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WOUND HEALING

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Abstract: ***Acute and chronic wounds are the two main categories of skin wounds. Traumatic or surgical wounds are considered acute wounds, and they typically heal over time in accordance with the standard wound-healing protocol. Therefore, one of the most intricate processes in the human body is skin restoration. When a wound occurs, the wounded blood arteries constrict and platelets activate to produce a fibrin clot. Incoming inflammatory cells can find scaffolding from the fibrin clot, which also stops blood flow. The clot instantly attracts neutrophils as their first line of defense against germs. Within 48 to 96 hours of an injury, monocytes are drawn in and at the wound site, they differentiate into tissue-activated macrophages. Complications of cutanecous wound healing are Deficient scar formation, Excessive formation of components of repair process and Contracture which results in deformities and commonly seen after burns and results in restricted movement.***

Keywords: ***Acute, Chronic, Cutanecous, Surgical Wounds.***

1. INTRODUCTION

Acute and chronic wounds are the two main categories of skin wounds. Traumatic or surgical wounds are considered acute wounds, and they typically heal over time in accordance with the standard wound-healing protocol. Acute skin wounds can range in depth from little scratches to major cuts that cause varying degrees of tissue loss, harm to internal organs, blood vessels, muscles, and other tissues. The body's reaction to injury intensifies with the size of the wound. The body's inflammatory and immunomodulatory cellular and humoral networks are involved in the systemic reactions to trauma. These systemic and local reactions could seriously harm organs if they are unable to start the healing process. The physiological process of acute wound healing is intricate and governed by numerous cell types, growth factors, cytokines, and chemokines. Above all, it is the body's natural response to harm in order to survive. Inflammatory cells, platelets, endothelial cells, fibroblasts, and keratinocytes are among the cells that go through certain preprogrammed changes in their gene expression and/or phenotype throughout the healing process. As a result, the wound environment moves through the traditional phases of wound healing—inflammation, the production of new tissue, and tissue remodeling—in order to reach homeostasis[1]–[6].

The complex interplay of multiple cell types and different types of intercellular signaling underlies the wound-healing program. By many weeks, most wounds heal quite rapidly and effectively based on the phases of regular wound healing. An important physiological process, cutaneous wound healing involves the cooperation of numerous cell types and their byproducts. The lesion caused by a localized aggression is attempted to be restored very early in the inflammatory stage. Ultimately, they lead to regeneration, which is the process of cell proliferation and posterior differentiation using stem cells and/or preexisting cells in the tissue, and repair, which is the replacement of specialized structures brought about by the deposition of

collagen. These methods do not exclude one another; that is, depending on the cell strains weakened by the injury, regeneration and repair can occur in the same tissue following a skin lesion. Following the commencement of the injury, processes of tissue regeneration and repair take place[7]–[10]. Whether as a result of the trauma or a particular clinical condition. All the stimuli that disrupt the physical continuity of functioning tissues result in the creation of a single lesion. Lesions can be brought on by internal or external stimuli that are physical, chemical, electrical, or thermal in nature. Furthermore, the lesions may cause harm to particular organelles or to the cells themselves.

The skin is the biggest organ in the human body and is essential for several functions, including excretion, heat management, vitamin D synthesis initiation, protection from toxins and infections, and hydration. Therefore, severe skin injury may be fatal. Healing a skin wound demonstrates a remarkable and unique cellular function process. The interplay of cells, growth factors, and cytokines involved in sealing the lesion is part of the repair process. The inconveniences resulting from injuries, especially those involving chronic wounds, are primarily attributable to wound repair limitations in treatment and management protocols rather than the restoration of tissue integrity (also known as "restitutio ad integrum"). In order to lower healthcare expenses, offer long-term relief, and eventually promote efficient scar healing, numerous studies are focused on developing more potent wound remedies. Skin wound treatments fall into one of two categories: "Regenerative" or "Conventional." Regardless of potential cosmetic or functional changes, conventional therapy results in the creation of scars. In the field of biomedical research, regenerative wound therapy is a relatively young and quickly expanding field that attempts to repair injured skin tissue and cells without leaving scars. Regeneration techniques should, in any event, be viewed as an adjunct to necessary traditional therapies like debridement[11]–[14].

