Foundations of Best Practice for Skin and Wound Management

Skin: Anatomy, Physiology and Wound Healing

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These 2017 updates build on the work of previous author teams and incorporate the latest research and expert opinion.

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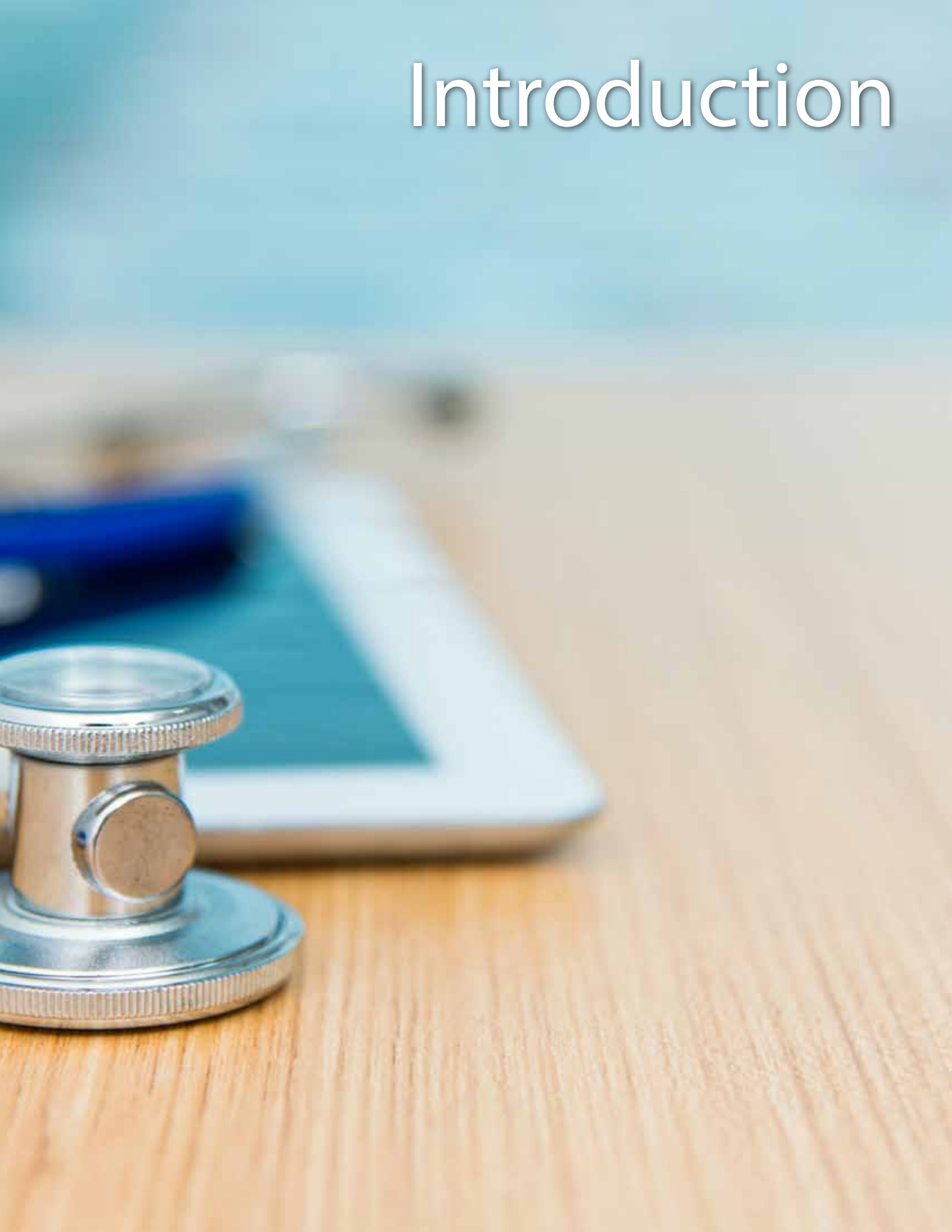
Introduction



Introduction

Skin is the largest organ of the body and consists of two layers—the epidermis and dermis—that are supported by a number of underlying structures. This organ has multiple functions. It is a barrier between the external environment and the internal organs, protecting against trauma from water, chemicals, micro-organisms, mechanical stress and radiation. It also performs sensory functions related to touch, pressure, temperature, pain and alerts for potential tissue damage. Additionally, it has a role in exchanging fluids, salts, gases and heat.[1–6]

Skin acts as a temperature regulator through a neural feedback mechanism that operates primarily through the hypothalamus. When skin temperature rises above 37°C, sweating helps to cool the body by drawing heat out through the process of evaporation. If skin temperature drops below 37°C, the body acts to conserve heat and increase heat production through the cessation of sweating. At the same time, the skin increases shivering and the secretion of norepinephrine, epinephrine and thyroxine to increase heat production and the erection of hair.[7]

Skin is also a window between the mind and body and the external world. Internal or external stimuli to the neuro-immuno-cutaneous-endocrine network can result in blushing, goose bumps or crawling skin. Skin colouration such as blushing is normally involuntary and triggered by emotional stress that could be associated with embarrassment, anger or romantic stimulation.

Skin is an endocrine organ and manufactures hormones such as vitamin D, steroids and thyroid hormone for its own use. Skin also makes many of the neurotransmitters and hormones found in the brain.[8] As an organ of the immune system, skin can release powerful signaling chemicals—such as histamine—that activate other components of the immune system, causing the skin to become red and swollen in the presence of foreign material.

Skin health is influenced by various internal and external factors. These factors also influence wound healing. Therefore, to support the health of skin and the healing of wounds, clinicians need to appreciate, recognize and comprehend both the complex nature of skin and what lies beneath.

