Chapter - I

Introduction
CHAPTER – I
GENERAL INTRODUCTION

1.1. SKIN

Skin is a vital tissue that maintains body temperature, controls loss of water, electrolytes and other body constituents. It prevents the entry of microorganism and unwanted compounds from the environment as well acts as radiation barrier against UV light. The skin is composed of two layers: the outer epidermis and the underlying dermis. A third subcutaneous layer is to be found below the dermis and is composed mainly of adipocytes (Figure 1 Adapted from www.healthy-skin-guide.com/skin-diagram.html). But these functions and integrity of skin tissue is disrupted by wounds caused by physical or chemical or immunological factors. Hence it is essential to take care of skin and to maintain its structure and smoothness by treating the wound immediately.

Figure 1: Structure of the skin
1.2. THE NORMAL RESPONSE OF THE SKIN TO INJURY

1.2.1. Wound—an overview

According to the Wound Healing Society, wounds are physical injuries that result in an opening or break of the skin that cause disturbance in the normal skin anatomy and function. They result in the loss of continuity of epithelium with or without the loss of underlying connective tissue (Ramzi et al., 1994; Strodtbeck, 2001). This includes injury of underlying tissues / organs caused by surgery, a blow, a cut, chemicals, heat/cold, friction / shear force, pressure or as a result of disease. On exposure to air, microorganism enters the wound which leads to wound contamination and finally development of infection. Wound may arise due to physical, chemical, microbial agents, thermal or immunological damage to the tissue.

1.2.2. Pathology of wounds

Wound infection is one of the most common diseases in developing countries because of poor hygienic conditions (Senthil Kumar et al., 2006). Proper healing of wounds is very essential for the restoration of disrupted anatomical continuity and disturbed functional status of the skin. Healing is a complex process initiated in response to an injury that restores integrity and function of damaged tissues of skin. Wound healing involves continuous interactions between cell-cell and cell-matrix that allow the process to proceed in three overlapping phases viz. inflammatory phase (0-3 days), cellular proliferation or proliferative phase (3-12 days) and remodeling phase (3-6 months) (Glynn, 1981; Martin, 1996, Clark Raf, 1996). Healing requires the collaborative efforts of various tissues and cell lineages (Martin, 1997). It involves aggregation of platelets, clotting of blood, fibrin formation, and an inflammatory response to injury, alteration in the ground substances, angiogenesis and re-epithelialization. Healing process is not complete until the disrupted surfaces are firmly knit by collagen (Buffoni, 1993). Wound healing process holds several steps which involve coagulation, inflammation, formation of granulation tissue, matrix formation, remodeling of connective tissue, collagenization and aquisition of wound strength (Suresh Reddy et al., 2002).
The basic principle behind optimal wound healing is to minimize tissue damage and provide adequate tissue perfusion and oxygenation, proper nutrition to tissue and moist wound healing environment to restore the anatomical continuity and function of the wound (Pierce & Mustoe, 1995). Cutaneous wound healing is accompanied by sequence of biological events starting with wound closure and progressing to the repair and remodeling of damaged tissue in an order (Phillips et al., 1991). In spite of tremendous advances in the pharmaceutical industry, the availability of drugs capable of stimulating wound repair processes is still limited (Udupa, 1995). Moreover, due to high cost therapy and presence of unwanted side effects, management of chronic wounds is another major problem (Porras-Reyes et al., 1993; Suh, 1998). It is agreed that reactive oxygen species (ROS) are deleterious to wound healing process, as they show harmful effects on cells and tissues. Absorbable synthetic biomaterials are considered to be degraded via ROS (Aliyeva et al., 2004). Cytoprotective enzymatic group of enzymes called Free-radical-scavenging enzymes (FRSE) plays an essential role in the reduction, de-activation and removal of ROS as well as in regulation of wound healing process. Inflammation, which is a part of acute response, results in a coordinated influx of neutrophils at the site of wound. These cells produce free radicals through their characteristic “respiratory burst” activity (Baboir, 1978). Free radicals are also generated by wound related non-phagocytic cells by non-phagocytic NAD (P) H oxidase mechanism (Griendling, 2000).

Thus, the wound site has rich concentration of both oxygen and nitrogen centered reactive species along with their derivatives. These radicals results in oxidative stress leading to lipid peroxidation, breakage of DNA, and enzyme inactivation, including free-radical scavenger enzymes. Evidence for the role of oxidants in the pathogenesis of many diseases suggests that antioxidants may be of therapeutic use in these conditions. Topical application of compounds with free-radical-scavenging properties in patients has shown to improve wound healing processes significantly and protects tissues from oxidative damage (Thiem and Grosslinka, 2003).
1.2.3. Types of wounds

There is no definite method of classifying wounds. There are many different types of wounds ranging from mild to severe to potentially fatal.

1.2.3.1. Based on anatomical site

Wounds can be referred to by their anatomical site, e.g. abdominal or axillary wound.

1.2.3.2. Based on underlying cause of wound creation

Wounds are classified as open and closed wounds.

1.2.3.2.1. Open wound

In this class, bleeding is clearly visible as blood escapes from the body. It is further classified as: incised wounds, laceration wounds, abrasions or superficial wounds, puncture wounds, gunshot wounds and penetration wounds (Schultz, 1999).

1.2.3.2.1.1. Abrasion or superficial wound

An abrasion is a scrape or graze. Typically, there is a superficial surface wound involving the epidermis and part of the dermis. As dermal nociceptors are exposed in the damaged dermis, these wounds are often very painful. Some abrasions can however, be deeper wounds involving tissues below the level of the skin. Abrasions are most commonly caused by friction injuries, falling off bikes is a common cause. These wounds need to be well cleaned to remove dirt and grit which may be sticking to the wound surface.

1.2.3.2.1.2. Laceration or tear wound

Laceration describes a wound made by a blunt object, and has often involved considerable force. The wound edges are usually split or torn with ragged edges as the skin has been burst rather than cut. After significant trauma, there may be lacerations involving internal organs. Lacerations of the liver, kidneys, or spleen may be associated with serious hemorrhage requiring urgent surgical attention. Hence traumatized patients should be nursed as at rest as possible, as movement may dislodge blood clots and result in more serious internal hemorrhage.
1.2.3.2.1.3. **Incised wound**

This is a cut caused by a sharp object. These wounds usually appear neat and the edges can be readily approximated to allow primary healing to take place. In incised wounds the cut may also involve deeper structures such as nerves, blood vessels or tendons. Incised wounds should always be assessed for such deeper injuries and treated as required.

1.2.3.2.1.4. **Puncture wound**

These may well present as misleadingly small wounds and are also described as penetrating wounds. They are made by pointed or sharp objects. As the edges of the wound may be closed above areas of bacterial contamination, infection is a potential hazard. Also puncture wounds may penetrate down into body cavities or other significant structures such as blood vessels. If the base of a wound cannot be seen it should be surgically assessed as a matter of urgency.

1.2.3.2.1.5. **Penetration wound**

Penetration wounds are caused by an object such as a knife entering and coming out from the skin.

1.2.3.2.1.6. **Gunshot wound**

They are caused by a bullet or similar projectile driving into or through the body.

