cells. **(3)** High-power (x900) view of the dermis showing adipose cells (A) and fibrous connective tissue (CT) [2].

1.1.3 Subcutaneous Tissue

Subcutaneous tissue (or *superficial fascia*) is the layer of connective tissue under the dermis of the skin. Bundles of collagenous fibers extend from the dermis into the *subcutaneous tissue*, thereby attaching the two structures firmly to each other. In most of us, both aerolar and adipose tissue compose the *subcutaneous tissue*. Adipose tissue, however, may be almost entirely missing in an emaciated individual but, in an obese person, may be several inches thick. In general, however, thin people have little fat in the *subcutaneous tissue*. The *subcutaneous tissue* is loosely attached to underlying structures in many regions of the body but is closely adherent over bony prominences. Subcutaneous tissue acts as an insulator against heat and cold and as a shock absorber against injury.

1.2 Functions of the Skin

The skin functions as a protector, a temperature regulator, and a multiple sensing device. In addition, the skin excretes fluid and electrolytes, stores fat and synthesizes vitamin D. Substances can also be absorbed through the skin, for example fat-soluble vitamins (A, D and K), estroegen, and corticoid hormones. The keratinized stratified squamous epithelial tissue that composes the epidermis make it a formidable barrier. It protects underlying tissues against invasion by unconquerable hordes of microorganisms, bars entry of most chemicals, and minimizes mechanical injury of the underlying structure. Also, melanin deposits deep in the epidermis prevent penetration of ultraviolet rays.

The skin is important in many ways in temperature regulation. Approximately one-third of the bloodstream flows through the skin and, as the blood vessels contract or relax in response to heat and cold, the skin acts as a thermostat that helps control body temperature. The two million sweat glands in the skin also regulate body temperature through the evaporation of perspiration. If body temperature rises above normal, blood vessels in the dermis dilate, and sweat secretion increases. More heat is therefore lost by radiation from the larger volume of blood in the skin and by evaporation of sweat on the skin's surface. Together, these changes tend to decrease blood temperature back to its normal level. Conversely, if blood temperature decreases below normal, skin blood vessels constrict and sweat secretion decreases.