This review specifically focuses on the advancements and developments in wound medication in the last several years. The review describes the primary issues with the healing process and the therapeutic care of long-term wounds. Furthermore discussed are cutting-edge skin regeneration therapy plans as well as experimental methods for skin tissue and cellular engineering. To get over the constraints of wound healing technology and apply customized therapy design, new skin regeneration approaches involving scaffolds activated with growth factors, bioactive compounds, and genetically modified cells are being utilized. Our skin is a highly adapted, multifunctional organ that has evolved over millennia of evolution to shield us from the everyday assault of chemicals, physical stresses, and UV radiation. Since skin injuries are frequently caused by the harsh outside world, it should come as no surprise that our skin has advanced healing mechanisms that enable rapid and effective skin repair. Even with a high degree of intrinsic repair capacity, some cellular components of an individual's wound healing response can weaken. Most frequently, pathogenic systemic changes—like those brought on by senior age or uncontrolled diabetes—cause this attenuation. It is true that the two main risk factors for getting

a chronic wound—one that takes longer than 12 weeks to heal—are getting older and having diabetes.

Regretfully, there is a great deal of unmet clinical need in relation to these chronic wounds, which are mostly pressure sores, diabetic foot ulcers, and venous ulcers. They are also becoming more prevalent worldwide. Here, we go over the state of knowledge on skin repair and provide examples of the dysfunctional cellular behaviors that underlie the pathology of chronic wound healing. Using cutting-edge research technologies will be crucial to understanding the cellular and molecular underpinnings of both pathological and acute repair. Ruptures in the epidermal layer of skin expose the underlying dermis to the air, resulting in wounding[15]–[18]. The tissues exposed to air range from blood vessels to bone, depending on the extent of the skin injury and the afflicted location. Wounds are therefore typically divided into three groups. A cut that merely affects the epidermal skin surface is considered superficial. A partial-thickness wound is one that affects deeper dermal layers, such as blood vessels, sweat glands, and hair follicles. This occurs when the deeper tissues or underlying subcutaneous fat rupture in a full-thickness incision. Burns are frequent skin injuries that pose serious problems for both prevention and regaining functionality and prevent scarring. Burn injuries are categorized as first-, second-, or third-degree wounds based on their level of superficial, partial, or full thickness. Fourth-degree burns cause damage to underlying tissues, muscles, tendons, ligaments, and even bone. The nerve endings are torn, resulting in a loss of feeling in the area of the wound.

In both humans and animals, the process of healing wounds is a significant yet intricate one that is controlled by a series of overlapping phases, such as the phases of hemostasis and inflammation, proliferation, and remodeling. Following a skin injury, the exposed sub-endothelium, collagen, and tissue factor will trigger platelet aggregation, which in turn will cause degranulation and the release of growth factors and chemotactic factors (chemokines) to form the clot. Successful hemostasis will be achieved through all of the aforementioned procedures. The first cells that arrive at the site of damage are neutrophils, which remove bacteria and debris to create an environment that is conducive to wound healing. Here, macrophages gather, aid in the phagocytosis of microorganisms, and cause tissue damage. The inflammatory and hemostasis phases typically take 72 hours to complete. It is clear that age affects one's capacity to heal wounds without excessive wound healing. The greater the likelihood of excessive wound healing, the older one becomes. The regeneration of normal dermal architecture, which includes the repair of dermal appendages and neurovasculature, is a characteristic of fetal wound healing.

A unique GF profile, a reduced inflammatory response with an anti-inflammatory cytokine profile, a decrease in biomechanical stress, an extracellular matrix rich in type III collagen and hyaluronic acid, and a possible function for stem cells are all involved in wound healing in the fetal skin. In contrast to fetal skin, adult skin is more likely to create scars. The ability of our skin to sense our surroundings, preserve thermal, physicochemical, and other homeostasis, store vital nutrients, offer both passive and active defense, and react to shock and injury is critical to our survival. Robust and efficient mechanisms that shield the skin from injury and insult as well as

restore or repair damaged or lost skin functions are necessary to maintain these vital functions. For thousands of years, people have been tending to their wounds[19]–[22]. The resources that are readily available or may be obtained locally, such as water, soil, and plant and animal products, are the limits of traditional wound care, which is frequently supplemented with ceremony and ritual as an extra precaution. Traditional remedies made from regional plants, animals, and natural products are the mainstay of wound care for millions of people throughout Asia, Africa, the Middle East, and Latin America; for some, they are their only source. Here, we go over some of the research that suggests using medicinal herbs to heal cutaneous wounds in an efficient and cost-effective manner.

The complex synchronization of several cell types in sequential phases is necessary for skin healing. The outermost layer of skin that is impermeable and resilient to the hostile external environment is called the epidermis in undamaged skin. Hair follicles, sweat glands, and sebaceous glands are also found in the epidermis. The dermis gives the skin its strength, nourishment, and immunity. It is rich in mechanoreceptors, extracellular matrix (ECM), and vascular. Beneath the dermis, subcutaneous adipose tissue serves as a store of energy. Additionally, it provides the dermis with growth factors continuously. Each layer also has resident immune cells that are always examining the skin for harm in addition to these cell types. To promote healing after a wound, different cell types in these three levels must work together at specific times. The following phases take place in a chronological order, but they also overlap: hemostasis, inflammation, angiogenesis, growth, re-epithelialization, and remodeling[23], [24].

