GENERAL SURGERY

TETANUS

- It was first documented by Hippocrates, and records dating back to the 5th century. Etiology of the disease was discovered in 1884 by Carle and Rattone.
- Tetanus is an illness characterized by an acute onset of ***hypertonia, painful muscular contractions (usually of the muscles of the jaw and neck), and generalized muscle spasms without other apparent medical causes.***
  - *Clostridium tetani*, an obligate anaerobic gram-positive bacillus, causes tetanus.
  - This bacterium is nonencapsulated and forms spores, which are resistant to heat, desiccation, and disinfectants. The spores are ubiquitous and are found in soil, house dust, animal intestines, and human feces.
  - Spores that gain entry can persist in normal tissue for months to years. Under anaerobic conditions, these spores geminate and elaborate tetanospasmin and tetanolysin. Tetanospasmin that is released by the maturing bacilli is distributed via the lymphatic and vascular circulations **to the end plates of all nerves.**
  - Tetanospasmin then enters the nervous system peripherally at the myoneural junction and is transported centripetally into neurons of the CNS.
  - These neurons become incapable of neurotransmitter release.
  - The neurons, which release gamma-aminobutyric acid (GABA) and glycine, the major inhibitory neurotransmitters, are particularly sensitive to tetanospasmin, leading to failure of inhibition of motor reflex responses to sensory stimulation.
  - This results in generalized contractions of the agonist and antagonist musculature characteristic of a tetanic spasm.
  - *The shortest peripheral nerves are the first to deliver the toxin to the CNS, which leads to the early symptoms of facial distortion and back and neck stiffness.*
  - Once the toxin becomes fixed to neurons, it cannot be neutralized with antitoxin. Recovery requires sprouting of new nerve terminals and new synapses.

History:

- The median incubation period is 7 days, and, for most cases incubation ranges from 4-14 days. Patients with clinical manifestations occurring within 1 week of an injury have more severe clinical courses.
- Patients with generalized tetanus present with trismus in 75% of cases.
  - Other presenting complaints include stiffness, neck rigidity, dysphagia, restlessness, and reflex spasms.
  - Subsequently, muscle rigidity becomes the major manifestation.
  - Muscle rigidity spreads from the jaw and facial muscles over the next 24-48 hours to the extensor muscles of the limbs.
  - Reflex spasms can be triggered by minimal external stimuli such as noise, light, or touch. The spasms last seconds to minutes; become more intense; increase in frequency with disease progression; and can cause apnea, fractures, dislocations, and rhabdomyolysis.
  - Laryngeal spasms can occur at any time and can result in asphyxia.
- Sustained contraction of facial musculature produces a risus sardonicus.

Physical:

- Autonomic dysfunction manifests as extremes in blood pressure, dysrhythmias, and cardiac arrest.
- Neonatal tetanus presents with an inability to suck 3-10 days after birth. Presenting symptoms include irritability, excessive crying, grimaces, intense rigidity, and opisthotonus.
- Tetanic seizures may occur and portend a poor prognosis.

    - Seizures frequently occur in the muscle groups causing opisthotonos, flexion and abduction of the arms, clenching of the fists on the thorax, and extension of the lower extremities.
- Cephalic tetanus usually is secondary to chronic otitis media or head trauma.
    - Cephalic tetanus is characterized by variable cranial nerve (CN) palsies; CN VII most frequently is involved.
- Ophthalmoplegic tetanus is a variant that develops after penetrating eye injuries and results in CN III palsies and ptosis.
- The diagnosis is clinically based on the presence of trismus, dysphagia, generalized muscular rigidity, and/or spasm.

Lab Studies:

- No laboratory tests specific for the diagnosis of tetanus exist.
- Laboratory studies may demonstrate a moderate peripheral leukocytosis.

Other Tests:

- An assay for antitoxin levels is not readily available. However, a level of 0.01 IU/mL or greater in serum generally is considered protective, making the diagnosis of tetanus less likely.
- Cerebral spinal fluid (CSF) studies usually are within normal limits.

TREATMENT

Emergency Department Care: Treatment of tetanus is directed toward the treatment of muscle spasm, prevention of respiratory and metabolic complications, neutralization of circulating toxin to prevent the continued spread, and elimination of the source.

- Admit patients to the ICU. Due to risk of reflex spasms, maintain a dark and quiet environment for the patient. Avoid unnecessary procedures and manipulations.
    - Consider prophylactic intubation in all patients with moderate-to-severe clinical manifestations.
    - Perform tracheostomy in patients requiring intubation for > 10 days.
- Surgical therapy includes debridement of wounds to remove organisms and to create an aerobic environment.
    - The current recommendation is to excise at least 2 cm of normal viable-appearing tissue around the wound margins. Incise and drain abscesses.
- The maintenance of nutrition is extremely important and should be carried out in seriously ill patients via nasoduodenal tubes, gastrostomy tube feedings, or parenteral hyperalimentation.

MEDICATION

Drugs used to treat muscle spasm, rigidity, and tetanic seizures include sedative-hypnotic agents, general anesthetics, centrally acting muscle relaxants, and neuromuscular blocking agents. Antibiotics are used to prevent multiplication of *C tetani,* thus halting production and release of toxins.

Medical Care: Passive immunization with human tetanus immune globulin (TIG) shortens the course and may lessen its severity. A dose of 500 U appears effective.

- Supportive therapy include ventilatory support and pharmacologic agents that treat reflex muscle spasms, rigidity, and tetanic seizures.
- Benzodiazepines have emerged as the mainstay of symptomatic therapy for tetanus. To prevent spasms that last longer than 5-10 seconds, administer diazepam intravenously, typically 10-40 mg every 1-8 hours. Vecuronium (by continuous infusion) or pancuronium (by intermittent injection) are adequate alternatives.
- Penicillin G, which has been used widely for years, has been the drug of choice. Metronidazole (eg, 0.5 g q6h) has comparable or better antimicrobial activity.
- Other drugs used are sedative hypnotics, narcotics, inhalational anesthetics, neuromuscular blocking agents, and centrally acting muscle relaxants (eg, intrathecal baclofen).

Complications:

- Prior to 1954, asphyxia from tetanic spasms was the usual cause of death. However, with the advent of neuromuscular blockers, mechanical ventilation, and pharmacologic control of spasms, sudden cardiac death has become the leading cause of death.
- Sudden cardiac death has been attributed to excessive catecholamine productions, direct action of tetanospasmin, or tetanolysin on the myocardium.
- Further complications include the following:
    - Long bone fractures
    - Glenohumeral joint and temporomandibular joint dislocations
    - Hypoxic injury, aspiration pneumonia, and pulmonary emboli
    - Adverse effects of autonomic instability, including hypertension and cardiac dysrhythmias
    - Paralytic ileus, pressure sores, and urinary retention
    - Malnutrition and stress ulcers
    - Coma, nerve palsies, neuropathies, psychological aftereffects, and flexion contractures

Prognosis:

- The prognosis is dependent on incubation period, time from spore inoculation to first symptom, and time from first symptom to first tetanic spasm.
- In general, shorter intervals indicate more severe tetanus and a poorer prognosis.
- Patients usually survive tetanus and return to their predisease state of health.
- Recovery is slow and usually occurs over 2-4 months.
- Some patients remain hypotonic.
- Clinical tetanus does not produce a state of immunity; therefore, patients who survive the disease require active immunization with tetanus toxoid to prevent a recurrence.

Gas Gangrene

- Gas gangrene is caused by exotoxin-producing clostridial species (large, gram-positive, spore-forming bacilli).
- These anaerobic organisms normally are found in soil and the gastrointestinal tract. *Clostridium perfringens* causes 80-95% of cases of gas gangrene.
- Spontaneous gas gangrene is caused by hematogenous spread (in immunocompromised or with diabetes). *Clostridium septicum* is the most common causative organism of spontaneous gas gangrene.
- Exotoxin, not bacterial proliferation, is responsible for rapid spread of infection.
- Exotoxin causes muscle destruction and creates an anaerobic environment conducive to further bacilli growth.
- Products of tissue breakdown (eg, creatine phosphokinase, myoglobin, potassium) cause secondary toxicity.
- Mortality from traumatic gas gangrene is greater than 25%.
- Mortality from nontraumatic gas gangrene caused by *C septicum* ranges from 67-100%.

Pathophysiology: An anaerobic, gram-positive, spore-forming bacillus of the genus *Clostridium* causes gas gangrene.

