

The mechanism of wound healing

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Wounds

Wounds and skin damage is a key feature of both the dermal pharmaceutical and skin care products industries, the only difference between them is the level of damage.

Definition

A wound occurs when the integrity of any tissue is compromised (e.g. skin breaks, muscle tears, burns, or a bone fractures). A wound may be caused as a result of a fall, or a surgical procedure; or by an infectious disease; or by an underlying condition.

Description

Types and causes of wounds are wide ranging, and health care professionals have several different ways of classifying them. They may be chronic, such as the skin ulcers caused by *diabetes mellitus*, or acute, such as a gunshot wound or animal bite. Wounds may also be referred to as open, in which the skin has been compromised and underlying tissues are exposed, or closed, in which the skin has not been compromised, but trauma to underlying structures has occurred (e.g. a bruised rib or cerebral contusion). Emergency personnel and first-aid workers generally place acute wounds in one of eight categories:

Abrasions. Also called scrapes, they occur when the skin is rubbed away by friction against another rough surface (e.g. rope burns and skinned knees).

Avulsions. Occur when an entire structure or part of it is forcibly pulled away, such as the loss of a permanent tooth or an ear lobe. Animal bites may cause avulsions.

Contusions. Are also called bruises and are the result of a forceful trauma that injures an internal structure without breaking the skin. Blows to the chest, abdomen, or head with a blunt instrument (e.g. a football or a fist) can cause contusions.

Crush wounds. Occur when a heavy object falls onto a person, splitting the skin and shattering or tearing underlying structures.

Cuts. Slicing wounds made with a sharp instrument, leaving even edges. They may be as minimal as a paper cut or as significant as a surgical incision.

Fish-hook wound. An injury caused by a fish-hook becoming embedded in soft tissue.

Incised wound: Any sharp cut in which the tissues are not severed; a clean cut caused by a keen cutting instrument. The wound may either be aseptic or infected, depending on the circumstances.

Lacerations. Also called tears, these are separating wounds that produce ragged edges. They are produced by a tremendous force against the body, either from an internal source as in childbirth, or from an external source like a punch.

Open wound. A contusion in which the skin is also broken, such as gunshot, incised or lacerated wound.

Penetrating wound. A wound in which the skin is broken and the agent causing wound enters subcutaneous tissue or a deep lying structure or cavity, e.g. nails, splinters, spikes etc.

Punctures. Deep, narrow wounds produced by sharp objects such as nails, knives, and broken glass. [Taber; Thivierge & Turkington]

2.2.1. Wound Healing

2.2.1.1. Normal Wound-Healing Phases.

A skin trauma will start a regime of organized and predictable sequence of events that has a cascade effect until the wound is bridged by scar tissue that binds and holds the wound in stasis. The successful treatment is one that minimizes the formation of scar tissue and reduces the amount of necrotic tissue that is produced during this process. The use of an hydrogel helps to produce a more rapid healing by creating a moist environment that reduces the build up of necrotic tissue through the apoptosis of cells (cell death) and help to minimize the build up of necrotic tissue. The beneficial effects of a moist versus a dry wound environment include: prevention of tissue dehydration and cell death, accelerated angiogenesis, increased breakdown of dead tissue and fibrin, i.e., pericapillary fibrin cuffs, and potentiating the interaction of growth factors with their target cells. [Field *et al*].

The response to injury, either surgically or traumatically induced, is immediate and the damaged tissue or wound then passes through three phases in order to effect a final repair:

- 1.1.1. the barrier protection
- 1.1.2. the inflammatory phase,
- 1.1.3. the fibroplastic phase, and
- 1.1.4. the remodelling phase.

2.2.1.1.1. The physical barrier

The most important action to take in the case of any wound is to protect it from the external environment and apply some form of a dressing. The modern thinking is to keep wounds in a moist environment and a hydrogel is a perfect medium to apply.

Wound care should support the natural healing process; i.e., such care should provide a moist dressing/wound interface, absorb or remove excess exudate, provide thermal insulation, prevent contamination, and provide an environment conducive to the body's natural defense mechanisms. Furthermore, dressings should cause little or no discomfort to the patient and be able to remain in place for a number of days to facilitate the healing process and reduce the cost of care [Wijetunge].

