Clinical Aspects of Pathology

Bone non-neoplastic conditions

Systems: Bone and Skin

Causes: genetic, metabolic, infection, degenerative

Quiz: IMED4121 – Musculo-skeletal

Introduction: Note Bone Tumours and Joint Diseases are in separate modules

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Wednesday, August 03, 2016


**CONGENITAL**

**Cretinism**

**Definition:** is a condition of severely stunted physical and mental growth due to untreated congenital deficiency of thyroid hormone.

**Sites affected:** thyroid, bone, brain, gonads, skin.

**Types:** endemic, genetic and sporadic.

**Incidence:** 1 in 4000 births. More common in babies with birth weight of 200 gms or less and when 4,500 gms or more. Also more common in twins where usually only one twin is affected.

**Age:** diagnosed in infancy or early childhood

**Gender:** F : M = 2:1

**Race:** The prevalence at birth is increased in Hispanics, particularly in Hispanic females, who have a birth prevalence of 1 in 1886 births. Black infants have about one third the prevalence rate of white infants.

**Demographics:** found in countries where dietary iodine deficiency is endemic such as inland China, the Himalayas, Africa

**Pathogenesis:** cretinism results from maternal iodine deficiency. Thyroid hormone regulates chondrocytes, osteoblasts and osteoclasts through production of cytokines. So there is defective cartilage maturation impairing linear growth with limbs disproportionately short compared with the trunk. Delayed closure of the fontanelles allows the skull to become unusually large. Closure of epiphyses is delayed.

**Genetic:** Cretinism may rarely be due to a genetic defect causing an in-born error of thyroid metabolism – called dyshormonogenetic goiter. Due to mutation in the thyroid peroxidase gene.

**Clinical features:** impaired development of the skeletal system and central nervous system with severe mental retardation, short stature, coarse facial features, a protruding tongue and an umbilical hernia. Photo of baby with these features, and one showing macro-glossia, courtesy of MS Daniel. Medscape Dec 2015.
As maternal thyroid hormones including T₃ and T₄ cross the placenta, when there is a deficiency before the development of the foetal thyroid gland, the mental retardation is severe.

**Pathology:** the chondrocytes do not follow the normal endochondral sequence. Maturation of the hypertrophied zone is retarded and the zone of proliferative cartilage is narrow. Endochondral ossification does not proceed correctly and transverse bars of bone in the metaphysis seal off the growth plate. The epiphysis is deformed due to incomplete penetration of the secondary centres of ossification. See diagram courtesy of Rubin's Pathology: Clinicopathologic Foundations of Medicine. 6th ed. 2012.
**Imaging:**

Epiphyseal dysgenesis (irregular, deformed and stippled epiphysis) is the radiological hallmark of longstanding untreated hypothyroidism. The appearance of ossification centres is very delayed and their growth when they do appear is slow. The centres are malformed and irregular in shape. The epiphysis for the proximal end of the femur shows a tendency to ossify from numerous irregular centres, instead of a single one, so the epiphysis does not grow properly so the femoral head develops a flattened shape. In the image below, courtesy of Paul and Juhl’s Essentials of Radiologic Imaging. 6th ed. 1993, the femoral head is abnormal and the femoral neck is broadened.

The delay in ossification is shown in the image below, comparing an 8 year old cretin’s hands – see arrows on epiphysis at the proximal end of the proximal phalanx of the index finger – the left image with black arrow, - with the same location in a normal 8 year child – right image and white arrow. Also courtesy of Paul and Juhl.

Spine may show platyspondyly and thoraco-lumbar kyphosis.

**Diagnosis** of Congenital Hypothyroidism is generally confirmed by measuring serum TSH and thyroxine concentrations.
Treatment: The main goal of the treatment is early detection and early initiation of treatment. When the diagnosis is made early, within the first two weeks of life, the effects of this condition to the brain and nervous system can be prevented by the thyroid hormone replacement. This is because they are not yet fully developed.

- The thyroid hormone replacement involves the administration of L-thyroxine. This is a synthetic thyroid hormone which comes in tablet forms. The amount and frequency of this medication is determined by the doctor and endocrinologist. As the child grows up, the dose is gradually increased. This is to be **given daily to the baby throughout his life**.
- L-thyroxine is in the form of small tablets. They are crushed and added into the milk formula of the baby and given 30 minutes before feeding.

Prognosis: Early diagnosis of the disease leads to better prognosis. The newborns that are diagnosed and treated within their first month of life usually have normal intelligence.

- On the other hand, newborns which are not treated immediately or at all, suffer from intellectual disability and delayed growth.
- According to some studies, some of the patients with cretinism have been found to have slight decreased performance in their IQ as well as in verbal and math. They have memory and attention deficits due to delayed diagnosis and treatment.

Glycosaminoglycans (formerly called Mucopolysaccharidoses)

Includes MPS 1 (Hurler syndrome), MPS II (Hunter syndrome), MPS III (San Filippo syndrome) and MPS IV (Morquio syndrome).

Morquio syndrome

Definition: this rare condition, the commonest in this group, is inherited as an autosomal recessive and is a disease of metabolism in which the body is unable to metabolize keratan sulphate due to a lysosomal enzyme deficiency so this is stored. That is, it is a type of lysosomal storage disease.

Incidence: 1 : 200,000 live births.

Types: This syndrome has two forms, Morquio A and Morquio B syndrome. The two forms are distinguished by the gene product involved; A involves a malfunction in the GALNS gene product (galactosamine-6 sulfatase), while B involves a malfunction of the GLB1 gene product (beta-galactosidase).

Age: apparent soon after birth.

Gender: equal involvement

Clinical presentation: clinical features are skeletal and neurologic. Both types of Morquio's syndrome are characterized by short-trunk dwarfism which is apparent within the first 2 years of life, fine corneal deposits, a skeletal dysplasia that is distinct from other mucopolysaccharidoses, and preservation of intelligence.

There is a dorsal kyphoscoliosis, muscular hypotonia, and weakness prominent in early childhood presentations. Also seen are coarse faces with short nose, broad mouth, widely spaced teeth with thinned enamel, corneal clouding due to mucopolysaccaridosis accumulating in the anterior chamber, ligamentous laxity, and joint stiffness. Adult height rarely exceeds 1.3 metres. Pectus carinatum (horizontal and protuberant sternum) and a shortened neck with the head appearing
sunken into the chest are the norm. Mental capacity is generally normal, but deafness often develops.

**Clinical appearance:** courtesy of Bye Bye Doctor November 2011.

![Clinical appearance image]

**Imaging:**  Courtesy of T Marlow and T Han. App Radiol. 2003; 32 (6).

Platyspondyly with central beaking is almost pathognomonic. There may be subluxation of C1 on C2 due to hypoplasia of the odontoid peg, which can cause spinal cord compression and sudden death.

![Imaging image]

The wings of the ilium flare laterally but constrict inferiorly giving a wine-glass appearance. The hips show enlarged acetabular cavities with rough margins and poorly formed femoral head epiphyses. The femoral necks are widened and one sees coxa valga.

![Imaging image 2]
Microscopy: of the cornea shows the most obvious abnormality to be mucopolysaccharide inclusions in the form of intracytoplasmic, multilaminar concentric bodies particularly within keratocytes but also affecting the epithelium and endothelium. The degree of keratocyte disruption is striking especially in the late stage of the disease. Bundles of abnormal collagen fibres, are present in the corneal stroma around the lacunae and there are areas of epithelial membrane bound vacuoles. The cornea may require a transplant. Other ocular abnormalities are cataracts and retinal abnormalities.

Diagnosis: Fibroblast culture of a skin biopsy shows reduced activity of N-acetyl-galactosamine-6-sulfate-sulfatase. Also urine analysis detects keratan sulphate.

Treatment: consists of prenatal identification and of enzyme replacement therapy. On 12 February 2014, the US Food and Drug Administration approved the drug elosulfase alfa (Vimizim) for treating the disease.

Prognosis: some can die as early as 2 or 3 years old, and some can live up to 60 or 70 years old and most patients survive into their third or fourth decade.

Hurler Syndrome – MPS I – gargoylism

Definition: is a genetic disorder, inherited as an autosomal recessive, resulting in the buildup of glycosaminoglycans – heparin sulfate and dermatan sulfate - due to a deficiency of alpha-L iduronidase, an enzyme responsible for the degradation of mucopolysaccharides in lysosomes.

Types: MPS 1 has 3 degrees of severity. Hurler syndrome is the most severe type. Scheie syndrome is the least severe and Hurler-Scheie patients are clinically between the other two in severity.

Age: symptoms appear during childhood and early death can occur due to organ damage.

Incidence: 1 per 100,000

Types: MPS I is divided into three subtypes based on severity of symptoms. All three types result from an absence of, or insufficient levels of, the enzyme α-L-iduronidase. MPS I H or Hurler syndrome is the most severe of the MPS I subtypes. The other two types are MPS I S or Scheie syndrome and MPS I H-S or Hurler-Scheie syndrome.

Genetics: Children born to an MPS I parent carry a defective IDUA gene, which has been mapped to the 4p16.3 site on chromosome 4. The gene is named IDUA because of its iduronidase enzyme protein product. As of 2001, 52 different mutations in the IDUA gene have been shown to cause Hurler syndrome.

Clinical features: Affected children may be large at birth and appear normal but may have inguinal or umbilical hernias. Growth in height is faster than normal initially but this slows before the end of the first year and ends about age 3 years.

Many children develop a short body trunk and a maximum stature of less than 1.3 metres. Distinct facial features become more evident in the second year (flat face, depressed nasal bridge, and bulging forehead).

There is progressive mental retardation, hepatosplenomegaly, dwarfism, loss of physical skills. Developmental delay is evident by the end of the first year, and patients usually stop developing between ages 2 and 4. Speech may be limited due to hearing loss and an enlarged tongue. The clear layers of the cornea become clouded and retinas may begin to degenerate. Carpal tunnel syndrome and restricted joint movement are common. By age 2, the ribs have widened and are oar-shaped.
The liver, spleen and heart are often enlarged. Children may experience noisy breathing and recurring upper respiratory tract and ear infections. Feeding may be difficult for some children. The photo below is courtesy of Dermatology Atlas www.atlasdermatologico.

**Imaging:**

**Skull** – macrocephaly, J-shaped sella, concave articular surface of the mandibular condyle

**Spine** – C1-C2 subluxation and narrowing of the foramen magnum due to a short C1 arch and dysplastic odontoid and thickening meninges and ligaments – all contribute to cord compression at the craniovertebral junction.

**Long bones** – are shortened and widened and the proximal metacarpals are pointed.

**Chest** – widening of the anterior ribs which look like oars/paddles and widening of the clavicles. Thoracolumbar kyphosis or hypoplastic vertebra at the thoracolumbar junction results in gibbus. The vertebrae show anterior inferior beaking.

**Heart** involvement - cardiac valve disease: early onset severe regurgitation and stenosis, coronary artery disease and cardiomegaly which is initially hypertrophic then dilated. The images below are courtesy of Jatin, K. Radiopaedia.org, rID 24387. Skull - arrow on J-shaped sella. Thoracic spine arrow on anterior-inferior beaking. Hand - arrow on pointed metacarpal.
Chest- arrow indicates flared anterior ribs. Xray of upper limb shows bone enlargement.

**Micro:** the vertebral body and cartilage display irregular trabeculae, remodelling and fibrous and reparative changes. The arrows on the image below indicate multiple osteoclasts.

**Diagnosis:** Diagnosis often can be made through clinical examination and urine tests for excess mucopolysaccharides. Enzyme assays for enzyme deficiency are used to provide definitive diagnosis of one of the mucopolysaccharidoses. Prenatal diagnosis using amniocentesis and chorionic villus sampling can verify if a foetus either carries a copy of the defective gene or is affected with the disorder. Genetic counseling can help parents who have a family history of the mucopolysaccharidoses to determine if they are carrying the mutated gene that causes the disorder.

**Treatment:** There is no cure for MPS I. Enzyme replacement therapies are currently in use reducing non-neurological symptoms and pain. BioMarin Pharmaceutical provides therapeutics for mucopolysaccaradosis type I (MPS I), by manufacturing laronidase (Aldurazyme), commercialized by Genzyme.
Bone marrow transplantation (BMT) and umbilical cord blood transplantation (UCBT) can be used as treatments for MPS. Abnormal physical characteristics, except for those affecting the skeleton and eyes, can be improved, and neurologic degeneration can often be halted.

**Prognosis:** Death is frequent by the age of 10 years from obstructive airway disease, respiratory infections, or cardiac complications.

