CHAPTER 1

INTRODUCTION

1.1 Skin [1]

The skin is, of course, the outer covering of the body. With its accessories – hair, nails, subcutaneous tissue, and sweat, sebaceous, and mammary glands – it is more properly called the **integument**. To most people, the skin is simply the protective surface of the body. In fact, it is far more than that. Its importance is illustrated by its very bulk. Next only to the muscles, it is the most massive organ-system of the body.

1.1.1 Activities of the Skin

Protection of the inner tissues is indeed an important function of the skin. As anyone can testify who has lost much skin by burn, sunburn, or other means, these delicate tissues suffer agonizing pain from exposure. The **retention of fluids** is equally important. In loss of skin, as from a burn, the most serious, and sometimes fatal, complication is shock due to loss of body water and salts.

In addition to simple conservation, the skin is an active factor in the **maintenance of water balance**. Whereas a person under average conditions excretes up to 1.5 liters a day in his urine, he excretes 0.7 liters or more in unnoticed perspiration and may excrete several times this amount in conditions of heat and/or extreme exertion. Uncompensated loss of this kind can have serious effects. That the skin is a major organ in the excretion of excess salt can be appreciated from the salty taste of sweat. In this instance, the skin is serving to regulate the balance of salts. A relatively minor shift in the proportion of, for example, sodium and potassium salts can have serious, even fatal, effects.

The skin also functions in the **regulation of body heat**. As is well known, a rise of a few degrees in body temperature causes intense drowsiness, as experienced by persons overcome in winter weather, and can even be used as an anaesthetic in some types of surgery. The skin helps to dissipate heat, first by the expanding of the rich web of capillary vessels near its surface, which acts as a radiator, and second by the outpouring of sweat, which absorbs heat when it evaporates. Heat is conserved by shutting down the vessels and sweat glands.

The integument is obviously a major **sense organ**. Extending nearly two square yards in a large person, its every square inch contains dozens to hundreds of tiny sense organs to detect light touch, pressure, heat, cold, and painful injuries. Loss of this widespread sensation (actually several sensations) would be very disabling. When such loss is induced experimentally, it causes mental disorganization.

1.1.2 The Structure of the Skin

The skin is composed of three layers (Fig. 1.1).

1) The Epidermis

The outer layer or epidermis is composed of many tiers of flattened cells which are continually replaced at the bottommost layer and lost at the most superficial layer. As the cells move to more superficial positions, they become impregnated with a waterproofing material called **keratin**, become transparent, and die. Simple rubbing or washing of the skin removes patches of such dead cells. They seem to have a sticky nature when in water which causes them to adhere to glossy surfaces such as to the wall of the bathtub. The sheet of "skin" which peels off our arms following a sunburn are actually several layers of such dead cells. Because there are no nerves or blood vessels in the epidermis, injuries restricted to this layer cause no bleeding or pain.

2) The Dermis

The dermis is a much thicker layer and much tougher than the epidermis. It is the "skin" from which leather is made, and is visible only after the epidermis has been scraped off. Here are located the glands, nerves, and blood vessels as well as the tough connective tissue which gives skin its strength. This connective tissue consists of strong collagenous fibers, similar to those of tendons and ligaments, as well as a quantity of elastic fibers. These elastic fibers are responsible for the smoothness of the skin regardless of whether it is stretched or relaxed. The elastic fibers also cause the normal separation of the cut surfaces of a wound, and necessitate the use of sutures in cases of injuries deep into the dermis. Aging of the skin includes a gradual failure of these elastic fibers and the skin wrinkling we associate with advancing age.

3) Subcutaneous Tissue

Underlying the dermis is a layer of subcutaneous tissue. Anyone who has skinned a rabbit or squirrel (or any mammal, for that matter) will remember the rather loose and liquid tissue which forms the layer of separation between the "skin" and the muscle, and can visualize such a layer in himself. This loose, often fatty, layer makes possible the movement of the skin over the underlying muscle in such areas as the back of the forearm. In certain areas such as the small of the back, the subcutaneous tissue measures two or more inches in thickness even in thin persons. In general, however, thin people have little fat in the subcutaneous layer, whereas most of the "fat" we associate with obesity is deposited here. In this sense, all of us, fat or thin, are pretty much alike once the skin is removed.

