TOR WO CHIU

# Stone's Plastic Surgery Facts

## A REVISION GUIDE

FOURTH EDITION

CRC Press
Taylor & Francis Group

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## Fourth Edition

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## Fourth Edition

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# Preface to the fourth edition

I remember buying the first edition of *Plastic Surgery: Facts* by Christopher Stone. I was not alone in appreciating the easy-to-read format, and the fact that it was born out of the author's revision notes made it all the more useful for those of us studying for our own exit examinations in plastic surgery.

I had the privilege of taking over the project for the previous (third) edition. The production of each new edition has added a large amount of new information. I focused on arranging the material for clarity and readability, and also to follow the syllabus of the Intercollegiate Surgical Curriculum Programme as closely as possible – the chapter layout is based on the Key Topics. There is also the excellent e-LPRAS resource that I have had the privilege of being able to contribute to.

Obviously, discussion of everything on the plastic surgery syllabus is not possible in a book of this size, nor is this intended to be the scope of this book. Each revision takes a great deal of time and effort; however, I was greatly encouraged to continue updating this book by the feedback from plastic surgery trainees. I was gratified to hear their comments and their appreciation of the philosophy of the book – it is very dense with information and deep insights. It is most useful after some prior reading of the subject.

The book has been thoroughly updated to include new materials including the surgical management of lymphoedema, the eighth edition of the 2018 Staging for Melanoma, updates in melanoma management such as PD1 protein inhibitors and inclusion of newer flaps such as the SCIP and MSAP. I have expanded the scope of the book somewhat to cover materials relevant to the US board exam. The article summaries have been a favourite feature of the book and have been retained and updated. Every reference has been rechecked and reviewed. I hope that new readers find this book useful.

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# Foreword

Taking the board exams marks the finale of a long training journey. During the preparation, it will probably be the last time you dive in deep to the whole broad spectrum of plastic surgery. It is during this time your general concept and understanding of plastic surgery is organised and stored as part of your knowledge. After this period of in-depth studying, you will be most likely to focus on a single or a couple of subspecialties in plastic surgery. At this time, your knowledge of that subspecialty field will continuously grow and expand, whilst the rest of the general knowledge stays dormant. My current work focuses on reconstruction of trunk and lower extremity, and the experience accumulated from this work allows me to evolve and provide new ideas and approaches. However, when a patient walks through the door, it is your job to notice the clues other than the subspecialties you focus on. This is when your fundamental knowledge of plastic surgery kicks in to observe the patient as a whole and not to miss obvious or hidden clues. That is why this opportunity to build your fundamentals and organise your thoughts and knowledge on plastic surgery is important as this will be the foundation of your future practice.

Dr Tor Chiu practices a wide spectrum of plastic surgery in one of the most prestigious training facilities in Hong Kong. His experience from the United Kingdom and Hong Kong allows him to have a wide exposure to plastic surgery, and lets him adapt to the new trends in this field. By training residents, he understands what is more essential in today's practice and how the fundamentals of plastic surgery evolve. He has added these new trends in this book, which gives you the opportunity to study and organise new topics as well as current knowledge in plastic surgery.

This book will help you develop and organise your knowledge in plastic surgery. It will guide you in your board exams; most of all, it will help you build your fundamentals in plastic surgery, which you can take along with you in your journey as a clinician.

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# 1

# Wound care



## A. WOUNDS AND WOUND HEALING

### I. WOUND HEALING AND TISSUE TRANSPLANTATION

#### WOUND HEALING

Wound repair proceeds through several stages that overlap somewhat:

- Inflammation (haemostasis, then increased vascular permeability and cell infiltration)
- Proliferation (re-epithelialization, fibroplasia)
- Remodelling (maturation)

#### INFLAMMATORY PHASE (DAYS 0–6)

**Haemostasis** – this phase is immediate, short-lived (lasting minutes) and characterised by **vasoconstriction** and **coagulation**. Haemostatic cascades lead to the formation of a thrombin–platelet plug (clot) that is adherent to type II collagen exposed by endothelial disruption. This clot has several functions:

- The **fibrin** acts as a scaffold for incoming cells and concentrates cytokines and growth factors such as platelet-derived growth factor (PDGF), transforming growth factors (TGF), α and β at the site.
  - It traps more platelets to perpetuate the cycle.
  - Fibrin is an essential component of wound healing.
- It releases chemotactic factors such as interleukin 2 (IL-2), tumour necrosis factor (TNF)-α, TGF-β.

**Inflammation** – this phase (lasting 3–5 days) is defined by the **vasodilation** (due to inflammatory mediators such as **histamine,** kinins, complement), **increased vascular permeability** and **cell infiltration. Cells** clear debris and initiate the proliferative phase; close regulation is needed to avoid overactivity (SIRS) or underactivity (chronic wounds – wounds that do not heal in an orderly set of stages in a timely manner, usually within 3 months; these are characterised by persistently elevated levels of matrix metalloproteinases, MMPs).

- **Neutrophils**
  - Within 12 hours of wounding, cells appear in the wound, attracted by chemotaxins including fibrin degradation products (FDPs), complement proteins, IL-1s, TGF-β, TNF-α, platelet factor 4 (PF4) and PDGF. Translocation of marginating neutrophils (at 24–48 hours) through capillary endothelium and basement membrane is facilitated by collagenase.
  - Neutrophils produce inflammatory mediators and cytokines, and remove debris; the response and population decline after a few days, whereupon the function of debris removal is taken over by macrophages. Neutrophils are not essential for wound healing.
- **Macrophage**s arrive after 48–96 hours and begin to phagocytose debris and release cytokines and growth factors, thus coordinating and promoting healing. They are **vital to wound healing**.
- **Fibroblasts** become the dominant cell type 1 week after injury, with a key role in the production of collagen. TGF-β promotes migration and proliferation of dermal fibroblasts.
- **T-lymphocytes** migrate into wounds after the macrophages (at 5–7 days) and persist for up to 1 week – a reduced response may lead to inferior wound healing. Their primary role seems to be to mediate in fibroblast recruitment and activation.
- **Keratinocytes** – differentiated cells are converted to immature cells that migrate over the wound surface.

#### PROLIFERATIVE PHASE (4 DAYS TO 3 WEEKS)

**Re-epithelialisation** begins within hours of wounding with migration of marginal keratinocytes over the matrix due to **loss of contact inhibition**, staying beneath the eschar. There is a phenotypic conversion of differentiated

keratinocytes into non-polarised cells expressing basal cytokeratins similar to cultured cells; increased mobility comes from dissolution of anchoring junctions and reorganisation of the cortical actin cytoskeleton to form lamellipodia. Cells stop migrating when they form a contiguous layer (contact inhibition). As the basement membrane is reconstituted, the cells are induced to adopt their previous morphology and form anchoring junctions with fibronectin. A **moist environment** increases the rate of (re)-epithelialisation.

