PHI™ technology
Technical Brochure

Understanding PHI™ technology

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3M

Chronic wounds

Chronic wounds have been defined as those that fail to progress through a normal, orderly and timely sequence of repair.[1, 2] Chronic wounds:

- Become out of balance and stall at some point along the healing cascade
- Fail to show signs of healing in two to four weeks

When a wound has stalled, the cells function different from normal because they are out of balance. That's why it's important to look at the normal healing process to understand where and how a wound gets stalled.

Wound healing

Wound healing is a complex regenerative process to repair or replace injured tissue.[1, 3] The injury often involves some form of ischemia and when injured, the natural balance between cells in tissue is disrupted creating an altered environment.[2, 4]

Cells in the injured tissue immediately begin a process to regain their pre-injury state. This process is comprised of a set of intricate biochemical interactions that take place in a well orchestrated series of events, or phases as shown in Figure 1.

Phases of healing

These 'phases' of wound healing overlap in time and the time for each phase may vary considerably based upon a person's age, general health and other key factors.[5, 6] Over the decades therapies for treating chronic wounds have focused on one or more of the phases, assuming that a defect lies in one of the phases and can be treated.

In fact, chronic wounds are more complicated and different defects that cause healing to stall can occur in different phases, e.g., diabetic wounds tend to have defects in the inflammation phase of healing while venous stasis ulcers have problems in the repair phase as shown in Figure 2.[7–9]

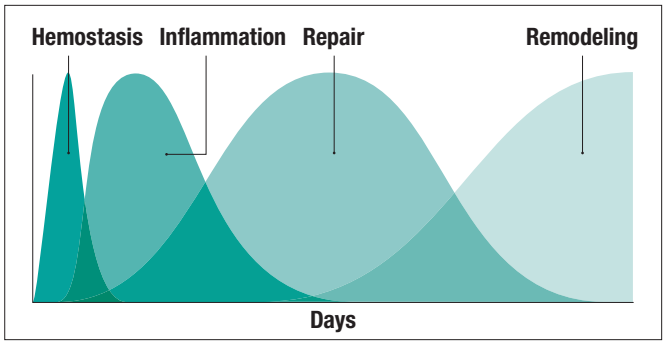

Figure 1: Natural Wound Healing Cascade of Events
Hemostasis – Vessels have ruptured followed by platelets that aggregate and then degranulate (release growth factors) along with fibrin clot formation
Inflammation – Neutrophils locate in the tissue and consume bacteria and debris and macrophages are present to provide stimulatory signals and matrix turn over
Repair – Migration/proliferation of cells
1. Angiogenesis – Formation of new blood vessels
2. Fibroplasia – Fibroblasts migrate into wound and replicate; collagen synthesis and deposition underway
3. Epithelialization – New skin cells migrate from wound margins and hair follicles
4. Contraction – Myofibroblasts pull on wound edges

Remodeling – Changes in matrix composition over time (scar)

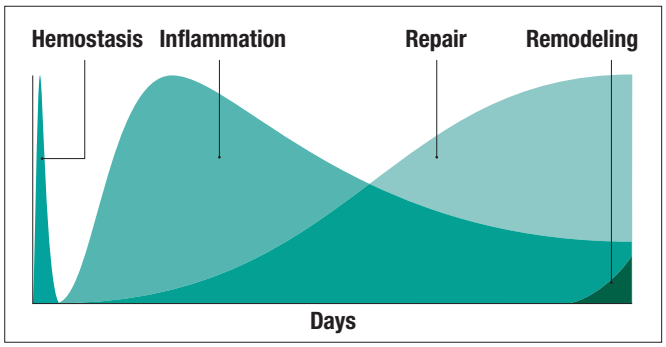

Figure 2: Chronic Wound Healing Cascade of Events
Hemostasis – May have been established before the skin was breached
Inflammation – Bacteria may be well established with high levels of MMPs and cytokines. Fewer neutrophils may be in the tissue to consume bacteria and debris and macrophages may be providing excessive stimulatory signals and there is excessive matrix turn over
Repair – Migration/proliferation of cells
1. Angiogenesis – Formation of new blood vessels is limited or non-existent
2. Fibroplasia – Fibroblasts are senescent and not migrating into wound or replicating; collagen synthesis and deposition is limited
3. Epithelialization – cells not replicating – granulation tissue may not be present
4. Contraction – Myofibroblasts may not have formed