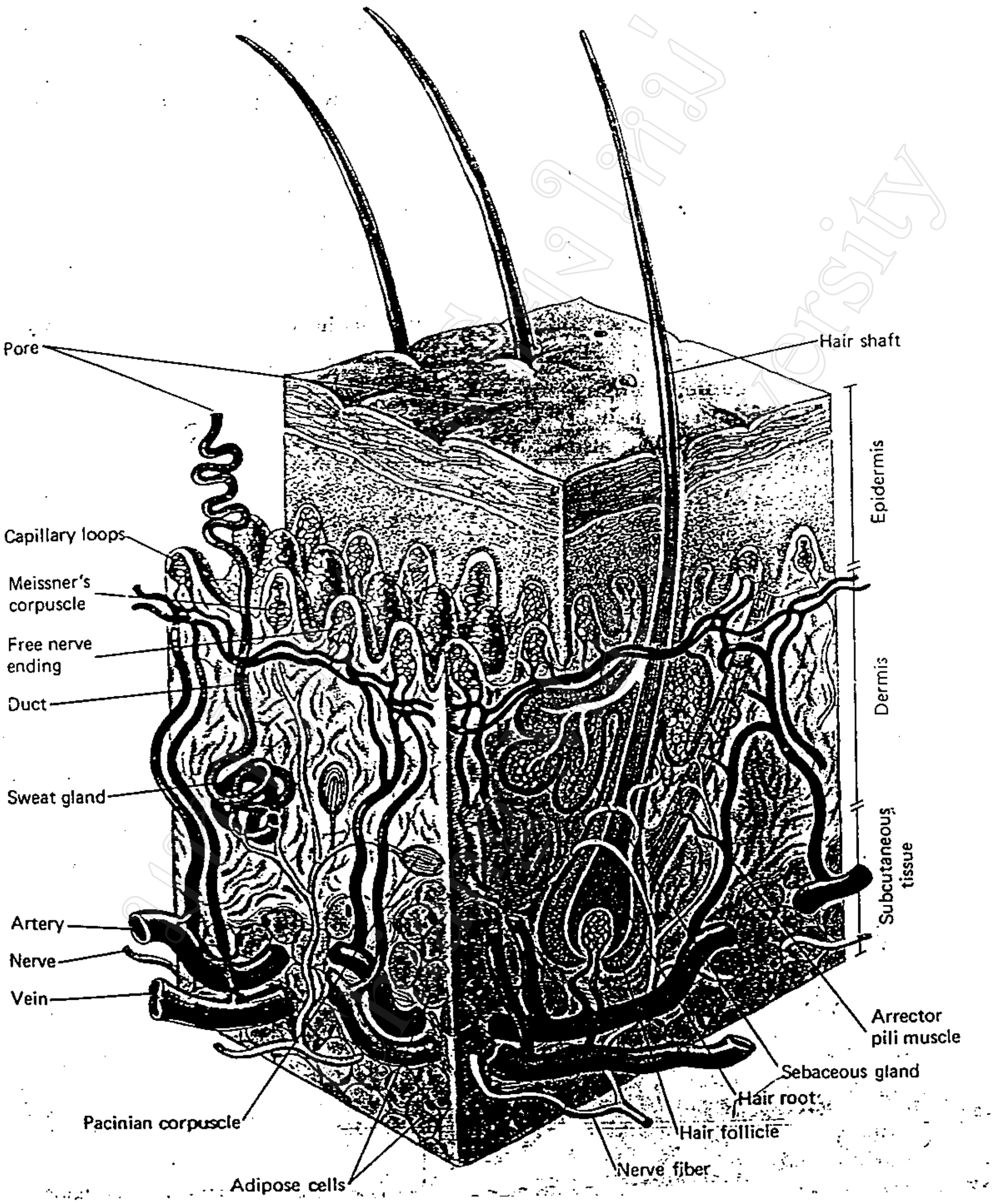


Figure 1.3 : A reconstruction of a block of skin, illustrating especially the skin vasculature, hairs, and other special skin structures [3].

Millions of microscopic sense organs lie in the dermis of all skin areas. They serve as antennas that detect stimuli which lead to sensation, not only to heat and cold, but also to pleasure, pain, and pressure. Vitamin D synthesis occurs in the skin and cells in the skin produce a protective pigmentation that determines its color and guards against overexposure to the ultraviolet rays of the sun. A steroid compound (7-dehydrocholesterol) normally present in the skin is converted by irradiation to vitamin D_3 (cholecalciferol). By absorption and elimination, the skin helps regulate the body's chemical and fluid balance. One of the miracles of the skin is that it constantly renews itself.

1.3 Burns and Other Thermal Injuries [5-7]

A severe thermal injury is one of the most devastating physical and psychological injuries a person can suffer. Approximately 6,000 or more people die each year of thermal injury. Burns are a common cause of death in young children. Burns involving over one-third to one-half of the body are often fatal, especially in children. The chief cause of death is shock, a fact of considerable significance in any effective plan of treatment.

Burns cause lesions of the skin accompanied by pain. The burn may be caused by heat (thermal burn), chemical cauterizing agents (chemical burns) or electricity (electrical burns). Sources include friction, lightning, or electromagnetic energy sources (ultraviolet light, x-rays, lasers, or atomic explosion). The types of burn that result from this various sources are relatively specific and diagonostic.

