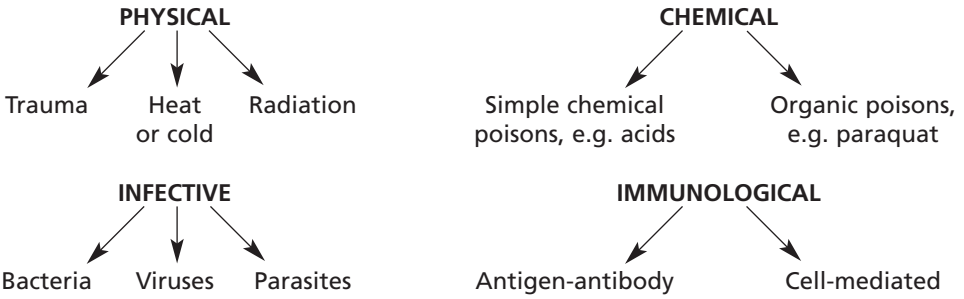
CHAPTER 2

INFLAMMATION

INFLAMMATION

Inflammation is the dynamic process by which living tissues react to injury. They concern vascular and connective tissues particularly.

Causes:
Various agents may kill or damage cells:



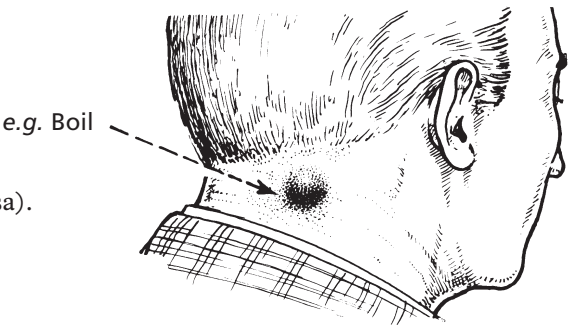
… and any other circumstance leading to tissue damage, e.g. VASCULAR or HORMONAL DISTURBANCE.

The inflammatory reaction takes place in the surviving adjacent vascular and connective tissues; the specialised parenchymal cells do not directly participate.

The initial stages are known as the **acute** inflammatory reaction. Where the process is prolonged the inflammation may be **subacute** or **chronic**.

ACUTE INFLAMMATION
The classical signs are:

REDNESS (rubor)
HEAT (calor)
SWELLING (tumour)
PAIN (dolor)
LOSS OF FUNCTION (functio laesa).



These gross signs are explained by changes occurring at microscopic level. Three essential features are:

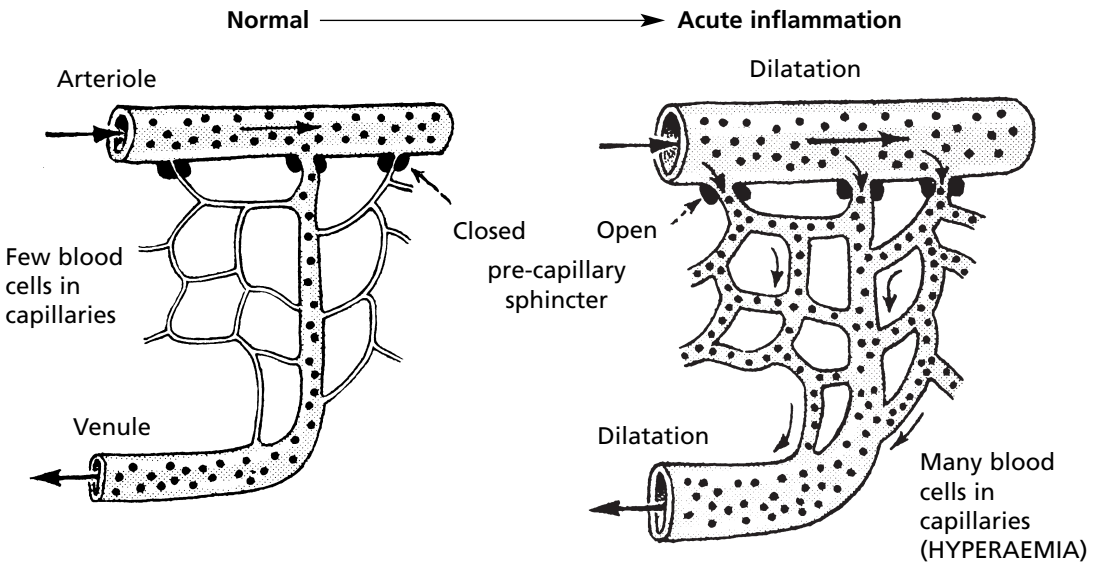
1. **HYPERAEMIA**
2. **EXUDATION OF FLUID**
3. **EMIGRATION OF LEUCOCYTES.**

ACUTE INFLAMMATION

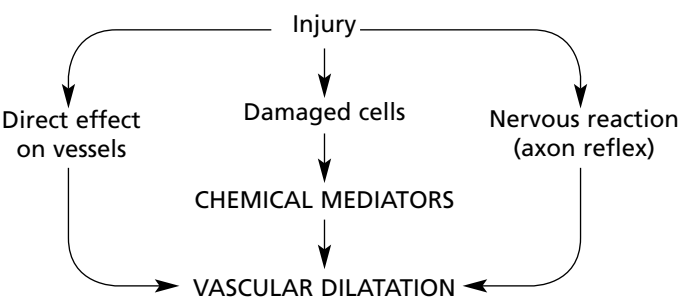
HYPERAEMIA

The hyperaemia in inflammation is associated with the well known microvascular changes which occur in Lewis' triple response – a FLUSH, a FLARE and a WEAL. It occurs when a blunt instrument is drawn firmly across the skin and illustrates the vascular changes occurring in acute inflammation.

The stroke is marked momentarily by a white line due to VASOCONSTRICTION.
The flush, a dull red line, immediately follows and is due to CAPILLARY DILATATION.
The flare, a bright red irregular surrounding zone, is due to ARTERIOLAR DILATATION.



Mechanisms involved are:



HYPERAEMIA explains the classical signs of REDNESS and HEAT.

ACUTE INFLAMMATION

EXUDATION

Exudation is the increased passage of protein-rich fluid through the vessel wall into the interstitial tissue. It explains the **weal** in Lewis' triple response.