1.2.3.2.1.7. **Fish-hook wound**

It is an injury caused by a fish-hook becoming embedded in soft tissue.

1.2.3.3. **Closed wound**

In closed wounds, blood escapes from circulatory system but remains in.

1.2.3.3.1. **Hematomas or blood tumor**

They are caused by damage to a blood vessel that consequently causes blood to collect under the skin.
1.2.3.3.2. Crush injury

Crush injury is caused when great or extreme amount of force is applied on the skin over a long period of time.

1.2.3.3.3. Contusion or bruises

A contusion is more commonly called a bruise. It is usually caused by a blunt blow, the overlying skin is unbroken, but tissues and blood vessels below are damaged. The discoloration is caused by bleeding from small vessels into the tissues. Red blood cells trapped in the tissue spaces become deoxygenated and dark coloured. Bruising can also develop behind deeper tissues, such as bones damage, and may become apparent only after a period of time as blood tracks towards the body surface. If blood collects in a discrete pool within the tissues this is described as a haematoma. As the blood in a haematoma is well consolidated it may cause pressure effects on surrounding tissues, these may include pain and nerve compression. There is a risk as haematoma may become infected and some need to be surgically evacuated.

![Structure of contusion](image.png)

Figure 2: Structure of contusion. A contusion or bruise represents the presence of blood cells in the tissue spaces. This causes a characteristic discoloration of the area. Initially a bruise is ‘black and blue’ due to the presence of reduced haemoglobin in the tissues. Over time macrophages phagocytose the red cells in the tissues and the haemoglobin is converted to bilirubin. This is why the discoloration changes from blue to yellow as the bruise fades.
1.2.3.4. Based on the basis of physiology of wound healing

Wounds are popularly categorized by their level of chronicity as either an acute or a chronic wound.

1.2.3.4.1. Acute wounds

Acute wound is an injury to tissue that normally proceeds through an orderly and timely reparative process that results in sustained restoration of anatomic and functional integrity. Acute wounds usually follow trauma or inflammation and are caused by external damage to intact skin and usually heal within six weeks. Surgical wounds, bites, burns, minor cuts and abrasions, and more severe traumatic wounds such as lacerations and crush or gunshot injuries are examples of acute wounds. Acute wounds are generally caused by cuts or surgical incisions and complete the wound healing process within the expected time frame (Lazarus, 1998).

1.2.3.4.2. Chronic wounds

Wounds that are failed to progress through the normal stages of healing and therefore enter into a state of pathologic inflammation. These wounds either require a prolonged time to heal or recur frequently. Most common frequent causes of chronic wounds are Local infection, hypoxia, trauma, foreign bodies and systemic problems such as diabetes mellitus, malnutrition, immunodeficiency or medications (Menke, 2007; Krishnan, 2006). Chronic wounds, in addition to failing to heal after six weeks, have characteristic pathological associations due to underlying endogenous mechanisms associated with a predisposing condition that ultimately compromises the integrity of dermal and epidermal tissue that inhibit or delay healing.

Pressure ulcers, venous leg ulcers, and diabetic foot ulcers are examples of chronic wounds (De la Torre and Chambers, 2008). These wounds are visible evidences of an underlying condition such as extended pressure on the tissues, compromised tissue perfusion as a consequence of impaired arterial supply (peripheral vascular disease) or impaired venous drainage (venous hypertension) and metabolic diseases such as diabetes mellitus (DM), or even poor nutrition.
1.2.3.5. Based on wounds with or without tissue loss

Wounds are generally classified as, wounds without tissue loss (e.g. in surgery), and wounds with tissue loss, such as burn wounds (Paul et al., 2004).

1.2.3.5.1. Avulsion

This term describes a wound where there is tissue loss, preventing the closure of the wound edges. An avulsion may be caused by gouging or tearing of tissue.

1.2.3.5.2. Strains

Strains are injuries to muscles, fascia or tendons caused by stretching forces. Patients complain of pain and stiffness and there may be some associated swelling. It is usually important to exclude other injuries such as fractures. Strain injuries usually resolve with rest followed by progressive mobilization.

1.2.3.5.3. Sprains

A sprain describes an injury to the fibrous tissues surrounding a joint. Fibrous ligaments around the joint are injured, usually as a result of excessive movement of the joint. A mild sprain may involve tearing a few of the fibers in a ligament, in more serious cases there will be associated haematoma formation. In severe cases there may be complete tearing and disruption of a ligament. Patients usually present with local heat, pain, swelling, disability and possible discolouration over the area. Ankles are commonly sprained; if the ankle is turned inwards there will be injury to the lateral ligaments. Sprains usually take longer to recover than strains.

1.3. WOUND SIGNS AND SYMPTOMS

♣ The most common symptoms of a wound are pain, swelling, and bleeding. The amount of pain, swelling, and bleeding of a wound depends upon the location of the injury and the mechanism of injury.

♣ Some large lacerations may not hurt very much if they are located in an area that has few nerve endings, while abrasions of fingertips (which has a greater number of nerves) can be very painful, for example, a paper cut.

♣ Some lacerations may bleed more if the area involved has a greater number of blood vessels, for example, the scalp and face.
1.4. WOUND CARE DIAGNOSIS

X-rays may be taken to look for broken bones (fractures). X-rays may also be helpful in looking for foreign objects that may have been embedded in the laceration. Fluoroscopy done at the bedside may help find foreign bodies that are deeply buried. Ultrasound may also be used to assist in diagnosis of foreign bodies in the wound.

1.5. WOUND PROGNOSIS

The prognosis for wound healing is individualized and depends upon the type of wound, the underlying injury, and the baseline health of the patient.

♣ Most minor wounds including simple lacerations and abrasions heal on their own and do not require medical care.

♣ The more complicated the patient and the more complicated the wound, the prognosis for a perfect outcome decreases. The goal for all wounds is to have healing that allows the return of the injured part to normal function.

♣ Outcome also depends upon the risk factors present. Wounds that are contaminated and very dirty are more likely to become infected, and heal poorly than those that are not. Contaminated wounds heal less well in individuals with diabetes or who have poor circulation.

♣ All lacerations will leave a scar but the health care practitioner will work to minimize the thickness and appearance of scars.

1.6. WOUND PREVENTION

Accidents happen and most people will sustain a wound regardless of how careful they might be. It is important to remember that when using tools at home or at work, to make certain that they are being used in the appropriate manner and the appropriate precautions are taken. Often accidents occur because the person was in a rush, takes a shortcut, or was using a tool in a way it wasn't designed. Protective gear is always appropriate. Wearing proper shoes or boots, wearing a bike helmet, or eye protection regardless of the situation, is reasonable to prevent an injury.
1.7. COMPLICATIONS ASSOCIATED WITH WOUNDS

Complications associated with wounds include infection, cellulitis, deformity, overgrowth of scar tissue (keloid formation), gangrene that may require bleeding (wound hemorrhage), overwhelming systemic infection (sepsis), tetanus and fatal infection of the nervous system. Open wounds involve decreased circulation (ischemia) and tissue death (necrosis) that require amputation of affected parts. Wounds involving nerve injury may be complicated by temporary or permanent loss of sensation or function of the affected body part. Trauma not involving direct nerve injury may lead to delayed involvement of the nervous system (reflex sympathetic dystrophy).