**Hunter syndrome – MPS II**

**Definition:** it is a very rare condition inherited as an X-linked recessive and caused by a deficient (or absent) enzyme, iduronate-2-sulfatase. The accumulated substrates in Hunter syndrome are heparan sulfate and dermatan sulfate

**Incidence:** 1 : 130,000 male live births.

**Age:** can be visible at age 18 months

**Gender:** nearly always occurs in boys, although occasionally reported in girls.

**Genetic:** the child inherits the lack of an essential enzyme from its mother. The gene is on Xq28.

**Clinical presentation:** features are not present at birth but appear between the ages of 2 and 4 years. The degree of severity ranges from mild to very severe. Seizures are a feature.

- An enlarged head (macrocephaly)
- Thickening of the lips
- A broad nose and flared nostrils
- A protruding tongue
- A deep, hoarse voice
- A distended abdomen, as a result of enlarged internal organs
- Diarrhea
- White skin growths that resemble pebbles
- Joint stiffness
- Aggressive behaviour
- Delayed development, such as late walking or talking
- Abnormal bone size or shape and other skeletal irregularities. The group of abnormalities is called dysostosis multiplex. Children with these abnormalities can develop irregularly shaped vertebrae and spines (kyphoscoliosis), ribs, arms, fingers, legs, and pelvises.
- Stunted growth. The skull may press down on or fuse with the cervical spine. These complications cause many people with Hunter syndrome to be abnormally short. Those with milder cases may reach normal or near-normal height.

**Macro:** All children with this disease do not die young. The photo below is of two adult brothers, both with Hunter’s syndrome. Courtesy of Global Genes Daily.
**Imaging:** the skeletal findings are similar to those of Hurler’s syndrome (MPS I). The main changes are usually in the central nervous system with progressive brain atrophy but as the brother on the left in the photo studied for a Masters of Business Administration successfully this is not always the case. This is also a feature in MPS I, III and VII.

Skeletal findings in patients with the mild type of Hunter syndrome are similar to those in patients with the severe type.

Dysostosis multiplex encompasses the multitude of findings seen in patients with all types of MPS and those with any other storage disease. Short stature is thought to be due to a failure of endochondral ossification in growth plates secondary to glycosaminoglycans deposition. Cranial manifestations include a J-shaped sella turcica and a thickened skull. Spinal involvement includes odontoid dysplasia and anterior beaking of the lower thoracic and upper lumbar vertebral bodies, sometimes resulting in a gibbus deformity or focal kyphosis. In the chest, the ribs and clavicles are thickened. In the pelvis, there is narrowing of the lower iliac bones, coxa valga, and shallow acetabula and flattening of the femoral heads, resulting in secondary osteoarthritis. Extremities show shortening of the long bones, narrow epiphyses, and irregular metaphyses. In the hands and feet, there is proximal pointing of metacarpals and metatarsals. Contractures develop secondary to glycosaminoglycan deposition in tendons, which can be surgically corrected if recognized early.

Orthopaedic complications, caused by a combination of direct bone involvement and severe arthropathy, can lead to significant disability. The destructive arthropathy, which especially affects the hip joints, is a feature of the skeletal disease in some patients and may be due to secondary events occurring within chondrocytes and/or osteoblasts as a result of storage.

Progressive arthropathy may affect all joints and leads to severe restriction of motion. The hip joints appear to be particularly vulnerable and severe erosive hip dysplasia can be especially disabling. Poor hand function, due to the characteristic claw-hand deformity, carpal tunnel syndrome and interphalangeal joint stiffness, is also common.

**Diagnosis:** A definitive diagnosis of Hunter syndrome is made by measuring enzyme iduronate-2-sulfatase (I2S) activity in serum, white blood cells, or fibroblasts from skin biopsy. In some people with Hunter syndrome, analysis of the I2S gene can determine clinical severity. Prenatal diagnosis is routinely available by measuring I2S enzymatic activity in amniotic fluid or in chorionic villi.

**Treatment:** There is no cure for Hunter’s syndrome. Treatment is aimed at management of symptoms and complications.

However, Idursulfase, a purified form of the lysosomal enzyme iduronate-2-sulfatase produced by recombinant DNA technology in a human cell line, underwent clinical trial in 2006 and was subsequently approved by the United States Food and Drug Administration as an enzyme replacement treatment for Hunter syndrome.
Complications: Complications can affect the lungs, heart, joints, connective tissue, and brain and nervous system.

Prognosis: Death is usually as a result of cardiorespiratory complications. Severe variant sufferers have average onset 2.5 years with an average age of death of ~12 years. However, some may survive into their thirties. Mild variant sufferers have an average age of onset of 4.3 years with average age of death 21.7 years. However, some may survive into their fourth decade and beyond. Cognitive impairment is associated with reduced life expectancy.

San Filippo Syndrome – MPS III

Definition: a rare autosomal recessive lysosomal storage disease caused by a deficiency in one of the enzymes needed to break down the glycosaminoglycan heparan sulfate (which is found in the extra-cellular matrix and on cell surface glycoproteins).

Types: there are 4 subtypes but all have the same clinical features.

Incidence: 1 : 60,000 in Australia.

Age: manifests in young children with infants appearing normal apart from mild facial dysmorphism

Clinical presentation: as the child grows, there is a slowing of development and the onset of behavior problems. Then there is progressive intellectual decline resulting in severe dementia and progressive motor disease. The behavior aspects include temper tantrums, aggressive behavior and sleep disturbances. In the late phases there is joint stiffness, hirsutism and the hair becomes coarse. In the final phase children become immobile and unresponsive requiring wheelchairs and develop difficulty swallowing and have seizures. The clinical features are mostly neurological but there may be dental caries and enlargement of the liver and spleen. There is a very wide range of clinical severity and the disease may even rarely present later in life as a psychotic episode.

Macroscopic: The photo of a young boy – courtesy of MPS Society 2008

Imaging: the findings include a thickened skull, flared anterior ribs, pointed metacarpals and flared wings of ilium which are very similar to other mucopolysaccaridoses.

Biochemistry: San Filippo syndrome is caused by deficiencies of four different enzymes which are involved in degradation of heparin sulphate; heparan N-sulfatase (type A), alpha-N-acetylg glucosaminidase (type B), acetyl-CoA-glucosaminide acetyltransferase (type C) and N-acetylg glucosamine-6-sulfatase (type D). Heparan sulfate is primarily found in the central nervous system and its accumulation in the brain is responsible for the numerous problems that affect
individuals with all types of MPS III. A urine analysis for glycosaminoglycans dermatin and heparin sulphate is important.

**Diagnosis:** The diagnosis of San Filippo disease can be confirmed with the urine using a simple, rapid and inexpensive CPC test, along with clinical and radiological features.

**Treatment:** Currently there is no cure for San Filippo Syndrome. In most cases, treatment is limited to reducing or controlling the symptoms of this disorder by making sure that neurologists, ophthalmologists, cardiologists, ENTs, orthopaedic surgeons, dentists and genetic counsellors are consulted routinely. Medications to control the behavioural problems associated with this disorder have not proven effective. Anticonvulsants may control seizures, and wheelchairs are often required as the disorder progresses to its final and immobile stage.

**Prognosis:** An affected child does not often live beyond the late teens or early twenties.

**Achondroplasia**

**Definition:** A genetic disorder disturbing normal growth of cartilage, resulting in a form of dwarfism characterized by usually a normal torso and shortened limbs, and usually inherited as an autosomal dominant trait.

**Incidence:** Achondroplasia is the most common type of short-limbed dwarfism. The condition occurs in 1 in 15,000 to 40,000 newborns.

**Genetic:** Two specific mutations in the FGFR3 gene are responsible for almost all cases of achondroplasia. The two mutations, G1138A and G1138C, cause increased function of the FGFR3 gene. These mutations cause decreased endochondral ossification, decreased cellular hypertrophy, decreased cartilage matrix production, and inhibited proliferation of chondrocytes in growth plate cartilage. About 98% of diagnosed patients have the G1138A mutation, resulting in a G-to-A point change. One percent of cases have a G-to-C point change at nucleotide 1138, causing the G1138C mutation. The FGFR3 gene makes a protein called fibroblast growth factor receptor 3. This protein is part of a family of four and provides instructions for making a protein that is involved in the development and maintenance of bone and brain tissue. Researchers believe that the FGFR3 protein in bone cells regulates bone growth by limiting the formation of bone from cartilage – ossification – particularly in the long bones. Cytogenetic Location: 4p16.3, which is the short (p) arm of chromosome 4 at position 16.3.

**Inheritance pattern:** Achondroplasia is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. About 80% of people with achondroplasia have average-size parents; these cases result from new mutations in the FGFR3 gene. In the remaining cases, people with achondroplasia have inherited an altered FGFR3 gene from one or two affected parents. Individuals who inherit two altered copies of this gene typically have a severe form of achondroplasia that causes extreme shortening of the bones and an underdeveloped rib cage. These individuals are usually stillborn or die shortly after birth from respiratory failure.

**Peak Age:**

**Gender:** Males and females are equally affected, as the FGFR3 gene is located on the fourth chromosome (an autosome) and not on a sex chromosome.

**Clinical presentation:** The average height of an adult male with achondroplasia is 131 centimeters (4 feet, 4 inches), and the average height for adult females is 124 centimeters (4 feet, 1 inch). Characteristic features of achondroplasia include an average-size trunk, short arms and legs with particularly short upper arms and thighs, limited range of motion at the elbows, and an enlarged
head - macrocephaly, a marked lumbar lordosis and lumbar and cervical canal stenosis. Fingers are typically short and the ring finger and middle finger may diverge, giving the hand a three-pronged appearance. People with achondroplasia are generally of normal intelligence.

A history of lower back numbness or pain, apnoea, ataxia, and incontinence may be due to cervicomедullary compression. Cord compression can lead to respiratory arrest and progressive quadriplegia. Surgical indicators to release this compression include a small foramen magnum, central hypopnea, and brisk reflexes.

The child may have recurrent otitis media so it is important to prevent conductive hearing loss, a factor related to speech delay.

Increased head size may indicate neurologic and respiratory complications.

**Imaging:** Note the photo of a hand (courtesy of NIH US National Library of Medicine), and an xray of a hand, pelvis, lower limbs and lumbar spine (courtesy of Paul and Juhl). The fingers are the same length and there is a divergent ring and middle finger. The spine shows a marked lumbar lordosis.
**Diagnosis:** For prenatal diagnosis, high resolution ultrasound exam at 16-28 weeks gestation for evaluation of bone length proportions and in a later trimester for head size.

All causal mutations occur at the exact same location within the gene; hence, molecular testing by targeted mutational analysis is easily done and interpreted.

**Complications:** cervicomedullary compression, spinal stenosis, restrictive and obstructive lung disease, otitis media, and tibial bowing, elbow distortion and hydrocephalus. Sleep apnoea is caused by foramen magnum stenosis.

**Treatment:** The availability of somatotropin (recombinant human growth hormone) has revolutionized the treatment of short stature. Growth hormone is currently being used to augment the height of patients with achondroplasia. The greatest acceleration in growth velocity is seen during the first year of treatment and in those with the lowest growth velocities before treatment. However, no long-term studies exist to determine final height. For maximum benefit, it is recommended that therapy be initiated at a young age (1-6 years).

Most of the orthopaedic problems encountered in patients with achondroplasia are related to the spine. Craniocervical stenosis, thoracolumbar kyphosis, spinal stenosis, angular deformities of the lower extremities, and lengthening of the short extremities are the orthopaedic problems commonly required in achondroplasia.

**Prognosis:** depends on the severity of the disease. Patients who have two copies of the deficient gene – homozygous - generally only survive a few weeks or months after birth. Those with one copy - heterozygous - have a normal life span and intelligence. They are usually independent in their daily activities and live a normal life.
Osteopetrosis

Definition: it is an inherited condition characterized by excessively dense bones as seen on x-rays and the bones are brittle and fracture easily due to osteoclasts failing to resorb bone.

Incidence: 1 per 100,000 population.

Age: it may be discovered at birth or soon after but it may not be diagnosed until adulthood.

Gender: equal in sexes

Clinical Presentation: growth is often stunted in the infantile form. Myelophthisic anaemia can be very severe and lead to death. Jaundice, hepatosplenomegaly and cranial nerve palsies and tooth disruption are common. Death often occurs within the first year of life. In the infantile form the disease can be diagnosed in utero and the baby may be stillborn.

Genetic: The infantile form is inherited as an autosomal recessive trait whereas the adult form may be either autosomal dominant, which accounts for the majority but may be autosomal recessive.

Imaging:

Skull: The base of skull shows the most marked sclerosis although all of the cranial bones may be involved. The sinuses and mastoids may show complete lack of pneumatization. As the cranial foramina are encroached upon, this leads to various cranial nerve palsies such as blindness and deafness. Teeth erupt late and soon develop caries. Dental infection may lead to osteomyelitis of the jaw. Images below courtesy of Dr Mohammad A El Bealy. Radiopaedia.org, rID: 25049.