Advantageous results

Fluid increase
↓
Dilution of toxins

Contents of fluid

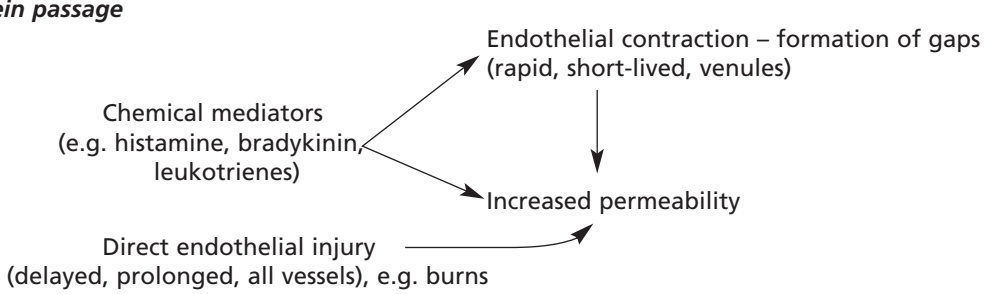
(a) Globulins → protective antibodies

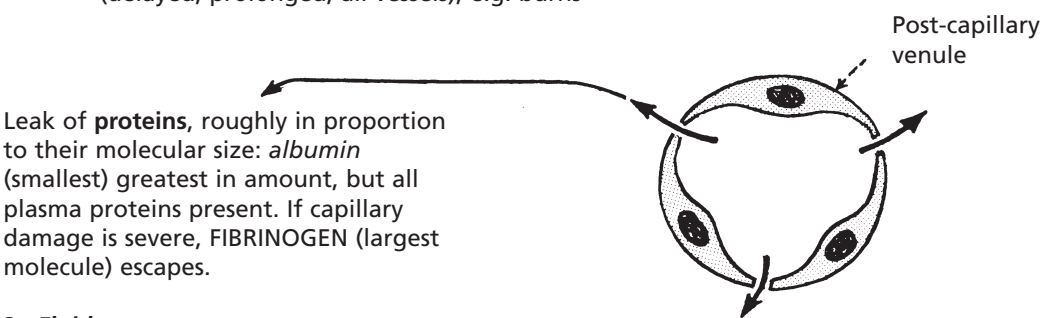
(b) Fibrin deposition → Helps to limit spread of bacteria

