A STUDY TO DETERMINE MARKET ACCEPTABILITY OF A SKIN REPLACEMENT THERAPY FOR THE TREATMENT OF CHRONIC WOUNDS

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An Abstract Presented to the Faculty of the Graduate School of Lindenwood College in Partial Fulfillment of the Requirements for the Degree of Master of Business Administration

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ABSTRACT

This thesis will focus on factors that would determine the market acceptability of a skin replacement therapy for the treatment of chronic wounds.

Because chronic wounds will probably become much more prevalent as the population ages, the best method to treat these wounds needs to be developed. In just the last couple of decades, the treatment of chronic wounds has been changing as new technologies are introduced into the marketplace.

The main purpose of this thesis is to evaluate some of the various therapies from traditional wound treatment to modern wound therapy to the more advanced therapies that may show some promising results in the next several years. Two of the most promising skin tissue engineered products and their cost effectiveness compared to the gold standard therapies readily available today are examined in detail. Specifically,

it is hypothesized that the cost/benefit ratio will not be great enough to insure rapid adoption of skin tissue engineered products for the vast population of patients suffering from chronic wounds.

After reviewing and carefully analyzing the most relevant clinical studies available to support the efficacy of skin tissue engineered products and comparing these results both clinically and economically to a major clinical study conducted utilizing current best available practices in treating chronic wounds, evidence suggests that the hypothesis is confirmed. Under the current managed care environment, both payers and providers will be unwilling to pay more than three times the cost for skin tissue engineered products for insignificant improvements in healing rates.

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Chapter I

INTRODUCTION

The Aging Population

The American population is becoming demographically older. In the United States, as well as the rest of the world, individuals over 65 are the most rapidly growing segment of the population. Those over 85 compose the largest portion of this group, and also represent the most frequent users of acute care beds (Wagner 5). In part, this aging population is the result of increased life expectancies brought about by improved health care. By 2020, the "Baby Boom" generation, age 65 and older, is expected to grow to about 52 million people, and account for 17.7 percent of the population (Syzcher and Lee 142-143).

With the aging of the population will come a proliferation of diseases that are prone to attack the geriatric population segment. One of the more prevalent diseases will be that which affects the skin in the form of chronic wounds, especially pressure

sores. Pressure sores are a leading cause of morbidity and mortality among older patients, especially bed-bound elders (Rousseau 85). Mortality increases in patients who develop pressure ulcers, with death rates being six times higher for those who do not or cannot heal an ulcer (Wagner 5). The greatest wound care problem faced in nursing homes is pressure sores. Already more than one-third of all the money spent on wound care products in nursing homes is for use on pressure sores (Frost & Sullivan, *U. S. Wound Management Markets* 2-16).

Chronic Wounds

Chronic wounds are those wounds that result from a combination of factors that lead to a deterioration of the skin rather than from a single, clearly defined incident that damages the skin. The single unifying factor in this class of wounds is that there is an underlying problem or group of problems with the patient that either cause these wounds to occur or inhibit them from healing. Chronic dermal wounds heal very slowly and often linger on the patient for weeks, months, or even years. Patients afflicted by these

wounds commonly experience secondary complications, including infections, metabolic and nutritional disorders, and other factors that make wound management more challenging (Szycher and Lee 144).

Types of Chronic Wounds

There are three major types of chronic wounds: pressure ulcers, diabetic ulcers, and venous stasis ulcers.

Pressure ulcers usually afflict people whose general health has somehow been compromised. They are often found in people who are confined to bed or wheel chairs such as elderly stroke victims or paraplegics. Ninety to 96 percent of pressure sores occur over bony prominences on the lower half of the body (Rousseau). Common sites include the sacrum or tail bone area, heels, elbows, shoulder blade area, and back of the head. Pressure ulcers can be caused by pressure, shear, friction, or moisture. Shear is created, for instance, from the raising of the head of a patient's bed, causing the sacral skin to remain fixed while the subcutaneous tissue glide downward.

Diabetic ulcers are unique to diabetics. These

wounds most often afflict the feet of the patient. Though the wounds can usually be treated successfully, neglect may result in the need to amputate the lower limb(s).

Most of the venous and arterial ulcers are the by-product of peripheral vascular disease; about 70 percent come from insufficient blood supply coupled with high blood pressure (Phillips 50).

Market Potential

The $1.57 billion U.S. market for wound management products grew at a rate of 10.1 percent in 1992 and is expected to nearly double in size, to $2.89 billion, by the end of the decade (Frost & Sullivan, *U. S. Wound Management Markets* 3.1). The reduction in healthcare dollars and a "graying America" require that nurse managers take serious action to reduce the incidence of pressure ulcers (Hausman 88R).

The market is very large, around 3.5 million chronic dermal ulcers per annum in the U.S. alone (Wilson 1). Leg ulcers are estimated to be 900,000, diabetic ulcers are estimated to be 600,000, and the largest portion, pressure ulcers, are estimated to be

two million cases per annum, and their prevalence is likely to rise as the population ages. They cause considerable disability, and the cost of treating these chronic wounds is enormous (Phillips 49). This figure will only grow larger as the population ages because many of these chronic wounds are directly related to being hospitalized or bedridden.

Therapeutic Strategies

Currently, a plethora of wound care products exists ranging from traditional therapies to advanced therapies. Traditional therapies focus on the acute issues of stopping blood loss, walling off and sealing the wound, and resisting infection. This would include natural products such as cotton and gauze for either packing the wound cavity or simply covering the wound itself. The advanced therapies try to fix the damaged tissue and return them to normal function and strength. It can be argued that the major differences between traditional wound care and advanced wound care is that traditional approaches focus on damage control and pay little attention to repair. Advanced approaches try to anticipate and manage repair without compromising the

process of damage control.

Advanced wound therapies include synthetic dressings such as hydrocolloids, thin films, polyurethane foams, and hydrogels. These dressings reduce pain, accelerate repair, add to the strength of the healed tissue, and lessen the amount of residual scarring. Advanced dressings improve the body's ability to affect repair by sealing in wound fluids and sealing out the outside environment (Frost & Sullivan, *U. S. Wound Management Markets* 2-10).

Current standards of care involve use of products such as the ones described above with tissue debridement (surgical removal of necrotic tissue) and antibiotic usage. Even under such ideal standards of care (and it should be noted that these do not always exist), the closure rates of chronic dermal ulcers are low and many wounds never heal (Wilson 3).

In short, there is an obvious need for advancements in wound healing products that not only increase closure rates but also deal with the more recalcitrant (non-healing) ulcers. As with other areas in biotechnology, the principle involved is to try and develop wound healing agents based upon a thorough

understanding of the molecular physiology of wound healing.

Active Healing

Many older wound care products are considered "passive" in nature, meaning they do not interact with the wound at all. Gauze dressings are perhaps the most obvious example of a passive wound care product. Many of the newer products on the market, and especially those under development, offer the advantages of taking an active role in the healing process. The whole concept of moist environment wound dressings, for instance, is that keeping the body's natural fluids in contact with the wound assists and accelerates the healing process.

