Acute Inflammation

Inflammation is the reaction of the tissue elements to injury. Vascular changes occur, resulting in the generation of a protein rich exudate. So long as the injury does not totally destroy the existing tissue architecture, the episode may resolve with restoration of original tissue architecture.

Vascular changes

- Vasodilation occurs and persists throughout the inflammatory phase.
- Inflammatory cells exit the circulation at the site of injury.
- The equilibrium that balances Starlings forces within capillary beds is disrupted and a protein rich exudate will form as the vessel walls also become more permeable to proteins.
- The high fibrinogen content of the fluid may form a fibrin clot. This has several important immunomodulatory functions.

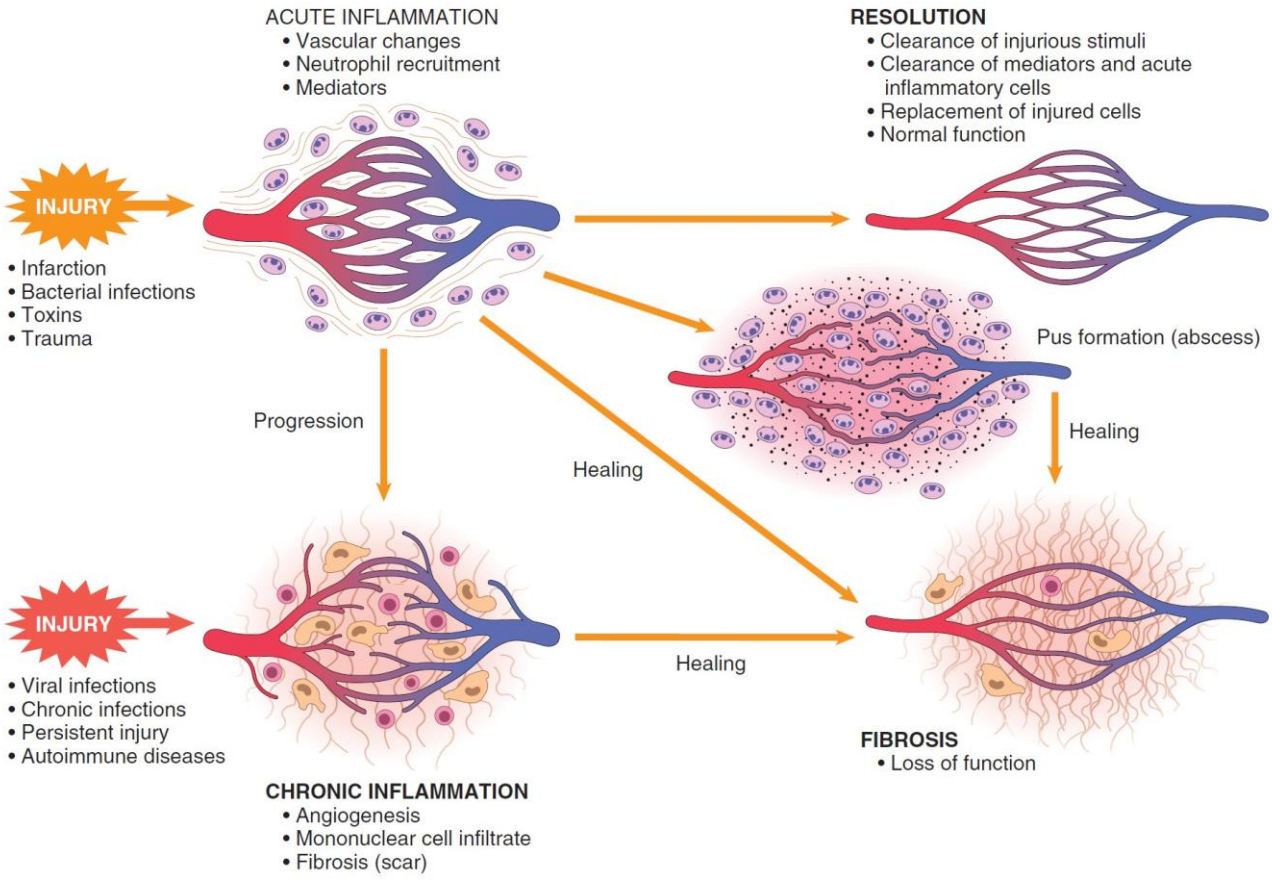
Presence of neutrophil polymorphs is a histological diagnostic feature of acute inflammation

Causes

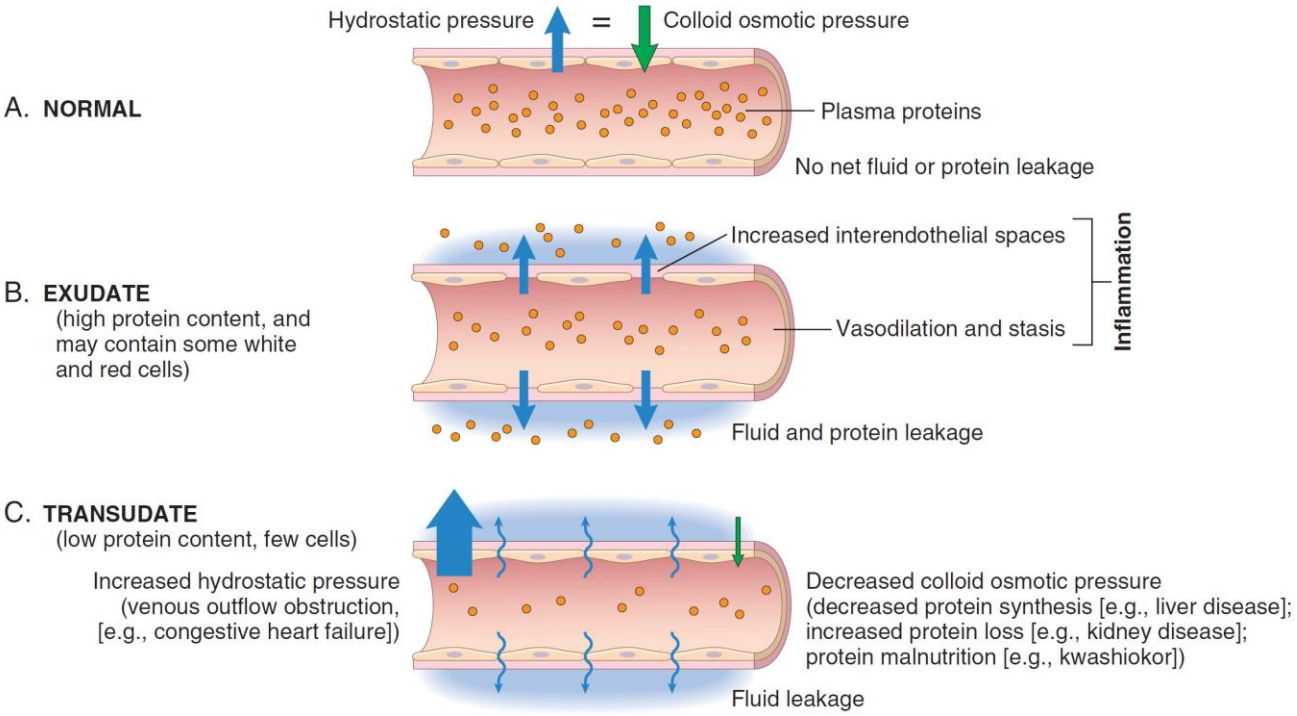
- Infections e.g. Viruses, exotoxins or endotoxins released by bacteria
- Chemical agents
- Physical agents e.g. Trauma
- Hypersensitivity reactions
- Tissue necrosis

Sequelae

Resolution	• Typically occurs with minimal initial injury • Stimulus removed and normal tissue architecture results
Organisation	• Delayed removal of exudate • Tissues undergo organisation and usually fibrosis
Suppuration	• Typically formation of an abscess or an empyema • Sequestration of large quantities of dead neutrophils
Progression to chronic inflammation	• Coupled inflammatory and reparative activities • Usually occurs when initial infection or suppuration has been inadequately managed



Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic inflammation. The components of the various reactions and their functional outcomes are listed.



Formation of exudates and transudates. (A) Normal hydrostatic pressure (blue arrow) is about 32 mm Hg at the arterial end of a capillary bed and 12 mm Hg at the venous end; the mean colloid osmotic pressure of tissues is approximately 25 mm Hg (green arrow), which is equal to the mean capillary pressure. Therefore, the net flow of fluid across the vascular bed is almost nil. (B) An exudate is formed in inflammation because vascular permeability increases as a result of retraction of endothelial cells, creating spaces through which fluid and proteins can pass. (C) A transudate is formed when fluid leaks out because of increased hydrostatic pressure or decreased osmotic pressure.

Chronic Inflammation

Overview

Chronic inflammation may occur secondary to acute inflammation. In most cases chronic inflammation occurs as a primary process. These may be broadly viewed as being one of three main processes:

- Persisting infection with certain organisms such as *Mycobacterium* tuberculosis which results in delayed type hypersensitivity reactions and inflammation.
- Prolonged exposure to non-biodegradable substances such as silica or suture materials which may induce an inflammatory response.
- Autoimmune conditions involving antibodies formed against host antigens.

Acute vs. Chronic inflammation

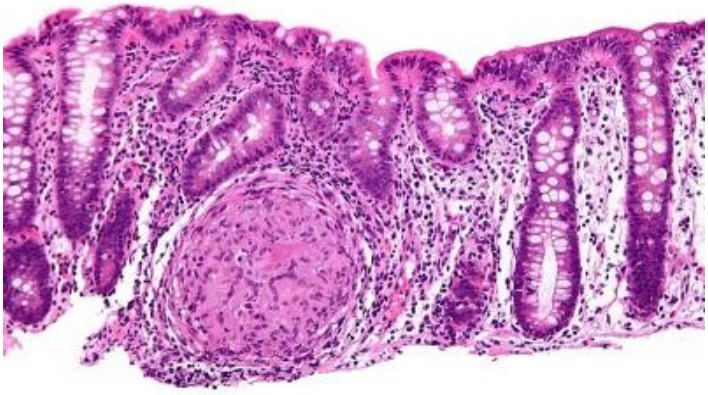
Acute inflammation	Chronic inflammation
Changes to existing vascular structure and increased permeability of endothelial cells	Angiogenesis predominates
Infiltration of neutrophils	Macrophages, plasma cells and lymphocytes predominate
Process may resolve with: • Suppuration • Complete resolution • Abscess formation • Progression to chronic inflammation • Healing by fibrosis	Healing by fibrosis is the main result