1.2 Requirements of Artificial Skins Used as Wound Dressings [2,3]

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 burns accidents is currently increasing. Currently available wound coverings have improved patient care significantly. The properties that serve to produce an ideal skin substitute or an optimally useful general dressing for discard and replacement as needed during wound care require careful consideration. The dressing must be rapidly and uniformly adherent and conform to the wound bed topography and contours so as to prevent air or fluid pocket formation.

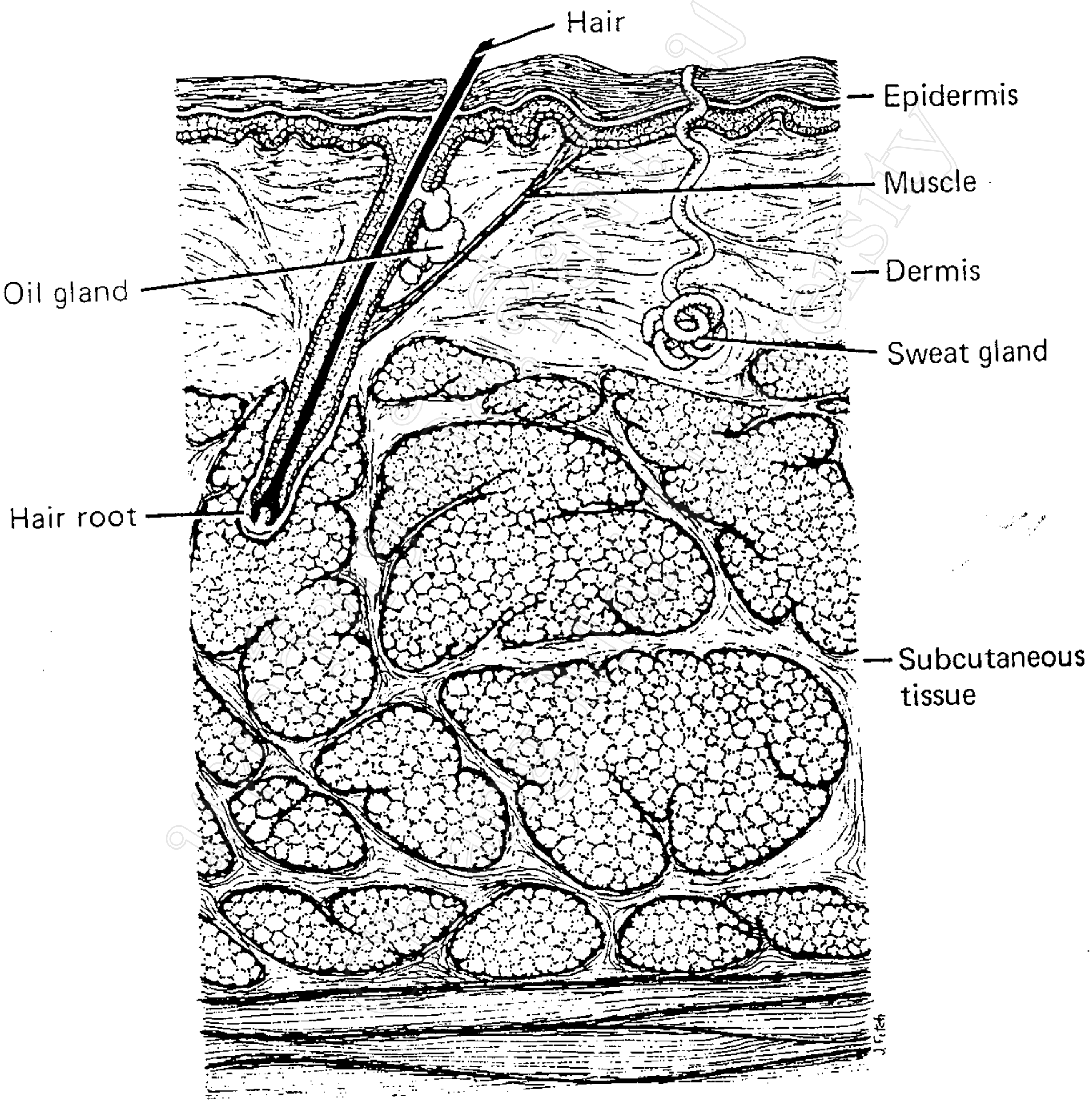


Fig. 1.1 : Microscopic section of the skin.

Good adherence reduces pain, facilitates decontamination, prevents peripheral channeling into the wound by bacteria, and promotes bonding to tissues. The dressing must be an absolute barrier to bacterial ingress, resist bacterial degradation, and prevent 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. Restricting the rate to that of normal water transmission through skin may be insufficient to prevent pooling over a wound area. The dressing must be compatible with body tissue (eg., permit ingrowth of vascular tissue), be nontoxic, nonantigenic, and nonallergenic.

The dressing should be a durable, stress–resistant (flexible and pliable) elastic material, and it should be easy to apply and remove without trauma during dressing changes, nonadherent over healed areas in the wound bed, or be sloughed off with the scab. It would be advantageous for the material to be antiseptic in nature and not only stop bacterial growth but reduce bacterial density in the wound, or at least be permeable to applied antibacterials. It would also be an advantage for the material to be hemostatic, transparent (in order to indicate the presence of infection), able to provide thermal insulation, accelerate healing, minimize scar formation, and finally, in some cases, be incorporated by the body (biodegradable) as it restores normal function to the skin.