The next generation wound care products will take an even greater role in accelerating the healing process. Wound therapies that can intervene in various phases of wound repair in order to stimulate, enhance and induce cellular migration and proliferation are being developed. Some of these newer dressings may include various growth factors or other biotechnology-derived substances. Others will use new designs or

blends of materials to improve outcomes.

There are three main approaches to active wound healing: growth factors, matrix enhancers, and skin replacement therapy. Growth factors are biopharmaceuticals that are naturally occurring or synthetically produced proteins or protein-like molecules that influence migration, division, and maturation of cells (Frost & Sullivan, *World Growth Factor Markets* 2-1). Growth factors stimulate cell migration or proliferation or affect collagen orientation enhancing the tensile strength of closed wounds (Turner 45). Extracellular matrix (ECM) is a dynamic structure with the capacity to modulate tissue development and regulate tissue repair (Skover 425). It is like scaffolding for the growth of new skin over wounds. Matrix enhancers help fill the dead space over a chronic wound and assist in cellular migration.

In theory, skin replacement products not only provide wound healing benefits but also immediate covering of the opening of the wound. Biotech companies are trying to treat disease by transplanting specific cells and tissues that they have engineered in the lab. There are companies that are using cells from

sources such as newborns and patients to grow skin for repairing burns and other wounds (Landeen et al 167).

Market Opportunity for Active Healing

The potential that active wound healing offers to companies that compete in the wound healing marketplace in a time of healthcare reform is the competitive advantage of being able to accelerate wound closure thus reducing the major cost component--labor cost--of the caregiver and improving the overall quality of life of the patient.

In the future, skin replacement therapy is likely to achieve a significant share of available procedures despite competition from available therapies.

Summary

The closure rates of chronic wounds are low and many wounds simply do not heal, even under the current standards of care regimes of tissue debridement and antibiotic usage. The cost of this level of care is substantial. Estimates of between $5 billion and $9 billion is spent per annum in the U.S. treating pressure ulcers and over $1 billion in outpatient care

of venous stasis ulcers. The surgical costs of amputations resulting from diabetic foot ulcers cost in excess of $1 billion (Wilson 3). The healthcare costs of treating just one foot ulcer is estimated to be as high as $36,000 (Wilson 3).

Wound healing as an area for investment features one very substantial positive: the market is very large, around 3.5 million chronic dermal ulcers per annum in the U.S. alone (Wilson 1).

Demographic trends combined with the development and introduction of new products and technologies drive growth. Demographics show that chronic wound healing will be a greater problem rather than a lesser problem as time goes on.

Statement of Purpose

It is incumbent upon any company that competes in the wound management field to investigate and study the new technologies that will have the greatest potential for the next generation of wound healing; therefore, this study will investigate the possibility that cell replacement offers the greatest potential at this time.

Chapter II

LITERATURE REVIEW

Overview of Skin

The skin is the body's largest organ and one of the most important. It may also be one of the most frequently abused, and is certainly one of the most commonly injured (Bark 2). Roughly 12 percent of an average individual's body weight is skin. (The World Book Encyclopedia 488). The skin plays a major role in temperature regulation and fluid balance. It houses the sense of touch and acts as a trigger in an individual's development process (The World Book Encyclopedia 489).

The skin is comprised of three principal layers: the epidermis, the dermis, and the subcutis. Each of these in turn has a different structure, including different cells and intracellular matrix. Interlaced throughout are the specialized cell structures such as hair follicles, nerve endings, sweat glands, and an infrastructure of blood vessels and muscles. The outermost layer of skin, the epidermis, is constantly

renewing itself with cells that move upward from its basal layer which rests on the basal lamina lining the dermal-epidermal junction. The tough dermis, which largely consists of connective tissue, gives the skin its strength and resiliency. Beneath the dermis, subcutaneous tissue stores fat to provide energy and insulation (Grossbart and Sherman, 19).

Epidermis

The epidermis is the outermost layer of skin. It is made up of three types of cells: keratinocytes, melanocytes, and Langerhans cells. Keratinocytes are the most plentiful and are the major cellular element in the epidermis, as well as the hair and nails (Grossbart 19). Langerhans cells play a key role in the cutaneous immune responses, protecting the body from external invasion (Barbul 282).

Dermis

The dermis is the thickest part of the skin and houses most of the specialized structures. Sebaceous glands, sweat glands and nerve endings are all found in this layer. Here lie the free nerve endings and epidermal appendages which give rise to pain sensation

and the micro-vessels and the capillary junctions that feed the skin and carry away waste products of cell metabolism. The dermis lies underneath the epidermis and consists of a complex meshwork of fibrous molecules (called the extracellular matrix, ECM) which acts as a support medium for special connective tissue cells called fibroblasts, the most common cell type in the human dermis. The latter are responsible for producing certain growth factors (such as PDGF—platelet derived growth factor and FGF--fibroblast growth factor), fibrous ECM protein molecules (such as fibronectin and collagen), and other molecules that provide skin with its structural integrity (Erlich 359).

Subcutaneous Tissue

The innermost layer of the skin is called the subcutis. This layer is made up primarily of fats called lipids, which are made in the predominate cell structure, the lipocyte (Clark 29). The subcutis layer provides cushioning for the body's internal structures, serves as an insulator for the regulation of body temperature, and stores energy in the form of fats.

Phases of Wound Healing

The spectrum of dermal wounds runs a broad gamut in terms of severity, cause, and the kinds of problems involved in their repair. There are ongoing debates about the proper classification of wounds, protocols for treatment, and material differences of opinion about just what is happening as a wound heals. However, many scientists believe that the repair of all wounds involves certain fundamental responses and common mechanisms that vary in response to the individual requirements of that wound (Cooper 3). In other words, the body will always try to stop fluid loss, wall off the site of the damage, and address contamination and infection. The body will always try to activate a cellular response to repair the damage and restore the tissue to near its original state and function.

The wound healing process is initiated with hemostasis and inflammation and passes through the stages of proliferation, maturation, and remodeling.

Hemostasis stops blood loss with fibrin clots and constricted vessels and walls off wounds. Local inflammatory molecules summon neutrophils and macrophages to engulf foreign matter. These

inflammatory cells release enzymes (lysozymes) which lyse fibrin and platelets causing release of wound repair factors to initiate repair (Clark 29).

Classification of Wounds

A Consensus Development Conference sponsored by the National Pressure Ulcer Advisory Panel was held in Washington, DC, in March 1989. As a result of this conference, a universally accepted staging system for use by all professional disciplines was developed. If these states are used by everyone, data about pressure ulcer prevalence, incidence, cost of prevention, and efficacy of treatment will be more easily communicated (Maklebust 30).

There are four classifications or stages of pressure ulcers. Stage I is erythema or redness of skin not going away within 30 minutes of pressure relief. The epidermis in this stage remains intact. Stage II is partial thickness loss of skin layers involving epidermis and possibly penetrating into but not through the dermis. The wound base looks moist and pink, is painful, and is free of necrotic tissue (tough, dry, dead skin, like a scab). Stage III is full-thickness tissue loss extending through dermis to

involve subcutaneous tissue. Looks like a shallow crater unless covered by eschar (a scab-like covering over the wound) and may also include necrotic tissue. Stage IV is deep tissue destruction extending through subcutaneous tissue to fascia and may involve muscle layers, joint, and/or bone. The stage IV wound looks like a deep crater (Tudahl 158).