(c) Various factors promoting subsequent healing

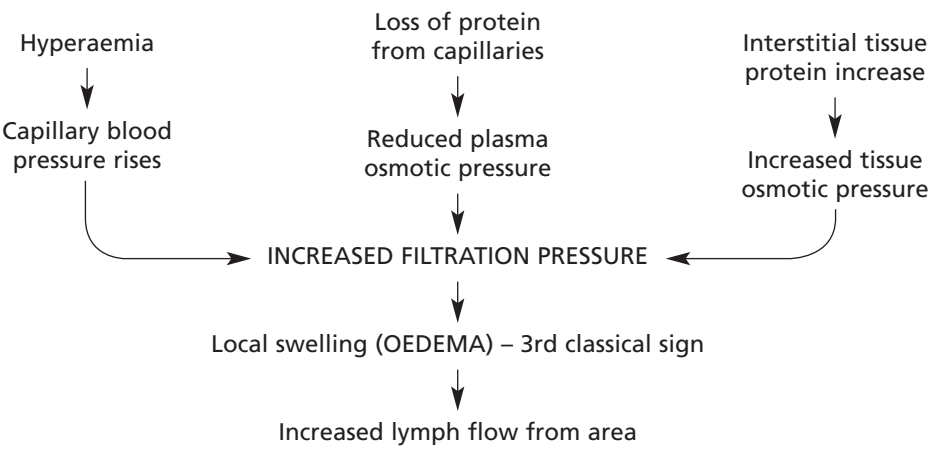
Mechanism

1. ***Protein passage***





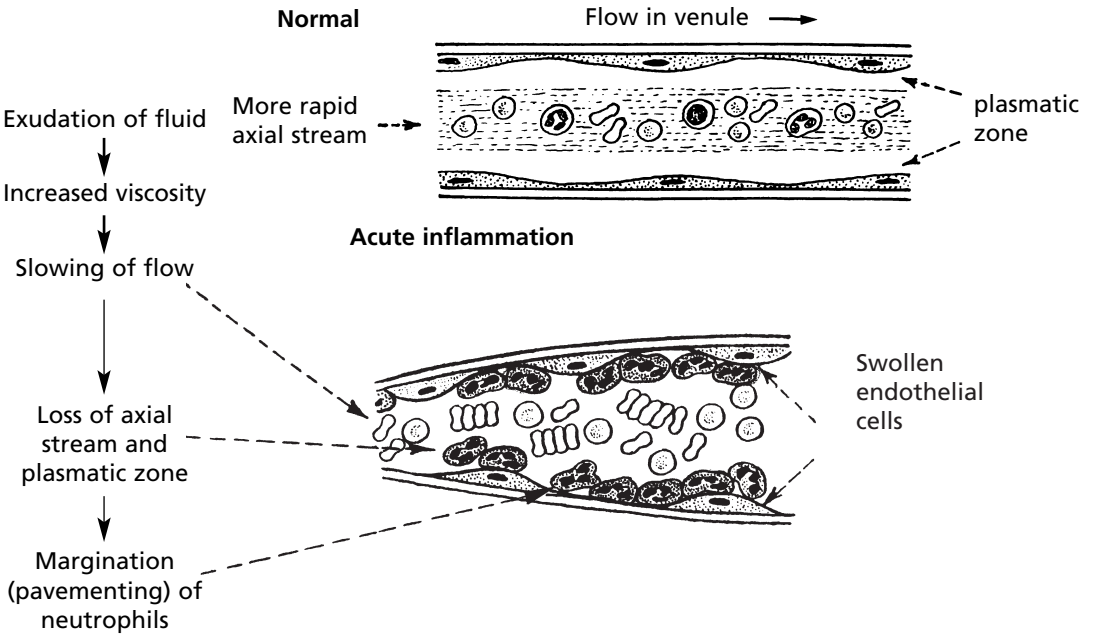
2. ***Fluid movement***

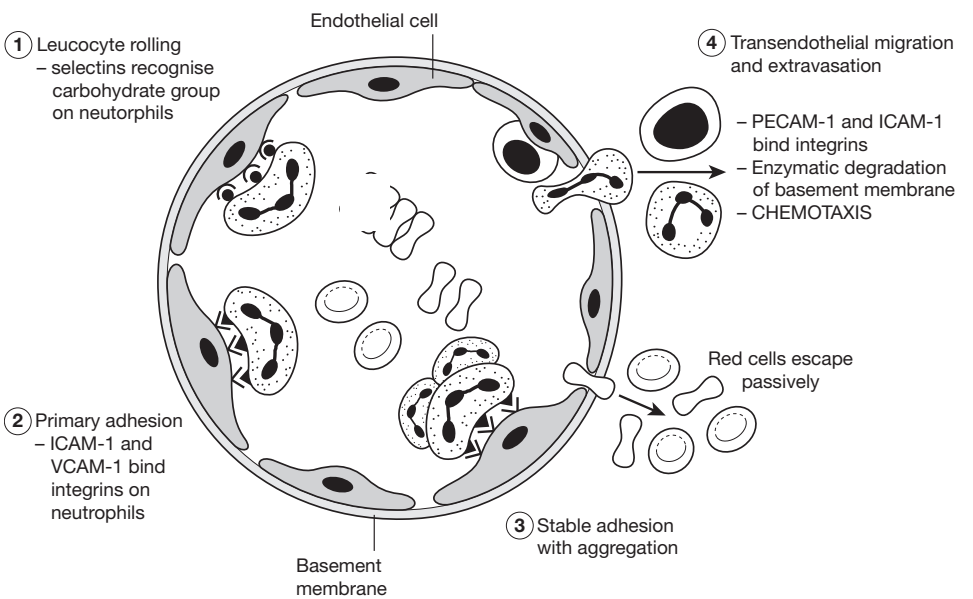


ACUTE INFLAMMATION

EMIGRATION OF LEUCOCYTES

Neutrophils and mononuclears pass between the endothelial cell junctions by amoeboid movement through the venule wall into the tissue spaces. In this process both neutrophils and endothelial cells are activated and both express cell adhesion molecules, initially SELECTINS and then INTEGRINS.



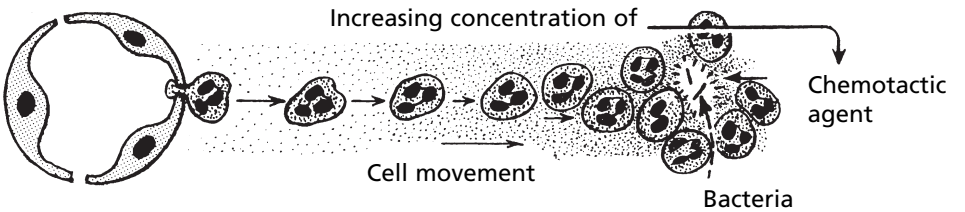


ACUTE INFLAMMATION

CHEMOTAXIS

The initial margination of neutrophils and mononuclears is potentiated by slowing of blood flow and by increased 'stickiness' of the endothelial surface.

After penetration of the vessel wall, the subsequent movement of the leucocytes is controlled by CHEMOTAXIS. The cell moves in response to an increasing concentration gradient of the particular chemotactic agent, usually a protein or polypeptide.



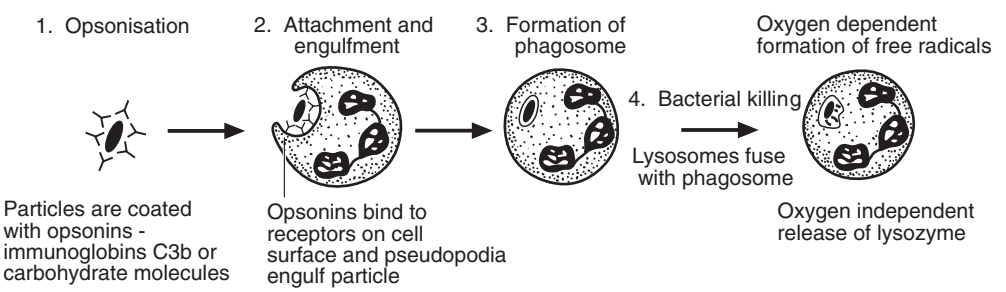
Important examples of chemotactic agents are:

Fractions of the COMPLEMENT SYSTEM (esp. C3a)
Factors derived from arachidonic acid by the neutrophils – LEUKOTRIENES (e.g. LTB4)
Factors derived from pathogenic BACTERIA
Factors derived from sensitised lymphocytes – CYTOKINES (e.g. IL-8).

The leucocytes move by extension of an anterior pseudopod with attachment to extracellular matrix molecules such as fibronectin using cell adhesion molecules. The cell body is then pulled forward by actin and myosin filaments.

PHAGOCYTOSIS

This is the process by which neutrophils and macrophages clear the injurious agent. It is an important defence mechanism in bacterial infections particularly.



There are 3 families of OPSONIN.

1. Immunoglobulin, especially IgG
   – recognized by Fc receptors on neutrophil surface.
2. Complement, especially C3b
   – recognized by C3b receptors on neutrophil surface.
3. Carbohydrate binding proteins, or lectins
   – bind sugar residues on bacterial cell walls.

The opsonic activity is enhanced when it is confined within a solid organ or rigid medium such as a fibrin network; where conditions are looser and more fluid, activity is diminished.

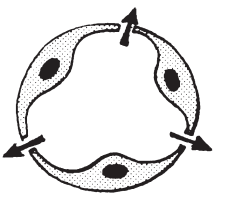
ACUTE INFLAMMATION

CHEMICAL MEDIATORS

Various chemical mediators have roles in the inflammatory process. They may be circulating in plasma and require activation or they may be secreted by inflammatory cells. Many of these mediators have overlapping actions.

Mediators dervived from:

1. Inflammatory cells



Histamine (Mast cells) → Increased vascular permeability

Histamine (Mast cells) → Vasodilatation

Serotonin (Platelets) ⇢ Vasodilatation

Arachidonic Acid Derivatives → Prostaglandins → Vasodilatation, oedema (PGE_2, PGI_2)