This paper presents the anatomy and normal functions of skin and underlying structures and provides the reader with an outline of the normal healing phases of wounded skin.

Skin Components

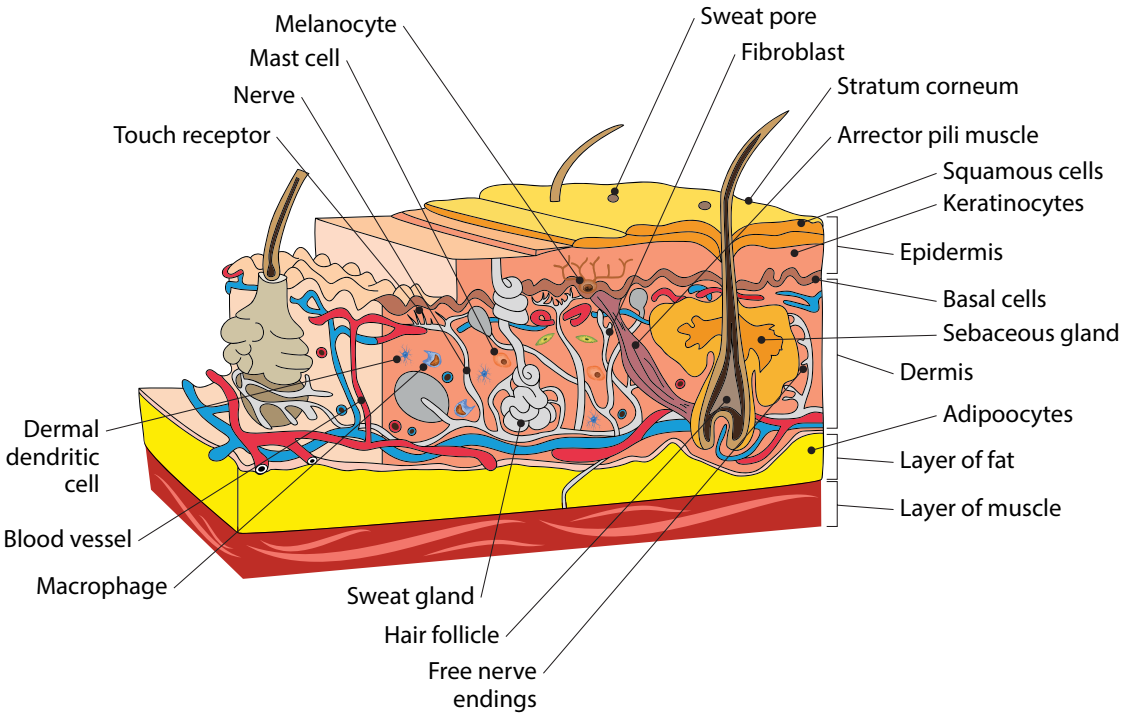
Skin Components

The epidermis is made of tightly woven epidermal, or skin, cells. The epidermis is the outermost layer of the skin and forms a waterproof barrier that both holds moisture in and keeps moisture out. Depending on its location in the body, the epidermis ranges from very thin (0.5 mm in the tympanic membrane, or eardrum) to very thick (6 mm on the sole of the foot).[9]

The epidermis has no blood vessels and gets its oxygen and nutrients from the deeper layers of the skin by diffusion from blood capillaries extending to the upper layers of the dermis. The epidermis is made up of several layers:

1. The **stratum corneum** is the outermost layer. It consists of stratified squamous keratinized epithelium. Cells in this layer migrate upward and are shed from the surface every 14 days. These cells require optimal moisture balance, temperature and pH in order to be active. The stratum corneum has an acidic pH, called the acid mantle, that protects the body from some bacteria and fungi.
2. The **stratum lucidum** is the innermost layer of the stratum corneum and is found on the palms of the hands and soles of the feet.
3. In the **granular cell layer** the squamous cells are in transition to becoming the stratum corneum and have lost their inner cell machinery, including the nuclei.
4. The **squamous cell layer** contains the Langerhans cells, which are derived from bone marrow and have an immune function.
5. The **basal cell layer** contains keratinocytes, melanocytes and Merkel cells. Skin cells are constantly shedding and regenerating. The keratinocytes, from the lowest layer of the epidermis, are continually pushed to the surface by the production of new cells beneath them. These cells fill with keratin as they migrate to the surface of the epidermis. Keratin gives skin protective qualities and makes it waterproof. When the cells reach the top layer of the skin they are dead flat sacs filled with keratin. Millions of these dead cells are shed daily, resulting in an entirely new epidermis every 35 – 45 days.[2–6,10] Melanocytes are wedged between the basal cells and produce melanin, which protects the skin from ultraviolet light. Merkel cells are thought to be sensory cells.

Figure 1. Skin Components



The epidermis is separated from the dermis by the basement membrane, a very thin membrane that attaches the epidermis firmly, though not rigidly, to the dermis.

The dermis lies just beneath the epidermis and above the subcutaneous tissue. The dermis is 0.3 to 4.0 mm thick and is divided into the papillary and reticular layers.[11]

The junction between the epidermis and the dermis has a series of finger-like structures called rete pegs that project up from the dermis. Similar structures project down from the epidermis. These projections increase the area of contact between the two layers and help to prevent the epidermis from being sheared off. These structures are not present in unborn babies and are almost nonexistent in premature neonates but develop rapidly after birth. As skin ages they get smaller and flatter.