- *C perfringens* is the most common cause of gas gangrene.
- Other common clostridial pathogens causing gas gangrene are *Clostridium bifermentans, Clostridium septicum, Clostridium sporogenes, Clostridium novyi, Clostridium fallax, Clostridium histolyticum,* and *Clostridium tertium.*
- These organisms are true saprophytes and are ubiquitous in soil and dust.
- Clostridia are obligate anaerobes, but some species are relatively aerotolerant. Bacterial multiplication and the production of soluble proteins called exotoxins require a low oxygen tension.
- *C perfringens* produces at least 20 exotoxins.
- Disrupted or necrotic tissue provides the necessary enzymes and a low oxidation/ reduction potential, allowing germination of spores.

- The typical incubation period for gas gangrene frequently is short (ie, <24 h), but extreme incubation periods of 1 hour to 6 weeks have been reported.
- Systemically, exotoxins may cause severe hemolysis. Hemoglobin levels may drop to very low levels and, when occurring with hypotension, may cause acute tubular necrosis and renal failure.
- Unconcentrated filtrate from *C perfringens*, purified alpha-toxin, and purified phi-toxins cause hypotension, bradycardia, and decreased cardiac output when injected into laboratory animals.

History:

- Incubation period usually is fewer than 3 days, with rapid onset of symptoms. Infection can advance as much as 1in/h.
- Pain commonly is out of proportion to physical findings.
- Progression to toxemia and shock can be rapid.

Physical:

- Local swelling and a serosanguineous exudate appear soon after the onset of pain.
    - The skin characteristically turns to a bronze color, then progresses to a blue-black color with skin blebs and hemorrhagic bullae.
    - Within hours, the entire region may become markedly edematous.
    - The wound may be nonodorous or may have a sweet mousy odor.
    - Crepitus follows gas production; at times, due to brawny edema, crepitus may not be detected with palpation.
    - Pain and tenderness to palpation disproportionate to wound appearance are common findings.
- Tachycardia disproportionate to body temperature is common.
- Late signs include hypotension, renal failure, and a paradoxical heightening of mental acuity.
- In summary, the typical signs and symptoms are severe pain and tenderness, local swelling to massive edema, skin discoloration with hemorrhagic blebs and bullae, nonodorous or sweet odor, crepitus, fever, relative tachycardia, and altered mental status.

Lab Studies:

- Gram stain of bullae fluid or muscle tissue: Pleomorphic, gram-positive bacilli with a paucity of leukocytes are considered diagnostic.
- Complete blood count: hemolysis and anemia secondary to release of toxins.
- Liver function tests: Hyperbilirubinemia and liver dysfunction.
- Electrolytes: Hyperkalemia can result from cell breakdown.
- Renal panel: Kidney dysfunction.
- Arterial blood gas: Gas gangrene can cause metabolic acidosis.
- Coagulation panel: Coagulopathy and thrombocytopenia can result.
- Myoglobin: Myoglobinemia and myoglobinuria dur to cellular breakdown.

Imaging Studies:

- Plain radiographs may reveal soft tissue gas within the fascial planes.
- Computed tomography demonstrates the extent of tissue involvement.

TREATMENT

Prehospital Care: Oxygenation/ Intravenous (IV) fluids/ Rapid stabilization of patient, because the disease may progress rapidly

Emergency Department Care: Resuscitation, supplemental oxygen, and aggressive volume expansion may be indicated.

- Use vasoconstrictors only if absolutely necessary; they can decrease perfusion to already ischemic tissue.
- Administer antibiotics.
- Tetanus toxoid and immune globulin may be administered if indicated.
- Surgical debridement is the definitive treatment.

Surgical Care:

- Fasciotomy for compartment syndrome may be necessary immediately.
- Daily debridement as needed to remove all necrotic tissue.
- Amputation of the extremity may be necessary and life-saving.
- Abdominal involvement requires excision of the body wall musculature.
- Uterine gas gangrene following septic abortion usually necessitates hysterectomy.
- ***Aggressive surgical debridement and intensive medical therapy are the mainstays of treatment of gas gangrene;*** however, HBO therapy has become an important adjunct therapy, especially in patients with truncal involvement.

MEDICATION

- Antibiotics may not penetrate the ischemic muscle but are important adjuncts to surgery.

***Antibiotics*:** Although penicillin G is effective against clostridial species, mixed infections are common, thus treatment include aminoglycosides, penicillinase-resistant penicillins, or vancomycin. If a patient is allergic to penicillin, alternative choices are clindamycin, third-generation cephalosporin, metronidazole, & chloramphenicol.

***Medicinal gas*:** Oxygen is used at a pressure greater than 1 atm in an attempt to minimize tissue necrosis caused by clostridial species.

- Typical therapy is 100% oxygen at 3 atm of pressure for 90 min with 2-3 dives in first 24 h, followed by 2-3 dives/d for a total of 7-10 dives

Toxoids -- Used to induce active immunity.

- **Adult Dose:** Primary immunization: 0.5 mL IM; administer 2 injections 4-8 wk apart; third dose 6-12 mo after second injection
- Booster dose: 0.5 mL q10y
- **Pediatric Dose:** Administer as in adults

Immunoglobulins -- Used to induce passive immunity.

- **Adult Dose:** Prophylaxis: 250-500 U IM in opposite extremity to tetanus toxoid lesion Clinical tetanus: 3,000-10,000 U IM
- **Pediatric Dose:** Prophylaxis: 250 U IM in opposite extremity to tetanus toxoid Clinical tetanus: 3,000-10,000 U IM

SHOCK

Hypovolemic Shock

- Hypovolemic shock refers to a medical or surgical condition in which rapid fluid loss results in multiple organ failure due to inadequate perfusion.
- Most often, hypovolemic shock is secondary to rapid blood loss (hemorrhagic).
- Hypovolemic shock can result from significant fluid (other than blood) loss. E.g. refractory gastroenteritis and extensive burns.

Pathophysiology:

The human body responds to acute hemorrhage by activating 4 major physiologic systems: the hematologic, cardiovascular, renal, and neuroendocrine systems.

- The hematologic system responds to an acute severe blood loss by activating the coagulation cascade and contracting the bleeding vessels (by local thromboxane A_2 release). In addition, platelets are activated and form an immature clot on the bleeding source.
- The cardiovascular system initially responds to hypovolemic shock by increasing the heart rate, increasing myocardial contractility, and constricting peripheral blood vessels. This response occurs secondary to an increased release of norepinephrine and decreased baseline vagal.
- The renal system responds to hemorrhagic shock by stimulating an increase in renin secretion from the juxtaglomerular apparatus. Renin converts angiotensinogen to angiotensin I, which

subsequently is converted to angiotensin II by the lungs and liver. Angiotensin II has 2 main effects, vasoconstriction of arteriolar smooth muscle, and stimulation of aldosterone secretion by the adrenal cortex. Aldosterone is responsible for active sodium reabsorption and subsequent water conservation.

- The neuroendocrine system responds to hemorrhagic shock by causing an increase in circulating antidiuretic hormone (ADH).

History:

- Symptoms, like weakness, lightheadedness, and confusion, should be assessed.
- Chest, abdominal, or back pain may indicate a vascular disorder.
- The classic sign of a thoracic aneurysm is a tearing pain radiating to the back. Abdominal aortic aneurysms usually result in abdominal or back pain.
- In patients with GI bleeding, inquire about hematemesis, melena, drinking history, excessive NSAID use, and coagulopathies (iatrogenic or otherwise).
- If a gynecologic cause is being considered, gather information about: last menstrual period, risk factors for ectopic pregnancy, vaginal bleeding, vaginal passage of products of conception, and pain.

Physical: The physical examination should always begin with an assessment of the airway, breathing, and circulation.

Once these have been evaluated and stabilized, the circulatory system should be evaluated for signs and symptoms of shock.

Do not rely on systolic BP as the main indicator of shock. Compensatory mechanisms prevent a significant decrease in systolic BP until the patient has lost 30% of the blood volume.

More attention should be paid to the pulse, respiratory rate, and skin perfusion.