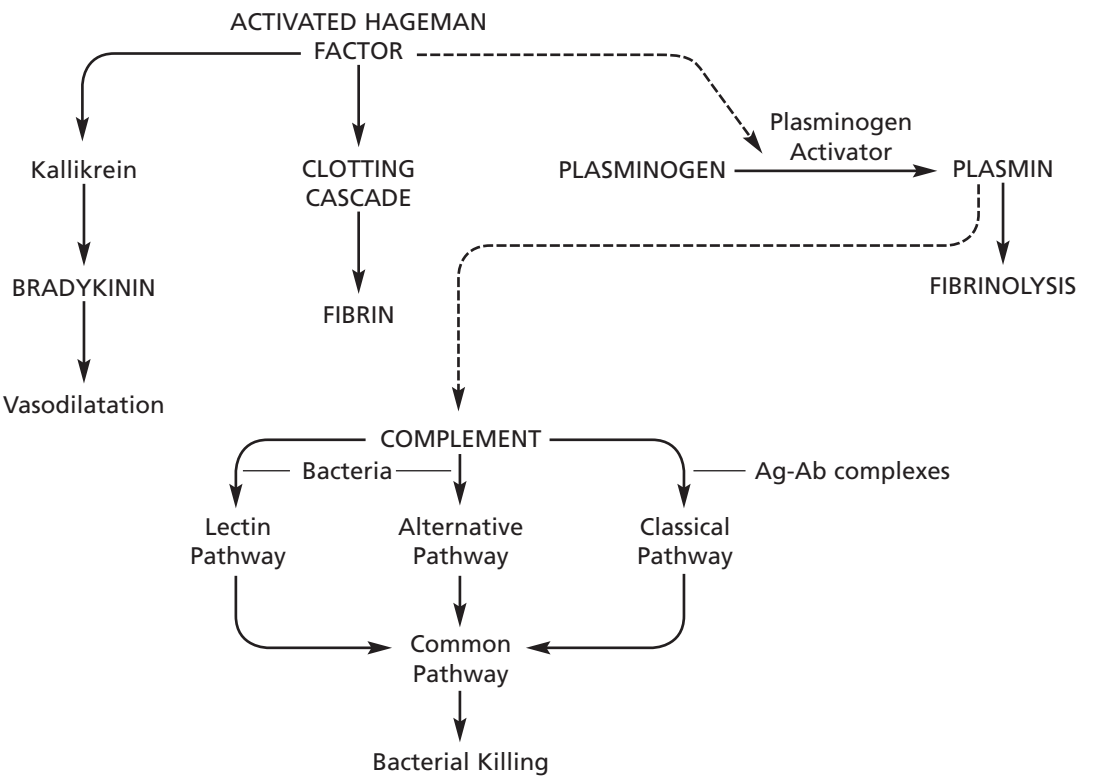
Arachidonic Acid Derivatives → Leukotrienes → Vasoconstriction; increased permeability

Cytokines (inflammatory cells, endothelium etc.) → IL-2, IL-4 → Stimulate lymphocyte proliferation

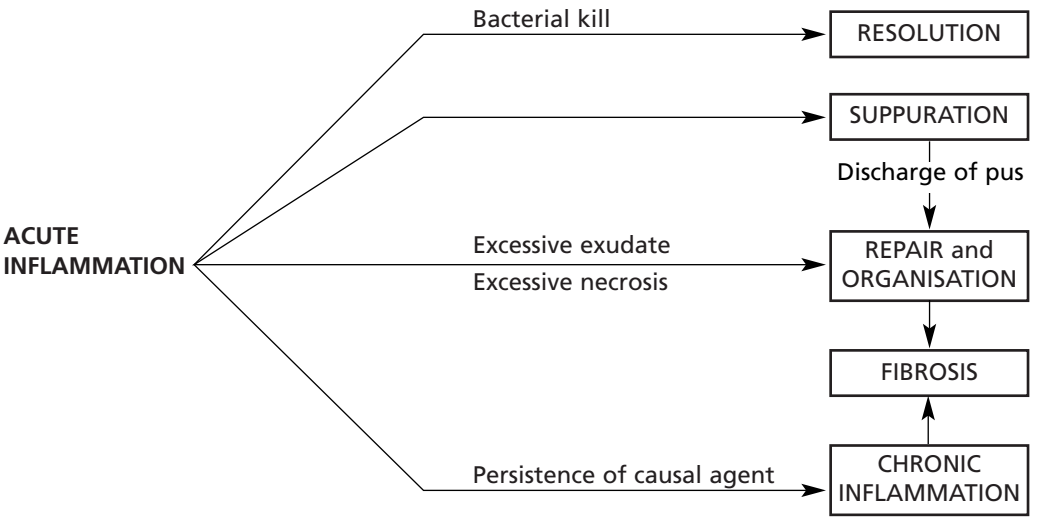
Cytokines (inflammatory cells, endothelium etc.) → IL-10, TGF-β → Suppress lymphocyte proliferation

Cytokines (inflammatory cells, endothelium etc.) → IFN-γ, TNF-α → Macrophage activation

2. Plasma. These pathways are all interrelated.



SEQUELS OF ACUTE INFLAMMATION

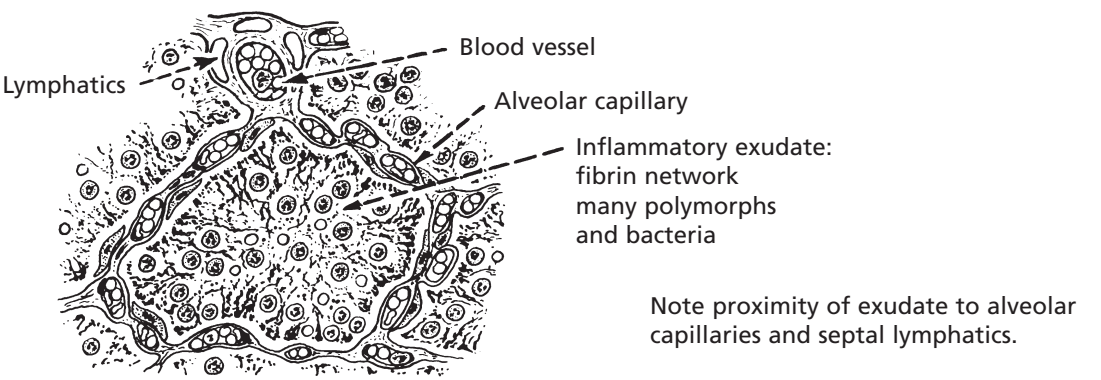


RESOLUTION

This means the complete restoration of normal conditions after the acute inflammation. The three main features which potentiate this sequel are:

1. minimal cell death and tissue damage
2. rapid elimination of the causal agent, e.g. bacteria
3. local conditions favouring removal of fluid and debris.