Granulomatous inflammation

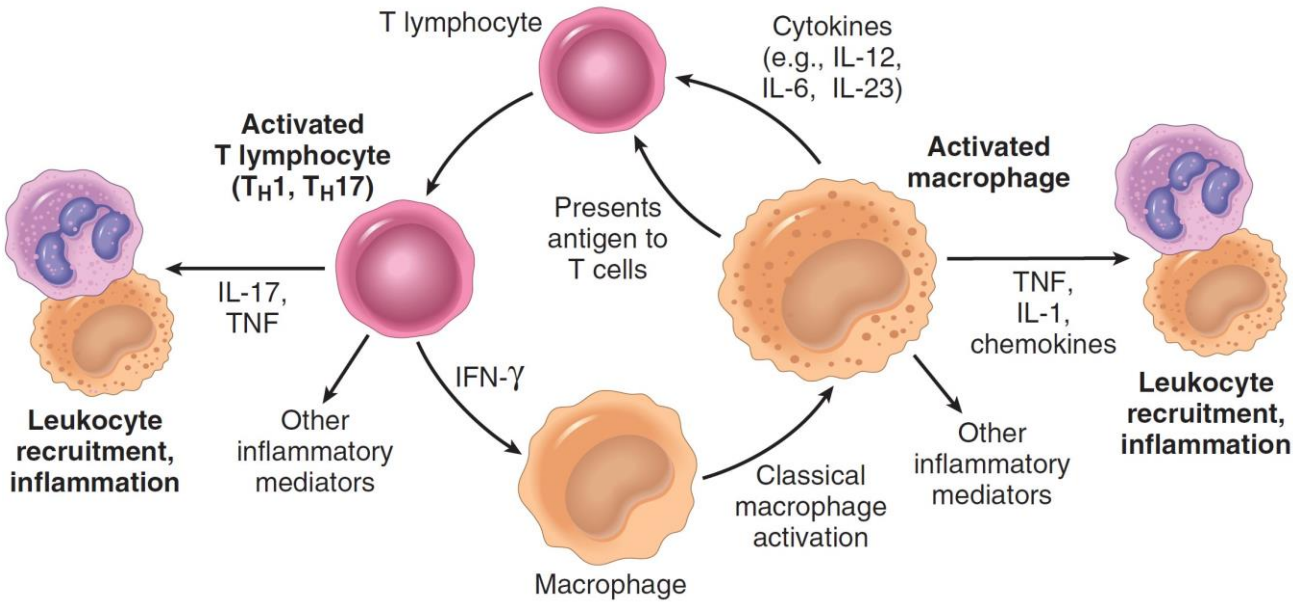
A granuloma consists of a microscopic aggregation of macrophages (with epithelial type arrangement = epitheliod). Large giant cells may be found at the periphery of granulomas.

Mediators

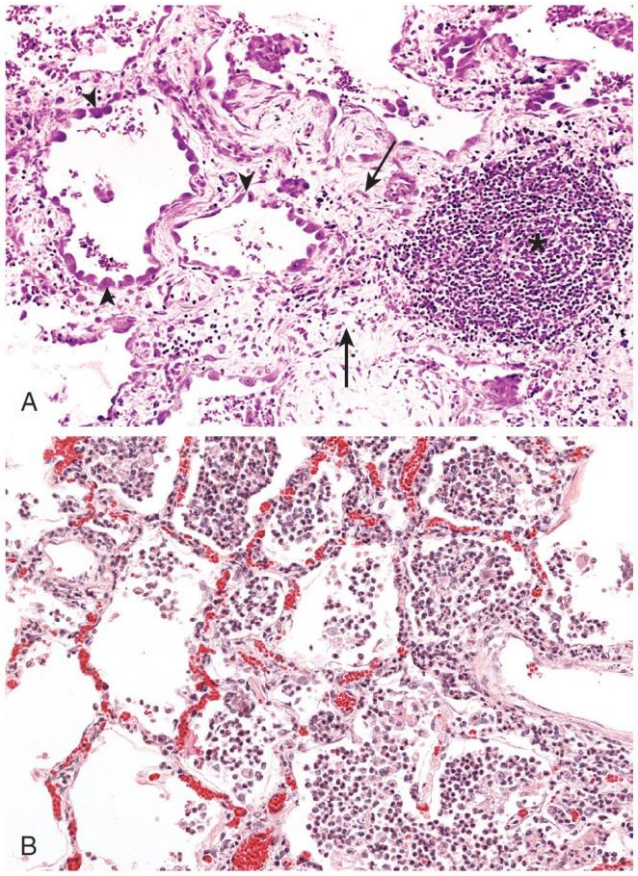
Growth factors released by activated macrophages include agents such as interferon and fibroblast growth factor (plus many more). Some of these such as interferons may have systemic features resulting in systemic symptoms and signs, which may be present in individuals with long standing chronic inflammation.



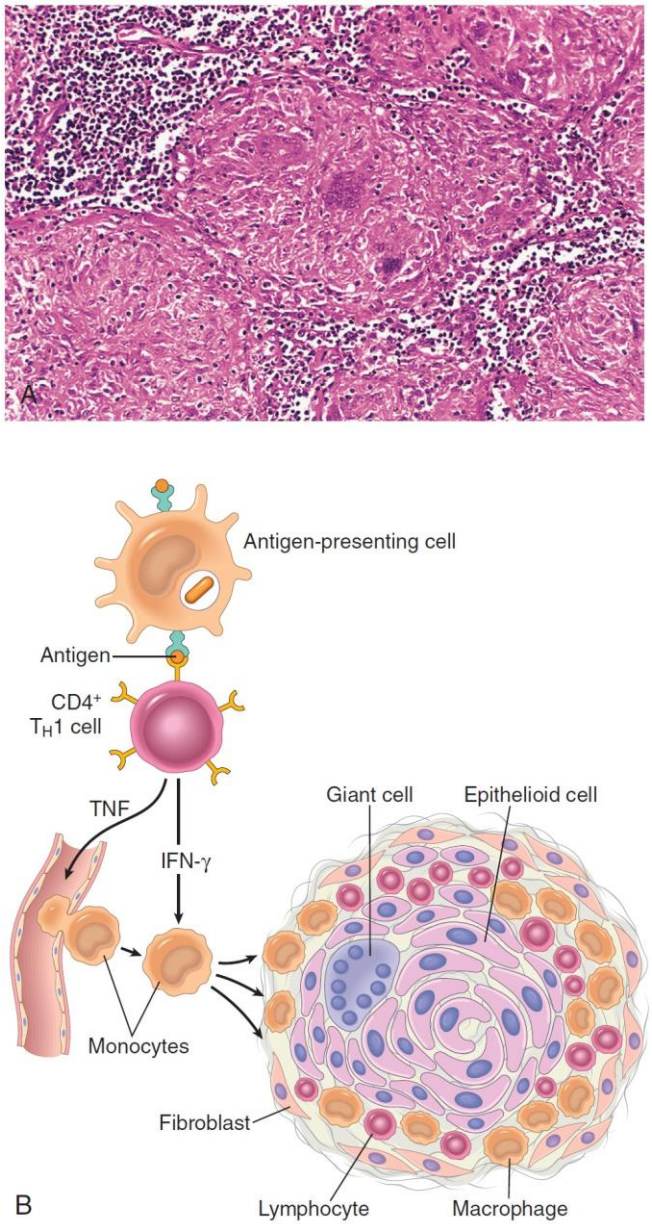
The finding of granulomas is pathognomonic of chronic inflammation, as illustrated in this biopsy from a patient with colonic Crohn's disease



Macrophage–lymphocyte interactions in chronic inflammation. Activated T cells produce cytokines that recruit macrophages (TNF, IL-17, chemokines) and others that activate macrophages (IFN-γ). Activated macrophages in turn stimulate T cells by presenting antigens and via cytokines such as IL-12.



(A) Chronic inflammation in the lung, showing all three characteristic histologic features: (1) collection of chronic inflammatory cells (*), (2) destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium, arrowheads), and (3) replacement by connective tissue (fibrosis, arrows).
(B) In contrast, in acute inflammation of the lung (acute bronchopneumonia), neutrophils fill the alveolar spaces and blood vessels are congested.



Granulomatous inflammation.
(A) A section of a lymph node shows several granulomas, each made up of an aggregate of epithelioid cells and surrounded by lymphocytes. The granuloma in the center shows several multinucleate giant cells.
(B) The events that give rise to the formation of granulomas in type IV hypersensitivity reactions, illustrating the role of TH1 cytokines. In some granulomatous disorders (e.g., schistosomiasis), TH2 cells also contribute to the lesions. The role of TH17 cells in granuloma formation is not proven.

Gastritis

Type of gastritis	Features
Type A	Autoimmune Circulating antibodies to parietal cells, causes reduction in cell mass and hypochlorhydria Loss of parietal cells = loss of intrinsic factor = B12 malabsorption Absence of antral involvement Hypochlorhydria causes elevated gastrin levels- stimulating enterochromaffin cells and adenomas may form
Type B	Antral gastritis Associated with infection with helicobacter pylori infection Intestinal metaplasia may occur in stomach and require surveillance endoscopy Peptic ulceration may occur
Reflux gastritis	Bile refluxes into stomach, either post-surgical or due to failure of pyloric function Histologically, evidence of chronic inflammation, and **foveolar hyperplasia** May respond to therapy with prokinetics
Erosive gastritis	Agents disrupt the gastric mucosal barrier Most commonly due to NSAIDs and alcohol With NSAIDs the effects occur secondary to COX 1 inhibition
Stress ulceration	This occurs as a result of mucosal ischaemia during hypotension or hypovolaemia The stomach is the most sensitive organ in the GI tract to ischaemia following hypovolaemia Diffuse ulceration may occur Prophylaxis with acid lowering therapy and sucralfate may minimise complications
Menetriers disease	Gross hypertrophy of the gastric mucosal folds, excessive mucous production and hypochlorhydria Premalignant condition

Acute Intermittent Porphyria

Acute intermittent porphyria (AIP) is a rare autosomal dominant condition caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem. The results in the toxic accumulation of delta aminolaevulinic acid and porphobilinogen. It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40 year olds. AIP is more common in females (5:1)

Features

- Abdominal: abdominal pain, vomiting
- Neurological: motor neuropathy
- Psychiatric: e.g. depression
- Hypertension and tachycardia common

Diagnosis

- Classically urine turns deep red on standing
- Raised urinary porphobilinogen (elevated between attacks and to a greater extent during acute attacks)
- Assay of red cells for porphobilinogen deaminase
- Raised serum levels of delta aminolaevulinic acid and porphobilinogen

*Neurological signs combined with abdominal pain is **Acute Intermittent Porphyria** OR **Lead poisoning** until proven otherwise*

Lead Poisoning

Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of abdominal pain and neurological signs