- **Epidermal growth factor** (EGF) – mRNA levels increase rapidly after wounding to promote re-epithelialisation. Abnormalities of EGF expression are thought to impair wound healing; glucocorticoids suppress EGF expression in cutaneous wounds but have less effect on EGF receptor levels.
- **Growth-related oncogene α** (GRO α), originally called 'melanocyte growth-stimulating activity' due to its mitogenic activity on melanocytes, is also a chemoattractant for neutrophils that is more potent than IL-8. Both GRO α and IL-8 stimulate keratinocyte proliferation in vitro; both are maximally expressed on day 1 after injury and subside after wound closure.
- **Insulin-like growth factor-1 (IGF-1)** and IGF-binding protein-1 have been demonstrated to act synergistically to accelerate the healing of adult skin wounds; exogenous IGF-1 increases myofibroblast expression in rat wound models (Achar RA, *Acta Cir Bras*, 2014). IGF-1 levels seem to be predictive of the response of diabetic foot ulcers in patients treated with HBO (Aydin F, *J Diabetes Res*, 2013).

**Fibroplasia** – there is an influx of fibroblasts over the fibronectin scaffold; they are activated by PDGF and TGF-β. These cells synthesise type **III collagen**, which with ongoing neovascularisation forms **granulation tissue**. Wound tensile strength increases during the fibroblastic phase.

- **Activin** is strongly expressed in wound skin. Overexpression in transgenic mice improves wound healing and enhances scar formation; activin A has been implicated in stimulating formation of granulation tissue whilst activin B mRNA has been localised to hyperproliferative epithelium at the wound edge.
- Secretion of glycosaminoglycans (GAGs) such as hyaluronic acid (HA), chondroitin sulphate and dermatan sulphate, which become hydrated to form an amorphous ground substance within which fibrillar collagen is deposited.
- Zinc, vitamins A (retinoids) and C are also required for normal collagen synthesis.

**Angiogenesis** – low oxygen tension in the wound leads to secretion of vascular endothelial growth factor (VEGF); MMPs degrade the extracellular matrix (ECM) to facilitate the passage of newly formed vessels.

## REMODELLING PHASE (3 WEEKS TO 18 MONTHS)

The ECM appears to modulate fibroblast activity through changes in composition during healing. When fibronectin initially predominates, fibroblasts actively synthesise HA and collagen, but in a maturing wound, when collagen becomes abundant, fibroblast proliferation and collagen production then cease – irrespective of any stimulation by TGF-β. At this point, the wound becomes a relatively acellular scar. This phase ends with the formation of the final scar.

- **Collagen remodelling.** Residual fibroblasts mature into myofibroblasts and form cell–matrix and cell–cell contacts that contract the wound (scar contracture). Type III collagen is gradually replaced by type I collagen by the activity of MMPs released by macrophages, keratinocytes and fibroblasts, slowly returning to the normal type I/III ratio of 3:1.
  - Collagen is initially disorganised but then becomes lamellar (and aligned along lines of stress).
- **Peak wound tensile strength** is achieved at ~60 days and is a maximum of ~80% of unwounded skin strength.
- **Vascular maturation.** The abundant capillaries regress.

## CYTOKINES AND GROWTH FACTORS

### Cytokines

Cyto, from Greek *kyttaro*, which means 'cell', and kines, from Greek *kinisi*, which means 'movement'.

Cytokines are small molecules (peptide, protein or glycopeptide) that are secreted predominantly by immune cells (mostly lymphocytes and macrophages) and affect the behaviour of other cells. They are important in cell-to-cell signalling and mediate in protective and reparative processes and also regulate cell growth and maturation. Interferon α (IFN-α) was the first cytokine to be discovered in 1957.

Cytokines tend to be pleiotropic (affects many different cells) and redundant (many do the same thing); they can be synergistic or antagonistic. One can try to classify them broadly according to their function:

- Non-specific (innate) immunity and inflammation – mostly made by macrophages, mast cells and endothelium.
  - Chemokines (chemotaxis)
  - TNF and IL-1
  - IFN-γ and Il-12 (chronic inflammation)
- Specific (acquired/adaptive) immunity – most are made by T-helper (TH) cells.
  - IFN- γ and IL-5 (cell activation)
  - IL-2 and IL-4 (lymphocyte proliferation)
- Haematopoiesis – made by endothelium, macrophages, etc.
  - Colony stimulating factors causing haematopoietic cell proliferation

### Tumour necrosis factor-α

TNF-α is released by macrophages/monocytes when stimulated by pathogens, tumour cells and toxins. It appears at wound sites 12 hours after wounding and peaks at 72 hours.

- Mediates in chemotaxis of inflammatory cells.
- Up-regulation of cellular adhesion molecules on endothelium.
- Other effects on collagen synthesis; may impair wound healing if it persists at high levels beyond natural peak, and excess TNF-α is associated with multisystem organ failure.

### Interleukin-1

Interleukins (ILs) are cytokines, classically made by leucocytes **that act on other leucocytes**. Interleukin-1 (IL-1) is produced by macrophages/monocytes as well as keratinocytes at wound sites. It is detectable at wound sites after 24 hours, peaking around day 2 with levels rapidly declining thereafter.

- Neutrophil activation and chemotaxis
- Increased collagen synthesis and keratinocyte maturation
- Similar action to TNF-α; also activates T helper cells
- High levels in chronic non-healing wounds; also called endogenous pyrogen and causes fever

### Interleukin-2

Interleukin-2 is produced by T lymphocytes.

- Sustains the post-injury inflammatory response via T-cell activation
- Promotes fibroblast infiltration at wound sites

### Interleukin-6

Interleukin-6 is released by macrophages/monocytes, polymorphs and fibroblasts.

- Promotes stem cell growth and B- and T-cell activation, and mediates in hepatic acute phase protein synthesis
- Stimulates fibroblast proliferation
    - High IL-6 increases scarring and high systemic levels have been described as a marker of **wound severity in major burns** and a poor prognostic indicator (Modi S, *Indian J Med Microbiol*, 2014).
    - Low IL-6 in elderly patients with impaired wound healing and at scar-less foetal wound sites.

### Interleukin-8

Interleukin-8 is released by macrophages and fibroblasts at wound sites.

- Neutrophil chemotaxis, adhesion and activation
- Promotes keratinocyte maturation and migration
- High levels in patients with psoriasis and low levels at foetal wound sites

### Interferon γ

Interferons **interfere** with viral replication. Interferons α and β are type 1 and interferon γ is type 2. Interferon γ is produced by T-helper cells primarily, but also by Tc and macrophages. It has many functions in both specific and non-specific immunity.

- Macrophage and polymorph activation
- Mediates in wound remodelling; reduces wound contraction
- Possible role for decreasing scar hypertrophy but may decrease wound strength

### Interleukin-4

Interleukin-4 is produced by T-cells, mast cells and B-lymphocytes.