Tubular bones: all may be affected and show a uniform, dense, structureless appearance and complete obliteration of normal trabecular architecture. The medullary canal shows dense sclerosis and merges with the cortex. The sclerosis is usually uniform in the infantile form. Sometimes there may be alternating bands of sclerotic and normal bone at the ends of the shafts. Bone length is usually normal and bones are club shaped due to failure of normal modelling. Epiphyseal ossification centres are dense but mature at the normal rate. In the adult, the increased density is limited to bands of sclerosis at the bone ends, sometimes alternating with bands of normal density. Hands and feet are involved the same as the long tubular bones.
The image below, courtesy of Paul and Juhl, is an infant showing radiolucent bands at the ends of the shaft of femur and tibia, due to periods of normal ossification.

**Spine:** vertebral bodies are uniformly involved by the sclerosis. In the adult type, the sclerosis may be limited to the upper and lower margins of the vertebrae, similar to that seen in renal osteodystrophy or secondary hyperparathyroidism. The image below is a 34 year old male.

**Microscopy:** Failure of osteoclasts to resorb skeletal tissue is the pathognomonic feature of true osteopetrosis. Remnants of mineralized primary spongiosa are seen as islands of calcified cartilage within mature bone. Woven bone is commonly seen. Osteoclasts can be increased, normal, or decreased in number.

**Biochemistry:** in the differential diagnosis, include conditions that can result in diffuse osteosclerosis. Such disorders may include congenital diseases (eg, pyknodysostosis, hypoparathyroidism, pseudohypoparathyroidism), chemical poisoning (eg, fluoride, lead, beryllium), malignancies (leukemia, myeloproliferative diseases), and sickle cell disease. Osteoblastic metastases should also be considered in the differential diagnosis.

Laboratory findings in infantile osteopetrosis include the following:

- Serum calcium - Generally reflects oral intake; hypocalcemia can occur and cause rickets if it is severe enough
- Parathyroid hormone (PTH) - Often is elevated (secondary hyperparathyroidism)
- Acid phosphatase - Increased due to increased release from defective osteoclasts
- Creatinine kinase isoform BB (CK-BB) - levels are increased due to increased release from defective osteoclasts

Laboratory findings in adult osteopetrosis include the following:

- Acid phosphatase and CK-BB - Concentrations are often increased in type II disease
- Serum bone-specific alkaline phosphatase - Values may also be increased in various types of the disease

Complications: bones frequently fracture.

**Treatment:** Bone marrow transplantation (BMT) has been tried but it is less likely to be successful in patients with crowded bone marrow.

**Infantile osteopetrosis** warrants treatment because of the adverse outcome associated with the disease. Vitamin D (calcitriol) appears to help by stimulating dormant osteoclasts, thus stimulating bone resorption. Large doses of calcitriol, along with restricted calcium intake, sometimes improve osteopetrosis dramatically. However, calcitriol usually produces only modest clinical improvement, which is not sustained after therapy is discontinued.
Treatment with gamma interferon has produced long-term benefits. It improves white blood cell function, greatly decreasing the incidence of new infections. With treatment, trabecular bone volume substantially decreases and bone-marrow volume increases. This results in increases in haemoglobin, platelet counts, and survival rates. Combination therapy with calcitriol is clearly superior to calcitriol alone.

Erythropoietin can be used to correct anaemia. Corticosteroids have also been used to treat anaemia, as well as to stimulate bone resorption. This effect on blood cells is due to reduced destruction in the reticuloendothelial system. Prednisone 1-2 mg/kg/day is usually administered for months to years. Steroids are not the preferred treatment option.

**Adult osteopetrosis** requires no treatment by itself, although complications of the disease may require intervention. No specific medical treatment exists for the adult type.

**Surgical treatment**

In pediatric osteopetrosis, surgical treatment is sometimes necessary because of fractures. In adult osteopetrosis, surgical treatment may be needed for aesthetic reasons (eg, in patients with notable facial deformity) or for functional reasons (eg, in patients with multiple fractures, deformity, and loss of function). Severe, related degenerative joint disease may warrant surgical intervention as well.

**Prognosis:** In infantile osteopetrosis, bone marrow failure may occur. If untreated, infantile osteopetrosis usually results in death by the first decade of life due to severe anaemia, bleeding, or infections. Patients with this condition fail to thrive, have growth retardation, and suffer increased morbidity. The prognosis of some patients with infantile osteopetrosis can markedly change after bone marrow transplantation (BMT). Patients with adult osteopetrosis have good long-term survival rates.

**Osteogenesis Imperfecta**

**Definition:** It is a rare inherited disorder characterized by excessive fragility of bone, leading to multiple fractures often from a trivial cause.

**Sites:** All bones

**Frequency:** 6 per 100,000 population.

**Types:** 8 forms of the disease exist but the most common are osteogenesis imperfecta congenita—Type II and osteogenesis imperfecta tarda—l.

**Age:** With the congenital type, it commences in utero and the baby will be born with multiple fractures. The tarda type will become obvious during childhood when there are frequent fractures. Also the joints are lax, so dislocations are frequent, deafness occurs due to otosclerosis and the teeth are discoloured, fragile and easily broken. Blue sclerae become apparent—see photo, courtesy of Flicker.com.
Gender: equally affects both sexes.

Racial: affects all races.

Genetics: Mutations in the COL1A1, COL1A2, CRTAP, and P3H1 genes cause osteogenesis imperfecta.

Mutations in the COL1A1 and COL1A2 genes are responsible for more than 90 percent of all cases of osteogenesis imperfecta. These genes provide instructions for making proteins that are used to assemble type I collagen. This type of collagen is the most abundant protein in bone, skin, and other connective tissues that provide structure and strength to the body.

Most of the mutations that cause osteogenesis imperfecta type I occur in the COL1A1 gene. These genetic changes reduce the amount of type I collagen produced in the body, which causes bones to be brittle and to fracture easily. The mutations responsible for most cases of osteogenesis imperfecta types II, III, and IV occur in either the COL1A1 or COL1A2 gene. These mutations alter the structure of type I collagen molecules. A defect in the structure of type I collagen weakens connective tissues, particularly bone, resulting in the characteristic features of osteogenesis imperfecta.

Mutations in the CRTAP and P3H1 genes are responsible for rare, often severe cases of osteogenesis imperfecta. Cases caused by CRTAP mutations are usually classified as type VII; when P3H1 mutations underlie the condition, it is classified as type VIII. The proteins produced from these genes work together to process collagen into its mature form. Mutations in either gene disrupt the normal folding, assembly, and secretion of collagen molecules. These defects weaken connective tissues, leading to severe bone abnormalities and problems with growth.

In cases of osteogenesis imperfecta without identified mutations in one of the genes described above, the cause of the disorder is unknown. These cases include osteogenesis imperfecta types V and VI.

Inheritance: Most cases of osteogenesis imperfecta have an autosomal dominant pattern of inheritance, so one copy of the altered gene in each cell is sufficient to cause the condition. Many people with type I or type IV osteogenesis imperfecta inherit a mutation from a parent who has the disorder. Most infants with more severe forms of osteogenesis imperfecta (such as type II and type III) have no history of the condition in their family. In these infants, the condition is caused by new (sporadic) mutations in the COL1A1 or COL1A2 gene.

Less commonly, osteogenesis imperfecta has an autosomal recessive pattern of inheritance.

Clinical Presentation: The most severe forms of osteogenesis imperfecta, particularly type II, can include an abnormally small, fragile rib cage and underdeveloped lungs. Infants with these abnormalities have life-threatening problems with breathing and often die shortly after birth.

Imaging: Skull – in the congenital type, the cranial bones are largely membranous at birth. If the infant survives, ossification progresses slowly, leaving wide sutures and multiple wormian bones. Later the sutures become of normal width.

Tubular bones – in the congenital type the baby is born with multiple fractures of the long bones.

See image below, courtesy of Paul and Juhl.
The shafts of the bones are wide and short due to the multiple fractures which heal rapidly. The callus can be so prominent that it can look like a malignant tumour. See image below of such a fracture in the femur. See image, courtesy of Paul and Juhl.

The bones become very misshapen due to the multiple fractures in the abnormally soft bone. The cortex is thin. See image below of the legs of a patient, courtesy of Paul and Juhl.
Spine: Although growth of the bone is normal, the vertebrae are osteoporotic with thin cortical margins, so compression fractures are common. Multiple bodies show biconcave disc surfaces (so-called cod-fish vertebrae). The disc spaces may widen and scoliosis is frequent.

Pelvis: changes are due to osteoporosis and protrusio acetabuli are common.

Treatment: there is no cure but there are ways to manage the symptoms. The goal of all treatment is to minimize fractures, enhance independent function, and promote general health. Treatment may include fracture care, physical therapy, surgical procedures, medications, life style features and mobility aides.

Medical: Goals for physical therapy include expanding and maintaining function and promoting independence. A typical program includes muscle strengthening and aerobic conditioning. Physical therapy often begins in infancy to counteract the delay in motor skill development many children experience due to related muscle weakness. Adaptive devices may be needed. Occupational therapy can help with fine motor skills and selection of adaptive equipment for daily living. As a child grows older and gains more independence, he or she will benefit from continued physical activity, such as adapted physical education. Adults also benefit from safe, regular exercise to maintain bone and muscle mass. Swimming and water therapy are particularly well-suited for people of all ages, as they allow independent movement with little fracture risk. Walking is also excellent exercise for those who are able.

Medications. Bisphosphonate drugs, which are currently approved by the FDA to prevent and treat osteoporosis are used off label to increase bone density in children and adults with moderate and severe osteogenesis imperfecta. Teriparatide, a drug based on the parathyroid hormone is also used to prevent age-related bone loss in adults.

Maintaining a healthy weight is important since extra weight adds stress to the skeleton, heart and lungs and reduces the ability to move easily. In addition, patients should avoid smoking, second hand smoke, excessive alcohol or caffeine consumption and steroid medications, all of which reduce bone density.

Surgery may be needed to repair a fracture, correct bone deformities such as bowing, stabilize the spine or repair bones in the middle ear and improve hearing. Many children undergo a surgical procedure (rodding), in which both non-expandable and expandable rods metal rods are inserted into the long bones to control fractures and improve deformities that interfere with function.

Prognosis: Many patients with Type 1 lead productive and fulfilling lives well into their adult years.

The congenital type has a high mortality resulting from intracranial haemorrhage at birth or from recurrent respiratory infections in the first 2 years of life.

Cleido-cranial dysostosis

Definition: is a congenital condition transmitted as an autosomal dominant trait, where there is delayed ossification of midline structures.

Sites: clavicles and skull most often affected but other bones can be involved such as mandible, pelvis, sacrum and coccyx.

Incidence: 1 : 1,000,000

Peak age: may be obvious at birth.
Gender: no difference between the sexes.

Genetics: caused by mutations in the CBFA1 gene (also called Runx2), located on the short arm of chromosome 6, which encodes transcription factor required for osteoblast differentiation which results in delayed ossification of midline structures of the body, particularly membranous bone. The condition can be inherited or be the result of a sporadic mutation in the CBFA1 gene.

CBFA1 is vital for differentiation of stem cells into osteoblasts, so any defect in this gene will cause defects in membranous and endochondral bone formation.

Clinical features:

Clavicles can be partly missing leaving only the medial part of the bone. In 10% cases, clavicles are completely missing. If the clavicles are completely missing or reduced to small nubbins, this allows hypermobility of the shoulders including ability to touch the shoulders together in front of the chest. The defect is bilateral 80% of the time. Partial clavicles may cause nerve damage symptoms and therefore have to be removed by surgery.

Skull - A soft spot or larger soft area in the top of the head where the fontanelle failed to close, or the fontanelle closes late.

The mandible is prognathic due to hypoplasia of maxilla. See image below, courtesy of Wikipaedia.

Panoramic view of the jaws showing multiple unerupted supernumerary teeth mimicking premolar, missing gonial angles and underdeveloped maxillary sinuses in cleidocranial dysostosis.

The permanent teeth include supernumerary teeth which may need to be removed as they will crowd the adult teeth in what already may be an underdeveloped jaw. Failure of eruption of permanent teeth may occur.

Hypertelorism.

Delayed ossification of the bones forming the symphysis pubis which may appear widened.

Coxa vara can occur which limits abduction.

Vertebral abnormalities can occur such as hemivertebrae. Basilar invagination of the skull may be present due to atlantoaxial impaction.
**Bones and joints** are underdeveloped – there may be short or absent fibulae and short or absent radius bones in the forearm and hypoplastic terminal phalanges.

**Imaging:** The clavicle ossifies from 3 centres and any segment may be missing. See the chest xray below (courtesy of Paul and Juhl) where the central segment of the right clavicle is absent.

![Chest Xray](image1.png)

The skull below, image courtesy of Dr Henry Knipe, Radiopaedia.org, rID:31114, shows the low density in the midline which is the widened anterior fontanelle – black arrow and the wormian bones around the occipital suture – white arrow.