The dermis contains extracellular matrix (ECM) made of collagen and elastic fibres that provide structure to the skin and are necessary for wound closure. The dermis also contains a capillary bed that is fed by the arterioles and drained by the venules. Interspersed in the capillary bed are the lymph capillaries. The hair follicles, sweat glands and sebaceous glands are lined with epithelial tissue that leads to the skin's surface and supports the regeneration of the skin at the surface. Sweat (from the sweat glands) helps to regulate body temperature, and sebum (from the sebaceous glands) helps to keep the skin from drying out.

Blood circulates within the capillaries of the dermis to supply nutrients and metabolites to the tissues and to collect waste products produced by the tissues. Without this nourishment and waste removal, tissue health cannot be sustained and tissue healing cannot occur. This exchange of constituents between the blood and tissues takes place via interstitial fluid (ISF), or tissue fluid.

The circulatory system moves blood through the body through the pumping action of the heart (arteries) and skeletal muscles (veins). Arterial blood carries oxygen from inhaled air to the tissues of the body via blood vessels of varying size. Venous blood carries carbon dioxide, a metabolic waste product produced by cells, from the tissues to the lungs to be exhaled.[11]

Blood is mostly water (90% by volume). It contains dissolved proteins, glucose, mineral ions, hormones, carbon dioxide, platelets and blood cells. Blood cells make up 55% of blood plasma and include red blood cells (erythrocytes), white blood cells (leukocytes: neutrophils, eosinophils, basophils, lymphocytes and monocytes) and platelets. The most abundant cells are red blood cells, which contain hemoglobin that enables the transportation of oxygen. Carbon dioxide is almost entirely transported extracellularly in the form of bicarbonate ions dissolved in plasma.[11]

Lymph is a straw-coloured fluid that forms in interstitial spaces. Water, glucose, amino acids and oxygen filter out of the capillaries, primarily on the arterial side. Lymph nourishes the cells and supports metabolism, creating waste products that are reabsorbed into the capillaries, primarily on the venous side.

Large protein molecules cannot cross the semi-permeable membranes of the walls of the capillaries and are not reabsorbed. However, lymphatic capillaries, which are interspersed in the capillary bed, have a unique structure that allows the absorption of these large protein molecules. The cells of the lymphatic capillaries have anchoring filaments and are able to separate from one another to create an opening through which fluids, proteins and macromolecules can flow into the lymphatic capillary. Lymphatic fluid primarily consists of water and protein filtrate but also may include lipids

(absorbed in the intestine), waste products of metabolism, matrix metalloproteases (MMPs), cytokines, polysaccharides and fibronectin. If there is an imbalance between filtration and absorption, fluid will accumulate in the interstitial space and is seen clinically as edema. If there is significant lymphatic dysfunction, the edema will have high protein content and is defined as lymphedema.

The lymphatic system consists of lymph vessels, lymph nodes, spleen, thymus, tonsils and Peyer's patches in the gut. In addition to its role of transporting lymph this system has a major role in the functioning of the immune system. The lymphatic capillaries connect to vertical pre-collectors. These drain into a common lymphatic collector that merges into a single lymph vessel (lymphangion). Smooth muscle in the lymphangion contracts once distended to propel lymph through the valves in a peristaltic manner. Normal lymph propulsion is aided by adjacent arterial pulsations, muscle contractions, body movements, respiration and skin distention. Lymph ultimately moves into the thoracic duct, which empties into the subclavian vein, returning the lymph to the circulatory system.

One immune function of the lymphatic system is particularly important in the skin. Bacterial antigens are picked up by presenter cells and carried through the lymph vessels to the lymph nodes. Here the antigens are presented to B-cells, which are stimulated to produce antibodies.

Skin pH

The pH of normal, healthy human skin is somewhere between 4.0 and 6.5 and varies with age. This slightly acidic pH is created from the combined excretion of oil and sweat from the skin's pores and excretions from normal skin microbiota (micro-organisms that live on the body without normally causing disease). The optimal pH of 5.5 is referred to as the "acid mantle" and it provides the body with defence against invading micro-organisms. This defence mechanism is not fully developed until puberty, leaving children more vulnerable to infections such as ringworm. The pH of the skin also influences barrier homeostasis, cohesion and desquamation by acting on the various enzymes within the stratum corneum.[12]

Underlying Structures

Underlying Structures

The following section discusses the underlying structures required for movement, support, protection and production of blood components as well as those that serve as a reservoir for essential minerals.[13]

Subcutaneous tissue, or hypodermis, is under the dermis and is made up of fat-filled cells called adipose cells. The hypodermis also contains connective tissue, larger blood vessels and nerves. One of its functions is to regulate skin and body temperature. The size of this layer varies throughout the body and from person to person. This layer of subcutaneous fat insulates the body, absorbs trauma and is a reserve energy source. It may be divided into two components, the fatty layer, or panniculus adiposus, and a deeper layer of muscle, the panniculus carnosus.[11]

Subcutaneous fat is loosely attached to muscles and bones by connective tissues. If the subcutaneous tissues have too much fat, the areas of attachment become more obvious and the skin cannot move as easily, giving rise to cellulite. Subcutaneous tissue is typically poorly vascularized and wounds that extend to the fatty tissues tend to heal more slowly.

Fascia is an uninterrupted, three-dimensional thin web of fibrous, strong connective tissue primarily consisting of collagen that extends throughout the body. Fascia acts as a shock absorber, maintains the structural integrity of the body and provides support and protection. The superficial fascia is found in the lowermost portion of the skin and surrounds nerves, blood and lymph vessels. The deep fascia is a dense layer that surrounds individual muscles and groups of muscles. The elastin fibres within it allow it to stretch and store kinetic energy. The deep fascia has few blood vessels but is rich in sensory receptors. All organs are covered with a double layer of fascia called the visceral or subserous fascia. Organs are suspended by fascia. After injury, it is the fascia that creates a scaffold for tissue repair.