Occlusion dressings can minimize necrotic tissue by preventing desiccation, aiding debridement, and providing a barrier against exogenous pathogenic organisms, thus limiting the resulting inflammatory cascade [Baxter]. The use of more moisture retentive dressings generally achieves environments supportive of earlier healing outcomes when compared to less moisture-retentive dressings. Maceration, an unwelcome occurrence with moisture-retentive dressing use on highly exuding wounds, is not consistently associated with increased adverse events. Evidence further suggests that greater dressing moisture retention is associated with fewer clinical infections, greater patient comfort, and reduced scarring. [Bolton *et al.*]. Concerns that moisture in wounds would increase the risk of clinical infection over traditional therapies are unfounded. [Field *et al*; Smith (2)].

Wounds will readily acquire bacteria, unless protective measures are taken. The bacterial protection afforded by conventional absorbent cellulose dressings has been shown to be limited, particularly in the presence of serous exudate that may compromise dressing integrity. In addition, dressings may shed particles that remain in the wound. By contrast, many modern dressings are impermeable to bacteria, are removed completely, have been found to optimize re-epithelialization rates and reduce the incidence of wound sepsis. Further, the numbers of bacteria per liter of air following removal of the hydrocolloid dressing were approximately 20% of those observed for gauze [Lawrence]

The sense of touch is the name given to a network of nerve endings that reach just about every part of our body. These sensory nerve endings are located just below the skin and register light and heavy pressure on the skin and also differences in temperature. These nerve endings gather information and send it to the brain. A graze to the skin will likely remove both the stratum corneum and in more severe cases the underlying epidermis as well. This will almost certainly expose nerve endings in the skin and so heighten their sensitivity so that they become extremely sensitive.

The application of an hydrogel will provide a soothing barrier that insulates the wound against hot and cold stimuli and also will act as a cushion against external physical influences such as pressure and touch.

The application of a hydrogel provides a cooling barrier that allows for water to evaporate from the surface and so produce a cooling effect. It is this cooling effect that helps to reduce the microcapillary circulation to the surface of the skin, so encouraging a reduction in erythema (skin redness), may lessen the build up of oedema and so reduce swelling to allow a more even cicatrisation (wound healing) to develop at the site. This cooling effect will bring a soothing comfort [Smith *et al*]. Pain is significantly reduced when wounds are

covered with an occlusive dressing. [Field *et al*; Metzger; Rheinecker]. Frequent dressing changes are time consuming and sometimes painful, and at the same time, patients are able to move freely and take showers, and nursing time spent on changing post-operative dressings is greatly reduced [Hulten *et al.*]. Dressings with large absorptive capacity reduce pain related to maceration of surrounding tissues and to pressure caused by the excess exudates [Ferrell & Coyle].

2.2.1.1.2. The inflammatory phase

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 fibroplastic phase rebuilds the structure, and then the remodelling phase provides the final form.

Tissues can heal at different rates, and even one wound can show various areas healing rapidly or slowly. The more rapid the healing process can be made leads to the better likelihood of a satisfactory outcome. The use of a moist healing environment like an hydrogel has been demonstrated to speed up the healing process when compared to a dry dressing scenario. Scar quality is significantly superior in those wounds treated with a moist dressing [Atiyeh (2003) *et al.*]. Scar assessment scores demonstrated marked prevention of unfavorable scars with improved cosmetic results following prophylactic therapy with a moist hydrogel type dressing [Atiyeh (2002) *et al.*]. The rate of wound infections is not increased when occlusive dressings are used following surgery. Finally, occlusive dressings have also been found to reduce inflammation and subsequent scarring [Hulten *et al.*; Kerstein *et al.*].

Inflammation is a normal and necessary prerequisite to healing. Changes in vascular flow are responsible for the clinical symptoms used to detect an inflammatory response. The majority of the specialised cells involved in this phase of the wound healing process come from blood.

Blood vessels that traversed the wound were severed at the time of injury and it was these cut vessels that allowed whole blood into the wound, which then coagulated, sealed off the injured vessels and lymphatic channels in order to close the wound and prevent further haemorrhage. The simultaneous release of histamine and other triggers by the injured tissue caused the intact vessels to dilate.

Histamine causes brief vasodilation in neighbouring non-injured vessels and it is this combination of whole blood exudate and serous transudate that creates a reddened, hot, swollen and painful environment. Bradykinins, derived from plasma in the area of the injury, contribute to more prolonged vascular permeability.