![Skull](image2.png)

**Treatment:** Around 5 years of age, surgical correction may be necessary to prevent any worsening of the deformity. If the mother has dysplasia, caesarian delivery may be necessary. Craniofacial surgery may be necessary to correct skull defect. Coxa vara is treated by corrective femoral osteotomies. If there is brachial plexus irritation with pain and numbness, excision of the clavicular fragments can be performed to decompress it. In the case of open fontanelle, appropriate headgear may be advised for protection from injury.

**Prognosis:**

The bone symptoms cause few problems in most cases. Appropriate dental care is important.

Complications include dental problems and shoulder dislocations.

**Ellis-van Creveld Disease (chondroectodermal dysplasia)**

**Definition:** It is inherited as an autosomal recessive and the patient has disproportionate dwarfism, polydactyly and congenital heart disease (especially an atrial septal defect).
Sites:

Incidence: 1:200,000. It is more common in the indigenous population of Western Australia and also in the Old Order of the Amish population in the United States.

Peak age: apparent at birth

Gender: equal both sexes

Genetics: Ellis-van Creveld syndrome can be caused by mutations in the EVC or EVC2 gene. Little is known about the function of these genes, although they appear to play important roles in cell-to-cell signalling during development. In particular, the proteins produced from the EVC and EVC2 genes are thought to help regulate the cell growth, cell specialization, and the normal shaping (patterning) of many parts of the body.

The mutations that cause Ellis-van Creveld syndrome result in the production of an abnormally small, non-functional version of the EVC or EVC2 protein. It is unclear how the defective proteins lead to the specific signs and symptoms of this condition. Studies suggest that they prevent normal signalling in the developing embryo, disrupting the formation and growth of the bones, teeth, and other parts of the body.

Together, mutations in the EVC and EVC2 genes account for more than half of all cases of Ellis-van Creveld syndrome. The cause of the remaining cases is unknown.

Clinical features: the patient has short stature especially short forearms and lower legs. The chest is narrow with short ribs. There are extra fingers and toes, as well as malformed fingernails and toenails and fused carpal bones (capitate and hamate). Dental abnormalities are common and 50% have a heart defect. Motor development and intelligence are normal. Photo image courtesy of Wikipedia.

Imaging: see image of hands, with polydactyly, fused 5th and 6th metacarpals and fused carpal bones, capitate and hamate. Courtesy of Paul and Juhl.
The shortening of the long tubular bones becomes more severe distally which is the opposite of what is found in achondroplasia. That is, the tibia and the fibula are much shorter than the femur and the distal phalanges more shortened than the proximal. The distal end of radius and proximal end of the ulna are somewhat enlarged. The radial head can be flared and then is frequently dislocated. The proximal end of the tibia also is widened. The intercondylar notch of the femur is shallow and the tibial spine is small. A severe cervical kyphosis with spinal cord compression may occur. The pelvis, vertebrae, ribs and skull are normal.

**Treatment:** It is often necessary to treat respiratory distress shortly after birth that results from a narrow chest and/or heart failure. Infants born with teeth -Natal teeth- should have these removed because they can interfere with feeding.

**Prognosis:** approximately 50% of patients with Ellis–van Creveld (EVC) syndrome die in early infancy as a consequence of cardiorespiratory problems. Most survivors have intelligence in the normal range.

Most importantly, early detection of growth hormone deficiency, known to occur in EVC syndrome, is important. Final adult height is 43-60 inches.

Usually, some limitation of hand function is observed, such as inability to form a clenched fist.

Dental problems are frequent.

End-organ involvement may include:

- Renal involvement including nephrotic syndrome, nephronophthisis, and renal failure
- Hepatic involvement, including a congenital paucity of bile ducts that leads to progressive fibrosis and hepatic failure
- Hematologic involvement ranges from myelodysplastic changes with dyserythropoiesis to acute leukemia

**Gaucher’s disease (sphingolipidosis)**

Please note that a more detailed description of Gaucher’s disease is found in the module called Liver and Gallbladder. Only the bone features will be discussed here.

**Definition:** it is the most common of the lysosomal storage diseases and it is the result of accumulation of glucocerebroside, a sphingolipid, especially in the liver and spleen but also in bone and bone marrow due to a deficiency of beta-glucocerebrosidase enzyme (also called GBA).

**Sites:** Abdomen - the liver and especially the spleen

**Skeletal abnormalities.** Gaucher’s disease can weaken bone, increasing the risk of painful fractures. It can also interfere with the blood supply to bones, which can cause portions of the bone to become necrotic.

**Blood disorders.** A decrease in healthy red blood cells (anaemia) can result in severe fatigue. Gaucher’s disease also affects the cells responsible for clotting, which can cause bruising and nose bleeds.

**Brain,** which may cause abnormal eye movements, muscle rigidity, swallowing difficulties and seizures. One rare subtype of Gaucher’s disease begins in infancy and typically results in death by the age of 2.
Types:

Gaucher’s disease type I (non-neuropathic) is the most common form of the disease, occurring in 40,000 live births. It occurs most often among persons of Ashkenazi Jewish heritage. Symptoms may begin early in life or in adulthood and include enlarged liver and grossly enlarged spleen and the spleen can rupture causing additional complications. **Skeletal weakness and bone disease may be extensive.** Spleen enlargement and **bone marrow replacement** cause anemia, thrombocytopenia, and leukopenia. The brain is not affected pathologically, but lung and, rarely, kidney impairment may occur. Patients in this group usually bruise easily (due to low levels of platelets) and experience fatigue due to low numbers of red blood cells. The range and severity of symptoms can vary greatly between patients.

Gaucher’s Disease type II (acute infantile neuropathic) typically begins within 6 months of birth and has an incidence rate around one 1 in 100,000 live births. Symptoms include an enlarged liver and spleen, extensive and progressive brain damage, eye movement disorders, spasticity, seizures, limb rigidity, and a poor ability to suck and swallow.

Gaucher’s Disease type III (chronic neuropathic) can begin at any time in childhood or even in adulthood, and occurs in about one in 100,000 live births. It is characterized by slowly progressive, but milder neurologic symptoms compared to the acute or type II version. Major symptoms include an enlarged spleen and/or liver, seizures, poor coordination, **skeletal irregularities**, eye movement disorders, blood disorders including anemia, and respiratory problems.

75% of patients develop visible bony abnormalities due to the accumulated glucosylceramide. A deformity of the distal femur in the shape of an Erlenmeyer flask is commonly described (aseptic necrosis of the femur).

**Incidence:** 1 : 40,000 live births.

**Gender:** affects males and females equally.

**Genetic:** inherited as an autosomal recessive condition. The disease is caused by a recessive mutation in the GBA gene located on chromosome 1. The gene instructs the lysosomes to make an enzyme called beta-glucocerebrosidase which will break down glucocerebroside into glucose and a fat molecule – ceramide. Cytogenetic Location: 1q21, which is the long (q) arm of chromosome 1 at position 21.

**Clinical features.** See detail under the heading Types.

**Imaging:** In the images below, courtesy of Paul and Juhl, the image on the left is the mid-tibia and fibula. It shows patchy bone destruction with endosteal scalloping. The image on the right is a femur showing the typical Erlenmeyer flask deformity of the distal femur caused by a lack of constriction of the metaphysis due to infiltration of the marrow by Gaucher’s cells. The image on the far right is the pelvis of an 8 year old girl showing a pathological fracture of the right femoral neck – see arrow - and the medial portion of the proximal femoral epiphysis on the left is sclerotic in keeping with avascular necrosis. In the left intertrochanteric region there is a swirled pattern of trabeculi due to the presence of Gaucher’s deposits within the intramedullary space.
**Microscopic appearance:** In the image below, courtesy of Wikipedia, note the crinkled paper cytoplasm and glycolipid-laden macrophages in the marrow space.

**Diagnosis:** Gaucher disease is suggested based on the overall clinical picture. Initial laboratory testing may include enzyme testing. Lower than 15% of mean normal activity is considered to be diagnostic. Decreased enzyme levels will often be confirmed by genetic testing. Numerous different mutations occur; sequencing of the beta-glucosidase gene is sometimes necessary to confirm the diagnosis. Prenatal diagnosis is available, and is useful when a known genetic risk factor is present. Cell analysis is shown in the microscopy image above.

Some lysosomal enzymes are elevated such as a human chitinase, chitotriosidase, an enzyme that has proved very useful for monitoring Gaucher's disease activity in response to treatment, and may reflect the severity of the disease.

**Treatment:**

For those with type-I and most type-III, enzyme replacement treatment with intravenous recombinant glucocerebrosidase such as Eliglustat (Cerdelga) approved in 2014, can decrease liver and spleen size, reduce skeletal abnormalities, and reverse other manifestations.

**Prognosis:** Depending on disease onset and severity, type I patients may live well into adulthood.

Type II affected children usually die by age two.
Type III patients often live into their early teen years and adulthood.

**Chromosome Abnormalities**

**Down’s syndrome – Trisomy 21**

**Definition:** is the result of an autosomal trisomy of chromosome 21 which occurs by random chance and is the most common chromosomal disorder. It is caused by the presence of all, or part of a third copy of chromosome 21 and is associated with physical growth delays, characteristic facial features, and mild to moderate intellectual disability.

**Incidence:** 1 : 600 births.

**Age:** may be detectable before birth.

**Gender:** Males have a slight preponderance.

**Genetic:** In 95% of cases, the chromosomal abnormality is trisomy of chromosome 21 due to meiotic non-disjunction (i.e. failure of a chromosome pair to separate during meiosis, so that both go to one daughter cell, and none to the other). The individual’s chromosome count is 47, rather than 46. Maternal non-disjunction accounts for about 95% of such cases.

An alternative chromosomal abnormality that results in the syndrome involves Robertsonian translocation of paternal chromosomal material, such that the overall number of chromosomes remains the same. This happens in about 3% of cases. Very rarely (2%) some individuals have mosaic trisomy 21 and these have a longer lifespan.

**Clinical features:** The I.Q is usually 50 -60 which is equivalent to a 9 year old child.

Physical characteristics: a small chin, slanted eyes, poor muscle tone, a flat nasal bridge, a single crease of the palm, and a protruding tongue due to a small mouth and relatively large tongue. These airway changes lead to obstructive sleep apnoea in 50% of those with Down syndrome. Other features include: a flat and wide face, a short neck, excessive joint flexibility, extra space between the great toe and second toe, abnormal patterns on the fingertips and short fingers. Instability of the atlantoaxial joint occurs in about 20% and may lead to spinal cord injury in 1–2%. Hip dislocations may occur without trauma in up to 30% of people with Down syndrome.

Growth in height is slower, resulting in the average height for men being 154 cm (5 feet 1 in) and for women is 142 cm (4 feet 8 in). Individuals with Down syndrome are at increased risk for obesity as they age.

**Risk factors:** maternal age is a risk factor for women over 35 years. The father’s older age is also a risk factor when the mother is older than 35, but not when the mother is younger than 35, and may partly explain the increase in risk as women age.

**Macroscopic:** see photo below, courtesy of Wikipaedia, of an 8 year old boy with Down’s syndrome.
Imaging:

**Pelvis:** during infancy the acetabular angles are flattened, the iliac bones large and flared and the ischia elongated and tapering. The changes are visible during the first 6 to 12 months of life. In the image (courtesy of Paul and Juhl) these features are present which produces the “Mickey Mouse ears” deformity of the pelvis.

**Hand:** shortening of the middle phalanx of the 5th finger.

**Sternum:** the manubrium may ossify from 2 or 3 centres instead of one.

**Ribs:** there are usually 11 ribs instead of 12.

**Lumbar vertebrae:** may be small in the anteroposterior diameter and increased in height.

**Skull:** atlantoaxial subluxation, hypoplastic nasal sinuses and decreased interorbital distance (hypotelorism).

**Cardiovascular:** congenital heart disease is usually an atroventricular canal and there is an increased frequency of an aberrant right subclavian artery.

**Abdominal:** duodenal atresia or annular pancreas.

**Diagnosis:** Down syndrome can be identified during pregnancy by prenatal screening followed by diagnostic testing, or after birth by direct observation and genetic testing. Since the introduction of screening, pregnancies with the diagnosis are often terminated.
When screening tests predict a high risk of Down syndrome, amniocentesis or chorionic villus sampling is needed to confirm the diagnosis which has a 5% false-positive rate. Amniocentesis and chorionic villus sampling are more reliable tests, but they increase the risk of miscarriage between 0.5 and 1%. The risk of limb problems is increased in the offspring due to the procedure. The risk from the procedure is greater the earlier it is performed, thus amniocentesis is not recommended before 15 weeks gestational age and chorionic villus sampling not before 10 weeks gestational age.