Resolution of lobar pneumonia (bacterial inflammation of lung alveoli) is a good example:



Following bacterial kill the mechanism is as follows:

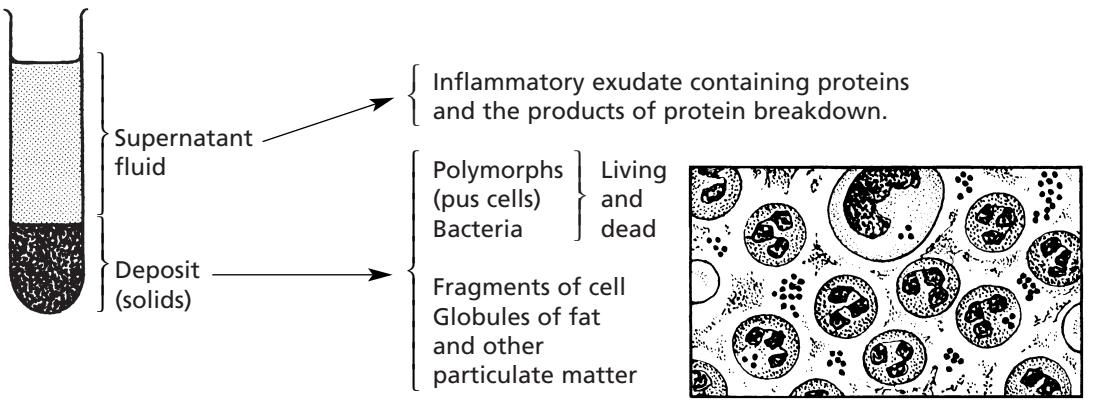
1. Solution of fibrin by enzyme action (polymorphs and fibrinolysin)
2. Removal of fluid by blood vessels and lymphatics
3. Removal of all debris by phagocytes to hilar lymph nodes
4. The capillary hyperaemia diminishes and restoration to normal is complete.

SEQUELS OF ACUTE INFLAMMATION

SUPPURATION

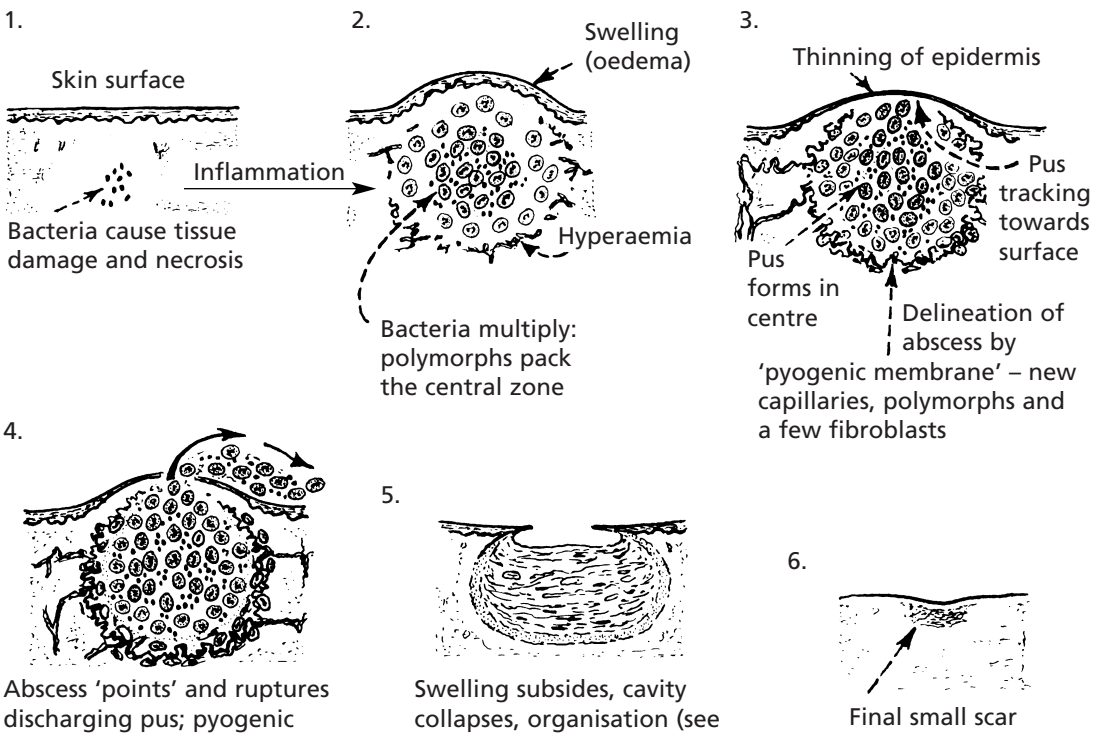
This means the formation of PUS; where pus accumulates an ABSCESS forms.

Infection by pyogenic (pus-forming) bacteria is the usual cause, e.g. staphylococcal abscess (or boil). The pus in this case is a thick, creamy yellow fluid which, on centrifugation, separates thus:



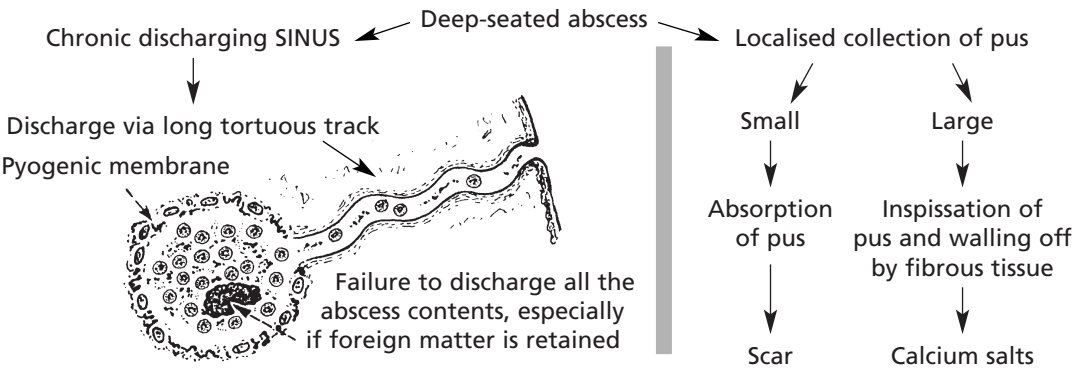
Evolution of an abscess

The usual evolution of an abscess is as follows:



SEQUELS OF ACUTE INFLAMMATION

Evolution of an abscess *(continued)*
When the abscess is deep-seated, the process may be modified as follows:

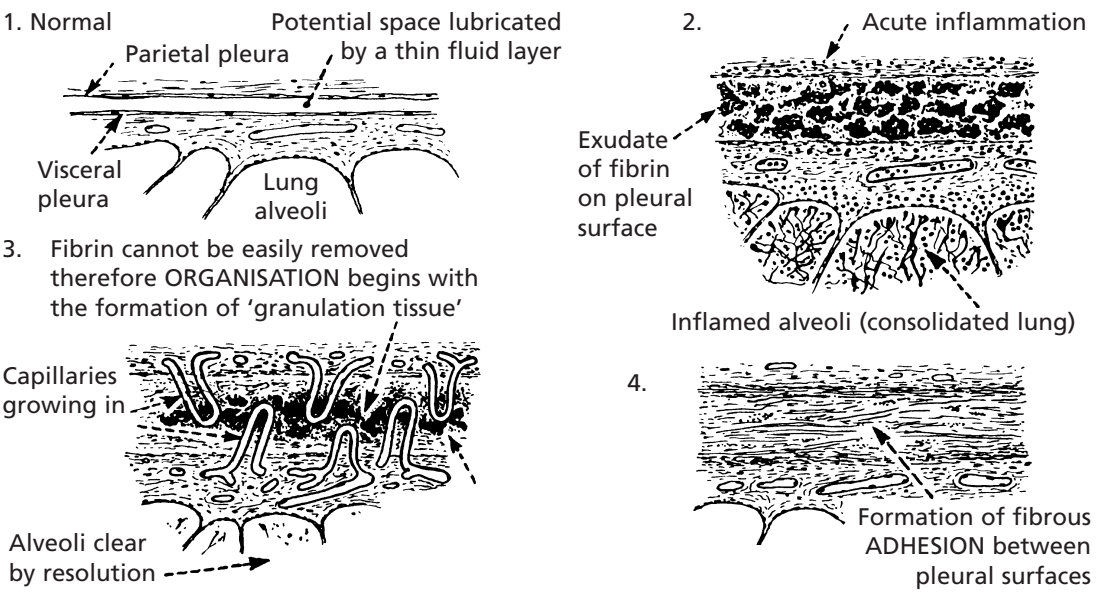


ORGANISATION AND FIBROSIS

Organisation occurs when, during the acute inflammatory process, (a) there is excessive exudation or necrosis or (b) when local conditions are unfavourable for the removal of exudate and debris. The term also applies to the local reaction to the presence of thrombus and also the necrosis associated with infarction.

The changes are similar to those described in wound healing viz – the growth of new capillaries into the inert material (exudate or thrombus), the migration of macrophages and the proliferation of fibroblasts resulting in FIBROSIS.

A good example of organisation following acute inflammation is seen in the pleura overlying pneumonia. The inflammation of the lung tissue proper usually resolves completely (p.264); in contrast the pleural exudate is not easily removed and organisation takes place.



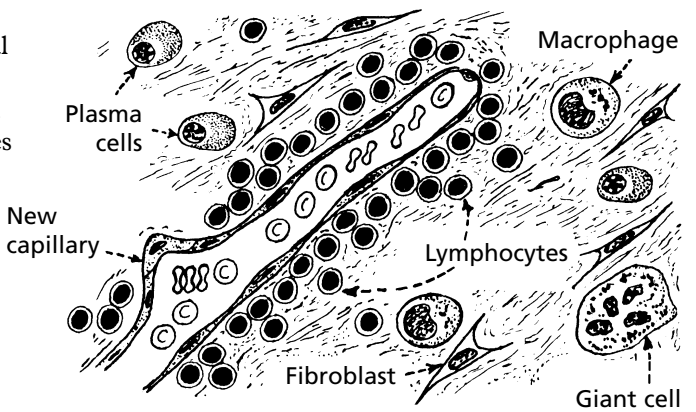
Other good examples of organisation are seen after infarction (see p.166).

CHRONIC INFLAMMATION

Chronic Inflammation may (a) follow acute inflammation if the causal agent is not removed: or (b) be 'primary', i.e. there is no pre-existing acute stage.

The essential changes are:

1. Absence of polymorphs (natural life span of 1–3 days); the appearance of lymphocytes and often plasma cells. Macrophages play an increasingly important role including removing dead polymorphs, presentation of antigenic material and granuloma formation.
2. Proliferation of vascular endothelium by 'budding' – formation of new capillaries (angiogenesis).
3. Proliferation of fibroblasts with collagen production leading to
4. Fibrosis.

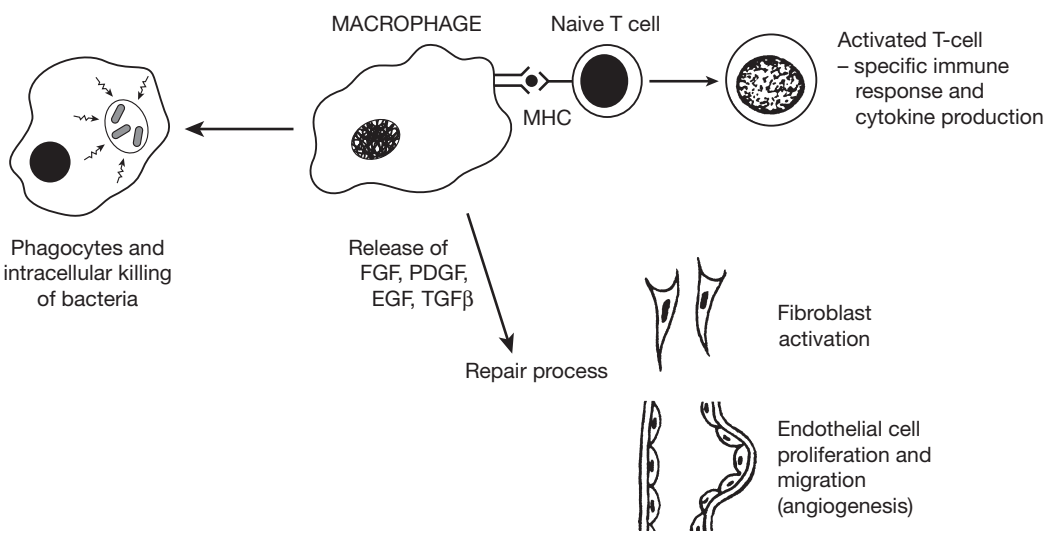


Common causes of 'primary' chronic inflammation include:

(a) Persistent infections, e.g. tuberculosis, leprosy – where the organisms are resistant to neutrophil attack and bacteria survive within macrophages.
(b) Foreign material, e.g. silicates, including asbestos.
(c) Auto-immune diseases, e.g. auto-immune thyroiditis.
(d) Conditions of unknown aetiology, e.g. sarcoidosis: Crohn's disease.

Cellular interactions

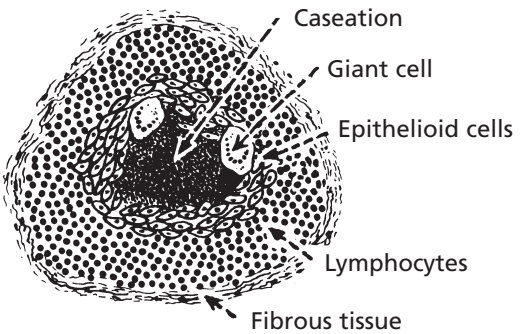
The macrophage is the key cell that directs the various cells involved in chronic inflammation.