1.8. PRIORITIES IN WOUND MANAGEMENT

1.8.1. Systemic stabilization

In any person with a wound, priority is always given to their systemic condition, only after this has been assessed and treated as required, is the wound considered in detail. Airway, breathing and circulation must all first be assessed and managed as required.

1.8.2. Hemostasis

Hemostasis may form part of systemic stabilization if blood loss is significant. Hemostasis is normally achieved by the application of firm direct pressure over the wound. This pressure will close off local blood vessels and give the blood time to clot. Direct pressure may need to be applied for some time before the bleeding stops. In some severe wounds pressure need to be applied continuously until surgery is made available. Direct pressure should not be applied if there is a foreign body in the wound as this will damage the foreign body to underlying tissues; in this case pressure is normally applied around the foreign body to reduce the blood supply to the area. If there is bleeding from an identified blood vessel, this may be clipped using artery forceps and tied off using suture thread by someone with the relevant surgical expertise. Tourniquet use is not normally recommended as a first aid measure in hemorrhage. However, with some wounds, bleeding should be encouraged. This is true when the wound is likely to be contaminated and when blood loss will not be too
severe. For example, in case of accidental needle stick injury bleeding to be encouraged as much as possible by squeezing the wound and running it under hot water. In this case, the outward flow of blood may wash out potential disease causing agents, such as bacteria and viruses. The same is true for other potentially dirty wounds such as animal or human bites.

1.8.3. Wound Assessment

After bleeding has been stopped the wound should be anaesthetised if required. The wound should be explored to carry out an accurate assessment. Whenever a practitioner is confronted with a wound, they must first identify the form of healing for the particular wound under consideration.

1.8.4. Wound healing

Healing is a survival mechanism and represents an attempt to maintain normal anatomical structure and function (Harshmohan, 2005). Wound healing or wound repair is an intricate process in which the skin repairs itself after injury (Nguyen et al., 2009). In normal skin, the epidermis and dermis exist in steady state equilibrium, following a protective barrier against the external environment.

1.8.4.1. Healing by primary intention

A wound will heal by primary intention if the edges of the wound can be approximated together. Some form of wound closure is normally employed to keep the wound edges closed. Common ways of achieving closure and stability of the wound edges include adhesive strips, sutures or super glue.

1.8.4.1.1. Advantages of healing by primary intention

Approximation and stabilization will allow the edges of a wound to heal directly into each other. In primary healing the process is fairly rapid, normally wound edges will be closed with sufficient tensile strength to remove the sutures after 7-10 days. However, it takes much longer than this to restore full strength to the wound, even after 2 weeks the wound only has 20% of full strength. If the edges of a wound are closed, the surface area of the wound is reduced. This means that there will be a minimal amount of scar tissue formed, giving good cosmetic and functional
results. As the wound is closed, there is less opportunity for secondary colonization or infection to enter the wound from outside sources

1.8.4.1.2. Potential problems with primary intention

Even the wound edges are closed; there is the possibility that foreign material or bacteria may be enclosed within the wound. This will allow any bacteria present to multiply and lead to wound infection with possible abscess formation. Also the presence of foreign material can lead to future complications such as pain and damage to tissues. If foreign material can be removed before closure, this particular complication may be prevented; this is one reason why wound exploration is so vital. If the wound is likely to be contaminated with bacteria from the implement which made the wound, then again it is unwise to close the wound, unless the practitioner feels they are able to adequately wash away the contamination with irrigation or other wound cleaning procedures. When primary healing is not possible, or is not advisable, healing by secondary intention will be used.

**Figure 3:** Cross section of a wound. An incised wound is a wound caused by a sharp object that has cut through the epidermis, dermis and some underlying tissues. When the skin is cut the edges ‘fall apart’ or ‘pull open’, this is because intact skin is under a degree of tension. The edges of this wound have been pulled together as close to their original position as possible after this approximation a suture has been inserted to hold the wound edges together to promote primary healing.
1.8.4.2. Healing by secondary intention

In this form of healing the wound is left open and allowed to heal by granulation. It is appropriate to use secondary healing when there is tissue loss and a wound cannot be closed because the edges will not approximate. In addition, if a wound is contaminated secondary healing may be chosen to prevent infective complications. All chronic wounds, such as ulcers, will be colonized with bacteria and so should not be closed. It is particularly dangerous to close a wound if there are anaerobic organisms present. If a wound is closed, the amount of oxygen the wound is exposed to is reduced; this lack of oxygen promotes the growth of anaerobic bacteria, such as Clostridium strains which may lead to tissue necrosis and gangrene. Prior to the advent of antibiotics, gangrene was the most common indication for limb amputation and for Tetanus, caused by Clostridium tetani, a gram positive anaerobic Bacillus.

1.8.4.2.1. Disadvantages associated with secondary intention

When the wound is left open to heal by granulation the time taken can be much longer than for primary healing. As secondary healing may be a protracted process, more nursing time will be required before the patient can be fully independent again. A large wound may take several months to heal, as the larger have more scar tissue formed, therefore the cosmetic and functional results are not as good as with primary healing. In secondary healing there is a risk that a wound may become infected from outside sources of contamination. All chronic wounds are colonized with various forms of bacteria but this does not adversely affect the healing process unless it develops into infection. Bacteria from a colonized or infected wound may however be transferred to another wound, or the wound of another patient, if we are not careful in preventing cross infection. Some wounds may be managed to open for a time so as to allow for cleaning or removal of devitalized tissue. After this time of cleaning such wounds may be subsequently closed, this is a delayed primary closure (or DPC).
Figure 4: Cross section of a wound healing by secondary intention; this involves the formation of granulation tissue which is progressively filling the wound. This will promote the processes of tissue healing with residual granulation eventually becoming scar tissue. An important part of management is the preservation of granulation tissue; this will involve the use of non adhesive dressings and the maintenance of a moist wound healing environment. Particular care needs to be taken not to damage this important but delicate tissue during procedures such as dressing changes.

1.8.4.3. Delayed primary closure

This means a wound is allowed to heal by primary intention, but only after being managed to open for a period of time after the initial injury. First the wound is treated so that it is clean enough to permit healing by primary intention. This may involve using cleaning agents and the removal of any devitalized tissue, which would necrosis if left as such. After this, the wound is closed to facilitate primary healing. Skin grafting is an example of a delayed primary closure. The donated skin is placed over the recipient area and heals in direct contact with the underlying tissue, so the healing is primary in nature.

1.8.4.4. Wound healing by regeneration and or repair

1.8.4.4.1. Specific Sites of wound healing

Wound healing occurs whenever there is injury to the tissues of the body. An injury describes an area of loss of continuity in any body tissue, this may occur as a result of trauma, infection or a pathological process. The mode of wound healing depends on the powers of regeneration of a particular tissue possesses. The following are some examples at specific sites.
Liver

Liver is able to regenerate very well. For example, acute hepatic injury caused by viral hepatitis or toxin exposure, can regenerate completely restoring full form and function. However, chronic insults such as ongoing exposure to alcohol or hepatitis C virus may result in the formation of collagen based scars and the development of cirrhosis. This latter process is associated with loss of functional liver tissue, so may progress to liver failure.