Prostaglandins are produced by all cells in the body and are released when there is any disruption of cell membrane integrity. Certain prostaglandins further contribute to long-term vascular vasodilation. The fibrin plugs that clotted in the wound to seal off leakage also formed in the lymphatic vessels. The blocking of the lymphatic flow not only seals

off the wound but also helps to stop the spread of any potential infection and they remain closed until later in the healing process.

The mast cells also release hyaluronic acid and other proteoglycans into the cocktail of chemicals building within the wound and these bind with the watery wound fluid to create a non-flowing gel that slows down leakage and fluid loss. The inflammatory oedema fills up all the spaces in the wound and surrounds all the damaged or repaired structures and binds them all together.

This type of oedema causes loss of dermal fat, thus thinning normal skin in the area. Some swelling in a wound is inevitable and to a degree it is required for successful healing to occur, because if there is no inflammation then healing does not begin and if too little inflammation occurs then healing may be slow. However, if too much inflammation occurs, then the likelihood of excessive scar is produced. This inflammatory fluid, derived from the blood, is high in fibrinogen. Fibrinogen coagulates in the wound and in the surrounding tissues that are now fluid filled. The coagulated fibrin will later mature into a dense, binding scar.

The soluble protein fibrinogen circulates in the blood and provides the material from which the insoluble fibrin clot is formed during blood coagulation. Fibrinogen, as an acute phase reactant, responds to infection and other short-term inflammatory stressors.

Excessive swelling, therefore, must not be permitted. Primary wound care ensures that all blood vessels have been repaired, cauterised, or clotted. Haematomas, the result of ongoing bleeding in the wound, create extra exudate, a powerful stimulus to scar formation.

The application of a hydrogel provides a vehicle into which the exudates may migrate and dissolve, so taking it away from the wound site without drying out the wound and allowing the formation of potential scar tissue to be reduced. The use of hydrocolloid dressings facilitates granulation tissue formation. Also, the use of these dressings solves many of the practical problems associated with the traditional methods of keeping the metal plates, exposed bone, and tissues moist [Sochen].

Secondary wound care addresses the contribution made by induced vasodilation, which continues in relation to the severity of the wound. This serous transudate can be diminished by the classic "RICE" regimen of rest, ice, compression, and elevation.

Pharmacological use of steroids and aspirin affects the transudative oedema. Their action aids in inhibiting prostaglandin release. All wounds, and even controlled surgical procedures, require oedema care.

For healing to commence, two prerequisite events must occur:

- 1) The wound must be decontaminated phagocytosis, and
- 2) a new blood supply (neovascularisation) must then be available.

2.2.1.1.2.1. Phagocytosis.

Within the blood vessels adjacent to the wound, white blood cells start to adhere to the dilated endothelial walls. Chemical changes in the wound induce and attract these cells to slip through the enlarged capillary pores and migrate to the site of injury.

The main purpose of this phase is to prevent or rid the wound of infection. All wounds, even under meticulous sterile conditions, are contaminated.

Hydrogel is non-cytotoxic to endothelial, fibroblast and keratinocyte cells and allows the cellular processes to occur unhindered.

Fortunately, the system of defense is perfectly adequate to prevent a minor contamination from developing into a major infection. Certain conditions can encourage an infection to develop: the types of bacteria present, the presence of foreign objects, necrotic tissue, poor oxygen supply, malnutrition, certain vitamin deficiencies, radiated tissues, and immuno-suppression may all lead to complications. The first white blood cells to reach the wound are polymorphonuclear leukocytes. These short-lived cells begin the process of phagocytosis by fixing to bacteria, extending their membrane around them, then enzymatically dissolving and digesting the invaders.

Phagocytosis is the cellular process of engulfing solid particles by the cell membrane to form an internal phagosome, or "food vacuole." and is a major mechanism used to remove pathogens and cell debris.

In a few days, another type of phagocyte will predominate and remain in the wound until all signs of inflammation cease. This cell, the macrophage, has two important roles in the process of repair and are cells within the tissues that originate from specific white blood cells called monocytes. Their role is to phagocytose (engulf and then digest) cellular debris and pathogens either as stationary or mobile cells, and to stimulate lymphocytes and other immune cells to respond to the pathogen.