Therefore, one of the most intricate processes in the human body is skin restoration. When a wound occurs, the wounded blood arteries constrict and platelets activate to produce a fibrin clot. Incoming inflammatory cells can find scaffolding from the fibrin clot, which also stops blood flow. The clot instantly attracts neutrophils as their first line of defense against germs. Within 48 to 96 hours of an injury, monocytes are drawn in and at the wound site, they differentiate into tissue-activated macrophages. To fight against foreign and self-antigens, the adaptive immune system, which consists of T cells, dermal dendritic cells, and Langerhans cells, is also activated. Understanding the heterogeneity among these immune cell populations is of increasing importance, particularly with regard to the relative roles played by different subsets in the resolution of infection vs the clearing of cellular debris.

2. LITERATURE REVIEW

Ana Cristina de Oliveira Gonzalez et al. [1] proposed that following the commencement of a tissue lesion, a series of molecular and cellular events take place as part of the regeneration and tissue repair processes, which aim to restore the damaged tissue. The phases of extracellular matrix remodeling, proliferative, and exsudative processes are sequential events that result from the integration of dynamic processes involving parenchymal cells, blood cells, and soluble mediators. After an injury, exsudative phenomena play a role in the development of tissue edema. The proliferative stage uses fibroplasia and myofibroblast contraction to try to lessen the

region of tissue damage. Angiogenesis and reepithelialization processes are still discernible at this point. The ability of endothelial cells to differentiate into mesenchymal components suggests that a group of signaling proteins that have been researched plays a precise role in this differentiation. The ability of endothelial cells to differentiate into mesenchymal components seems to be carefully controlled by a group of signaling proteins that have been researched in the literature. We call this route Hedgehog. This review aims to delineate the diverse cellular and molecular elements implicated in the process of skin healing.

Erika Maria Totto et al. [2] said that the skin wound healing demonstrates a remarkable, one-of-a-kind cellular function mechanism involving the interaction of several cells, growth factors, and cytokines. Although tissue integrity is restored through physiological wound healing, the process is frequently restricted to wound repair. Current research endeavors to procure enhanced efficacious wound remedies with the goal of mitigating inpatient expenditures, furnishing enduring alleviation, and promoting efficient scar healing. This thorough review's primary objective is to highlight the advancements in wound care and how they have changed over time. The review describes the primary issues with the healing process and the therapeutic care of long-term wounds. Furthermore discussed are cutting-edge skin regeneration therapy plans as well as experimental methods for skin tissue and cellular engineering. To get over the constraints of wound healing technology and apply customized therapy design, new skin regeneration approaches involving scaffolds activated with growth factors, bioactive compounds, and genetically modified cells are being utilized.

Holly N. Wilkinson et al. [3] said that In order to effectively restore injured tissue, wound healing is a complicated, dynamic process backed by a wide range of cellular activities that need to be closely coordinated. Chronic, non-healing wounds can develop as a result of disruption in wound-linked cellular behaviors, which is seen in diabetes and aging. Because these wounds are so common and frequently repeat, they pose a substantial socioeconomic burden. Therefore, a better molecular and clinical knowledge of the mechanisms underlying wound repair is desperately needed. Here, we go over the biological underpinnings of tissue restoration and talk about how our growing knowledge of wound pathology may help create more effective wound treatments in the future.

Xiaoxuan Deng et al. [4] proposed that the intricate process of wound healing is essential to the restoration of the skin's barrier function. Many illnesses have the potential to impede this process, leading to chronic wounds that are a significant medical burden. These types of wounds do not heal according to the prescribed stages and are frequently made worse by an environment that is pro-inflammatory due to a build-up of germs, hypoxia, and elevated proteinases. The complicated symptoms brought on by the metabolic dysfunction of the wound microenvironment make the comprehensive treatment of chronic wounds still considered a major unmet medical need. To address the chronic wound environment and promote skin tissue regeneration, a number of cutting-edge medical devices have been created, including surgical sutures, wearable wound monitoring, negative pressure wound therapy devices, and wound dressings. The majority of

medical devices are made up of a broad range of products that include both synthetic and natural polymers (polyvinyl alcohol, polyethylene glycol, poly[lactic-co-glycolic acid], polycaprolactone, polylactic acid, collagen, hyaluronic acid, alginate, and silk fibroin), as well as bioactive molecules (chemical drugs, silver, growth factors, stem cells, and plant compounds). The goal of this study is to provide a crucial theoretical framework for future studies on chronic wound healing by addressing these medical devices with an emphasis on biomaterials and applications.