Remodeling – Little if any remodeling occurs

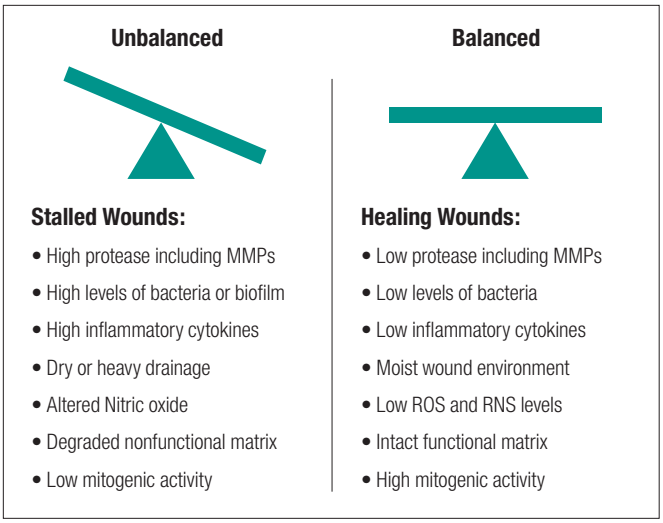

Figure 3: Environments of Stalled and Healing Wounds [19]

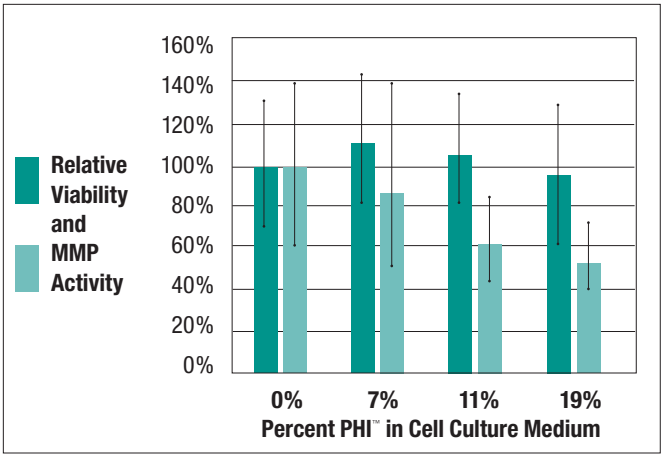

Figure 4: PHI™ technology Affects MMP Activity[20]
The above graph represents the *in vitro* effect of PHI™ technology on MMP activity in human foreskin fibroblasts cultured in 10% serum supplemented medium. The percent PHI™ approximates what may be present in a wound situation. This graph shows the measured relative activity of MMPs in the medium decreases as a function of PHI™ technology.

Introducing PHI™ technology

All of biology follows a simple sequence: a stimulus reaches a cell and sends a 'message' causing DNA in our genes to send a 'reply' in the form of a biochemical change, commonly associated with proteins.[10–13]

In chronic wounds, proteins include destructive enzymes known as the matrix metalloproteinases (MMPs). This is important because in chronic wounds, an imbalance in the production of MMPs and their natural inhibitors (TIMPs) has been shown to slow down the healing process.[14–16] Prolonged MMP expression destroys growth factors, impairing the wound's ability to heal.

Research has revealed that wound bioburden and protease enzyme imbalance, in particular differential expression of MMPs and their inhibitors (TIMPs), are strongly associated with delayed healing in chronic wounds.[17, 18]

We have taken advantage of these points in the development of PHI™ technology, a patented blend of cations found naturally in the body including potassium, zinc, calcium, and rubidium, in a mixture of polyethylene glycols and citric acid. PHI™ technology helps rebalance the wound environment allowing stalled wounds to progress toward healing.

In vitro laboratory data illustrates that when PHI™ technology is used to alter the environment of diabetic fibroblast cells, these cells alter their expression of over 10,000 genes. Among the various genes affected are those impacting the biochemical pathways involving MMPs and TIMPs.

Figure 4 shows that PHI™ technology is not cytotoxic to cells but the activity of MMPs is decreased with increasing amounts of PHI™ technology in the environment surrounding the cells.[20]