The macrophage has a great influence on scar production. As a scavenger cell, the macrophage not only attacks and engulfs bacteria but also disposes of necrotic tissue in the wound and is capable of phagocytosing in poorly nourished tissues with low oxygen levels or can consume oxygen at over 20% of the basal rate for enhanced phagocytosis. Because ischemic tissues are more prone to infection than normal tissues, the oxygen state of the wound is a critical factor.

Ischemia (Greek ισχαιμία, isch- is restriction, hema or haema is blood) is a restriction in blood supply, generally due to factors in the blood vessels, with resultant damage or dysfunction of tissue.

The maintenance of an adequate arterial oxygen supply for optimum phagocytosis is dependent on there being a sufficient blood volume and is also a function of the

percentage of atmospheric oxygen breathed (as opposed to local, topically applied oxygen). Macrophages ingest microorganisms and excrete products of digestion, namely ascorbic acid, hydrogen peroxide, and lactic acid as a result of phagocytosis. Hydrogen peroxide aids in controlling anaerobic microbial growth, while the level of ascorbic and lactic acids are interpreted as a need for the need for more macrophages. The cycle is cyclic with more macrophages producing more by-products and so leads to a more intense and prolonged inflammatory response.

Most wounds heal without infection because of the microbiocidal capacity of the macrophage population. Chronically activated macrophages create a chronically inflamed wound. An hydrogel can potentially mitigate this process by assisting the macrophage in its work by providing a moist, exudate-solubilising environment.

Another cell called the fibroblast soon responds to the chemical signals issued from the macrophage. The healing process evaluates the extent of the wound and mobilises a sufficient number of repair cells.

Fibroblasts provide a structural framework for many tissues, and play a critical role in wound healing and are the most common cells of connective tissue and secrete the precursors of all the components of the extracellular matrix, primarily the ground substance and a variety of fibres.

The macrophage influences repair by chemically influencing the number of fibroblastic repair cells activated. It is a local platelet derived growth factor released from the platelets during clotting and from the macrophages that signals fibroblasts. The macrophage is a key factor in regulating the stages of the inflammatory period. Its presence is vital as a phagocytic agent and appraiser of damage and the presence of fibroblasts are significantly related to the final amount of scar produced. It is of interest to note that the use of steroids may inhibit the macrophage level and result in a lowering in the rate of wound debridement and so lead to a delay in scar production.

Neovascularisation. The inflammatory response requires the re-growth of new blood vessels, since healing will not proceed unless new, functioning blood vessels are present to supply oxygen and nourishment to the injured tissue.

It is likely that it is the macrophage signals this vascular regeneration to begin. Patent vessels in the outlying wound area develop small 'buds' or 'sprouts' that grow into the wound area and it is these outgrowths that will eventually come in contact with and join up with other arteriolar or venular buds to form a functioning capillary loop.

These new circulatory loops fill the wound, creating a highly pink to reddish colour throughout the one wound. As a result the young wound will remain much redder in contrast to the normal adjacent tissues throughout healing because of the high concentration of capillary loops. Those areas that remain grey in appearance or have a delayed whitening following pressure show an inadequate circulation. As the wound approaches final maturity the majority of these loops cease to functioning and then they

retract. As a result, the fully matured scar appears whiter than adjacent tissue. The success of wound healing may therefore be determined by the colour of scar and be a guide to the prognosis of any further changes in scar characteristics. The capillary sprouts, when first formed, lack full thickness, which renders them delicate and easily disrupted, so immobilisation is essential during this phase to permit the vascular re-growth and prevent any micro-haemorrhages from forming.

As this phase comes to a close, fibrinolysin in blood vessels is produced to assist in dissolving clots and the lymphatic channels open to assist in reducing the wound oedema.

In normal conditions, all these events happen within the first four days after injury and the main objective in treatment is to minimise all the factors that can prevent or prolong inflammation and in this respect an hydrogel has been shown to be effective.

2.2.1.1.3. Fibroplastic Phase

With the inflammatory phase completed, rebuilding can commence. This phase is named for the primary cell of scar production - the fibroblast.

Many different cells are involved in the inflammatory phase, but there are fewer types of cells operate in the fibroplastic phase which lasts about three weeks. During this phase the wound is resurfaced and strength imparted to the wound. The fibroblasts originate from mesenchymal cells which are located in loose tissue around blood vessels and fat. In response to chemotaxis the precursors of the fibroblast transform into cells with migratory ability.