Melanie Rodrigues et al.[6] said that one of the most intricate processes in the human body is wound healing. Numerous cell types with different roles in the phases of hemostasis, inflammation, growth, re-epithelialization, and remodeling are synchronized both spatially and temporally. The development of single-cell technology has made it feasible to identify functional and phenotypic variation within a number of these cell types. Rare stem cell subsets in the skin have also been found; these subsets are unipotent when the skin is healthy but become multipotent after skin damage. Understanding the functions of each of these cell types and how they interact with one another is crucial to comprehending the processes involved in healthy wound closure. Impaired stages of wound healing are directly caused by changes in the microenvironment, which include modifications in mechanical forces, oxygen levels, chemokines, extracellular matrix, and growth factor production. In order to develop effective therapeutic treatments for healing wounds, single cell technologies can be employed to understand these cellular modifications in pathological states, such as in chronic wounds and hypertrophic scarring.

T Velnar et al. [5] said that wound healing is still a difficult clinical issue, and effective wound care is crucial. A lot of work has gone into wound care, with a focus on developing new therapeutic strategies and technological advancements for the management of both acute and chronic wounds. Multiple cell types, the extracellular matrix, and the action of soluble mediators including growth factors and cytokines are all involved in wound healing. Despite being an ongoing process, healing can be loosely separated into four stages: (i) hemostasis and coagulation; (ii) inflammation; (iii) proliferation; and (iv) remodelling of the wound with the creation of scar tissue. The clinical result can be effectively influenced by the appropriate approach to wound treatment. This overview covers wound classification, wound treatment techniques, and the physiology of the wound healing process.

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3. METHODOLOGY

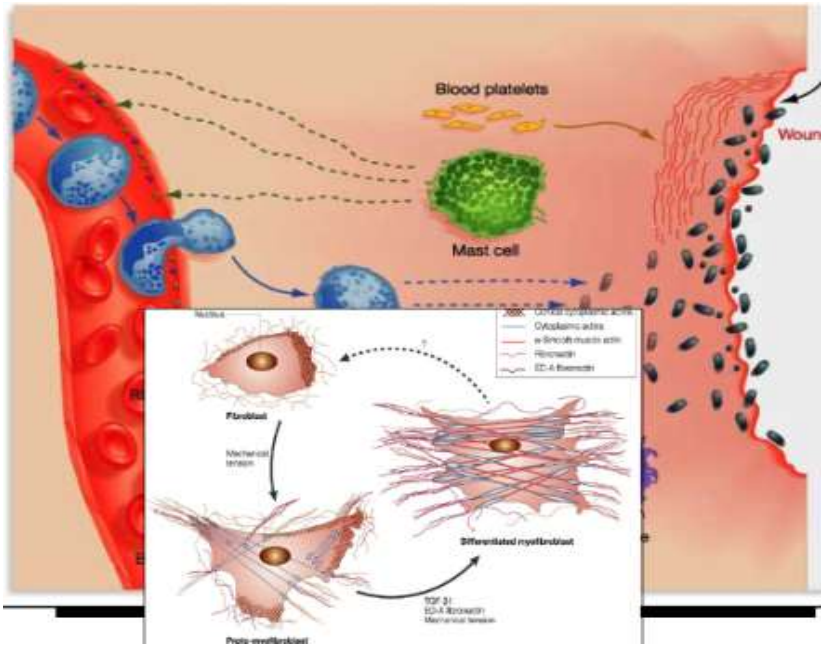

Fig 1 shows the inflammation

Factors influencing repair process –

- The tissue environment-(Proliferative capacity of cells of tissue)
- Extent of tissue damage- (Integrity of extracellular matrix)
- The intensity and duration of the stimulus- (Resolution or Chronicity of injury and inflammation)

ANGIOGENESIS

Vasculogenesis – is formation of blood vessels in embryonic stage in which a primitive vascular network is established from endothelial cell precursors called angioblasts

Angiogenesis – or Neovascularization is the process of blood vessel formation in adults.

Angiogenesis occurs in 2 ways –

1.Branching and extention of pre-existing vessel.

2.Recruitment of endothelial progenitor cells.