In 1993, Marge Meehan conducted a survey of patients with pressure ulcers. The sacrum (the tail bone area) was the most common location for ulcers, with 36 percent of all ulcers reported; the heel was the second most common site with 30 percent (Meehan 28).

Stage I ulcers represented 46.95 percent making them the most frequently reported, with Stage II a close second at 32.66 percent. Stages III and IV were a much smaller percentage (Meehan 29).

The focus of this study is specifically leg ulcers and pressure ulcers. In these wounds, skin breaks down as a result of disruption of blood flow to the skin caused either by prolonged pressure over a localized area or by chronic diseases which affect the circulatory or peripheral nervous systems. In many of these patients, skin ulcers are open, often painful

wounds which are resistant to healing for many months or years.

Demographics, Prevalence, and Incidence

It is well accepted that the prevalence of chronic skin ulcers increase with age. Elderly patients are among those with the highest risk of developing pressure ulcers, and the projection for the United States is for a growing population of elderly patients at high risk of developing pressure ulcers (Erwin-Toth 12). According to Healthcare Financing Statistics, 120 per 100,000 persons aged 45-64, 150 per 100,000 persons aged 65-74, and 800+ persons per 100,000 aged 75 and older will have a chronic skin ulcer (1992 HCFA Statistics 50).

Prevalence is the number of patients with pressure ulcers at a point in time and incidence is the number of patients who acquire pressure ulcers in one year. Incidence, not prevalence, will drive the continuing wound care market.

There is no single source of reliable statistics about the incidence of chronic leg and pressure ulcers either worldwide or in the United States. Available statistics are based on some regular reporting, ad hoc

research studies of particular industries or particular settings, and hospital settings rather than nursing homes where the majority of chronic wounds are treated (Erwin-Toth 12). There is very little data on recurrence, the impact of deaths on the numbers, and the number of patients versus number of ulcers. There may be under-reporting of pressure ulcers because pressure ulcers are not usually the primary reason for admission to hospitals, pressure ulcers are not separately reimbursed if acquired in the hospital, and there is a stigma attached to a patient having a pressure ulcer because they are usually preventable by good nursing practice.

The prevalence of pressure ulcers in United States hospitals is widely quoted as three to ten percent of one million patients at any one point in time (i.e., 30,000 to 110,000 patients (Raney 46). The incidence of new pressure ulcer patients is quoted at one to five percent of the 35 million admissions per year (i.e., 350,000 to 1,750,000 new patients)(Raney 46). The incidence data for pressure ulcers in nursing homes and the community generally are incomplete.

Despite occasional reports that most pressure ulcers occur in nursing homes, the incidence numbers

indicate that most pressure ulcers occur in hospitals and are treated there. However, there are patients admitted to hospitals with pressure ulcers and it is sometimes the primary cause for admission; although more frequently is the secondary cause for admission due to reimbursement issues (Raney 47). With early discharge incentives at hospitals, nursing homes claim a high proportion of patients from hospitals who have pressure ulcers on arrival. More pressure ulcers are treated in a nursing home setting than originate there, primarily due to early hospital discharge. Leg ulcers usually originate at home but are then treated in the hospital, physician's office and other specialized outpatient/clinic settings (Langemo 49).

Current Approaches to Wound Healing

Basically all wound care dressings are divided into two broad segments: dry, traditional products such as gauze and tape, and advanced moist-healing products such as hydrocolloids, transparent films, polyurethane foams, and calcium alginates.

Today, sales of advanced products represent about 40 percent of total sales of wound care products (Frost & Sullivan 3-6). In the next few years, that is

expected to grow at a rate of 10-15 percent (Cassack 28). With the greater differentiation and technological innovation has come a dizzying complexity. Go to any advanced wound care meeting today and one gets some feel for the blur that clinicians must be feeling. It is one product after another, with only the subtlest of differences between them. For any given wound, there are 25 or 30 different products that could be used to achieve the same results (Cassack 29).

Evolution of Wound Healing Technology

As previously discussed, the wound management industry has witnessed an evolution in the manner in which wounds have been treated over the past several decades. In the 1960's, the traditional treatment was with cotton and gauze and basically maintaining a dry environment for healing to take place (Roma 3). In the early 1970's, Smith & Nephew introduced a new technology called "thin film" dressings which for the first time created a moist environment for the healing process to take place (Roma 6). However, one major drawback with this technology was that it could not deal with the amount of exudate or fluid that the wound

was producing. In the early 1980's, a company called ConvaTec addressed this exudate problem by offering one product that would create a moist environment and manage moderate exudate in a single product called Duoderm (hydrocolloids). In the 1990's, a barrage of new products based upon a combination of thin films, hydrocolloids, polyurethane foams, and calcium alginates make up the advanced wound care market. The next evolution in wound care will take place in the late 1990's and it will be based upon active wound healing products that may have the potential to accelerate the healing process (Wysocki 166).

Currently, these active technologies can be categorized into three areas: 1) growth factors, 2) matrix enhancers, and 3) skin tissue engineering. For the purposes of this thesis, the focus will be on skin tissue engineering, which appears at this time to have the best clinical results and which, more than likely, will be first to the market.

Skin Tissue Engineering

Skin tissue engineering is the ability to create living tissue and collagen matrix structures capable of being remodeled into functional skin by the body's own

cells (Wilson 3). Skin tissue engineering encompasses a number of approaches to skin tissue cultures and its use directly or in combination with other biological or synthetic materials. Homologous skin covering products are prepared based mainly on cells called fibroblasts taken from neonatal foreskins, which are discarded from circumcisions (Hamilton 77). In contrast, autologous products are cultured from a patient's own skin through a biopsy procedure and grown in a special skin culture engineering laboratory. One of the constraints with autologous products is that they may take ten to twenty days to grow a significant amount of skin to cover a chronic wound (Hamilton 77).

Because homologous products use human tissue derived from sources other than the patient himself or herself, there is a possibility that certain diseases (including AIDS and hepatitis) could be transmitted to the patient using them. There are millions of blood transfusions each year, hundreds of thousands of artificial inseminations, bone marrow transplants, and thousands of burn skin grafts, cornea transplants, and heart valve replacements. Real or perceived risks of disease transmission do not appear to be a significant factor in these procedures. The actual record in the

United States has been excellent. These conditions, however, are very serious, life-threatening conditions. Chronic wounds are generally not viewed as life-threatening and therefore, disease transmission may be more of an issue. This perception of disease transmission may be a threat to the widespread adoption of homologous skin tissue engineering. Due to this, many patients may prefer the autologous products because there is no threat of disease transmission since the skin cells are derived from the patient's own body. However, homologous products may have a better chance of being commercially successful in the marketplace due to the convenience and reduced time required to deliver the product to the patient. "Skin tissue engineering will be here in five years, I'm sure," said FDA biotechnology chief Dr. Philip Noguchi in June 1996 (Bucks County Courier Times, 2A).

Recalcitrant Segment

Recalcitrant segment wounds are defined as those patients whose wounds have not healed despite the repeated applications of existing products and/or current standards of care. If a market exists for skin tissue engineering, the writer believes it will start

in the recalcitrant segment.