These migratory fibroblasts follow the fibrin meshwork created earlier in the wound fluid milieu, which enveloped all injured structures and the fibroblasts have access to all depths of the wound. Once in place, the fibroblast initiates its synthesis of the collagen molecule. Three processes occur simultaneously in this phase to achieve coalescence and closure:

- 1) epithelialisation,
- 2) wound contraction, and
- 3) collagen production.

Topical application of an hydrogel to the wound site enhances wound healing and it has been demonstrated that L-arginine increases collagen biosynthesis. [Witte & Barbul] and reduces cell apoptosis [Sauermann *et al.*]. Arginine is the physiologic substrate for NO synthesis, and systemic arginine administration improves wound healing in normal individuals as well as in individuals with impaired wound healing. [Yamasaki *et al.*] Arginine enhances wound healing and lymphocyte immune responses in humans [Barbul *et al.*] and stimulates wound healing and immune function in elderly human beings [Kirk *et al.*]. Administration of agents known to enhance T lymphocyte function, such as thymotrophic arginine, leads to increases in wound breaking strength and collagen deposition [Regan & Barbul; Barbul & Retura *et al.*].

Several studies indicate impaired wound healing after trauma and shock. Wound immune cell dysfunction seems to be responsible for altered wound healing after trauma-haemorrhage. In this respect, administration of the amino acid L-arginine normalized wound immune cell function under those conditions [Wittman *et al.*]. and was also shown to support the successful wound healing of diabetic ulcers [Arana *et al.*]. Arginine is beneficial in enhancing wound healing, and was shown to reduce hospital stay days in severe trauma patients and with little side-effects [Peng *et al.*]

2.2.1.1.4. Remodelling Phase

2.2.1.1.4.1. Epithelialisation.

The factors critical to tissue survival are phagocytosis, blood flow, and the provision of a surface covering and these events occur early in the healing process. The provision of even a one-cell layer will provide protection from external invading organisms. A protective barrier like an hydrogel not only protects against these organisms but will further aid healing by preventing loss of fluid from the wound. Neuropathic ulcers respond well to reducing the pressure that caused the ulcer, removing necrotic materials and to secure protection with a hydrocolloid dressing. These wounds have been found to heal, on an outpatient basis, after approximately 6 weeks. All diabetic foot ulcers are contaminated with a variety of organisms, but antibiotic treatments are usually unnecessary [Laing *et al.*]

Within hours after injury, undamaged epithelial cells at the wound margin begin to reproduce. Epithelial mitosis causes an accelerated reproduction and leads to a ridge forming around the periphery of the wound. These new cells are true epithelial cells and therefore, this is a regeneration process.

Surviving epidermal structures such as hair shafts and sweat glands also give rise to epithelial mitosis. If the wound bed is viable and there is good blood supply available, then migration of these new cells begins, with those from the periphery moving in and those from appendages moving out. These migratory cells remain attached to their parent cells and their movement causes a tension on the normal skin around the wound edge.

The advancing edge of the epithelium seeks out moist, oxygen-rich tissue. Dressings, kept moist and not permitted to dry out, will facilitate this migration. An hydrogel is quite specific in this action and is not only helpful in the case of exudating wounds, but also in those that are prone to drying out.

In dry skin conditions, the inclusion of a blend of humectants (Cetearyl Ethylhexanoate and Stearyl Heptanoate/Stearyl Caprylate registered in the German Pharmacopoeia) helps to retain the precious balance of skin hydration and prevent the wound from drying out. The excipient used to formulate the hydrocolloid structure of an hydrogel delivers a feeling of moisture, richness and comfort to the skin.

The dressings will adhere to this thin skin, if the wound is allowed to dry and subsequent removal will result in microdebridement of this healing tissue.

Should the epithelial edge meet eschar, foreign material, sutures, or blood clots, it will plunge under it in order to maintain a contact with the vascular loop network in the wound.

The epithelial margin must release lytic enzymes, which act to cleave the attachments of nonviable tissue from the viable wound bed and so as this epithelial margin gradually undermines it loosens the eschar which eventually loosens and detaches from the wound.

