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The Physiology of Healing Wounds

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ABSTRACT
A complex biological process called wound healing leads to the recovery of tissue integrity. Haemostasis, inflammation, proliferation, and tissue remodelling are the four main physiological processes that it goes through. This page explains the extracellular signalling systems that regulate wound healing as well as the biological underpinnings of it. In-depth consideration is given to the role of platelets, neutrophils, macrophages, and fibroblasts. The idea of healing by primary and secondary intention is examined. Malnutrition, hypoxia, immunosuppression, chronic illness, and surgery are just a few of the conditions that have been shown to negatively affect healing. In order to reduce patient morbidity from delayed healing, surgeons must have a thorough understanding of the fundamental physiological mechanisms involved in healing.
Keywords: wound healing, tissue remodelling, proliferation, and hemostasis.

1. INTRODUCTION

A wound is created when the integrity of the skin, mucosal surfaces, or organ tissue is compromised. A wound's origin can be unintentional or purposeful, or it can emerge as a result of a disease process. [1] When an insult occurs, numerous cellular and extracellular pathways are activated in a carefully controlled and coordinated manner with the goal of restoring tissue integrity. Haemostasis, inflammation, proliferation, and tissue remodelling are the four separate phases that make up the traditional division of this wound-healing process. It is amazing how frequently the healing cascade occurs without complications given how intricate it is. Numerous variables may obstruct this process, which could lead to poor cosmetic results, a delay in the healing of the wound, and an increase in patient morbidity and death. Because they are challenging to fully quantify, the health economic costs of chronic wounds and the psychological repercussions for patients are frequently underestimated. However, it has been calculated that the annual cost of wound-related issues in the USA alone surpasses $1 billion.[2] This article aims to give surgeons a fundamental understanding of the physiology of wound healing, explore the cellular mechanisms involved in each of the four phases, and emphasise the clinical aspects that may lead to wound problems.

Chronic and acute wounds

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The wound repair procedures are the same regardless of the aetiology. The most common cause of acute wounds is trauma, which can be either blunt or penetrating (e.g., surgical incisions, gunshots, animal bites). When tissue is damaged by a wound, a coordinated physiological response is triggered to provide haemostasis and to start the inflammatory, proliferative, and remodelling processes. [3] Surgical incisions and acute wounds typically go through these stages very quickly. Chronic wounds are defined as those that show delayed healing 12 weeks after the initial trauma, frequently as a result of protracted pathological inflammation. Surgical incisions often result in little tissue damage and loss and are clean. The likelihood of wound infection after surgery can be predicted using the classification of surgical wounds (i.e. clean, clean contaminated, contaminated, and unclean) based on the degree of contamination. These wounds can be sutured shut right away and usually mend quickly. This is known as closure with the main purpose. It is referred to as delayed primary healing when the wound is contaminated, left open to prevent infection, and wound closure is carried out after a few days. The reparative procedure takes longer since the defect must be filled with significant granulation tissue when the tissue loss has been more severe, the edges cannot be approximated, or the wound must be left open owing to sepsis. By secondary intention, this procedure is referred to as closure. Large defects can be repaired in this way, although the cosmetic outcome is frequently poorer to those that are closed principally.

Haemostasis

Vascular damage happens during surgical incisions on a macro- or microvascular scale. The body's first response is to stop exsanguination and encourage hemostasis. Increased cytoplasmic calcium levels cause damaged arterial arteries to rapidly constrict by the contraction of smooth muscle in the circumferential layer of the vessel wall. 4Vessels as small as 5 mm in diameter can entirely shut by contracting, but only if the lesion is in a transverse plane. The decreased blood flow caused by arteriole constriction causes tissue hypoxia and acidosis within a short period of time. Nitric oxide, adenosine, and other vasoactive metabolites are produced more readily as a result, resulting in reflex vasodilation and relaxing of the arterial arteries. Histamine production from mast cells simultaneously increases vascular permeability and vasodilatation, which makes it easier for inflammatory cells to enter the extracellular area around the wound. This explains why early wounds have the recognisable warm, red, swollen appearance. The creation of a clot, which is accomplished through three main methods, also stops more blood loss at this stage.