**Treatment:** There is no cure and support aims to improve the quality of life.

**Prognosis:** Life expectancy is around 50 to 60 years in the developed world, with proper health care. Between 5 and 15% of children with Down syndrome in Europe attend regular school. Some graduate from high school; however, most do not. Of those with intellectual disability in the United States who attended high school about 40% graduated. Many learn to read and write and some are able to do paid work. Many are able to live semi-independently but they often require help with financial, medical, and legal matters. Those with mosaic Down syndrome usually have better outcomes.

Individuals with Down syndrome have a higher risk of early death. This is most often from heart problems or infections. Following improved medical care, particularly for heart and gastrointestinal problems, the life expectancy has increased. **Currently between 4 and 12% of individuals die in the first year of life.** The probability of long-term survival is partly determined by the presence of heart problems. In those with congenital heart problems 60% survive to 10 years and 50% survive to 30 years of age. In those without heart problems 85% survive to 10 years and 80% survive to 30 years of age. About 10% live to 70 years of age.

Males with Down’s syndrome usually do not father children, while females have lower rates of fertility relative to those who are unaffected.

**Trisomy 18 (Edward’s syndrome)**

**Definition:** is a chromosomal abnormality caused by the presence of all, or part of, an extra 18th chromosome. This genetic condition almost always results from nondisjunction during meiosis. It is the second-most common autosomal trisomy, after Down syndrome, which carries to term.

**Incidence:** At the first trimester screening the incidence is 1 in 400 but due to high spontaneous loss, the birth prevalence is 1 in 6000 live births. Incidence increases as maternal age increases.

**Gender:** 80% are female.

**Genetics:** Edwards syndrome is a chromosomal abnormality characterized by the presence of an extra copy of genetic material on the 18th chromosome, either in whole (trisomy 18) or in part (such as due to translocations). **The additional chromosome usually occurs before conception.** The effects of the extra copy vary greatly, depending on the extent of the extra copy, genetic history, and chance.

Trisomy 18 (47,XX,+18) is caused by a meiotic nondisjunction event. With nondisjunction, a gamete (sperm or egg cell) is produced with an extra copy of chromosome 18; the gamete thus has 24 chromosomes, instead of 23. When combined with a normal gamete from the other parent, the embryo has 47 chromosomes, with three copies of chromosome 18.

If only some of the body’s cells have an extra copy of chromosome 18, resulting in a mixed population of cells with a differing number of chromosomes this is mosaic Edwards syndrome.
Very rarely, a piece of chromosome 18 becomes attached to another chromosome (translocated) before or after conception. Affected individuals have two copies of chromosome 18 plus extra material from chromosome 18 attached to another chromosome. With a translocation, a person has a partial trisomy for chromosome 18, and the abnormalities are often less severe than for the typical Edwards syndrome.

The smallest extra region necessary for expression of serious anomalies of trisomy 18 appears to be 18q11-12.

**Race:** occurs in all races.

**Age:** it can be detected prenatal and in the newborn.

**Clinical features:** Prenatal history in trisomy 18 - Maternal polyhydramnios possibly related to defective sucking and swallowing reflexes in utero and oligohydramnios secondary to renal defects. There can be a small placenta. The foetus has a single umbilical artery, shows weak activity and has growth retardation.

Postnatal in trisomy 18 – infant has apnoeic attacks, feeds poorly and fails to thrive. Low-set, malformed ears and recession of the chin due to mandibular and maxillary hypoplasia is visible. There is ulnar deviation of the fingers with the hand held as a clenched fist. Bone age is retarded. There are short, hypoplastic first metacarpal and pseudo-epiphysis for the metacarpals, equinovarus and “rocker-bottom” feet with hammer toe deformities, short first toe and hypoplastic distal phalanges. The ribs are thin and short and there is an under-segmented sternum and an increase in the A.P. diameter of the chest. There is a narrow transverse diameter of the pelvis due to anterior rotation of the ilia (anti-mongoloid pelvis), hypoplasia or absent medial third of clavicle, hypoplastic, dislocated femoral heads with increased acetabular angles. Cranial bones are thin with a prominent elongated posterior fossa and a shallow J-shaped sella. The thin ribs and antimongoloid pelvis are the most diagnostic skeletal features.

Congenital cardiac abnormalities are frequent and are usually a ventricular septal defect or patent ductus arteriosus. Eventration of the diaphragm and malformation of the kidneys (double ureters, multicystic kidneys, horseshoe kidneys and hydronephrosis) are common.

**Imaging:** The clenched hand is characteristic of the condition. In the image below, courtesy of Dr H. Chen, Medscape Feb 5th 2016 see the index finger overlapping the middle finger and the 5th finger overlapping the 4th.

This condition can be detected by prenatal ultrasound, with many abnormalities shown including microcephaly and the Dandy-Walker malformation (enlarged posterior fossa associated with cerebellar hypoplasia. Refer back to clinical features.
Biochemistry Diagnosis: Low levels of human chorionic gonadotrophin (hCG) and low unconjugated oestriol (uE3) in maternal serum during mid trimester are useful predictors for an increased risk for trisomy 18.

A first-trimester biochemical screening for trisomy 18 is possible; reduced levels of pregnancy-associated plasma protein A (PAPP-A) and free beta–human chorionic gonadotropin (β-hCG) at 8-13 weeks' gestation

The multiples of the mean (MoM) in affected pregnancies is 0.25 for PAPP-A and 0.34 for free beta-hCG.

Screening for trisomy 18 using a combination of maternal age, PAPP-A, and beta-hCG has a detection rate of 76.6% with a false-positive rate of 0.5%.

Amniocentesis is routinely recommended at 14-16 weeks' gestation when trisomy 18 is suspected. It remains the criterion standard with which all other invasive diagnostic tests are compared. Amniocentesis testing for chromosome disorders is 99.5% accurate.

Chorionic villus sampling (CVS) is performed at 10-13 weeks' gestation. The accuracy (96-98%) is less than that of mid trimester amniocentesis.

Treatment: medical care is required for the congenital heart defects and respiratory problems. Rarely correction of for example, oesophageal atresia would be undertaken, as the prognosis is so poor.

Prognosis: The majority of foetuses with the syndrome die before birth. The syndrome has a very low rate of survival, resulting from heart abnormalities, kidney malformations, and other internal organ disorders. When translocations occur that result in partial trisomy or mosaic trisomy, the clinical picture is less severe and the child survives longer.

A small number of children with trisomy 18 survive beyond the first year, and few live into their teens and twenties. Survival rates for Edward’s syndrome are as follows:

- Newborns have a 40% chance of surviving to age 1 month.
- Infants have a 5% chance of surviving to age 1 year.
- Children have a 1% chance of surviving to age 10 years.

Trisomy 13 (Patau’s syndrome)

Definition: is a chromosomal condition associated with severe intellectual disability and physical abnormalities - heart defects, brain or spinal cord abnormalities, microphthalmia, polydactyly, a cleft lip with or without a cleft palate, and weak muscle tone. Due to the presence of several life-threatening medical problems, many infants with trisomy 13 die within their first days or weeks of life. Only 5%-10% of children with this condition live past their first year.

Incidence: 1 in 16,000

Age: can be diagnosed prenatally with ultrasound.

Gender: slightly more common in females.
**Genetic:** Most cases of trisomy 13 are not inherited but result from having three copies of chromosome 13 in each cell in the body instead of the usual two copies. The extra genetic material disrupts the normal course of development, causing the characteristic features of trisomy 13.

Trisomy 13 can also occur when part of chromosome 13 becomes attached (translocated) to another chromosome during the formation of reproductive cells (eggs and sperm) or very early in foetal development. Affected people have two normal copies of chromosome 13, plus an extra copy of chromosome 13 attached to another chromosome. In rare cases, only part of chromosome 13 is present in three copies. The physical signs and symptoms in these cases may be different than those found in full trisomy 13.

A small percentage of people with trisomy 13 have an extra copy of chromosome 13 in only some of the body’s cells. In these people, the condition is called mosaic trisomy 13. The severity of mosaic trisomy 13 depends on the type and number of cells that have the extra chromosome. The physical features of mosaic trisomy 13 are often milder than those of full trisomy 13.

Translocation trisomy 13 can be inherited. An unaffected person can carry a rearrangement of genetic material between chromosome 13 and another chromosome. These rearrangements are called balanced translocations because there is no extra material from chromosome 13. A person with a balanced translocation involving chromosome 13 has an increased chance of passing extra material from chromosome 13 to their children.

**Risk factors:** advanced maternal age – mean 35 years.

**Imaging:** prenatal ultrasound is able to detect the skeletal and cardiac abnormalities.

**Diagnosis:** foetal chromosome testing will show trisomy 13.

**Treatment:** is medical support for the cardiac and other organ abnormalities.

**Prognosis:** 80% die in the first year of life.

**Turner’s syndrome**

**Definition:** Turner syndrome is caused by the absence of one complete or partial copy of the X chromosome in some or all the cells, so the female is 45X instead of XX

**Incidence:** 1 in 2000 live female births. 99% of foetuses abort spontaneously.

**Age:** detectable pre-natal and at birth.

**Gender:** exclusively females.

**Genetic:** it is not an inherited condition.

**Race:** the condition affects all races.

**Clinical features:** Often, a short and webbed neck, low-set ears, low hairline at the back of the neck, short stature, and swollen hands and feet are seen at birth. Typically, females are without menstrual periods, do not develop breasts, and are unable to have children. Heart defects, diabetes, and low thyroid hormone occur more frequently. Most have normal intelligence. Many, however, have troubles with spatial visualization such as that needed for mathematics. Vision and hearing problems occur more often.
**Risk factors:**  mother’s age does not play a role, unlike Trisomy 21, 18 and 13.

**Imaging:**  there is characteristic shortening of the 4th metacarpal. Image courtesy of Paul and Juhl.

![Image of bone shortening](image)

Bones may become osteoporotic and in the spine this can lead to scoliosis. Also this will lead to an increased risk of fractures.

**Diagnosis:**  Turner syndrome may be diagnosed prenatal by amniocentesis or chorionic villus sampling during pregnancy. Also can be identified by abnormal ultrasound findings (*i.e.* heart defects – especially coarctation of the aorta and aortic valve abnormalities, kidney abnormality, cystic hygroma or ascites.

Turner syndrome can be diagnosed postnatally at any age. Often, it is diagnosed at birth due to heart problems, an unusually wide neck or swelling of the hands and feet. In the photograph, courtesy of Wikipedia, one can see severe lymphoedema of the feet of an infant.

![Image of lymphoedema](image)

However, it is also common for it to go undiagnosed for several years, typically until the girl reaches the age of puberty/adolescence and she fails to develop breasts or menstruate.

A karyotype or chromosome analysis, analyses the chromosomal composition of the individual. This is the test of choice to diagnose Turner syndrome.

**Treatment and Prognosis:**  There is no cure but growth hormone can be offered to a child to increase its adult height, starting when the child is just a toddler. Oestrogen supplements may be given to promote the development of breasts. Prognosis for Turner syndrome can be good, with careful and consistent monitoring of a person’s health and early treatment of problems that can occur. Many women with Turner syndrome lead full and active lives and can expect a normal lifespan.
ACQUIRED Non-neoplastic Conditions

Fractures

Can be **Open (compound)** – is when there is perforation, laceration or avulsion of the overlying skin and soft tissues by the broken bone. OR

**Closed** – the soft tissues are not involved and skin is intact. However, if surgery is required to reduce and fix the fracture with metal plates or bone grafts, the fracture site is then potentially ‘Open’ with the risk of infection.

**Terminology for description of fractures**: the distal fragment is mentioned first as displaced in relation to the proximal fragment. The same phraseology applies to dislocations; for example forearm bones are displaced with respect to the humerus. If there is an angular deformity, consider it is angled in relation to the proximal fragment. One must also refer to apposition, overlap or over-riding and number of fragments.

**Classification:**

**Complete fracture** – when there is complete discontinuity or disruption of bone with separation into two or more fragments.

**Incomplete fracture** – when the fracture does not extend across the entire width of the bone.

**Occult fracture** – when a fracture is suspected on clinical grounds but the radiograph is normal. These cases need either a nuclear medicine scan to follow or a follow-up radiographs a few days later. A common site for this to occur is the scaphoid bone in the wrist. There is loss of bone occurring along the fracture line shown on the second radiograph.

**Bone bruise** – represents haemorrhage and oedema associated with trabecular micro fractures sustained as a result of compression or impaction forces applied to the joint surface. MRI is very useful to demonstrate this condition. It is often associated with meniscal or ligamentous injuries but can occur in isolation.

**Hairline fracture** – an undisplaced fracture with minimal separation of fracture fragments.

**Comminuted fracture** – this has more than two fragments.

**Avulsion and chip fracture** – occurs when the fragment is pulled away from a tuberosity or bony process at the end of a bone at sites of ligament or tendon attachment. When the fragment is very small it is called a chip or sprain fracture or flake fracture.