- Promotes B-cell proliferation and IgE-mediated immunity and inhibits the release of pro-inflammatory cytokines by macrophages.
- Promotes fibroblast proliferation and collagen synthesis at wound sites.
- High levels are found in patients with scleroderma.

### Interleukin-10

Interleukin-10 is produced by activated macrophages and T-cells; it has mostly **inhibitory** actions.

- Inhibits production of pro-inflammatory cytokines at acute wound sites
- Persistently high levels at chronic wound sites, e.g. venous ulcers; contributes to impaired wound healing

### Growth factors

Growth factors are polypeptides whose primary role is in regulation of cell growth and maturation.

#### *Platelet-derived growth factor*

PDGF is released from platelet α granules and by macrophages.

- Recruitment and activation of immune cells and fibroblasts in the early post-injury phase.
- Later stimulates the production of collagen and GAGs; reduced levels are found in non-healing wounds.
- Three isomers of PDGF (2 polypeptide chains 'A' and 'B'):
    - AA – elevated at acute wound sites
    - BB – most useful clinically, used for chronic and diabetic ulcers (**Regranex®,** see below)
    - AB

#### *Transforming growth factor β*

TGF-β is released by macrophages, platelets and fibroblasts; it has mostly **inhibitory** actions.

- Blocks macrophage activation; inhibits the action of other cytokines on neutrophils and endothelium.

- Fibroblast maturation, collagen and proteoglycan synthesis.
- Inhibition of proteases.
- There are three isomers – TGF-β1, TGF-β2 and TGF-β3.
  - TGF-β1 and TGF-β2 are associated with hypertrophic and keloid scarring, and neutralising antibodies decrease scarring at rat wound sites (Shah M, *J Cell Sci*, 1994).
  - Low TGF-β levels at foetal wound sites.
  - TGF-β3 shown to decrease scarring.
  - Ratio of TGF-β1 and β2 – TGF-β3 determines nature of scar.

### *Fibroblast growth factor*

Fibroblast growth factor (FGF) is released from fibroblasts and endothelial cells.

- Regulates angiogenesis and keratinocyte migration at wound sites.
- Two main forms – acidic FGF (or FGF-1) and basic FGF (or FGF-2) that binds to the same receptors as aFGF but is 10 times more potent.
- Application of exogenous bFGF to wound sites accelerates re-epithelialisation.
- Eight other isoforms – FGF-7 is keratinocyte growth factor (KGF) 1, which is low in diabetics and steroid immunosuppression. Recombinant KGF has been shown to improve wound re-epithelialisation.

### *Epidermal growth factor*

EGF is released from keratinocytes.

- EGF promotes epithelialisation.
- Promotes collagenase release from fibroblasts (for remodelling).
- Inhibits wound contraction at foetal wound sites.

### *Vascular endothelial growth factor*

VEGF is mainly released from keratinocytes; there is a minor contribution from macrophages and fibroblasts.

- Promotes angiogenesis at wound sites.
- Mediates in the formation of granulation tissue.

### *Insulin-like growth factor*

At wound sites, IGF is released by macrophages, neutrophils and fibroblasts; levels rise to a peak within 24 hours of wounding and persist for several weeks.

- Promotes fibroblast and keratinocyte proliferation, with possible role in angiogenesis.
- Two isoforms – IGF-1 and IGF-2.
- Low IGF levels are observed in diabetic and steroid-suppressed wounds.

## COLLAGEN

Collagen forms about one-third of the total protein in the human body. It is a triple helix formed from three α-helical chains; 25 different α-chains have been identified, each encoded by a separate gene. There are at least 16 different types of collagen. Their structural differences determine the ability of their helical and non-helical regions to associate, form fibrils and sheets or cross-link different collagen types; 90% of body collagen is type I. In normal skin, the ratio of types I/III = 3:1. See Table 1.1.

- Type I – most common and predominates in bone, tendon and skin
- Type II – hyaline cartilage, cornea
- Type III – immature scar, blood vessels, bowel, uterus
- Type IV – basement membrane
- Type V – foetal and placental tissue

The initial product is the pro-α-chain. Post-translational hydroxylation of proline and lysine residues (requires vitamin C and iron) is important for structural strength and stability by cross-linking the triple helix, as well as being necessary for its export from the cell.

- Procollagen – three polypeptide chains in a triple helix form tropocollagen. All types contain a repeating Gly-Pro-X sequence that allows folding.
- Tropocollagen units form collagen filaments.
- Filaments form fibrils, which form fibres with enormous tensile strength. The typical 'fibrous' collagens are I, II, III and V.

Early collagen is thin and randomly orientated parallel to the skin surface; collagen that is laid down during the later stages of wound healing is thicker and lies along stress lines, thus increasing wound strength.

- Initially, type III collagen production is high and then type I replaces type III until a ratio of 3–4:1 is achieved.

**Table 1.1** Common types of collagen

| Number | Distribution | Disorders |
|---|---|---|
| I | Bone, skin, tendon, ligaments, cornea | Deficient in osteogenesis imperfecta |
| II | Cartilage, vitreous humour of eye | Deficient in chondrodysplasia |
| III | Skin, blood vessels, intestines, uterus | Excessive: early wound, early Dupuytren's contracture, hypertrophic scar<br>Deficient: Ehlers–Danlos syndrome |
| IV | Basal laminae, lens | Deficient in vascular Ehlers-Danlos syndrome (EDS type IV - 13 types described in 2017) |
| V | Associated with type I | Found in active stage Dupuytren's contracture |

- Myofibroblasts cause wound contraction that reduces the wound size (not the same as a contracture that is excessive scar contraction across a mobile surface). There is gradual decrease in vascularity.

See 'Syndromes associated with altered healing'.

## FACTORS AFFECTING WOUND HEALING

Discussions generally divide factors into patient factors and wound factors.

### Wound factors

- **Hydration** increases the rate of epithelialisation, hence the rationale for occlusive dressings (see 'Moist wound healing'). The mechanisms proposed for this improved healing include thermal insulation, altering wound oxygen/carbon dioxide/pH, maintaining growth factors as well as acting as a physical barrier.
- **Infection** – the presence of $>10^5$ organisms (or lower concentrations of β-haemolytic streptococcus) **prolongs the inflammatory phase.** Endotoxins reduce tissue oxygenation and stimulate phagocytosis and the release of collagenases and radicals that may damage normal tissue. **Taking swabs of open wounds is generally pointless;** colonisation does not equate to infection and would not normally inhibit wound healing.
- **Foreign bodies** (or necrotic tissue) prolong the inflammatory phase, are obstacles to healing and are nidi for bacteria.
- **Ischaemia** – energy in the form of glucose and oxygen is required for proliferation (cell replication and protein synthesis) as well as fibroblast and neutrophil activity. Reduced oxygen tension causes inefficient keratinocyte migration. Fibroblasts, in particular, are oxygen-sensitive and an oxygen tension of >40 mmHg augments fibroblastic activity and is required for the hydroxylation of proline and lysine in the collagen α-chain. Oxygen also facilitates cell-mediated killing of pathogens in the wound. **Ischaemia and reduction of local oxygen tension may be a component of other processes**:
  - Oedema – reduces tissue perfusion and leads to capillary closure.
  - Protein extravasation forms a diffusion barrier.
  - Radiation – direct DNA damage, impaired inflammatory response, endarteritis obliterans.
  - Diabetes mellitus (DM).
  - Smoking.
- **Tissue expansion** – increased rate and strength of healing.
- **Low serum protein** – prolonged inflammatory phase and impaired fibroplasia.
- **Increased ambient temperature (30°C)** – accelerates wound healing.