Consideration of what takes place in the damaged tissues clarifies many points of treatment. At first, capillary permeability is altered in the local injured area; that is, permeability is increased, resulting in a loss of plasma and weeping of the surface tissue. If the burn is at all extensive, considerable amounts of plasma fluid may be lost in a relatively short time. This depletes the blood volume and causes a decreased cardiac output and diminishes blood flow. Unless the situation is rapidly brought under control, irreparable damage may result from the rapidly developing tissue anoxia. Lack of sufficient oxygen and the accumulation of waste products from inadequate oxidation result in loss of tone in the minute blood vessels, and the increased capillary permeability then extends to tissues remote from those suffering the initial injury. Thus, a generalized edema often develops and the vicious cycle once estabished tends to be self-perpetuating. One of the aims of the treatment of burns is therefore to stop the loss of plasma insofar as it is possible and to replenish that which is lost as quickly as possible.

Partial or full-thickness burns must be thought of as open wounds with the accompanying danger of infection. The infection must be prevented or treated. The treatment, however, must be such that it will not cause any further destruction of tissue or of the small islands of remaining epithelium from which growth and regeneration can take place.

1.4 Classification of Burns [5-9]

The depth of the burn significantly affects all subsequent clinical events. The depth may be difficult to determine and in some cases is not known until after spontaneous healing has occurred or when the eschar is removed and granulation tissue is seen.

When burns are classified by degree, the degree of the burn is determined by the depth of skin involved within a geographic designation. First-degree burns involve only the epidermis, causing erythema with characteristic dry, painful reddening and edema without blistering or vesiculation (e.g., overexposure to the sun or flash burn). Second-degree burns involve the epidermis extending into the dermis and may be superficial or involve deep dermal necrosis. Epithelial regeneration may extend from the deep skin appendages such as hair follicles and sebaceous glands that penetrate the dermis. This burn is characterized by a moist, blistered, very painful surface (e.g., flash or scald burns from nonviscous liquids). Third-degree burns involve destruction of the entire dermis and epidermis characterized by white, lustrous, or opaque skin; dry, leathery skin; or coagulated, charred skin without sensation as a result of the destruction of nerve endings (e.g., flame burns or hot viscous liquids). Deep third-degree burns extend into subcutaneous fat, muscle, or bone; they cause scarring and may require skin grafting. These various burns are compared in Figure 1.4 and Table 1.1.

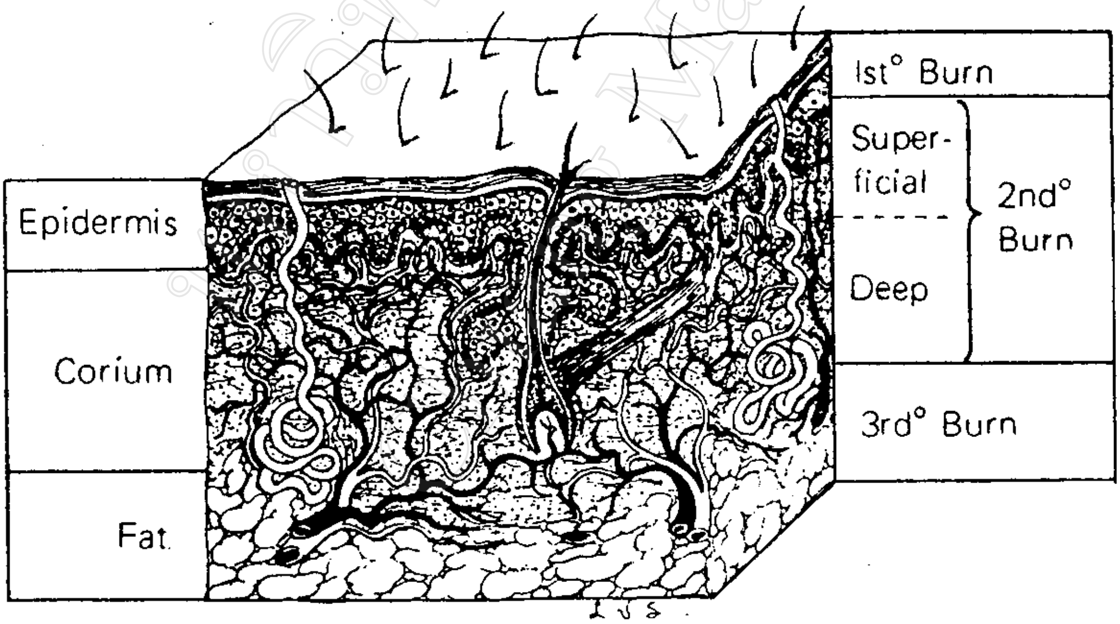


Figure 1.4 : Layers of the skin showing the comparative depths of first, second, and third-degree burns [5].

