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# WOUND HEALING AND IT'S IMPORTANCE- A REVIEW



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Article Info	ABSTRACT
Received 25/11/2013	A chronic wound should prompt the health care professional to begin a search for
Revised 16/12/2013	unresolved underlying causes. Healing a chronic wound requires care that is patient
Accepted 18/12/2013	centred, holistic, interdisciplinary, cost effective and evidence based. In many cases the
	underlying causes and factors interfering with wound healing may be mutlifactorial, an
Key words: Wounds,	elderly patient who suffered trauma. Wounds may be classified by several methods, their
Remodeling,	aetiology, location, type of injury presenting symptoms, wound depth and tissue loss or
Maturation,	clinical appearance of the wound Research work on acute wounds in an animal model
Inflammation.	shows that wounds heal in four phases. It is believed that chronic wounds must also go
	through the same basic phases. Some authors combine the first two phases. The phases of
	wound healing are Hemostasis, Inflammation, Proliferation or Granulation and Remodeling
	or Maturation, While there is still no superior substitute for reconstruction using patients
	own tissues and carefully thought-out reconstructive procedures; new products can help
	facilitate eventual healing by providing prophylaxis against barriers to healing,
	augmentation of wound healing factors, assistance in temporizing and bridging time to
	definitive repair, and optimization of the ultimate results of wound reconstruction.

#### **INTRODUCTION**

Wound healing is a complex and dynamic process with the wound environment changing with the changing health status of the individual. The knowledge of the physiology of the normal wound healing trajectory through the phases of haemostasis, inflammation, granulation and maturation provides a framework for an understanding of the basic principles of wound healing [1]. Through this understanding the health care professional can develop the skills required to care for a wound and the body can be assisted in the complex task of tissue repair. A chronic wound should prompt the health care professional to begin a search for unresolved underlying causes. Healing a chronic wound requires care that is patient centred, holistic, interdisciplinary, cost effective and evidence

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based. This is one of five articles made available by the Canadian Association of Wound Care to assist the wound care clinician develop an increased understanding of wound healing. This article explores [2].

- Why wounds happen.
- How wounds heal.

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- When a wound is considered chronic
- The nature of good chronic wound care

It is hoped that these basic principles will provide a framework for further study and exploration into the complex area of wound care [3].

#### Why Do Wounds Happen?

In any natural disaster the damaging forces must be identified and stopped before repair work can begin. So too in wound care the basic underlying causes and factors that affect healing must be identified and controlled as best we can before wound healing will begin. Following are some of the common underlying causes or factors, which may interfere with wound healing are as follows

• Trauma (initial or repetitive)



- Scalds and burns both physical and chemical
- Animal bites or insect stings
- Pressure
- Vascular compromise, arterial, venous or mixed
- Immunodeficiency
- Malignancy
- Connective tissue disorders
- Metabolic disease, including diabetes
- Nutritional deficiencies
- Psychosocial disorders

In many cases the underlying causes and factors interfering with wound healing may be mutilifactorial. An elderly patient who suffered trauma was shown in figure 1. The ulcer drains copious amounts of chronic wound drainage causing irritation to the surrounding skin. The patient sits most of the day in a dependent position which worsens the leg edema [4]. How can the wound fluid be controlled to enable healing? The clinician working in wound care needs to be a good detective and needs to consider all possible factors influencing healing adverse effects of medications [5].

### CLASSIFICATION OF WOUND

Wounds may be classified by several methods, their aetiology, location, type of injury presenting symptoms, wound depth and tissue loss or clinical appearance of the wound [6]. Separate grading tools exist for Pressure Ulcers, Burns, Diabetic Foot Ulcers and General Wounds. General wounds are classified as being

- Superficial (loss of epidermis only)
- Partial thickness (involve the epidermis and dermis)

• Full thickness (involves the dermis, subcutaneous fat and sometimes bone)

The most common method for classification of a wound is identification of the predominant tissue types present at the wound bed, black necrotic and the respective amount of each expressed as a percentage. This classification method is very visual, supports good assessment and planning and assists with continuous reassessment [7].

### What is a Wound?

A wound may be described in many ways; by its aetiology, anatomical location, by whether it is acute or chronic, by the method of closure, by its presenting symptoms or indeed by the appearance of the predominant tissue types in the wound bed. All definitions serve a critical purpose in the assessment and appropriate management of the wound through to symptom resolution if viable, healing [8].