Muscle is specialized tissue made up of cells that have the ability to contract and conduct electrical impulses. There are three types of muscles: smooth involuntary muscle (such as the muscles in the stomach), striated voluntary muscle (such as the muscles in the arms and legs) and striated involuntary muscle (such as in the heart). Muscle is contractile; it is not easy to grab with tissue forceps and tears easily.[11]

Tendons are tough bands of fibrous connective tissue that connect muscle to bone and are capable of withstanding tension. Tendons and muscles work together and can only exert a pulling force. Tendons have a high concentration of elastin fibres, which allow the stretched tendon to store kinetic energy. Tendons are covered with connective tissue sheaths that produce synovium to reduce friction between the tendon and surrounding structures. Paratenon, which is located between the fascia and tendon, surrounds and nourishes some tendons. When functioning normally, tendons glide easily and smoothly as the muscles contract. If the normal smooth gliding motion of the tendon is impaired, the tendon will become inflamed and movement will become painful. This is called tendinitis. When tendons are damaged they heal slowly because they are poorly vascularized. If they are exposed to the air and are allowed to dry out the paratenon is destroyed and the tendon may be damaged. Infection tends to spread quickly along the tracts that the sheaths around the tendons create.

Ligaments are short bands of fibrous connective tissue that connect bones to other bones to form a joint. Ligaments often have an overlying vascular layer, the

Table 1. Physiology at a Glance

Structure	Function	Implications for Wounds
Epidermis	• provides protection against trauma and harmful environment and organisms	Abrasion occurs if epidermis is damaged.
Dermis	• provides skin flexibility and strength	Bleeding occurs and the body's first line of defence is breached. Healing is multifactorial.
Arterial blood	• supplies oxygen to the body	Poor arterial flow leads to ischemia and impaired healing.
Venous blood	• removes metabolic waste products from the body	Venous hypertension leads to edema and interferes with healing.
Lymph fluid	• removes waste and supports immune response	Lymphedema often accompanies venous edema. Lymphedema is rarely acknowledged and poorly understood.
Subcutaneous tissue	• provides protection, cushioning, insulation and energy storage	Poorly vascularized tissue leads to slow healing.
Fascia	• gives structure, protection, support	Entry into fascial plane leads to infection.
Muscles	• perform voluntary and involuntary movement	Muscles are very vascular and tear easily.
Tendons	• attach muscles to bones	Exposed tendons should be kept moist. They are poorly vascularized and therefore slow to heal. Loss of tendon means loss of function.
Ligaments	• attach bones to bones to form a joint	Exposed ligaments should be kept moist. They are poorly vascularized and therefore slow to heal. Loss of ligament means loss of function.
Bones	• provide protection, strength and support	Exposed bone usually leads to osteomyelitis. Bone (periosteum) should not be allowed to dry out.
Joints	• facilitate movement and mechanical support	Joint involvement in wounds usually leads to osteomyelitis.
Synovium	• lubricates to reduce friction	Appearance of synovium in wounds indicates exposure to joint cavity.
Cartilage	• connects bones	Exposed cartilage should be kept moist. Exposure leads to osteomyelitis.

epiligament, covering their surface. This layer is often indistinguishable from the actual ligament and merges into the periosteum of the bone around the attachment sites of the ligament. Some ligaments limit the mobility of articulations or prevent certain movements altogether. Double-jointedness, hyperlaxity and hypermobility refer to individuals with more elastic ligaments that allow joints to stretch and contort further than normal. Ligaments are most often torn in traumatic joint injuries and can result in either partial or complete ligament discontinuities. As with tendons, ligaments heal slowly and if exposed should not be allowed to dry out.

Bones consist of hard, white, dense connective tissue with a periosteum covering that provides an external blood supply. Bones provide rigid strength and support. Like skin, they are continually turning over and remodeling. Bones can granulate but must

be kept moist to preserve the periosteum, which is the nutritional source for bones. If there is no periosteum the bone will die. Exposure of bone can quickly result in infection, which can lead to osteomyelitis.

Joints are the locations at which two or more bones make contact. They are constructed to allow movement and provide mechanical support. Joints are classified based on their structure and function.

- Structure:
  - Fibrous joints are joined by fibrous connective tissue.
  - Cartilaginous joints are joined by cartilage.
  - Synovial joints are not directly joined.
- Function:
  - Synarthrosis joints permit little or no mobility. Most synarthrosis joints are fibrous joints (e.g., those in the skull).
  - Amphiarthrosis joints permit slight mobility. Most amphiarthrosis joints are cartilaginous joints (e.g., vertebrae).
  - Diarthrosis joints permit a variety of movements. All diarthrosis joints are synovial joints (e.g., shoulder, hip, elbow, knee).

Synovium is a thin layer of tissue only a few cells thick that lines the joints and tendon sheaths to control the environment. Synovium acts as a membrane to determine what can pass into the joint space and what must stay outside. As well, synovium produces a thick, viscous, sticky lubricant called synovial fluid that reduces friction in the joint during or with movement. If synovial fluid is noted in a wound bed, joint involvement and osteomyelitis should be suspected.

Cartilage is the dense connective tissue found in many areas in the body, including the articular surface of the bones, rib cage, ears, nose, bronchial tubes and intervertebral discs. Its mechanical properties are an intermediate between bone and dense connective tissue like tendon. Unlike other connective tissues, cartilage does not contain blood vessels. Compared with other connective tissues, cartilage grows and repairs more slowly.