There are few reliable data sources for this segment. Quoted figures are that 30 percent of venous ulcers are severe and candidates for tissue engineering products. Twenty percent of leg ulcers remain unhealed for over two years and about ten percent of pressure ulcers are recalcitrant. There are approximately 50,000 amputations per year due to diabetes, and at least 10 percent of diabetic ulcers are severely recalcitrant. For leg ulcers, the recalcitrant segment is about 15 percent of the total leg ulcer numbers. For pressure ulcers, the recalcitrant segment is about 10 percent of Stage III and Stage IV ulcers only (Bolton 33).

A clinical study was conducted by Bristol-Myers Squibb to test the efficacy and safety of an oral product (Ifetroban) versus a placebo in patients with recalcitrant venous leg ulcers. One of the results of this study was that managing recalcitrant wounds with the use of a moist wound environment using a hydrocolloid dressing and the use of compression was found to be efficacious and sets the standard of care (Bristol-Myers Squibb 5).

Clinical Efficacy and Patient Outcomes

Clinical efficacy, cost effectiveness, and improved patient outcomes will be the most significant hurdles for skin tissue engineering products. The demonstration of unequivocal clinical efficacy and statistical significance will be necessary to convince a very cautious Federal Drug Administration (FDA) to grant approval for use a result of the above, clinicals will be larger, more expensive, and more difficult to control.

There are many problems in clinical comparisons. One problem is that there are no established standards of care for use in wound care clinicals. Many different control dressings are being used, from gauze to hydrocolloids. Standards of care also encompass the patient turning regimen for pressure ulcers or appropriate compression for venous ulcers, wound debridement, use of topical agents, etc. Another problem is that the conventional wisdom is that a fully-healed wound is the desired and necessary end-point. However, even this causes debate as to the underlying tissue condition. Other suggested end-points for clinicals include rate of healing, percentage healed, pain reduction, restoration of function or

mobility, prevention of recurrence (Plackett 3). Another problem is that leg or foot ulcers and pressure ulcers have high rates of recurrence. This has yet to be fully explored in clinical trials.

At a more fundamental level, there is clearly a lack of scientific understanding of the complete wound healing process. This will be of increasing significance as more interactive products enter the market. Some clinicians suggest that *any* improvements would be acceptable for venous ulcers, which are extremely difficult to heal; but clinical results will need to be significant to satisfy the FDA.

International Committee on Wound Management

The International Committee on Wound Management (ICWM) was established in 1992 in response to a growing confusion surrounding wound management (Wound Management in the Elderly 130). The ICWM is composed of wound healing experts from around the world. The Committee has addressed the key issues and defined the responsibilities of the health care provider as they relate to wound management. The subject of ICWM's third meeting in 1995 was the measuring of the cost effectiveness of wound management (Plackett 1). These

experts established that cost effective wound management should take into account the cost of achieving wound care results, such as healing, not just the cost of a single product use.

Cost

Cost effectiveness of wound management is an important issue because health care professionals and reimbursement agencies around the world have a constant struggle to provide high quality wound care while containing health costs.

Over the past 15 years there has been a general commoditization of medical products. For instance, two decades ago, even products like surgeons' gloves were considered appropriately a matter of surgeon preference (Cassak 26). Today, gloves, along with an increasing number of other products, are finding themselves covered under hospital group purchasing agreements that all but ignore features and benefits in the name of securing lower prices. This trend has greatly affected the wound care market as well. Traditional wound care products--gauze and tape and bandages--have felt the full force of such pressures.

Many wound care companies have successfully

resisted such pricing and margin pressures by focusing on a key technological shift in the treatment of wounds--the shift from dry to moist healing. Today, advanced wound care products such as hydrocolloids, foams, and calcium alginates are booming, taking more and more share from traditional dressings and doing so at prices and margins that have just begun to come under price scrutiny because of the evolution of managed healthcare. Money-saving measures in the treatment of chronic wounds may actually increase cost while reducing the quality of care (Bolton 32). Cost-effectiveness must be taken into account.

Rapid technological innovation is inviting a host of new companies into the market, introducing fierce competition. The influence of a managed care environment will have dramatic effects on wound care companies to validate the cost effectiveness of not only new technologies but also existing therapies.

Studies of cost to treat chronic wounds have produced a wide range of results, typically ranging from $2,000 to $40,000 or even higher (NPUAP 24). The cost to heal a complex, full-thickness pressure ulcer may run as high as $70,000 (Gallagher 28). However, these estimates are not established as any basis for

comparison of skin tissue engineering. Clearly there is a major need for actual cost information and cost to heal wounds (cost effectiveness); some of this information will be developed in the near future with the assistance of software programs in tracking treatments and outcomes. Until now, the dressing/material cost has been a relatively small portion of the overall cost of treatment. With the projected cost of skin tissue engineering products ranging from $500 to $2,000 per application, they will undoubtedly be perceived as very expensive. This, of course, will be another major hurdle for skin tissue engineering products, particular given the lack of an established, accepted "real" cost of existing treatment.

Reimbursement

Current reimbursement mechanisms are based on average per procedure, per diem, or per visit costs; they currently do not specifically reflect the expensive-to-treat recalcitrant segment. With this in mind, the current reimbursement mechanisms tend to work against the adoption of skin tissue engineering. One recent example is Procuren, a platelet derived wound

healing factor from Curative Technologies (Platelet 28). Procuren was initially reimbursed by Medicare but subsequently overturned partly because of lack of demonstrated clinical efficacy and outcome benefits (Platelet 28). Another problem with Medicare reimbursement for Procuren was that it was a self administered product.

It is the writer's belief that reimbursement will be fundamental to the adoption of any skin tissue engineering technologies. Pioneering companies will have a major task in educating the reimbursement agencies on the efficacy of these skin tissue engineered products.

Currently, Medicare, and to a lesser extent Medicaid, are the most important programs in wound care reimbursement. Medicare is a Federal reimbursement program, and Medicaid is a s
ate-sponsored reimbursement program. Since none of the skin tissue engineering technologies are yet cleared by the FDA, they are therefore not candidates for reimbursement.

Accessibility of Treatment Setting

Limited market accessibility for the sale and

delivery of skin tissue engineering technologies will exist due to limited capabilities to deliver and preserve the actual skin tissue engineered products. Skin tissue engineered products require special packaging to ensure preservation if not used within 24 hours. Currently they must be stored at -80° C (Karlsson, 243). Generally, only hospitals and large nursing home chains may be able to properly handle the advanced products, which means only patients in these settings will have access to skin tissue engineered products. Overall, approximately 63 percent of pressure ulcer patients and approximately 75 percent of leg ulcer patients are accessible for treatment with skin tissue engineering (Sittinger et al, 237). Patients using home health agencies generally would not be accessible to the skin tissue engineering products because of these agencies' lack of facilities to store and preserve the products and because of the lack of large purchasing volumes which would facilitate the necessary training and support functions required with these products.

Skin Tissue Engineering Companies

Currently there are two major companies that are

developing potential skin replacement products that will have application for wound healing. The two companies are Organogenesis, Inc. and Advanced Tissue Scientists (ATS). Each of these two major biotechnology companies involved in the chronic wound healing market have somewhat different approaches to the healing of chronic wounds.