1. Contact activation pathway, an intrinsic mechanism of the clotting cascade Tissue injury causes endothelial destruction, which exposes the sub-endothelial tissues to blood and activates factor XII (Hageman factor).
2. Extrinsic pathway of the clotting cascade (tissue factor pathway) e Endothelial damage results in tissue factor (which is present in most cells) being exposed to circulating blood, which activates factor X, which converts prothrombin to thrombin, causing the conversion of fibrinogen to fibrin and the formation of a fibrin plug. As a result, factor VII and the rest of the extrinsic pathway of the clotting cascade are activated, which eventually activates thrombin.
3. Platelet activation e Platelets undergo a change in morphology and secrete the contents of their alpha and dense granules after being activated by thrombin, thromboxane, or ADP.[5] In order to create a platelet plug and momentarily stop bleeding, activated platelets cling to exposed collagen sites. The actin and myosin filaments found within the platelets, as well as

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the von Willebrand factor and fibrin, all contribute to the strength of this plug. Unnucleated megakaryocyte pieces from bone marrow make up platelets. They are essential to the process of healing wounds. In addition to being crucial for blood clot formation, they also generate a variety of growth factors and cytokines that continue to control the healing cascade. More than 300 signalling molecules that affect and regulate the operation of other platelets, leukocytes, and endothelial cells have been identified from active platelets.[6] The primary functions of chemicals formed from platelets. In addition to these elements, arachidonic acid is converted into a number of strong signalling molecules, including prostaglandins, leukotrienes, and thromboxanes, which play roles in promoting the inflammatory response, in response to the damaged cell membranes induced by the wounding stimulation.

Inflammation

The primary objective of this stage of wound healing is to stop infection. No matter how the wound was caused, the mechanical barrier that served as the first line of defence against encroaching microbes is now damaged. The 'initial responders,' neutrophils, are highly motile cells that penetrate the wound within an hour of the insult and travel steadily for the first 48 hours. This is done through a number of chemical signalling processes, such as the complement cascade, interleukin activation, and TGF-B signalling, which causes neutrophils to chemotactically move down a chemical gradient towards the direction of the wound. [3] For removing debris and microorganisms, neutrophils primarily use three different processes. A mechanism known as phagocytosis allows them to first directly absorb and eliminate foreign particles. Second, neutrophils have the ability to degranulate and produce a range of poisons (such as cathepsin, neutrophil elastase, lactoferrin, and proteases), which can be used to kill both bacteria and dead host tissue. Recent research has revealed that neutrophils are also capable of producing protease and chromatin "traps" that may capture and eliminate bacteria in the extracellular environment. Byproducts of neutrophil activity include oxygen free radicals, which not only have bactericidal qualities but can also interact with chlorine to sterilise the wound. When the neutrophils have finished their job, they either go through apoptosis, are sloughed off the surface of the wound, or are phagocytosed by macrophages.

At 48 to 72 hours following damage, the concentration of macrophages, which are phagocytic cells that are significantly bigger, peaks in the injured area. The chemical messengers that platelets and injured cells emit draw them to the wound, and they may live in the more acidic wound environment that is now present. [1] Growth factors like TGF-b and EGF, which are abundant in macrophages and play a key role in controlling the inflammatory response, promoting angiogenesis, and improving the creation of granulation tissue, are among the many growth factors that can be found in them. Lymphocytes are hypothesised to play a crucial role in controlling wound healing by producing an extracellular matrix scaffold and remodelling collagen after 72 hours since lymphocytes first arrive in the wound. According to experimental research, inhibiting T cells reduces the tensile strength of the wound and impairs collagen synthesis. [7] Displays a list of the cells that contribute to inflammation.

In order to ensure that all surplus bacteria and debris from the site are removed, the inflammatory phase of wound healing will last as long as it's necessary. A chronic wound can develop as a result of prolonged inflammation, which can also cause significant tissue damage, delayed proliferation, and other problems. It is believed that a number of substances, including lipoxins and the byproducts of arachidonic acid metabolism, have anti-inflammatory qualities that suppress the immune reaction and enable the development of the next stage of wound healing.[8]

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Proliferation

The proliferative stage of the healing cascade can start to repair the defect once the damaging stimulus has stopped, haemostasis has been accomplished, the inflammatory response is balanced, and the wound is clear of debris. This multi-step process includes simultaneous angiogenesis, granulation tissue development, collagen deposition, epithelialization, and wound retraction.