Features

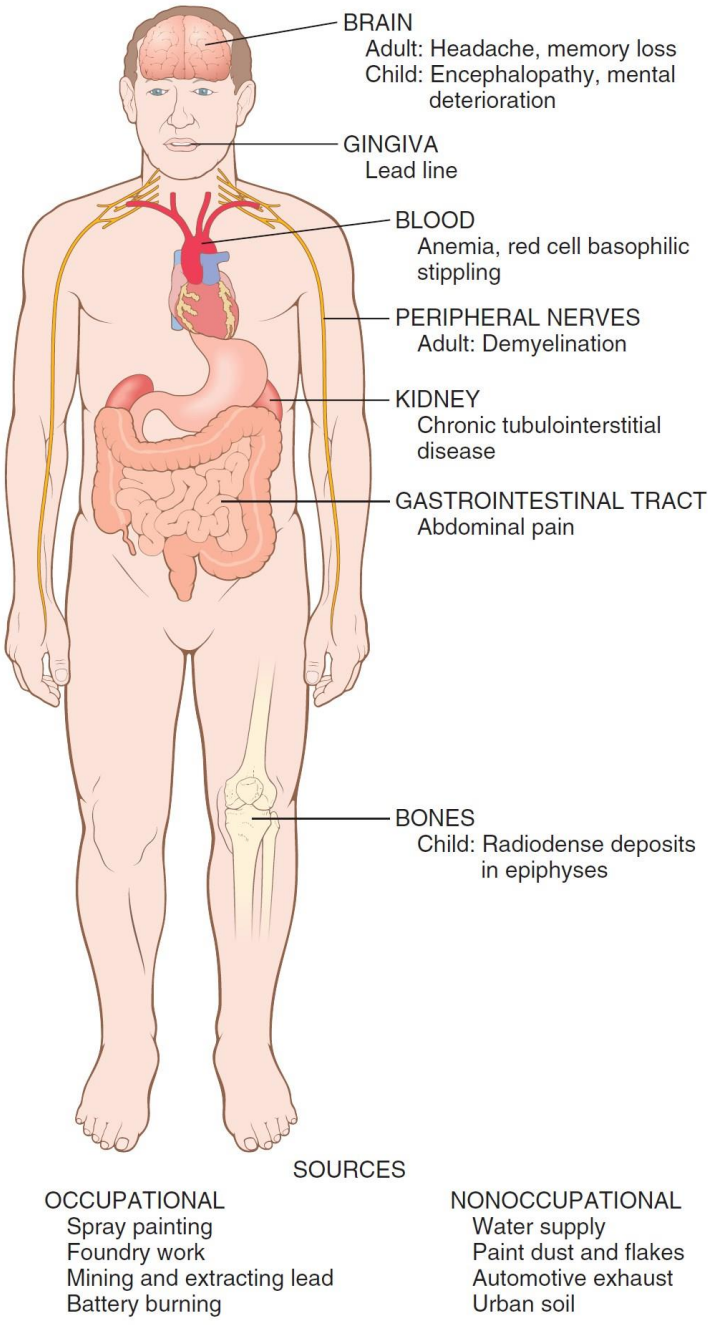
- Abdominal pain
- Peripheral neuropathy (mainly motor)
- Fatigue
- Constipation
- Blue lines on gum margin (only 20% of adult patients, very rare in children)

Investigations

- The blood lead level is usually used for diagnosis. Levels greater than 10 mcg/dl are considered significant
- Full blood count: microcytic anaemia. Blood film shows red cell abnormalities including **basophilic stippling** and clover-leaf morphology
- Raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria
- Urinary coproporphyrin is also increased (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased)

Management - various chelating agents are currently used:

- Dimercaptosuccinic acid (DMSA)
- D-penicillamine
- EDTA
- Dimercaprol



Pathologic features of lead poisoning.

Cell Death

Cells can die via two mechanisms; necrosis and apoptosis. These are outlined below:

Necrosis

Necrosis is characterised by bioenergetics failure. Loss of tissue perfusion results in hypoxia and an inability to generate ATP. The integrity of the cellular membrane is lost and the loss of ATP results in loss of energy dependent cellular transport mechanisms. There is an influx of water, ionic instability and cellular lysis. The release of intracellular contents may stimulate an inflammatory response. Several types of necrosis are recognised; coagulative, colliquative, caseous, gangrene, fibrinoid and fat necrosis. The type of tissue and the underlying cause determine the predominant necrosis pattern.

Coagulative necrosis

- The commonest type, occurs in most organs
- Tissue is initially firm, later becomes soft as tissue is digested by macrophages
- In the early phases the histological appearances may demonstrate little change
- In later stages cellular outlines are seen with loss of intracellular detail

Colliquative necrosis

- Occurs in tissues with no supporting stroma
- Dominant necrosis pattern in the CNS
- Necrotic site may eventually become encysted

Caseous necrosis

- No definable structure seen in the necrotic tissue
- Amorphous eosinophilic tissue may be seen histologically
- Classically seen in tuberculosis

Gangrene

- Necrosis with putrefaction of tissue
- May complicate ischaemia
- Haemoglobin degenerates and results in the deposition of iron sulphide (which is why the tissue is black)
- Both wet and dry gangrene may occur, in wet gangrene there is often a liquefactive component and super-added infection (which usually smells!)

Fibrinoid necrosis

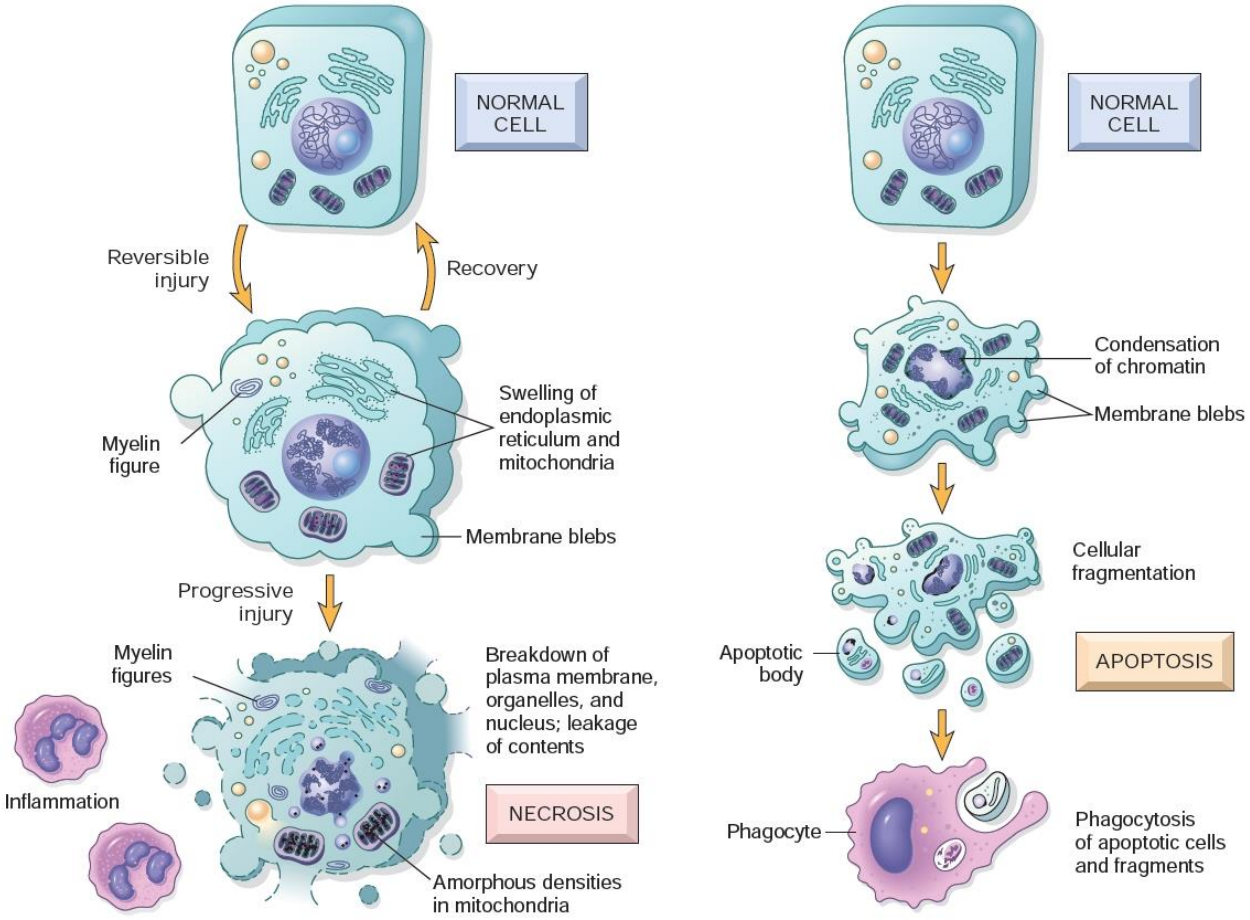
- Classically seen in arterioles in patients with hypertension (malignant type)
- Necrosis of the smooth muscle wall occurs and plasma may extravasate into the media with fibrin deposition

Fat necrosis

- Direct trauma to fat can result in rupture of adipocytes
- Lipids incite a local inflammatory reaction
- Inflammatory cells phagocytose the lipid with eventual fibrosis

Apoptosis

- Also known as programmed cell death
- Energy dependent pathways are activated via a number of intracellular signalling mechanisms
- It is the result of the activation of caspases triggered by the bcl-2 family or the binding of the FAS ligand to its receptor
- DNA fragments, mitochondrial function ceases, nuclear and cellular shrinkage occurs
- Phagocytosis of the cell does not occur, instead the cell degenerates into apoptotic bodies


NORMAL CELL
Reversible injury
Recovery
Myelin figure
Swelling of endoplasmic reticulum and mitochondria
Membrane blebs
Progressive injury
Myelin figures
Breakdown of plasma membrane, organelles, and nucleus; leakage of contents
Inflammation
NECROSIS
Amorphous densities in mitochondria
NORMAL CELL
Condensation of chromatin
Membrane blebs
Cellular fragmentation
Apoptotic body
APOPTOSIS
Phagocyte
Phagocytosis of apoptotic cells and fragments

Disseminated Intravascular Coagulation (DIC)

Simultaneous coagulation and haemorrhage caused by initially formation of thrombi which consume clotting factors (factors 5,8) and platelets, ultimately leading to bleeding

Causes include:

- Infection
- Malignancy
- Trauma e.g. major surgery, burns, shock, dissecting aortic aneurysm
- Liver disease
- Obstetric complications

Key points

- Clinically bleeding is usually a dominant feature, bruising, ischaemia and organ failure
- Blood tests: prolonged clotting times, thrombocytopenia, decreased fibrinogen, increased fibrinogen degradation products
- Treat the underlying cause and supportive management

DISSEMINATED
Dx: D dimer
Immune complexes
Snakebite, shock, heatstroke
SLE
Eclampsia, HELLP syndrome
Massive tissue damage
Infections: viral and bacterial
Neoplasms
Acute promyelocytic leukemia
Tumor products: **T**issue Factor (TF) and TF-like factors released by carcinomas of pancreas, prostate, lung, colon, stomach
Endotoxins (bacterial)
Dead fetus (retained)

Disseminated Intravascular Coagulation - Diagnosis

Under homeostatic conditions, coagulation and fibrinolysis are coupled. The activation of the coagulation cascade yields thrombin that converts fibrinogen to fibrin; the stable fibrin clot being the final product of hemostasis. The fibrinolytic system breaks down fibrinogen and fibrin. Activation of the fibrinolytic system generates plasmin (in the presence of thrombin), which is responsible for the lysis of fibrin clots. The breakdown of fibrinogen and fibrin results in polypeptides (fibrin degradation products). In a state of homeostasis, the presence of plasmin is critical, as it is the central proteolytic enzyme of coagulation and is also necessary for fibrinolysis.

In DIC, the processes of coagulation and fibrinolysis are dysregulated, and the result is widespread clotting with resultant bleeding. Regardless of the triggering event of DIC, once initiated, the pathophysiology of DIC is similar in all conditions. One critical mediator of DIC is the release of a transmembrane glycoprotein (tissue factor =TF). TF is present on the surface of many cell types (including endothelial cells, macrophages, and monocytes) and is not normally in contact with the general circulation, but is exposed to the circulation after vascular damage. For example, TF is released in response to exposure to cytokines (particularly interleukin 1), tumor necrosis factor, and endotoxin. This plays a major role in the development of DIC in septic conditions. TF is also abundant in tissues of the lungs, brain, and placenta. This helps to explain why DIC readily develops in patients with extensive trauma. Upon activation, TF binds with coagulation factors that then triggers the extrinsic pathway (via Factor VII) which subsequently triggers the intrinsic pathway (XII to XI to IX) of coagulation.