CHRONIC INFLAMMATION

GRANULOMATOUS INFLAMMATION

This is the term given to forms of chronic inflammation in which modified macrophages (epithelioid cells) accumulate in small clusters surrounded by lymphocytes. The small clusters are called GRANULOMAS. The basic lesion in TUBERCULOSIS is a good example.



Similar granulomas are seen in:

Sarcoidosis – a rare inflammatory disease of unknown aetiology affecting especially the lymph nodes and lungs, but also many other organs.

'Talc' granuloma – where particulate silicates introduced into the tissues evoke an inflammatory reaction after a latent period (usually years).

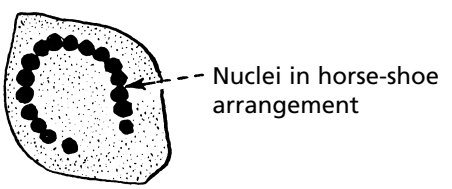
Crohn's disease – a chronic inflammatory disease affecting the terminal ileum and colon (see p.309).

Lymph nodes draining ulcerated areas in which breakdown of lipid is occurring.

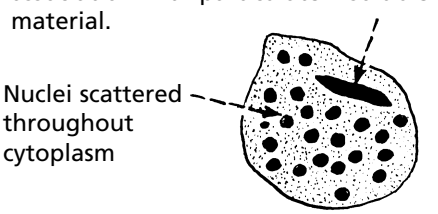
N.B. In all of these granulomatous diseases the basic lesion may be identical, but CASEATION only occurs in tuberculosis.

The epithelioid cells of the granulomas are modified macrophages, and giant cells are derived from macrophages usually by cell fusion but occasionally by nuclear division without cytoplasmic separation.

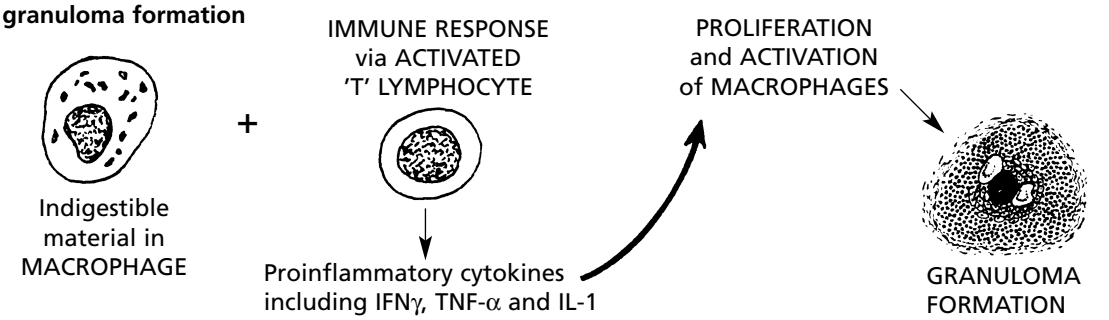
The Langhans' giant cell – seen in chronic granulomata, e.g. tuberculosis and sarcoidosis.



The foreign body giant cell – seen in association with particulate insoluble material.



Mechanism of granuloma formation



ULCERATION – BENIGN

ULCERATION is a complication of many disease processes.

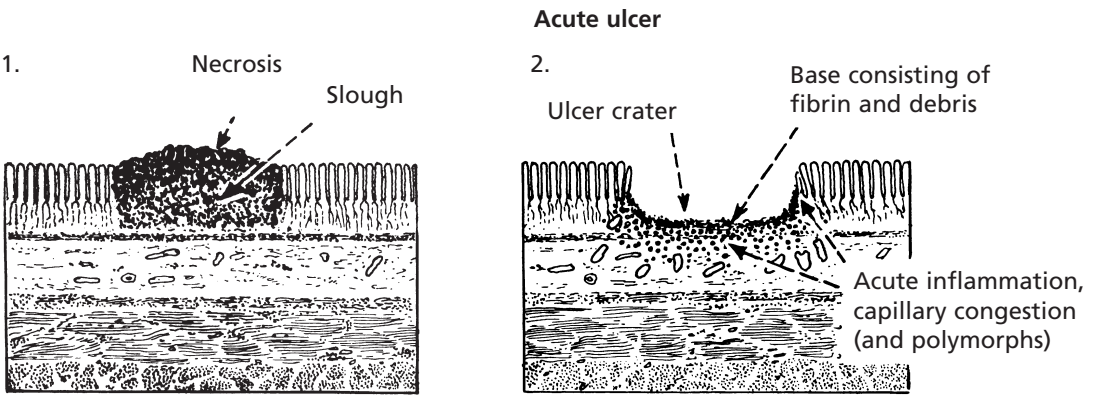
An **ulcer** is formed when the surface covering of an organ or tissue is lost due to necrosis and replaced by inflammatory tissue.

The most common sites are the alimentary tract and the skin.

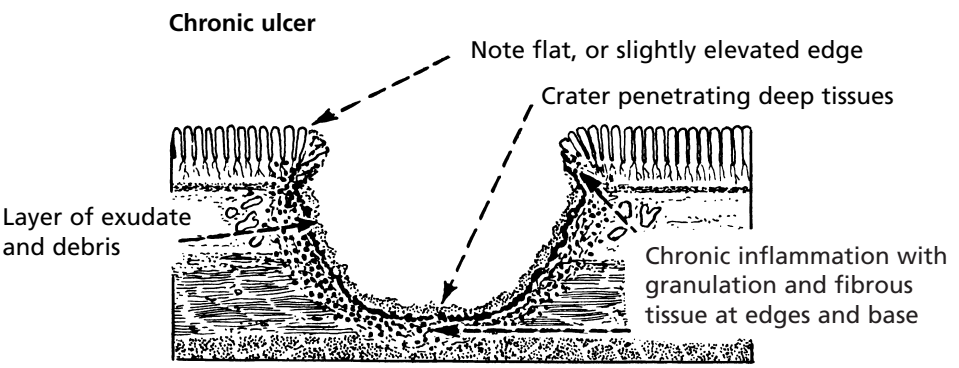
Ulcers are divided into two main groups: 1. BENIGN (inflammatory) and 2. MALIGNANT (cancerous).

The word 'benign' is used here in the limited sense of contrasting with 'malignant': 'benign' ulcers may have serious consequences.

Evolution of a benign ulcer



Healing can occur at this stage with restoration to normal, but if irritation (e.g. bacterial action, slight trauma, digestive juices and acid) continues, a CHRONIC ULCER forms.

