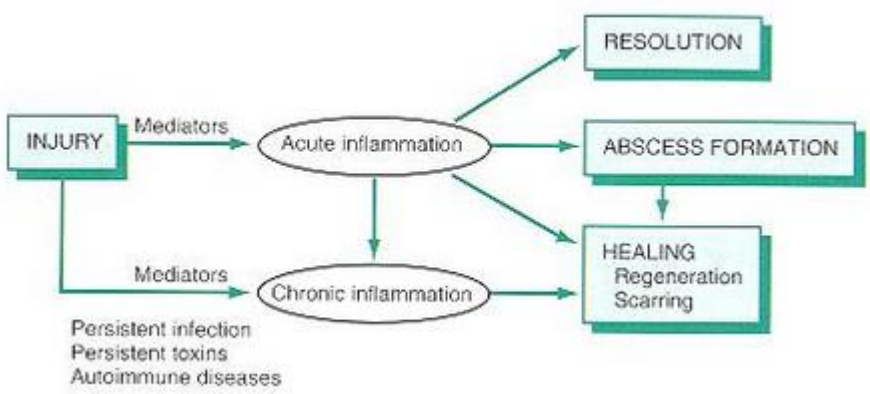
Group A revamp for healing: Shaylee Wang & Zamira Imin

Healing

Objectives

- Cell injury, cell death
- Acute and chronic inflammation
- What is healing
- Factors which influence wound healing
- Pathological aspects of wound repair
- Describe the healing of skin and mucosal wounds
- Describe the healing of bone fractures
- Describe the healing of a tooth socket
- Alveolar osteitis



Cell Injury: can occur in two ways

- Reversible injury
- Irreversible injury

Causes

1. Oxygen Deprivation
2. Physical agents (Trauma, Extreme temperatures, Radiation, electric shock)
3. Chemical agents (Simple chemical in high concentration, Poisons)
4. Infectious agents (Bacteria, viruses, fungi)
5. Immunologic reactions (Autoimmune disease)
6. Genetic derangements
7. Nutritional imbalance (Protein, vitamin deficiencies)

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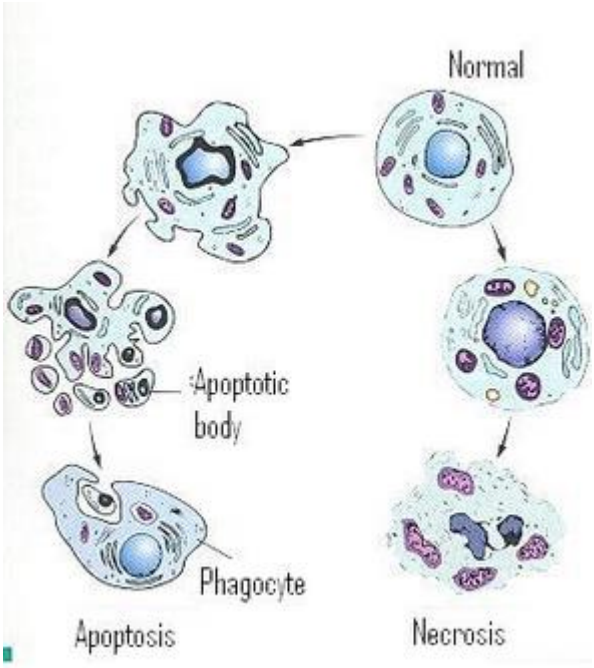
Cell death: may occur through necrosis or apoptosis

Necrosis will depend on:

1. The cellular response to injurious stimuli , type of injury, its duration and severity
2. The consequence of cell injury depends on the type, state and adaptability of the injured cell
3. Four vulnerable intracellular systems

- Maintenance of cell membrane integrity
- Aerobic respiration
    - There is inability to reverse mitochondrial dysfunction
    - There is profound disturbances in membrane function
- Protein synthesis
- Preservation of the integrity of the genetic apparatus



Apoptosis

- Programmed cell death (designed to eliminate unwanted host cells) and may occur
- During development
- homeostatic mechanism to maintain cell populations
- Defense mechanism (immune reaction)
- damage by disease or noxious agents
- Aging

Other Cellular responses to physiologic or pathologic stimuli:

1. Hyperplasia- An increase in the number of cells
2. Hypertrophy- increase in cell size (may lead to an increase in size of the organ), may be *physiologic* or *pathologic*
3. Atrophy- Shrinkage in the size of cell by loss of cell substance (disuse, denervation, diminished blood, inadequate nutrition, loss of endocrine stimulation, aging)
4. Metaplasia reversible change in which one cell type is replaced by another (Columnar to squamous

Acute and Chronic inflammation

Exogenous and endogenous stimuli causing cell injury can provoke a complex reaction in the vascularised connective tissue called inflammation:

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1. Acute inflammation: immediate and early response to an injurious agent. Three major components: alteration in vascular calibre increasing blood flow; structural changes in the microvasculature affecting permeability; emigration of leukocytes from vessels to site of injury
2. Chronic inflammation: inflammation of prolonged duration (weeks to months) and may arise due to persistent infection, prolonged exposure to toxic agents; autoimmunity
3. Granulomatous inflammation - distinct pattern of chronic inflammation in which activated macrophages with a modified epithelial-like(epitheliod) appearance predominate. *Granuloma is a focal area of granulomatous inflammation (aggregation of macrophages as above surrounded by a collar of mononuclear leukocytes)*

Features of Inflammation
Exudate- inflammatory extra vascular fluid with high protein, debris
Transudate- fluid with low protein concentration (ultra filtrate of plasma)
Oedema- denotes an excess of fluid in the interstitial or serous cavities
Pus (purulent exudate)- inflammatory exudate rich in leukocytes (mainly neutrophils) and cell debris
Characterised by infiltration with mononuclear cells (macrophages, lymphocytes, plasma cells); tissue destruction; Attempts at healing by CT replacement of damaged tissue through angiogenesis and fibrosis
Cells in Chronic inflammation: Lymphocytes (antibody and cell mediated immunity); Mast cells have receptors that bind IgE (Anaphylactic, drug reactions, foods etc); Eosinophils (associated with IgE)

WHAT IS HEALING?

Healing is the replacement of necrotic tissue by living tissue. To do this the body must: -

1) <u>Remove</u> the necrotic tissue-termed demolition
2) <u>Replace</u> the demolished tissue with living tissue

These two processes are closely co-ordinated.

WHAT ARE THE TYPES OF HEALING?

In humans there are two types of healing: -

1) <u>Regeneration</u>: This is when the necrotic cells are replaced with cells of the same type 2) <u>Repair</u>: When a collagen scar replaces the damaged tissue

Often a wound heals with a mixture of regeneration and repair.

There are two requirements for regeneration of a tissue:

1. The remaining cells of the tissue must be capable of dividing to produce new cells to replace those destroyed.
2. The collagen framework of the tissue must be intact to provide a scaffolding for the new cells.

So, the possibility of healing by regeneration depends on the type of cell injured and the type of injury. Cells can be divided into three groups depending on their ability to divide in mature tissue. These groups are: -

1. Labile cells - found in tissues with a continuous turnover of cells throughout life *e.g.* skin, epithelium lining the respiratory and gastro-intestinal tracts, including the oral mucosa.
2. Stable cells - these are long lived cells which are capable of dividing and are found in tissues with a low rate of cell turnover *e.g.*hepatocytes, fibroblasts, osteocytes.
3. Permanent cells - These are unable to divide postnatally and regeneration is therefore impossible. Examples are neurones and cardiac muscle cells

As well as the type of injured cell, the type of injury is important in determining whether a tissue heals by regeneration. Orderly regeneration can only occur when the collagen framework of the tissue is intact to act as a scaffold for the new cells to attach to. In most tissues the basement membrane forms the framework. In an abscess the enzymes released often destroy the collagen framework and healing, even in a tissue composed of labile or stable cells, will take place by repair.

HEALING BY REGENERATION

As described above. Examples of healing by regeneration are the healing of the oral epithelium after trauma *e.g.* a cut with the bristles of a new toothbrush. The oral epithelial cells are labile cells and the basement membrane provides the scaffold. Phagocytic cells remove damaged cells. Growth factors stimulate proliferation of the epithelial cells and growth inhibitors suppress proliferation once sufficient new cells have been formed. Once the process of regeneration is complete the tissue will be exactly the same as it was before the injury.

HEALING BY REPAIR

The tissue damage would have initiated an acute inflammatory response with changes in vascular permeability and emigration of white cells. Healing by repair begins with phagocytic cells, especially macrophages removing necrotic tissue (demolition). Immature granulation tissue is then formed. Granulation tissue is made up of a) fibroblasts which synthesise collagen and extracellular matrix molecules, b) endothelial cells and new capillaries which re-establish a good blood supply to the area and c) macrophages for phagocytosis and secretion of growth factors. Two to three days after the injury fibroblasts and endothelial cells begin to proliferate in the living tissue adjacent to an area of necrosis. Over the next few days they migrate together as granulation tissue into the necrotic zone. Some fibroblasts in granulation tissue are able to contract (myofibroblasts) and draw the ends of a wound together-wound contraction. This leads to faster healing and a smaller scar. As granulation tissue matures an increasing amount of collagen is deposited and the fibroblasts reduce in size and number. The vessels also reduce in size and number. The end result is a dense fibrous scar. This appears pearly white clinically.