Kidneys

In the kidneys, epithelial tissues lining renal tubules may regenerate but whole nephrons do not. This means that mild damage to the kidneys will heal completely but more extensive injuries will result in scar formation. The glomeruli are the balls of capillaries within Bowman’s capsule and do not regenerate after injury. However, if one kidney is removed, the glomeruli in the other kidney enlarge to compensate.

Lungs

Damage to the alveoli may occur as a result of infection, inhalation of irritants or shock. As long as the basement membranes of the alveoli remain intact there can be complete healing. However, more severe damage can lead to areas of pulmonary fibrosis. The epithelial lining of the respiratory tract may regenerate effectively after injury, provided that the underlying structures and extracellular matrix framework is preserved. In the trachea and bronchial passages, there is restoration of epithelium from adjacent cells after injury.

Muscle

Skeletal and cardiac muscle cells do not have the potential for significant mitosis in adults. This means that damaged muscle cells are not replaced. In skeletal muscles, if there is a relatively small area of injury, other muscle cells can enlarge to restore overall muscle strength. Damage to the myocardium which results in necrosis is permanent, as cardiac muscle cells do not divide. Healing is by the formation of granulation tissue and fibrosis (i.e. fibrous scar tissue). This means affected areas of myocardium become non-contractile. This is why early thrombolytic is so important after coronary thrombosis, to prevent necrosis.
Nervous System

Neurons do not divide and are not capable of mitosis after injury. Any functional recovery which occurs after death of Central Nervous System (CNS) neurons is only as a result of reorganization of surviving nerve cells to re-establish neural connections. In the peripheral nervous system axons may slowly regrow, but even this does not occur in most of the CNS. Damage to the CNS results in the formation of gliosis, this is a permanent scarring of the nervous system. Gliosis occurs as a result of proliferation of glial cells, which are the supportive and structural non-neuronal cells of the nervous system. Once gliosis is established, there is no ongoing recovery of neurons; this explains why transverse spinal cord injuries cause permanent paralysis, and why dementia is irreversible.

Healing of wounds occurs by two physiological processes called regeneration and repair. In regeneration the wound heals as the lost tissue is replaced by cells from adjacent healthy tissue. Mitosis occurs in these adjacent cells to replace the cells lost as a result of the injury. This means the tissue is restored, more or less as it was, by the process of cellular and tissue regeneration. This is the ideal form of healing giving good cosmetic and functional results. Repair is an efficient method of closing and ‘patching’ damaged tissues. The damaged specialized tissue is replaced with collagen. Collagen is a tough protein with high tensile strength; it is the main component of fibrous scar tissue. In repair, the original tissue is replaced with fibrous tissue, so the functional and cosmetic results are poor. Most wounds heal by a combination of regeneration and repair although the wound-healing process varies among different tissue types; there are more similarities than differences between them. In this discussion, skin is considered as a representative tissue type. There are also different types of acute skin wounds, including incisional wounds, partial thickness injuries, and wounds involving significant tissue loss. Different types of wounds involve different phases of the healing process to varying degrees, although the phases themselves remain the same.
1.9. MECHANISM OF WOUND HEALING

It is traditional to describe wound healing in terms of stages; however in practice there is overlap. These stages and the physiology involved apply to wounds healing by primary and secondary intention. Healing of an acute wound follows a predictable chain of events (Figure 5). This chain of events occurs in a carefully regulated fashion that is reproducible from wound to wound. The phases of wound healing are overlapping, but are described in a linear fashion for the purpose of clarity. The five phases that characterize wound healing include (1) hemostasis, (2) inflammation, (3) cellular migration and proliferation, (4) protein synthesis and wound contraction, and (5) remodeling (Figure 6).

![Diagram of the acute wound-healing cascade](image)

**Figure 5:** The acute wound-healing cascade. The progression of acute wound healing from hemostasis to the final phases of remodeling is dependent on a complex interplay of varied acute wound-healing events. Cytokines play a central role in wound healing and serve as a central signal for various cell types and healing cascade.
1.9.1. Hemostasis

All significant traumas create a vascular injury and thereby initiate the molecular and cellular responses that establish hemostasis. The healing process cannot proceed until hemostasis is accomplished. Primary contributors to hemostasis include vasoconstriction, platelet aggregation, and fibrin deposition resulting from the coagulation cascades. The end product of the haemostatic process is clot formation. Clots are primarily composed of fibrin mesh and aggregated platelets along with embedded blood cells (Lawrence, 1998).

The inflammatory phase prepares the area for healing and immobilizes the wound by causing it to swell and become painful, so that movement becomes restricted. The fibroblastic phase rebuilds the structure, and then the remodeling phase provides the final form (Figure 7).
1.9.2. The inflammatory phase

The inflammatory phase starts immediately after the injury that usually last between 24 and 48 hrs and may persist for up to 2 weeks in some cases (Figure 7). The inflammatory phase launches the haemostatic mechanisms to immediately stop blood loss from the wound site. Clinically recognizable cardinal sign of inflammation, rubor, calor, tumor, dolor and function-læsa appear as the consequence. This phase is characterized by vasoconstriction and platelet aggregation to induce blood clotting and subsequently vasodilatation and phagocytosis to produce inflammation at the wound site (Li et al., 2007).

1.9.3. Cellular migration and proliferation

The cellular environment in wounds changes dramatically in the first week post acute injury. The initial fibrin-fibronectin matrix is heavily populated by inflammatory cells, whereas fibroblasts and endothelial cells will predominate as healing progresses. Reestablishment of the epithelial surface is also initiated within the first several days after injury, as is revascularization of the damaged area. Cytokine networks continue to be a part of the process as cytokine release contributes to fibroplasias, epithelialization, and angiogenesis (Fauci, 1996).

1.9.4. Protein synthesis and wound contraction

Synthesis and deposition of proteins and wound contraction are the wound-healing events that begin to predominate 4 to 5 days after wounding. The quality and quantity of matrix deposited during this phase of healing significantly influence the strength of a scar (Bullard, 1999). Collagen constitutes more than 50% of the protein in scar tissue, and its production is essential to the healing process (Nimmi, 1974). Fibroblasts are responsible for the synthesis of collagen and other proteins regenerated during the repair process (Figure 8). Collagen synthesis is stimulated by TGF-b, PDGF, and EGF (Ignocz and Massaugue, 1986). Collagen synthesis is affected by patient’s conditions and the nature of the wound together with age, tension, pressure, and stress (Caterson and Lowther, 1978). Collagen synthesis continues at a maximal rate for 2 to 4 weeks and subsequently begins to slow.
1.9.5. The Remodeling phase

This phase lasts for 3 weeks to 2 years (Figure 8). New collagen is formed in this phase. Tissue tensile strength is increased due to intermolecular cross-linking of collagen via vitamin-C dependent hydroxylation. The scar flattens and scar tissues become 80% as strong as the original (Madden and Peacock, 1968; Prockop et al., 1979).