The mode of development of hypoxic conditions in wound fluid has been studied. 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 wound dressings. Leukocyte viability and function under an air–permeable cover is significantly greater than under an air–impermeable one. As for nonmedical virtues, the wound cover should be an inexpensive, readily available, sterile material with minimal storage requirements and an indefinite shelf life.

Although many of the criteria for an ideal dressing have been realized to a greater or lesser extent in currently produced materials, there is no one material or composite that serves for all types of wound, including donor sites, burns (large and small ; superficial, deep partial, or full thickness), chronic ulcers, and various other pathologies of interest to medical practitioners. Clinicians, faced with a given lesion, may therefore pursue differing therapeutic modalities.

These requirements of skin substitutes for use as wound dressings are summarized in Table 1.1.

1.3 Synthetic Dressings

It is obvious that the only material which will wholly satisfy the list of requirements in Table 1.1 is human skin itself. However, substitutes, both natural and synthetic, have been available for some time now and these can partially fulfill these requirements.

The growing number of commercially produced or experimentally available skin–substitute wound coverings that may be classified as synthetics, organics, or composites of synthetic and organic origin are described in Table 1.2. Of particular interest in this project are the ***synthetic hydrogels*** of the 'Hydron'–type, as listed at the top of Table 1.2.

Table 1.1 : Ideal properties of a skin substitute [4].

Medical	Safety	General	Economic
Good adhesion to the wound bed	Sterility	Oxygen permeability	Availability
Maintenance of moist environment	Nonpyrogenicity	Water vapour permeability	Reasonable shelf life
Occlusiveness to microorganisms	Nontoxicity	Flexibility	Minimal storage requirements
Control of evaporative water loss	Nonantigenicity	Transparency	Cost effectiveness
Absorption or control of wound exudate	Lack of release of materials or particles that could interfere with healing		
Antisepticity or compatibility with antiseptic agents			
Ability to improve the healing process			
Pain control			
Durability			
Ease of application and removal			