Organogenesis, Inc. - Company Background

Organogenesis Inc. (OI) is using its unique, proprietary technology to develop a variety of innovative medical devices that will serve as replacements for damaged tissues and organs. The Company, incorporated in 1985, is based in Canton, Massachusetts.

Since its founding in 1985, Organogenesis has assembled an impressive team of scientists and engineers with complementary skills in biotechnology. This team has developed premier tissue engineering capabilities and a substantial body of knowledge rooted in strong skills in cell biology, immunology, and collagen matrix biochemistry (Organogenesis 4).

Organogenesis' technology represents a significant development in the historical evolution of tissue

repair/engineering. Today, OI is a leader in the development of products based on tissue engineering products created for biologically derived materials rather than from synthetic materials that can substitute for damaged or diseased human tissues or organs in a way that allows the patient's own cells to remodel the implant into new tissue. The Organogenesis product that may have an impact on chronic wounds is called Graftskin.

On January 17, 1996, Sandoz Ltd. in Basel, Switzerland, and OI in Canton, Massachusetts jointly announced the execution of an agreement that gives Sandoz the licensing rights to Graftskin (PR Newswire 1/17/96, 1). Under the terms of the agreement, Sandoz will have exclusive worldwide marketing rights to Graftskin and OI will supply Sandoz's global requirements for the product. Shortly after this announcement, Sandoz changed its name to Novartis.

Graftskin

Organogenesis' Graftskin is a living, tissue-engineered, homologous skin substitute consisting of two layers derived from circumsized skin of newborn males. The upper layer contains human keratinocytes

(the most common cell type in human epidermis) which form a well differentiated epidermal layer. The lower dermal layer contains collagen with human fibroblasts (the most common structural protein and cell type, respectively, in the human dermis) (Graftskin 50).

Currently, Graftskin is the only full-thickness, living skin equivalent in human trials. In clinical applications, Graftskin has been shown to cover and protect wounds, eliminate the need to create a second wound site on the patient, accelerate wound healing, and reduce hospital stays. No immunological rejection has been observed with Graftskin. It is not perceived to be "foreign" by the body because its basic structure is similar to that of human skin.

Graftskin offers some advantages to the chronic wound patient. First of all, Graftskin is designed for easy handling, which is important in surgical procedures. Secondly, in clinical applications, where skin grafting or replacement is required, Graftskin can provide coverage and protection of wounds, eliminating the need to create a second patient wound site because it is a homologous product. Since the body's immune system does not reject Graftskin, the patient's skin should gradually replace the graft with its own skin

tissue.

Clinical Evidence - Graftskin

In a controlled study, Graftskin dressing under foam and compression was compared to foam and compression alone on venous ulcers. This study continued at least six months with 61 percent of the venous ulcers healed in a median healing time of 57 days for Graftskin versus 44 percent healed in 80 days for the control (Sabolinski et al, 311).

Advanced Tissue Sciences (ATS) - Company Background

ATS is also a leading tissue engineering company engaged in the development of living human tissue products for therapeutic application. The company has successfully replicated a variety of human tissues including skin.

Leading ATS' product development efforts are therapeutic skin products that address the diabetic foot ulcer market. The products, based on Dermagraft, were developed to treat conditions where the dermis has been injured or destroyed such as in chronic skin ulcers.

Dermagraft

On April 29, 1996, ATS signed an agreement with Smith & Nephew to form a fifty-fifty joint venture for the worldwide commercialization of Dermagraft for the treatment of diabetic foot ulcers. With sales and marketing capabilities in over 90 countries, Smith & Nephew is a major force in the global wound care market (PR Newswire 8/7/96, 1).

Currently in pivotal clinical trials on diabetic foot ulcers, Dermagraft is being used to provide a healthy, metabolically active dermal tissue replacement to promote healing and closure. Advance Tissue Scientists utilizes a one-layer approach. Although literature reports have indicated recurrence rates ranging from 20 to 50 percent within the first year following healing, Dermagraft-treated patients who healed during the pilot study had no recurrence of their ulcers after being followed for an average of 14 months (Advanced 8).

Clinical Evidence - Dermagraft

A pilot study was conducted to determine the effectiveness of Dermagraft for the healing of diabetic foot ulcers. Three dosage regimens of Dermagraft were

compared to standard therapy in a controlled multi-center, randomized trial. After 12 weeks, 30 percent of the Dermagraft treated and 8 percent of the control ulcers healed completely (Gentzkow et al, 330).

Hypothesis

The cost/benefit ratio will not be great enough to insure rapid adoption of skin tissue engineered products for the vast population of patients suffering from chronic wounds.

Chapter III

SELECTIVE REVIEW AND EVALUATION OF RESEARCH

Studies

Three studies will be evaluated in this chapter. The first study is "Cultured Skin as a 'Smart Material' for Healing Wounds: Experience in Venous Ulcers" by M. L. Sabolinski, O. Alvarez, M. Auletta, G. Mulder, and N. L. Parenteau as presented in Biomaterials 1996, Vol. 17, No. 3, pages 311-320. The second study is "Use of Dermagraft, a Cultured Human Dermis, to Treat Diabetic Foot Ulcers" by Gary D. Gentzkow, Scott D. Iwasaki, Kenneth Hershon, Marvin Mengel, Joseph J. Pendergast, John Ricotta, David Steed, and Scott Lipkin, which was published in Diabetic Care in April 1996. The third study is "A Multi-Center, Double-Blind, Parallel Group Efficacy and Safety Comparison of Ifetroban and Placebo in Venous Leg Ulcers," conducted by Bristol-Myers Squibb.

Research Methods - Sabolinski Study

In the Sabolinski article, the researchers are testing the hypothesis that living tissue can act as a "smart material" to heal wounds. By "smart material" the authors mean a wound covering that responds to its environment to bring about healing. Graftskin from Organogenesis was the "smart material" used in this controlled study. The 233 patients with venous ulcers were treated and evaluated in a prospective, controlled, parallel group, clinical trial at 15 centers. Patients with significant arterial disease were excluded from the study (see Table 1). All patients had failed on previous venous ulcer treatments in the community and had open ulcers for at least one month. The median duration of ulcers of patients who were enrolled into the trial was approximately one year. The median size of the ulcers treated out of 233 patients in the study was approximately 400 mm^2. All patients were treated for their ulcers at weekly visits for eight weeks. Graftskin was compared to multilayered compression therapy control in a randomized trial. Demographic data of the two treatment groups is shows in Table 2. Statistical comparisons between groups showed that the

TABLE 1

PATIENT POPULATION

Inclusion	Exclusion

-- Ulcers secondary to CVI
  -- Venous filling time <20s
  -- Clinical criteria characteristic of venous disease
-- > 1 month Hx of non-healing
-- IRB approved informed consent
-- Expected availability 1 year follow-up
-- 18-85 years
	-- Ulcers < ½" x ½" or >4" x 8"
	-- Arterial disease (ABI <0.65)
	-- Vasculitis, RA, other colagen vascular diseases
	-- Pregnancy or lactation
	-- Medical conditions that would impair wound healing
	-- Cellulitis
	-- Osteomyelitis
	-- Necrotic or avascular wound bed
	-- Ulcer with exposed bone, tendon or fascia
	-- Uncontrolled diabetics
	-- Corticosteroids, immuno-suppressive agents, radiation, or chemotherapy
	-- Enrolled in other studies within 3 months

TABLE 2

COMPARISON OF THE TWO TREATMENT GROUPS' DEMOGRAPHIC INFORMATION (n = 233)

		Control	Graftskin
GENDER	Female	50.5%	46.8%
	Male	49.5%	53.2%
RACE	Asian	0.9%	0.0%
	Black	17.8%	15.1%
	Caucasian	74.8%	80.2%
AGE (years)	Median	62.0	62.0
ULCER AREA (mm^2)	Median	339.1	515.1

patient populations were comparable in every respect.