A red, highly vascular wound with a thin, almost transparent covering appears once the eschar is detached. A scab forms as a temporary barrier for the wound and should not be disturbed until the epithelialisation is complete. An hydrogel helps reduce the extent of this scab and other necrotic tissue, eschars and other non-viable tissue allowing a cleaner and more uniform re-epithelialisation.

If the necrotic tissue or the wound is too extensive or oxygen availability is poor, epithelial migration cannot proceed. If sufficient capillary circulation is not available to maintain epithelial integrity then wound dehiscence can occur.

Dehiscence is a premature bursting open or splitting along natural or surgical suture lines. It is a complication of surgery that occurs secondary to poor wound healing. Risk factors include diabetes, advanced age, obesity and trauma during the post-surgical period.

When epithelial cells from one direction meet similar migratory cells, contact inhibition causes cessation of movement. Although clean, approximated wounds are clinically resurfaced within 48 hours larger open wounds require a longer period. Several weeks are required for this thin covering to become multi-layered and to differentiate into the various strata of normal epidermis. The thickening process skin healing is called intussusceptive growth. Skin healed in this manner, however, never truly develops a full basal layer of cells and will always be thinner in appearance.

Epithelialisation can be facilitated by maintaining moist dressings such as an hydrogel protecting the wound from minor repetitive trauma, avoidance of chemical irritants or infection and debridement.

Important:

When new skin cells start to form and the wound is closing, only apply a thin layer of an hydrogel to prevent weakening. If necessary, protect the wound edges.

2.2.1.1.4.2. Wound contraction.

Epithelialisation closes the wound surface, but contraction pulls the entire wound together in effect shrinking the defect. A successful contraction results in a smaller wound to be repaired by scar formation.

Minimising the area to be healed is truly beneficial in certain tissues with fixed, deep structures covered by mobile, loose skin. Wound contraction, however, may be harmful in those areas that require every millimetre of skin and tissue length – those areas like the hands and face.

Allowing uncontrolled contraction is a potential problem as it will distort the topography of the skin and cause the tissue to be drawn abnormally towards the site of healing causing disfigurement and discomfort. There is a specialised cell called a myofibroblast that is involved in this contraction process.

Myofibroblast is a cell that is in between a fibroblast and a smooth muscle cell in differentiation.

The myofibroblasts attach to the skin margins and pull the entire epidermal layer inward and are a feature in hypertrophic scars. An hydrogel may help to avoid this condition by providing a rapid and moist environment that restricts the contractual element of wound healing. Occlusive dressings shorten the time for healing, decrease pain, reduce wound contamination, and improve the cosmetic result. Control of wound contraction and scar formation at the time of wound formation is useful in order to control the direction of wound contraction and prevent distortion [Zitelli].

2.2.1.1.4.3. Collagen production.

The conclusion to the wound healing process is collagen production which is essential if wound healing is to occur. The migratory fibroblasts discussed earlier are now present throughout the wound and it is this environment that stimulates the fibroblasts to synthesise and secrete collagen. The build-up of lactic acid influences the amount of collagen produced. Adequate supplies of oxygen, ascorbic acid, and other cofactors such as zinc, iron, and copper are needed to create the proper background for fibroplasia.

Fibroplasia is the production of fibrous tissue, usually implying an abnormal increase of non-neoplastic fibrous tissue.

The fibroblast synthesises three polypeptide chains which coil to form a right-handed helix. These spiralled chains (procollagen) are then extruded from the fibroblast out into the extracellular space. Once exocytosed, the triple-helical molecule undergoes cleavage at specific terminal sites and becomes tropocollagen.

Tropocollagens spontaneously associate in an overlapping array and eventually convolves with other tropocollagen molecules to form a collagen fibril. These filaments lay disorganised in the wound and are still in a gelatinous state. There is little strength in this collagen mass which requires cross-links and other bonding to be formed before wound durability or tensile strength is achieved.

The fibroblast also synthesises glycosaminoglycans (GAG) which fill in the space between and around collagen. This GAG ground substance, combined with water,

provides lubrication and acts as a spacer between moving collagen fibres. New cross-links are formed that turn mobile tissue immobile. The relationship between GAG ground substance and collagen dictates scar architecture. A bulky, rough, tender, red scar is visible and palpable.