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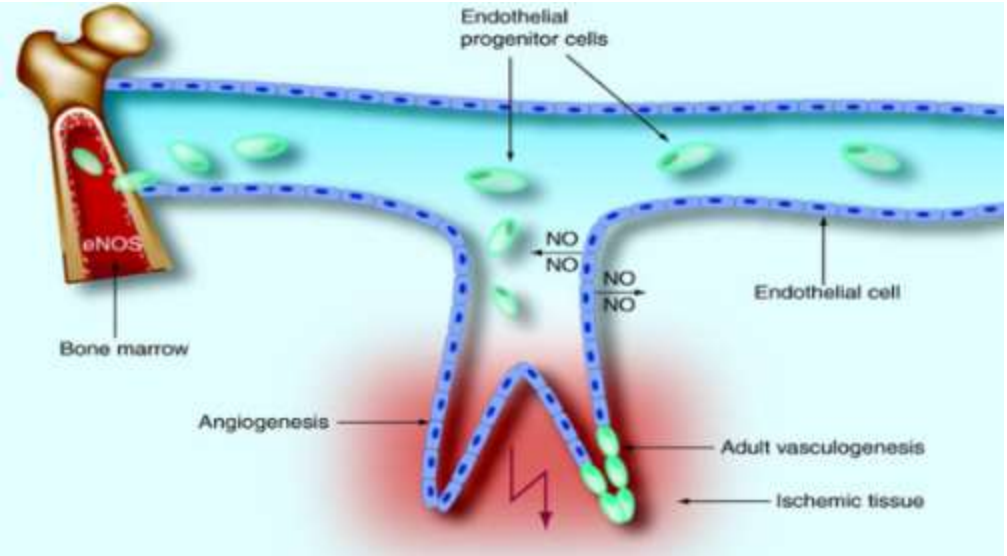