### Patient factors

- **Age** – there is a reduction in the cellular multiplication rate with age. Tensile strength and wound closure rates also decrease with age – the various stages of wound healing are all protracted.
- **Nutrition** (see 'Nutrition') – malnutrition is associated with impairment of fibroblast function and reduced wound tensile strength.
  - Protein malnutrition especially deficiencies of arginine and methionine compromises wound healing.
  - Vitamin C – essential for hydroxylation of collagen.
  - Vitamin E – antioxidant actions neutralise lipid peroxidation (and thus cell damage) caused by ionising radiation, for example.
  - Minerals – many are cofactors in collagen production, e.g. zinc influences re-epithelialisation and collagen deposition.
- **Systemic illness** – such as anaemia or pulmonary disease may impair oxygen delivery and collagen synthesis.
- **Smoking** (multifactorial) – the nicotine in one single cigarette causes vasoconstriction that lasts 90 minutes, cyanide impairs oxidative enzymes whilst carbon monoxide (CO) impairs the oxygen-carrying capacity of haemoglobin. Stopping smoking will ameliorate the effects of
  - CO after >12 hours.
  - Free radicals (1 week).
  - Nicotine effects (10 days).
  - CDC recommends quitting 4 weeks before surgery, but there is no consensus. The highest risk is in surgeries where tissues may have reduced vascularity, e.g. composite grafts/replants, extensive tissue undermining, e.g. facelifts.
  - There is no evidence that nicotine replacement therapy affects wound healing, but it is probably prudent to avoid in high-risk surgery.
- **Diabetes mellitus** (see 'Diabetic ulcers') – multiple factors are at work in addition to the microvascular disease that reduces oxygenation. These patients are prone to infections that should be treated aggressively. However, with adequate glycaemic control, most surgical wounds should heal satisfactorily.
  - Glycosylation of proteins may alter functions, e.g. glycosylated haemoglobin has a higher affinity for oxygen, which impairs oxygen delivery to the tissues.
  - Increased blood glucose impairs cellular function.
    - Sorbitol by-products are toxic.
  - Sensory neuropathy decreases protective reflexes and increases vulnerability to ischaemia.
  - Autonomic neuropathy leads to anhydrosis (dry skin) and arteriovenous shunting.
  - Reduced fibroblast numbers and immune dysfunction.
  - Vascular disease and ischaemia.
- **Drugs.**

  - **Steroids** – anti-inflammatory actions affect wound healing in many ways including **impaired macrophage and fibroblast** function, reduced angiogenesis and contracture. Vitamin A is usually said to reverse steroid effects and increases collagen synthesis.
  - **Non-steroidal anti-inflammatory drugs (NSAIDs)** – almost halve collagen synthesis in some studies, which is related to the reduction in prostaglandin production.
  - **Chemotherapy** – e.g. cyclophosphamide is anti-inflammatory whilst methotrexate potentiates infections.
- **Syndromes associated with altered healing**
  - **Ehlers–Danlos** – a group of patients with defects in collagen metabolism (e.g. lysyl oxidase) commonly affecting **type III collagen**, though some have deficiencies of types I and V. The skin is really stretchable and recoils without wrinkles. Patients exhibit joint hyper-extensibility with tissue fragility and **poor healing** with post-operative bleeding, wound infections (defective immune response) and wider atrophic scars. Non-essential surgery is not recommended.
  - **Cutis laxa** – variable modes of inheritance. There is an elastin defect causing the skin to be thin and stretchable (but does not recoil due to the lack of elastin), with easy bruising; joints are normal. **Essential surgery can be** performed, though there is an association with cardiorespiratory disease.
  - **Homocystinuria** – autosomal recessive (AR) inherited deficiency of cystathionine synthase that is needed to metabolise methionine. Accumulated homocysteine initiates the clotting cascade, and causes arterial sclerosis, thrombosis, poor perfusion and platelet malfunction. There is a high risk of developing cardiovascular disease.
  - **Osteogenesis imperfecta** – patients have a **defective collagen I gene**, and wounds typically heal with wide scars.
- **Dystrophic epidermolysis bullosa** is a hereditary disease of skin and mucosa that causes blistering after trivial trauma and heals by scarring. It is associated with mutations of **collagen VII**, which form anchoring fibril-specific proteins. Typically, there is cocooning of the digits in an atrophic scar – pseudosyndactyly and flexion contracture; the digits are generally quite mobile despite the deformity, but surgical release is generally not rewarding as recurrence is almost inevitable. Exsanguination during any surgery should be performed by elevation and not bandaging; tourniquets need extra padding. Grafts can be taken with hand knives; both donor and recipients heal fairly well, but haemolytic streptococcal colonisation is not uncommon. Patients generally die young (third decade) from squamous cell carcinoma (SCC).

## ADJUNCTS TO HEALING

There are a plethora of modalities and products put forward for enhancement of wound healing. The strength of evidence is variable but overall is fairly low.

