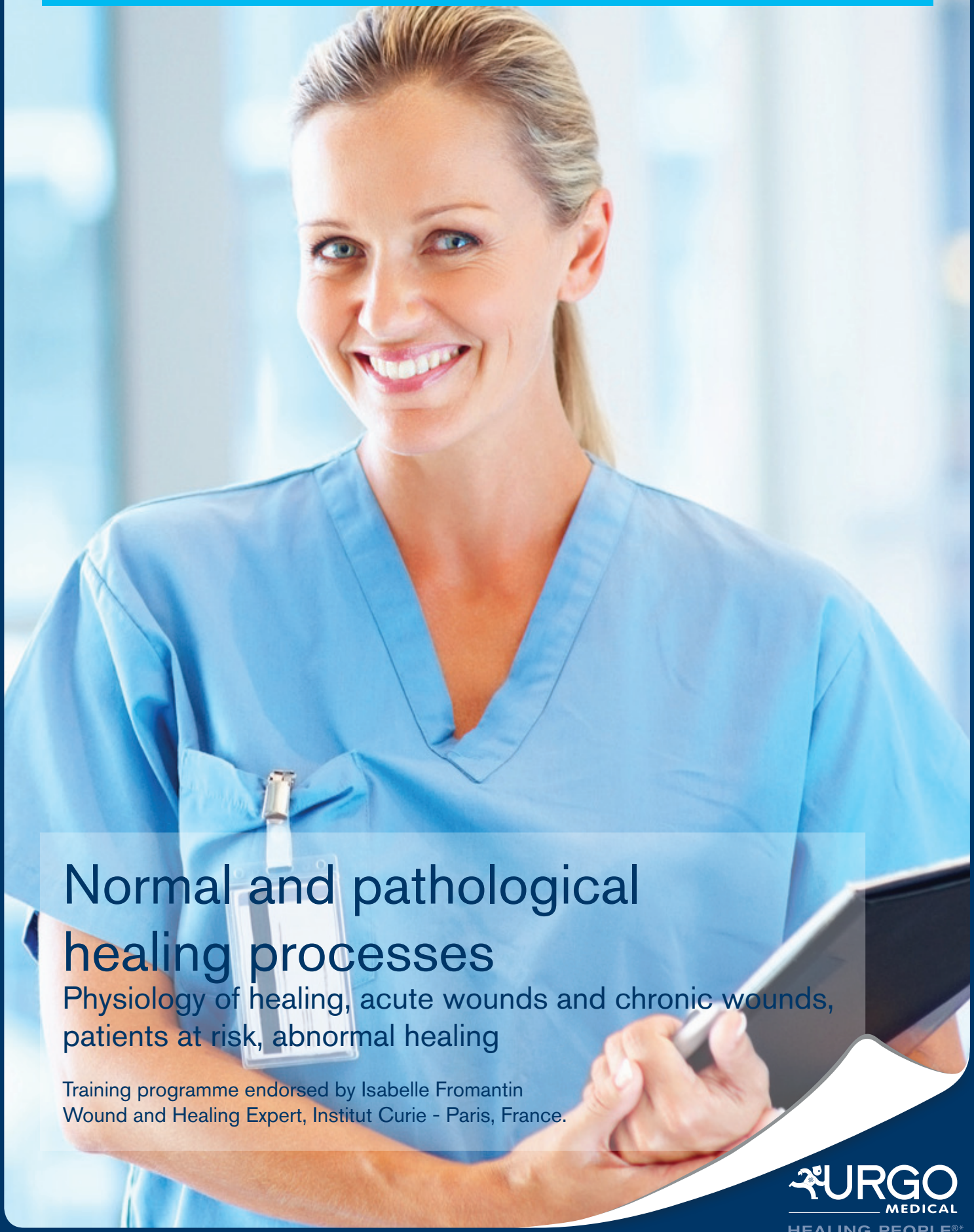
Training module



Normal and pathological healing processes

Physiology of healing, acute wounds and chronic wounds, patients at risk, abnormal healing

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Normal and pathological healing processes

Following a wound, a succession of complex events combines to repair damaged tissue. Cellular phenomena play a role, orchestrated by mediators that act as messengers between the different factors involved in the healing process. The tissue and skin repair process is triggered immediately and continues for several weeks. A variety of situations can compromise the speed and quality of the healing process.