- Class I hemorrhage (loss of 0-15%)
    - In the absence of complications, only minimal tachycardia is seen.
    - Usually, no changes in BP, pulse pressure, or respiratory rate occur.
    - A delay in capillary refill of longer than 3 seconds corresponds to a volume loss of approximately 10%.
- Class II hemorrhage (loss of 15-30%)
    - Clinical symptoms include tachycardia (rate >100 beats per minute), tachypnea, decrease in pulse pressure, cool clammy skin, delayed capillary refill, and slight anxiety.
    - The decrease in pulse pressure is a result of increased catecholamine levels, which causes an increase in peripheral vascular resistance and a subsequent increase in the diastolic BP.
- Class III hemorrhage (loss of 30-40%)
    - By this point, patients usually have marked tachypnea and tachycardia, decreased systolic BP, oliguria, and significant changes in mental status, such as confusion or agitation.
    - In patients without other injuries or fluid losses, 30-40% is the smallest amount of blood loss that consistently causes a decrease in systolic BP.
    - Most of these patients require blood transfusions, but the decision to administer blood should be based on the initial response to fluids.
- Class IV hemorrhage (loss of >40%)
    - Symptoms include the following: marked tachycardia, decreased systolic BP, narrowed pulse pressure (or immeasurable diastolic pressure), markedly decreased (or no) urinary output, depressed mental status (or loss of consciousness), and cold and pale skin.
    - This amount of hemorrhage is immediately life threatening.

Lab Studies:

- Initial laboratory studies should include analysis of the CBC, electrolyte levels (eg, Na, K, Cl, HCO_3, BUN, creatinine, glucose levels), prothrombin time, activated partial thromboplastin time, ABGs, and urinalysis (in patients with trauma). Blood should be typed and cross-matched.

TREATMENT

Prehospital Care:

- Most prehospital interventions involve immobilizing the patient (if trauma is involved), securing an adequate airway, ensuring ventilation, and maximizing circulation. Appropriate treatment usually can be initiated without delaying transport. Some procedures, such as starting intravenous (IV) lines or splinting of extremities, can be performed while a patient is being extricated.

Emergency Department Care: Three goals exist in the emergency department treatment of the patient with hypovolemic shock as follows:

(1) Maximize oxygen delivery - completed by ensuring adequacy of ventilation, increasing oxygen saturation of the blood, and restoring blood flow,

(2) Control further blood loss, and

(3) Fluid resuscitation; Should be rapid and appropriate.

Whether crystalloids or colloids are best for resuscitation continues to be a matter for discussion and research. Many fluids have been studied for use in resuscitation; these include isotonic sodium chloride solution, lactated Ringer solution, hypertonic saline, albumin, purified protein fraction, fresh frozen plasma, hetastarch, pentastarch, and dextran 70.

- current recommendations still advocate the use of normal saline or lactated Ringer solution.

Another area of interest regarding resuscitation is whether the goal should be to restore normal circulating volume and BP prior to definitive control of bleeding.

- Current recommendations are for aggressive fluid resuscitation with lactated Ringer solution or normal saline in all patients with signs and symptoms of shock, regardless of underlying cause.

A common error in the management of hypovolemic shock is failure to recognize it early.

This error leads to delay in diagnosing the cause and in resuscitating the patient.

- This error often is caused by a reliance on BP or initial hematocrit level, rather than signs of decreased peripheral perfusion, to make the diagnosis.
- Injuries in patients with trauma can be missed. This error can be avoided by a full physical examination, continuously and closely monitoring the patient's status.
- Elderly individuals have less tolerance for hypovolemia.
- In patients who require extensive volume resuscitation, care should be taken to prevent hypothermia, because this can contribute to arrhythmia or coagulopathy.
- Patients taking beta-blockers or calcium-channel blockers and those with pacemakers may not have a tachycardic response to hypovolemia.
- Coagulopathies can occur in patients receiving large amounts of volume resuscitation.

Cardiogenic Shock

- Cardiogenic shock is a physiologic state in which inadequate tissue perfusion results from cardiac dysfunction, most commonly following acute myocardial infarction (MI).
- The clinical definition of cardiogenic shock is decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume. Hemodynamic criteria for cardiogenic shock are sustained hypotension (systolic blood pressure <90 mm Hg for at least 30 min) and a reduced cardiac index (<2.2 L/min/m^2) in the presence of elevated pulmonary capillary occlusion pressure (>15 mm Hg).
- The diagnosis of cardiogenic shock can sometimes be made at the bedside by observing hypotension and clinical signs of poor tissue perfusion, which include oliguria, cyanosis, cool extremities, and altered mentation. These signs usually persist after attempts have been made to correct hypovolemia, arrhythmia, hypoxia, and acidosis.

Pathophysiology:

Myocardial pathology

- Patients who develop cardiogenic shock from acute MI consistently have evidence of progressive myocardial necrosis with infarct extension. Decreased coronary perfusion pressure and increased myocardial oxygen demand play a role in the vicious cycle that leads to cardiogenic shock.

Cellular pathology

- Tissue hypoperfusion, with consequent cellular hypoxia, causes anaerobic glycolysis, the accumulation of lactic acid, and intracellular acidosis. Also, myocyte membrane transport pumps fail, which decreases transmembrane potential and causes intracellular accumulation of sodium and calcium, resulting in myocyte swelling. If ischemia is severe and prolonged, myocardial cellular injury becomes irreversible and leads to myonecrosis, which includes mitochondrial swelling, the accumulation of denatured proteins and chromatin, and lysosomal breakdown.

Reversible myocardial dysfunction

- This potentially reversible dysfunction is often described as myocardial stunning or hibernating myocardium.
- By definition, myocardial dysfunction from stunning eventually resolves completely. The mechanism of myocardial stunning involves a combination of oxidative stress, abnormalities of calcium homeostasis, and circulating myocardial depressant substances.

Cardiovascular mechanics of cardiogenic shock

- The main mechanical defect in cardiogenic shock is that the left ventricular end-systolic pressure-volume curve shifts to the right because of a marked reduction in contractility. As a result, at a similar or even lower systolic pressure, the ventricle is able to eject less blood volume per beat. The attempt to enhance cardiac output by this mechanism comes at the cost of having a higher left ventricular diastolic filling pressure, which ultimately increases myocardial oxygen demand and causes pulmonary edema.

Systemic effects

- Systemic perfusion is compromised by decreased cardiac output, with tissue hypoperfusion intensifying anaerobic metabolism and instigating the formation of lactic acid, which further deteriorates the systolic performance of the

Shock state

- Shock state, irrespective of the etiology, is described as a syndrome initiated by acute systemic hypoperfusion that leads to tissue hypoxia and vital organ dysfunction. All forms of shock are characterized by inadequate perfusion to meet the metabolic demands of the tissues. A maldistribution of blood flow to end organs begets cellular hypoxia and end organ damage, the well-described multisystem organ dysfunction syndrome. The organs of vital importance are the brain, heart, and kidneys.

History:

- Patients demonstrate clinical evidence of hypoperfusion (low cardiac output), which is manifested by sinus tachycardia, low urine output, and cool extremities. Systemic hypotension, defined as systolic blood pressure below 90 mm Hg or a decrease in mean blood pressure by 30 mm Hg, ultimately develops and further propagates tissue hypoperfusion.
- Patients also may report associated autonomic symptoms, including nausea, vomiting, and sweating.
- Other associated symptoms are diaphoresis, exertional dyspnea, or dyspnea at rest. Presyncope or syncope, palpitations, generalized anxiety, and depression are other features indicative of poor cardiac function.

Physical: Cardiogenic shock is diagnosed after documentation of myocardial dysfunction and exclusion of alternative causes of hypotension, such as hypovolemia, hemorrhage, sepsis, pulmonary embolism, pericardial tamponade, aortic dissection, or preexisting valvular disease. Shock is present if evidence of multisystem organ hypoperfusion is detected upon physical examination.

- Patients in shock usually appear ashen or cyanotic and have cool skin and mottled extremities.
- Peripheral pulses are rapid and faint and may be irregular if arrhythmias are present.
- Jugular venous distention and crackles in the lungs are usually (but not always) present. Peripheral edema also may be present.
- Heart sounds are usually distant, and both third and fourth heart sounds may be present.
- The pulse pressure may be low, and patients are usually tachycardic.

- Patients show signs of hypoperfusion, such as altered mental status and decreased urine output.
- A systolic murmur is generally heard in patients with acute mitral regurgitation or ventricular septal rupture.
- The associated parasternal thrill indicates the presence of a ventricular septal defect, whereas the murmur of mitral regurgitation may be limited to early systole.
- The systolic murmur, which becomes louder upon Valsalva and prompt standing, suggests hypertrophic obstructive cardiomyopathy (idiopathic hypertropic subaortic stenosis).

