1.0. Aims

1. To identify the components of chronic inflammation.
2. To identify the components of repair (organisation).
3. To understand how the process of chronic inflammation participates in and leads on to repair (organisation).
4. To apply these principles to complex disease situations.
5. To further practice the identification of pathological processes and the writing of succinct, descriptive pathological reports.

2.0. Introduction

**Chronic inflammation** describes a process of prolonged duration with tissue destruction, inflammation and healing all proceeding simultaneously.

Chronic inflammation may:

1. follow acute inflammation
2. result from repeated bouts of acute inflammation
3. be a smouldering, low-grade response to persistent infections, sustained chemical injury, or long-term exposure to non-degradable, toxic substances
4. be associated with harmful immune responses, such as hypersensitivity (e.g. allergic reactions) and/or autoimmunity.

The key features and cellular components of chronic inflammation include:

A. tissue destruction;
B. infiltration by macrophages, lymphocytes and plasma cells (occasional eosinophils);
C. repair by granulation tissue (capillaries & fibroblasts) laying down fibrous tissue (mostly collagen), thus producing a scar – this process is also called organisation.

In ideal situations, dead cells and inflammatory exudate would be completely cleared by macrophages, a process called **Resolution**. Sometimes this is not possible and other responses are set in motion. This leads to **Organisation**, which is the gradual conversion of the unwanted non-viable tissue into fibrous tissue – in lay terms a scar. The entire process is often described by the generic term **Repair**. Accompanying this process there may also be replacement of damaged epithelium by **Regeneration** to form new epithelium to cover a surface defect. Thus, the process of **Healing** involves a combination of regeneration and repair.
In chronic inflammation, monocytes in the blood are recruited to the site, where they mature in the tissue to form macrophages. Lymphocytes also enter the tissue. The macrophages secrete cytokines that are chemoattractant for endothelial cells and fibroblasts. The endothelial cells participate in the formation of new blood vessels (angiogenesis) that provide oxygen and nutrients to the area, whilst the fibroblasts synthesise the collagenous fibrous tissue. The lymphocytes respond to persistent foreign antigens and the B cells differentiate into plasma cells that synthesise immunoglobulin (antibody). This combination of capillaries and fibroblasts forming collagenous fibrous tissue is referred to as granulation tissue.

Thinking in 3-dimensions you can picture granulation tissue as the new formation of a complex maze of tiny capillary vessels made by the endothelial cells (angiogenesis). Macrophages clear debris, but at the same time macrophages secrete mediators that promote the growth of new capillaries and recruit and stimulate fibroblasts, forming granulation tissue. The capillaries establish a temporary circulation to the area, with beneficial effects, which include bringing oxygen and nutrients. The migrating fibroblasts synthesize collagen, forming the fibrous tissue to fill in the space left by clearance of damaged tissue. You could think of the granulation tissue as providing a 'bridge' between unwanted necrotic tissue and inflammatory exudate on the one hand and the final repair on the other. Usually the fibrous tissue forms gradually, the early scar grows to fill the space to be repaired, then eventually there is remodelling of the fibrous tissue and it shrinks to form a mature scar.
Macrophages are the central figures in chronic inflammation, as they can interact with lymphocytes, secrete factors involved in tissue injury (reactive oxygen species, proteases, inflammatory mediators), clear debris, as well as coordinate the granulation tissue response by inducing angiogenesis (via secretion of FGF & VEGF) and recruiting fibroblasts for synthesis of fibrous tissue (by secretion of FGF & TGF-beta).

3.0. Organisation of inflammatory exudate

3.1 Organising pericarditis of the heart (H&E and trichrome stains to show fibrin) – NDP Images: 3.1: 83.204; 3.2: 83.204 (Trichrome)
Glass Slides: 83.204; 3.2: 83.204 (Trichrome)
Photos: P3.1A & P3.1B

This heart was examined at post mortem (photos P3.1A and P3.1B). You can see the major vessels clearly. Note on the surface of the heart there is a thin layer of fibrinous exudate.

The pericardium refers to the thin layer of cells forming a sac around the heart, the cardiac equivalent of the peritoneum. Inflammatory exudate has formed over the heart. The section shows the thin atrial wall covered by a layer of eosinophilic, compacted fibrin. Growing into it from the base are new capillaries springing from the pre-existing blood vessels. Between them are many macrophages with a few lymphocytes, plasma cells and fibroblasts.

This pericarditis was caused by metabolic injury (an example of sustained chemical injury) resulting from renal failure. (Why retained waste products in the blood commonly injure the pericardium specifically is a mystery).

Q1. What is the special name given to this combination of fibroblast cells and new blood vessels?