Wound present more than 30 days or wounds failing to improve with multiple treatments or therapies are diabetic foot ulcers, lower leg ulcers, pressure ulcers, burns, bone infection, (osteomyelitis), gangrene, skin tears or lacerations, radiation burns, post-operation infections, slow or non-healing surgical wounds, brown recluse spider wounds failing or compromised skin muscle grafts or flaps.

1.10. FACTORS WHICH IMPAIR WOUND HEALING

Wounds come in various forms and result from a multitude of factors, such as hypoxia, trauma, or pressure, improper diet, insufficient oxygen supply and tissue perfusion to the wound area, elderly age, bacterial infection, nutritional deficiency, drugs, sterility, obesity, movement of wound edges, site of wound and wasting diseases.

Sussman (2007) reported that haemorrhheologics, pentoxyfilline (Trental), other methyl xanthenes, retinoid, phenytoin, prostaglandins, vitamin A and C, zinc and some growth factors are the drugs which are having the potential in improving the healing of wounds.

Local and systemic factors may influence the rate of wound healing. Local factors describe the conditions in the immediate wound environment while systemic
factors refer to ‘whole body’ influences on the local wounded area. Several factors delay or reduce wound healing including bacterial infection, necrotic tissue, interference due to blood supply, lymphatic blockage, diabetes and other disease conditions. When unabated, wound healing progresses in an orderly and predictable fashion: inflammation (reactive), proliferation (regenerative), and maturation (remodeling). Numerous factors, however, play a detrimental role in the wound-healing process (Table 1). A precise understanding of these mechanisms of impairment is necessary when treating acute or chronic wounds.

Table 1: Factors that interfere with wound healing

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<tr>
<td>10.</td>
<td>Arterial insufficiency</td>
<td>21.</td>
<td>Medications</td>
</tr>
</tbody>
</table>

1.10.1. Infection

It is a common observation that infected wounds heal slowly, if at all. Infection means that bacteria are present in the wound and are generating an inflammatory host response. Living bacteria secrete waste products of their metabolism referred to as exotoxins. These substances are toxic, and so inhibit the normal function of local cells and tissues e.g. they may interfere with protein synthesis. Infected wounds need to be well cleaned and often systemic antibiotics are needed. Any foreign bodies in a wound are also likely to be associated with infection.
1.10.2. Poor hygiene

Patients with poor personal hygiene may infect their wounds from other areas of their body or from outside sources of contamination. This can also be a problem in treating people with wound and in wound dressings.

1.10.3. Local blood supply

Good blood supply to a wound is one of the main factors for promoting healing. Wounds on areas of the body with copious blood supplies, such as the face or scalp, tend to heal quickly. Conversely areas of the body with a poorer blood supply, such as the back or feet, heal more slowly. Blood supplies leucocytes, nutrients, oxygen, remove waste products, and keep the wound warm. Wound ischemia may occur as a result of the initial trauma, if blood vessels are damaged or compressed by swelling. Pre-existing vascular insufficiency is a significant adverse factor in healing. Ischemia results in very poor rates of healing or no healing at all. For example, foot or leg wounds in patients with peripheral vascular disease are notoriously difficult to heal. Venous deficiency is an adverse factor in wound healing, as seen in venous leg ulceration. Systemic conditions affecting the cardiovascular system may also reduce local wound perfusion; these may include heart failure or shock. Immobility will also reduce the circulation of the blood and so reduce wound perfusion.

1.10.4. Oedema

The presence of oedema, for whatever reason, adversely affects wound healing. All cells of the body receive nutrients and oxygen from the capillary blood, via tissue fluid, by the process of diffusion. If there is an increased volume of tissue fluid, as is the case in oedema, then there will be an increase in the distance from the capillaries to the tissue cells. This increased distance means nutrients and oxygen need to travel further to reach the cells, so supplies are reduced. The result is that cells become relatively embarrassed and their functional ability is reduced. If cell function is reduced wound healing will be correspondingly adversely affected.

1.10.5. Wound hypoxia (Inhibited wound oxygenation)

This may occur secondary to wound ischemia. Lack of oxygen in the wound is a consequence of a poor blood supply, as it is the blood which transports oxygen to the area. Any systemic cause of hypoxia will also reduce wound oxygenation and
healing rates. This means if any one is able to improve any underlying causes of wound hypoxia, such as respiratory infection or anemia, wound healing will be promoted. Decreased oxygen in a wound is detrimental to wound healing (Hunt et al., 1969; Stadelmann et al., 1998; Xia et al., 2001) and results in the formation of a non-healing ulcer or impaired healing of an incision (Winter, 1977). Although hypoxia is a stimulus for angiogenesis, the wound will not proceed through the later stages of healing without higher tissue oxygen levels. Many clinical conditions affect blood vessels and can be associated with impaired healing. In the microenvironment of the skin, tissue oxygen tension levels below 35 mm Hg are associated with poor healing. At this level, wound fibroblasts are unable to replicate, and collagen production is severely impaired. Although the exact mechanism is not known, evidence suggests that impaired diffusion of oxygen from the capillaries to the surrounding tissue is the cause. In the past, anemia has been considered a risk factor for impaired healing (Hugo et al., 1969).

1.10.6. Smoking

Cigarette smoking has long been known to have a detrimental effect on wound healing. Nicotine causes vasoconstriction, therefore reduces blood supply to the skin and periphery. This reduces the perfusion of wounds. Smoke also contains carbon monoxide which increases the proportion of carboxyhaemoglobin in the blood. Smoke causes the breakdown and increased excretion of vitamin C from the body, resulting in a chronic shortage. As vitamin C is essential for collagen formation, wound healing will be correspondingly inhibited. Collagen production is reduced in smokers (Jorgensen et al., 1998). Nicotine is known to have an inhibitory effect on the proliferation of red blood cells, macrophages, and fibroblasts. These effects combine to impair wound healing (Kwiatkowski et al., 1996).

1.10.7. Cooling of the wound

Cooling leads to localized vasoconstriction which reduces wound perfusion. As wound healing is dependent on a good blood flow which is necessary to supply nutrients and oxygen, if there is a decreased blood flow due to vasoconstriction the process will be inhibited. Removal of metabolic and respiratory waste products will
also be correspondingly inhibited. Wound cooling will inhibit the biochemical processes in local cells as this chemistry is dependent on the action of intracellular enzymes. Enzymes are made of proteins and function within a narrow temperature range. Wound cooling should therefore be prevented as far as possible and should be a considered in wound redressing procedures. In hypothermia when the whole body is cool, peripheral vasoconstriction will result in wound bed cooling. Besides when the body is hypothermic, all metabolic processes will be retarded.

1.10.8. Insufficient diet or malnutrition

For a wound to heal it needs to be supplied with the nutritional building blocks required for the regeneration of tissues. To optimize wound healing the patient should eat an adequate balanced diet including adequate proteins, carbohydrates, fats, vitamins, minerals, fiber and water. Balanced means the dietary components should be eaten in the profile required by the body. Adequate means the components must be eaten in sufficient quantities. Lack of proper caloric intake and nutritional balance may delay wound healing (Reynolds, 2001) (Table 2).