Approach to the initial clinical evaluation of a patient in shock

Shock is identified in most patients based on findings of hypotension and inadequate organ perfusion, which may be caused by either low cardiac output or low systemic vascular resistance (SVR).

Circulatory shock can be subdivided into 4 distinct classes

Hypovolemic shock

- Hypovolemic shock results from loss of blood volume caused by gastrointestinal bleeding, extravasation of plasma, major surgery, trauma, and severe burns.

Obstructive shock

- Obstructive shock results from impedance of circulation by an intrinsic or extrinsic obstruction. Pulmonary embolism, dissecting aneurysm, and pericardial tamponade all result in obstructive shock.

Distributive shock

- Distributive shock is caused by conditions producing direct arteriovenous shunting and is characterized by decreased SVR or increased venous capacitance because of the vasomotor dysfunction. These patients have high cardiac output, hypotension, high pulse pressure, low diastolic pressure, and warm extremities with good capillary refill. Such findings upon physical examination strongly suggest a working diagnosis of septic shock.

Cardiogenic shock

- Cardiogenic shock characterized by primary myocardial dysfunction causes the heart to be unable to maintain adequate cardiac output. These patients demonstrate clinical signs of low cardiac output, with adequate intravascular volume. The patients have cool and clammy extremities, poor capillary refill, tachycardia, narrow pulse pressure, and low urine output.

Medical Care:

Initial management includes fluid resuscitation to correct hypovolemia and hypotension, unless pulmonary edema is present.

Central venous and arterial lines are often required.

Swan-Ganz catheterization and continuous percutaneous oximetry are needed. Correction of electrolyte and acid-base abnormalities, such as hypokalemia, hypomagnesemia, and acidosis, are essential.

Hemodynamic support

- Dopamine, norepinephrine, and epinephrine are vasoconstricting drugs that help maintain adequate blood pressure during life-threatening hypotension and help preserve perfusion pressure for optimizing flow in various organs.
- In patients with inadequate tissue perfusion and adequate intravascular volume, initiation of inotropic and/or vasopressor drug therapy may be necessary. Dopamine increases myocardial contractility and supports the blood pressure; however, it may increase myocardial oxygen demand. Dobutamine may be preferable if the systolic blood pressure is higher than 80 mm Hg and has the advantage of not affecting myocardial oxygen demand as much as dopamine.
- If the patient remains hypotensive despite moderate doses of dopamine, a direct vasoconstrictor (eg, norepinephrine) should be started at a dose of 0.5 mcg/kg/min and titrated to maintain an MAP of 60 mm Hg.

Vasopressor supportive therapy:

- Dopamine is a precursor of norepinephrine and epinephrine and has varying effects according to the doses infused.

- Norepinephrine is a potent alpha-adrenergic agonist with minimal beta-adrenergic agonist effects. Norepinephrine can increase blood pressure successfully in patients who remain hypotensive following dopamine.
- Epinephrine can increase the MAP by increasing the cardiac index and stroke volume, along with an increase in SVR and heart rate. Epinephrine may increase oxygen delivery and consumption and decreases the splanchnic blood flow. Administration of this agent is associated with an increase in systemic and regional lactate concentrations. The use of epinephrine is recommended only in patients who are unresponsive to traditional agents.

Inotropic supportive therapy

- Dobutamine (sympathomimetic agent) is a beta1-receptor agonist, although it has some beta2-receptor and minimal alpha-receptor activity.
- Phosphodiesterase inhibitors (PDIs), currently inamrinone (formerly amrinone) and milrinone, are the PDI inotropes that have proved valuable.

Thrombolytic therapy

- Although thrombolytic therapy (TT) reduces mortality rates in patients with acute MI, its benefits for patients with cardiogenic shock secondary to MI are disappointing.
- Patients who are unsuitable for invasive therapy should be treated with a thrombolytic agent in the absence of contraindications.

Intra-aortic balloon pump

- The use of the IABP reduces systolic left ventricular afterload and augments diastolic coronary perfusion pressure, thereby increasing cardiac output and improving coronary artery blood flow.
- The IABP is effective for the initial stabilization of patients with cardiogenic shock. However, an IABP is not definitive therapy.

Ventricular assist devices

Distributive Shock

- Shock may be defined as a state in which alterations in tissue perfusion result in end-organ dysfunction.
- Distributive shock is characterized by hypotension (systolic blood pressure <90 mm Hg) due to a severe reduction in systemic vascular resistance (SVR), with normal or elevated cardiac output in most instances.
- Septic shock is the most commonly encountered form of distributive shock.
- Other causes of distributive shock include systemic inflammatory response syndrome (SIRS) due to noninfectious inflammatory conditions; toxic shock syndrome (TSS); anaphylaxis; drug or toxin reactions, including insect bites, transfusion reaction, and heavy metal poisoning; addisonian crisis; hepatic insufficiency; and neurogenic shock due to brain or spinal cord injury.

Pathophysiology:

- Decreased tissue perfusion in distributive shock results primarily from arterial hypotension caused by a reduction in SVR.
- In addition, a reduction in effective circulating plasma volume often occurs due to a decrease in venous tone and subsequent pooling of blood in venous capacitance vessels, and loss of intravascular volume into the interstitium due to increased capillary permeability also occurs.
- Finally, primary myocardial dysfunction often is present as manifested by ventricular dilatation, decreased ejection fraction (despite normal stroke volume and cardiac output).
- Tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-1b, and IL-6 act synergistically with other cytokines and phospholipid-derived mediators to produce the complex alterations in vascular and myocardial function, which leads to maldistribution of blood flow.

History:

- Patients with shock frequently present with dyspnea or respiratory distress, mental status changes, and obtundation.

- Patients with septic shock or SIRS may have prior complaints suggesting infection or inflammation of the respiratory tract, urinary tract, or abdominal cavity.
- Streptococcal TSS is associated with recent soft tissue injury, surgery, pharyngitis, and nonsteroidal anti-inflammatory drug (NSAID) use.
- Staphylococcal TSS still is observed most commonly in women who are menstruating, but it also is associated with cutaneous infections, postpartum and cesarean section wound infections, and focal staphylococcal infections, such as abscess, empyema, pneumonia, and osteomyelitis.

Physical:
Cardinal features of distributive shock include the following:

- Hypotension - With systolic blood pressure less than 90 mm Hg or a reduction of 40 mm Hg from baseline
- Heart rate - Greater than 90 beats per minute
- Respiratory rate - Greater than 20 breaths per minute
- Extremities - Frequently are warm with bounding pulses and increased pulse pressure (systolic minus diastolic blood pressure)

Pneumonia
Urinary tract infection
Intraabdominal infection or acute abdomen
Anaphylaxis
Toxic shock syndrome
Adrenal insufficiency
A pulmonary artery (PA) catheter should be considered when potential benefit from information obtained outweighs potential adverse consequences.
PA catheter measurements may be useful in differentiating shock due to state of low cardiac output (hypovolemic, cardiogenic, extracardiac obstructive) from distributive shock in certain patients.
Pulmonary Artery Catheter Findings in Common Shock States

Diagnosis	**Pulmonary Capillary Wedge Pressure**	**Cardiac Output**
Cardiogenic shock*	Increased	Decreased
Extracardiac obstructive shock 1. Pericardial tamponade† 2. Pulmonary embolism	 Increased Normal or decreased	 Decreased Decreased
Hypovolemic shock	Decreased	Decreased
Distributive shock 1. Septic shock 2. Anaphylactic shock	 Normal or decreased Normal or decreased	 Increased or normal Increased or normal

*In cardiogenic shock due to a mechanical defect such as mitral regurgitation, forward cardiac output is reduced though the measured cardiac output may be unreliable. Large V waves commonly are observed in the pulmonary capillary wedge tracing in mitral regurgitation.
†The hallmark finding is equalization of right atrial mean, right ventricular end-diastolic, PA end-diastolic, and pulmonary capillary wedge pressure.

TREATMENT

Medical Care: all patients with shock should be admitted to an ICU.

- Vital signs and fluid intake and output should be measured and charted on an hourly basis. Adequate intravenous access should be obtained.
- A central venous access device should be considered if vasoactive drug support is required.
- Placement of PA and arterial catheters should be considered.
- All patients should be treated prophylactically against thromboembolic disease, gastric stress ulceration, and pressure ulcers of the skin.
- The 2 primary goals of treatment in patients with distributive shock are to reverse the initiating cause of shock (treat infection) and to stabilize the patient hemodynamically.
    - Oxygen should be administered immediately by mask.
    - In all patients with suspected sepsis, empiric antibiotic therapy should be initiated immediately.
- 0.4 mg/kg IV q12h for 48 h with first dose administered with or just before antibiotics.