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Factors which influence wound healing

Local

- Infection, the most important cause of delayed healing
- Impaired blood supply may delay healing
- Foreign bodies in the wound e.g. glass, dirt, bone, sutures
- Mechanical factors such as early movement of the wound may delay healing
- Size, location and type of wound: Wounds in well vascularized areas such as the oral mucosa heal more easily than those in areas with a lesser blood supply.

Systemic

- Diabetes
- Medications e.g. corticosteroids, chemotherapy , bisphosphontes.
- Nutritional deficiency e.g. protein deficiency and vitamin C deficiency inhibit collagen synthesis and retard healing.
- Systemic illness.

Pathological aspects of wound repair

Complications of wound healing arise from abnormalities in the basic repair process and are usually grouped into three categories

1. deficient granulation tissue/scar formation
2. excessive formation of repair tissue
3. formation of contractures

Deficient Granulation Tissue/Scar Formation:

In skin wounds inadequate formation of granulation tissue or assembly of the scar can results in wound dehiscence (rupture) or ulceration. Wound dehiscence is usually seen in abdominal surgery and ulceration of a wound is usually associated with inadequate vascularization during healing. A dry socket (see below) fits in this category.

Excessive Formation of Repair Tissue

Keloid or hypertrophic scar tissue is due to excessive amounts of collagen forming after an injury. Excessive granulation tissue (exuberant granulation tissue) may develop in a wound.

Formation of Contractures

Contracture is an exaggeration of the normal contraction process in healing and may result in deformities in the wound and surrounding area. This is seen most often after burns.

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HEALING OF SKIN / MUCOSAL WOUNDS

Healing by first intention

Healing of skin involves regeneration of the surface epithelium and repair of the dermis/submucosa (healing by regeneration on the top, healing by repair occurring on the bottom). The steps involved in the healing of a clean skin incision (clean skin incision: A wound characterized by a clean cut, as by a sharp instrument such as by knives or broken glass, razor etc.) (Healing by first intention; primary union) are as follows

1-48 hours:

The **inflammatory phase** is the body's natural response to injury. After initial wounding, the blood vessels in the wound bed contract and a clot is formed this will dry to form a scab.
Once haemostasis has been achieved, There will be an increase in vascular permeability, and vasodilation allow essential cells; neutrophils, macrophages, growth factors, enzymes and nutrients to reach the wounded area. At this stage the characteristic signs of inflammation can be seen; erythema, heat, oedema, pain and functional disturbance. The predominant cells at work here are the phagocytic cells; 'neutrophils and macrophages'; mounting a host response and phagocytise any necrotic tissue

2-3 days- 3 weeks

During **proliferation**, the wound is 'rebuilt' with new granulation tissue which is comprised of collagen and extracellular matrix and into which a new network of blood vessels develop, a process known as 'angiogenesis'. Immature granulation tissue is then formed. Granulation tissue is made up of a) fibroblasts which synthesise collagen and extracellular matrix molecules, b) endothelial cells and new capillaries which re-establish a good blood supply to the area and c) macrophages for phagocytosis and secretion of growth factors. Two to three days after the injury fibroblasts and endothelial cells begin to proliferate in the living tissue adjacent to an area of necrosis. Over the next few days they migrate together as granulation tissue into the necrotic zone. Healthy granulation tissue is dependent upon the fibroblast receiving sufficient levels of oxygen and nutrients supplied by the blood vessels. Healthy granulation tissue is granular and uneven in texture; it does not bleed easily and is pink / red in colour. The colour and condition of the granulation tissue is often an indicator of how the wound is healing. Dark granulation tissue can be indicative of poor perfusion, ischaemia and / or infection. Epithelial cells finally resurface the wound, a process known as 'epithelialisation'.
The surface epithelium will slowly appears normal. Granulation tissue fills the site of the incision, neovascularization is maximal and collagen fibres are more abundant and begin to bridge the incision.

3 weeks -6 month

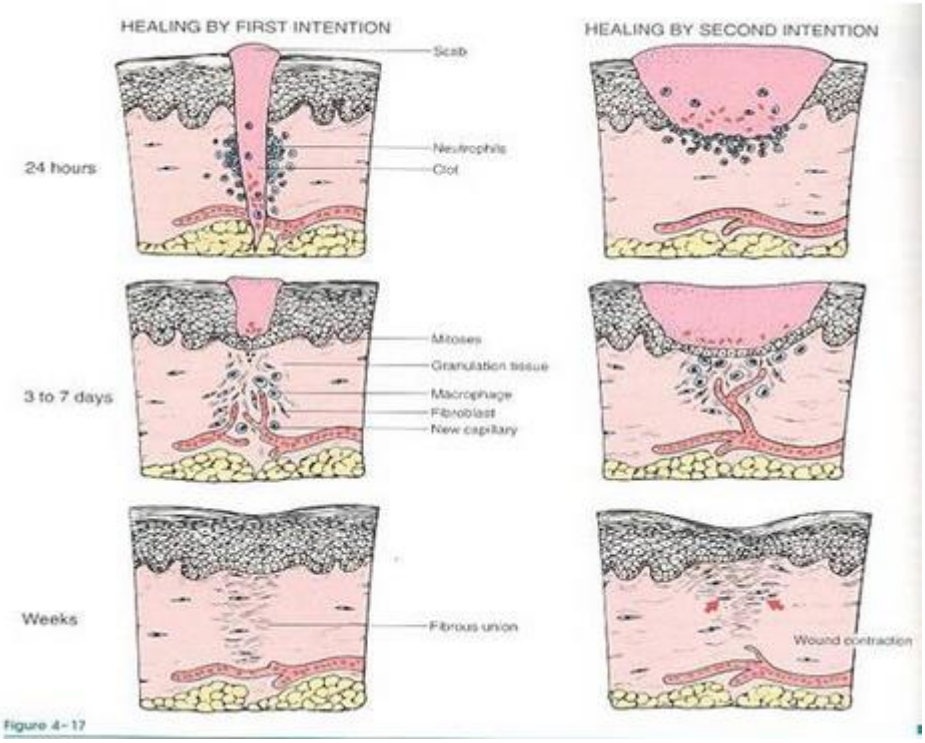
This phase involves remodelling of collagen. Cellular activity reduces and there is decrease in vascularity in the wounded. There will be an increase in tensile strength of the wound to restore its strength however, it will restore to only 70% of original strength.

Important to note epidermal appendages (skin, sebacous gland, sweat gland, arrector pilli) do not regenerate

Healing by second intention

The healing of a large gaping wound (healing by second intention) varies from healing by primary intention in three main ways:-

- There is a larger tissue defect with fibrin and necrotic debris that has to be removed, hence the inflammatory reaction is more intense
- A much larger amount of granulation tissue is necessary to fill the defect
- Wound contraction is an important feature and is more pronounced than in healing by primary intention.



HEALING OF BONE FRACTURES

The 4 steps involved in the healing of an uncomplicated fractured bone are as follows:

1. Hematoma formation

- A **haematoma** develops between the fractured bone ends and surrounds the area of bone injury. It provides a fibrin mesh, which helps to seal off the fractured area and provides a framework for the ingrowth of fibroblasts, new vessels and inflammatory cells.
- Inflammatory cells migrate to the area and release factors that activate osteoprogenitor cells in the periosteum and medullary cavity and stimulate osteoclastic and osteoblastic activity

2. Fibrocartilagenous callus forms

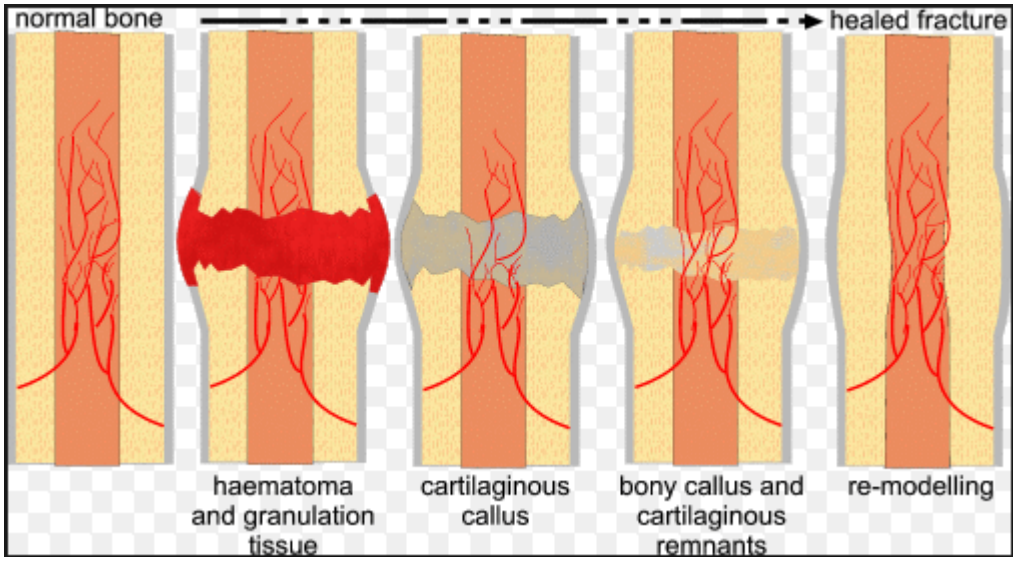
- By end of first week the haematoma is organising, the adjacent tissue is ready for matrix production and the fractured bone ends are being remodelled. The soft tissue surrounds the fracture and anchors the bone ends, but provides little support thus it is known as **soft tissue callus or procallus**

3. Fibrocatilagenous callus to bony callus

- Activated progenitor cells produce trabeculae of woven bone. Some cells may differentiate into chondroblasts and make cartilage. The repair tissue reaches its maximum size by about the third week. Newly formed cartilage will undergo endochondral ossification and eventually the bony ends are bridged by a **bony callus**, which will increase in strength as mineralisation continues.