Table 2: Nutritional deficiencies associated with delayed wound Healing

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Malnutrition</th>
<th>S. No.</th>
<th>Malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Decreased protein levels</td>
<td>8.</td>
<td>Decreased vitamin A deficiencies</td>
</tr>
<tr>
<td>2.</td>
<td>Carbohydrate depletion</td>
<td>9.</td>
<td>Excess vitamin E</td>
</tr>
<tr>
<td>3.</td>
<td>Decreased levels of amino acids</td>
<td>10.</td>
<td>Trace element</td>
</tr>
<tr>
<td>4.</td>
<td>Arginine</td>
<td>11.</td>
<td>Zinc</td>
</tr>
<tr>
<td>5.</td>
<td>Glutamine</td>
<td>12.</td>
<td>Iron</td>
</tr>
<tr>
<td>6.</td>
<td>Vitamins</td>
<td>13.</td>
<td>Copper</td>
</tr>
<tr>
<td>7.</td>
<td>Decreased vitamin C</td>
<td>14.</td>
<td>Magnesium</td>
</tr>
</tbody>
</table>

1.10.9. Malnutrition delays healing

1.10.9.1. Proteins

Proteins in the diet are broken down into component amino acids during digestion. Amino acids then circulate in the blood and are taken up by tissues where they are needed. Human proteins contain 20 different forms of amino acids. A single protein may contain hundreds or thousands of amino acid units. For a wound to heal
new cells and tissues must be constructed, amino acids are required as building block components for the new proteins. Without amino acids from the diet, wounds fail to heal properly and may even break down. Lack of protein specifically inhibits angiogenesis, collagen and matrix synthesis and fibroblast proliferation. This result in decreased synthesis, accumulation, and remodeling of collagen (Breslow, et al., 1993; Daly et al., 1990). The degree of protein depletion necessary to impair wound healing, however, is not clearly understood. Severe lack of protein will also lead to hypoproteinaemia and consequent oedema. Protein depletion can be caused by trauma, sepsis, nephritic syndrome, liver disease, chronic open wounds, and burns.

![Collagen synthesis](image)

**Figure 9: Collagen synthesis**

1.10.9.2. Aminoacids

Specific amino acids such as arginine and glutamine have been shown to enhance wound healing. The role of arginine in wound healing is slightly better understood. It is thought that the metabolism of arginine via the nitric oxide pathway (which increases NO) is one mechanism by which arginine enhances wound healing.

1.10.9.3. Carbohydrates

Carbohydrates are energy giving foods. Wound healing is a very energy demanding process so carbohydrates are important to fuel metabolic processes in the cells and tissues involved. Patients with extensive wounds, e.g. large burns, will need an increased intake of energy giving foods. When adequate carbohydrates are available the body does not need to break down amino acids for energy production.
1.10.9.4. Fats

Fats are composed of sub-units called fatty acids in much the same way proteins are composed of amino acids. Some components of cells and tissues e.g. cell membranes, are composed of fatty acids, so a supply of these is required for tissue regeneration. In addition to supplying essential fatty acid building blocks, fats also act as a source of energy for cell metabolism in a similar way to carbohydrates.

1.10.9.5. Vitamins

Vitamins are micronutrients which are vital in the diet. Vitamins A, D, E and K are fat-soluble and so may be stored in the body. Vitamins B\textsubscript{1}, B\textsubscript{11} and C are water soluble so cannot be stored. Vitamins C, A, E, and K play important roles in the wound healing process.

1.10.9.5.1. Vitamin C

Vitamin C (Ascorbic acid) deficiency to be the only true vitamin deficiency to impair wound healing. Vitamin C’s critical role in wound healing was first linked to scurvy in the early days of the British Navy. Vitamin C is a cofactor in the hydroxylation of proline and lysine for procollagen formation. Procollagen residues are then altered intra-cellularly to form collagen. Any deficiency of ascorbic acid will impact both the rate and the quality of collagen production, with the net result being marked delay in healing, weaker scars, and abnormal capillary formation. Severe vitamin C deficiency can even result in the dehiscence of previously healed wounds. In addition to impairing collagen formation, vitamin C deficiency results in an immune system compromise. Vitamin C allows wounds to resist infection by facilitating leukocyte migration into a wound. It also plays a bactericidal role by contributing to the formation of neutrophils superoxide. Vitamin C (ascorbic acid) is particularly important for wound healing as it is essential for protein and collagen formation when a person is deficient in vitamin C; old wounds may also fall apart as collagen in scar tissue is not adequately maintained. Vitamin C appears to facilitate wound healing by preventing molecular damage.
1.10.9.5.2. Vitamin A

Vitamin A is important for regenerative processes such as re-epithelialization, collagen synthesis and angiogenesis. Vitamin A also helps to reverse the anti-inflammatory effects of corticosteroid drugs and so may promote wound healing in such patients. Vitamin A has been shown to influence most of the stages of wound healing, adversely affecting monocyte and macrophage stimulation, fibronectin deposition, cellular adhesion, and tissue repair (Weinzweig, 1990). Vitamin A does play a fundamental role in the immune response. Vitamin A contributes to lysosomal membrane stabilization and phagocytosis in a wound, and functions in cell-mediated cytotoxicity, cytokine production, and antibody responses (Ross, 1992).

1.10.9.5.3. Vitamin E

The role of vitamin E (α-tocopherol) in wound healing is controversial, because possesses positive and negative effects. Vitamin E is a known antioxidant that has anti-inflammatory properties. It alters prostaglandin production by inhibiting phospholipase A\(_2\) activity, resulting in decreased collagen production and decreased inflammation. Although the exact role of vitamin E in wound healing is not understood, it appears to involve cell differentiation, epithelialization, cell-mediated immunity, the early inflammatory response, and angiogenesis (Tanka et al., 1979; Taren et al., 1987).

1.10.9.5.4. Vitamin B

Vitamin B is needed to facilitate the action of several enzymes needed for normal tissue regeneration.

1.10.9.5.5. Vitamin K

Vitamin K is vital in the normal clotting cascade. Because the initial events of the inflammatory stage of wound healing depend on blood clotting, deficiencies in vitamin K will affect the synthesis of pro-thrombin and factors II, VII, IX, and X. Adequate vitamin K is needed for blood clotting and the prevention of haematoma formation.
1.10.9.6. Trace elements

Minerals are inorganic nutrients required in small quantities for health. Trace elements are critical for wounds to heal properly. The elements most often implicated in delayed wound healing are zinc and iron.

1.10.9.6.1. Zinc

Zinc is an essential cofactor in normal cellular growth and replication, and is involved in more than 100 different enzymatic reactions. Those reactions that are specifically related to wound healing include the production of DNA polymerase (essential for cellular proliferation) and superoxide dismutase. Zinc directly imparts epithelialization and fibroblast proliferation through its effects on metalloenzymes, such as RNA polymerase, DNA polymerase, and DNA transcriptase. Zinc is also involved in many aspects of the immune response, including phagocytosis, cellular and humoral immunity, and bactericidal activity.