- **Hyperbaric oxygen** therapy (HBOT) increase oxygen delivery to wounds but its use in wound healing in general is controversial. It may be useful in selected wounds, e.g. ischaemic (acute arterial insufficiency, crush injuries), radionecrosis, necrotising fasciitis (NF)/gas gangrene and diabetic ulcers. Medicare covers its use if there are 'no measurable signs of healing for at least 30 days of standard wound therapy'.
- **Negative pressure** – the exact mechanism is unclear but reportedly removes interstitial fluid and oedema to improve oxygenation, removes deleterious inflammatory mediators, reduces bacterial counts and speeds up formation of granulation tissue (see 'Negative pressure wound therapy').
- **Growth factors** – some are commercially available and used in some localities, e.g. PDGF, GM-CSF and KGF2. However, the evidence is generally not that convincing, and their use is regarded as mostly experimental. Recombinant PDGF B-chain (becaplermin) is marketed as Regranex®, the only agent shown to be efficacious in double-blind studies. It has FDA approval; however, there is a warning that there is an increased cancer mortality in patients who use three or more tubes. Recombinant human EGF is used in South Korea for wound healing; one product has been used to reduce radiation dermatitis (Kang HC, *Radiat Oncol*, 2014).
  - Apligraf® is a bioengineered product, initially marketed as a skin substitute. Although some wounds did heal, it became evident that the material was not actually incorporated – it acted as a wound stimulator – in chronic wounds, there would be outgrowth of previously dormant keratinocytes at the wound edges (see below). Activskin® is a similar product made in China (CRMI).
- **Electrostimulation (ES)** therapy – the premise is that there is an endogenous electric field in wounds and that cells are sensitive to and respond to an applied field. Multiple animal studies seem to have demonstrated some efficacy, but good clinical evidence is lacking; some attribute this to a paucity of uniform protocols/products (e.g. DC or pulsed current at low frequency or high voltage, pulsed EM field, etc.). There were weak recommendations from the pressure sore advisory panels (NPUAP, EPUAP and PPPIA) in 2014.
  - NICE 2015 does not recommend ES as an adjunctive treatment for diabetic foot problems unless as part of a clinical trial.
  - Cochrane reviews (Aziz Z, *Cochrane Database Syst Rev*, 2010, updated in 2015) demonstrated a lack of level 1 evidence.

- **Lasers** – low-level laser therapy (LLLT), aka 'biostimulation', is said to increase cellular activity especially of fibroblasts and keratinocytes. Light is administered at wavelengths of 680–890 nm, over several applications; it does not generate heat and is thus often referred to as 'cold' laser.
  - LLLT was introduced in the 1960s by Mester E. Devices have FDA approval (1994) for relief of minor muscle and joint pain and improvement of superficial circulation. The consensus seems to be that it is not more effective for temporary pain relief than heat therapy; most insurance companies do not cover its use.
  - There seems to be some evidence for a role in reducing post-irradiation oral mucositis (Kumar SP, *Indian J Palliat Care,* 2013).
- **Ultrasound** (low frequency, i.e. ~20 kHz, traditionally used to relieve muscular spasms). Cavitation (gas bubbles) and streaming (unidirectional steady mechanical force) seem to alter the characteristics of cell membranes.
  - Use in venous ulcers and pressure sores yields inconsistent results.
    - Systematic reviews in *BMJ Clinical Evidence* (2007) deem it to be of 'unknown effectiveness'.
    - NICE 2011 stated that there was promise but the low level evidence, and lack of comparisons, meant that its use in the NHS was not supported.
  - Most insurance companies will not cover its use.

See other chapters for healing of bone, tendon and nerves.

## WOUND MANAGEMENT

Management of wounds involves a comprehensive assessment of the patient as a whole, as well as the wound itself. This includes looking for conditions/factors that can affect healing, and also the nutritional status.

## NUTRITION

Whilst there has been much research on the subject, as yet, there is no simple, single reliable method of assessing nutritional status. Criteria that have been used for this include the following:

- **Clinical**, e.g. recent weight loss, signs of loss such as muscle wasting/loss of fat, oedema. Unplanned weight loss of more than 10% over 6 months is associated with a poor response to injury.
  - BMI < 18.5 implies nutritional impairment whilst BMI < 15 is associated with significant mortality.
  - Skin fold thickness of triceps, mid-arm circumference.
- **Biochemical markers** – transferrin, retinol binding protein but most commonly prealbumin. **Prealbumin** has a half-life of 2–3 days and is thus a better measure of protein nutrition than albumin (half-life 20 days, and may be reduced by sepsis/inflammation as well as malnutrition). Closure of surgical wounds is more successful if the albumin is >30).
- Nutrition Risk Index = (1.519 × albumin g/L) + 0.417 × (present weight/usual weight × 100). A score below 100 indicates malnutrition.
- Lymphocyte function and body nitrogen are primarily research tools.

NICE recommends nutritional support for patients who have 5 days or more of reduced intake, or those with poor absorption, high losses or increased requirements. Nutrition can be supported by various means:

- Oral supplements – over and above a normal hospital diet, is simple and relatively effective.
- Enteral feeding for those with inadequate oral intake, is cheaper and safer than parenteral feeding and numerous studies have shown benefit.
- Parenteral feeding (peripheral or central) is reserved for those with non-functioning gut, e.g. short bowel, high output fistula. Some trials show that preoperative TPN reduces complications but not mortality in malnourished patients; there is less support for the use of post-operative TPN and it may actually be harmful.

Whilst many **micronutrients** are important in healing, replacement is only indicated in deficiency states.

- **Vitamin A** is one of the exceptions to this rule. Administration reverses most of the steroids' effects on inflammation, except for infections and wound contraction. It may be considered in those on chronic steroid therapy.
- Vitamin E supplements do not have any beneficial effects on wound healing, and large doses may actually inhibit healing (decreased tensile strength).
- Taking large doses of vitamin C does not improve healing.
- The benefit of glutamine is most well studied particularly in burns; arginine seems to have mixed effects.

## SPECIFIC WOUND MANAGEMENT

The fundamentals of wound management are usually summarised with the acronym TIME (or DIME).

- Tissue management (or Debridement)
- Infection control
- Moisture balance
- Edge advancement

### Debridement

Debridement of necrotic, non-viable tissue, which also reduces bacterial load, bioburden (**and biofilm**) is an important part of wound management. The word comes from the French *debridement* (old French *desbrider*), meaning to take

away the bridle, and the procedure is usually attributed to Napoleonic war surgeons (Desault). The aim is to convert a chronic wound into an acute wound.