Oedema, infection and rough handling can cause the wound to become re-inflamed. Any mobilisation aimed at breaking scar tissue may create a new wound, ultimately with further scar formations. A secondary inflamed wound will result in collagen deposition in addition to that already present and so the quantity of scar produced is an indication of the final outcome.

2.2.1.1.4.4. Synthesis-lysis balance. Despite the fact that collagen synthesis continues at a high rate, no further increase in scar mass occurs. At this point new collagen is created and old collagen is broken down in a balanced fashion with the aid of an enzyme collagenase.

Collagen turnover is accelerated as old fibrous tissue is removed and as new fibrous tissue is formed. This process continues until the remodelling phase ends at six months to a year post injury, depending on the state of the injury. The high rate of collagen turnover in this stage can be either beneficial or detrimental. As long as the scar exhibits a rosier appearance than the normal, remodelling is under way. It should be remembered that the speed of collagen synthesis and the laying down of new collagen is age related and decreases with advancing years.

2.2.1.1.4.5. Collagen fibre orientation

During the remodelling phase collagen turnover allows the randomly deposited scar tissue to be arranged, in both linear and lateral orientation. Scar tissue is non-elastic and attempts to mimic the characteristics of the tissue in which it is healing. The tissue structure induces the collagen weave, thus, dense tissues induce dense, highly cross-linked scar; pliable tissues induce a loose, coiled, less cross-linked scar. Scar can adapt through the remodelling forces of synthesis and lysis. Sometimes the process does not function as expected and results in unwanted scar tissue in the form of hypertrophic or keloid scars.

Hypertrophic scar. Two types of scars are the result of the body overproducing collagen, which causes the scar to be raised above the surrounding skin. Hypertrophic scars take the form of a red raised lump on the skin, but do not grow beyond the boundaries of the original wound, and they often improve in appearance after a few years.

Keloid scar. This is a type of scar which results in an overgrowth of tissue at the site of a healed skin injury. Keloids are firm, rubbery lesions or shiny, fibrous nodules and can vary from pink to flesh-colored or red to dark brown in color. A keloid scar is benign, non-contagious and usually accompanied by severe itchiness, sharp pains and changes in texture. In severe cases, it can affect movement of skin.

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GLOSSARY

Bradykinins (BKs) belong to a family of short, structurally similar peptides that are important metabolites of the kallikrein-kinin system. They are vasoactive nonapeptides formed by action of proteases on the high-molecular-weight kininogen during the contact phase of blood coagulation, resulting in endothelium-dependent vasodilatation and stimulation of tissue plasminogen activator release from human endothelial cells. Bradykinin is released from mast cells in damaged tissues as a pain signal, and may act as a neurotransmitter. Bradykinin also contracts smooth muscles, and is a potent stimulator of nitric oxide formation by vascular endothelium. Bradykinin is involved in oedema resulting from trauma or injury and aids in dissolving blood clots. When it is secreted by eccrine sweat glands, it causes the surface of blood vessels to dilate and help radiate excessive heat from the body surface, making it an important peripheral thermoregulatory molecule.

Chemotaxis is the phenomenon in which bodily cells, bacteria, and other single-cell or multicellular organisms direct their movements according to certain chemicals in their environment. This is important for bacteria to find food (for example, glucose) by swimming towards the highest concentration of food molecules, or to flee from poisons (for example, phenol). In multicellular organisms, chemotaxis is critical to development as well as normal function. Chemotaxis is called positive if movement is in the direction of a higher concentration of the chemical in question, and negative if the direction is opposite.

Collagenases are enzymes that break the peptide bonds in collagen. They assist in destroying extracellular structures in bacteria pathogenesis. They are an exotoxin (a virulence factor). Collagenase production can be induced during an immune response, by cytokines which stimulate cells such as fibroblasts and osteoblasts, and cause indirect tissue damage.

Eschar from the Greek word eschara (scab) an eschar (IPA: /ɛskɑr/) is a piece of dead tissue that is cast off from the surface of the skin, particularly after a burn injury, but also seen in gangrene, ulcer, fungal infections and late exposure to anthrax. Eschar is sometimes called a "black wound" because the wound is covered with thick, dry, black necrotic tissue. Eschar may be allowed to slough off naturally, or it may require surgical removal (debridement) to prevent infection, especially in immunocompromised patients (e.g. if a skin graft is to be conducted).