**Impacted fracture** – fragments are driven into one another either along the entire line of fracture or only along one side. At the line of impaction the bone is denser than normal due to condensed bony trabeculae. Common sites are the Colles’ fracture of the distal end of the radius and subcapital fracture of the neck of the femur. When it occurs in the spine, it is called a compression fracture.

**Greenstick fracture** occurs in infancy and childhood and there are 3 types;

(a) a transverse fracture in the cortex which extends into the centre of the bone and then becomes orientated along the long axis of the bone without disrupting the opposite cortex.
(b) a buckling fracture due to impaction. The cortex is buckled but there is no disruption of the cortex.

(c) a bow fracture when the bone is curved but without fracture or buckle. This is most common in the forearm, followed by the fibula and rarely occurs in the femur, clavicle and humerus.

**Epiphyseal fracture** – this follows the Salter-Harris classification. See the diagrams below, courtesy of Paul and Juhl.

**Pathological fracture** – is when a fracture occurs through diseased bone such as involvement with either a primary benign tumour (e.g. enchondroma) or metastasis from a malignant tumour or Paget’s disease. In children, the underlying process is usually benign, e.g. osteogenesis imperfects, simple bone cysts. The fracture is usually transversely orientated at right angles to the shaft of the bone. The edges may show bone destruction, the shaft show endosteal erosion and periosteal new bone.

**Pseudofracture** – this has transverse fissures that extend partly or completely through the bone e.g. osteomalacia. The fissures are infractions of bone in which osteoid is formed in the defect but calcium deposition fails.

**Birth fractures** – may occur when a big baby has a long labour or a breech presentation. Bones that may fracture are the clavicle, humerus and femur.

**Apophyseal fractures** – the apophyses are growth centres for bony projections and tuberosities and serve as attachments for muscles, tendons and ligaments. They can be avulsed by one of those structures pulling it off e.g. ischial tuberosities in the pelvis and the medial epicondyle of the elbow.

**Insufficiency fractures** – are the result of normal activity in weakened bone. A common place is the pelvis of elderly osteoporotic women. Also occurs with rheumatoid arthritis, renal osteodystrophy, steroid use and after pelvic irradiation. Diagnosis is confirmed by CT scan which shows patchy sclerosis, with fissure-like fractures and no associated soft-tissue mass. This distinguishes it from metastatic disease which would be in the differential diagnosis of this age group. These may also occur after joint replacement for osteoarthritis in osteoporotic individuals.

**Stress fractures** – occur in normal bone of healthy individuals in response to the stress of repeated activities. One sees a thin line of transverse or oblique radiolucency or a fluffy or compact periosteal callus without an obvious underlying fracture. Another feature is that it may appear as a band of increased density showing healing or compression of medullary bone e.g. distal shaft of the metatarsals (so-called march fracture), tuberosity of the calcaneum, shafts of tibia, fibula, neck of femur, pubic bones. A radionucleide scan may be very useful to confirm its presence, when the patient complains of pain over the site but the radiograph is negative.
Fractures of the skull and spine are covered in modules titled Head Injuries and Spinal Injuries.

Healing of Fractures: a haematoma forms about the fracture site. The blood supply to the cells adjacent to the fracture is interrupted so those cells die. Hence the edges of the fracture have dead bone back as far as the junction of collateral vascular channels. A network of fibrin is precipitated in the clot and collagenoblasts penetrate the haematoma from the adjacent mesenchyme. The haematoma is organised into a mass of granulation tissue. Viable osteoblasts begin to produce osteoid and new fibroblasts mature into osteoblasts and chondroblasts. In addition there is production of new bone between the periostium and the old cortex and a solid mass of bone replaces the marrow tissue. The new bone extends toward the fracture line and meets with the similar bone produced on the opposite side of the fracture. This new bone is called callus.

Initially the new bone consists of woven bone but this has to be replaced with compact adult bone to withstand functional loads. Eventually the callus decreases as the stronger adult bone replaces the weaker woven bone. When there is destruction of the periostium healing is delayed. Also any movement of the edges of the fracture delays the healing process and increases the size of the callus. Patients who are taking long-term anticoagulants, which are Vitamin K antagonists, are reported to take longer to unite a fracture because Vitamin K is one factor required for new bone formation.

Osteonecrosis (avascular necrosis)

Definition: osteonecrosis is death of bone tissue due to a lack of blood supply.

Causes:

- fracture of the bone or dislocation of a joint.
- Corticosteroid administration
- Infection
- Radiotherapy
- Pregnancy
- Gaucher’s disease
- Sickle cell disease
- Chronic pancreatitis
- Epiphyseal disorders
- Tumours

Sites: In the medullary cavity of the metaphysis or diaphysis and the subchondral region of the epiphysis.

Pathology: medullary infarcts which involve both cancellous bone and marrow. The cortex is usually unaffected because of collateral blood flow.

In subchondral infarcts there is a triangular segment of tissue, with its apex pointing to the centre of the bone, that undergoes necrosis, and it has the subchondral bone plate as its base. The articular cartilage over that remains viable because it receives nutrients from the synovial fluid. Eventually there is collapse of the necrotic cancellous bone and the articular cartilage will fracture or slough off.

Clinical features: Medullary infarcts are clinically silent except when occurring in sickle cell disease and Gaucher’s disease. As a rule these remain stable. Subchondral infarcts cause chronic pain which becomes constant. Often the site of these collapse and cause secondary osteoarthritis.
Imaging: The plain radiograph may show the abnormality. See the arrow on the pelvis, with avascular necrosis in the right femoral head – courtesy of Dr Abhijit Datir, Radiopaedia, rID 36031.

However, MRI is much more sensitive - 95% pick-up and shows abnormalities before plain radiographs. The image below, courtesy of Dr Ahmed Abd Rabou, Radiopaedia.org, rID 22964, shows avascular necrosis in the talus. It has the double-line sign which consists of a peripheral/outer dark (sclerosis) and an inner bright (granulation tissue) on T2 weighted images. This finding is diagnostic.

Radionuclide bone scan is nearly as good as MRI (85% pick up) and might be preferred in cases where there is a high risk of multiple bones having avascular necrosis, such as sickle cell disease.

Treatment: The goal of treatment is to reduce the load on the affected part and to promote revascularisation.

Treatment varies with location and includes:

- conservative: anti-inflammatory drugs, analgesia, and reduced/non-weight bearing
- core decompression
- joint replacement for end-stage disease
Infection - osteomyelitis

Types: bone infection can be divided into pyogenic and non-pyogenic and this can be classified further as subacute, acute or chronic (active and inactive) depending upon the severity of the infectious process and the clinical symptoms. Also one could consider a diffuse form and a localized form, the latter being called a bone abscess.

Source of infection:

- via the bloodstream (haematogeneous) - the most common method
- Contiguously from local areas of infection as in cellulitis
- Penetrating trauma
- iatrogenic causes such as joint replacements or internal fixation of fractures or secondary periapical periodontitis in teeth

PYOGENIC OSTEOMYELITIS – acute and chronic

Organisms:

Staphylococcus aureus – causes 90% of the cases of pyogenic osteomyelitis and is part of the normal flora found on the skin and mucous membranes. However, in sickle cell disease the most common agent is Salmonella, with a relative incidence more than twice that of S.aureus.

Escherichia coli, Pseudomonas and Klebsiella infections occur in patients with genitourinary tract infections or who are intravenous drug abusers.

Haemophilus influenzae and group B streptococci are frequent in the newborn.

Sites: tibia, femur, humerus, vertebrae, the maxilla, and the mandibular bodies are especially susceptible to osteomyelitis. Abscesses of any bone, however, may be precipitated by trauma to the affected area. In infants, the infection can spread to a joint and cause septic arthritis. In children, large subperiosteal abscesses can form because the periosteum is loosely attached to the surface of the bone.

Pathogenesis: The area usually affected when the infection is contracted through the bloodstream is the metaphysis of the bone. Once the bone is infected, leukocytes enter the infected area, and, in their attempt to engulf the infectious organisms, release enzymes that lyse the bone. Pus spreads into the bone's blood vessels, impairing their flow, and areas of devitalized infected bone, sequestra, form the basis of a chronic infection. Often, the body will try to create new bone around the area of necrosis. The resulting new bone is called an involucrum. On histologic examination, these areas of necrotic bone are the basis for distinguishing between acute osteomyelitis and chronic osteomyelitis. Osteomyelitis is an infective process that encompasses all of the osseous components, including the bone marrow. When it is chronic, it can lead to bone sclerosis and deformity.

In the neonate the metaphyseal vessels penetrate the growth plate, resulting in frequent infection of the metaphysis, epiphysis or both. In older children the organisms localize in the metaphysis. When the growth plate closes, the metaphyseal vessels reunite with their epiphyseal counterparts and provide a route for bacteria to seed the epiphyses and subchondral regions in the adult.

Clinical features: it may present as a systemic illness plus severe pain over the affected bone. In infants there may only be a fever and in adults there may only be the pain, with no fever.
**Imaging:** the first sign of bone infection on an radiograph is soft-tissue oedema and loss of fascial planes. This occurs within 24 – 48 hrs of the infection. The earliest changes in the bone on radiograph and radionuclide bone scan, is evidence of a destructive lytic lesion within 7 – 10 days of the onset of infection. Within 2 – 6 weeks there is progressive destruction of cortical and medullary bone, an increased endosteal sclerosis indicating reactive new bone formation and a periosteal reaction.

In 6 – 8 weeks sequestra indicating areas of necrotic bone usually become apparent and these are surrounded by a sheath of periosteal new bone (involutrum). This can be shown on CT scan. The involucrum develop as the result of an accumulation of inflammatory exudate which penetrates the cortex and strips up the periosteum. This stimulates the inner layer to form new bone.

However, the new bone is then infected and the barrier causes the cortex and spongiosa to be deprived of a blood supply and it becomes necrotic. This stage is **chronic osteomyelitis** and a draining sinus tract often forms. If the sequestra are small these will be resorbed or exit via the sinus tract to the exterior. The photograph below left, courtesy of Robbins and Cotran. Pathologic Basis of Disease, is an excised surgical specimen showing a sequestrum – see arrow – within an involucrum.

On the right is a radiograph of a radius, courtesy of Paul and Juhl, with chronic osteomyelitis of the entire shaft. Irregular cavities are the site of chronic abscesses and there is a large, dense sequestrum - see arrow - surrounded by involucrum within the cavity in the distal end of the shaft. The original cortex has been completely replaced.

In the images below, courtesy of Paul and Juhl, there is acute osteomyelitis of the distal radius. Image A is the first examination and shows irregular lysis and destruction in the distal metaphysis. Epiphysis is not involved. Image B is a radiograph 9 days later and shows obvious destruction, which now extends to the diaphysis. Destruction of the cortex and marked overlying soft-tissue swelling are evident. There is also some periosteal new bone formation.
Follow-up at 8 weeks – see below - shows healing with compact periosteal reaction filling in a portion of previously destroyed bone.

**Treatment:** osteomyelitis often requires prolonged antibiotic therapy for at least 6 weeks. A PICC line or central venous catheter can be placed for long-term intravenous medication administration. It may require surgical debridement in severe cases, or even amputation.

Initial first-line antibiotic choice is determined by the patient's history and regional differences in common infective organisms. Local and sustained availability of drugs have proven to be effective in achieving prophylactic and therapeutic outcomes. Open surgery is needed for chronic osteomyelitis, whereby the involucrum is opened and the sequestrum is removed. Hyperbaric oxygen therapy has been shown to be a useful adjunct to the treatment of refractory osteomyelitis.

**Complications:** fractures of the bone, amyloidosis, endocarditis, or systemic sepsis.

**NON PYOGENIC bone infection**

**Types:** tuberculosis, syphilis and fungal infections.

**Tuberculous osteomyelitis:** occurs as a secondary phenomenon from a primary focus in the lung or the genitourinary tract. In 15% bone involvement occurs without joint involvement. TB has a predilection for the metaphyseal segment of the long bones. In adults the joints are more often affected.

**Imaging of TB osteomyelitis**

In the long and short bones, progressive destruction of the medullary region with abscess formation is demonstrated on radiographs. There is evidence of osteoporosis but in the early stage of the disease little reactive sclerosis is present.
A short tubular bone of the hand or foot may have destruction in the mid diaphysis and produce a fusiform enlargement of the entire diaphysis.

In children there may be multiple disseminated lytic lesions in the short tubular bones – called cystic tuberculosis.

**Fungal osteomyelitis**

The most common organisms are coccidioidomycosis, blastomycosis, actinomycosis, cryptococcosis and nocardiosis. The infection is usually low grade with the formation of an abscess and a draining sinus. It can resemble a tuberculous skeletal infection because the abscess is usually found in cancellous bone with little or no reactive sclerosis or periosteal reaction.