Initial hemodynamic support should be in the form of fluid resuscitation. Crystalloid fluids, such as 0.9% NaCl or lactated Ringers solution, should be infused rapidly in 250- to 500-cc boluses, with frequent reassessment of blood pressure, extremities, skin turgor, and urine output to determine response to therapy.
If the blood pressure fails to improve after 2-3 L of rapid crystalloid infusion or after reaching the target pulmonary capillary wedge pressure, vasoactive drug therapy should be initiated with dopamine.
If an adequate hemodynamic response is not achieved with dopamine infusion rates of 15-20 mg/kg/min or if excessive tachycardia or tachyarrhythmias develop, norepinephrine (Levophed) or phenylephrine (Neo-Synephrine) may be added to or substituted for dopamine.
Dobutamine may be added to the therapeutic regimen when cardiac output is low, recognizing that this drug acts primarily as a positive inotropic agent and may further decrease SVR.
Vasoactive Drugs in Sepsis and Usual Hemodynamic Responses

Drug	Dose	Cardiac Output	Blood Pressure	Systemic Vascular Resistance
Dopamine*	2.5-20 mcg/kg/min	+	+	+
Norepinephrine†	0.05-2 mcg/kg/min	+	++	++
Epinephrine	0.05-2 mcg/kg/min	++	++	+
Phenylephrine	2-10 mcg/kg/min	-	++	++
Dobutamine‡	2.5-10 mcg/kg/min	+	+/-	-

*Dopamine is the usual drug of first choice. At doses >10 mcg/kg/min, effects are similar to norepinephrine. Tachycardia may limit use.
†Norepinephrine may be effective when dopamine is inadequate to increase blood pressure. Evaluate for hypovolemia or low cardiac output if norepinephrine fails to increase blood pressure adequately.
‡Dobutamine is useful when low blood pressure is due to decreased cardiac output. Dobutamine may further lower blood pressure due to peripheral vasodilatation.
Patients with distributive shock should be evaluated thoroughly to identify a potential nidus of infection. Surgical drainage or debridement should be performed promptly.

FLUID AND ELECTROLYTES

Distribution of body fluids

- ✓ Total Body Water (TBW) = 50 70% of body weight (BW)
- ✓ Depends upon
  - Lean body mass
  - Age

Fluid Compartments

Rapidly equilibrating with each other

1) Intracellular fluid (ICF) - 40% of Body Weight.
2) Extracellular fluid (ECF) - 20% of Body Weight
   a. Interstitial fluid (IF) - 14-15%BW
   b. Intravascular fluid (IVF)-5%-6% BW
3) Third space fluid & transcellular fluid - fluid outside the first two compartments.

- New born - 75%
- 1 Year - 65% (Constant throughout childhood)
- Adult Male-60%

Adult Female 55% (more s/c fat & small muscle mass)
(Blood volume= roughly 7-8% body wt)

Electrolyte	Intracellular fluid	Plasma	Intestinal fluid
Sodium	10	142	144
Potassium	150	5	4
Magnesium	40	3	2
Calcium	-	5	3
Total	200	155	153
Chlorides	-	103	114
Phosphates	120	2	2
Sulfates	30	1	1
Bicarbonaies	10	27	30
Protein	40	16	1
Organic acids	-	6	5
Total anions	200	155	153

	ICF	ECF
Principal cation	K^+ 97% intracellular (Mg^{2+} is second)	Na*(represents 90% of all ECF cations)
Principal anion	Phosphate	CI (although an accurate index of ECF volume, but total plasma chloride can change as a consequence of changes in acid base status)

Osmolarity (Osmotic pressure)

- Depends upon actual number of osmotically active particles in the solution and not their size
- ECF osmolality (mosm/Kg) = 2 (Na^+) mEq/1 + Glucose/18 rag/dl + BUN/2.8 mg/dl Normal serum osmolality is 285-290 mosm/1

Colloid Osmotic pressure (COP) [oncotic pressure)

It is the osmotic pressure generated by the presence of colloid on one side of a membrane which is impermeable to them. It is primarily responsible for effective osmotic pressure

between the plasma and the interstitial fluid compartment. It is normally about 25 mmHg and tends to draw fluid into the intravascular compartment.

Composition of GI fluid loss

SOURCE	DAILY LOSS (ML)	[NA*]	*an*	[CL1	[$HC0_3$]
Saliva	1000	30-80	20	70	30
Gastric	1000-2000	60-80	15	100	0
Pancreas	1000	140	5-10	60-90	40-100
Bile	1000	140	5-10	100	40
Small bowel	2000 - 5000	140	20	100	25-50
Large bowel	200- 1500	75	30	30	0
Sweat	200-1000	20-70	5-10	40-60	0
Total secretions = 8-10 litres. Almost all reabsorbed in intestines (jejunum 6000, ileum 2000-3000).					

Daily electrolyte requirements & commonly use I/V fluids

	Daily requirement
Sodium	1 - 2 meq/kg
Potassium	0.5 -1.0 meq/kg
Calcium	0.2 - 3.0 meq/kg
Magnesium	0.35 - 0.45 meq/kg

Solution	**PH**	**Na+**	**CI-**	**K+**	**Ca+2**	**Bicarbonates**
Plasma mEq/1	**7.4**	**135-145**	**90-110**	**3.5-4.5**	**3-5**	**22-27**
D5%	5		-	-	-	-
Normal saline (NS) 0.9%	4.5	154	154	0	0	-
Lactated Ringer's (LR)	6.5	130	109	4	3	28 meq/L (Lactates)
Darrows	6.5	124	104	36		56 meq/L (Lactates)
3% saline	-	513	513	-		-
5% saline	-	855	855	-	-	-

	Prerenal Oliguria	**Renal Oliguria**
1. Urine Osmolality (mosm/1)	>500	~ 300
2. BUN / S.cretinine	> 10	< 10
3. Urine sodium mEq/L	<20	>40

4. U/P creatinine	>40	<20
6. Renal failure Index (RFI) UNaxPCr/UCrxlOO	< 1	> 1
7. Fractional excretion of sodium UNa/PNax PCr/UCrxlOO	<1	>1
8. Urine specific gravity	>1.020	~ 1.010
9. Urinary Sediment	Hyaline casts	Granular cast
Examples	Prerenal azotemia, acute GN, hepatorenal syndrome, early sepsis	ATN, severe obstructive uropathy, preexisting CRF, diuretic use

Electrolytes Imbalance

Sodium balance
Normal range - 135 - 145 mEq/L
Hyponatremia

Types:

1. Hypovolemic hyponatremia [TBS i]
   - Severe isotonic dehydration (ECF volume loss).
2. Hypervolemic hyponatremia [Edematous states TBS t]
   - Occurs in conditions of
     a. Cirrhosis, CHF, nephrotic syndrome - 'Effective' volume decreases because of low cardiac output (CHF) or sequestration of fluid outside the central circulation e.g.-↓ plasma oncotic pressure resulting in reduced renal perfusion
     b. Acute stress, trauma, hypovolemia - endocrine response to injury
3. Isovolemic hyponatremia [TBS normal]
   a. SIADH is the most prevalent etiology of euvolemic hyponatremia.
      i. Specific diagnostic criteria that define SIADH include the following:
         a. Hyponatremia
         b. Hypotonicity
         c. Inappropriately concentrated urine
         d. Elevated urine sodium concentration
         e. Clinical euvolemia
         f. Normal renal, adrenal, and thyroid function
         g. No edema
      ii. Excess ADH may emerge from the pituitary gland or an ectopic source:
         a. CNS disorders: Head trauma. Stroke, Neonatal hypoxia, Brain tumor, Hydrocephalus, Cerebral abscess. Meningitis, Encephalitis, Subarachnoid hemorrhage e.t.c.
         b. Malignancies: neoplasms with a potential to synthesize, store, and secrete ADH (eg, increased levels of ADH found in -60% of patients suffering from small cell carcinoma of the lung). Others:

Brain, Pancreas, Prostate, Ovary, Lymphoma, Leukemia, Thymoma.

c. Pulmonary disease: Pneumonia. Tuberculosis, Empyema, Abscess, Asthma, COPD
d. Endocrine disorders: Hypothyroidism / myxedema, deficiency
e. Drugs
   - Analgesics (eg, narcotics, NSAIDS)
   - Antidepressants (eg, MAO inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors)
   - Barbiturates
   - Carbarn azepine
   - Cyclophosphamide Clofibrate
   - Diuretics (especially thiazides)
   - Neuroleptics (eg, phenothiazines)
   - Oral hypoglycemics (eg, chlorpropamide, tolbutamide)

- Treatment: For asymptomatic or mildly symptomatic hyponatremia, water restriction.
- Demeclocycline- Interferes with action of ADH at renal collecting duct.