Patients randomized into the Graftskin group received up to five applications of Graftskin during the first three weeks of treatment. Approximately 70 percent of the Graftskin treated patients received one, two or three applications. Application of Graftskin was determined on the basis of clinical observation at each study visit. If less than 50 percent of the wound area remained covered with Graftskin, another piece was applied; if more than 50 percent persisted, no fresh piece of Graftskin was applied. A non-adherent primary dressing was placed over the Graftskin, followed by a secondary, non-occlusive dressing (cotton gauze) folded as a bolster, and a self adherent elastic wrap. No Graftskin application was made subsequent to week 3. After eight weeks, healed patients were placed in elastic stockings. Patients who were not healed continued with the three-layer dressing regimen for up to six months. After eight weeks, all patients were followed for one year with visits scheduled at three-month intervals. The three-layer dressing regimen provided a sustained pressure of between 10 and 20 mmHg pressure at the ankle.

Patients randomized into the active control group

received a multilayered compression wrap, overlying bolster, zinc oxide impregnated paste bandage, and were treated at identical time intervals as for the Graftskin group. The purpose of the multilayered compression regimen was to provide sustained therapeutic compression between 30 and 40 mmHg at the ankle, more than twice the compression of the Graftskin group. As with the Graftskin group, healed patients were placed in elastic stockings after eight weeks. If not healed, patients were continued with multilayered compression for up to eight months and followed for one year.

The primary endpoints of the study were the frequency of and time to complete (100%) wound closure as assessed by clinical observation and wound tracings. Secondary endpoints included assessments of relief of pain and itching, reduced drainage, and progressive wound healing measured as a percentage of the original ulcer area.

Researchers' Conclusions as Supported by Data - Sabolinski Study

Analysis of 233 patients followed over six months shows median times to 100 percent wound closure of 57 days for Graftskin versus 181 days for standard care.

Of the 127 Graftskin treated patients, 78 or 64.1 percent achieved complete wound closure, while only 47 of 109 or 44.3 percent of the control patients achieved 100 percent closure. In addition, comparison of healed wounds in the control and treatment groups showed distinct differences in the quality of repair. It is clear from the study results that the healing in control patients was different from that of the patients in the Graftskin group.

Limitations - Sabolinski Study

Table 4 is misleading. While ulcer size in patient A is the sum of the areas of four wounds (the study wound being about 82 cm^2), the ulcer size in patients B and C represents single wounds. The unit for ulcer size is not consistent throughout the paper and is confusing to the reader. Secondly, the authors do not report percentage "take" of Graftskin in the study group. It appears that in chronic wounds, allogenic grafts would "take" only in small wounds such as in patient C.

Research Methods - Gentzkow Study

In the Gentzkow study, a randomized, controlled,

prospective, 20-center, single blinded study treating patients with full thickness neuropathic foot ulcers was performed using Dermagraft to assess the safety and effectiveness of Dermagraft in the healing of plantar diabetic foot ulcers. The study enrolled 235 diabetic patients with neuropathic, full thickness, plantar surface foot ulcers of the forefoot or heel greater than or equal to 1.0 cm^2 in size and eliminated ulcers that showed initial rapid healing in response to standard care during a screening period. The 126 patients selected randomly for control treatment received conventional therapy with sharp debridement, infection control, saline moistened gauze dressing, and standardized off weighting (including special shoes and custom inserts). The patients selected for Dermagraft treatment received identical conventional therapy plus an application of Dermagraft on Day 0 and at Weeks 1, 2, 3, 4, 5, 6, and 7 for a total of up to eight applications or until wound closure. The two groups of patients were demographically similar (See Table 3).

The primary objective of the study was to show a difference in the proportion of patients reaching complete closure by week 12 compared to patients receiving conventional therapy. In addition, the time

TABLE 3

Dermagraft Diabetic Ulcer Pivotal Trial Demographics

Dermagraft Range	Control	Dermagraft All	Therapeutic
N	128	109	61
Age	55.5	55.3	57.1
Gender (male/female %)	72/28	73/27	71/29
Ulcer Size (cm^2)	2.8	2.9	2.9
Ulcer Duration (weeks)	46.5	44.4	56.6

to healing and status of the wound at 32 weeks were assessed.

Researchers' Conclusions as Supported by Data - Gentzkow Study

The primary efficacy end point of the study was to complete healing of the ulcer by 12 weeks, and 31.7 percent of the patients in the conventional care group, compared to 50.8 percent in the group receiving the Dermagraft healed completely. In addition, when patients were followed out to 32 weeks, six months after the last application of the product, healing rates of 42.4 percent in the conventional care and 57.7 percent of the Dermagraft treated patients were seen.

Limitations - Gentzkow Study

Initially, 109 patients were treated with Dermagraft and the improvement in healing at 12 weeks (38.5 versus 31.7 percent) was not statistically significant because 48 of these patients received tissue that did not have the required metabolic activity at the time of implantation. No other limitations were noted in the study.

Research Methods - Bristol-Myers Study

A total of 203 patients with one or more venous leg ulcers was enrolled in a multi-center, randomized, double-blind parallel study in 48 centers across the United States to study the efficacy and safety of oral Ifetroban against a placebo. One hundred sixty-four patients were subsequently randomized to either the placebo or the Ifetroban. One hundred fifty subjects completed the study.

The study was divided into two treatment periods (A and B); period A was a two to four week single-blind placebo lead-in, during which ulcers were completely debrided and any clinical infection was treated and controlled with appropriate antibiotics. Ulcers greater than or equal to 1 cm^2 in surface area were selected. Patients were stratified into two groups based on ulcer surface area sizes greater or less than 10 cm^2.

During Period B, patients received daily treatment with 250 mg Ifetroban or matching placebo for 12 weeks. In addition, all randomized patients received the same local management of all ulcers with a hydrocolloid dressing and graduated compression of the lower limb(s) using a zinc oxide past bandage and a cohesive bandage.

The reference ulcer was measured weekly. Treatment with compression only was continued for 12 weeks if the reference ulcer healed (100 percent re-epithelialization) earlier.

The primary objective of the study was to determine whether Ifetroban would increase the proportion of patients who experienced complete healing of the reference venous leg ulcer compared to placebo following 12 weeks of active treatment. Secondary objectives considered 50 percent healing of the reference ulcer, total healing of all ulcers, time to total healing of the reference ulcer, change in area of reference ulcer, and change in total ulcer area.