A wound by true definition is a breakdown in the protective function of the skin; the loss of continuity of epithelium, with or without loss of underlying connective tissue following injury to the skin or underlying tissues/organs caused by surgery, a blow, a cut, chemicals, heat/cold, friction shear force, pressure or as a result of disease, such as leg ulcers or carcinomas [9]. Wounds heal by primary intention or secondary intention depending upon whether the wound may be closed with sutures or left to repair, whereby damaged tissue is restored by the formation of connective tissue and regrowth of epithelium [10].

#### PHASES OF WOUND HEALING

Whether wounds are closed by primary intention, subject to delayed primary closure or left to heal by secondary intention, the wound healing process is a dynamic one which can be divided into three phases. It is critical to remember that wound healing is not linear and often wounds can progress both forwards and back through the phases depending upon intrinsic and extrinsic forces at work within the patient [11].

The phases of wound healing are

Inflammatory phase

Proliferation phase

Maturation phase

The inflammatory phase is the body's natural response to injury. After initial wounding, the blood vessels in the wound bed contract and a clot is formed. Once haemostasis has been achieved, blood vessels then dilate to allow essential cells, antibodies, white blood cells, growth factors, enzymes and nutrients to reach the wounded area. This leads to a rise in exudate levels so the surrounding skin needs to be monitored for signs of inflammation can be seen, erythema, heat, oedema, pain and functional disturbance. The predominant cells at work here are the phagocytic cells; neutrophils and macrophages, mounting a host response and autolysing any devitalised necrotic sloughy tissue was shown in figure 2 [12].

During proliferation, the wound is rebuilt with new granulation tissue which is comprised of collagen and extracellular matrix and into which a new network of blood vessels develop, a process known as angiogenesis. Healthy granulation tissue is dependent upon the fibroblast receiving sufficient levels of oxygen and nutrients supplied by the blood vessels. Healthy granulation tissue is granular and uneven in texture, it does not bleed easily and is pink/red in colour. The colour and condition of the granulation tissue is often an indicator of how the wound is healing. Dark granulation tissue can be indicative of poor perfusion, ischaemia. Epithelial cells finally resurface the wound, a process known as epithelialisation. Maturation is the final phase and occurs once the wound has closed. This phase involves remodelling of collagen from type III to type I. Cellular activity reduces and the number of blood vessels in the wounded area regress and decrease [13].

### Theory of Moist Wound Healing

The principle of moist wound healing challenges the normal physiological process of wound repair, dry healing seen by the formation of a scab. It is recognised that in moist occlusive semi-occlusive environments, epithelialisation occurs at twice the rate when compared to



a dry one. Moist wound healing can be achieved with advanced wound care dressings, a wet environment can be detrimental as this can lead to maceration and tissue breakdown. Moist wound healing is not suitable for all wounds. Necrotic digits due to ischaemia and neuropathy should be kept dry or monitored very closely. These patients experience problems fighting infection. Modern wound dressings can be used but the wound needs to be monitored closely to identify for early signs of clinical infection and to prevent maceration. Skin barrier preparations which are easy to use, do not sting even on vulnerable or sore skin, such as LBF 'no sting' barrier wipes may be used around the wound if exudate levels are high and a risk of maceration is present [14].

#### **Patient Assessment**

Patient assessment is critical to ensure good wound healing outcomes. A unified patient centred approach should be adopted which takes into account the systemic, regional and local factors which may affect wound healing [15]. It is important to assess the patient and the wound to aid appropriate dressing selection and then accurate treatment interventions can be planned. A multi-disciplinary approach should always be considered was show in figure 3.

#### **Assess the Patient**

Assess the patient and consider systemic factors which may affect wound healing. These include comorbidities disease processes such as cardiovascular, diabetes, immune suppressant conditions, carcinomas, psychosocial conditions, medication, age and nutritional status. Any known allergies should be recorded.

#### Assess the Regional Area

Regional factors to consider include vascular disease, infection and pain.

#### Assess the Local Wound Area

The local wound bed should be assessed in terms of the type and amount of each respective tissue type present and also the level of pain, infection, exudate and odour present.