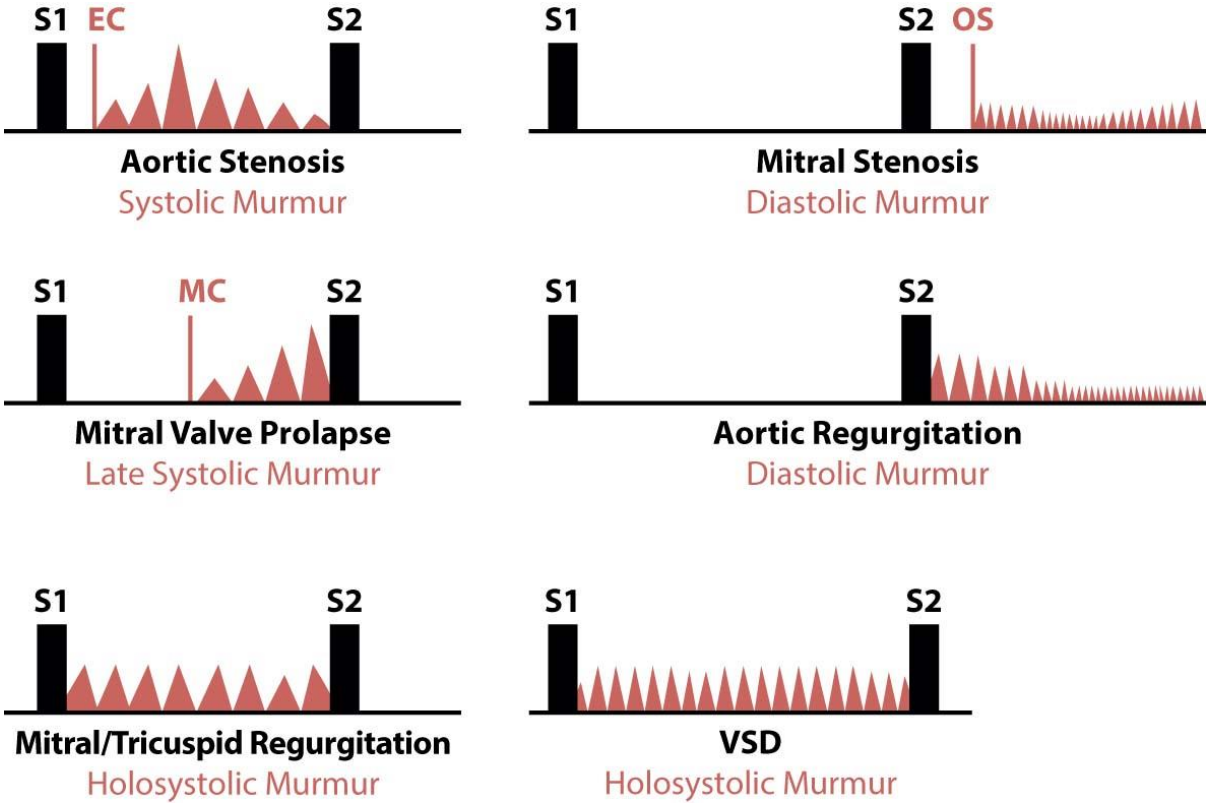
Diagnosis

Fibrin degradation products are often raised.

Disorder	PT / INR	aPTT	Thrombin time	Platelet count	Bleeding time
Heparin	↔ / ↑	↑↑	↑↑	↔	↔
DIC	↑↑	↑↑	↑↑	↓	↑
Liver disease	↑	↑	↔ / ↑	↔ / ↓	↔ / ↑
Platelet defect	↔	↔	↔	↔	↑(↑)
Vitamin K deficiency / Warfarin	↑↑	↑	↔	↔	↔
Haemophilia	↔	↑↑	↔	↔	↔
von Willebrand's disease	↔	↑↑	↔	↔	↑(↑)
Aspirin	↔	↔	↔	↔	↑

Cardiac Murmurs

Type of Murmur	Conditions
Ejection systolic	Aortic stenosis Pulmonary stenosis, HOCM ASD, Fallot's
Pan-systolic	Mitral regurgitation Tricuspid regurgitation VSD
Late systolic	Mitral valve prolapse Coarctation of aorta
Early diastolic	Aortic regurgitation Graham-Steel murmur (pulmonary regurgitation)
Mid diastolic	Mitral stenosis Austin-Flint murmur (severe aortic regurgitation)



Nerve Injury

Definitions	Nerve fiber	• A single axon. 3 types: large/myelinated fibers are fast, small/unmyelinated are slow • Efferent fibers (axons) transmit motor signals from CNS via ventral horn to peripheral muscles • Afferent fibers (axons) transmit sensory signals from peripheral receptor via DRG to CNS
	Fascicle	• A group of nerve fibers surrounded by perineurium • Fascicles unite and divide (form plexi) continuously along the course of the nerve
	Peripheral nerve	• One or more fascicles surrounded by epineurium • Most peripheral nerves have both motor and sensory fascicles

Classifications

- **Seddon**: 3 categories of injury: neurapraxia, axonotmesis, and neurotmesis
- **Sunderland**: 5 degrees (axonotmesis subdivided into 3 based on intact endo, peri, or epineurium)

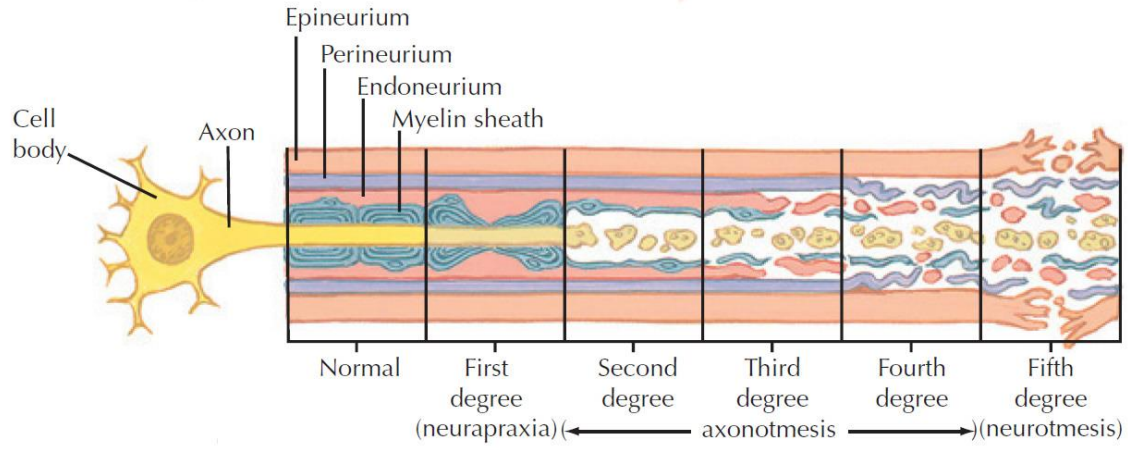
Neuropraxia	• Nerve intact but electrical conduction is affected • Full recovery • Autonomic function preserved • Wallerian degeneration does not occur
Axonotmesis	• Axon is damaged and the myelin sheath is preserved. The connective tissue framework is not affected. • Wallerian degeneration occurs.
Neurotmesis	• Disruption of the axon, myelin sheath and surrounding connective tissue. • Wallerian degeneration occurs.

Wallerian Degeneration

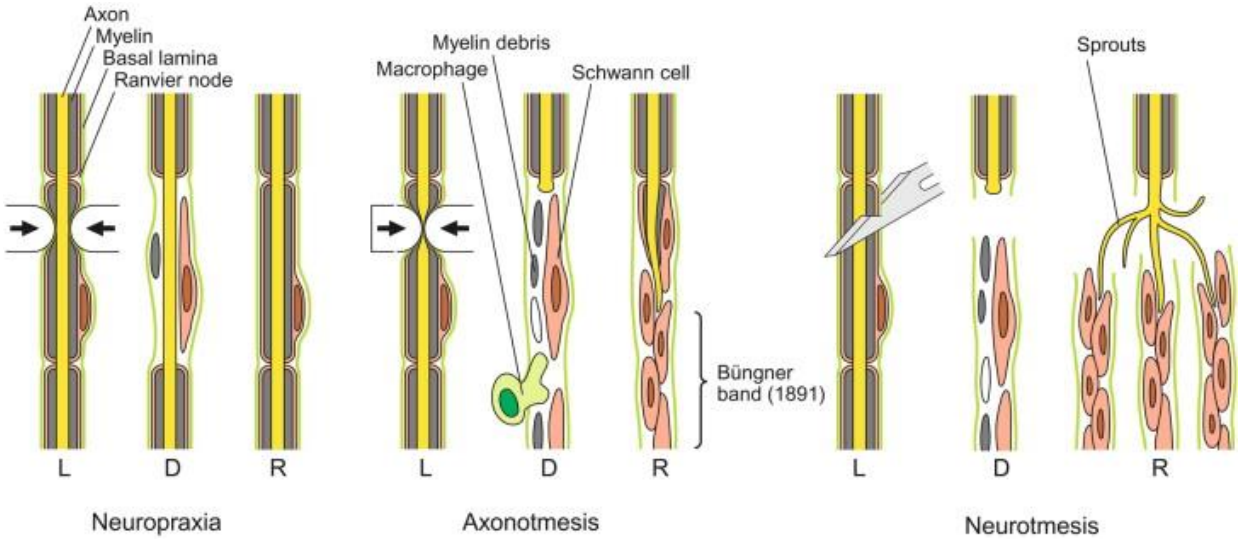
- Axonal degeneration distal to the site of injury.
- Typically begins 24-36 hours following injury.
- Axons are excitable prior to degeneration occurring.
- Myelin sheath degenerates and is phagocytosed by tissue macrophages.

Nerve repair

Neuronal repair may only occur physiologically where nerves are in direct contact. Where a large defect is present, the process of nerve regeneration is hampered. It may not occur at all or result in the formation of a neuroma. Where nerve regrowth occurs it is typically at a rate of 1mm per day.



Classification of nerve injury by degree of involvement of various neural layers



Absence of The Vas Deferens

- Absence of the vas may be unilateral or bilateral
- Cystic fibrosis CFTR gene mutations are the cause in 40% of cases
- Some non CF cases are due to unilateral renal agenesis
- Sperm harvesting may allow for assisted conception

Choanal Atresia

- Congenital disorder with an incidence of 1 in 7000 births.
- Posterior nasal airway occluded by soft tissue or bone.
- Associated with other congenital malformations e.g. coloboma
- Babies with unilateral disease may go unnoticed.
- Babies with bilateral disease will present early in life as they can then only breathe through their mouth.
- Treatment is with fenestration procedures designed to restore patency.