**Sites:** favour location at a joint or bony prominence such as the acromion, coracoid process, olecranon or styloid process of the radius or ulna.

**Coccidioidomycosis**

**Route of infection** is inhalation of the organism from dust. So the primary site of infection is the lung and often asymptomatic. Dissemination of the organism is rare but there are exceptions in the at-risk group. Bone involvement occurs in 50% of patients with disseminated disease.

**Risk factors:** pregnancy, children under the age of 5 years, adults over the age of 50 years and immunosuppressed patients.


**Imaging:** usually seen as well-marginated, punched-out osteolytic lesions involving long and flat bones. Lesions are unilocular usually but there is a permeated type seen sometimes with a periosteal reaction. In the latter soft tissue swelling and osteoporosis are common. The other variety has joint involvement and changes in joints are periarticular osteoporosis, a permeative pattern involving both articular surfaces, soft-tissue swelling and sometimes periostitis. However, joint involvement in coccidioidomycosis is exactly the same picture as tuberculosis. The vertebral column can be affected and may present as a disc space infection. Paraspinal extension into the soft tissues is common.

Nucleotide scan is useful to evaluate patients with disseminated disease. CT and MRI define bony involvement and assess the extent of soft-tissue disease.
In the CT image below, again courtesy of BD Mirochnik et al, see multiple well circumscribed lesions involving sternum and manubrium.

Nocardia asteroids is another fungal infection and reported in patients with the human immunodeficiency virus (HIV) who have developed the acquired immune deficiency syndrome (AIDS). The clinical features and the imaging are very much like tuberculosis. The bone infection is due to spread from soft-tissue infection in most cases.

Syphilitic osteomyelitis – organism is a spirochete Treponema pallidum

Congenital syphilis – the infection is transmitted from mother to foetus and the features can be a chronic osteochondritis, periostitis or osteitis.

Site: most frequent site is the tibia.

Macroscopic: the lesions are wide-spread and symmetrical. Destructive change is usually in the metaphysis at the junction with the growth plate. In late cases, the tibia shows anterior bowing referred to as ‘saber tibia’.

Acquired syphilis - shows either a chronic osteitis with irregular sclerosis of the medullary cavity or as syphilitic abscesses called gumma. The gumma variety looks like pyogenic osteomyelitis but there are no sequestra which occur in the pyogenic type.

Imaging: congenital syphilis – see radiograph A – courtesy of Paul and Juhl – there is a fine line of periosteal new bone formation paralleling the diaphysis of the long bones, as well as focal areas of destruction in the medial aspects of the metaphysis of the proximal tibia, distal femur and distal tibia bilaterally. In radiograph B of the newborn, the linear periosteal new bone formation is visible in both femurs. A focal area of bone destruction at the medial margin of the proximal metaphysis of the tibia is present – see the arrow.
Acquired syphilis  showing chronic syphilitic osteoperiostitis of the tibia causing a bilateral saber shin deformity which is diagnostic of tertiary syphilis. See image, also courtesy of Paul and Juhl.

Leprosy – caused by Mycobacterium leprae.

There are two forms; a cutaneous form (lepromatous leprosy) which is not associated with abnormalities in the skeletal system and a neural form (tuberculoid leprosy) which frequently does so. In the tuberculoid type nerves become enclosed within granulomatous inflammatory reactions and are destroyed. Nerve degeneration means there is skin anaesthesias and skin and muscle atrophy. Minor trauma can result in chronic ulcers. Contractures, paralyses and autoamputation of fingers and toes follows. Hence the organism itself does not damage the bone which is secondary to the loss of sensation.

In the image, courtesy of Paul and Juhl, all of the phalanges of the foot have been resorbed, with the exception of the 4th toe and the base of the great toe. Tapered thinning of the distal ends of the metatarsals is evident.
OSTEOPOROSIS

**Definition:** it is a generalized metabolic bone disease characterized by inefficient formation or increased resorption of bone matrix that results in decreased bone mass and microscopic deterioration of bone. The bone matrix that is present is *normally mineralised*.

**FLAG:** The converse is present in osteomalacia where there is *faulty mineralization of bone matrix*.

**Classification of osteoporosis** initially divides the condition into generalized involvement of the skeleton and localized involvement.

Within the generalized category there is primary and this includes senile and postmenopausal.

Most of the causes in the generalized category show osteoporosis secondary to the presence of other conditions: genetic, endocrine, neoplasia, gastrointestinal, drugs and others.

**Pathogenesis:** Peak bone mass is achieved in young adults. The degree is influenced by hereditary factors, physical activity, diet and hormonal factors. As a natural phenomenon, there is loss of bone mass at the rate of 0.7% per year affecting both sexes equally.

**Senile and postmenopausal osteoporosis**

**Pathogenesis:** osteoblasts from elderly persons have reduced proliferative and biosynthetic potential when compared with osteoblasts from young persons. Proteins bound to the extracellular matrix lose their biologic potency. Thus there is a reduced ability to make bone. Women are much more affected than men with an earlier onset and greater loss of bone. This is attributed to the loss of stimulation by oestrogen in women. Resorption of bone occurs in 3 locations; the endosteal surface with thinning of the cortex, the haversian canals causing porosity of the cortex and the trabeculae within intramedullary bone. The changes are more prominent in non-weight bearing areas.

**Sites:** the first sites affected are the periarticular regions where the cortex is anatomically thinner. In the long bones, the thickness of the cortex decreases, the bones become brittle and there is increased clinical incidence of fractures, especially in the proximal femur, the proximal humerus, the distal radius and the ribs.

**Clinical evaluation of Osteoporosis** – patterns of trabecular bone loss correlate well with increasing severity of osteoporosis.
**Imaging:** The most used method – the Singh index - is to examine a radiograph of the proximal femur observing the femoral neck for the pattern of the principal compressive group of trabeculae, the secondary compressive group of trabeculae and the principal tensile group of trabeculae.

**Singh trabecular index**

- **grade 1:** only thin principal compression trabeculae visible – most severe degree  
- **grade 2:** principle compression trabeculae present, other trabeculae nearly resorbed  
- **grade 3:** principle tensile trabeculae thinned and breakage in continuity present  
- **grade 4:** principal tensile trabeculae thinned without loss of continuity  
- **grade 5:** principle tensile and compression trabeculae readily visible with prominence of Ward triangle  
- **grade 6:** all trabeculae visible and of normal thickness

Grade 3 and below indicate definite osteoporosis.

At the confluence of principal tensile, principal compressive and secondary compressive trabeculae there is a triangle of radiolucency called Ward’s triangle. The compressive trabeculae are more important than the tensile trabeculae. Diagram is courtesy of Dr Matt Skalski, Radiopaedia.org, rID:19963.

**Generalised osteoporosis - Secondary**

Endocrine disorders: hyperparathyroidism, hyperthyroidism, hypothyroidism, hypogonadism, pituitary tumours, diabetes type 1, Addison’s disease.

Gastrointestinal: malnutrition, malabsorption syndromes, liver insufficiency, **vitamin C** and D deficiencies.

Drugs: anticoagulants, corticosteroids, anticonvulsants (phenytoin), alcohol

Neoplasia: multiple myeloma, carcinomatosis and Congenital – osteogenesis imperfecta.

****Only Scurvy due to vitamin C deficiency and hyperparathyroidism (primary and secondary) will be discussed in the text that follows.
A deficiency of ascorbic acid (vitamin C) in the diet causes bone disease in children and both haemorrhages and healing defects in children and adults. It is required for normal osteoblastic activity, so the organic matrix of bone cannot be laid down without it. The function of vitamin C is to support intracellular substances of mesenchymal derivation e.g. connective tissue, osteoid tissue in bones and dentine in teeth. Deficiency causes a haemorrhagic tendency which leads to subperiosteal bleeding and abnormal function of osteoblasts and chondroblasts which will result in defective osteogenesis.

**Imaging:** bone lesions are caused by cessation of endochondral bone ossification caused in turn by failure of the osteoblasts to form osteoid tissue. As osteoclastic resorption continues without adequate formation of new bone, one sees the appearance of osteoporosis, with generalized osteopenia and thinning of the cortex.

However, deposition of calcium phosphate continues in the osteoid tissue formed, so an area of increased density develops adjacent to the growth plate. These are referred to as the “white lines of scurvy”. A ring of increased density is also seen around any secondary centre of ossification (called the Wimberger ring sign).

Fractures of the metaphysis are common, producing the “corner sign” or “Pelkan’s beak”. As there is increased capillary fragility subperiosteal and soft-tissue bleeding occurs which in turn can be responsible for a periosteal reaction. In adults the bleeding can extend into joints.

The images below of an infant (courtesy of Paul and Juhl) show on the left; black arrow indicates the white line of scurvy in the distal femur. The short white arrow is a Pelkan’s beak and the long white arrow indicates the Wimberger ring sign around the epiphysis. The image on the right is the same infant soon after beginning treatment but now shows there is an epiphyseal fracture, with lateral displacement of the right lower femoral epiphysis. Large calcifying subperiosteal haematomas are present bilaterally around the femoral shafts in the image on the right.
HYPERPARATHYROIDISM

Types:  Primary and secondary

Primary is associated with increased parathyroid hormone secretion from a parathyroid tumour which is usually a solitary adenoma but can be multiple adenomas and rarely parathyroid carcinoma.

Secondary:  is caused by alterations in renal function, such as due to glomerular nephritis or chronic pyelonephritis in adults and congenital structural abnormality of the urinary tract such as polycystic disease, congenital obstructions of the ureters, bladder outlet or urethra in children and adolescents, causing hyperplasia of all parathyroid glands. The combination of both soft-tissue and skeletal abnormalities is called renal osteodystrophy. The term includes increased osteoclastic bone resorption, delayed matrix mineralization (osteomalacia), osteosclerosis, growth retardation and osteoporosis.

Pathogenesis:  the excess of parathyroid hormone causes excessive bone resorption which results in increase in the levels of serum calcium and reduces serum phosphorus. The parathyroid hormone increases the number of osteoclasts with subsequent osteoporosis. It can also decrease the resorption of phosphate by the proximal renal tubules. When the renal threshold is exceeded calcium is excreted in increased amounts. Renal stones can form and calcification occurs in the kidney as nephrocalcinosis. These additional changes further impair renal function aggravating the retention of phosphate and the loss of calcium.

Clinical features:  patients often present with urinary tract calculi, peptic ulcer or pancreatitis. Some complain of pain of the peripheral joints or vertebral column.

Diagnosis:  is by biochemistry – hypercalcaemia, hypophosphataemia, increased urinary excretion of calcium and phosphate and increased serum alkaline phosphatase. These findings are present in 40% before the radiographs show an abnormality.


Subperiosteal resorption is diagnostic of hyperparathyroidism. It is most common along the radial aspects of the middle phalanx of the index and middle finger. This creates a fine irregularity along the outer margins of the cortex and creates a lace-like pattern. Resorption of the terminal tufts occurs in the distal phalanges. Similar changes occur in the medial, proximal metaphyseal surfaces of the tibia, humerus and femur and both superior and inferior margins of the ribs. In the image below, courtesy of DK McDonald, L Parman, VO Speights. RSNA Radiographics 25 (3) May-June 2005 – see diffuse osteopaenia with subperiosteal resorption especially of the radial aspect of the shafts of the 2nd and 3rd phalanges (solid arrows). Prominent acr-o-osteolysis (arrowheads) and intra-cortical tunneling involving multiple phalanges (open arrows).
**Subchondral resorption:** also occurs and at the acromioclavicular, sternoclavicular, symphysis pubis and sacroiliac joints. This widens these joints.

**Subligamentous resorption:** and erosions occur at the site of tendon and ligament attachment to bone, most frequent at the trochanters, the ischial and humeral tuberosities, the inferior surface of the calcaneus and the inferior aspect of the distal clavicle.

**Intracortical bone resorption** within the haversian canals may show as intracortical linear lucencies.

**Endosteal bone resorption** causes a scalloping of the endosteal surface and **trabecular resorption** results in a granular appearance with loss of trabecular detail. The latter is evident in the skull vault where it is called “salt and pepper skull”.

**Chondrocalcinosis:** is found in 50% of patients with primary hyperparathyroidism and is uncommon in secondary hyperparathyroidism. The calcification is in the joint cartilage.

**Osteosclerosis:** is a feature of secondary hyperparathyroidism or renal osteodystrophy. This is seen most often in the superior and inferior margins of the vertebral bodies as broad bands of increased density resulting in the “rugger-jersey” spine. The sclerotic bands on the superior and inferior endplates of the vertebral bodies represent accumulations of excess osteoid and appear opaque because of their increased volume when compared to normal bone. See image below with the arrows indicating those bands (courtesy of Venkata Ganesh, Radiopaedia.org, rID 36455).