- Non-selective
  - **Mechanical**, which includes
    - Wet-to-dry dressings – characteristically painful
    - Scrubbing
    - Hydrotherapy
  - **Hydrogen peroxide** (usually 3%) – this is a source of reactive oxygen species that when applied to tissues bubbles due to the reaction with tissue catalase releasing water and oxygen. Staphylococci tend to be catalase-positive whilst Streptococci do not have catalase and are thus said to be more susceptible to peroxide. It is commonly used as a wound antiseptic, and whilst it shows broad in vitro activity, the few clinical studies generally show that it is relatively ineffective in reducing bacterial load, though it does appear not to delay wound healing. The AMA (Roderheaver GT, *Chronic Wound Care: A Clinical Source Book for Healthcare Professionals*, 2nd Edn, 1997) suggested that the effervescence may have some mechanical benefit in loosening debris and necrotic tissue.
  - **Antiseptics** such as chlorhexidine (works within 20 seconds but lasts only 6 hours), povidone iodine 10% (equivalent to 1% availability, needs 1 minute to work), alcohol, etc. have a wide spectrum of activity and low risk of resistance, but may damage healthy cells.
  - **Topical antimicrobials** include the usual antibiotics mupirocin, fucidic acid and neomycin, but some include silver, honey and cadexomer iodine (Iodosorb, Smith and Nephew). They do not harm healthy tissue, but antibiotics should only be used for 1–2 weeks due to concerns over sensitisation and resistance.
- Selective debridement
  - **Surgical** (some would put this in the non-selective category). This is the most common method and involves blades/curettes, etc.; some use more complicated systems such as the Versajet®.
  - **Enzymatic** – selectively digest dead tissue/slough. Iruxol Mono® is a collagenase, clostridiopeptidase A, but takes several days to work. Others such as Nexobrid® (bromelain, derived from pineapple stems) may work quicker (Rosenberg L, *Burns*, 2004) but is not widely available.
    - **Autolytic** – the combination of moist dressings, e.g. hydrocolloids and endogenous proteolytic enzymes, can lead to the liquefaction of necrotic tissue that then separates. It can be enhanced with hydrocolloids/hydrogels/occlusive films and products such as medical honey.
  - **Biological** – **maggots** of certain species, e.g. *Lucilia sericata*, can cause benign myiasis, i.e. the larvae only digest dead tissue, extracorporeally through chymotrypsin-like enzymes (note that some species cause malignant myiasis, damaging healthy tissue). There are reports of an antimicrobial action and promotion of healing. There may be pain after 2–3 days, supposedly due to alkaline secretions, whilst other secretions may cause irritation/excoriation of normal skin
    - Maggots have been used in military wounds for a long time. Crile demonstrated that soldiers with maggot-infested wounds actually did better. Following the increasing use of antibiotics, maggot therapy declined, but it has had a resurgence since the 1980s. In the United Kingdom, they can be prescribed and used in the community. They are useful in infected necrotic wounds including diabetic ulcers and pressure sores, particularly those unfit for surgery. One study showed healing of 90% of MRSA-infected wounds after one to two maggot applications over 4–6 days.
    - Maggots take 10–14 days to pupate, requiring a dry place; thus, it is important to keep them in the wound and to dispose of them quickly.

## Infection control

- **Contamination** – there are low numbers of non-replicating bacteria.
- **Colonisation** – bacteria are replicating but are not provoking an inflammatory response. It does not normally inhibit normal wound healing.
- **Infection** – there are a large number of bacteria that are invading wound tissue and are provoking an inflammatory reaction.

Taking wound swabs for bacterial culture is a very common practice but not that useful; swabbing open wounds is particularly pointless. Quantitative analysis of tissue biopsy is the gold standard; $>10^5$ is regarded as significant.

- **Biofilms** are polymeric glue-like structures with collections of bacteria within them. Their significance is that the bacteria are relatively protected from the immune system as well as simple wound care. They often require physical removal, e.g. debridement, as well as topical antiseptics/antimicrobials or systemic antibiotics; Prontosan® (betaine-polyhexanide) uses electrostatic disruption/surfactant action to disrupt a biofilm.

## Moisture balance

There are many wound dressings available; but in simple terms,

- If the wound is dry, add moisture with hydrogels, hydrocolloids or films.
- If the wound is too wet, remove moisture with foams or alginates.

### MOIST WOUND HEALING (WINTER G, *NATURE*, 1962)

This concept is a mainstay of modern wound healing and is promoted by occlusive dressings such as hydrocolloids, hydrogels and films.

- Maintains hydration and temperature
- Prevents scab/eschar formation
- Promotes epithelialisation
- Autolysis
- Slightly acidotic environment
- Growth factors more active

### EDGE ADVANCEMENT

The wound edge may be undermined or rolled due to excessive proliferation. Failure of wound edge migration may be due to persistent/inadequately debrided slough, prolonged wound inflammation or senescent cells.

## ULCERS

An ulcer is a breach in the epithelium and there are multiple causes. The ulcer characteristics, particularly the edge and base, provide important information. The surrounding tissues specifically skin condition, circulation and sensation (e.g. glove and stocking neuropathy) also provide clues. Long-standing ulcers should be biopsied to exclude malignancy (**Marjolin's ulcer**); other problems to consider include vasculitis/autoimmune disease, sickle cell, infection or

- **Hydroxyurea** (an antineoplastic agent used to treat haematological malignancies) can cause painful leg ulcers (usually after prolonged use) that are refractory to local care until the drug is discontinued.
- **Pyoderma gangrenosum** is a necrotising cutaneous vasculitis that may be associated with inflammatory bowel disease or rheumatoid arthritis. Histological findings are non-specific and the diagnosis is clinical. Ulcers in IBD patients may improve when the bowel disease improves. Surgery is contraindicated.

### VENOUS ULCERS

This is the commonest cause of leg ulcers in developed countries (70%–90%), affecting 1.7% of the elderly in the United Kingdom and costing 600 million GBP a year in health costs. A minority will also have an arterial component.

- Typically a painless (unless infected) ulcer over medial malleolus (**gaiter area** – a gaiter being a protective item that covers the ankle to the instep area. They also cover the lower trouser, differentiating them from spats). Aching and swelling at the end of the day are improved by elevation.
- The typical skin changes are lipodermatosclerosis (scarring) and pigmentation due to haemosiderin deposition.
- Valvular dysfunction leads to **venous hypertension;** a history of DVT was found only in 28% (Moffat CJ, *QJM*, 2004). This leads to protein extravasation and formation of a perivascular fibrin cuff. Duplex ultrasound studies have shown that superficial venous incompetence is found in most patients with venous ulceration (Magnusson MB, *Eur J Vasc Endovasc Surg*, 2001), sometimes with deep venous reflux, but isolated reflux in deep or perforating veins is uncommon.
- There are many dressings to choose from, and there is little evidence that any one product demonstrates superiority to the others, though hydrocolloids/foams may help reduce pain.
  - **Pentoxifylline** (Trental®), normally used for intermittent claudication through increases in microcirculatory blood flow, may be more effective than placebo, with or without compression (Jull AB, *Cochrane Database Syst Rev*, 2012). Most of the side effects were gastrointestinal. SIGN (2010) suggests that it may be used; however, it is an unlicensed indication.
- **Compression therapy** (to counteract venous hypertension) by trained nurses is a key treatment. There are some regional preferences but results are similar.
  - Four-layer bandaging (4LB) is popular in the United Kingdom; full healing is achieved in 8 weeks.
  - Short stretch bandaging is preferred in Europe.
  - Unna boots made from zinc oxide and calamine-impregnated bandages, changed once every 1–2 weeks, are common in the United States. They facilitate ambulation.
- **Superficial vein surgery** (various forms of venoablation including high ligation and GSV stripping, sclerotherapy and RFA or endovenous laser) is much more beneficial for ulcer healing/recurrence than deep vein surgery, which has significant complications. The evidence for subfascial perforator ligation in ulcer healing remains unconvincing. Venous surgery/referral to a vascular surgeon does not need to be delayed in patients with healthy granulating ulcers with no evidence of infection. The **ESCHAR trial** (2004) found no difference between compression alone (89% at 3 years) vs. compression with surgery for superficial reflux (93%), but the latter group has a reduced recurrence rate and more 'ulcer-free time'.
- **Surgery to the ulcer** can be considered if conservative treatment fails. Skin grafts work reasonably well, but recurrence is almost inevitable without dealing with the venous insufficiency; flaps are a major undertaking but import vascularity.