Achondroplasia

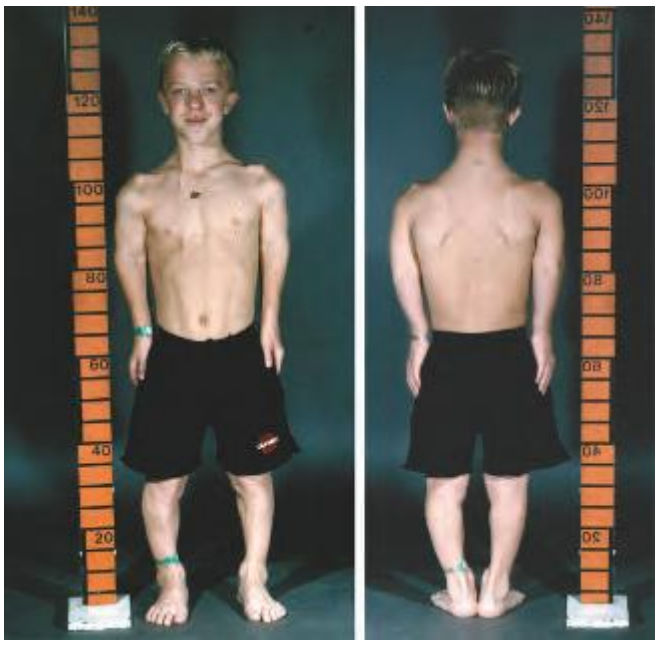
Achondroplasia is a common cause of dwarfism and is caused by defects in the fibroblast growth factor receptor. In most cases (approximately 70%) it occurs as a sporadic mutation. The main risk factor is advancing parental age at the time of conception. Once present it is typically inherited in an autosomal dominant fashion.

Radiological features

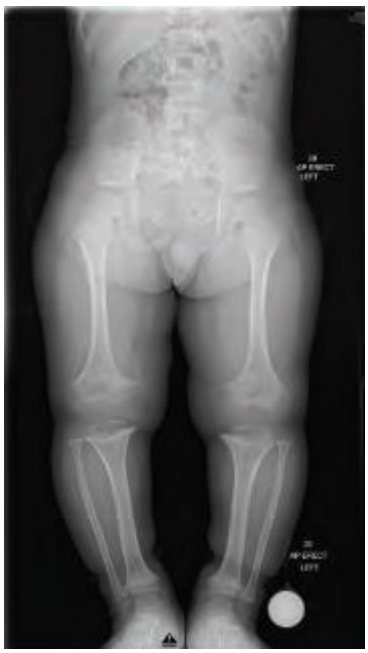
- Large skull with narrow foramen magnum
- Short, flattened vertebral bodies
- Narrow spinal canal
- Horizontal acetabular roof
- Broad, short metacarpals

Treatment

There is no specific therapy. However, some individuals benefit from limb lengthening procedures. These usually involve application of Ilizarov frames and targeted bone fractures. A clearly defined need and end point is the cornerstone of achieving success with such procedures.



Clinical photograph of a child with achondroplasia.



Standing leg length/alignment radiograph of a different child with achondroplasia showing short limbs, flared/ widened metaphysis, an overlong fibula and slight bowing, The acetabulum is very horizontal and the pelvic wings seem square: all classical features of this condition.

Cleft Lip and Palate

Cleft lip and palate are the most common congenital deformity affecting the orofacial structures. Whilst they may be an isolated developmental malformation they are also a recognised component of more than 200 birth defects. The incidence is as high as 1 in 600 live births. The commonest variants are:

- Isolated cleft lip (15%)
- Isolated cleft palate (40%)
- Combined cleft lip and palate (45%)

The aetiology of the disorder is multifactorial; both genetic (affected first degree relative increases risk) and environmental factors play a role.

Cleft lip

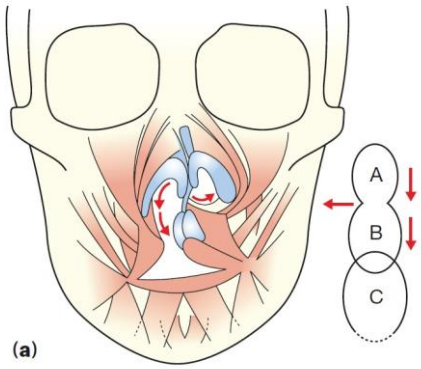
Cleft lip occurs as a result of disruption of the muscles of the upper lip and nasolabial region. These muscles comprise a chain of muscles viz; nasolabial, bilabial and labiomental. Defects may be unilateral or bilateral.

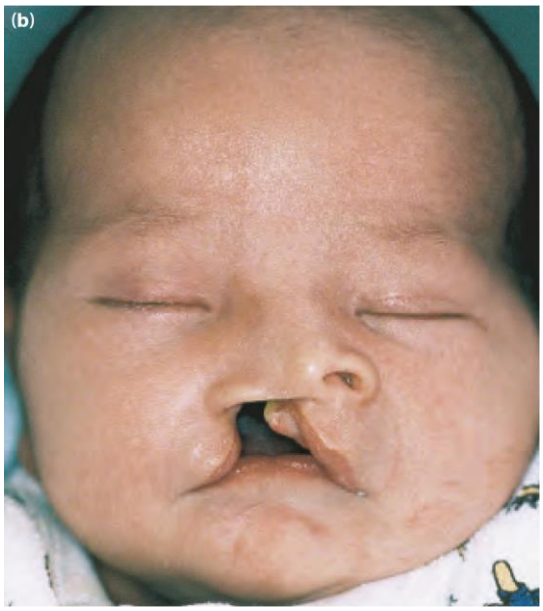
Cleft palate

The primary palate consists of all anatomical structures anterior to the incisive foramen. The secondary palate lies more posteriorly and is sub divided into the hard and soft palate. Cleft palate occurs as a result of non-fusion of the two palatine shelves. Both hard and soft palate may be involved. Complete cases are associated with complete separation of the nasal septum and vomer from the palatine processes.

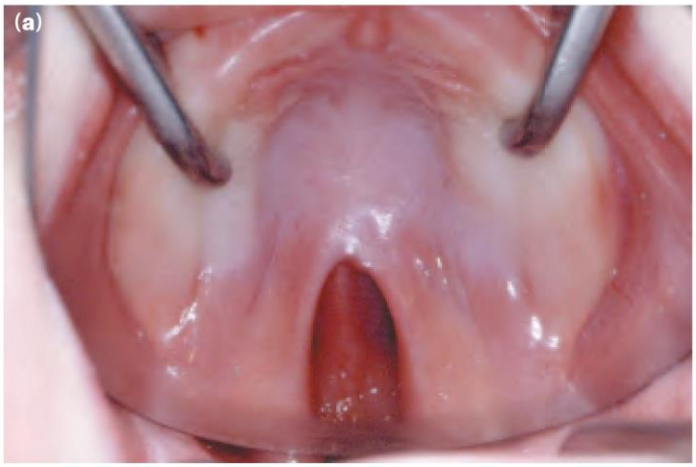
Treatment

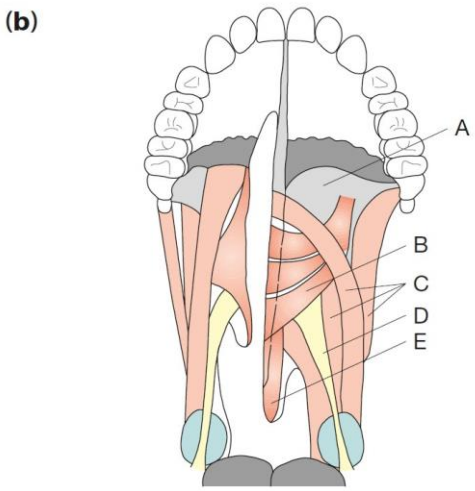
Surgical reconstruction is the mainstay of management. The procedures are planned according to the extent of malformation and child age. Simple defects are managed as a single procedure. Complex malformations are usually corrected in stages. Affected individuals have a higher incidence of hearing and speech problems.





(a) Schematic representation of disruption of the nasolabial and bilabial muscle chains in unilateral (left) cleft lip. A, nasolabial; B, bilabial; C, labiomental.
(b) Unilateral cleft lip before muscular reconstruction.





(a) Cleft of soft palate and incomplete cleft of hard palate.
(b) Muscles of the soft palate: left, cleft palate; right, normal anatomy. A, tensor palati; B, levator palati; C, palatopharyngeus; D, palatoglossus; E, musculus uvulae.

Genetics and Surgical Disease

Li-Fraumeni Syndrome

- Autosomal dominant
- Consists of germline mutations to p53 tumour suppressor gene
- High incidence of malignancies particularly sarcomas and leukaemias
- Diagnosed when:
    - Individual develops sarcoma under 45 years
    - First degree relative diagnosed with any cancer below age 45 years and another family member develops malignancy under 45 years or sarcoma at any age

BRCA 1 and 2

- Carried on chromosome 17 (BRCA 1) and Chromosome 13 (BRCA 2)
- Linked to developing breast cancer (60%) risk.
- Associated risk of developing ovarian cancer (55% with BRCA 1 and 25% with BRCA 2).

Lynch Syndrome (HNPCC, Hereditary nonpolyposis colorectal cancer)

- Autosomal dominant
- Develop colonic cancer and endometrial cancer at young age
- 80% of affected individuals will get colonic and/ or endometrial cancer
- High risk individuals may be identified using the Amsterdam criteria

Amsterdam criteria

- Three or more family members with a confirmed diagnosis of colorectal cancer, one of whom is a first degree (parent, child, sibling) relative of the other two.
- Two successive affected generations.
- One or more colon cancers diagnosed under age 50 years.
- Familial adenomatous polyposis (FAP) has been excluded.

Gardner's syndrome

- Autosomal dominant familial colorectal polyposis
- Multiple colonic polyps
- Extra colonic diseases include: skull osteoma, thyroid cancer and epidermoid cysts
- Desmoid tumours are seen in 15%
- Mutation of APC gene located on chromosome 5
- Due to colonic polyps most patients will undergo colectomy to reduce risk of colorectal cancer
- Now considered a variant of familial adenomatous polyposis coli

Tumour Markers

Tumour markers may be divided into:

- Monoclonal antibodies against carbohydrate or glycoprotein tumour antigens
- Tumour antigens
- Enzymes (alkaline phosphatase, neurone specific enolase)
- Hormones (e.g. calcitonin, ADH)

It should be noted that tumour markers usually have a low specificity

Monoclonal antibodies

Tumour marker	Association
CA 125	Ovarian cancer
CA 19-9	Pancreatic cancer
CA 15-3	Breast cancer

NB: The breast cancer tumour marker is not specific or sensitive enough to be used routinely.

Tumour antigens

Tumour marker	Association
Prostate specific antigen (PSA)	Prostatic carcinoma
Alpha-feto protein (AFP)	Hepatocellular carcinoma, teratoma
Carcinoembryonic antigen (CEA)	Colorectal cancer

Hodgkins Lymphoma

Presenting features

- Asymptomatic lympadenopathy
- Cough, Pel Ebstein fever, haemoptysis, dyspnoea
- B Symptoms - 10% weight loss, fever, night sweats

Staging

All patients are staged with CT scanning of the chest, abdomen and pelvis
The Ann Arbor staging system is commonly used

Stage	Features
I	Single lymph node region
II	Two or more regions on the same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm
IV	Involvement of extra nodal sites

Sub types

Classical Hodgkin lymphoma is classified into the following 4 types:

- Nodular sclerosing Hodgkin lymphoma (NSHL)
- Mixed-cellularity Hodgkin lymphoma (MCHL)
- Lymphocyte-depleted Hodgkin lymphoma (LDHL)
- Lymphocyte-rich classical Hodgkin lymphoma (LRHL)

*A **Reed Sternberg** cell may be identified histologically.*
A fifth sub type, Nodular lymphocyte-predominant Hodgkin lymphoma, is characterised by a different cell type Reed-Sternberg cells are rarely seen.