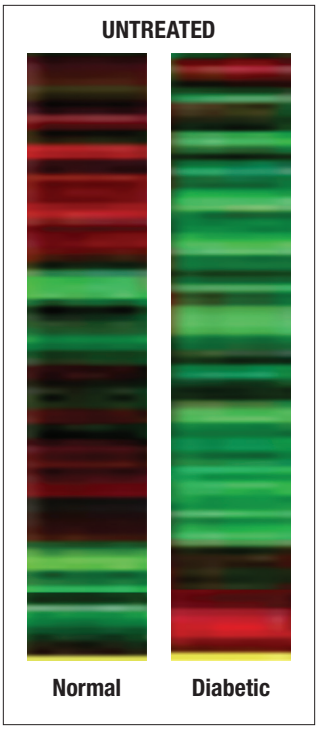

Figure 5: Gene array of normal and diabetic fibroblasts before treatment

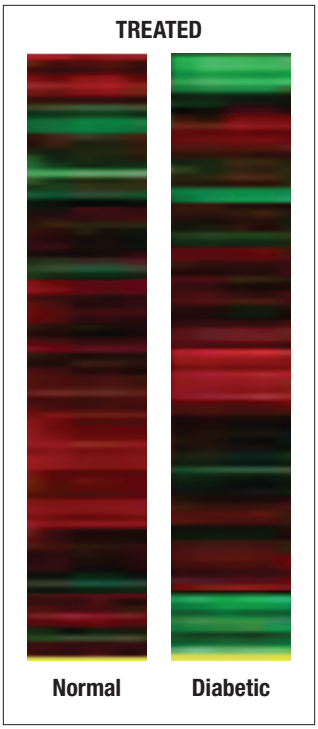

Figure 6: Gene array of normal and diabetic fibroblasts after exposure to PHI™ technology

DNA microarrays can be used to show how PHI™ technology changes gene response. The red indicates genes with increased activity and the green color indicates genes with reduced activity. Figure 5 illustrates how different diabetic and normal fibroblasts are from one another before exposure to PHI™ technology. This is consistent with clinical settings where diabetic patients differ significantly from non-diabetic patients. Figure 6 illustrates the response of a selected portion of all the genes available for analysis from normal and diabetic fibroblasts when exposed to PHI™ technology. The diabetic fibroblasts become more like normal fibroblasts after exposure to PHI™ technology.[20]

Altering the wound environment

Clinicians understand that they must do something to alter the wound environment in their efforts to jump-start a wound. That is why they change treatments whenever a wound fails to respond after a couple of weeks. There are few diagnostic tools available to benchmark the condition of a wound before treatment begins and to monitor the changes as healing progresses. Nonetheless, experienced clinicians have sharp observational skills and have developed techniques to assess when a chronic wound is responding favorably to treatment without knowing precisely why.

A wound dressing can alter the environment of a wound bed by:

- Absorbing excess fluid
- Helping to manage microbes in the wound
- Absorbing and altering the activity of MMPs
- Impacting the signaling of nitric oxide
- Influencing any of the numerous integrated biochemical pathways and environmental factors

The result will be manifested in observable changes in the appearance and size of the wound.

PHI™ technology is proving to be effective

The case studies on the following pages demonstrate some of the favorable results observed with the use of PHI™ technology.

Patient GJ
Non-healing diabetic foot ulcer

Patient History

Patient GJ is a 51 year old male with a history of Type 2 diabetes (insulin requiring), asthma, hepatitis C, hypertension, and smoking. He had a long-standing ulcer at the level of the first metatarsal-phalangeal joint of his right foot. The patient had previous injuries, surgical intervention, and skin grafting that left him with a partially marsupualized lesion over the medial aspect of his right foot, limited mobility, and a chronic wound which was fibrous and dystrophic.

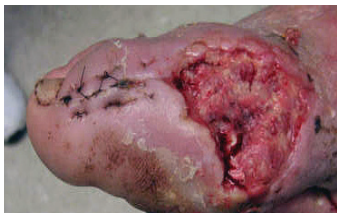

Figure 6: August 11, 2006. The initial wound (full thickness, 4.4 cm X 3.8 cm).

Initial Wound Description

Prior to use of Tegaderm™ Matrix dressing (Figure 6), the ulcer was full-thickness, measured 4.4 cm X 3.8 cm and had been present to varying degrees for about 2 years. There was moderate to heavy drainage that was serous and non-purulent. There was no malodor or bloody discharge noted. The peri-wound skin was pink, indurated, and somewhat macerated. The wound bed contained 100% fibrous slough with no granulation tissue present.

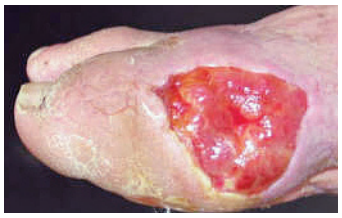

Figure 7: September 7, 2006. The wound after 4 weeks of Tegaderm™ Matrix dressing use.

Prior Wound Management

Off-loading and in-office sharp and enzymatic debridement were completed with little success.