Table 1.2 : **Examples of skin-substitute dressings.**

Trade Name	Composition	Salient Uses and General Characteristics
Synthetics		
Hydron	methacrylate-PEG mixture[a]	for superficial and partial thickness burn wounds (up to 20 % area) ; adheres well and takes wound contour ; antimicrobials may be incorporated in dressing ; poor durability when wet, surface cracking when dry Caution : serum pooling, infection
Epigard	polypropylene film over polyurethane foam	bioadherent (entrapment of coagulum and granulation tissue) ; useful for debridement, conservative management of partial and full thickness wounds Caution : irregular adherence, submembrane suppuration
Opsite Tegaderm Bioclusive	polyurethane films with adhesive that sticks to normal skin	no significant differences between these three temporary wound dressings ; semiocclusive barrier tapes most suitable for light use in various supportive and protective functions ; may be used on superficial (donor site and surgical closure) wounds ; used on venous ulcers to encourage exudation and painless debridement as well as on clean wounds of moderate size and depth Caution : [b] low rate of vapour permeability is conducive to membrane lifting or leaking, growth of microorganisms ; removal of tape in residence over three days may lift off newly formed tissue
Vigilon	poly(ethylene oxide)-water gel backed by polyethylene film	nonadherent, neutral, absorbent hydrogel dressing ; useful in dermabrasion, excisional surgery, over hair-transplant sites ; protective uses

a poly(ethylene glycol) solubilized poly(2-hydroxyethyl methacrylate) powder

b The clinical use of unilaminated films as dressings for invariably contaminated burn wounds has been universally unsuccessful

Table 1.2 : (continued)

Material	Composition	Salient Uses and General Characteristics
Organics		
Collagen-based synthetic skin	collagen (crosslinked) sponge	for partial thickness burns ; absorbs wound exudate, provides cell migratory scaffolding, promotes adherence, helps reduce bacterial count
Poly-nag	chitin or chitosan powders or mats	accelerated wound healing claimed after insufflation with chitin or chitosan powder
Stra Cor II	chitosan-keratinate	for contact layer over various types of chronic ulcer ; extreme vapour permeability allows use over hypertrophic granulation tissue ; may be manufactured with antimicrobials incorporated ; bioadherent after equilibration with wound exudate ; requires initial absorbent overwrap ; indefinite residence until sloughed off ; may also serve as temporary dressing Caution : subject to long-term enzymatic degradation over moist areas, cracking over dry healed areas
Chitosan-gelatin	blended chitosan-gelatin film	proposed as a general wound dressing and especially for deep burns ; adheres well to (pig) subcutaneous fat

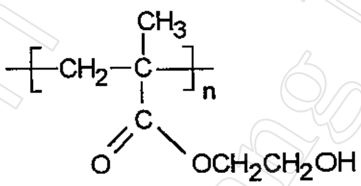
Table 1.2 : (continued)

Trade Name	Composition	Salient Uses and General Characteristics
Composites		
Biobrane	nylon-collagen peptide-silicone membrane	for partial and full thickness clean burn wounds ; semiocclusive, adheres well, easily removable ; can transmit antimicrobials through membrane ; not biodegradable, may be stripped off or allowed to slough with scab; recommended maximum residence : 30 to 50 days
Stage I, MIT	polysiloxane cover bonded to cross-linked collagen-chondroitin 6-sulfate	for extensive deep burns and excised wounds ; must be fitted and sutured ; fibroblasts and capillaries enter and degrade organic layer to form a base (neodermis) over which epithelial cells grow from periphery or via implants . Caution : microbial infection; maximum residence for over 50 to 60 days
Duoderm	adhesive polyurethane-backed gelatin-pectin-carboxymethyl cellulose-polyisobutylene mixture	completely occlusive dressing ; useful for various chronic leg ulcers; maximum recommended residence on wound : 7 days Caution : bacterial growth, hypertrophic granulation, retarded re-epithelialization

1.4 Rationale and Aims of this Study

A modern trend nowadays in polymer research is the interest 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 synthesis. 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. There is an urgent need in hospitals in Thailand for a new type of "artificial skin", particularly in the treatment of burns patients. Hopefully, this project can go some way towards meeting this need.

The main objective of this initial study is to synthesize some film–forming hydrogel polymers which have properties appropriate to their potential use as synthetic temporary skin substitutes in wound dressings. 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)

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