![Image of vertebral bodies with sclerotic bands](image)

**Treatment:** **surgery** is the method of choice for primary hyperparathyroidism to remove the adenoma and will produce a cure in 95%. If all 4 parathyroid glands are involved, the surgeon will remove three and a part of the 4th leaving some functioning parathyroid tissue.

**Medication - Calcimimetics.** Mimic calcium circulating in the blood so may trick the parathyroid glands into releasing less parathyroid hormone. This drug is sold as cinacalcet (Sensipar). This drug was approved to treat secondary hyperparathyroidism due to chronic kidney disease but some doctors prescribe it to treat primary hyperparathyroidism if the patient is not a good candidate for surgery.
OSTEOMALACIA (and RICKETS in children)

**Definition:** is a condition where an insufficiency of vitamin D causes the process of bone removal and formation to not be in balance, so bone removal continues but formation is arrested. It occurs when insufficient amounts of calcium, phosphorus and vitamin D are available, so proper calcification of osteoid cannot occur with resultant demineralization.

In adults this is called osteomalacia but when it occurs in children, the same process is called rickets. The basic derangement in both is an excess of unmineralised matrix.

**Etiology:** lack of vitamin D due to living in a habitat lacking in sunlight and also due to lack of calcium, phosphorus and vitamin D in the diet. The main effect of vitamin D is to increase absorption of calcium and phosphorus from the gastrointestinal tract. In addition vitamin D has a direct effect on bone.

90% of vitamin D is obtained by endogenous production in the skin which has been exposed to ultraviolet light of the sun. The compound in the skin is 7-dehydrocholesterol and when this is irradiated forms cholecalciferol (vitamin D3). This is bound to plasma α1-globulin and transported to the liver. Vitamin D is converted there into 25-hydroxycholecalciferol (25-OH-D) by 25-OHase. This is then converted into 1,25-hydroxyvitamin D in the kidney which is the most active form of vitamin D.

Parathyroid hormone regulates the level of blood calcium

**Pathogenesis of osteomalacia/rickets:** in children, the process affects bone already formed as in adults but in addition it affects new bone formed in the epiphyseal complex; namely the metaphysis and epiphysis.

The process in children commences with overgrowth of epiphyseal cartilage due to insufficient initial calcification and also failure of the cartilage cells to mature and disintegrate.

Osteoid matrix is deposited on inadequately mineralized cartilaginous remnants. This is followed by disruption of the normal replacement of cartilage by osteoid matrix with enlargement of the osteochondral junction.

There is abnormal overgrowth of capillaries and fibroblasts in the disorganized zone due to micro-fractures in the inadequately mineralized bone. Lastly there is deformity of the bones due to loss of structural rigidity.

**Sites:** the bone softening affects the skull in the *newborn* with flattening of the occiput and frontal bossing. The ribs are pulled inwards by respiration, causing the sternum to protrude outwards – pigeon breast deformity

**Imaging of Rickets.** After the child starts walking, deformities due to bone softening are noticed in the spine, pelvis and tibia.

The image below, courtesy of Dr Angela Byrne. Radiopaedia.org, rID 8116 shows the marked bowing of the lower limbs.
Clinical features:

In the child: the infant is usually 6 – 18 months of age and is restless and sleeps poorly. Closure of the fontanelles is delayed and there is softening of the skull vault causing it to change shape. Enlargement of the cartilage at the costo-chondral junction of each rib produces a knob which is the basis of the name – ‘rachitic rosary’. Serum levels of calcium and phosphorus are low and alkaline phosphatase is increased.

In the older child, about 30 months of age: they may have vitamin D resistant rickets. It is also known as familial vitamin D-resistant (or hypophosphataemic) rickets. This is a congenital disorder, transmitted as a sex-linked dominant trait. It occurs as a result of mutation of PHEX gene which is found on the X-chromosome. This gene normally produces an enzyme zinc-metallopeptidase. Loss of function of the enzyme results in circulatory clearance of fibroblast growth factor 23 (FGF-23) that acts on the kidneys to increase phosphate excretion and decrease alpha-1 hydroxylase activity. This results in hypophosphataemia but serum calcium levels are normal. Patients are short and bow-legged. Radiographs show ectopic calcifications and ossifications in the axial and appendicular skeleton.

In the adult: osteomalacia commonly presents with bone pain and muscle weakness.

Imaging of the adult with osteomalacia: there is generalised osteopaenia and multiple, bilateral often symmetric radiolucent lines in the cortex perpendicular to the long axis of the bone – Looser zones. The defects are cortical stress fractures filled with poorly mineralised callus, osteoid and fibrous tissue. Common sites of Looser zones (insufficiency fractures) – see arrows below on the right femoral neck and the left superior pubic ramus - are the axillary margins of the scapulae, the medial margin of the femoral neck, the proximal dorsal aspect of the ulnae, the ribs and the pubic and ischial rami. Image courtesy of Dr Mohammad Taghi Niknejad, Radiopaedia.org, rID 20086.
Microscopic of Osteomalacia: there are excessive quantities of inadequately mineralised bone matrix (osteoid) coating the surfaces of trabeculae in spongy bone and lining the haversian canals in the cortex. In the images below, courtesy of Courses Washington Bone Gallery 2012, see the normal situation upper picture and osteomalacia below. The mineralised bone is green and the osteoid is orange.
PAGET’S DISEASE (osteitis deformans)

**Definition:** A chronic bone disorder that typically results in enlarged, deformed bones due to excessive breakdown and formation of bone tissue that can cause bones to weaken and may result in bone pain, arthritis, deformities or fractures.

**Sites:** 85% cases are polyostotic (vertebral column & femora in 80% of these)  
15% monostotic – tibia, ilium, femur, skull, vertebrae, humeri.  
Unusual to involve ribs, fibula, bones of hands and feet.

**Prevalence:** common in the UK, France, Austria, Australia, New Zealand, U.S.A but rare in China, Japan, Africa and Scandinavia.

**Age:** average age of onset is between 45 years and 55 years. Rare before the age of 40 years.

**Gender:** M : F = 3 : 2

**Etiology:** : possibly a slow virus – a paramyxovirus. Paracrystalline inclusions resembling paramyxovirus are seen in the nuclei of the osteoclasts but no virus has been isolated from tissue cultures.

**Clinical features:** Only 20% of patients are symptomatic, usually complaining of pain at the site of involvement. Most cases are incidental findings at the time of radiographs of the abdomen for other purposes.  
- Pain is common due to microfractures and bone overgrowth compressing the spinal & cranial nerves.
- Compression of the medulla with subsequent nerve palsies.
- Develop malignant change, for example 5-10% develop into a sarcoma

**Biochemistry:** the serum alkaline phosphatase is elevated as much as 20 times normal. Serum calcium and phosphorus are normal but calcium may be elevated in patients with Paget’s disease who are immobilized. Renal calculi or nephrocalcinosis may develop from hypercalciuria under these conditions.

**Imaging:** The radiographic appearance is dependent upon the phase of the disease: lytic, reparative or mixed. The affected bone is enlarged and there is a thick, coarse cortex and thick, coarse cancellous bone. There are areas of radiolucency and patches of dense bone plus evidence of bone softening. In long bones the process almost always involves the end of the bone extending into the diaphysis. In the pelvis it usually involves some portion of the acetabulum.

Paget bone takes up radionuclide bone scanning agents avidly so the diagnosis of Paget’s disease can be made with this tool with the characteristic location of involvement and evidence of softening by bowing of long bones and flattening of vertebrae.

CT scan and MRI show similar findings to plain films.
The image of the vertebral body – courtesy of SE Smith et al. Radiographics 22(5)Sept 2002, shows in the reformatted image trabecular thickening (arrowheads) with extension into the posterior vertebral elements – see asterisk.

The CT image of the skull, courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID 2639, shows a marked increase in the thickness and a coarse, thickened inner and outer table and a widened diploic space. There is a coarse trabecular pattern in the diploic space and small foci of increased density which give rise to the “cotton wool” appearance of the skull. The foci of sclerosis alternate with foci of lucency within the diploic space.

The image of the tibia, courtesy of Paul and Juhl, shows anterior bowing, irregular thickening of the cortex, coarse trabecular pattern and several linear horizontal radiolucencies in the anterior cortex which are Looser zones (pseudofractures).
Microscopic appearance:
Regions of furious osteoclastic bone resorption.
Period of fast bone formation – osteoblastic.
When bone cell activity settles down there is an increase in bone mass and it looks osteosclerotic
New bone is disorganized and followed by progressive fibrosis of marrow spaces. It is structurally unsound so can fracture. The example below, courtesy of SE Smith, MD Murphey, K Motomedi, ME Mulligan, CE Resnick & FH Gannon. RSNA Radiographics 22 (5) Sept 2002 is a case which has the lytic to mixed active phase. It reveals multiple osteoclastic giant cells (black arrowheads) and osteoblasts (arrows) causing bone resorption (white arrowhead) and formation. The asterisk indicates the marrow cavity replaced by fibro-vascular tissue.

Complications: . CT and MRI are most useful for the assessment of the complications of Paget’s disease – spinal cord and nerve compression, basilar invagination of the skull and sarcomatous degeneration. The radiograph is end stage Paget’s disease in the femur with a transverse insufficiency fracture through the proximal femoral shaft. Courtesy of P.A.Cripe, Medscape May 15, 2016.

When there is sarcomatous degeneration in Paget’s disease, it is usually an osteogenic sarcoma, especially if the patient is over the age of 50 years, and less commonly a fibrosarcoma. The image which follows is an osteogenic sarcoma developing in Paget’s disease. The proximal humerus shows a thickened cortex of Paget’s disease. The arrow indicates the tumour which is extending into the
soft tissues. The homogeneous quality of the density indicates osteoid matrix. Courtesy of Paul and Juhl.

![Image of bone structure](image_url)

**Treatment:** Calcitonin & diphosphonates are used to heal the lytic phase.

**FIBROUS DYSPLASIA**

**Definition:** it is a condition whereby the normal lamellar cancellous bone is replaced by an abnormal fibrous tissue that contains small, abnormally arranged trabeculae of immature woven bone formed by metaplasia of the fibrous stroma. Some group it with benign tumours but others regard it as a developmental arrest.

**Gender:** In the monostotic type both sexes are equally affected but in the polyostotic, males slightly more than females.

**Age:** the polyostotic type is seen between 2 years and 20 years and the monostotic in early adolescence, usually stopping at the time of growth plate closure.

**Genetics:** it is considered due to mutation in the GNAS1 gene, the defect that prevents osteoblasts to form normal lamellar bone. There are two common mutations associated with fibrous dysplasia, both occurring at codon 201, with arginine being substituted for either cysteine or histidine, R201C and R201H respectively. A third mutation has recently been reported Q227L which represents only 5% of the GNAS1 mutations in this condition.

**Sites:** the condition can be polyostotic or monostotic.

**Types:** the monostotic type accounts for 70% of cases and most commonly affects the femur, especially the femoral neck, as well as the tibia and ribs.

**Macro:** the lesion arises centrally in the bone, sparing the epiphysis and is rarely seen in the articular end of the bone in adults. As the lesion increases in size, it expands the medullary cavity. The radiographic appearance varies depending upon the proportions of osseous to fibrous content. The image below of proximal femur, courtesy of Dr Yi-jin Kuok, Radiopaedia.org, rID 17974.
Micro: fibrous dysplasia presents as an aggregate of dense fibrous connective tissue with bony trabeculae arranged irregularly instead of the stress-oriented distribution of normal cancellous bone. The trabecular are curved and with branches but few connections with each other. The trabeculae show no evidence of osteoblastic activity. It is the same appearance in both types.

Polyostotic type: shows a predilection for one side of the body in 90% of cases.

Sites: pelvis is the most frequently affected then the long bones, skull and ribs but again the proximal end of the femur, like monostotic, is a common site.

Pathogenesis: the lesions usually progress in number and size until the completion of skeletal maturation then become static. 5% do continue to enlarge.

Imaging: the changes may occur in a small or a large portion of long bones. The cortex is left uninvolved but can be thin purely because of the expanding nature of the lesion. Radionuclide bone scan will show the distribution of multiple lesions. CT scan is useful to show the extent of bone involvement, especially in the craniofacial region.

Treatment: lesions that fracture are treated with surgery. Bisphosphonates are sometimes given to relieve bone pain.

Complications of polyostotic: the most common is fracture.

Sarcomatous transformation can occur in both types but is very rare. It can occur spontaneously or following radiotherapy. The tumour is a fibrosarcoma and affects both sexes equally and appears in the elderly age group. These present as an enlarging painful mass usually in the metaphysis of long bones and pelvic flat bones and pathologic fracture is frequent. Prognosis varies depending upon the grade of the tumour with those high grade that are difficult to resect have a very poor prognosis.

END