Normal Changes and Differences in Skin

Normal Changes and Differences in Skin

Infant Skin

Infant skin differs from adult skin in several ways. The thickness of infant skin is 40% to 60% that of adult skin. Weak rete ridges provide limited surface attachment to an immature dermis. As well, an infant's ratio of body surface area to weight is up to five times that of an adult. These factors place the infant at greater risk for skin damage.[14]

At birth, the surface layer of the skin is relatively neutral (pH about 6.5) and gradually becomes more acidic over the first few postnatal weeks. The acid mantle forms as a result of changes on the skin surface, such as the presence of sweat, sebum and normal microbiota as well as metabolic processes within the stratum corneum, such as lactic acid and free fatty acid production. Over the first few postnatal weeks the skin's pH falls to about 5.5, a level that is beneficial for antimicrobial defence through the inhibition of the growth of pathogenic bacteria.[15] Acidification also maintains epidermal barrier integrity by stabilizing the double-lamellar structure of intracellular lipids.[15]

Skin Changes in the Adolescent

Adolescence brings about the maturation of the hair follicles, sebaceous (oil-producing) glands and sweat glands in the skin. Stimulation of the sebaceous glands, caused by a surge in the sex hormones estrogen, androgen and progesterone, results in increased production of oil, or sebum. These sex hormones are also responsible for the development of apocrine glands in the pubic region and armpits. The resulting thick sweat mixed with bacteria on the surface of the skin can cause body odour. At the same time hair growth occurs in these areas.

An increase in the lipid content during this time enhances the heat-insulating properties of skin, improving temperature regulation. The higher fat content also helps to retain moisture, making teenage and young adult skin less susceptible to drying out.[15,16]

Skin Changes in the Older Adult

As individuals age, skin goes through many changes based on genetics, environment, lifestyle and any existing chronic disease states. However, despite these individual variations, the normal aging process of all skin causes many predictable changes.

With increasing age there is a 50% decrease in the turnover of the epidermal layer. The

pH of the skin becomes more neutral (less acid) and thus more susceptible to bacterial growth and infections. Interestingly, the pH value rises above 6 when a person actually experiences a skin problem or skin disease.

Thinning of the outer epidermal layer can cause a 1% decrease in collagen per year. Since collagen gives skin tensibility, this loss leads to wrinkling. There is also a decrease in melanocytes, the pigment-producing cells. Langerhan's cells, which serve as macrophage and immune moderators of the epidermis, also decrease. Blood supply is reduced and the dermis becomes increasingly avascular as the body ages.

The skin's aging process also results in biochemical changes in collagen and elastin, the connective tissues underlying the skin, which give the skin its firmness (collagen) and elasticity (elastin). The rate of the loss of skin firmness and elasticity differs from individual to individual depending on genetic makeup, general health, exposure to the sun, skin care regimen and other factors.

Elastin fibers significantly decrease in size and number over time, which leads to decreased elasticity. Elastin maintains the skin's elasticity and recoil so this loss leads to wrinkling. The skin's ability to perceive sensation to pressure and light touch is also reduced, resulting in an increased threshold for pain. As the skin becomes less elastic, it also becomes drier. The underlying fatty tissue begins to disappear and skin begins to sag. The skin is less supple and wrinkles begin to form. Atrophy of subcutaneous fat in the hands, face, shins, waist (men) and thighs (women) results in sagging and folds. At this stage, skin is more easily injured, heals more slowly and tends to dry out more quickly.[16,17]

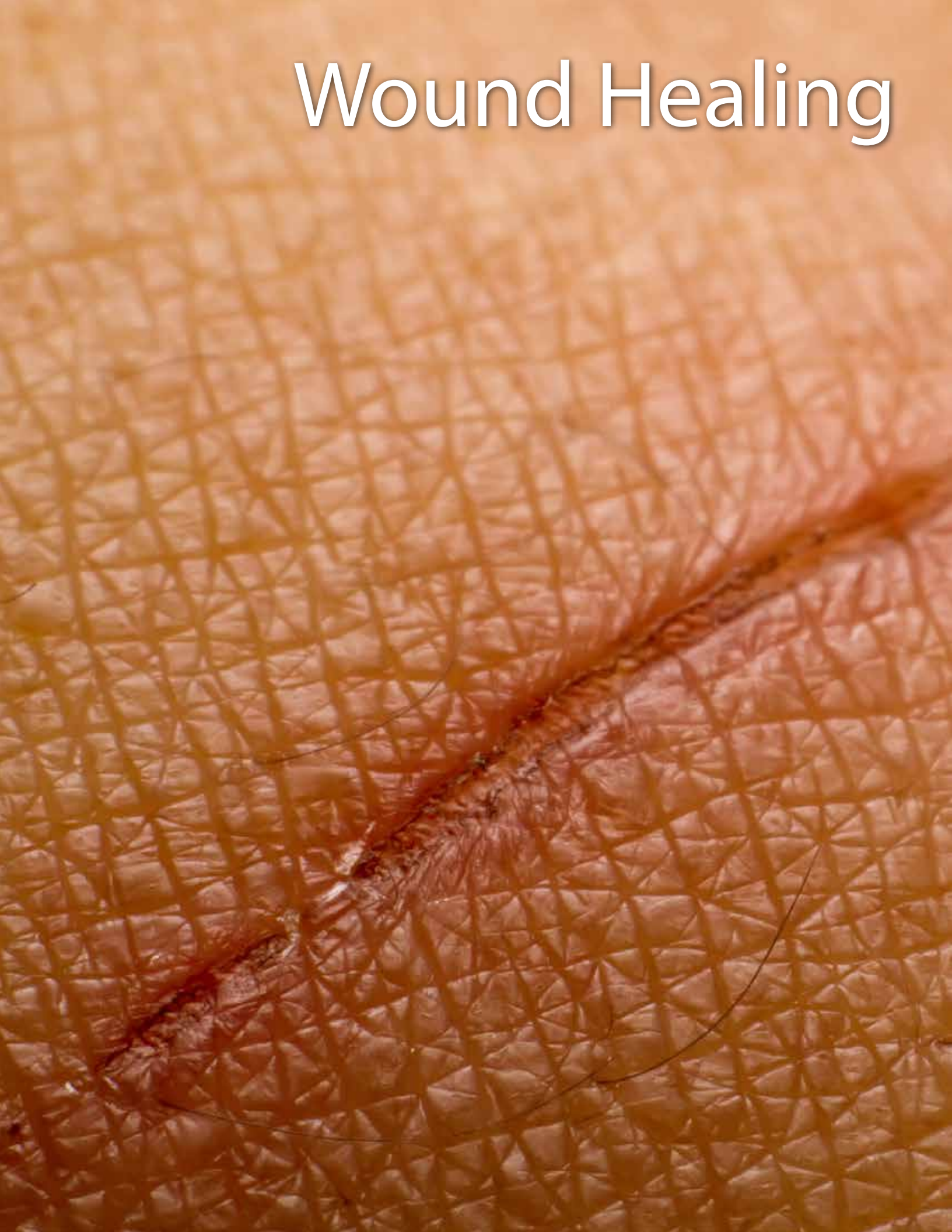
Melanocytes, the pigment-producing cells, decrease in quantity during the aging process. Hair follicles also decrease in number and growth rate, with associated greying due to the decrease and loss of melanin.