Treatment

This may be multimodal and both chemo and radiotherapy are used.

Diagnosis

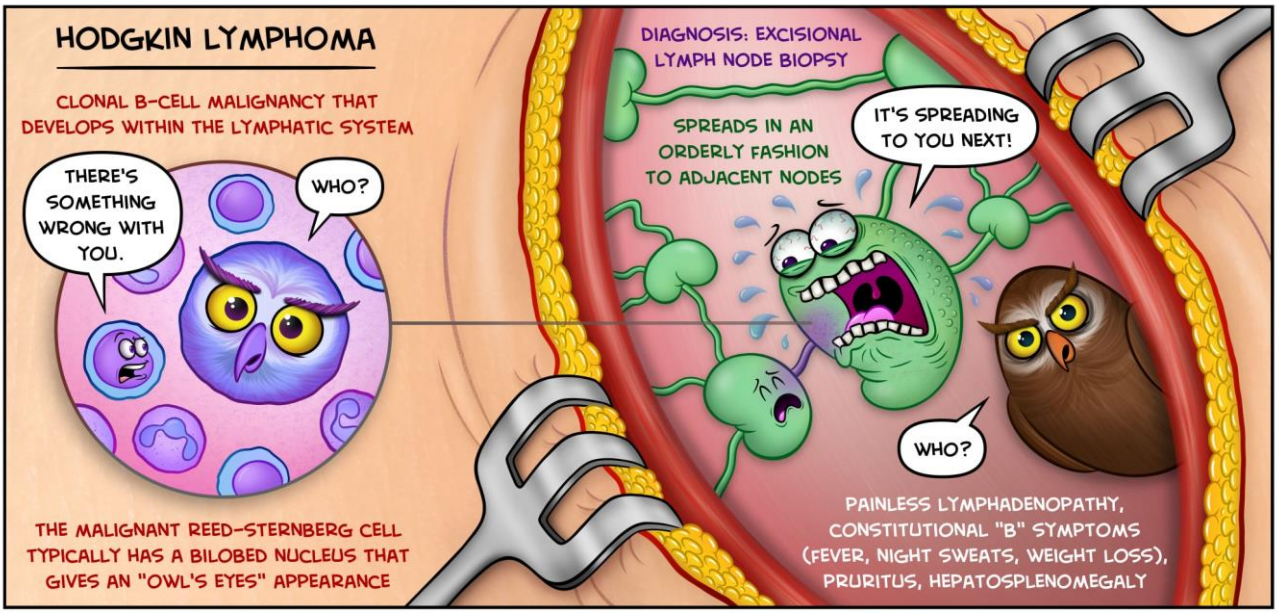
This is made by excision of a complete lymph node that is then submitted for detailed histological evaluation.

Pathogenesis

Infection with Ebstein Barr virus is linked to the condition (particularly mixed cellularity lymphoma).

Prognosis

Stage I disease is associated with survival figures of up to 85% at 5 years. The lymphocyte rich classical lymphoma has the best prognosis. Lymphocyte depleted Hodgkins lymphoma, advancing age, male sex and stage IV disease are all associated with a worsening of prognosis.

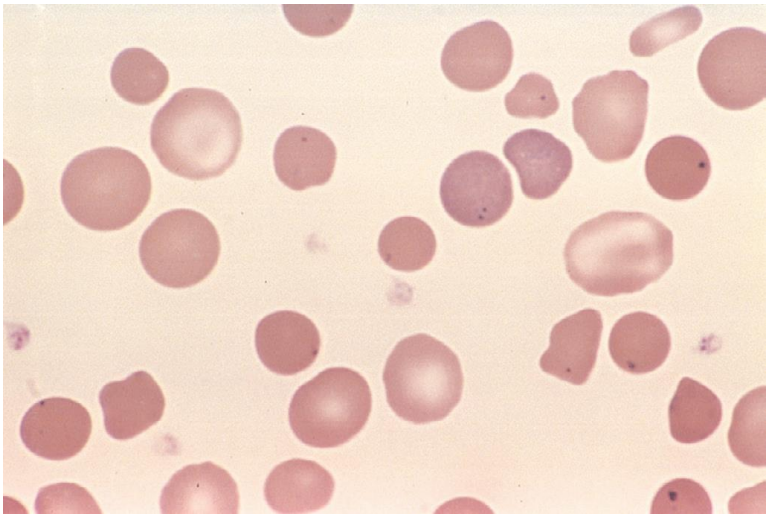


Aggressive Fibromatosis

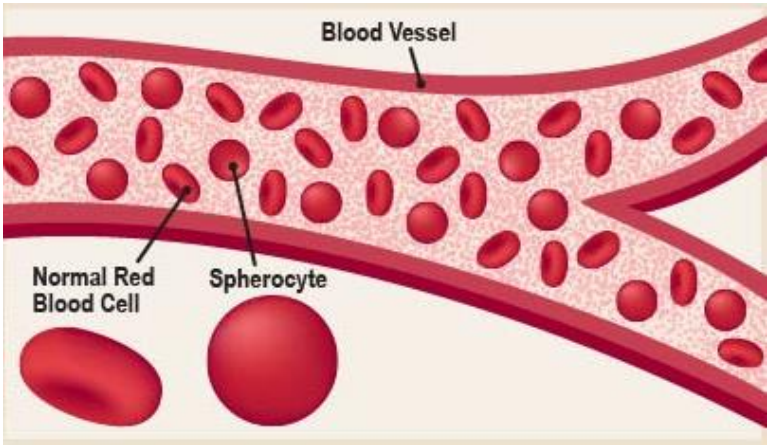
Aggressive fibromatosis is a disorder consisting of desmoid tumours, which behave in a locally aggressive manner. Desmoid tumours may be identified in both abdominal and extra-abdominal locations. Metastatic disease is rare. The main risk factor (for abdominal desmoids) is having APC variant of familial adenomatous polyposis coli. Most cases are sporadic. **Treatment**: Surgical excision.

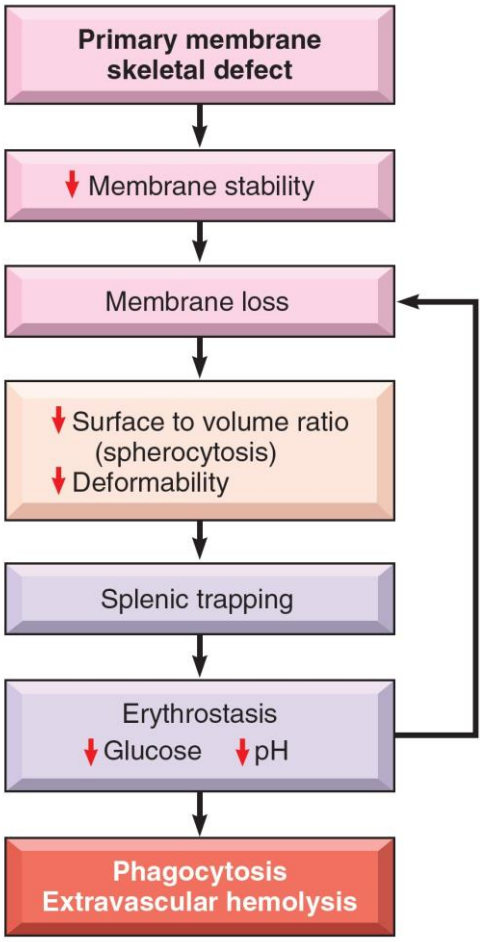
Hereditary Spherocytosis

Most common disorder of the red cell membrane, it has an incidence of 1 in 5000. The abnormally shaped erythrocytes are prone to splenic sequestration and destruction. This can result in hyperbilirubinaemia, jaundice and splenomegaly. In older patients an intercurrent illness may increase the rate of red cell destruction resulting in more acute symptoms.
Severe cases may benefit from splenectomy.



Hereditary spherocytosis (peripheral smear). Note the anisocytosis and several dark-appearing spherocytes with no central pallor. Howell-Jolly bodies (small, dark nuclear remnants) also are seen in some of the red cells of this asplenic patient.





Pathophysiology of hereditary spherocytosis.

Hypersensitivity Reactions

The Gell and Coombs classification divides hypersensitivity reactions into 4 types

	Type I (Immediate)	*Type II (Anti-body Mediated)*	*Type III (Immune Complex-Mediated)*	*Type IV (T-Cell Mediated)*
Description	Anaphylactic	Cytotoxic	Immune complex	Delayed type
Mediator	IgE	IgG, IgM	IgG, Ig A, IgM	T-cells
Antigen	Exogenous	Cell surface	Soluble	Tissues
Response time	Minutes	Hours	Hours	2-3 days
Examples	• Asthma • Hay fever	• Autoimmune • Haemolytic anaemia • Pemphigus • Goodpasture's	• Serum sickness • SLE • Aspergillosis	• Graft versus host disease • Contact dermatitis

Mnemonic for the reactions and the mediators involved ***ACID EGG-T***

ACID

- Type 1 **A**naphylactic
- Type 2 **C**ytotoxic
- Type 3 **I**mmune complex
- Type 4 **D**elayed type

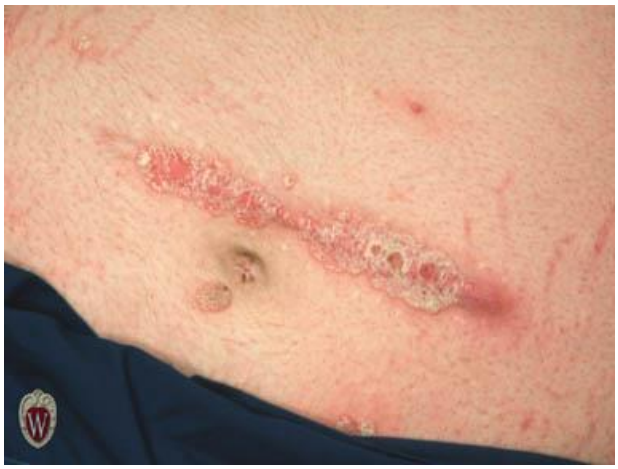
EGG T (mediators)

- IgE
- IgG
- IgG
- T cells

Koebner Phenomenon

The Koebner phenomenon describes skin lesions which appear at the site of injury. It is seen in:

- Psoriasis
- Vitiligo
- Warts
- Lichen planus
- Lichen sclerosus
- Molluscum contagiosum



This patient with psoriasis has the scaly psoriatic lesions along the line of a ventral hernia repair.

Pheochromocytoma and Adrenal Lesions

Neuroendocrine tumour of the chromaffin cells of the adrenal medulla. Hypertension and hyperglycaemia are often found.

- 10% of cases are bilateral.
- 10% occur in children.
- 11% are malignant (higher when tumour is located outside the adrenal).
- 10% will not be hypertensive.

Familial cases are usually linked to the Multiple endocrine neoplasia syndromes (considered under its own heading). Most tumours are unilateral (often right sided) and smaller than 10cm.