Fig 2 shows the occurrence of Angiogenesis

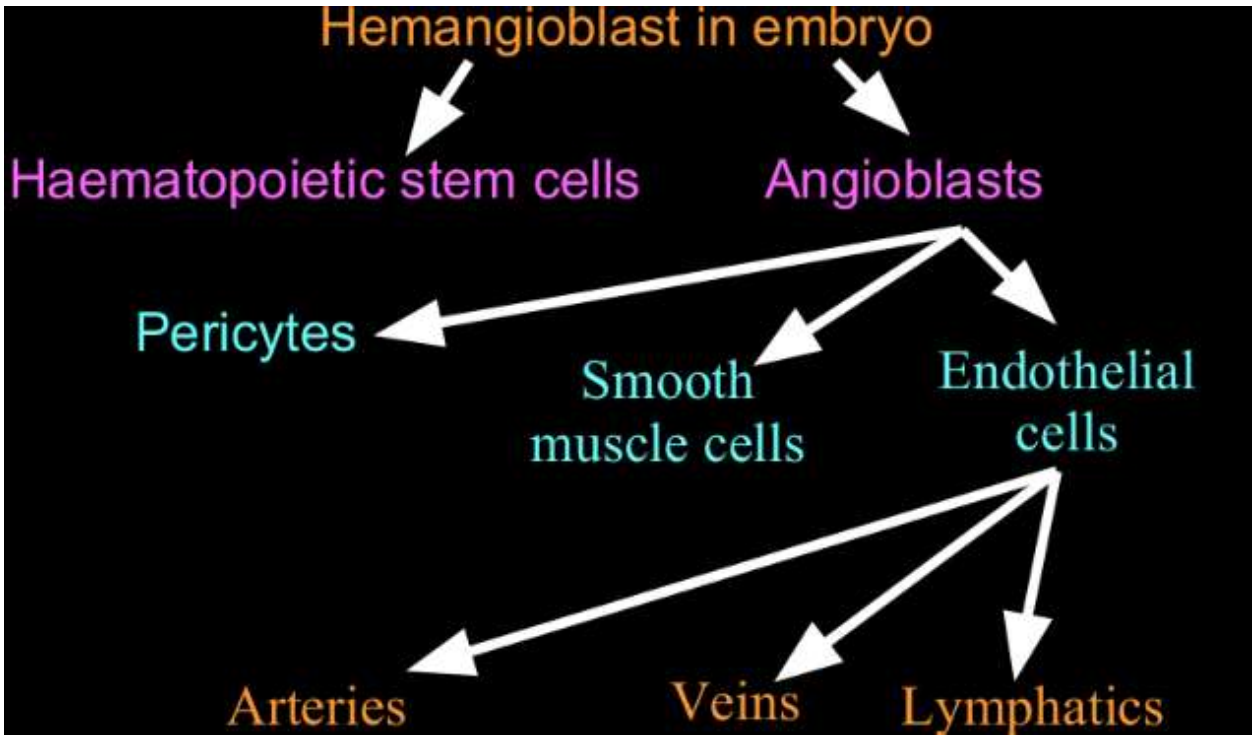

Fig 3 shows Angiogenesis from Endothelial precursor cells

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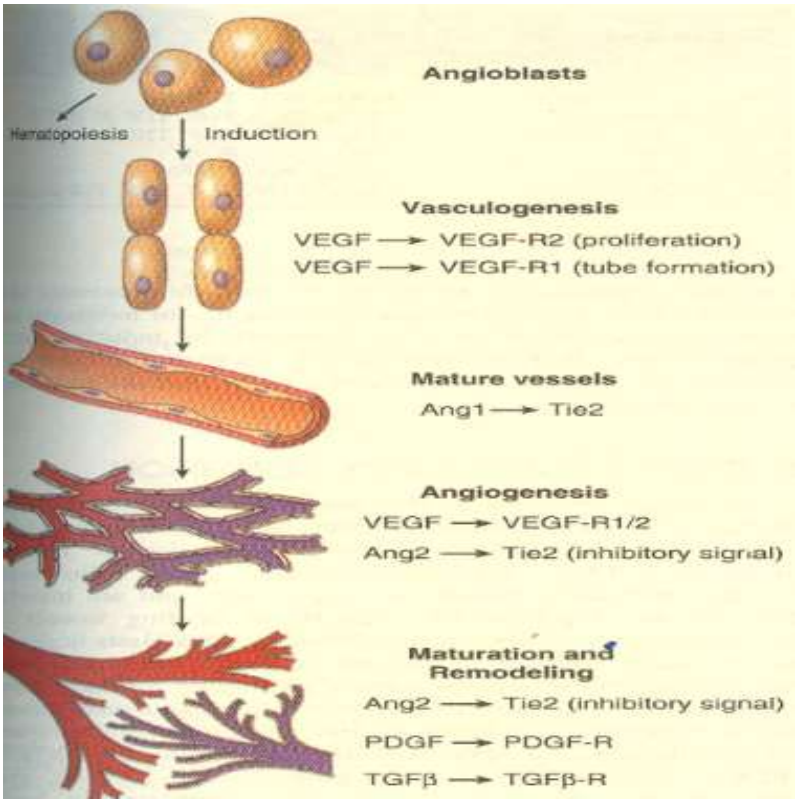

Fig 4 shows growth factors and receptors involved in angiogenesis

Cutaneous Wound Healing

- In superficial wounds epithelium is reconstituted
- Epidermal appendages do not regenerate so a scar is always seen

Healing can be by –

- Primary intention
- Secondary intention

Cutaneous wound healing occurs in 3 phases that overlap

1 Inflammation

2 Granulation tissue formation and re-epithelization

3 Wound contraction, ECM deposition and remodeling.

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4. RESULTS AND DISCUSSION

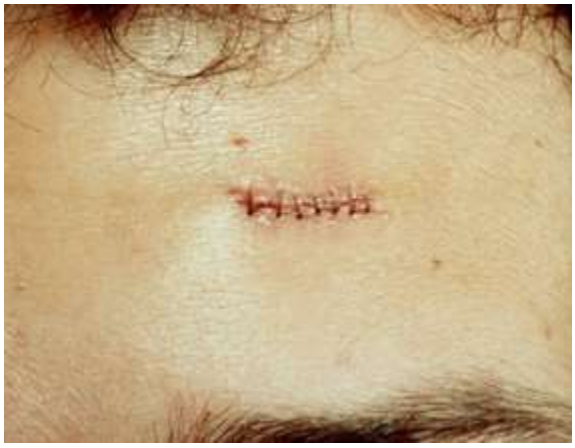

Fig 5 shows first intention healing

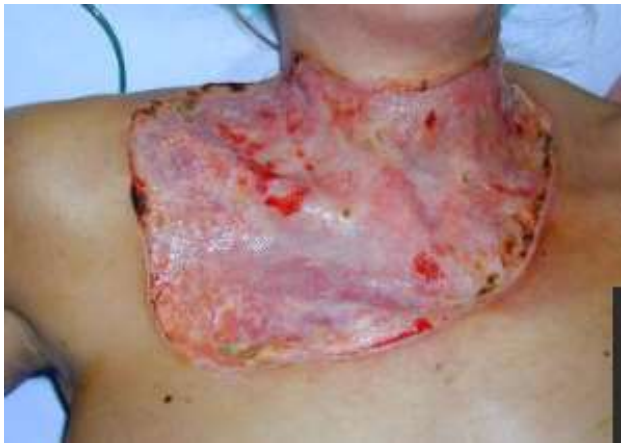

Fig 6 shows second intention healing

Healing by First Intention

- Occurs in small wounds that close easily
- Epithelial regeneration predominates over fibrosis
- Healing is fast, with minimal scarring/infection

Examples:

- Paper cuts, Well-approximated surgical incisions
- The site fills with clotted blood containing fibrin and blood cells, which dehydrates to form scab.

24 hours

- Neutrophils appear at margins of incision
- Spurs of epithelium move towards each other
- Thin continous layer of epithelium closes wound.