C/F of hyponatremia:

- Neurological dysfunction
- Intracellular movement of water -brain cell edema ↓→ flCT→HT, lethargy, confusion, coma. Later tissue signs of excessive intracellular water e.g. - "Finger printing sign"
- If Hyponatremia develops rapidly, signs of hyper excitability - irritability, muscular twitches & hyperactive deep tendon reflexes

Treatment

Asymptomatic hyponatremia are managed with free water restriction.
Severe, Symptomatic hyponatremia should be treated with hypertonic saline.
Rapid correction of hyponatremia can pontine myelinolysis
Once S. Sodium levels reach 130mEq/L, the further correction is carried out more slowly by water restriction.

Hypernatremia

Causes:

Solely due to water loss

- Extrarenal- insensible loss- skin/lungs.
- Renal-Diabetes insipidus

Water loss with sodium loss

- Extrarenal- sweat
- Renal- osmotic diuresis-glycosuria, urea.

Due to sodium gain

- Iatrogenic
- Adrenal hyperfunction- hyperaldosteronism, Cushing's.

Principal C/F

CNS system
Due to dehydration of brain cells
↑ neuromuscular excitability, twitching, seizures, stupor & coma
Tissue signs - "dry sticky mucous membranes" are characteristic of this condition

Treatment

I/V infusion of free water (5% dextrose)
Correction advised slowly over days.
Rapid correction may lead to cerebral edema

Potassium balance: hyperkalemia & Hypokalemia

98% of potassium is intracellular, with the concentration gradient maintained by the sodium- and potassium-activated adenosine triphosphatase (Na^+/ K^+-ATPase) pump that is controlled by insulin and p-2 receptors
Cellular concentration is approx 40 times the ECF.
The normal potassium level is 3.5-5.0 mEq/L.

Potassium balance:
Minute-to-minute levels of potassium are controlled by intracellular to extracellular exchange. A balance of GI intake and renal potassium excretion achieves long-term potassium balance. *All regulation of K+ excretion occurs at distal nephrons.* The excess K^+ is excreted prompdy. The filtered K^+ is nearly completely reabsorbed in the proximal segments and the K^+ in urine is derived almost entirely from K^+ secreted in the distal convoluted tubules. K^+ secretion is influenced by:

- Aldosterone
- Distal tubular fluid flow rate
  - Increased distal delivery of fluids, e.g. loop diuretics, favors K^+ excretion,
- Acid base balance
  - Alkalosis enhances and acidosis depresses renal potassium secretion, probably by inducing corresponding changes in tubular cell potassium.

Hyperkalemia:
Defined as a potassium level greater than 5.5 mEq/L

Causes:

- Pseudohyperkalemia
  - Sample hemolysis
- Redistribution
  - Acidosis
  - Insulin deficiency
  - Drugs
    - Beta-blockers
    - Acute digoxin intoxication or overdose
    - Succinylcholine (releases K* from muscles by depolarizing cell membranes)
    - Arginine hydrochloride - used to treat metabolic acidosis (drives K^+ out of cells)
  - Hyperkalemic familial periodic paralysis -1 [K^+] is associated with repeated attacks of muscle paralysis. Mechanism obscure.
- Excessive endogenous potassium load
  - Trauma
  - Burns
  - Hemolysis
- Excessive exogenous potassium load
- Diminished renal potassium excretion (principal cause)
- Potassium-sparing diuretics (spironolactone, triamterene, amiloride)
- ↓ Effective circulating volume.
- Laboratory error

History:

- Patients may be asymptomatic or report the following:

- Generalized fatigue & weakness
- Paresthesias
- Paralysis
- Palpitations

ECG changes:

- Peaked (tented) T waves (earliest)
- PR interval prolongation
- QRS widening
- Loss of P wave
- Sine wave
- Ventricular fibrillation or cardiac arrest in asystole.

Treatment:

1. Calcium: Calcium chloride or calcium gluconate
2. Alkalinizine agents: Sodium bicarbonate
3. Beta-agonists: Albuterol
4. Loop diuretics: Purosemide (Lasix)
5. Binding resins: Sodium polystyrene sulfonate (Kavexalate)
6. Dialysis

Hypokalemia

Hypokalemia is defined as a plasma potassium level of less than 3.5 mEq/L.

Causes:

- Gasrointestinal losses
  - Gastrointestinal losses from vomiting, diarrhea, NG suction e.t.c.
- Renal
  - Metabolic alkalosis (excess bicarbonate delivery to the distal nephron)
  - Diuretics (MC cause of |[K*]
    - Thiazides
    - Loop diuretics
    - CA inhibitors
  - Excessive mineralocorticoid effects
  - Renal tubular disease
- Hypokalemia due to shifts into the cells (no depletion)
  - Hypokalemic periodic paralysis - sudden movement of potassium into the cells
  - Insulin effects o Alkalosis
  - Increased β- adrenergic activity (or ↓ α - adrenergic activity).
- Drugs
  - P-agonists and a-blockers.
  - Theophylline
  - Verapamil (with overdose)
  - High-dose penicillin
  - Ampicillin
    - Carbenicillin

Signs of ↓ **K*:**

- Absent tendon reflexes & paralaytic ileus

A) Complications

- Cardiac arrhythmias and acute respiratory failure from muscle paralysis.
- TT sensitivity to digitalis → arrhythmias

Lab Studies:

- Serum electrolytes

> Unlike hyponatremia, serum potassium may not accurately reflect total body stores.

- Blood gas analysis
    - o Assess acid-base status.
    - o Alkalosis may induce hypokalemia

Other Tests:

- ECG
    - o T-wave flattening
    - o Appearance of U waves
    - o ST-segment depression
    - o Prolongation of PR interval
    - o QT prolongation.
    - o Cardiac arrest in systole

• Symptomatic or severe hypokalemia should be corrected with a solution of intravenous potassium.

- Potassium chloride -- First choice for IV therapy. 10-40 mEq IV infused over 2-3 h; not to exceed 10 mEq/h (40 mEqA with monitoring)

Calcium regulation; Hypercalcemia & Hypocalcemia

• Approximately 99% of calcium is found in bone, and 1% is found in extracellular fluid. Of this 1 %, 50% is in the free (active) ionized form (1-1.15 mmol/L), 40% is bound to protein (predominantly albumin), and 10% circulates bound to anions (phosphate, carbonate, citrate, lactate, sulfate).

- Normal S. calcium levels - 8 to 10 mg / dL (2.0 to 2.5 mmol/ L or 4 to 5 mEq/L).
- Normal ionized calcium levels - 4 to 5.6 mg / dL (1 to 1.4 mmol / L).
    - Clinical signs and symptoms are observed only with decreases in ionized calcium concentration. Alkalemia increases binding, thereby decreasing the ionized calcium. Plasma [Ca^{2+}] is maintained within the reference range by a complex interplay of 3 major hormones, PTH, 1,25-dihydroxyvitamin D (i.e. calcitriol), and calcitonin.

Actions of the Hormones Involved in Calcium Homeostasis

Hormone	Effect on bones	Effect on gut	Effect on kidneys
Parathyroid hormone ↑Ca^{++}, 4'$P0_4$ levels in blood	Supports osteoclast resorption	Indirect effects via ↑ calcitriol from 1-hydroxylation	Supports Ca^{++} resorption and $P0_4$ excretion, activates 1-hydroxylation
Calcitriol (vitamin D) ↑Ca^{++}, ↑$P0_4$ levels in blood	Indirect effects. Supports osteoblasts	↑Ca^{++} and $P0_4$ absorption	No direct effects
Calcitonin causes ↑Ca^{++}, ↓$P0_4$ levels in blood when hypercalcemia is present	Inhibits osteoclast resorption	No direct effects	Promotes Ca^{++} and $P0_4$ excretion

Hypercalcemia

• Hypercalcemia is defined as a serum calcium level greater than 10.5 mg/dL.