Table 1.1 : Descriptions of the variours burn ratings by degree.

Degree	Description
First - degree burn	Superficial injury involving only the epidermis. Characterized by pain, red skin without blistering, and perhaps, swelling. This is a mild partial thickness burn that will heal without scarring.
Second - degree burn	Burn extends from epidermis into the dermis area. Pain is intense, skin surface will be red, blistered, and may have a mottled appearance. This type of burn usually has edema and blistering for 2 days after the initial burn injury. This is a partial thickness burn that generally leaves minimal scarring if properly treated.
Third - degree burn	This burn involves destruction of the epidermis and dermis and may extend into fat, muscle, or tissue. Some areas will be charred black, person will complain of severe pain or no pain at all if nerves have been destroyed. This is a full - thickness burn that may require skin grafting. Healing results in significant scarring.

1.5 Requirements of Temporary Skin Substitutes Used as Burn Dressings [10,12]

Burn injuries are probably the most traumatic and most difficult to tend of all external injuries with many complications arising from the initial loss of skin. The number of burn accidents is currently increasing. Patients with burn injuries lose large amounts of body fluid through evaporation from the open wound and are also susceptible to infections. The treatment of burns therefore requires a temporary skin substitute as a barrier for protection. The dressing must be rapidly and uniformly adherence and conform to the wound bed topography and contours so as to prevent air or fluid pocket formation.

Adherence has been considered an important requirement for an ideal skin substitutes. A temporary skin substitute should adhere rapidly to the dry and wet wound surface with sufficient strength to resist lifting and slipping. The dressing must be an absolute barrier to bacterial, ingress, resist bacterial degradation, and prevent the egress of wound organisms to the dressing's surface. It must be permeable to water vapour to the extent that a moist exudate under the dressing is maintained without pooling, but excess fluid absorption and evaporation leading to desiccation of the wound bed are prevented. Adherence must be intimate and uniform because small areas of nonadherence will lead to the formation of fluid-filled pockets which are ideal for bacterial proliferation. A uniform adherence will not only reduce infection but can also reduce pain and promote wound healing.

The control of moisture content is important in preventing damage as a result of dehydration. It is believed that epidermis cell movement is slower under dry conditions because the cells are physically impeded by collagen fibres at the interface of the scab and the underlying dermis. Wounds covered with an occlusive dressing do not form scab, so epidermis cells are able to move rapidly over the surface of the dermis, through the exudate which collects at the wound - dressing interface.

Angiogenesis is fundamental to the wound healing process. It was shown that limited hypoxia actually stimulates the formation of new blood vessels and granulation tissue, and thus speeds up the healing process. Although the partial pressure of oxygen under an air-impermeable or air-permeable dressing is therefore uniformly low, oxygen-permeability is still deemed to be an important attribute for a wound dressing. Leukocyte viability and function under an air-permeable cover is significantly greater than under an air-impermeable one.

In summary, wound dressings should be semipermeable materials, e.g., films which are permeable to moisture vapour when one is placed on the wound. The aqueous component of the exudate is lost through the back of the dressing in the form of water vapour, while the cellular material remains trapped at the surface of the wound. The dressing must be compatible with body tissue, be nontoxic, nonantigenic and nonallergenic. Also, the dressing should be a durable, stress-resistant (flexible and pliable) elastic material, easy to apply and remove without trauma during dressing changes, and be nonadherent over healed areas in the wound bed or be sloughed off with the scab. It would also be an advantage for the material to be haemostatic, transparent, accelerate healing, able to provide thermal insulation, and minimize scar formation. Finally, for its nonmedical virtues, the wound cover should be a low cost, sterile material, with minimal storage requirements, readily available and have a long shelf-life.