Difference between Male and Female Skin

Skin is affected by sex hormones. Estrogen increases collagen and skin moisture and promotes wound healing, while testosterone stimulates oil production and the growth of facial hair. Of note, men and women have *both* sex hormones; skin is able to convert testosterone to estrogen and ovaries produce a small amount of testosterone.

Women's skin is generally thinner and less oily than men's. Therefore, women are more likely to experience wrinkles because thinner, drier skin is more prone to damage from the sun and cigarette smoke. Women also sweat less than men and thus are more likely to suffer heat stroke. During menopause, the loss of sex hormones accentuates wrinkles and estrogen-deprived skin thins, loses collagen and slows down its cell renewal.[14]

Wound Healing



Wound Healing

Skin's Response to Damage

When skin is damaged or wounded it attempts to regenerate itself so it can continue to protect the larger organism.

Research on acute wounds in animal models shows that wounds heal in four phases. (Note: some authors combine the first two phases.)

1. Hemostasis
2. Inflammation
3. Proliferation (also known as granulation and contraction)
4. Remodeling (also known as maturation)

Dean Kane created a wound-repair analogy that compared wound healing to the repair of a damaged house.[18] As with the repair of a house, the process relies on the right materials (cells) being delivered to the site (wound) in the right order and at the correct time (see Table 2). A successful repair also depends on access to the damaged areas with the high-quality materials (adequate blood supply and an active immune system) necessary to get the job done well.[18]

Table 2. Phases of Wound Healing and the Kane Analogy[18]

Phase of Healing	Time Post Injury	Cells Involved in Phase	Function or Activity	Analogy to House Repair
1. Hemostasis	immediate	• platelets	• clotting • release of growth factors	• cap off broken utilities
2. Inflammation	days 1 – 4	• neutrophils • macrophages • monocytes	• phagocytosis	• unskilled labourers clean up the site
3. Proliferation (granulation and contraction)	days 4 – 21	• macrophages • pericytes • lymphocytes • angiocytes • neurocytes • fibroblasts • keratinocytes • epithelial	• fill defect • re-establish skin function • closure	• contractor or supervisor • specific labourers • plumbers • electricians • framers • roofers and siders
4. Remodeling (maturation)	day 21 – 2 yrs.	• fibrocytes • fibroblasts	• develop tensile strength	• remodelers

1. Hemostasis Phase

Hemostasis occurs within minutes of the initial injuries unless there are underlying clotting disorders. Once the source of damage (such as fire or flood) to a house has been removed and before work can start, utility workers must come in and cap damaged gas or water lines. Similarly, in wound healing, the source of the damage (e.g., pressure or heat) must first be identified and removed and then blood vessels must

be sealed. In wound healing, the platelets are the cells that act as the utility workers, sealing off the damaged blood vessels. The blood vessels themselves constrict in response to injury, but this spasm ultimately relaxes. Although the platelets secrete vasoconstrictive substances to aid in this process, their primary role is to form a stable clot, thereby sealing the damaged vessel. Under the influence of ADP (adenosine diphosphate) leaking from damaged tissues, the platelets adhere to the exposed type I collagen. Platelets become activated and secrete adhesive glycoproteins that stimulate further platelet aggregation. They also secrete factors that interact with and stimulate the intrinsic clotting cascade through the production of thrombin, which in turn initiates the formation of fibrin from fibrinogen. The fibrin mesh strengthens the platelet aggregate into a stable hemostatic plug. Finally, platelets secrete growth factors such as platelet-derived growth factor (PDGF), which is recognized as one of the first factors secreted in initiating the subsequent healing steps. The growth factors also recruit neutrophils and monocytes and stimulate epithelial cells to recruit fibroblasts, thereby initiating the next phase of wound healing: inflammation.