Causes:

- ✓ Hyperparathyroidism is overall the most common cause of hypercalcemia. Malignancy is the second most common cause.

- ✓ Hyperparathyroidism is the most common cause of hypercalcemia on routine screening.
- ✓ Malignancy is the commonest cause of hypercalcemia in hospitalized patients.

PTH-mediated hypercalcemia (Primary hyperparathyroidism)

- It is overall the commonest cause of hypercalcemia. Usually in 3-5 decades.
- The incidence of primary hyperparathyroidism is considerably higher in women.

Non-PTH-mediated hypercalcemia
Malignancies:

- Hypercalcemia is the most common life-threatening metabolic disorder associated with neoplastic diseases.
- Bronchogenic carcinoma (MC), followed by CA Breast, RCC, and hematological disorders e.g. multiple myelomas, leukemias or lymphomas (specially theT cell variant).

✓ The remaining 10% of cases of hypercalcemia are caused by many different conditions, including vitamin D-related problems, disorders associated with rapid bone turnover, thiazides or renal failure, and, in rare cases, familial causes.

Causes related to vitamin D:

- Vitamin D toxicity
  → Excessive ingestion of vitamin D t intestinal calcium absorption
- Granulomatous disease (especially sarcoidosis)
  → Abnormal metabolism of vitamin D.
- Idiopathic infantile hypercalcemia (Williams syndrome)

Causes related to high bone turnover:

- Hyperthyroidism
- Immobilization
- Thiazides
- Vitamin A intoxication

Causes related to renal failure:

- Severe secondary hyperparathyroidism due to progressive renal damage,
- Milk-alkali syndrome
- Aluminum intoxication as occurs in patients with chronic dialysis

Other causes related to particular mechanisms:

- Decreased renal calcium excretion (or increase renal calcium reabsorption)
  - Familial hypocalciuric hypercalcemia
  - Thiazide diuretics
  - Hypophosphatasia

Signs and symptoms

- Symptoms relate to CNS, renal, GI, and cardiac. CNS **symptoms are the most common and the earliest symptom usually is lethargy or feeling tired.**
- Central nervous system:
  - Irritability
  - Memory loss
  - Apathy
  - Depression
  - Dementia
  - Lethargy
  - Confusion
  - Coma
- Renal effects:

  - Polyuria
  - Nocturia
  - Volume contraction
  - Thirst .
- Gastrointestinal effects:
  - Anorexia
  - Pain
  - Nausea
  - Vomitings
  - Constipation (due to dehydration) & Fecal impaction

ECG Changes:

- QT interval shortening.
- PR interval prolongation.
- QRS interval lengthening (at very high levels)
- T waves flattening or inversion(at very high levels)
- A variable degree of heart block.(at very high levels)
- Digoxin effects are amplified.
- **Treatment**
- Volume expansion with NS followed by Loop Diuretics
- Inhibition of bone resorption
  - Calcitonin
  - Bisphosphonates
  - Mithramycin (Plicamycin)
  - Gallium nitrate
- Mobilization
- Reduction of gastrointestinal calcium absorption
  - Reduction of dietary calcium
  - Oral phosphate - forms insoluble calcium phosphate in the gut.
- Dialysis

Surgical Care:

- Parathyroidectomy is the definitive treatment for hyperparathyroidism.
- Hypercalcemia due to malignancy may require surgical resection of the tumor.

Hypocalcemia:

- A serum calcium level less than 8.5 mg/dL

Causes:

- PTH deficiency
- Vitamin D deficiency
- Miscellaneous disorders
  - Acute pancreatitis
  - Toxic shock syndrome.
  - Hypoalbuminemia.
  - Infiltrative disease: Sarcoidosis, tuberculosis may infiltrate & dysfunction parathyroids,
- Drugs
  - Calcitonin and bisphosphonates.
  - Diuretics - Furosemide.
  - Estrogen inhibits bone resorption.

Clinical features:

- Numbness and tingling sensations in the perioral area (earliest sign).

- Muscle cramps; may progress to carpopedal spasm (i.e. tetany).

- Neurological symptoms, including irritability, confusion, depression, and personality changes, hallucinations, dementia, extrapyramidal manifestations, and seizures.
- Respiratory - laryngospasm and bronchospasm.
- Subclinical tetany
  1. Chvostek sign
  2. Trousseau sign
- ECG changes:
  1. ↑ Q T interval-used to monitor serum calcium

Medical Care:
10 ml of 10% calcium gluconate.
Vit D supplement & Calcium
PTH if required

Magnesium

- Magnesium (Mg) is the second-most abundant intracellular cation and, overall, the fourth-most abundant cation.
- The intracellular concentration is 40 mEq/L, while the normal serum concentration is 1.5-2.0 mEq/L. Serum levels do not necessarily reflect the status of total body stores.
- Approx. 60% of total body magnesium is located in bone, 38% in the soft tissues (intracellular) and only less than 2% is present in the ECF compartment. Of this serum component, 30% is protein bound, 20 % is complexed, and the remaining 50% is ionized. Analogous to plasma calcium, the free (ie.ionized) fraction of magnesium is the active component.
- Almost all enzymatic processes using phosphorus as an energy source (eg, adenosine triphosphatase [ATPase]) require magnesium for activation. It is involved in nearly every aspect of biochemical metabolism (eg, deoxyribonucleic acid [DNA] and protein synthesis, glycolysis, oxidative phosphorylation).
- Magnesium is a component of chlorophyll and is present in high concentrations in all green plants. Seed grains, nuts, peas and beans are rich source. Less than 40% of dietary magnesium is absorbed, predominantly in the jejunum and ileum, and excreted in stool and urine.
- Elimination is predominantly renal. The kidney is the main regulator of magnesium concentrations. Normally, only 3% of filtered magnesium appears in urine; thus, 97% is reabsorbed by the renal tubules. When serum levels rise above 2.5 mEq/L, magnesium excretion increases dramatically. Conversely, the magnesium retention by the kidneys is very efficient i.e. the kidney retains a strong capacity to resorb magnesium, and the main site for reabsorption is the thick ascending loop of Henle (THAL). Several factors may impair renal reabsorption, such as volume expansion, ethanol ingestion, hypercalcemia, and diuretic administration (eg, osmotic, thiazide, loop). Of these 3 types of diuretics, loop diuretics have the greatest effect on renal magnesium wasting because of their site of action.

Hypermagnesemia:
Hypermagnesemia is a rare electrolyte abnormality because the kidney is very effective in eliminating excess magnesium by rapidly reducing its tubular reabsorption to almost negligible amounts.
Causes:
MC cause: Renal insufficiency
II MC Cause: Iatrogenic, especially errors in calculating appropriate infusions.
Additional causes include the following:

- Acidosis

- Ingestion of magnesium-containing substances such as vitamins, antacids, or cathartics by patients with chronic renal failure
- Acute renal failure (oliguric phase)
- Neonates bom to eclamptic mothers treated with magnesium, which passes through the placental circulation.
- Decreased GI elimination and increased GI absorption of magnesium due to intestinal hypomotility.
- Tumor lysis syndrome, by releasing massive amounts of intracellular magnesium.
- Adrenal insufficiency (secondary hypermagnesemia).
- Rhabdomyolysis, like tumor lysis syndrome, by releasing significant amounts of intracellular magnesium
- Milk-alkali syndrome
- Hypothyroidism
- Hypoparathyroidism
- Neoplasm with skeletal muscle involvement
- Lithium intoxication by supposedly decreasing urinary excretion, although the mechanism for this is not completely clear.
- Extracellular volume contraction, as in diabetic ketoacidosis (DKA)
- Familial hypocalciuric hypercalcemia- This autosomal dominant disorder is characterized by very low excretion of calcium and magnesium, and the increase in magnesium reabsorption appears to occur from an abnormal sensitivity of the loop of Henle to magnesium ions.

Signs an,d symptoms;

- ✓ Hypermagnesemia affects the neuromuscular, CNS and cardiac organ systems.
- ✓ Symptoms of hypermagnesemia usually are not apparent unless the serum magnesium level is greater
- ✓ than 2 mmol/L.
- ✓ Concomitant hypocalcemia, hyperkalemia, or uremia exaggerates the symptoms of hypermagnesemia at any given level
    - **Nonspecific symptoms (earliest, at** 2-4 **mmol**/1)
    - These symptoms include nausea (earliest), vomiting, and cutaneous flushing.