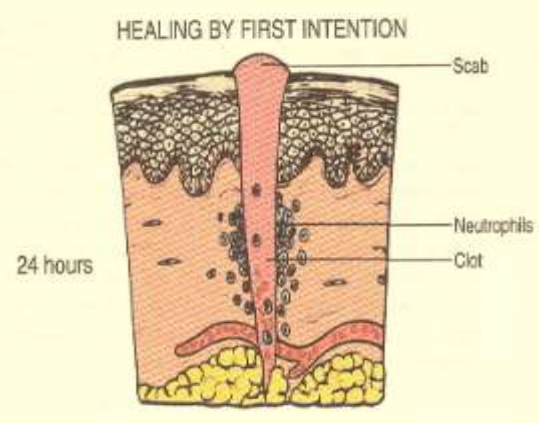

Fig 7 shows healing by first intention in 24 hours

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Day 3-7

- Neutrophils are replaced by macrophages
- Granulation tissues invades space
- Collagen fibers are first vertically later horizontally oriented
- Epithelial layer thickness

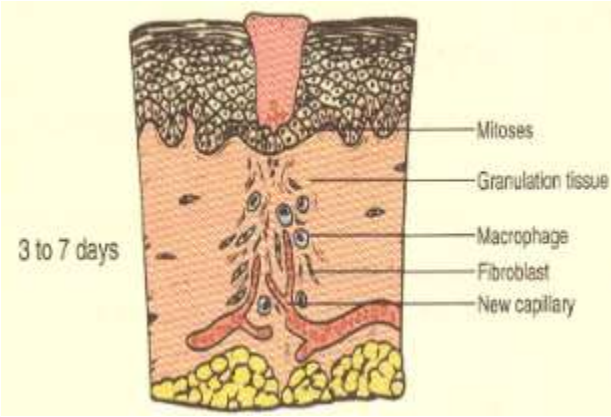

Fig 8 shows healing in 3 to 7 days

2nd Weeks –

- Accumulation of collagen and proliferation of fibroblasts.
- Regression of vascular channels
- Blanching begins

End of 1st Month –

Wound is made up of-

-cellular connective tissue

- without inflammation

-covered with epithelium.

Healing by Second Intention

- Occurs in larger wounds that have gaps between wound margins
- Fibrosis predominates over epithelial regeneration
- Healing is slower, with more inflammation and granulation tissue formation, and more scarring
- Examples:

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- Infarction , Large burns and ulcers

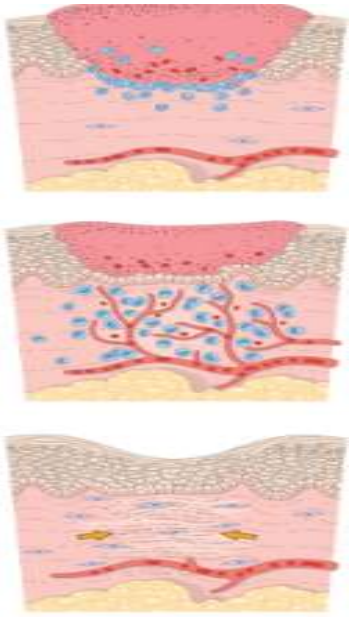
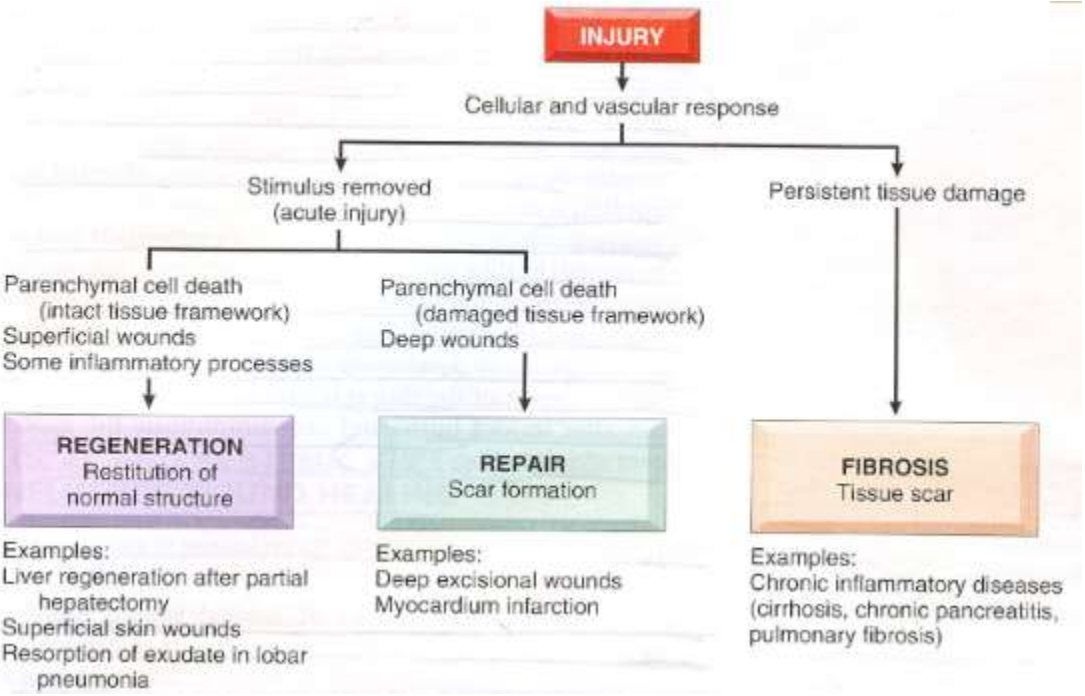