4. Bone remodelling

- The repairing bone reduces in size as a result of remodelling and replacement of woven bone with lamellar bone until the shape of the normal bone and the medullary cavity is restored.
- Normal bone architecture may not be restored in cases where bone ends are displaced and/or there is a comminute fracture or in cases that are inadequately immobilised.



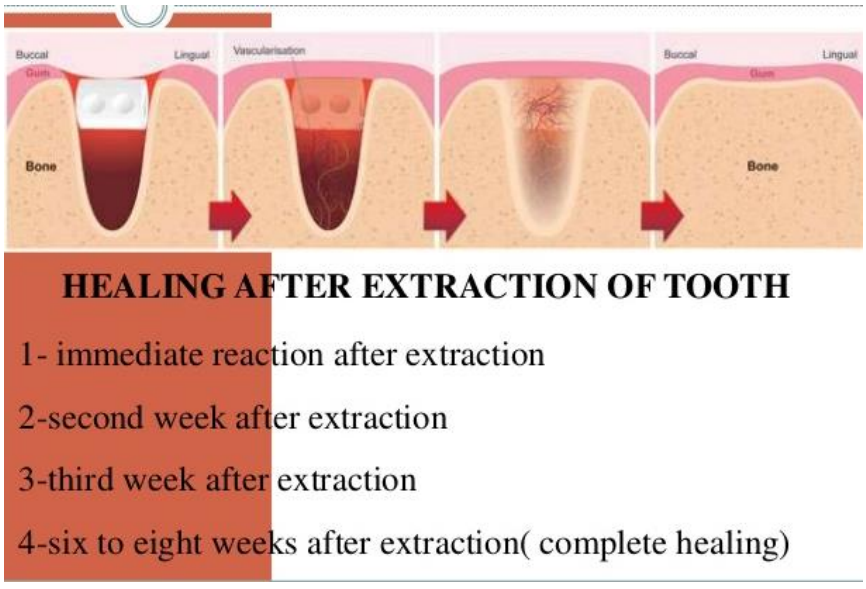
HEALING OF A TOOTH SOCKET

The healing of a tooth extraction socket is the same as for other wounds of the body except for the anatomical site. All the time the wound is bathed in saliva that contains numerous bacteria. In all oral wounds the blood clot doesn't dry out and so a scab does not form.

- Immediately after extraction: A blood clot fills the socket and the ends of the torn blood vessels in the periodontal ligament become sealed off. It is very important that the blood clot does not get dislodged since it forms the scaffold for the healing process to proceed. The unsupported gingival tissue collapses across the socket and helps maintain

the clot in position. Within the first 24-48 hours the remaining vessels in the periodontal ligament dilate and neutrophils mobilise to the area.

- First week: Within the first week there is proliferation of fibroblasts and endothelial cells from the remnants of the periodontal ligament which begin to grow into the clot. The clot is gradually being replaced by granulation tissue. Acute and chronic inflammatory cells are present, especially on the surface of the clot. The epithelium at the periphery of the wound will be proliferating. The crest of the alveolar bone at the margin of the socket will show osteoclastic activity
- Second week: Further granulation tissue formation is seen. The remnants of the periodontal ligament are no longer recognisable. Further epithelial proliferation over the surface of the wound occurs, but particularly in molar teeth, the epithelium is not yet intact. Bony margin shows prominent osteoclastic activity. Fragments of bone, which may have fractured from the rim of the socket, are being resorbed or undergoing sequestration.
- Third week: Maturing granulation tissue is present. Delicate trabeculae of osteoid forming from pluripotent cells of the original periodontal membrane are seen. The cortical bone of the socket remodels to become less dense and the crest of the alveolar bone is rounded off. The surface of the socket is completely epithelized.
- Fourth week: There is continued deposition and remodelling of bone. Radiographic evidence of new bone formation is seen at about 6-8 weeks and the outline of the socket will be observed radiographically for 4-6months.



Dry socket (alveolar osteitis)

Definition and epidemiology

- The loss of the blood clot in a tooth extraction socket prevents normal healing and leads to a condition known as a dry socket. It is seen most often in the posterior mandible and may follow the extraction of 25-30% of mandibular 3rd molars. It is seen most often in people aged between 20-40years and there is no significant sex predilection.

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Aetiology, pathogenesis and predisposing factors

- Fibrinolysis leads to destruction of the clot. This is secondary to transformation of plasminogen to plasmin, leading to lysis of fibrin and production of kinins. Local trauma, (difficult extraction, inexperienced surgeon), oestrogens (OCP) and bacteria (prior infection) can stimulate fibrinolysis. Inadequate irrigation at surgery and tobacco smoking have also been related to dry socket.

Clinical features

- The patient complains of severe pain and a bad taste and smell about 3-4 days after the extraction. Examination shows a bony socket with bare bony walls or containing a small amount of grey clot.

Investigations

- A radiograph should be taken to confirm there are no retained tooth or bone fragments.

Management

- The socket is irrigated and packed with dressing allowing healing to proceed slowly.

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CASES

In this section you will be required to look at five cases, look at images and respond to questions at the end of each case

Case 1: Curettings from a tooth socket

This specimen is from a 55-year-old female who presented complaining of intense pain in the 36 socket. The 36 had been extracted about a week previously. On examination the socket was empty with an exposed piece of bone visible

Figure 1:

Under LA, the small amount of soft tissue associated with the socket was removed and submitted for histological assessment (Figures 2,3,4,5)

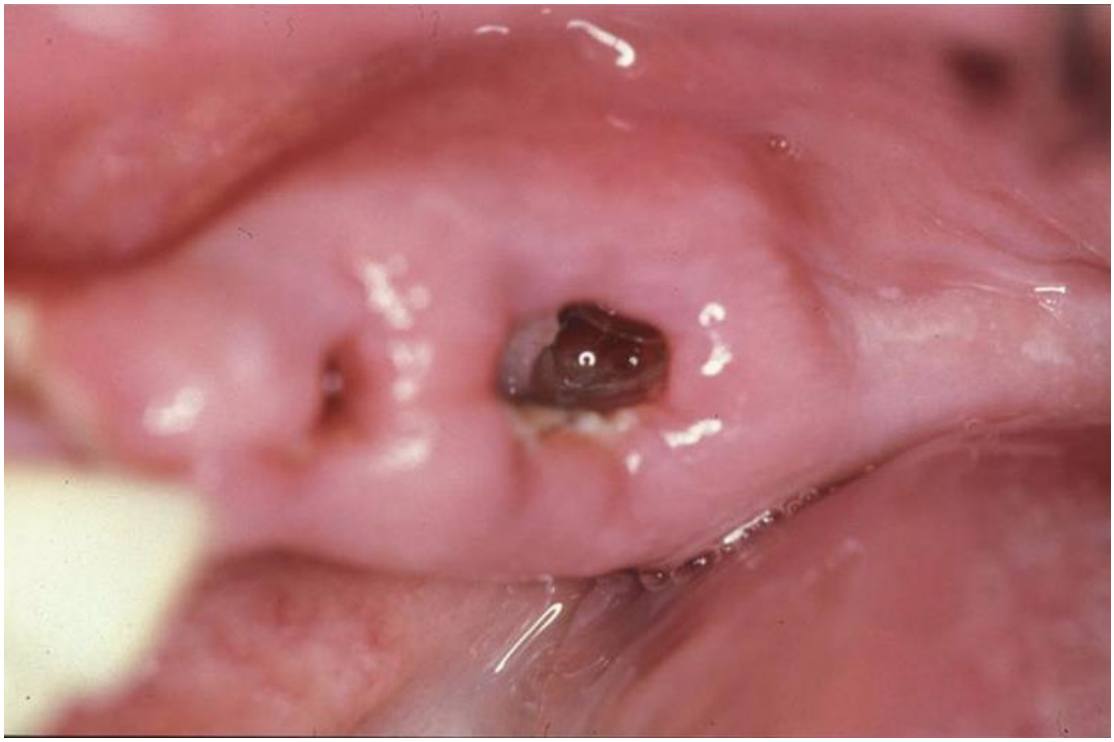


Figure 2:

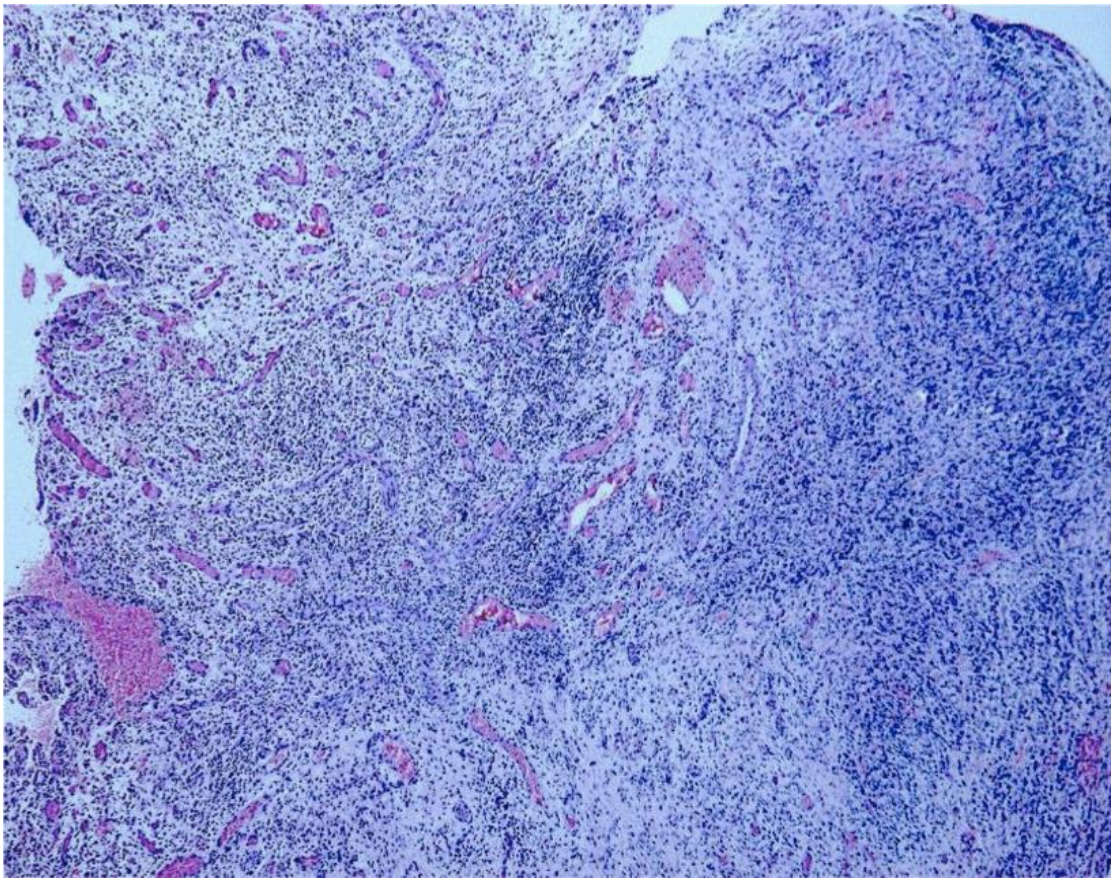


Figure 3:

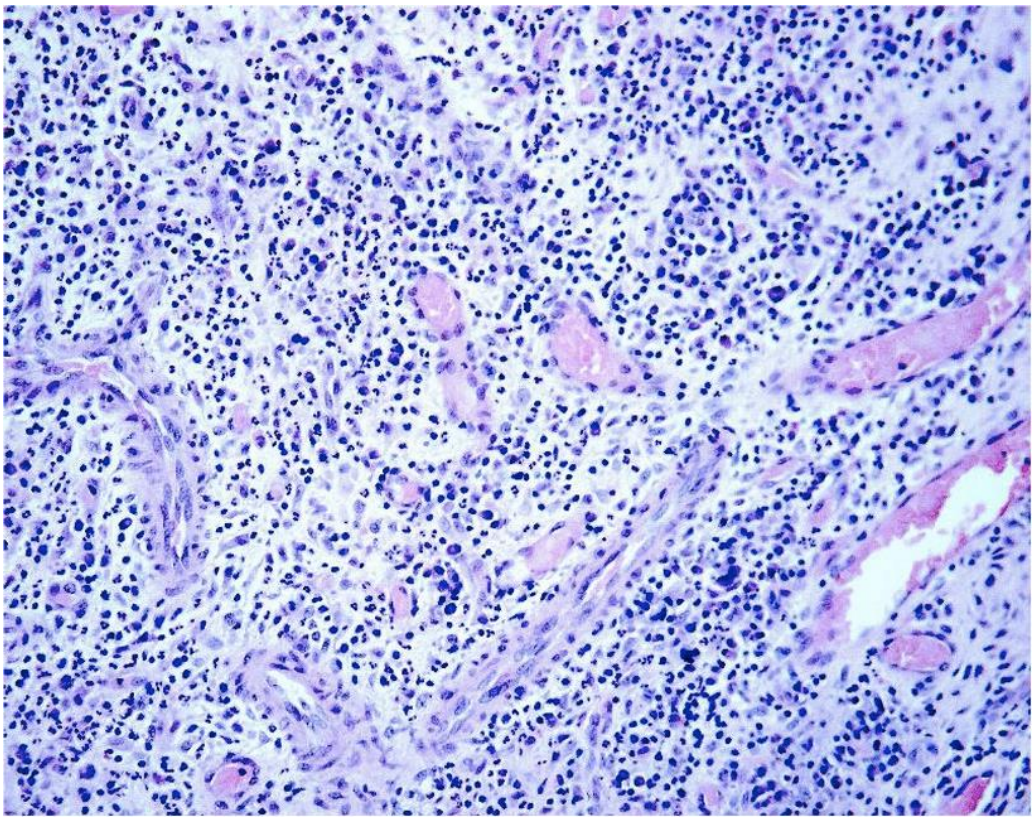


Figure 4:

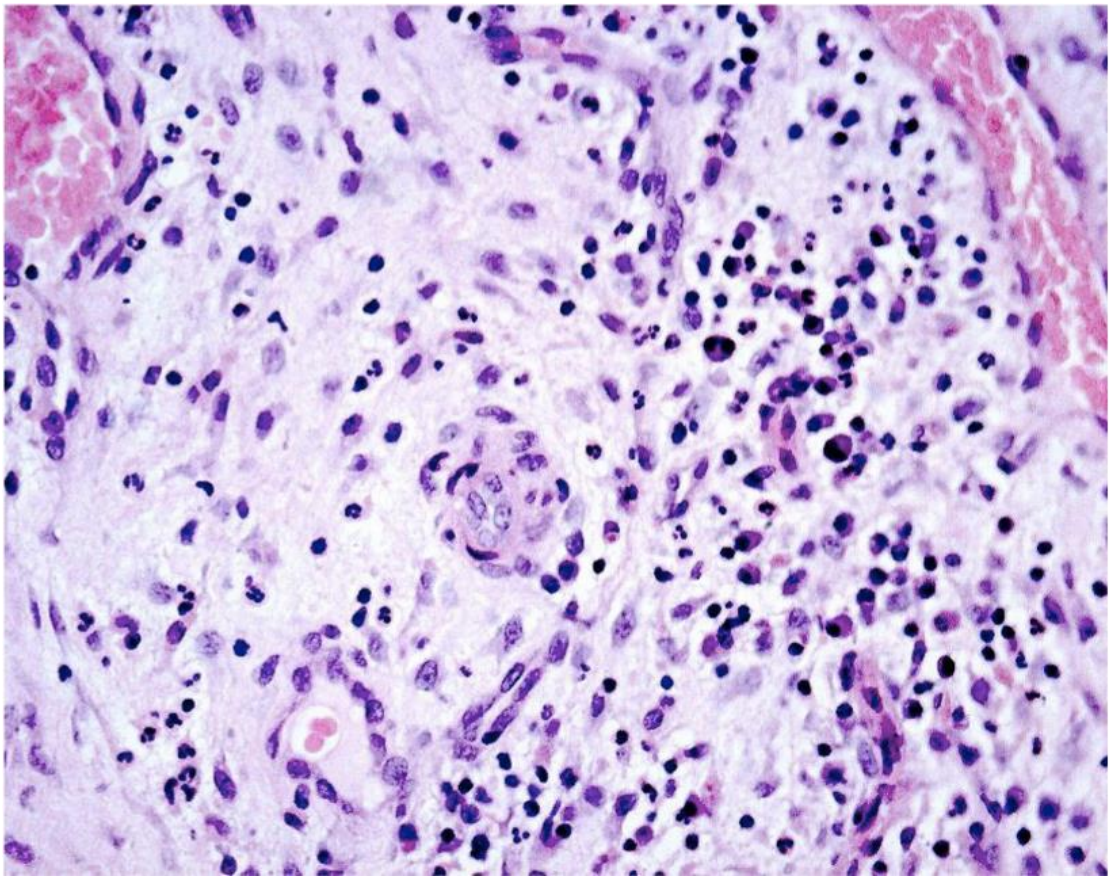
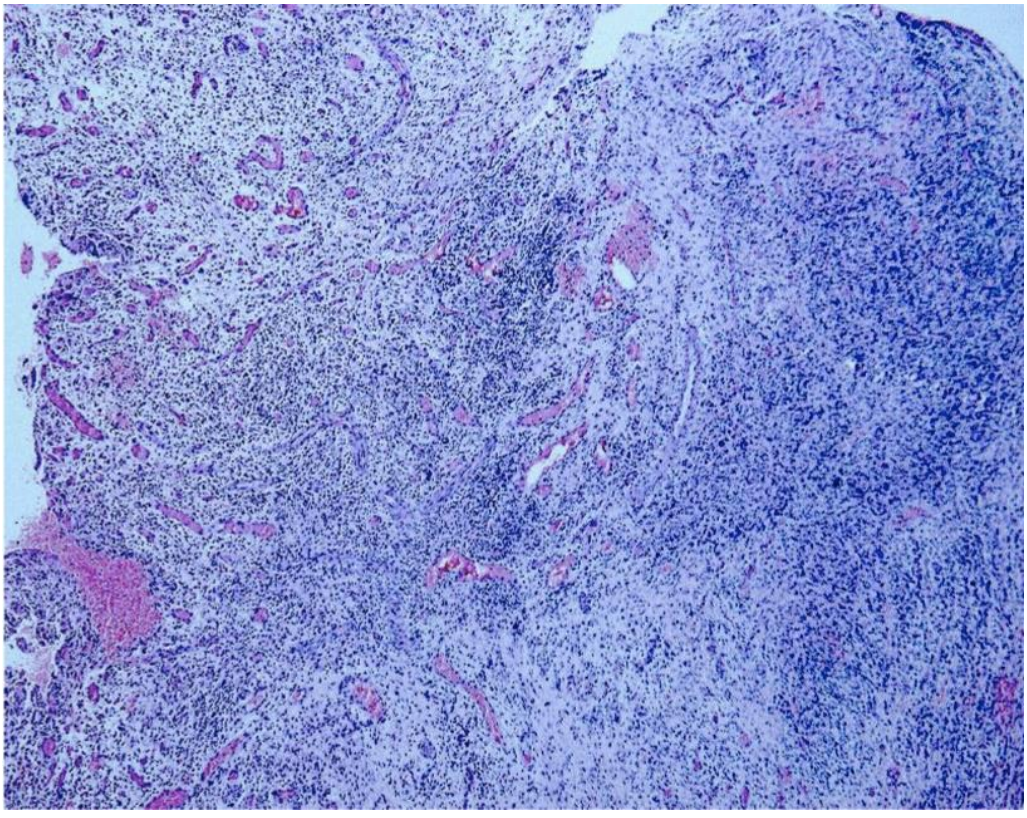


Figure 5:



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Questions

1. Identify the general cell types and tissue in this specimen? List and describe the cell/tissue types you see.
2. What pathological processes are involved?
3. What is the clinical diagnosis?

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Case 2: Curettings from a tooth socket

This patient presented complaining of 'bits of bone coming out of my tooth socket'. The 46 had been extracted a month previously. The socket was curetted and the tissue sent for histological examination (Figs 1,2,3,4)

Figure 1:

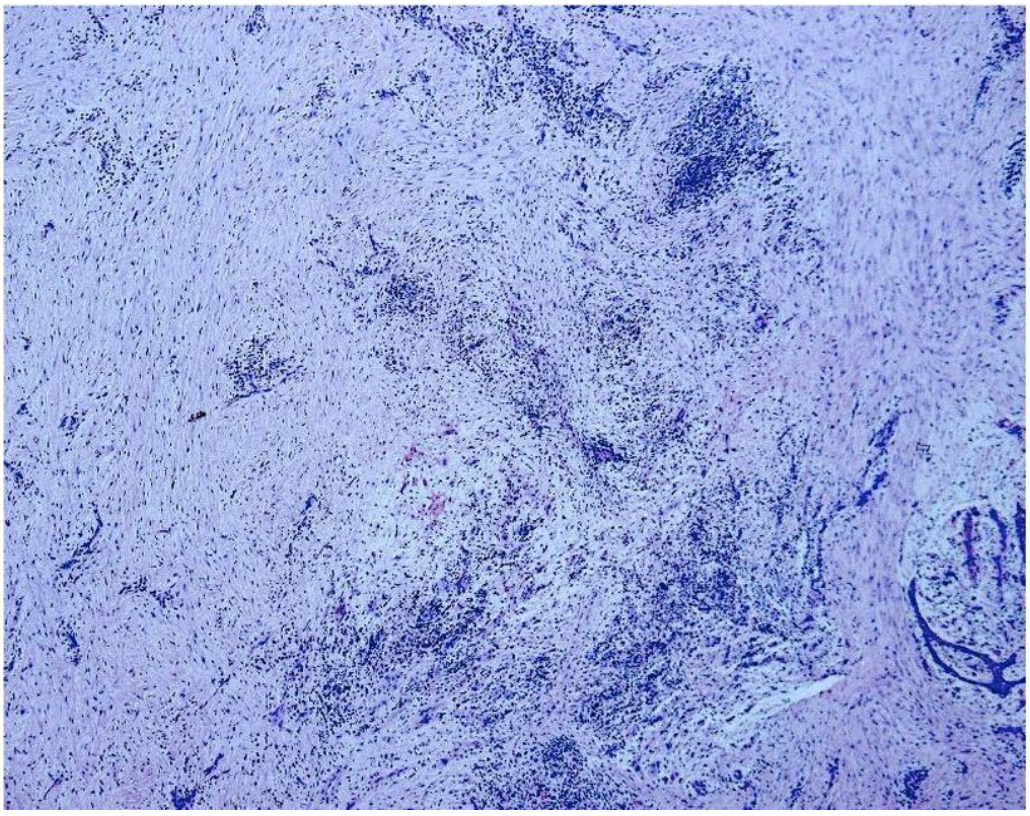

Figure 2:

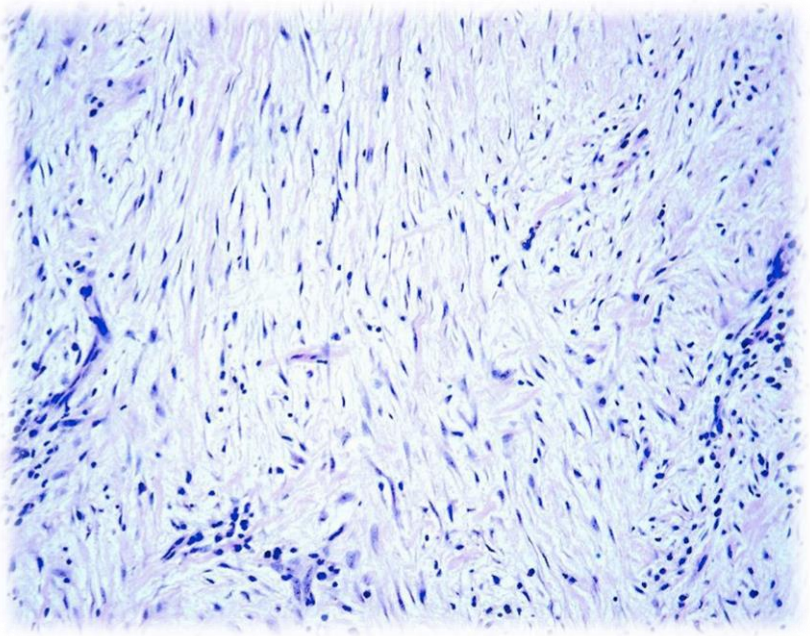

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Figure 3:

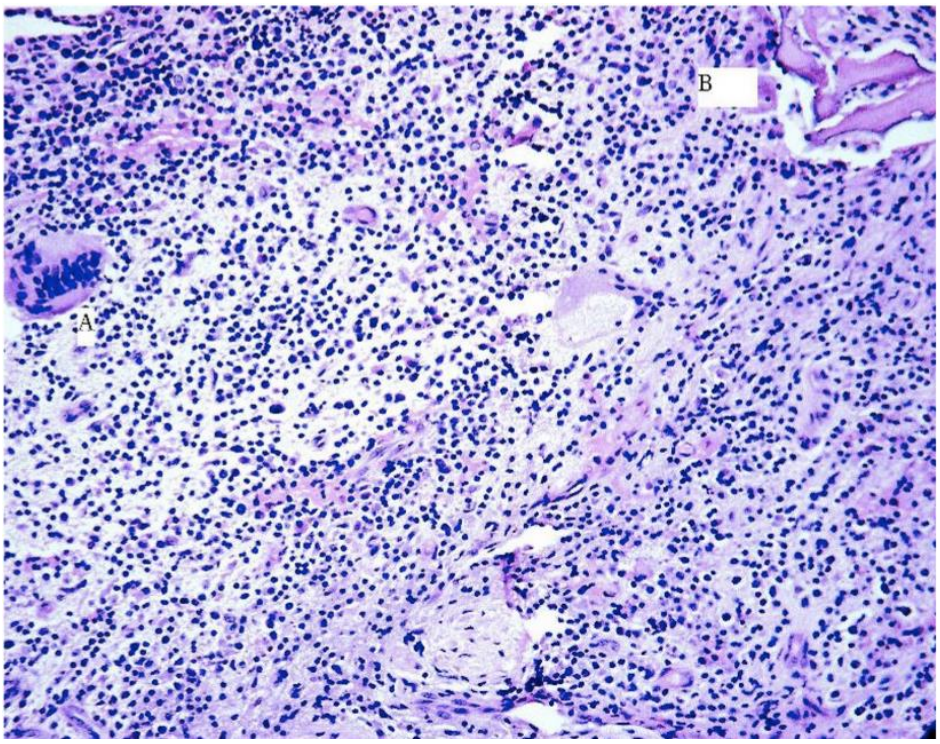
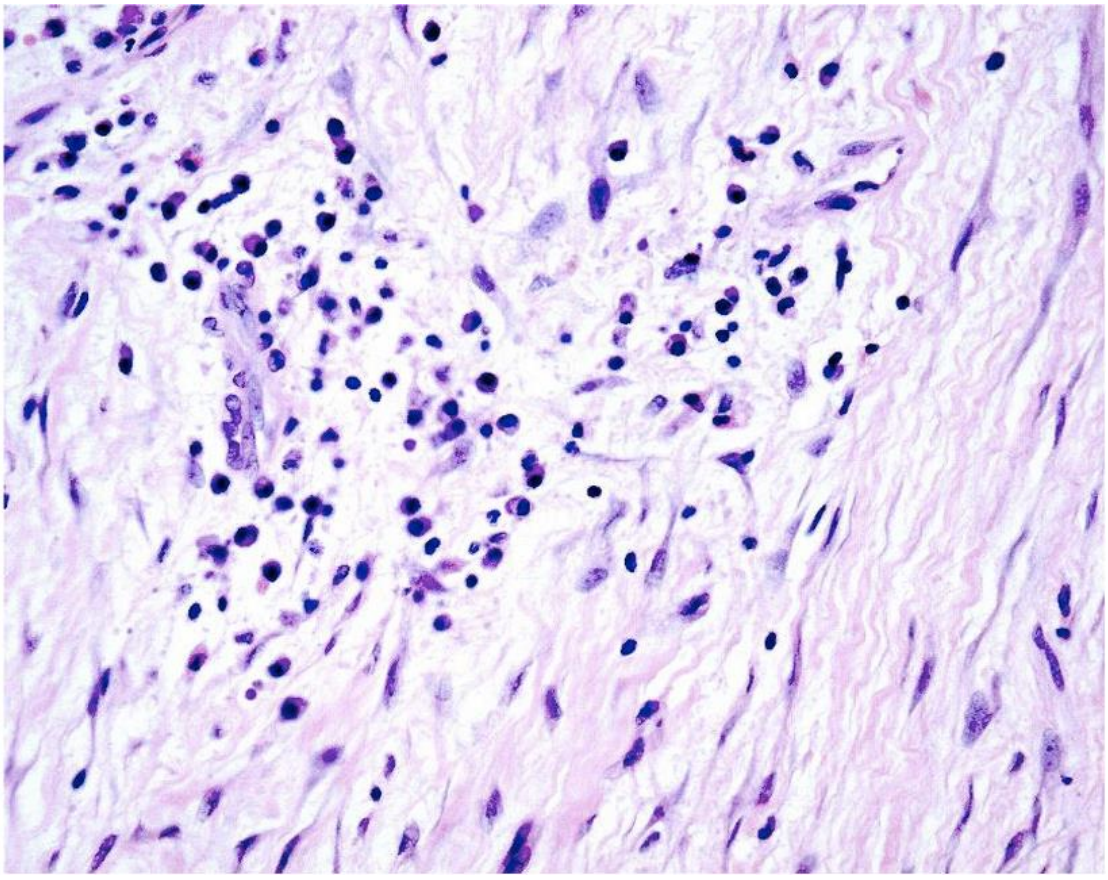


Figure 4:



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Compare the features of this specimen with Case 1

Questions:

What is the structure to the right of label A and above label B in Fig 3?

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Case 3: Scar tissue

One year ago this 11 year old female fell off her bike resulting in a through and through laceration of her lower lip. She presents now with excessive scar tissue in her lower lip. This has been removed surgically and submitted for histological examination (Figs 1, 2, 3)

Figure 1:

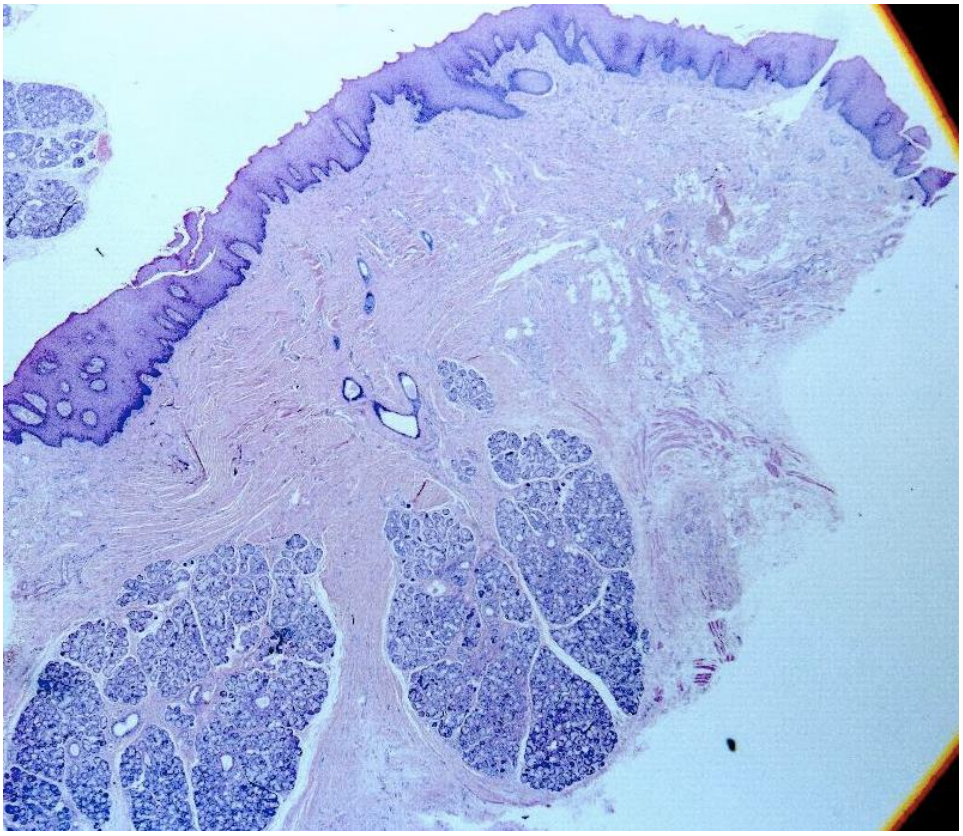

Figure 2:

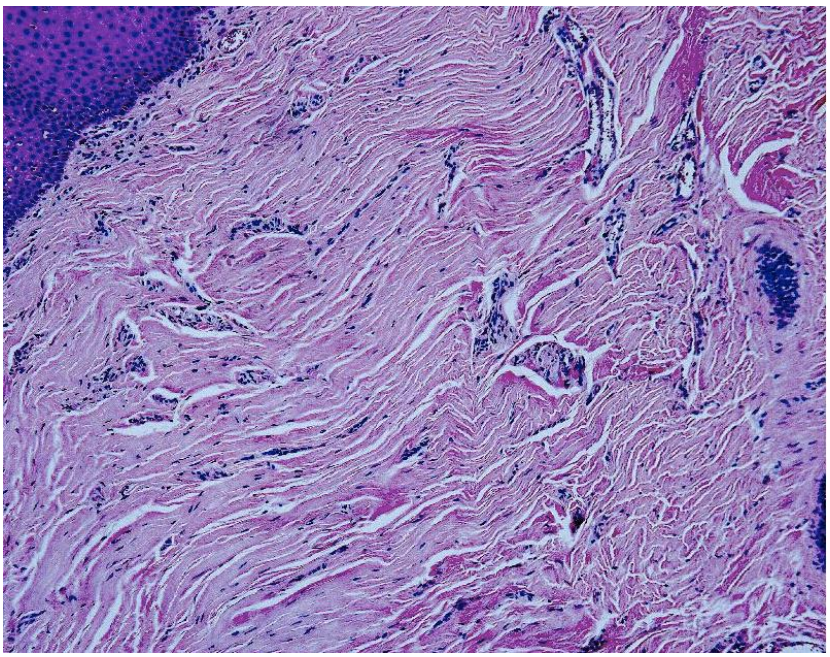

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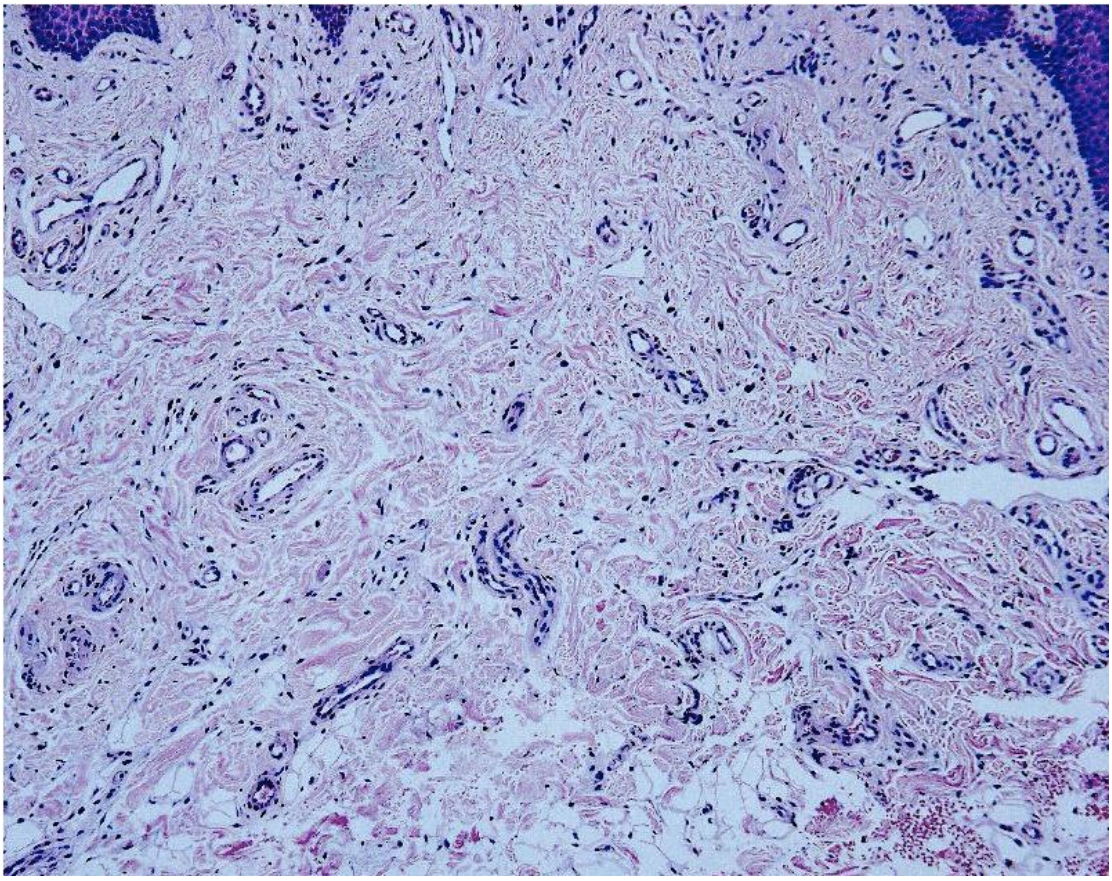
Figure 3:



Questions:

1. Look at Figure 1 and identify all the tissues.
2. Look at Figure 2 and Figure 3, one slide shows normal lamina propria and submucosa of the lower lip and one shows fibrosis. Which is which, and why?
3. What are the histological features of scar tissue?

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Case 4 - Periapical Scar

Look at Figures 2 and 3 first. These specimens are from a radiolucent lesion associated with the apex of 23. The tooth had been the root filled five years previously. Look at the questions then refer to Figure 1.

Figure 1: (not the same patient - see below)

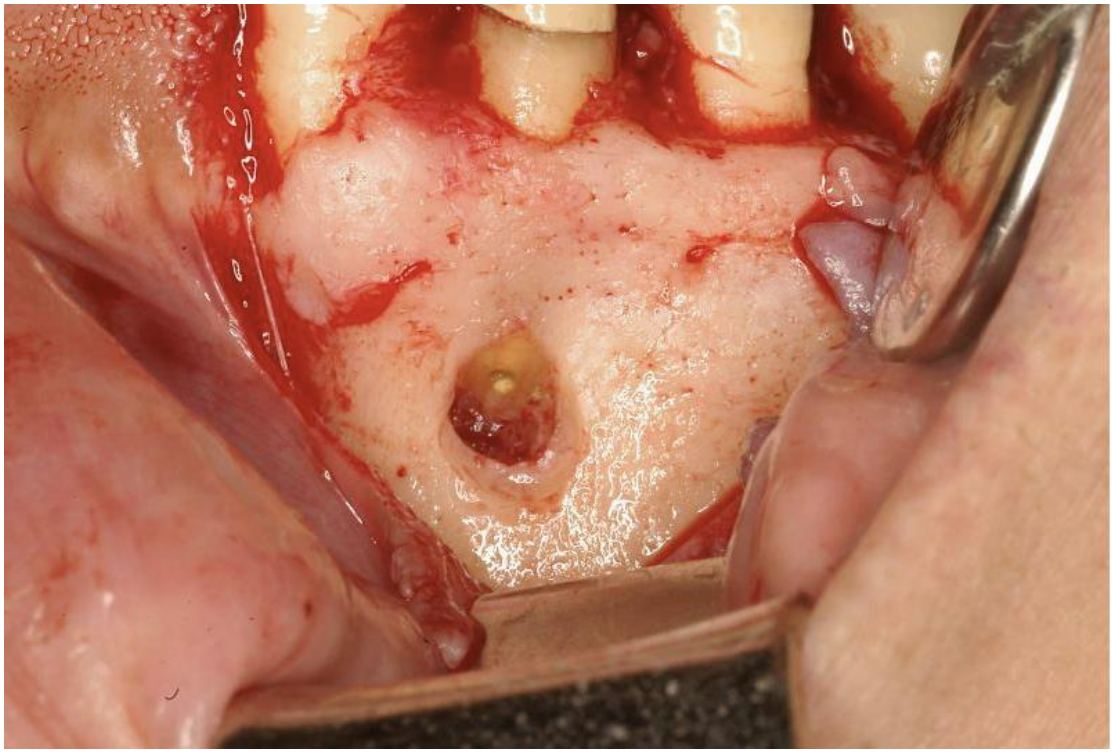


Figure 2:

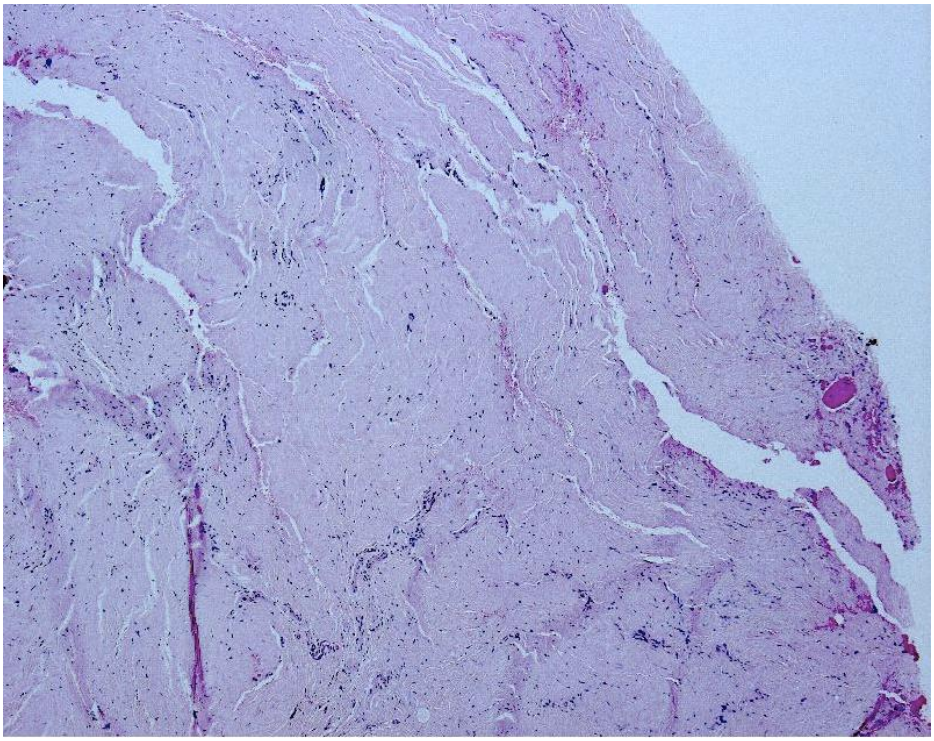
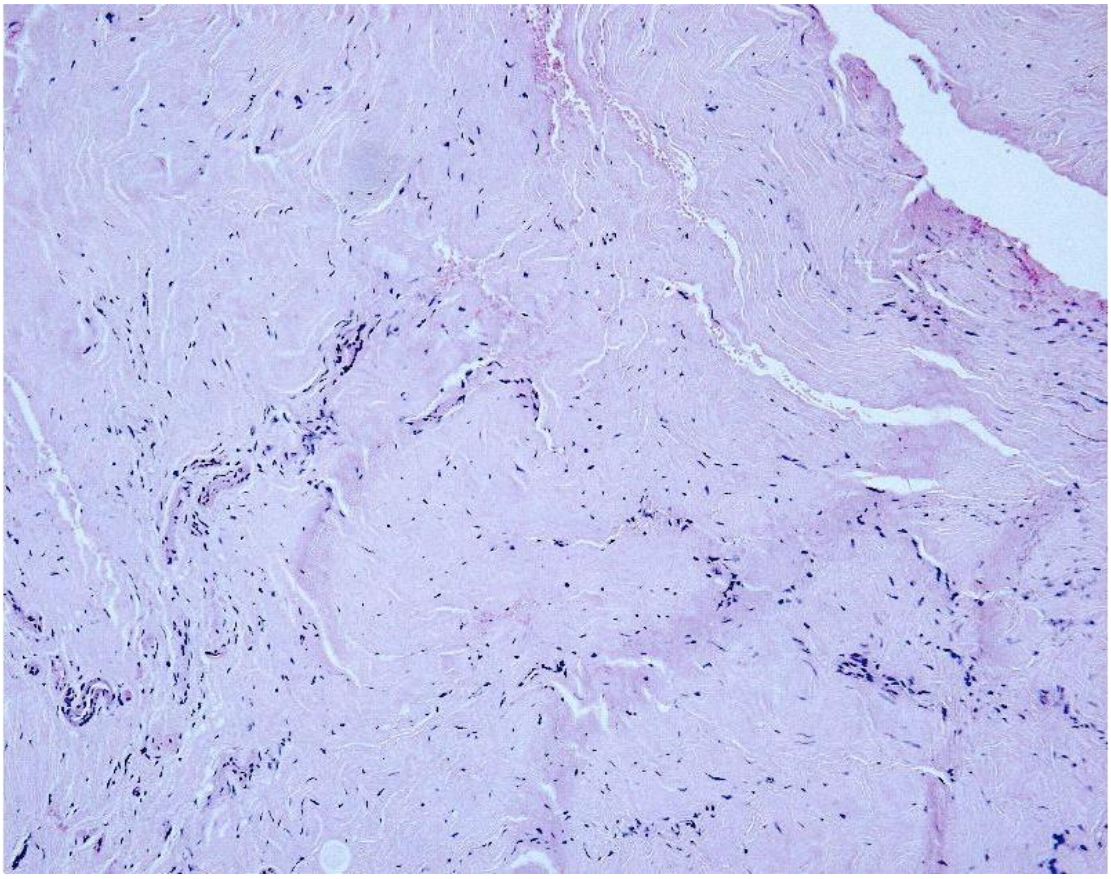


Figure 3:



Questions:

1. How would this specimen have been obtained? (the tooth was not extracted) Hint, have a look at Figure 1, from a different patient, but showing the same procedure.
2. Describe the histological features seen in figures 2 and 3.
3. What may a periapical film taken one year previously have shown?

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Case 5: Parotid Gland with Fibrosis

Fibrosis can also occur in other tissues of the body such as salivary glands as a result of chronic disease process.

This 60-year-old female presented with a complaint of 'lumpiness' in her right parotid gland. She had no significant medical history. The area was biopsied and sent for histological examination (Figures 1 and 2)

Figure 1:

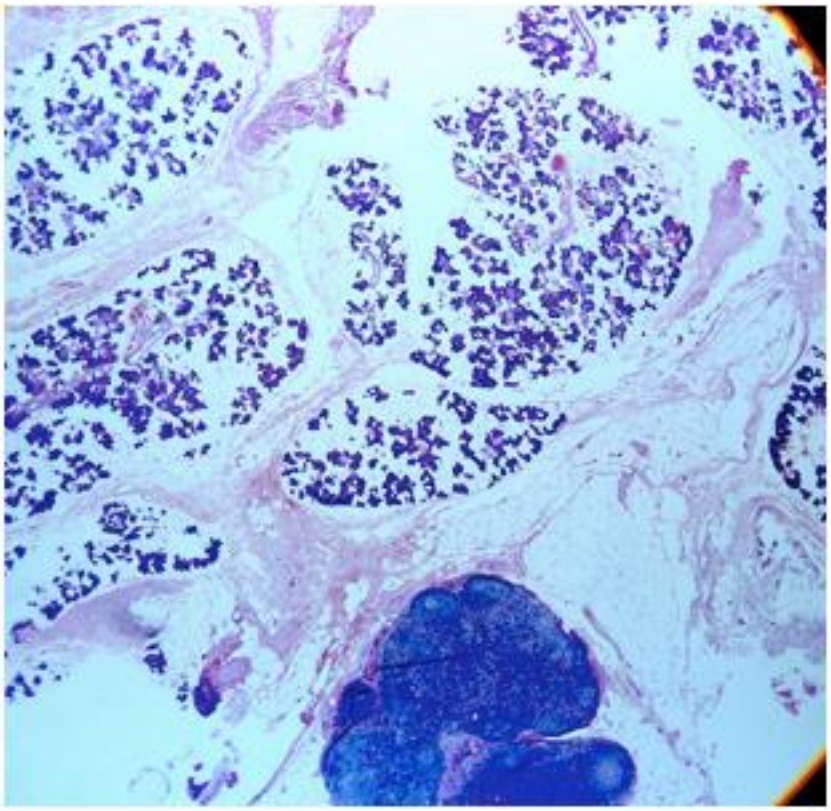
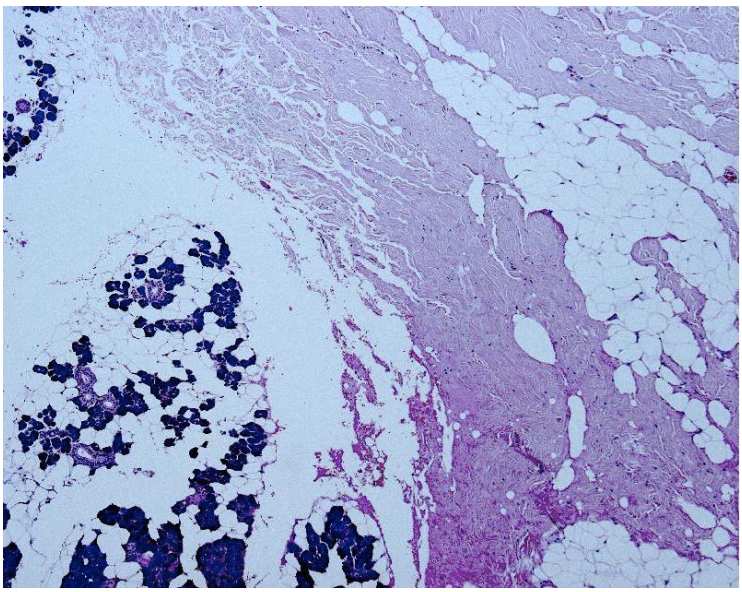


Figure 2:



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Questions:

1. Revise the normal histology of the parotid gland and identify the tissues in Figures 1 and 2.
2. Which areas are normal and which are abnormal?

Healing Self-Assessment Task

Please answer the following questions:

1. What is granulation tissue?
2. How does scar tissue differ from ordinary fibrous tissue?
3. Are the following true or false?

Soon after an uncomplicated tooth extraction the patient should be advised to

a) Rinse vigorously to assist with prevention of infection
b) Apply pressure to the socket e.g. with gauze, to reduce bleeding
c) Take the next three weeks off work/study
d) Take aspirin for pain relief

MULTIPLE CHOICE:

Which is <u>not true</u> about the difference between healing by first and second intention:

A) There is a larger tissue defect with fibrin and necrotic debris that has to be removed, hence the inflammatory reaction is more intense in second intention healing
B) Epithelial spurs are only seen in primary intention and not in secondary intention healing
C) Wound contraction is an important feature of both types of healing
D) A much larger amount of granulation tissue is necessary in secondary healing
E) All of above are true

Clinically, dry sockets:

A) 2 weeks after extraction
B) will bleed profusely
C) patients complains of foul smell but no pain
D) are asymptomatic hence rarely diagnosed
E) patients will usually present with symptoms 3-4 days after extraction

Cell injuries occur due to:

A) oxygen deprivation
B) infectious agents
C) genetic derangements
D) immunologic reactions
E) all of the above

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Acute inflammation composes of:

A) alteration in vascular caliber increasing blood flow
B) prolonged duration
C) lack of leukocyte activity
D) autoimmunity
E) no alterations in microvasculature