Diagnosis

- Urine analysis of vanillymandelic acid (VMA) is often used (false positives may occur e.g. in patients eating vanilla ice cream!)
- Blood testing for plasma metanephrine levels.
- CT and MRI scanning are both used to localise the lesion.

Treatment

Patients require medical therapy first. An irreversible alpha adrenoreceptor blocker should be given, although minority may prefer reversible blockade. Labetalol may be co-administered for cardiac chronotropic control. Isolated beta blockade should not be considered as it will lead to unopposed alpha activity.

These patients are often volume depleted and will often require moderate volumes of intra venous normal saline perioperatively.

Once medically optimised the phaeochromocytoma should be removed. Most adrenalectomies can now be performed using a laparoscopic approach. The adrenals are highly vascular structures and removal can be complicated by catastrophic haemorrhage in the hands of the inexperienced. This is particularly true of right sided resections where the IVC is perilously close. Should the IVC be damaged a laparotomy will be necessary and the defect enclosed within a Satinsky style vascular clamp and the defect closed with Prolene sutures. Attempting to interfere with the IVC using any instruments other than vascular clamps will result in vessel trauma and make a bad situation much worse.

Incidental Adrenal Lesions

Incidentaloma of the adrenal glands have become increasingly common as CT scanning of the abdomen is widely undertaken. Prevalences range from 1.5-9% in autopsy studies. Overall, 75% will be nonfunctioning adenomas. However, a thorough diagnostic work up is required to exclude a more significant lesion.

Factors suggesting benign disease on CT include:

- Size less than 3cm
- Homogeneous texture
- Lipid rich tissue
- Thin wall to lesion

Investigation

- Morning and midnight plasma cortisol measurements
- Dexamethasone suppression test
- 24-hour urinary cortisol excretion
- 24-hour urinary excretion of catecholamines
- Serum potassium, aldosterone and renin levels

Management

The risk of malignancy is related to the size of the lesion and 25% of all masses greater than 4cm will be malignant. Such lesions should usually be excised. Where a lesion is a suspected metastatic deposit a biopsy may be considered. Smaller, innocent lesions are usually followed up by serial CT scans at 6, 12 and 24 months.

All patients with incidental lesions should be managed jointly with an endocrinologist and full work up as described above. Patients with functioning lesions or those with adverse radiological features (Particularly size >3cm) should proceed to surgery.

Glucagonoma

- Rare pancreatic tumours arising from the alpha cells of the pancreas.
- Glucagon levels markedly elevated.
- Symptoms include diarrhoea, weight loss and **necrolytic migratory erythema**.
- A serum level of glucagon >1000pg/ml usually suggests the diagnosis, imaging with CT scanning is also required.
- Treatment is with surgical resection. However, careful staging is required for these tumours are usually malignant and non resectable.

Glioma

Glioma is a tumour that is typically found in the CNS. These tumours arise from glial cells. They are sub categorised according to the cell type they most closely resemble.

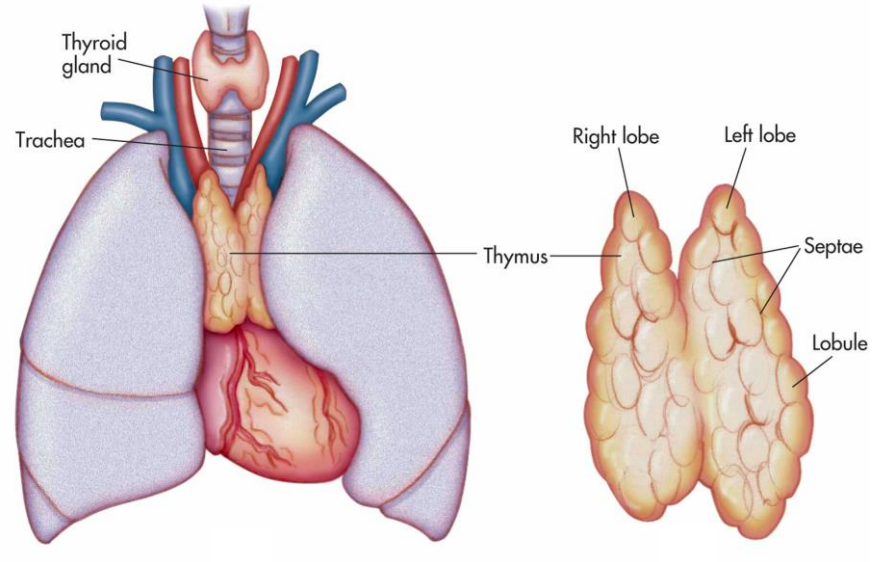
Glioma sub types

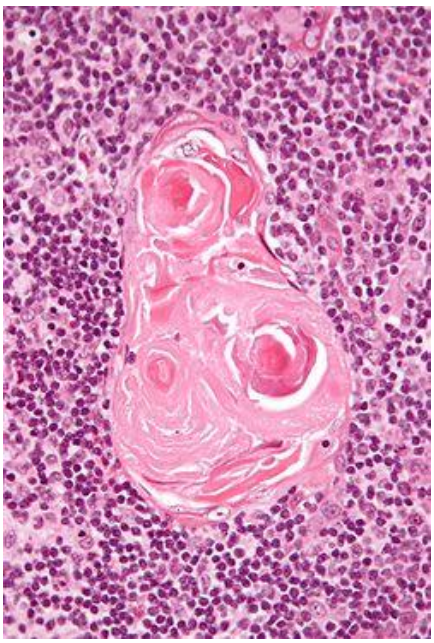
- Ependymomas- Ependymal cells
- Astocytomas- Astrocytes (including glioblastoma)
- Oligodendrogliomas- Oligodendrocytes
- Mixed- e.g. oligoastrocytomas

Gliomas are categorised as being either high or low grade lesions (the former has the worse prognosis). They may be either supra or infra tentorial. Their symptoms will typically reflect their site of origin. Glioblastoma multiforme has the worst prognosis and few patients will survive beyond 12 months.

Thymus

The thymus develops from the third and fourth pharyngeal pouches. It descends to lie in the anterior superior mediastinum. It is encapsulated and is subdivided into lobules, these consist of a cortex and a medulla. The cortex is composed of tightly packed lymphocytes. The medulla consists largely of epithelial cells. The medullary epithelial cells are concentrically arranged and may surround a keratinized centre, known as Hassall's corpuscles.
The inferior parathyroid glands also develop from the third pharyngeal pouch and may also be located with the thymus gland.
Its arterial supply is from the internal mammary artery or pericardiophrenic arteries. Venous drainage is to the left brachiocephalic vein.





Hassall's corpuscles stained with H+E

Sarcomas

Malignant tumours of mesenchymal origin

Types (*May be either bone or soft tissue in origin)*

Bone sarcomas include:	*Soft tissue sarcomas* include:
• Osteosarcoma • Ewing's sarcoma (although non-bony sites recognised) • Chondrosarcoma - originate from Chondrocytes	• Liposarcoma - *adipocytes* • Rhabdomyosarcoma - *striated muscle* • Leiomyosarcoma - *smooth muscle* • Synovial sarcomas - *close to joints* *(cell of origin not known but not synovium)*
Malignant fibrous histiocytoma is a sarcoma that may arise in both soft tissue and bone.	

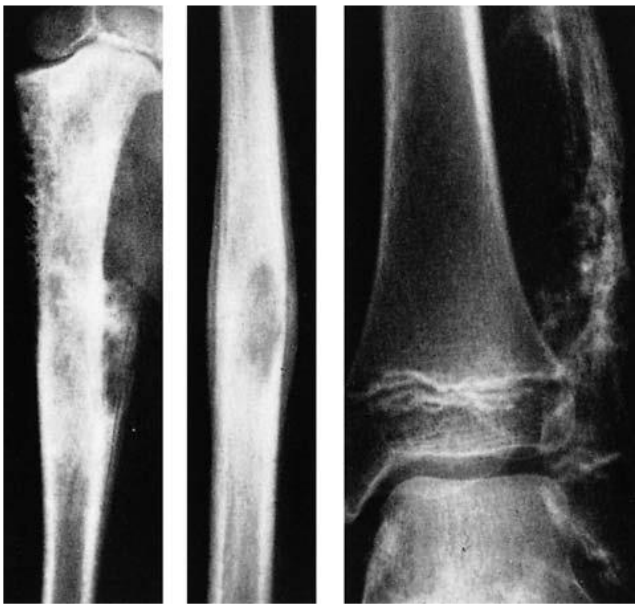
Features

Certain features of a mass or swelling should raise suspicion for a sarcoma these include:

- Large > 5cm soft tissue mass
- Deep tissue location or intra muscular location
- Rapid growth
- Painful lump

Assessment

Imaging of suspicious masses should utilise a combination of MRI, CT and USS. Blind biopsy should not be performed prior to imaging and where required should be done in such a way that the biopsy tract can be subsequently included in any resection.



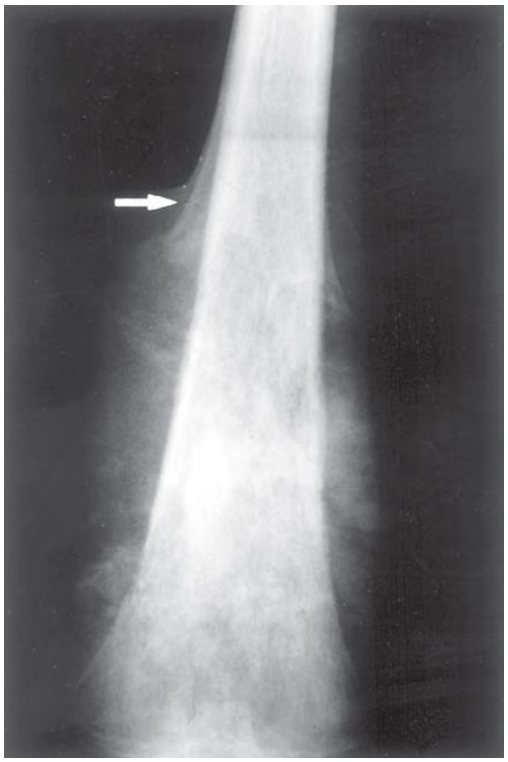
Examples of Ewing's tumour in
(a) the humerus, (b) mid-shaft of the fibula and (c) the lower end of the fibula.

Ewing's sarcoma

- Commoner in males
- Incidence of 0.3 / 1, 000, 000
- Onset typically between 10 and 20 years of age
- Location by femoral diaphysis is commonest site
- Histologically it is a small round tumour
- Blood borne metastasis is common and chemotherapy is often combined with surgery
- XR: maybe permeative (moth-eaten) or onion skin appearance

Osteosarcoma

- Mesenchymal cells with osteoblastic differentiation
- 20% of all primary bone tumours
- Incidence of 5 per 1,000,000
- Peak age 15-30, commoner in males
- Osteosarcoma may complicate Paget's disease of bone in up to 10% cases
- Limb preserving surgery may be possible and many patients will receive chemotherapy
- XR: sunburst appearance, Codman triangle



Distal femoral osteosarcoma with prominent bone formation extending into the soft tissues. The periosteum, which has been lifted, has laid down a proximal triangular shell of reactive bone known as a Codman-triangle arrow).