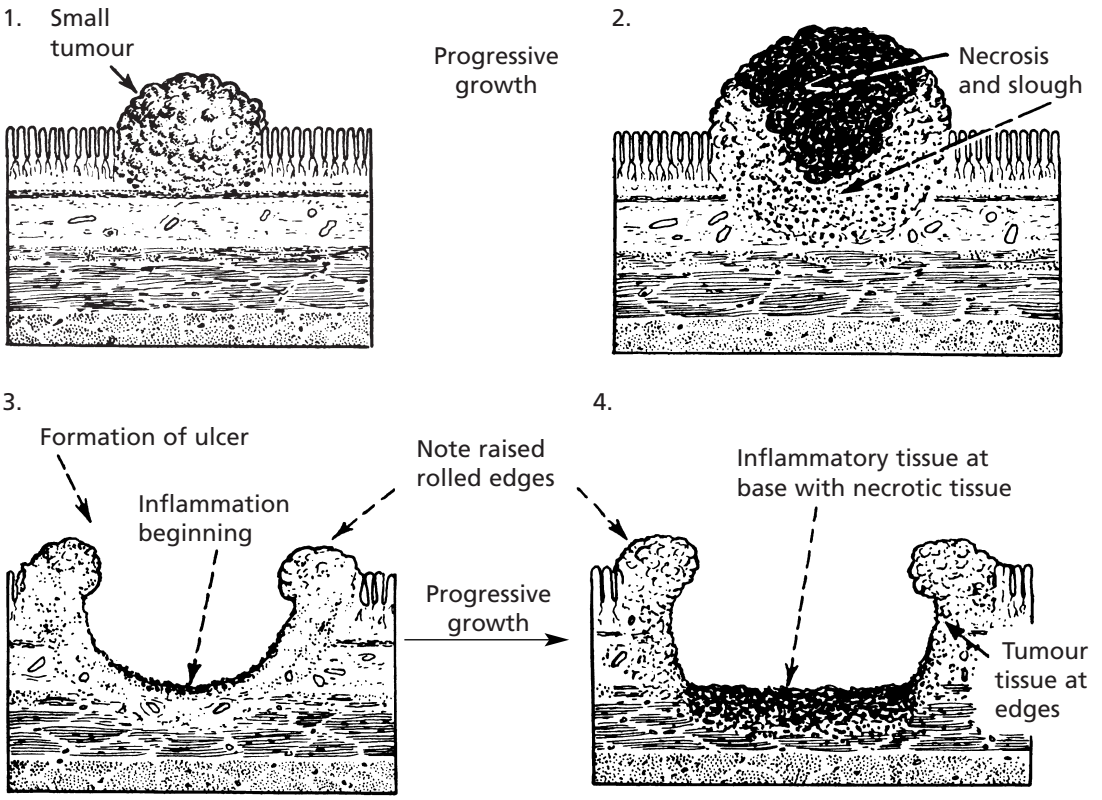


Healing of a chronic ulcer may be impeded by the secondary obliterative changes in the blood vessels due to the chronic inflammation, and it is inevitably associated with a variable amount of scarring.

ULCERATION – MALIGNANT

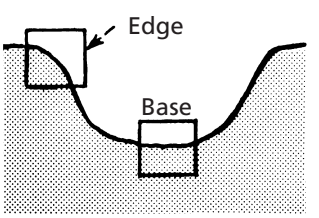
Evolution of a malignant ulcer (ulcerated tumour)

Such an ulcer is the result of the growth of a malignant tumour.



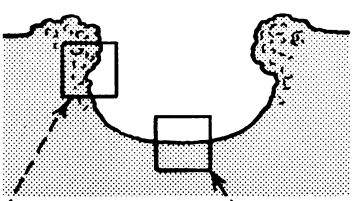
The differences between benign and malignant ulcers are most prominent at the edges – from which a diagnostic biopsy should be taken. It is worth remembering that cancers often ulcerate but benign ulcers rarely undergo malignant change.

Benign ulcer



Biopsies from edge and base both show inflammation

Malignant ulcer



Biopsy from edge likely to show malignant tumour

Biopsy from base may miss malignant tumour

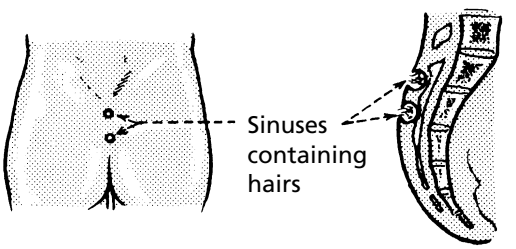
INFLAMMATION – ANATOMICAL VARIETIES

SINUS

A sinus is a tract lined usually by granulation tissue leading from a chronically inflamed cavity to a surface. In many cases the cause is the continuing presence of 'foreign' or necrotic material.

Examples include:

- **Sinuses associated with osteomyelitis** (inflammation of bone).
  Where necrosis of bone occurs, chronic sinuses form over it.
- **Pilonidal sinus**
  (pilonidal = nest of hairs).
  Seen in the mid-line over the sacrum (natal cleft) where hairs which have penetrated deeply under the skin are associated with chronic relapsing inflammation.



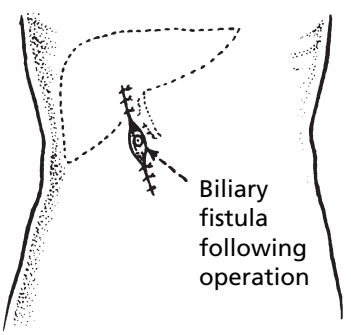
FISTULA

A fistula is a track open at both ends, through which abnormal communication between two surfaces is established.

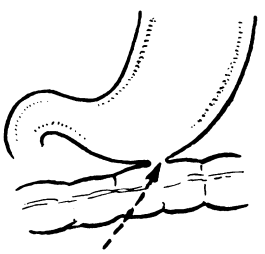
There are two main types:

1. **Congenital** – due to developmental abnormality: any inflammation is superimposed, e.g. tracheoesophageal fistula which can lead to choking and coughing during feeding in a newborn.
2. **Acquired** – due to:

(a) Trauma

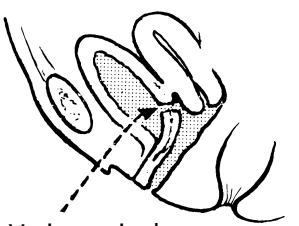


(b) Inflammation



Gastrocolic fistula in Crohn's disease

(c) Necrosis – particularly of tumour



Vesicovaginal fistula following radionecrosis in treatment of cancer of cervix

An **EMPYEMA** is a collection of pus in a body cavity or hollow organ. The term refers usually to the pleural cavity or the gall bladder.

CELLULITIS occurs when inflammation spreads in the connective tissue planes.