### DIABETIC ULCERS

Approximately 15% of diabetic patients suffer from ulcers. The aetiology is often mixed: one-third are purely

neuropathic, one-third are neuropathic and ischaemic whilst one-fourth is purely ischaemic. **Neuropathy** is important and has anatomic, ischaemic and metabolic contributing factors:

- Elevated blood sugar levels reduce sodium pump activity and increase intracellular sorbitol, leading to nerve swelling and intraneural compression.
- Alterations in microcirculation lead to focal nerve loss.
- May have 'double crush' phenomenon, e.g. concomitant carpal tunnel, cubital tunnel syndrome.
- Sensory neuropathy leads to loss of protective sense.
- Autonomic neuropathy – anhidrosis, dry cracked skin from AV shunting.

Wound care in diabetics is a particular challenge.

- **Off-loading** is very important.
- **Increased infection risk** (usually Staphylococci or Streptococci) due to impaired lymphocyte function and impaired phagocytosis. Antibiotics should be used judiciously; some countries have banned the use of topical antibiotics in diabetic wounds due to resistance problems.
- **HBOT** reduces amputation rates and is covered by Medicare if ulceration has been unresponsive to 30 days of standard treatment.
- **Apligraf** (see later) use is covered in non-responsive diabetic and venous ulcers, though insurers have recently cut back on the reimbursement per treatment.

Microangiopathy does not contribute significantly to the development of ulcers in diabetics; thus, vascular reconstruction can be beneficial. It may be more useful for foot ulcers compared to calf ulcers. Diabetic patients have atherosclerosis similar to non-diabetics but often with different distributions – they tend to have tibioperoneal disease with long segment occlusion and calcification, whilst any femoral disease tends to be diffuse. The peak flow improvement occurs 1 week after a bypass but takes up to 1 month after an endovascular intervention; the latter also has a higher rate of short-term failure.

- **Amputation** – toe fillet, plantar VY, ray/transmetatarsal amputation are choices for gangrenous toes; >½ of all amputations performed are secondary to diabetic disease.
- **Reconstructions** may be 'simplified' with the use of negative pressure wound therapy (NPWT) to reduce bacterial counts, improve the formation of granulation tissue especially over non-favourable wounds with exposed tendons, bones and joints and improve the take of skin grafts.
- The current consensus is to aggressively postpone the need for amputation:
  - 1/3 need a more proximal amputation due to poor healing.
  - 1/2 have a contralateral limb amputation within 5 years.
  - The 5-year survival after amputation is 40%.

**Diabetic foot reconstruction using free flaps increases 5-year survival rate. (Oh TS, *J Plast Reconstr Aesthet Surg*, 2013)**
A retrospective review of 121 reconstructive procedures in diabetic foot wounds. A variety of free perforator flaps (ALT, SCIP, anterior or upper medial thigh flaps) were used with 91.7% success, with overall limb salvage rate at 5 years being 86.6%. Statistical analysis shows improved 5-year survival in patients who had foot reconstruction compared to those who had an above ankle amputation (86.8% vs. 41.4%).

## TISSUE TRANSPLANTATION

- **Immunology**
- **Skin grafts**
- **Bone grafts**
- **Tendon healing and tendon grafts**
- **Tissue allografts, xenografts and alloplasts**

## IMMUNOLOGY

Major histocompatibility antigens (MHC, also called human leucocyte antigens – HLA, in humans) are found on the surface of cells.

- Type 1 – all nucleated cells and platelets
- Type 2 – antigen-presenting cells (APCs): Langerhans cells, macrophages and lymphocytes

## RESPONSE TO MHC-ALLOANTIGENS

- APCs present alloantigen to T-cells and express IL-1.
- IL-1 causes T-helper (CD4+) to produce IL-2.
- IL-2 causes clonal expansion of T-helper cells and B-lymphocytes.
- IL-2 also activates Tc-cells and NK cells (cellular immunity).
- B lymphocytes mediate antibody-mediated cell lysis (humoral immunity).

## ALLOGRAFT REJECTION

Unmatched tissue grafts from another patient, i.e. allografts, will be rejected; skin is the most allogenic tissue – rejection in hand/face transplants is first manifested as a blotchy rash.

- **Acute rejection** occurs after 7–10 days due to T-cell infiltration (cellular immunity). It may be delayed in immunocompromised patients until the immunodeficient state has passed, e.g. recovery from a severe burn or stopping immunosuppressant drugs.
- **Late rejection** is due to antibody-mediated cell lysis (humoral immunity).
- **Hyperacute rejection** is due to preformed antibodies and the rejection response begins immediately.

- **Graft versus host reaction** occurs when allograft containing lymphoid tissue reacts against an immunocompromised host, and is a particular risk in bone marrow transplant.

Immunosuppressant drugs are needed to block rejection in allotransplantation:

- Cyclosporin blocks IL-2, which blocks clonal expansion of Tc-cells.
- Azathioprine inhibits T-cell-mediated rejection by preventing cell division.
- Prednisolone blocks the generation and release of T-cells.

## BIOMATERIALS

These are biological materials used to replace or augment tissues in the human body and can be classified as

- Autograft – living tissue from host
- Isograft – from a genetically identical twin
- Allograft – tissue from same species
- Xenograft – tissue from different species
- Alloplast – derived from synthetic material.

The biological reactions to a foreign body include

- Immediate inflammation with early rejection
- Delayed rejection
- Fibrous encapsulation
- Incomplete encapsulation with continuing cellular reaction
- Slow resorption
- Incorporation

## TISSUE ALLOGRAFTS, XENOGRAFTS AND ALLOPLASTS

### Tissue allografts

These generally do not contain living cells due to processing to reduce antigenicity, though bone allograft may have osteoconductive and osteoinductive properties. They are usually incorporated into host tissues providing a structural framework for the ingrowth of host tissues.

- Their advantages include a plentiful supply; a donor site is not required and operation time is usually reduced.
- Disadvantages include a potential for infection/disease transmission, and they demonstrate a variable amount of resorption.

Examples include

- Lyophilised fascia (dura mater, fascia lata) – risk of Creutzfeldt–Jakob disease (CJD) transmission in the former. Typically there is a 10% resorption rate.
- Homologous cartilage – greater tendency for resorption, replacement with fibrous tissue, ossification and more infection compared with autologous tissue. A tissue is said to be homologous if it performs the same basic function in the recipient as the donor.
- Homologous bone – acts generally as scaffold for formation of new bone; slower to become incorporated and revascularised.
- AlloDerm® (Lifecell Corp) – cadaveric dermis that has been processed to remove cellular elements, allowing incorporation into the host.
- Glyaderm® (Euro Skin bank) is a glycerolised acellular human dermis, which can be used as a dermal substitute, which is then covered by a thin autograft.