2. Inflammation Phase

The vasoconstriction in the hemostasis phase is followed by vasodilation in this phase, to provide an increase in blood flow to the traumatized site. Therefore, clinically, inflammation (the second phase of wound healing) presents as erythema, swelling and warmth often associated with pain; the classic "*rubor et tumor cum calore et dolore*." This stage usually lasts up to four days post injury. In the wound healing/house repair analogy, the second job to be done once the utilities are capped is to clean up the debris. In a wound, this cleaning is done by the first inflammatory cells on the scene: neutrophils, or PMNs (polymorphonuclear neutrophilic leukocytes). The inflammatory response causes the blood vessels to become leaky and release plasma and PMNs into the surrounding tissue. The neutrophils phagocytize debris and micro-organisms, thus providing the first line of defence against infection. They also enhance the effectiveness of antibiotics through oxidative killing of bacteria. As they digest bacteria and debris, the neutrophils die. Monocytes then become the primary white blood cell in the wounded tissues and release intracellular enzymes in the surrounding matrix, further digesting tissue. Fibrin is broken down as part of this clean-up process, and the degradation products attract the next cells involved: fibroblasts and epithelial cells, which are aided by local mast cells.

The Role of Micronutrients

Each step of the wound-healing process is dependent on circulating amino acids, lipids and carbohydrates. The most important micronutrients known to be associated with wound healing are iron, zinc and vitamins A and C. Deficiencies in the intake of proteins and vitamins are particularly common in the elderly. Infected wounds often require that patients increase their nutritional intake.

The task of repairing a house is complex and requires someone, such as a contractor,

to direct activity. Similarly, wound repair requires co-ordinated activity of the cells and reliable cell-to-cell communication. Cells communicate through soluble proteins called cytokines and growth factors. These cytokines and growth factors are released by one cell and bind to receptors on target cells. Once a cytokine binds to a target cell, it stimulates that cell to move. Growth factors, on the other hand, stimulate the target cell to either divide and produce more cells or to synthesize and release substances such as the collagen required to form the extracellular matrix. The extracellular matrix also plays an active role in wound healing by interacting with the cells through receptors called integrins. Examples include platelet activation, epithelial migration and fibroblast movement.

Macrophages are also involved in the co-ordination of cell activity in wound repair. Within two days, circulating monocytes differentiate into macrophages after they exit the blood vessels and come into contact with the extracellular matrix. Macrophages are able to phagocytize bacteria and provide a second line of defence. Macrophages also secrete extracellular enzymes to degrade necrotic tissue and apoptotic cells (including neutrophils), thus paving the way to resolving inflammation. These enzymes belong to a family of substances called matrix metalloproteinases (MMPs). There are approximately 20 different types of MMPs secreted by many different cells, including neutrophils, macrophages, epithelial cells and fibroblasts under the influence of inflammatory cytokines such as tumour necrosis factor alpha (TNFα) and the interleukins (IL-1 and IL-6). MMPs require calcium for functional shape and zinc for activation. MMPs act on all components of the extracellular matrix and are responsible for removal of devitalized tissue, repair of lost or damaged tissue and remodeling. MMPs are balanced by tissue inhibitors of metalloproteinases (TIMPs), which are released locally by cells and bind reversibly to the MMPs to deactivate them. Uncontrolled activity of MMPs may result in degradation of newly formed tissue or destruction of growth factors. An imbalance in protease activity can result in a prolonged inflammatory phase and a delay in wound healing.

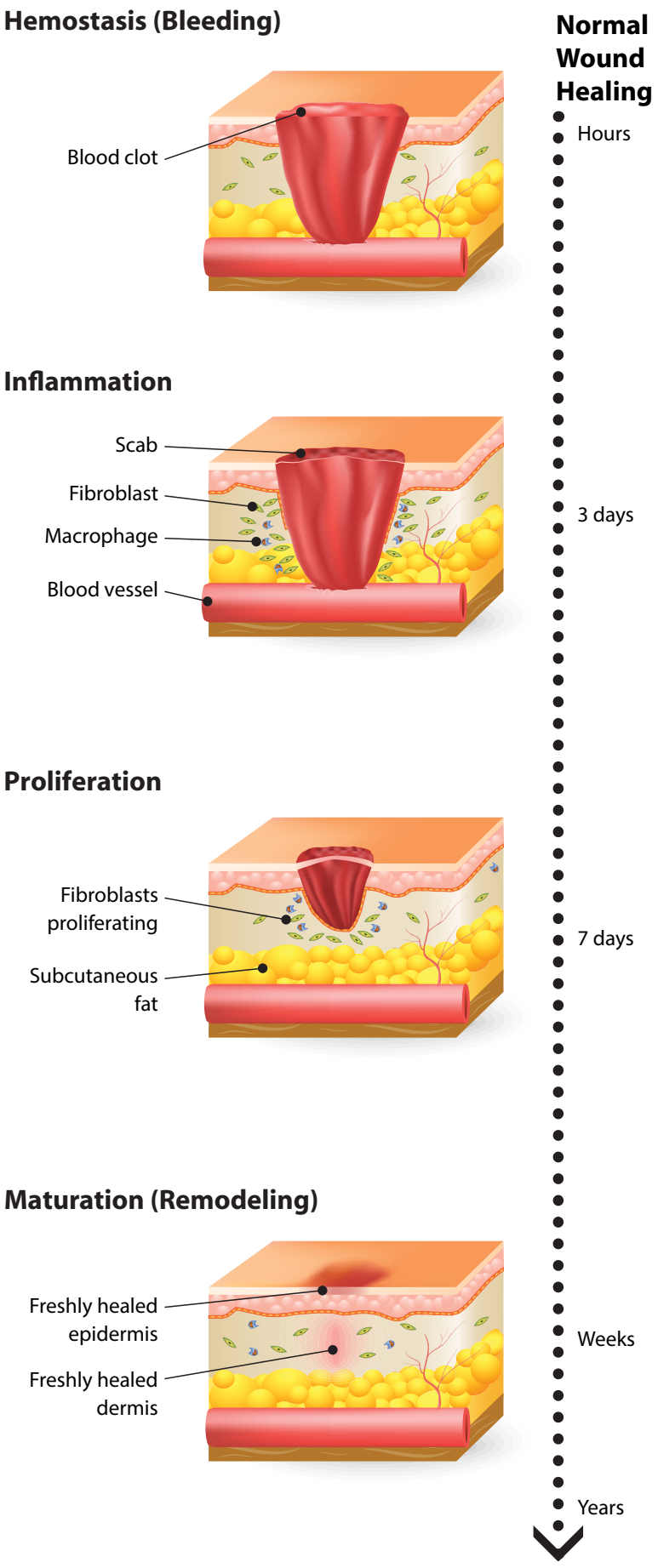
Macrophages secrete a variety of cytokines and growth factors such as fibroblast growth factor (FGF), epidermal growth factor (EGF) and transforming growth factor beta that can stimulate keratinocytes, fibroblasts and angiogenesis. As such, macrophages promote the transition to the proliferative phase of healing.[19]