#### Assess the Current Dressing Regime

Assess the current dressing for signs of leakage and strikethrough and assess efficacy in terms of wear time, pain at dressing change and in situ. At assessment the wound should be measured and the depth of tissue loss expressed as a grade. If the wound is a cavity, then all areas of undermining should be probed, measured and documented. Ideally all wounds should be mapped and photographed. A treatment plan should be selected providing clear rationale for the dressings selected and frequency of dressing changes [16].

#### HOW DO WOUNDS HEAL

Research work on acute wounds in an animal

model shows that wounds heal in four phases. It is believed that chronic wounds must also go through the same basic phases. Some authors combine the first two phases. The phases of wound healing are

- Hemostasis
- Inflammation
- Proliferation or Granulation
- Remodeling or Maturation

Kane's analogy to the repair of a damaged house provides a wonderful frame work to explore the basic physiology of wound repair [17].

#### Hemostasis

Once the source of damage to a house has been removed and before work can start, utility workers must come in and cap damaged gas or water lines. So too in wound healing damaged blood vessels must be sealed. In wound healing the platelet is the cell which acts as the utility worker sealing off the damaged blood vessels. The blood vessels themselves constrict in response to injury but this spasm ultimately relaxes. The platelets secrete vaso constrictive substances to aid in this process but their prime role is to form a stable clot sealing the damaged vessel. Under the influence of ADP (adenosine diphosphate) leaking from damaged tissues the platelets aggregate and adhere to the exposed collagen. They also secrete factors which interact with and stimulate the intrinsic clotting cascade through the production of thrombin, which in turn initiates the formation of fibrin from fibrinogen. The fibrin mesh strengthens the platelet aggregate into a stable hemostatic plug. Finally platelets also secrete cytokines such as platelet derived growth factor (PDGF), which is recognized as one of the first factors secreted in initiating subsequent steps. Hemostasis occurs within minutes of the initial injury unless there are underlying clotting disorders.

#### **Inflammation Phase**

Clinically inflammation, the second stage of wound healing presents as erythema, swelling and warmth often associated with pain. This stage usually lasts up to 4 days post injury. In the wound healing analogy the first job to be done once the utilities are capped is to clean up the debris. This is a job for non-skilled laborers. These nonskilled laborers in a wound are the neutrophils or PMN's (polymorphonucleocytes). The inflammatory response causes the blood vessels to become leaky releasing plasma and PMN's into the surrounding tissue4. The neutrophils phagocytize debris and microorganisms and provide the first line of defense against infection. They are aided by local mast cells. As fibrin is broken down as part of this clean-up the degradation products attract the next cell involved. The task of rebuilding a house is complex and requires someone to direct this activity or a contractor. The cell which acts as contractor in wound healing is the macrophage [18].



#### **TREATMENT** Biological Based Treatments

Cryo preserved human cadaver skin (used in the UK), and human amniotic membrane and frog skin (used in other parts of the world) have long been used to treat wounds, particularly burns. More recently, artificial skin substitutes and growth factors have been developed to help achieve healing in chronic, non-healing wounds of varying aetiologies. These treatments target different stages of the healing process and, in the case of skin substitutes, replace lost tissue. Artificial skin substitutes, products of tissue engineering, consist of a micro engineered, biocompatible, polymer matrix in combination with cellular and extracellular elements such as collagen. Several growth factors (proteins involved in coordinating and regulating various interrelated processes during wound healing) produced by recombinant DNA technology have also been developed to aid healing of such wounds [19].

#### Products targeting inflammatory phase

The production and activity of several proteases including metallo proteinases, serine proteases, and neutrophil elastases, which are tightly regulated in acute wound healing, may be altered in chronic wounds. Raised levels of such proteases can be detrimental to wound healing, and products aimed at counteracting their effect have been developed. One such product is Promogran, which is designed to inactivate proteases and also protect the host's naturally produced growth factors. It may be useful in the treatment of chronic wounds refractory to conventional treatments, but it is not effective in infected wounds or those with unhealthy wound beds shown in figure 4.

### **Growth factors**

Fibroblasts, the key type of cell in the healing process, are attracted to the wound site by several growth factors, including platelet derived growth factor (PDGF) and TGF- $\beta$ . They proliferate and produce the matrix proteins fibronectin, hyaluronan, and later, collagen and proteoglycans, all of which help to construct the new extracellular matrix in figure 5 [20].