## SKIN 'ALLOGRAFTS'

Cadaveric skin was first used as temporary cover in burns by Brown in 1953. It has not been satisfactorily used as a skin transplant (i.e. a true allograft) in major burns (Mahdavi-Mazdeh M, *Int J Organ Transplant Med*, 2013).

- The skin must be retrieved within 24 hours of death from a refrigerated cadaver under aseptic conditions (screening serology for hepatitis B and C viruses, human immunodeficiency virus and skin samples for culture of bacteria, yeast and fungi). It is stored in nutrient media at 4°C for up to 1 week ('fresh') or sterilised (e.g. irradiation) and cryopreserved (controlled freezing at 0.5–5°C/min to –196°C with liquid nitrogen and a cryoprotectant solution). When needed, it is rapidly rewarmed to 10–37°C (~3–4 min). Alternatively it can be processed with 85% glycerol (Euro Skin), which is a slow-acting but effective bactericide.
- Donor exclusion criteria – high-risk categories for HIV, i.e. male homosexuals, drug abusers, those with tattoos, prostitutes and haemophiliacs, those with infection/sepsis, neoplasia and autoimmune disease. Only two cases of viral transmission in 3 million tissue transplants (including skin) have been described.

Cadaveric skin is the best **biological dressing** for areas of full thickness skin loss; however, it is temporary due to rejection through HLA-DR and Langerhans cells; thus, they are strictly not allografts. Burns patients are immunosuppressed so rejection may be delayed – some cases demonstrate up to 85% viability at 1 year (see 'Burns').

- Coverage of areas of full thickness skin loss, e.g. after burn debridement, in the face of inadequate donor skin. The cadaveric dermis will adhere tightly to the (fibrin of the) wound bed and keep it clean and reduce losses, whilst the donor sites heal and become available for a second harvest.
- It can also be laid over widely meshed autograft to reduce wound desiccation (Alexander/sandwich technique).
- Some use cadaveric skin or porcine skin as 'test grafts' to see if a wound bed is ready to support autografts, e.g. in debrided chemical burns.

## CULTURED EPITHELIAL AUTOGRAFT

Epithelial culture (Rheinwald JG, *Cell*, 1975) begins with a full thickness skin biopsy of several square centimetres taken from the patient. After culturing for 2–3 weeks, there will be enough cells to cover a 1.8 $m^2$ sheet five cells thick. The cells take by adhesion more than revascularisation; overall take is 80% under favourable conditions, though late loss can occur.

- Cultured epidermal cells express fewer MHCII/HLA-DR antigens and thus *allogenic keratinocytes* could potentially be used. Animal studies have shown temporary take contributing to wound closure, but the cells do not persist for more than a week – they may accelerate wound healing by interaction with host cells, and through cytokines and growth factors. The results so far have been too costly and time-consuming to be clinically useful.

## TISSUE XENOGRAFTS

Animal-derived wound dressings have been used as early as 1500 BC. The dressing dries and falls off as the burn heals; they are 'ejected' rather than rejected, and thus the term 'xenograft' should be avoided for these materials. Similarly, whilst other animal-derived products are used for permanent incorporation, they are acellular after significant processing, and probably do not qualify as true xenografts.

- **Surgisis®** (Cook) – derived from pig small intestine submucosa (SIS); an updated product Biodesign was released in 2008. It is often used for fascia replacement; the acellullar matrix allows tissue ingrowth; it received FDA clearance in 1988 as a hernia repair material.
- Similar products include – Cellis®, Strattice® (Lifecell) and Permacol® (Covidien). There are no good clinical data for its effectiveness over other biological meshes or standard mesh. Some of these are being promoted for use in (covering) breast implants; however, it is much less elastic than human ADMs and is associated with higher seroma rates.

## TISSUE ALLOPLASTS

Alloplasts have abundant supply without donor site morbidity, but tend to be expensive and elicit a host reaction of some sort as they are foreign materials. Silicone and Medpor® are the commonest types of implant materials used in the face.

- **Silicone** is a silicon polymer and its physical state depends on the amount of cross-linking. It is generally inert, which means it tends to be encapsulated rather than incorporated.
- **Medpor®** (high-density porous polyethylene) – allows vascular ingrowth and reduced tissue reaction, but it is expensive and can be difficult to remove.
- **Hydroxyapatite** – a calcium phosphate salt available in dense (high-pressure compaction) or porous hydroxyapatite. A natural source of hydroxyapatite comes from coral. It allows a degree of vascular ingrowth but is brittle and can be difficult to shape. It is also available for use as a tissue filler (Radiesse®).
  - Nanocrystalline hydroxyapatite (NanoBone®) – new bone formation is seen after 5 weeks. There is a size limit; clinical studies suggest that (cranial) defects larger than 4–5 cm will be incompletely ossified. Such materials are unable to tolerate load bearing. Note that autologous bone is prone to resorption in the absence of load bearing, and thus would offer a few advantages over biomaterials under these circumstances.
  - Calcium carbonate also derived from coral (but without additional conversion to phosphate) is resorbed and totally replaced. However, it is not very strong.
- **Gore-Tex®** – expanded polytetrafluoroethylene (ePTFE) – is available in many different forms. It provokes a weaker foreign body reaction and reduced ingrowth in comparison to polypropylene mesh, and thus is said to have weaker interface with tissues (almost no capsule formation) with potentially more herniation but fewer adhesions and fistulae. However, major differences are not evident in studies.
- **Metals**, e.g. stainless steel, vitallium alloy, titanium alloys (10 times stronger than bone and well tolerated but has low fatigue tolerance).
- **Polylactide compounds**, e.g. Lactosorb® plating system used in craniofacial surgery, poly-L-lactic acid (PLLA) tissue fillers (Sculptra®). These are completely resorbed and thus have fewer long-term risks.
- **Polyglactin** – is available as a suture (Vicryl), film or mesh.

## BONE AND BONE HEALING

Bone is composed of 35% organic material (mostly type I collagen), 60% mineral (mainly hydroxyapatite) and 5% trace elements.

## TYPES OF BONE

### Developmental classification

- Endochondral bone – laid down as cartilage first, usually at an epiphysis, followed by ossification. This occurs in long bones.
- Membranous bone (skull, facial, clavicle) – osteoid is laid down directly by osteoblasts without a cartilaginous stage. Also occurs in primary bone healing.
  - Membranous bones are said to undergo less absorption than endochondral when used as onlay grafts on facial bones (Zins JE, *Plast Reconstr Surg*, 1983).