The body's inflammatory response to trauma can be confused with infection. Inflammation is a normal response to trauma and the inflammation subsides as the trauma is resolved. Chronic inflammation is often the result of repetitive trauma, hypoxia, foreign bodies and persistent bacteria, with the presence of persistent bacteria being the most common cause of chronic inflammation that inteferes with wound healing.

3. Proliferation Phase (Granulation and Contraction)

The proliferation phase starts approximately four days after wounding and usually lasts until day 21 in acute wounds, depending on the size of the wound. It is characterized by angiogenesis, collagen deposition, granulation tissue formation, wound contraction and epithelialization. Clinically, proliferation is observed by the presence of pebbled red tissue, or collagen, in the wound base and involves replacement of dermal tissues (sometimes subdermal tissues in deeper wounds) as well as contraction of the wound. In the wound healing/house repair analogy, once the site has been cleared of debris, under the direction of the contractor, the framers move in to rebuild the framework of the house. Subcontractors can now install new

Figure 2. Phases of Normal Wound Healing



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plumbing and wiring on the framework and siders and roofers can finish the exterior of the house.

The "framer" cells are the fibroblasts, which secrete the collagen framework on which further dermal regeneration occurs. Specialized fibroblasts are responsible for wound contraction. Angiogenesis, the process of development of new blood vessels, occurs via pericytes, the "plumber" cells that regenerate the outer layers of capillaries and endothelial cells that produce the lining. The "roofer" and "sider" cells are the keratinocytes. They are responsible for epithelialization. In the final stage of epithelialization, contracture occurs as the keratinocytes differentiate to form the protective outer layer, or stratum corneum. Just as with building a new house, a sound infrastructure must be in place before the finishing components can be added, and the environment must be favorable for the finishing touches to be completed. The wound bed must fill in from the bottom up with collagen and must be maintained in an optimal environment (appropriate moisture balance) before the epithelial cells will begin to proliferate and migrate across the wound's surface to close the wound. Epithelial cells migrate based on contact inhibition, meaning they spread in only one layer and only where they are in contact with each other and the collagen framework of the granulating wound bed.

In a healing wound, growth factors cause cells to divide to produce new cells and cytokines cause these cells to migrate to where they are needed. A balance between the MMPs and TIMPs results in a net production of new tissue. In contrast, in chronic wounds that are stalled with suppressed cell division and migration, high levels of inflammatory cytokines and MMPs and low levels of TIMPs and growth factors inhibit new cell development. In this environment cells are often senescent and unresponsive to the growth factors. This chronic inflammatory state may be caused by increased bacterial burden, presence of devitalized tissue, chronic ischemia or repetitive trauma, which must be addressed in order for the wound to progress to healing.

4. Remodeling Phase (Maturation)

Once the basic structure of the house is completed interior finishing may begin. Similarly, in wound repair, the healing process involves the remodeling and realignment of collagen. Collagen type III is initially produced by the fibroblasts. This is later replaced by type I collagen. With time the fibres cross-link and align along tension lines to increase the tensile strength of the wound. A subgroup of fibroblasts called myofibroblasts also assists in wound shrinkage.[19] Tensile strength will not be more than 70 – 80% of what it was before the injury occurred.[20] In addition, cell and capillary density decreases following the presence of a wound. In the acute epithelialization phase, thin layers of scar tissue form and thicken over time. Initially scar tissue is deep pink in colour. This changes to bright pink, regardless of normal skin pigmentation. In the chronic epithelialization phase, scar tissue may be hypertrophic, keloid or hyperkeratotic. In the absence of epithelialization, weak scar tissue may be friable, break or wash out. The main cells involved in remodeling are the fibroblasts. The process of remodeling can take up to two years after wounding. This is why closed wounds can break down so dramatically and quickly if attention is not paid to the initial causative factors.

Normal wound healing is depicted in Figure 2. The process flows through the above stages with overlap between.

Defining the Wound Repair Process

Not all wounds heal in a timely fashion and clinicians need to determine why.

- Acute wounds heal in a normal, orderly sequence of repair as described above. This usually occurs because the cause of the wound has been removed and an optimum environment for healing has been created. Time to heal depends on the dimensions of the wound.
- Chronic wounds are wounds that have failed to progress through a normal, orderly and timely sequence of repair due to unresolved factors that interfere with healing. These wounds may eventually pass through the repair process without restoring sustained anatomical and functional results. This usually occurs when the cause(s) or co-factors of the wound have not been corrected and there is not an optimum environment for healing.

Summary

For health-care professionals, knowledge of the anatomy and physiology of skin and the healing process is essential to prevent, assess, treat and manage acute and chronic wounds effectively.

Resources and References

Resources and References

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