Fig 9 shows healing by second intention

Differences from healing by first intention:

- More inflammation
- More granulation tissue
- More scar



- Fig 12 shows the summary

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5. CONCLUSION

Wound strength

End of 1st week – sutures are removed wound strength 10% of unwounded skin

End of 3rd month – 70-80% tensile strength of unwounded skin

1- Collagen synthesis = First 2 mths

2- Continuous crosslinking

3- Increase in fiber size

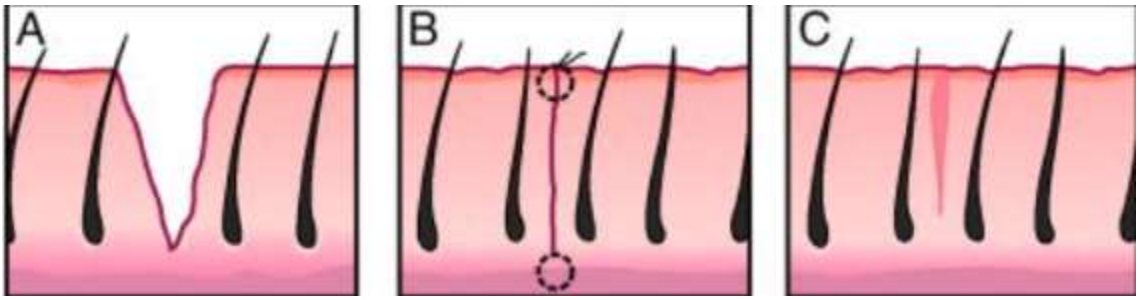

Fig 10 shows Primary healing of skin wound closure

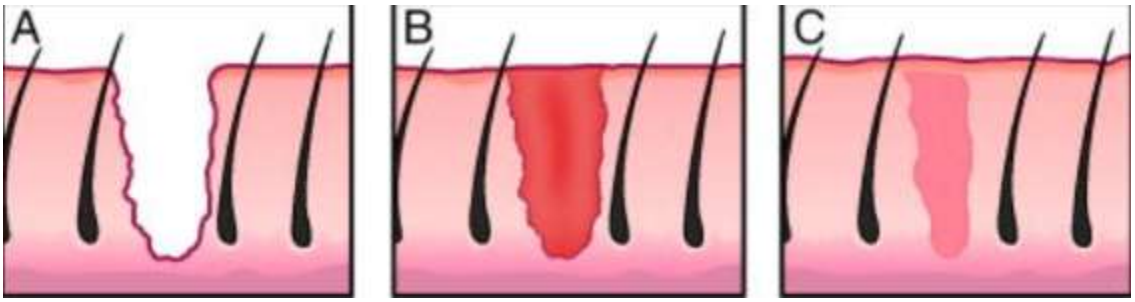

Fig 11 shows Primary healing of skin wound closure

Factors Affecting Wound Healing

- Blood Supply
- Denervation
- Local Infection
- Foreign body
- Hematoma
- Mechanical stress
- Necrotic tissue

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- Protection (dressings)
- Size of wound
- Type of tissue

Systemic Factors

- Age
- Anemia
- Drugs
- Genetic disorders
- Hormones
- Diabetes
- Systemic infection
- Malignant disease
- Malnutrition
- Obesity
- Temperature
- Trauma, hypoxia,
- hypovolumia
- Uremia
- Vitamin /Trace
- metal deficiency

Complications of cutanecous wound healing

1. **Deficient scar formation**
    (a) Excessive formation of repair components
    (b) Formation of wound contractures
    (c) Inadequate granulation tissue leads to-
        i. Dehiscence / rupture of a wound
2. **Excessive formation of components of repair process**

a-Hypertrophic scar – excessive laying down of collagen during healing

b-Keloid –beyond the boundaries of the original wound and does not regress

c-Proud flesh - Exuberant granulation tissue

d-Desmoid /aggressive fibromatosis between benign and malignant tumours.

3. **Contracture**

- Results in deformities
- Commonly seen after burns and results in restricted movement.

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