Museum Specimens
Fibrinous pericarditis of the heart due to uraemia (renal failure) - P77.770
From a woman, who died of renal failure at the age of 60. Certain metabolic products (e.g. urea) in excess can cause tissue damage. Although it is not clear why, the pericardium is unusually susceptible. The presence of damaged or dead cells causes the release of inflammatory mediators, which affect blood vessels causing dilatation, increased permeability and the other processes of acute inflammation.
Fibrinogen escaped with other plasma proteins and was converted to fibrin, forming this yellowish film over the surface of the heart.

Fibrinous - purulent pericarditis - 21.60
No history is available.
Acute fibrinous pericarditis - P77.693
This followed a recent myocardial infarction. The presence of necrotic cells causes release of inflammatory mediators, which affect surviving blood vessels causing dilatation, increased permeability and the other processes of acute inflammation. Fibrinogen escaped with other plasma proteins and was converted to fibrin, forming this yellowish film over the surface of the heart.

Fibrino - purulent pericarditis – 28.200
No history is available

3.2. Organisation of exudate within the lung (H&E and Elastic Ponceau-S)
NDP Images: 3.3: 65.93; 3.4: 65.93 (Elastic Ponceau-S)
Glass Slides: 3.3: 65.93; 3.4: 65.93 (Elastic Ponceau-S)
Image Maps: A_CI_ON_LU_57; A_CI_ON_LU_13
Lung tissue several weeks after a case of pneumonia which failed to resolve.

Lung has many small air spaces, which may fill with inflammatory exudate during pneumonia. Macrophages often clear the exudate completely, leading to
resolution, but if the injury is prolonged, the exudate may not be cleared rapidly by absorption, coughing and macrophages. Then the inflammatory exudate undergoes repair / organisation with conversion into fibrous tissue. The basic process is the same as before, only the pattern is different.

New capillaries grow inwards, followed by fibroblasts. As the exudate shrinks, fibroblasts arrange themselves over it and secrete a 'basketwork' of collagen fibres. A special stain, Elastin Ponceau-S, can make this clearer. The pre-existing framework of lung tissue contains elastic fibres, which stain black with the stain, whereas the newly synthesised collagen fibres are dull red. Look for the outline of the pre-existing alveolar walls lining the air spaces in black (as they contain elastin fibres), whereas within some of the alveolar spaces there are loose 'baskets' of reddish collagen fibres resulting from organisation of exudate (see diagram). Other alveolar spaces have been cleared of exudate and contain only macrophages.

Q2. What would be the effect on lung function of permanent thickening of the alveolar walls by fibrous tissue?

Museum Specimens

**PLEURA: fibrous adhesions - R60.393**
Delicate fibrous adhesions bind the layers of the pleura together. This is the end result of a previous pleurisy (inflammation of the pleura).

**PLEURA: fibrous adhesions - P80.809**
Fibrous adhesions bind the surface of the lung to the pleura overlying an adjacent rib. Many such adhesions were found incidentally in an elderly man, probably due to past episodes of pneumonia with pleurisy.

Numerous fibrous adhesions are present involving the parietal (outer layer of the two layers of) the peritoneum. Some areas of the visceral peritoneum (the inner layer which overlies and adheres tightly to the small intestine,) also appear dull, due to the presence of a delicate, off-white layer of fibrinous exudate. Here we see both fibrinous and fibrous material. Which is likely to have come first chronologically?

3.3. Organising purulent exudate forming an abscess in adipose tissue.

**NDP Images: 3.5: 89.757 & 72.667**
**Glass Slides: 3.5: 89.757 & 72.667**
**Image Maps: A_CI_AB_SK_08; A_CI_AB_SK_37**

The most conspicuous feature is an irregular central area (often slit-shaped) of purulent exudate (central pus), mainly neutrophils, with a few macrophages phagocytosing them. There are some new capillaries running through the surrounding paler tissue of the abscess wall. The capillaries are made up of large, plump endothelial cells surrounding vascular spaces and you may have difficulty
in recognizing them at first. Around the edges, the process of organisation is occurring and there is fibrous tissue (collagen laid down by fibroblasts), forming the abscess wall that separates the central pus from the surrounding adipose tissue. A smaller number of chronic inflammatory cells (lymphocytes and plasma cells) can be seen in the abscess wall, including a few lymphoid aggregates (in some but not all sections). This is another example of chronic inflammation following on from acute inflammation. The chronic inflammation then leads on to repair in a sequential process.

Q3. What is the central cell co-ordinating the process of organisation of angiogenesis with fibrosis?

4.1. Repair of a skin wound – a common example of healing

4.2. A recent wound of the skin

Seventeen days earlier, what was thought to be a pigmented mole had been excised from the shoulder of a 38 year old woman by her G.P. It proved to be a type of skin cancer known as a malignant melanoma, which develops from the melanocytes of the epidermis. Therefore a wider excision was done and the original sutured wound is included in this section (an example of skin healing, [see diagrams below] in which the two sides of the wound are stitched together with only mild tissue damage and mild inflammation).