Thus, the essential requirements for an ideal temporary skin substitute can be listed as follows [11]:

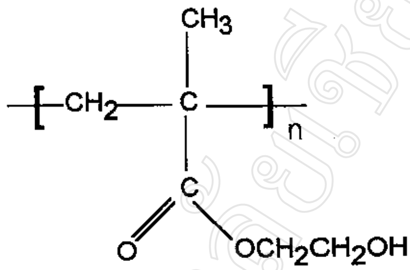
1. Controlled water vapour permeability
2. Uniform adherence to the wound surface
3. Allowance of gaseous exchange
4. Tensile strength, elasticity and pliability
5. Impermeability to micro-organisms
6. Absorption of excess exudate and toxic substances from the wound surface

7. Nontoxic and nonantigenic
8. Easy to apply and remove
9. Provision of thermal insulation
10. Ability to deliver antimicrobial agents
11. Easy to sterilize
12. Long shelf life and minimal storage requirements
13. Inexpensive
14. Haemostatic

1.6 Rationale and Aims of this Study

Nowadays, in polymer research, interest is being shown in high- value speciality polymers for purpose-designed applications. However, the strict property requirements usually demanded in such applications mean that strict microstructural control needs to be exerted during polymer systhesis. This is especially true in the case of polymers for use in biomedical applications. The real research challenge in this project lies in the fact that it requires both knowledge and experience in polymer chemistry combined with a sound appreciation of the medical problems involved.

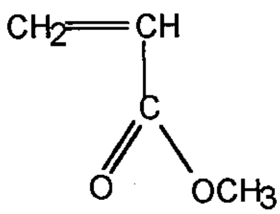
The main objective of this research project is to develop a new synthetic polymer which could be used as a temporary skin substitute. The main application of this type of material is as a wound covering for burns patients. Indeed, there is an urgent need for materials such as this in hospitals around the country to replace the conventional cotton gauze dressings which require daily changing and which tend to adhere to the wound surface. An ideal temporary skin substitute would be a material that could be left in place for a period of between 1-3 weeks before it required changing. The initial objective of this research work, therefore, is to develop a material with a usage period of at least 2 days. The class of polymer chosen for this study is *synthetic hydrogels* because of their known biocompatibility and potential for controlling water vapour transmission through structural modification. The starting point for this study is to design and prepare materials based on the well-known hydrogel: poly(2-hydroxyethyl methacrylate), P(HEMA), a polymer widely used in soft contact lenses.



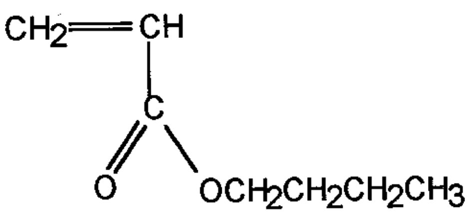
P(HEMA)

poly(2-hydroxyethyl methacrylate)

However, P(HEMA) alone does not posses the required balance of properties; in particular, its mechanical properties require improvement . This improvement may be brought about by copolymerisation of HEMA with a suitable comonomers especially chosen to modify P(HEMA)'s mehanical properties. The comonomers to be studied in this work are:



and



methyl acrylate (MA)

butyl acrylate (BA)

The resultant copolymers, P(HEMA-co-MA) and P(HEMA-co-BA),are then to be charecterised and their properties tested. From the results, their suitability as potential new materials for use as temporary skin substitutes will be assessed.

It is hoped that, by the end of this research project, a valuable insight will have been gained into how the complex property requirements of polymers in this highly specialized application can be fulfilled.