Angiogenesis

As soon as the haemostatic plug has formed, platelets start to release TGF-b, PDGF, and FGF. This starts angiogenesis. VEGF is generated in reaction to hypoxia, and when combined with other cytokines, it causes endothelial cells to stimulate neovascularization and the healing of damaged blood vessels. Invading neutrophils in hypoxic tissue activate a family of enzymes known as mixed metalloproteinases (MMP). Through VEGF liberation and extracellular matrix remodelling, they encourage angiogenesis (ECM). [9] In the beginning, the wound's centre is comparatively avascular since it only receives diffusion from the undamaged capillaries near the wound's margin. An extensive vascular network of capillaries is created throughout the wound as the angiogenesis process develops from the outgrowths of healthy vessels. Capillaries are initially brittle and porous, which adds to tissue oedema and the development of healing granulation tissue.

Fibroblast movement

Growth factors released from the haemostatic clot after the wound insult encourage fibroblasts to multiply and move to the wound (predominantly by TGF-b and PDGF). By the third day, the wound has a high concentration of fibroblasts, which create collagen and fibronectin by laying down extracellular matrix proteins such hyaluronan, fibronectin, and proteoglycans. Granulation tissue is the pink, vascular, fibrous tissue that develops in place of the blood clot at the site of a lesion. Compared to unwounded tissue, this has a different range of collagens (with a higher proportion of type 3 collagen). When enough matrix has been deposited, fibroblasts transform into myofibroblasts and produce pseudopodia. This makes it possible for them to attach to nearby fibronectin and collagen proteins and aid in wound contraction. Additionally, myofibroblasts stimulate angiogenesis by regulating MMP activity. [10] The main factor in giving tissues strength is collagen produced by fibroblasts. Collagen deposition is at its peak in wounds sealed by primary intention by day 5, and this is frequently felt as a "wound ridge" beneath the skin. A wound is at danger of dehiscence when the ridge along the wound is not palpable. Hypertrophic scarring can result from excessive collagen production. Hypertrophic scars continue to be erythematous and elevated while still being contained within the boundaries of the initial wound. Wound infections and those in areas with high stress are risks for their development.

Epithelialization

A complete layer of epithelial cells covers the wound and binds to the matrix below fairly quickly after the initial insult. Epithelial cells move from the edges of the lesion in this manner. Epithelial cells acquire motility and move across the wound surface thanks to an embryological process known as epithelial-mesenchymal transition (EMT). [11] This stage can be finished in 24 hours in wounds that have mostly healed. Changes in cytokine concentration cause epithelial cells to change from a motile to a proliferative phenotype in

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order to replenish epithelial cell numbers and finish wound repair. [12] The area missing epithelial cells in wounds that heal by secondary intention can be rather big, and the wound must significantly close before epithelialization can be finished. In other circumstances, this might never happen, and the defect can be covered via skin grafting.

Wound healing

Seven days after an injury, wounds start to close, primarily through the action of myofibroblasts. Actin and myosin interactions draw the cell bodies closer together, reducing the amount of tissue that needs to repair. Shorter scars can result from contraction that happens at a pace of 0.75 mm each day. Numerous factors, including the geometry of the wound, affect how quickly it heals, with circular wounds healing more slowly than linear ones. Deformity and the development of contractures might result from disorders during this healing phase. [13]

Remodelling

The maturation of the scar tissue and the creation of normal epithelium are the outcomes of the final stage of wound healing, which can last up to 2 years. As the collagen and other proteins deposited in the wound grow more and more structured, production and degradation are balanced at this stage. They will eventually regain a structure like that of unwounded tissue (replacing type 1 collagen with type 3 collagen). Despite this, wounds never attain the same degree of tissue strength, with an average of just 80% long-term and 50% of the initial tensile strength after 3 months. The degree of vascularity reduces as the scar ages, and it gradually transitions from red to pink to grey.

Essential elements for the healing of wounds

Nutrition

The ability of nutritional condition to affect wound healing has long been known. Vasco de Gama, a Portuguese explorer, observed that seafarers with scurvy frequently had skin sores that did not heal in the fifteenth century. It wasn't until James Lind, a Scottish surgeon, showed how citrus fruits might effectively treat scurvy and speed up wound healing, in 1747. Through prolonged inflammation, fibroblast function inhibition, decreased angiogenesis, and decreased collagen synthesis, malnutrition negatively impacts recovery. Numerous critical nutrients are crucial for wound healing, such as vitamin A (engaged in epidermal growth), carbohydrates (for the synthesis of collagen), and omega-3 fatty acids (modulate arachidonic acid pathway). The use of nutritional support approaches to speed up wound healing has been proven to be beneficial in recent years by in-depth study in the field of clinical nutrition. Several recent review papers have covered this subject. [14]