1.10.9.6.2. Iron

Iron is an essential cofactor in the replication of DNA. In conjunction with ribonucleotide reductase, iron is involved in producing the deoxyribonucleotides needed for DNA synthesis. Ferrous iron is a cofactor in the hydroxylation of proline and lysine in collagen synthesis. Without this, the normal collagen triple helix is not possible. Increased free iron and an increase in reactive oxygen species released from neutrophils represent pathologic key steps (via the Fenton reaction) that are thought to be responsible for the persistent inflammation, increased connective tissue destruction, and lipid peroxidation that contributes to the pro-oxidant hostile environment of chronic wounds (Wenk et al., 2001). Thus, by contributing to toxic free radicals, iron may also impair wound healing (Vaxman et al., 1996).

1.10.9.6.3. Copper and magnesium

Two other trace elements that merit reference are copper and magnesium. Through its promotion of vascular endothelial growth factor, copper may be harnessed to accelerate wound healing by stimulating angiogenesis (Sen et al., 2002). Magnesium has been observed to enhance the mechanical properties of scar, although the precise mechanism is poorly understood (Vaxman, 1996).
1.10.10. Psychological stress

Stress has adverse effects on the immune system; this may make wound infection more likely. During periods of anxiety, people release the hormone adrenaline from the adrenal medulla. Epinephrine (adrenaline) is a very powerful vasconstricting agent. Peripheral vasoconstriction will reduce perfusion of the wound, with a corresponding reduction in local blood supply. Steroid hormones, such as hydrocortisone, are released during periods of stress from the adrenal cortex; these hormones inhibit the inflammatory response. As in other conditions, the way practitioners approach and communicate with patient has the potential to significantly reduce their anxiety levels. If the patient believes that the doctors are trying their best to help them and have the ability to do so, they will feel psychologically better and should therefore heal more rapidly.

1.10.11. Delayed inflammatory response

The inflammatory response may be delayed for local or systemic reasons. If the area is cold, there will not be significant inflammation as the vasoconstrictions reaction to cold will act against the vasodilators effect of the inflammatory process. A reduced inflammatory response is also seen in patients who are receiving corticosteroids as these drugs are anti-inflammatory. Corticosteroids work by decreasing capillary permeability and inhibiting fibroblast activity and the phagocytic capacity of leucocytes. Inflammation is the first essential stage in the physiology of wound healing so any factor which reduces this response will delay wound healing.

1.10.12. Age effects

Children and young adults usually heal well. It is important to remember that children with wounds need adequate nutrients for wound healing, in addition to the normal requirements of growth and development. Wound healing in the elderly may be slow due to a reduced number of fibroblasts in their tissues and consequent reduced rates of collagen formation. Re-epithelialization and wound contraction are also slower in older people. The elderly are more likely to have underlying disease processes which may adversely affect wound healing such as diabetes mellitus, heart disease and peripheral ischaemia. They are more likely to have reduced mobility, with increased risk of pressure sore formation.
1.10.13. Poorly managed or unrecognized diabetes mellitus

It is a common observation that people with diabetes mellitus often have poor wound healing. Adverse effects on wound healing are related to poor glycaemic control. Higher blood sugar levels inhibit wound healing. Reasons for this include high levels of glucose in the tissue fluids and basement membrane thickening in arterioles, capillaries and venules.

1.10.14. Drugs

Many drugs are known to impair wound healing (Table 3). Many more possess the ability to delay healing but are overlooked because the patient has more significant comorbid factors.

Table 3: Medications associated with delayed wound-healing

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Medications</th>
<th>S. No.</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Anticoagulants</td>
<td>11.</td>
<td>Dakin’s solution (sodium hypochlorite .25%)</td>
</tr>
<tr>
<td>2.</td>
<td>Antihistamines</td>
<td>12.</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>3.</td>
<td>Antimicrobials (some)</td>
<td>13.</td>
<td>Immunosuppressive agents</td>
</tr>
<tr>
<td>4.</td>
<td>Aspirin</td>
<td>14.</td>
<td>Lathyrogens</td>
</tr>
<tr>
<td>5.</td>
<td>Azathioprine</td>
<td>15.</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>6.</td>
<td>B-amino propio nitrile (BAPN)</td>
<td></td>
<td>Nonsteroidal anti-inflammatory agents</td>
</tr>
<tr>
<td>8.</td>
<td>Chemotherapeutic agents</td>
<td>17.</td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>9.</td>
<td>Chlorhexidine</td>
<td>18.</td>
<td>Quinoline sulfate</td>
</tr>
<tr>
<td>11.</td>
<td>Dakin’s solution (sodium hypochlorite .25%)</td>
<td>20.</td>
<td>Thiphenamil hydrochloride</td>
</tr>
</tbody>
</table>

1.10.14.1. Chemotherapeutic agents

Drugs used to treat cancer are by far the largest group known to delay wound healing. Wound healing and tumor growth share many physiologic and metabolic pathways. Drugs that impair tumor growth will also impair wound healing because
they target rapidly dividing cells. Nine different classes of chemotherapeutic agents are commonly used to treat cancer (Table 4). Many of these are thought to work in a similar manner to impair wound healing. These drugs tend to attenuate the inflammatory phase of healing by interfering with the vascular response. Delays in the cellular infiltration in the healing wound and decreased fibrin deposition lead to poor or incomplete scaffolding for healing. These delays interfere with DNA and RNA production, protein synthesis, and cell osmosis. The primary cells affected are the fibroblasts, with decreased collagen synthesis. The myofibroblasts are also impaired, causing delayed wound contraction in treated animals (Devereux, 1980; Engelmann, 1983; Falcone and Nappi, 1984).

**Table 4: Classification of chemotherapeutic agents**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Chemotherapeutic agents</th>
<th>S. No.</th>
<th>Chemotherapeutic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Adrenocorticosteroids</td>
<td>6.</td>
<td>Estrogen progestogens</td>
</tr>
<tr>
<td>3.</td>
<td>Antiestrogens</td>
<td>8.</td>
<td>Plant alkaloids</td>
</tr>
<tr>
<td>5.</td>
<td>Antitumor antibodies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**1.10.14.2. Steroids**

Systemic glucocorticosteroids have been shown to impair wound healing by directly blunting the cellular response. This impairs fibroblast proliferation and ultimately collagen synthesis. The formation of granulation tissue and extracellular matrix is also decreased in steroid-treated animals. As expected, both epithelialization and wound contraction are decreased in a dose-dependent manner. Gene transcription particularly that associated with production of platelet derived growth factor is also impaired. As stated earlier, the anti-inflammatory effects of steroids can be reversed by the administration of vitamin A (Ehrlich and Hunt, 1973; Ehrlich and Hunt, 1969). Steroids stabilize lysosomal membranes, which are necessary to initiate part of the inflammatory response during wound healing. Vitamin A is thought to antagonize this effect and allow the release of the lysosomal products. The effect of steroids on
wound strength is dose and time dependent. Low doses given for short periods will not interfere with wound healing. With chronic administration, however, wound healing is impaired for up to 1 year after cessation of the drug.

1.10.14.3. Nonsteroidal anti-inflammatory agents

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a relatively newer class of analgesics. It is still unclear as to whether low or moderate doses of these drugs impair wound healing. Lower doses of these drugs may in fact cause delays in wound healing (Riley et al., 2001; Haws et al., 1996). Some-what less controversial is that high doses of NSAIDs have been implicated in delayed healing (Riley et al., 2001; Haws et al., 1996). In ischemic wounds, NSAIDs may limit necrosis and actually improve healing (Quirinia et al., 1997).