The exact appearance of the wound varies in different sections, but the regenerated epidermis has a flat inferior border, lacking normal rete ridges. Where the skin edges were brought together, there is irregularity and islands of epidermis have been pushed downwards into the dermis. This contains some apparently empty areas, which contain oedema fluid.

In the superficial part of the wound, fibroblasts are beginning the repair process. Deeper in, are pieces of suture material, (brown or refractile), surrounded by neutrophils and also, some large, multinucleated macrophages. The latter are formed by the fusion of macrophages and are called foreign body GIANT cells, responding to the suture material (acting as a foreign body that is not easily phagocytosed or broken down by ordinary macrophages).

Q4. Where is the REPAIR taking place? What cells types are involved in REPAIR?

Q5. Where is the REGENERATION taking place? What cells types are involved in REGENERATION?
Do not confuse the terms **fibrinous** and **fibrous**:

**Fibrinous exudate** = fibrinogen leaking from blood vessels forms fibrin threads in tissue

**Fibrous** = fibroblasts synthesising and secreting collagen fibres into the extracellular matrix

Please examine photograph P3.2: Small intestine, examined at post mortem.

Numerous fibrous adhesions are present involving the outer layer (peritoneum) of the intestines. There are several off-white bands of fibrous material, which adhere tightly to the small intestine. Sometimes the intestines may twist around such adhesions and become obstructed. This is a good example of how previous injury
has led to inflammation that has healed by repair with formation of fibrous tissue bridges – called adhesions.

Q6. What is the origin of plasma cells and what is their function? What are the other main cell types involved in chronic inflammation?

Q7. What is granulation tissue? What are the two main cell types present?

Q8. What chemical mediators trigger the onset of the repair process? Which cell secretes these mediators?

Q9. Draw a graph showing the numbers of neutrophils, macrophages, lymphocytes, plasma cells and fibroblasts as time passes in a focus of tissue injury. What factors contribute to the changes in cellular composition that your graph shows?

Q10. What is the difference between repair and regeneration?

5.0. Pathological process identification and report writing - Middle ear biopsy

NDP Images: 3.7: 78.1003
Glass Slides: 3.7: 78.1003

This tissue is taken from the middle ear of a patient with a longstanding (chronic) infection of the middle ear.

Please draw a diagram, write a description and provide an interpretation with identification of the pathological process.

Q11. Which cells of chronic inflammation and/or repair are most prevalent in this case?

6.0. Additional scanned slide images of chronic inflammation

If you have time, please take the opportunity to use the computer NDP system to view the following scanned slide images (not available as glass slides):

A) Stomach peptic ulcer: 50.520
We will discuss peptic ulceration in detail in the forthcoming problem solving exercise class.

B) Lung asbestosis: 69.139

C) Lung silicosis: 60.229
The importance of environmental exposure to agents that induce fibrosis in the lungs is demonstrated in these 2 sections of asbestosis (asbestos exposure) and silicosis (silica particle exposure). Certain foreign agents can activate macrophages that stimulate excessive fibrosis.
D) **Kidney amyloidosis: **63.493 **(Congo Red)**

In amyloidosis, certain over-produced proteins (e.g. immunoglobulin light chains or certain inflammatory proteins - SAA) are abnormally deposited in tissues (such as kidney and many other organs) as beta-pleated sheets. These abnormal protein deposits interfere with tissue function and can be stained by special stains (Congo Red stains amyloid red and shows apple green birefringence with polarised light).

**7.0. Words used**

<table>
<thead>
<tr>
<th>Fibrinous</th>
<th>containing fibrin</th>
<th><strong>Fibrinous exudate</strong></th>
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<tbody>
<tr>
<td>Purulent</td>
<td>containing pus (ie. containing cells, in particular neutrophil leukocytes)</td>
<td><strong>Fibrino-purulent exudate</strong> (ie. An exudate containing fibrin and pus)</td>
</tr>
<tr>
<td>Fibrous</td>
<td>connective tissue, mainly collagen</td>
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<tr>
<td>Epi (Greek)</td>
<td>upon heart</td>
<td><strong>Epicardium</strong> – the shiny surface layer over the heart. Commonly called visceral pericardium (to distinguish from parietal pericardium lining the pericardial sac)</td>
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<tr>
<td>Peri (Greek)</td>
<td>around heart</td>
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<tr>
<td>Cardia (Greek)</td>
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<td>Granulation tissue</td>
<td>This curious but important term arose because early military surgeons saw (and approved) shining tiny granules at the base of wounds that were about to heal. The granules were of course the sprouting endothelial buds: hence the association with a favourable outcome.</td>
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