New Wound Management

On August 11, 2006, a new regimen was initiated. The wound was surgically debrided and Tegaderm™ Matrix dressing was placed over the clean wound bed and covered with sterile gauze and gauze wrap. The dressings were changed daily at home by the patient, and Tegaderm™ Matrix dressing was cut to fit the size of the wound. The patient was seen weekly for about a month by the Foot and Ankle Surgeon, and then every 2 weeks until the wound closed. Sharp debridement was performed as needed.

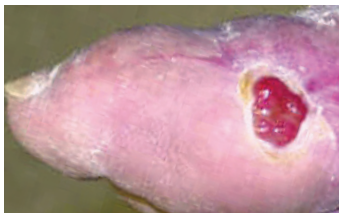

Figure 8: November 30, 2006. The wound approaching closure after 16 weeks of Tegaderm™ Matrix dressing use.

Case Study Results

Marked improvement in the wound was noted within the first 4 weeks of using Tegaderm™ Matrix dressing (Figure 7), with progressive improvement through the 16th week visit (Figure 8), and to eventual closure of the wound (Figure 9). The exact date of wound closure is not known, but occurred before the January 25, 2007 visit.

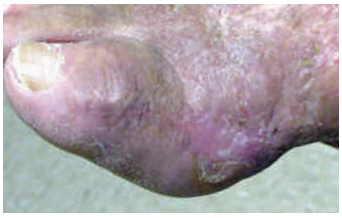

Figure 9: January 25, 2007. Wound closure occurred sometime prior to this visit.

Case Summary

This case study highlights a 51 year old patient with Type 2 (insulin requiring) diabetes and a full thickness, long-standing chronic wound over the medial aspect of his right foot that was stalled in a non-healing state for approximately 2 years. After initiating treatment with sharp debridement and Tegaderm™ Matrix dressing, the wound responded and attained complete closure.

Patient ES
Non-healing diabetic foot ulcer

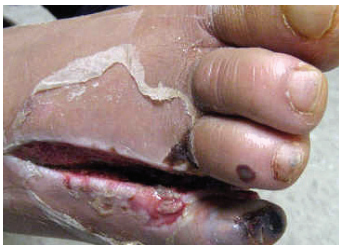

Figure 10: August 7, 2006, 6 days post-surgery. Tegaderm™ Matrix dressing use was initiated.

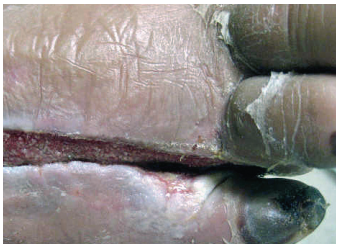

Figure 11: August 17, 2006, 16 days post-surgery and 10 days after initiation of Tegaderm™ Matrix dressing use. Marked improvements in the wound were noted.

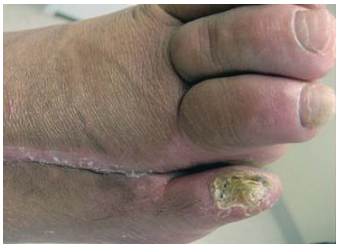

Figure 12: October 23, 2006, 11 weeks post after initiation of Tegaderm™ Matrix dressing use.

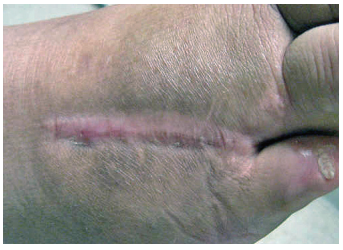

Figure 13: February 12, 2007, wound closure after 27 weeks of Tegaderm™ Matrix dressing use.

Patient History

Patient ES is a 54 year old male with a history of diabetes, peripheral neuropathy and a previous partial right foot amputation. On July 24, 2006 he was initially seen as an in-patient for an abscess and suspected 4th metatarsal osteomyelitis. On July 29, 2006 he was taken to the OR for debridement, resection of non-viable bone and soft tissue, and lavage. On August 1, 2006 the 4th toe was amputated with a partial 4th Ray resection.

Initial Wound Description

Prior to use of Tegaderm™ Matrix dressing (Figure 10), there was a large open surgical wound between the 3rd and 5th Rays. There was no extension of abscess, no purulence, and no foul odor. There was superficial desquamation of the skin, and questionable viability of the 3rd and 5th digits.

Prior Wound Management

None.