1.10.15. Radiation

Radiation has both acute and chronic effects on the skin. Acute effects include erythema, dry desquamation at moderate dose levels, and moist desquamation at higher dose levels. Delayed effects include increased or decreased pigmentation, thickening and fibrosis of the skin and subcutaneous tissues, telangiectasias, and alterations in sebaceous and sweat gland function. Further chronic effects can include necrosis and ultimately tumorigenesis. These effects lead to delays in wound healing because radiation therapy impacts the various components of skin and their roles in wound healing, including keratinocytes, fibroblasts, cutaneous vasculature, and adnexal structures. Radiation damage affects the blood vessels of the skin, creating a hypoxic skin bed. Radiation therapy is most effective on cells in the active part of the cell cycle. The cells most frequently injured by irradiation are the fibroblasts. As in the epidermis, irradiation causes an intense inflammatory response within the dermis. This subsequently leads to edema of the collagen bundles. Coupled with a diminished ability of the dermal fibroblasts to proliferate, this causes decreased breaking strength. If the radiation injury is severe enough, full-thickness loss may ensue with necrosis and ulceration.
1.10.16. Risk factors

Certain risk factors may lead to chronic wounds, such as Malnutrition and diet, Blood flow problems, Infection, Aging, Diabetes, Hyperglycemia - especially blood sugars over 150, Arthritis, Kidney disease, Medications, Swelling, Weight, Smoking, Inability to adhere to individual plan of care.

1.11. MEDICATIONS FOR WOUNDS

Medical treatment of wound includes administration of drugs either locally (topical) or systemically oral or parenteral (Savanth and Shah, 1998). The topical agents used include antibiotics such as Oxacillin, Mezlocillin, and Gentamicin and antiseptics (Chulani, 1996), desloughing agents (chemical debridement, e.g. hydrogen peroxide, eusol and collagenase ointment) (Savanth and Mehta, 1996), wound healing promoters exist like Tretinoin, Aloe vera extract, honey, comfrey, benzoyl peroxide, chamomilia extract, dexpanthenol, tetrachlordecaxide solution, clostebol acetate and the experimental cytokines. Various growth factors like platelet derived growth factor, macrophage derived growth factor, monocyte derived growth factor (Mather et al., 1989) etc. are necessary for the initiation and promotion of wound healing. Many substances like tissue extracts (Udupa et al., 1991), vitamins & minerals and a number of plant products (Dahanukar et al., 2000) have been reported by various workers, to possess pro-healing effects. Antimicrobial ointments such as silver sulfadiazine, mafenide, silver nitrate, and povidone-iodine are used to reduce risk of infection. Nitrofurazone used for open wounds. Prescription pain medications such as acetaminophen with codeine, morphine, or meperidine and anabolic steroids such as oxandrolone, may be used for severe burns to help in decreasing the time of wound healing. Nitrofurazone ointment is used as a standard drug for comparing the wound healing potential of the extract in the animal studies. Some of the commonly available drugs used in the healing of wounds are, NSAIDs ibuprofen (non-steroidal anti-inflammatory drug), colchicines, corticosteroids, antiplatelets (aspirin), anticoagulants (heparin), warfarin and vasoconstrictors e.g., nicotine, cocaine and adrenaline (Grey and Harding, 2006).

Several drug classes have been used in the management of wounds. Among these are the antibiotics. Penicillin and Streptomycin have been widely employed in
combating postoperative infections in man and animals (WHO, 1985). The antibiotics are chosen based on their ability to destroy or inhibit the growth of pathogenic organisms, while the tissue is left unharmed. Antibiotics used should be applied to achieve maximum concentration in the tissue as quickly as possible and continued until 48 h after disappearance of symptoms unless signs of toxicity are shown (Fazly-Bazzaz et al., 2005).

1.12. SIDE EFFECTS

Leukopenia has been reported as well following prolonged silver sulfadiazine application and could be secondary to medullar toxicity (Chaby et al., 2005) silver sulfadiazine remains the main topical product used in burn units (Dunn and Edwards-Jones, 2004; Fakhry et al., 1995). Various toxic effects observed confirmed that topical application of this cream should not be used for long periods on extensive wounds (Chaby et al., 2005). Impaired reepithelialization has been described. Bone marrow toxicity with silver sulfadiazine is observed 0.5%. Silver nitrate is the standard and most popular silver salt solution widely used for topical burn wound therapy. Concentrations exceeding 1% silver nitrate are toxic to the tissues. Bacterial resistance to silver nitrate has been described by (Bishara et al., 2007). The same is observed in case of antibiotics.

1.13. MANAGEMENT OF WOUND HEALING

The objective in wound management is to heal the wound in the shortest time possible, with minimal pain, discomfort, and scarring to the patient or to minimize the undesired consequences (Myers et al., 1980). Attention should be directed towards discovering an agent, which will accelerate wound healing either when it is progressing.

Management of wound healing, particularly the under healing is complicated and expensive programme. Research on wound healing drugs is a developing area in modern biomedical sciences. Several drugs from plant sources are known to have wound healing properties. Some of these plants have been screened scientifically for evaluation of their wound healing activity in different pharmacological models and patients, but the potential of most remains unexplored. In a few cases, active chemical constituents were identified (Biswas and Mukherjee, 2003). Hence, there is a dearth of safe, economic and effective prohealing agents for the wound management programme,
which can enhance healing as well as control. Therefore the aim of treating a wound is to either shorten the time required for healing or to minimize the undesired consequences (Myers et al., 1980). Attention should be directed towards discovering an agent, which will accelerate wound healing either when it is progressing normally (Myers et al., 1980), or when it is suppressed by various agents like corticosteroids (Ehrlich and Hunt, 1968), anti-neoplastics (Raju and Kulkarni, 1986), or non-steroidal anti-inflammatory agents.

1.14. NEED FOR STUDY

Traditional medicines holds a great promise as an easily available source as effective medicinal agents to manage a wide range of ailments among the people particularly in tropical developing countries like India. In this context, the people consume several plants or plant derived formulations to cure helmintic infections (Satyavati, 1990) and to treat wounds (Raina et al., 2008). Plants or chemical entities derived from plants need to be identified and formulated for treatment and management of wounds. In this direction a number of herbal products are being investigated at present. Various herbal products have been used in management and treatment of wounds over the years.

Current trend observed among the public is to resort to herbal medicine, as they are free from side effects and easily affordable ones. Hence in the present dissertation also focus is made towards herbs in the management and treatment of wounds. Brief literature review suggested that herbs and herbal products are capable of healing wounds without any serious side effects due to the presence of various phytoconstituents such as flavones, sesquiterpenes lactones and alkaloids.

Till date, there is no evidence available to assess the traditional claim about the wound healing property of Centratherum punctatum Cass. leaf extracts. Hence the present study was undertaken to investigate the wound healing activity of Centratherum punctatum Cass. using animal models and also to investigate supporting studies like analgesic and anti-inflammatory activity and thereby to provide scientific evidence to the same.

A detailed literature review was carried out which is presented and discussed in sequel. Based on this review a common herb with wound healing potential is selected and studied from standardization and validation point of view.