1 The skin

The skin accounts for 15% of our body weight and its thickness varies from 1 to 8 mm. The skin on the soles of our feet is 10 times thicker and the skin on our eyelids is the thinnest. It is made up of three layers:

A

The epidermis has a barrier function (protection, waterproofing). On average, it is 1/2 mm thick, and up to 5 mm thick on the soles of the feet. It does not contain any blood vessels and does not require treatment in the event of very superficial scratches. Keratinocytes are the main cells present in the epidermis and skin appendages; these make keratin, which gives the skin its protective properties. The deepest layer of the epidermis is the **basal layer** where the cells ensure constant regeneration of the epidermis: a basal cell produces daughter cells, which rise up through the epidermis, flattening and then dying at its surface: the full cycle takes 21 days. Melanocytes, which give our skin its colour, are contained in the basal layer. The intermediate layer (**germinal layer**) is the thickest, and is composed of daughter cells. The upper layer (**horny layer or stratum corneum**) is covered by a hydrolipid film produced by sweat and sebaceous gland secretions. This film has an acidic pH (4 to 6.81) and maintains the balance of the skin's normal flora, protecting it against the multiplication of pathogenic microorganisms.

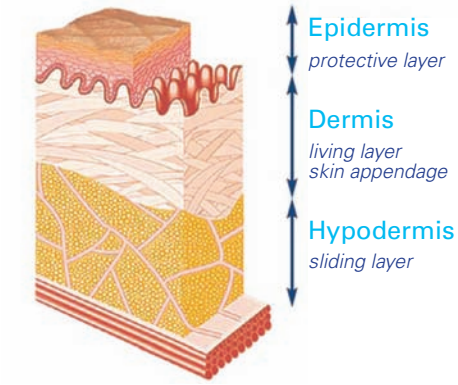
B

The dermis is around 2 mm thick and is composed of cells within a network of collagen and elastin fibres: the **extracellular matrix** (ECM). The main cells are star-shaped **fibroblasts**, which synthesise the fibres of the ECM: collagen (solidity), elastin (elasticity), proteoglycans (laminin, fibronectin). Macrophages are also present in the dermis, along with nerve receptors, blood vessels and sweat and sebaceous glands.

C

The hypodermis or subcutaneous tissue is a cellular-fatty layer forming the transition with the underlying tissues and enabling the skin to slide over the deep structures. It is in the hypodermis that fat stores are formed, the distribution of which varies depending on gender.

The 3 layers of the skin
The epidermis and the dermis are clearly separated by the epidermal basal layer, solidly anchored in dermal papillae.



2 | The normal healing process

The healing mechanism varies depending on the extent of damage to the skin's different layers. A purely epidermal or superficial dermal and epidermal wound will heal without any residual effects, whereas a wound involving the deep dermis or the hypodermis will leave a scar.

A | Three phases that overlap in time[1]

The inflammatory phase starts immediately: a clot formed of blood platelets and fibrin stops the bleeding. Attracted by mediators secreted by the platelets, leukocytes and macrophages flood into the region to get rid of bacteria and devitalised tissue (desloughing).

• **The granulation phase** begins a few hours to a few days after formation of the wound. It is initially marked by a proliferation of cells whose role is to reconstruct the tissue: endothelial cells form new blood vessels and fibroblasts synthesise the essential components of the new extracellular matrix (ECM). Fibroblasts proliferate until the loss of substance is filled by granulation tissue; they acquire the characteristics of muscle cells (myofibroblasts) and allow the wound to contract, reducing its surface area and speeding up its closure. Re-epithelialisation is due to colonisation of the granulation tissue by keratinocytes from the wound edges, hair follicles and sweat glands.

• **Remodelling** begins from the moment the granulation tissue forms and continues until the definitive scar is obtained after a few months. The ECM is gradually reorganised and enriched with new components to increase its density and resistance.

Healing phases	Key cells	Start	Duration
Haemostasis Inflammation	Platelets Neutrophils then macrophages +++	Immediate A few minutes	A few hours 2/3 days
Granulation	Fibroblasts +++ Keratinocytes	A few hours to a few days	1 to 3 weeks
Remodelling	Macrophages Fibroblasts	Around 1 week (reorganisation of ECM components)	A few months to a few years

[1] Some authors break it down into 5 because they do not include haemostasis in the inflammatory phase or re-epithelialisation in the granulation phase.