New Wound Management

Tegaderm™ Matrix dressing was used as a wound packing and primary dressing beginning 6 days after the surgical resection and amputation was complete (Figure 10). The dressing was held in place with sterile gauze and gauze wrap and changed daily. After discharge from the hospital, use of Tegaderm™ Matrix dressing continued at home. The dressings were changed daily by the patient with Tegaderm™ Matrix dressing packed to the depths of the wound. The patient was seen weekly for about a month by the Foot and Ankle Surgeon, and then every 2 weeks until the wound closed. Sharp debridement was performed as needed.

Case Study Results

Marked improvements in the wound were noted within the first 2 to 3 weeks of using Tegaderm™ Matrix dressing (Figure 11), with continued and progressive improvements observed throughout the period of use (Figure 12). Wound closure occurred by the February 12, 2007 visit, after approximately 27 weeks of use (Figure 13).

Case Summary

This case study highlights a 54 year old patient with a history of diabetes and a large surgical debridement and resection wound of the 4th metatarsal due to abscess and osteomyelitis. After debridement and resection, the wound responded to Tegaderm™ Matrix dressing and progressed toward closure over a 27 week period.

Tegaderm™ Matrix dressing has not been studied in a randomized clinical trial to confirm the results of these case studies.

Glossary

Angiogenesis – The process of developing new blood vessels.

Biochemical – The substances making up bodily tissues and fluids.

Biofilm – A structured community of microorganisms encapsulated within a self-developed polymeric matrix and adherent to a living or inert surface.

Contraction – Around a week after the wounding takes place, fibroblasts have differentiated into myofibroblasts and the wound begins to contract. In full thickness wounds, contraction peaks at 5 to 15 days post wounding and can last for several weeks and continues even after the wound is completely reepithelialized. Contraction occurs in order to reduce the size of the wound.

Epithelialization – The process where epithelial cells migrate over granulation tissue in the wound bed to form a barrier between the wound and the environment. Cells advance in a sheet across the wound site and proliferate at its edges, ceasing movement when they meet in the middle.

Extracellular matrix – Created and modified by fibroblasts consisting of a network of collagen.

Fibroblasts – A type of cell in wounds that synthesizes and maintains the extracellular matrix (the structural framework for many tissues) and plays a critical role in wound healing. They are the most common cells of connective tissue in animals.

Fibroplasia – A stage in wound healing normally beginning 2-5 days after the injury and ending 2-4 weeks later.

Granulation tissue – Tissue consisting of new blood vessels, fibroblasts, inflammatory cells, endothelial cells, myofibroblasts, and the components of a new, provisional extracellular matrix. Required for a wound to heal.

Hemostasis – A response occurring shortly after injury. Bleeding creates fibrin clots at the ends of severed blood vessels. The clots become a temporary matrix responsible for promoting coagulation of blood cells and migration of cells that trigger the release of various growth factors.

Inflammation – The complex biological response of tissues to harmful stimuli, such as bacteria, damaged cells, or irritants. It is a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue. Inflammation is not a synonym for infection.

Inflammatory cytokines – Signaling biomolecules responsible for communication between cells.

Ischemia – A restriction in blood supply resulting in damage of tissue.

Macrophages – Cells essential to wound healing. They replace neutrophils as the predominant cells in the wound by two days after injury. Attracted to the wound site by growth factors released by platelets and other cells. The main role of the macrophages is to engulf and remove bacteria and damaged tissue, and it also debrides damaged tissue by releasing proteases.

Mitogenic activity – Leading to cell division.

Mitotically competent cells – Cells capable of dividing.

MMP – Matrix metalloproteinases – Enzymes that break down proteins. They are also thought to play a major role in many different cell functions.

Myofibroblasts – A cell that is in between a fibroblast and smooth muscle cells that are then capable of speeding wound repair by contracting the edges of the wound.

Neutrophils – White blood cells normally found in the bloodstream that react within an hour of tissue injury and are the hallmark of acute inflammation.

Protease – An enzyme that breaks down proteins.

Remodeling – Part of the wound healing process where repaired tissue is modified to become more like uninjured tissue.

Repair – Regenerative process to replace tissue lost to injury.

RNS – Reactive nitrogen species – Produced through the reaction of nitric oxide with superoxide (O2–) to form peroxynitrite (ONOO–). They act together with ROS to carry out detrimental effects on cells.

ROS – Reactive oxygen species – Natural byproducts of the normal cell metabolism of oxygen and have important roles in cell signaling. These can increase dramatically leading to significant damage to cell structures.

Stalled wound – Wound that is not healing and is not reducing in size or improving in appearance.

TIMP – Tissue inhibitors of metalloproteinases (TIMPs).

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