Fibrinolysin attacks and inactivates fibrin molecules occurring in undesirable exudates on the surface of the human body and on human mucosa, e.g., in superficial wounds and burns.

Fibroblast. A fibroblast is a type of cell that synthesizes and maintains the extracellular matrix of many tissues. Fibroblasts provide a structural framework (stroma) for many tissues, and play a critical role in wound healing. They are the most common cells of connective tissue. The main function of fibroblasts is to maintain the structural integrity of connective tissue by continuously secreting precursors of the extracellular matrix. Fibroblasts secrete the precursors of all the components of the extracellular matrix, primarily the ground substance and a variety of fibres. The composition of the extracellular matrix determines the physical properties of connective tissues. Fibroblasts can also migrate slowly over substratum as individual cells, again in contrast to epithelial cells. While epithelial cells form the lining of body structures, it is fibroblasts and related connective tissues which sculpt the "bulk" of an organism.

Hyaluronan (also called hyaluronic acid or hyaluronate) is a non-sulfated glycosaminoglycan distributed widely throughout connective, epithelial, and neural tissues. It is one of the chief components of the extracellular matrix, contributes significantly to cell proliferation and migration, Hyaluronan is also a major component of skin, where it is involved in tissue repair.

Hydrocolloid dressings are occlusive and reduce pain by preventing exposure of the wound to air. They have adhesive properties and can cause pain if removed improperly.

Hydrogel dressings are non-adherent, reducing pain during dressing changes. Calcium alginates, alginate, collagen dressings and exudate absorbing beads, flakes, pastes or powders absorb large amounts of drainage.

Hypertrophic scar. Two types of scars are the result of the body overproducing collagen, which causes the scar to be raised above the surrounding skin. Hypertrophic scars take the form of a red raised lump on the skin, but do not grow beyond the boundaries of the original wound, and they often improve in appearance after a few years. The other type is a keloid scar.

Intussusceptive growth. the folding in of an outer layer so as to form a pocket in the surface. The growth in the surface area of a cell by the deposit of new particles between existing particles in the cell wall

Keloid scar. This is a type of scar which results in an overgrowth of tissue at the site of a healed skin injury. Keloids are firm, rubbery lesions or shiny, fibrous nodules and can vary from pink to flesh-colored or red to dark brown in color. A keloid scar is benign, non-contagious and usually accompanied by severe itchiness, sharp pains and changes in texture. In severe cases, it can affect movement of skin. Keloids should not be confused with hypertrophic scars, which are raised scars that do not grow beyond the boundaries of the original wound and may reduce over time.

Lytic. The lytic cycle is one of the two cycles of viral reproduction, the other being the lysogenic cycle. These cycles should not, however, be seen as separate, but rather as somewhat interchangeable. The lytic cycle is typically considered the main method of viral replication, since it results in the destruction of the infected cell.

Macrophage (Greek: "big eater", from makros "large" + phagein "eat") are cells within the tissues that originate from specific white blood cells called monocytes. Monocytes and macrophages are phagocytes, acting in both nonspecific defense (or innate immunity) as well as specific defense (or cell-mediated immunity) of vertebrate animals. Their role is to phagocytose (engulf and then digest) cellular debris and pathogens either as stationary or mobile cells, and to stimulate lymphocytes and other immune cells to respond to the pathogen.

Neovascularization. Neovascularization is the formation of functional microvascular networks with red blood cell perfusion and differs from angiogenesis in that angiogenesis is mainly characterized by the protrusion and outgrowth of capillary buds and sprouts from pre-existing blood vessels.

Phagocytosis is the cellular process of engulfing solid particles by the cell membrane to form an internal phagosome, or "food vacuole." The phagosome is usually delivered to the lysosome, an organelle involved in the breakdown of cellular components, which fuses with the phagosome. The contents are subsequently degraded and either released extracellularly via exocytosis, or released intracellularly to undergo further processing. Phagocytosis is involved in the immune system and is a major mechanism used to remove pathogens and cell debris. Bacteria, dead tissue cells, and small mineral particles are all examples of objects that may be phagocytosed.

Prostaglandin: One of a number of hormone-like substances that participate in a wide range of body functions such as the contraction and relaxation of smooth muscle, the dilation and constriction of blood vessels, control of blood pressure, and modulation of inflammation. Prostaglandins are derived from a chemical called arachidonic acid.