Hypoxia

Due to the disruption of the local vascular supply, all wounds are partially hypoxic. While some hypoxia is necessary to encourage re-epithelialization, adequate oxygen is crucial for wound healing. In surgical practise, it is evident that older patients and those with peripheral vascular disease heal wounds slowly, while hyperbaric oxygen speeds up the process. Although oxygen is necessary for phagocytosis and for the best function of neutrophils and macrophages, hypoxia is one of their chemoattractants. Supplemental oxygen provided during the perioperative period was shown to lower the risk of wound infections in a

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randomised controlled experiment. [15] Due to its role as a substrate in the hydroxylation of proline and lysine residues, oxygen is also crucial for collagen deposition.

Smoking

Smoking interferes with the inflammatory phase's chemotaxis, migratory function, and oxidative bactericidal processes. Additionally, it reduces the migration and proliferation of fibroblasts. Smoking also has an impact on immune system performance and collagen synthesis and deposition. [16]

Infection

Before making a surgical incision, antibiotic prophylaxis has been shown to lower the incidence of wound infections, initially in guinea pigs in 1958 and then in people in 1960. When suturing highly polluted wounds, one should think about delaying primary closure or closing with a secondary aim because these techniques have been demonstrated to reduce wound infection rates.

Immunosuppression

Immunosuppression is seen in patients with HIV, cancer, and malnutrition, and it can impede the healing of wounds. Additionally, any medication that reduces the inflammatory response can prevent the healing cascade from happening. Prednisolone and other oral steroids have been proven to lower cytokine levels during wound healing, which in turn results in less collagen deposition. Additionally, radiotherapy and chemotherapy may hinder the healing of wounds. Vascular endothelial growth factor (VEGF), a crucial regulator of the angiogenesis stage of wound healing, is impacted by chemotherapy drugs. [17] Radiation damage to the skin's top layer produces tissue ischemia, which can result in skin ulcers. Surgery on irradiated tissue increases the risk of wound complications, and these wounds heal slowly.[18]

Chronic illness

The availability of oxygen and other nutrients necessary for wound healing may be severely impacted by any chronic condition that affects the cardio-respiratory system. Diabetes patients' ability to heal wounds is greatly hampered since their immune systems are already damaged and because diabetes affects leukocyte function. Diabetes alters MMP expression and function, which impairs wound healing and causes a variety of additional vascular problems. [19] Diabetes also results in long-term microvascular damage that affects the delivery of nutrients and tissue oxygen levels.

Management of wounds

Successful wound healing requires a healthy wound environment. More than 250 distinct kinds of wound dressing exist, and they all work to protect the wound, keep it moist, and absorb excessive exudates to speed up healing. Later in this issue, these are covered in more detail.

Age

The epidermal layer is thinner in older patients, and it inflammatory, migratory, and proliferative responses are slower. Additionally, these individuals have a higher likelihood of

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having a chronic illness, which together results in slower wound healing and a higher risk of wound complications such dehiscence.

Genetics

The proliferation of scar tissue that spreads past the borders of the wound leads to keloid scars. Steroids, cryotherapy, or radiation therapy may help with their itching and suffering, as well as their high risk of recurrence. They are uncommon below the waist and most frequently appear on the upper chest, shoulders, and arms. Keloid development has a substantial genetic component and affects people of Black, Hispanic, and Asian racial backgrounds far more frequently. The formation of incisional hernias has also been linked to greater levels of type 3 collagen, suggesting that incisional hernias may have a hereditary component that results from abnormalities in the synthesis of collagen. [20]

Surgical procedure

Clearly, good surgical technique is essential for maximising wound healing. Incision complications can be reduced with careful tissue handling, stringent aseptic procedures, avoiding stress across the wound, and suture selection. To decrease infectious problems, intraoperative hypothermia should be avoided and postoperative supplementary oxygen should be administered.

2. CONCLUSIONS

Clearly, good surgical technique is essential for maximising wound healing. Incision complications can be reduced with careful tissue handling, stringent aseptic procedures, avoiding stress across the wound, and suture selection. To decrease infectious problems, intraoperative hypothermia should be avoided and postoperative supplementary oxygen should be administered.

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