Researchers' Conclusions as Supported by Data - Bristol-Myers Study

For the primary efficacy variable, 54.32 percent of the ulcers in the placebo group achieved healing (100 percent re-epithelialization) of the reference ulcer prior to the end of the study, compared to 55.42 percent in the Ifetroban group. A combined total of 137 patients (83.5 percent) achieved a reduction of greater than 50 percent of reference ulcer size during the study. The researchers concluded that Ifetroban had no significant statistical difference in the

healing rates of recalcitrant venous leg ulcers.

Limitations - Bristol-Myers Study

No limitations were acknowledged in the Bristol-Myers study.

Chapter IV

RESULTS

Results of Sabolinski Study

Based upon the hypothesis that living tissue (Graftskin) can act as a "smart material" to heal wounds, the researchers reported on three patients (Patient A, B, and C) out of the 233 patients in the study (See Table 4). Patient A had a 14.3 x 5.7 cm ulcer having a depth of 5 mm on the leg. It should be noted that this patient also had three non-study ulcers, which comprised a total ulcer area of 400 mm^2. Patient A had Graftskin applied four times, at study days 1, 5, 14 and 21 respectively. The patient responded immediately with relief of pain and marked reduction in wound exudate. Fifty percent of wound closure was achieved by study week 2, and 75 percent closure by week 12. Complete wound healing was reported at study week 25. Graftskin in this case of a large, highly exuding ulcer functioned as a skin graft which promoted the migration of the patient's own

TABLE 4

PATIENT SUMMARY

Patients Healing	Ulcer Size (cm^2)	Wound depth (mm)	Duration of ulcer(s)	Number of Graftskin applications	Time reported healed (100%)	Type of
A intention	400.0	5	> 30 years	4	Week 25 (1 ulcer) Week 24 (3 ulcers)	Secondary
B closure	11.0	3.5	5 months	2	Week 12	Persistent
C	3.2	0.5	3 months	2	Week 2	Appearance frank take

keratinocytes over the open wound bed.

Patient B had a leg ulcer that measured 4.4 x 2.5 cc with a depth of 3.5 mm. On Patient B, Graftskin was applied on study days 1 and 14. By week 2, greater than 50 percent wound closure was observed. Graftskin was again applied in study week 2. This dressing was left on for an additional six weeks, through study week 8. At the next clinic visit at study week 12, complete clinical healing was reported. Graftskin treatment was shown to promote healthy, granulating tissue within two weeks so that the second application of Graftskin adhered to the wound bed.

Patient C had a leg ulcer measuring 2.5 x 1.3 cm with a depth of 0.5 mm. Graftskin was applied on days 1 and 7. The depth of the ulcer had improved by day 71, when greater than 75 percent wound closure was reported. The ulcer was observed to be completely healed by study day 14 with the clinical assessment of 100 percent graft take.

The multi-layered compression therapy used on the control group represents the standard of care in the medical community and is generally able to heal approximately 20 to 40 percent of venous ulcers.

Two patients (D and E) were the control patients

discussed in the study. Patient D received Graftskin and was assessed as healed at study week 7. Patient E received the compression therapy and was only assessed as completely healed at study month 6. Patient D's tissue appeared resilient and pliable from time of healing through the course of the study (one year). The healed skin achieved in patient E appeared fragile. Patient E's ulcer reopened within two weeks following the six month check-up.

Tables 5 and 6 show the results for frequency of and median time to complete wound closure. Analysis of 233 patients followed over 6 months shows median times to 100 percent closure of 57 days for Graftskin versus 181 days for standard care. Of the 127 Graftskin treated patients, 78 or 64.1 percent achieved complete wound closure, while only 47 of 109 or 44.3 percent of the control patients achieved 100 percent closure.

Results - Gentzkow Study

Figures 2 and 3 summarize the healing data obtained at 12 and 32 weeks. By week 12, 31.75 percent of the patients in the conventional care group healed completely compared to 50.8 percent of the group receiving the Dermagraft. When patients were followed

TABLE 5

FREQUENCY OF COMPLETE WOUND CLOSURE BY 6 MONTHS

Treatment attained	n	Number attained	%
Graftskin	127	78	51.4
Control	106	47	44.3

TABLE 6

MEDIAN TIME TO COMPLETE WOUND CLOSURE BY 6 MONTHS

	Graftskin	Control
All patients (n = 233)	57 days	181 days

out to 32 weeks, six months after the last application of the product, healing rates were 42.4 percent for the conventional care and 57.7 percent for the Dermagraft patients.

This clinical study confirms the importance of Dermagraft as a living, human, metabolically active tissue, which is a key determinant of wound healing. In addition, the clinical study confirmed that Dermagraft within therapeutic range healed more ulcers faster than traditional therapy; i.e., cotton/gauze. Defining this therapeutic range of optimal metabolic activity was an important outcome to support the science of tissue engineering.

Results - Bristol-Myers Study

There was no statistical significance betwen the placebo and the Ifetroban group for any of the outcomes listed in the primary or secondary objectives, including total healing of reference ulcer, 50 percent healing of reference ulcer, time to total healing of reference ulcer and change of area of reference ulcer from baseline. For the primary efficacy variable, 54.32 percent of the ulcers in the placebo group achieved healing (100 percent re-epithelialization) of

the reference ulcer prior to the end of the study, compared to 55.42 percent in the Ifetroban group (see Table 7).

TABLE 7

ANALYSIS OF PATIENTS ACHIEVING 100% HEALING OF REFERENCE ULCER

	Ifetroban	Placebo
Healed	55.42%	54.32%
Not Healed	44.58%	45.68%

CHAPTER V

DISCUSSION

Summary

There are several important factors that must be considered when dealing with or treating chronic wounds. First and possibly most important is that of treating the underlying pathology as the very first step in any treatment plan. For example, in pressure ulcers, proper nutrition along with pressure relief from the prominent sties most susceptible to breakdown is a key factor. This may be accomplished with a variety of practices including nutritional evaluations, turning regimens, therapeutic support surfaces (i.e., specialty beds), and pressure reducing pads. In leg ulcers, the arterial disease that is compromising the patient's lower extremity blood flow must be corrected. One should also be aware of the well documented benefits of graduated compression therapy in treating venous leg ulcers. In diabetic foot ulcers, as a final example, the underlying pathology involves the

multi-organ disease diabetes. Particular attention must be given to the metabolic control of high blood glucose. If a diabetic patient develops a foot ulcer due to neuropathy or arteriopathy, then proper off-loading of the pressure in the neuropathic foot is essential to achieve healing. Without first treating the underlying disease, the type of topical therapy (whether traditional, modern, or tissue engineered products), will have little success in healing the chronic wound.

As the cost/benefit of tissue engineered products versus modern/moist products is investigated, one must understand that this challenge will be far greater than that of proving the cost/benefit evolution from traditional (gauze) products to modern/moist products. The market transformation over the past twenty years from traditional gauze products to moist wound healing has been slow. Over 50 percent of chronic wounds are still treated with traditional gauze-type products, despite modern/moist products' accelerated healing claims and labor savings. This statement is based upon the labor savings of treating a particular wound several times a day with traditional gauze-type products versus treating a wound only several times a

week with modern/moist wound healing products. Even though the modern/moist wound dressing is more expensive per dressing unit, the material cost is an insignificant factor to the total cost of treating a wound. As mentioned, in addition to the labor savings, it is also well documented that modern/moist products achieve faster healing than that of traditional gauze products. The cost of an extra day in the hospital easily offsets that of more costly dressings.