B | Cytokines, enzymes and growth factors

During all the healing phases, these substances enable the cells and the extracellular matrix to communicate, in order to organise the different steps in the process. Cytokines are synthesised by immune cells and act remotely to regulate the activity of other cells.
The different growth factors stimulate proliferation of fibroblasts, their differentiation and the secretion of ECM components. Within this complex sequence of events enabling the healing process to progress, degradation of the ECM by proteinases during the inflammatory phase is necessary for cell migration phenomena. In the course of normal healing, this degradation is limited and primarily occurs during the desloughing phase. If certain proteinases are produced in excessive amounts, the inflammatory phase is abnormally prolonged and healing can no longer progress. An excessively high quantity of proteinases is systematically found, therefore, in chronic wounds such as pressure sores, leg ulcers and malum perforans pedis (perforating diabetic foot ulcers).

3 | Slow healing

A number of local or systemic factors can delay the healing process by abnormally prolonging the inflammatory phase.

A | Local factors

The natural desloughing that occurs at the start of the process is essential if the various phases are to progress normally. The presence of tissue debris in the wound, the development of an infection and cutaneous hypoxia prolong inflammation, as do continuous or repeated traumas to the wound. Chronic wounds, defined by a healing time of more than 4 or 6 weeks as a result of one or more healing delay factors, are the site of excess metalloproteinases, in contrast with acute wounds, which heal more quickly.

Bacteria and wounds

A wound is systematically colonised by bacteria (normal flora), but that does not automatically mean that it is the site of an infection, since this depends on the microorganisms present, their number and the quality of the host's immune defences. The normal flora creates a barrier against pathogenic microorganisms.
Local infection is accompanied by several inflammatory signs (pus, foul odour, pain, redness, fragile granulation tissue that bleeds easily, deepening of the wound, development of a second wound). If regional signs are present (swollen lymph nodes, lymphangitis, erysipelas) or if the patient develops a fever, systemic antibiotic treatment is necessary.

B | Systemic factors

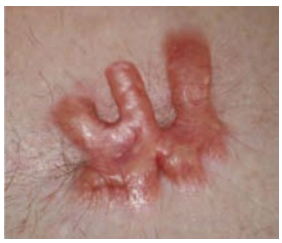
Certain chronic conditions slow down healing, either because they cause tissue hypoxia (arterial disease, diabetes, smoking) or because they disrupt cell responses (immune deficiencies, under-nutrition). Drug treatments can also cause delayed healing, for example corticosteroids.
Age is another source of slow healing because elderly subjects have an accumulation of risk factors: chronic conditions causing tissue hypoxia, thin, fragile skin, reduced mobility, nutritional deficiencies.

4 | Abnormal scars

Sometimes, even after a small wound (acne, piercing +++), an accumulation of ECM can cause excessive development of scarring. This is unpredictable but always occurs in the upper part of the body (chest, head and neck especially). As with all scars, these abnormal scars may be accompanied by pruritus or hypersensitivity.

A | Hypertrophic scars

These resemble a normal scar but are bulkier and more raised; their surface is smooth and they may affect only a portion of the whole scar. They tend to reduce, but it may take years.



B | Keloid scars

These are nodular, often painful and extend beyond the wound edges. Black skins are more prone to them. They never disappear spontaneously and are more likely to worsen over time.

5 | Improving the appearance of a scar

The remodelling phase continues for months after wound closure, restoring the skin's original appearance. A "fresh" scar must be protected from UV light to prevent hyperpigmentation: massages will prevent it from adhering to the dermis and developing a hard appearance. The use of moisturising cream is also recommended.

Training module

The main points to be remembered

- Fibroblasts are key cells.
- Proteinases are necessary for wound desloughing; but they can be present in excessive quantities in chronic wounds.
- A chronic wound is defined as a healing time of more than 4 or 6 weeks as a result of one or more healing delay factors (HAS – French Health Authority).
- Following wound closure, local treatments are recommended to improve the appearance of the scar.

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