Growth factors, including granulocyte colony stimulating factor (G-CSF) and transforming growth factor- $\beta$  (TGF- $\beta$ ), have also been used to target this phase of healing. G-CSF, an endogenous haemopoietic growth factor, induces terminal differentiation and release of neutrophils from the bone marrow, enhances neutrophil and macrophage function, and promotes keratinocyte proliferation. Recombinant human G-CSF, injected subcutaneously, has been shown to enhance healing in infected diabetic foot ulcers. TGF-B is chemotactic for macrophages, induces the production of collagen and fibronectin, and inhibits metalloproteinase activity. TGFβ1 has been shown to accelerate wound healing in animal models, and topical application of TGF-B2 has been shown to be effective in the healing of diabetic foot ulcers. PDGF attracts keratinocytes and promotes the formation of granulation tissue. Recombinant PDGF was developed to expedite the proliferative phase. Becaplermin is the only growth factor currently licensed for commercial use in the United Kingdom. A multicentre, double blind randomized controlled trial in patients with chronic diabetic foot ulcer showed topical PDGF to be superior to placebo in promoting healing. Its effectiveness was further enhanced when used in conjunction with debridement of the wound bed, emphasising the importance of good basic wound care in figure 6 [21].

FGF promotes fibroblast proliferation and collagen accumulation and accelerates the formation of granulation tissue. VEGF plays a crucial role in angiogenesis in figure 7.

#### Cell and matrix based treatments

Autologous fibroblasts seeded onto a matrix derived from hyaluronic acid have been shown to be useful in treating diabetic foot ulcers and venous leg ulcers. Similarly, acellular collagen based matrices designed to mimic the extracellular matrix have been successfully used to treat chronic ulcers of varying aetiologies shown in figure 8.

Allogenic fibroblasts, obtained from neonatal human foreskin and cultured in vitro, have been used to provide the dermal replacement in such wounds. They are seeded either on a biologically absorbable scaffold on a nylon mesh. The proliferating fibroblasts secrete collagen, matrix proteins, and growth factors and promote healing. They are designed to provide dermal replacement in a variety of wounds, though most evidence to date comes from the treatment of diabetic foot ulcers and burns.

#### **OTHER CONCERNS**

Most biological based products contain bovine, porcine, or human constituents and thus have religious and ethical implications. Tissue engineered skin substitutes and growth factors produced by recombinant DNA technology are expensive, which may limit their widespread use [22]. Current areas of research include regulation of target genes of cells involved in wound healing, new methods of delivery of specific cell products to the wound, use of adult pluripotent stem cells, which are capable of differentiating into essential cells involved in wound healing. To date, there is only experimental evidence for gene and stem cell therapy in the treatment of chronic wounds

Cutaneous wound healing is a multistep process requiring the interaction and coordination of many different cell types and molecules including growth factors and proteases. Given the multiple molecular mechanisms involved, no single mediator, growth factor, or gene is likely to be successful in accelerating healing. Similarly, there is heterogeneity within wound types, identification of the cellular and molecular dysfunction in individual wounds and targeting or supplementing them is one of the goals for the future. Fig 1. Patient who suffered from trauma











Fig 5. Topical application of recombinant platelet derived growth factor on a diabetic foot ulcer





Fig 6. Venous leg ulcer suitable for use of dermal or composite skin substitute Fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) are active in this phase of repair



(1)



### Fig 7. Partial thickness burn suitable for an epidermal skin substitute

Fig 8. Wounds suitable for therapies aimed at the remodelling and epithelialisation phases of wound healing Loss of the dermal layer occurs frequently in deep ulcers and burns



#### CONCLUSION

The field of wound care is ever expanding with advances in technology. While there is still no superior substitute for reconstruction using patients own tissues and carefully thought-out reconstructive procedures; new products can help facilitate eventual healing by providing prophylaxis against barriers to healing, augmentation of wound healing factors, assistance in temporizing and bridging time to definitive repair, and optimization of the ultimate results of wound reconstruction. Current wound healing products and modalities increase the armamentarium of the wound practitioner to address all aspects of wound care.

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