Therefore, any hopes for tissue engineered products to achieve a positive cost/benefit ratio, companies will need to conduct significant clinical trials that drastically improve healing rates over current best treatment standards to justify the increased unit product cost (see Table 8).

For example, if one looks closely at the Bristol-Myers Squibb Ifetroban study, the healing results with a modern/moist product along with good compression therapy showed healing rates of approximately 55 percent in both the study group and the control group. If the costs of the individual products used in the Ifetroban data to achieve these healing rates are compared to the Sabolinski study, which utilized tissue engineered products (Graftskin) and compression

TABLE 8

BRISTOL-MYERS SQUIBB
IFETROBAN STUDY

Treatment Period = 12 weeks

Products used and unit cost

Modern/moist product @ $4/unit
Graduated compression System @ $11/unit

Total cost per unit of product = $15.00

No. of treatments/treatment period = 24
(2 times per week X 12 weeks)

Estimated labor cost/treatment = $30.00

Total Direct Treatment Cost

Total Product Cost ($15 x 24) = $360

Total Labor Cost ($30 x 24) = $720

Total Direct Cost = $1,080

$1,080 for 55 percent healed in 12 weeks

SABOLINSKI STUDY

Treatment period = 28 weeks

Products used and unit cost

Graftskin = $400 per unit

Compression = $11 per unit

Total cost per unit of product = $411

No. of treatments/treatment period = 3
(based on study average)
Estimated labor cost/treatment = $30

Total Direct Treatment Cost

Graftskin product cost (3 x $400)	= $1,200
# of traditional/compression treatments (28 wks. X 2 x $11)	= $ 616
Estimated labor cost (28 wks. X 2 x $30)	= $1,680
Total Direct Cost	= $3,496

$3,496 for 60 percent healed in 28 weeks

therapy, one can easily conclude that the additional expense of the tissue engineered products does not justify the expense.

At this time, with the increasing downward pressure of managed care in the United States and stricter reimbursement guidelines, both inside the United States and internationally, the commercial viability of an advanced product such as tissue engineering will have no chance of being adopted as a standard of care for chronic wounds unless the higher product unit cost is justified by significantly shorter healing times.

Today the most significant barrier to getting a new product or technology approved for reimbursement is providing enhanced outcomes over existing products and technologies. In the pertinent studies relating to this thesis, there was no mention of the economic difference behind the results. As discussed in Chapter II, cost effectiveness must be taken into account. Companies developing advanced technologies that will have better outcomes for wound healing must very clearly prove to be cost effective over current best healing practices.

Based upon the hypothesis, the cost/benefit ratio

will not be great enough to insure rapid adoption of skin tissue engineered products for the vast population of patients suffering from chronic wounds. With careful examination of Table 8 as well as a review of the pertinent studies presented in this thesis, the initial hypothesis is well supported and documented.

Limitations

It is the writer's opinion that in both of the most pertinent studies currently available on tissue engineered products (Sabolinski and Gentzkow), the authors chose to use a regimen of standard care of ulcer healing that is clearly suboptimal as compared to current widely accepted standard clinical practice.

In the Sabolinski study, conclusions are based on results that are presented at six months, not eight weeks. Proportions of subjects who healed should have been presented at eight weeks and each three month follow-up visit. This is important because the subjects go for three full months without investigator interaction or standardized assessment. How compliant they were with the protocol is unclear. The authors also claim the graft acts as a "smart" material and responds to its environment. This too may be an

exaggeration. In small wounds that are normally easier to heal there is evidence of successful graft take. However, in larger wounds, which are normally much more difficult to heal, the grafts tend not to take. Yet the author points out that the results are better than the control, which may be simply due to changes in wound conditions caused by physical or chemical properties of the by growth factors, matrix proteins, and so on. There is no evidence that these products add value beyond that of moisture-retentive hydrocolloid dressings. Based on the above comments one would have to question if these conclusions/results are repeatable and valid as compared to the best available clinical care.

Also in the Sabolinski study, statistical comparisons at baseline indicated comparable treatment groups. However, due to lack of information in the study, procedures were not identified to validate that there were comparable treatment groups. However, the issue regarding the potential center by center treatment interaction was not addressed. This leads to the question of whether or not the data was poolable. For example, does the information differ from center to center? Only three case studies were presented in the

study, which is unusual and possibly irrelevant in a comparative study of this size. One would think that out of 233 subjects, regardless of what is being studied, one could find some good and some bad cases to highlight or elect not to discuss. Finally, the Sabolinski study is unclear regarding the accounting of the subjects; i.e., withdrawals, lost to follow-up, adverse events, etc. No adverse events are reported. With a study of this size, one would have to believe that the possibility of some adverse events would be highly probable.

The Gentzkow study reported on the effect of cultured dermal fibroblasts (Dermagraft) in the healing of diabetic foot ulcers. Only 7.7 percent of the patients receiving "standard care" achieved wound closure by 12 weeks, and even the "treatment" group that achieved the best results only demonstrated full closure in 50 percent of the lesions by 12 weeks. These results are in stark contrast to documented higher healing rates of similar ulcers of patients using total contact cast therapy, which once again addresses the issue that, in the Gentzkow study, the best standard of care was not utilized. In addition, the control group was treated with saline and moist

gauze (traditional therapy) along with therapeutic shoes. Based upon current clinical evidence, one of the major problems in the Gentzkow study was inadequate pressure relief of the ulcer site. The standard of care that the authors elected to utilize in the Gentzkow study was based on the premise that it should be one that is widely used by expert practitioners, does not exclude a substantial segment of the population of interest, and allows for uniformity of care across multiple treatment centers. Elimination of variables that can confound the results is the challenge facing all studies, but especially wound healing studies. When doing a comparative clinical study, the best treatment available should be utilized for the control group if the results are to have any validity at all. One should not be biased by suboptimal standards of care that are supported only on the basis that they are widely used. In the Gentzkow study, it is well documented that patients utilizing total contact casts without bioengineered skin replacements heal in 4.4 to 6.3 weeks. Therapeutic shoes were used in the Gentzkow study. Even though the patients were told not to put any pressure on their feet, when a patient is given a shoe, he or she is

likely to walk in it. With the total contact cast, the patient cannot put any pressure on his or her foot, which eliminates this problem.

Suggestions for Future Research

Continued research is clearly needed to develop more innovative and effective methods to treat chronic wounds. It has been shown that with use of tissue engineered products, there is obviously some type of biological effect. However, the results do not clearly substantiate their efficacy over the current best standard of care. Now that the Ifetroban data is being published, at least as they relate to managing venous leg ulcers, future studies should be designed in accordance with the highest clinical trial standards in order to unequivocally validate the efficacy of tissue engineered products. This undoubtedly leaves the door open for additional studies in this area. Recommended studies comparing new technology effects to best standard of care would include epidemiology, healing, reoccurrence, cost effectiveness, and quality of life of patient, stratified for risk levels.

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