Sarcomas in which Lymphatic Metastasis is seen:
'RACE For MS'

- R: Rhabdomyosarcoma
- A: Angiosarcoma
- C: Clear cell sarcoma
- E: Epithelial cell sarcoma
- For: Fibrosarcoma
- M: Malignant fibrous histiocytoma
- S: Synovial cell sarcoma

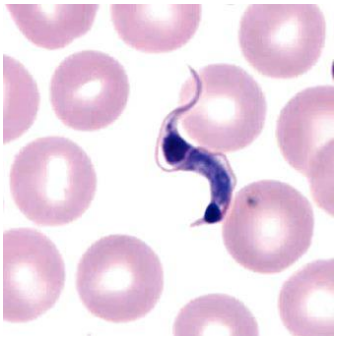
Liposarcoma

- Malignancy of adipocytes
- Rare, approximately 2.5 per 1,000,000. They are the second most common soft tissue sarcoma
- Typically located in deep locations such as retroperitoneum
- Affect older age group usually >40 years of age
- May be well differentiated and thus slow growing although may undergo de-differentiation and disease progression
- Many tumours will have a pseudocapsule that can misleadingly allow surgeons to feel that they can 'shell out' these lesions. In reality, tumour may invade at the edge of the pseudocapsule and result in local recurrence if this strategy is adopted
- Usually resistant to radiotherapy, although this is often used in a palliative setting

Malignant Fibrous Histiocytoma

- Tumour with large number of histiocytes
- Most common sarcoma in adults
- Also described as undifferentiated pleomorphic sarcoma (PUS, UPS) (i.e. Cell of origin is not known)
- 4 major subtypes are recognised: storiform-pleomorphic (70% cases), myxoid (less aggressive), giant cell and inflammatory
- Rx is usually with surgical resection and adjuvant radiotherapy as this reduces the likelihood of local recurrence

Trypanosoma Cruzi



- Protozoan
- Causes Chagas disease
- Carried by bugs which infect the skin whilst feeding
- Penetrate through open wounds and mucous membranes
- Intracellular proliferation
- Major infective sites include CNS, **intestinal myenteric plexus** (causing clinical picture **similar to achalasia**), spleen, lymph nodes and cardiac muscle.
- Chronic disease is irreversible, nifurtimox is used to treat acute infection

Actinomycosis

Chronic, progressive granulomatous disease caused by filamentous gram positive anaerobic bacteria from the Actinomycetaceae family.

Actinomyces are commensal bacteria that become pathogenic when a mucosal barrier is breached.

The disease most commonly occurs in the head and neck, although it may also occur in the abdominal cavity and in the thorax.

The mass will often enlarge across tissue planes with the formation of multiple sinus tracts.

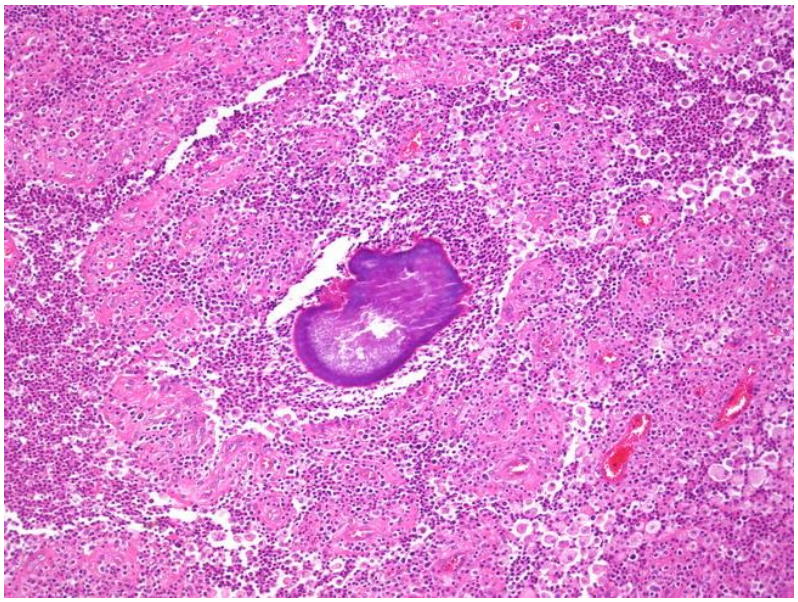
Abdominopelvic actinomycosis occurs most frequently in individuals that have had appendicitis (65%) cases.

Pathology

- On histological examination gram positive organisms and evidence of sulphur granules.
- **Sulphur granules** are colonies of organisms that appear as round or oval basophilic masses.
- They are also seen in other conditions such as nocardiosis.

Treatment

- Long term antibiotic therapy usually with penicillin.
- Surgical resection is indicated for extensive necrotic tissue, non-healing sinus tracts, abscesses or where biopsy is needed to exclude malignancy.



The image shows an actinomycotic (sulfur) granule enveloped by an infiltrate composed of neutrophils, foamy histiocytes, lymphocytes and plasma cells.

Burns

Burns may be thermal, chemical or electrical. In the former category are burns which occur as a result of heat. Chemical burns occur when the skin is exposed to an extremely caustic or alkaline substance. Electrical burns occur following exposure to electrical current. The immediate management includes removal of the burning source which usually includes irrigation of the burned area. A detailed assessment then needs to be made of the extent of the burns and a number of charts are available for recording this information. The degree of injury relates to the temperature and duration of exposure. Most domestic burns are mainly scalds in young children.

Following the burn, there is a local response with progressive tissue loss and release of inflammatory cytokines. Systemically, there are cardiovascular effects resulting from fluid loss and sequestration of fluid into the third space. There is a marked catabolic response. Immunosupression is common with large burns and bacterial translocation from the gut lumen is a recognised event. Sepsis is a common cause of death following major burns.

Type of burn	Skin layers affected	Skin appearance	Blanching	Management
Epidermal/Superficial	Epidermis	Red, moist	Yes	
Superficial partial thickness	Epidermis and part of papillary dermis affected	Pale, dry	Yes	Normally heals with no intervention
Deep partial thickness	Epidermis, whole papillary dermis affected	Mottled red colour	No	Needs surgical intervention (depending on site)
Full thickness	Whole skin layer and subcutaneous tissue affected	Dry, leathery hard wound	No	Burns centre

Depth of burn assessment

- Bleeding on needle prick
- Sensation
- Appearance
- Blanching to pressure

Percentage burn estimation

- Lund Browder chart: most accurate even in children
- Wallace rule of nines
- Palmar surface: surface area palm = 0.8% burn

>15% body surface area burns in adults needs urgent burn fluid resuscitation

Transfer to burn centre if:

- Need burn shock resuscitation
- Face/hands/genitals affected
- Deep partial thickness or full thickness burns
- Significant electrical/chemical burns

Management

The initial aim is to stop the burning process and resuscitate the patient. Intravenous fluids will be required for children with burns greater than 10% of total body surface area. Adults with burns greater than 15% of total body surface area will also require IV fluids. The fluids are calculated using the Parkland formula which is; volume of fluid= total body surface area of the burn % x weight (Kg) x4. Half of the fluid is administered in the first 8 hours. A urinary catheter should be inserted. Analgesia should be given. Complex burns, burns involving the hand perineum and face and burns >10% in adults and >5% in children should be transferred to a burns unit.

Circumferential burns affecting a limb or severe torso burns impeding respiration may require escharotomy to divide the burnt tissue.

Conservative management is appropriate for superficial burns and mixed superficial burns that will heal in 2 weeks. More complex burns may require excision and skin grafting. Excision and primary closure is not generally practised as there is a high risk of infection.

There is no evidence to support the use of anti-microbial prophylaxis or topical antibiotics in burn patients.

Escharotomies

- Indicated in circumferential full thickness burns to the torso or limbs.
- Careful division of the encasing band of burn tissue will potentially improve ventilation (if the burn involves the torso), or relieve compartment syndrome and oedema (where a limb is involved)

Collagen

Collagen is one of the most important structural proteins within the extracellular matrix, collagen together with components such as elastin and glycosaminoglycans determine the properties of all tissues.

- Composed of 3 polypeptide strands that are woven into a helix, usually a combination of **glycine** with either proline or hydroxyproline plus another amino acid
- Numerous hydrogen bonds exist within molecule to provide additional strength
- Many sub types but commonest sub type is I (90% of bodily collagen), tissues with increased levels of flexibility have increased levels of type III collagen
- Vitamin c is important in establishing cross links
- Synthesised by fibroblasts

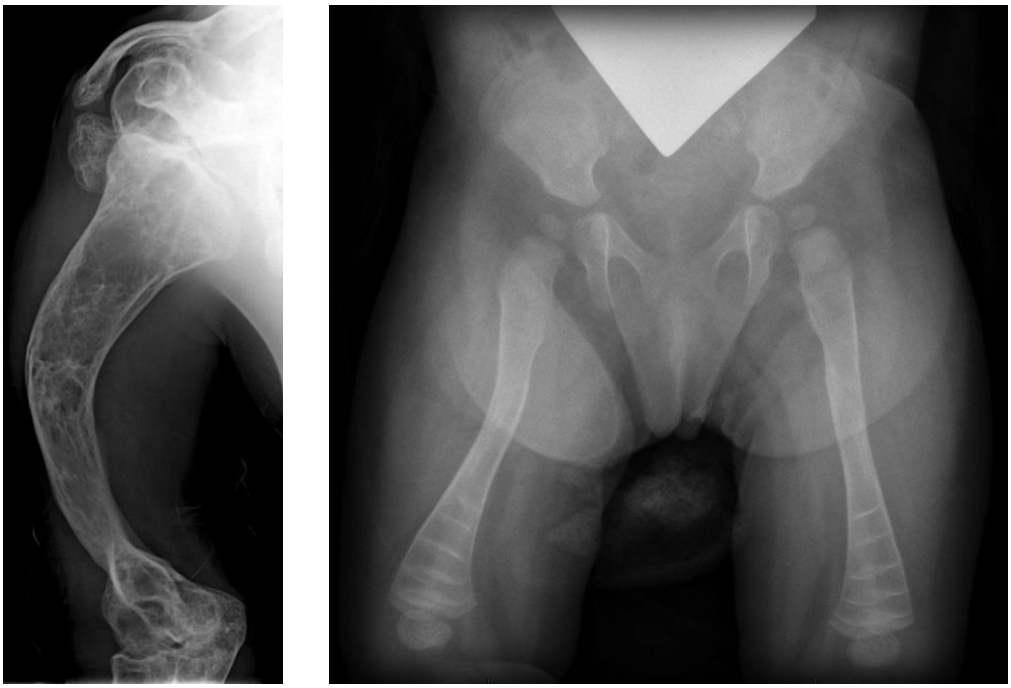
Glycine is present in all types of collagen

Collagen Diseases

Osteogenesis imperfecta:

- 8 Subtypes
- Defect of type I collagen
- Type I - The collagen is normal quality but insufficient quantity
- Type II - Poor quantity and quality
- Type III - Collagen poorly formed, normal quantity
- Type IV - Sufficient quantity but poor quality

Patients have bones which fracture easily, loose joint and multiple other defects depending upon which sub type they suffer from.



Examples of osteogenesis imperfecta on plain x-ray

Ehlers Danlos:

- Multiple sub types
- Abnormality of types 1 and 3 collagen
- Patients have features of hypermobility.
- Individuals are prone to joint dislocations and pelvic organ prolapse. In addition to many other diseases related to connective tissue defects.