Neuromuscular symptoms

These are the most common presenting problems.

Hypermagnesemia causes blockage of neuromuscular transmission by preventing presynaptic acetylcholine release. **One of the earliest symptoms is loss of deep-tendon reflex.**

- Facial paresthesias also may occur at moderate serum levels.
- Muscle weakness is a more severe manifestation, occurring at levels greater than 5 mmol/L. This manifestation can proceed to flaccid paralysis, then to depressed respiration, and, eventually, to apnea.

• **CNS system**

- Lightheadedness
- Depressed levels of consciousness.
- Stupor or coma

• **Conduction system symptoms**

- Hypermagnesemia depresses the conduction system of the heart and sympathetic ganglia.

- Hypotension
- Bradycardia
- Intraventricular conduction delay
- Arrhythmia, including atrial fibrillation
- Complete heart block and cardiac arrest may occur at levels greater than 7 mmol/L

- **Hypocalcemia**
  - Discussed already

Lab Studies:

- Electrolytes, including potassium, magnesium, and calcium levels
  - Elevation in magnesium level is usually not found as an isolated electrolyte abnormality,
  - Hyperkalemia and hypercalcemia are often present concurrently.
- BUN and creatinine levels
- Arterial blood gases (ABG) may reveal a respiratory acidosis.

Other Tests:

- An ECG and cardiac monitor may show prolongation of the PR interval or intraventricular conduction delay, which are nonspecific findings.
- The ECG findings may reflect other electrolyte abnormalities such as hyperkalemia.

Treatment:

- In patients with mildly increased levels, simply stop the source of magnesium.
- In patients with higher concentrations or severe symptoms, other treatments are necessary as follows:
  - **Intravenous fluids with diuretics:**
    - Intravenous fluids e.g. NS, cause the dilution of the extracellular magnesium. These are used with diuretics to promote increased excretion of magnesium by the kidney. Furosemide (Lasix) is the diuretic of choice. It acts at loop of Henle to promote magnesium diuresis.
  - **Calcium gluconate:**
    - Calcium directly antagonizes the neuromuscular and cardiovascular effects effects of magnesium. Reserved for patients with severe or symptomatic hypermagnesemia. 10% IV solution
  - **Dialysis:**
    - Best used when levels exceed 8 mEq/L, when life-threatening symptoms are present, or in patients with poor renal function.

Hypomagnesemia

Causes: Most causes are related to renal and GI losses.

- **GI losses or low intake**
  - Malabsorption.
  - GI secretions in large amounts, e.g. chronic diarrhea, laxative abuse, inflammatory boweldisease, or neoplasm,
  - Prolonged TPN.
- **Renal losses**
  - Primary renal disorders - by decreased tubular reabsorption of magnesium.

Clinical effects:

- Neuromuscular irritability (Earliest, at serum magnesium levels less than 1.0 mEq/L)
  - Hyperactive deep tendon reflexes
  - Muscle cramps
  - Trousseau and Chvostek signs
- CNS hyperexcitability
  - Irritability
  - Psychosis

Treatment:

- Magnesium is administered PO (oxide or gluconate form) for patients with mild depletion,
- IV replacement, as a sulfate salt is indicated for severe clinical effects.

Miscellaneous Facts:

Pyloric Stenosis

- K, *I* CL\ metabolic alkalosis with paradoxical acidosis
- Rx = replace ECF with Isotonic NaCl & K^+

Anion gap

Anion gap = $(Na^+ + K^+) - (CI + HC0_3)$
= 10-15 meq/1

Metabolic acidosis

↑ Anion Gap.	(N) Anion Gap.
-Commonest = shock	- Diarrhea
-Diabetic ketoacidosis	- Small bowel fistula
-Alcohol intoxication	-Uretrosigmoidostomy
-Uraemia	-Proximal RTA
-Salicylate toxicity	- Distal RTA
-Oxaloisis	- Dilutional acidosis

TOTAL PARENTERAL NUTRITION (TPN)

ASSESSMENT OF THE PATIENT (Prior to initiation of TPN)

Method of assessment	Moderately malnourished	Severely malnourished
Ideal Weight	60-80%	<60%
Creatinine Height Index (24 Hrs urinary creatinine ×100 / Ideal for height & sex)	60-80	<60
S. Albumin (mg/dl)	2.1-3	<2.1
S. Transferrin (mg/dl)	100-150	<100
TLC (cmm)	800-1200	<800
Delayed Hypersensit. Index *	1	0
Prognostic Nutritional index #	40-50	>50

* Delayed hypersensitivity index quantitates the amount of induration elicited by skin testing with a common antigen such as candida, trychphyton or mumps.
Induration grade: 0= < 0.5 cm.; 1= .5 cm. 2= 1cm.
PMI % = 158-1.66 × albumin (gm/l) – (0.78 × triceps skin fold in mm.)- (2 × transferrrin gm/l) – 5.8 × delayed hypersensitivity index)

REQUIREMENTS TO BE CALCULATED.

After assessing the nutritional status of the patient, requirement is calculated in terms of:

A: Fluid requirement B: Energy Requirement
C: Protein or AA requirement D: Mineral & Vitamin.

A: FLUID REQUIREMENT:

Normal Daily fluid requirement:

Infants: 120ml/kg body weight. Adults: 40ml/lg body weight.
For each 0C rise of Temp. add 200 ml/day.
Abnormal losses are added to daily requirements.

B: ENERGY REQUIREMENT:
Patients BASAL ENERGY EXPENDITURE (BEE) is calculated using HARRIS BENEDICT EQUATION.
For women: 655.10 + 9.56 (W) + 1.85 (H) - 4.68 (A) Kcal/day
For men: 665.47 + 13.75 (W) + 5 (H) - 6.76 (A) Kcal/day
W= wt. In Kg. H= height in cm. A= age in years.
To the BEE should be added:

- A value of 20% of BEE for a pt. without significant metabolic stress.
- 50% of BEE for patients with marked stress like sepsis and trauma.
- 100% of BEE for pt. with severe stress like >40% burn.

Harris Benedict equation is based on the data related to healthy subjects. So it may not correctly assess the caloric need of a hospitalized malnourished patient. Here assessment of ***Resting energy expenditure*** is a better guide.

- Men REE: (789 × BSA) + 137
- Women REE: (544 × BSA) + 414

BSA is Basal surface area.
A factor of 20% above REE estimates the need of most of the hospitalized patients, and 40-100% above REE for >40% burn.
C: PROTEIN AND AMINO-ACIDS REQUIREMENT:
Recommended dietary protein allowance:

- In non-stressed patients = 0.8 gm/kg body wt./day.
- Catabolic patients require = 1.2-1.7 gm/kg body wt./day

Protein balance = Protein intake – protein loss
Protein loss = 24 hrs. Urine urea nitrogen (g) × 6.25.
6.25 Gm of protein = 1 Gm of nitrogen.
Calorie to nitrogen ratio should be 100-150: 1 (To minimize protein catabolism).
D: MINERALS & VITAMIN REQUIREMENT.
The parenteral requirement of some of the vitamins may be higher than the enteral requirements, due to:

- The micronutrients are delivered into the systemic rather than portal system thereby by-passing the liver and rapidly excreted by the kidneys.
- Many patients requiring TPN have large GUT losses that results in Na, CL, K, and bicarbonate wasting and also loss of divalent cations and vitamins.
- The tubing and exposure to the oxygen and light can also absorb and destroy vitamins (eg. Vit. A) before it reaches the patient.

PRESCRIBING PARENTERAL NUTRITION: - Steps are:
Step I: Calculate patient's expenditure for caloric need & protein need.
Step II: identify appropriate amount of Dextrose/ Fat Calorie and amount of amino acids to supply nitrogen acid.
Step II: Order necessary electrolyte, mineral, vitamins & trace elements.
Step IV: Calculate fluid need in which TPN will be given.

Step I: Already described.
Step II:

Dextrose-

- In TPN concentrated Dextrose or Glucose is the most commonly prescribed caloric source.
- Dextrose provide 3.4% Kcal/gm.
- Thus 500 ml of 50% Dext. Supplies 850 Kcal.
- The basic conc. Of dext. is final solution = 20-25% dextrose.

Fat-

- Fat is needed to prevent essential fatty acids deficiency and also as a source of non-protein calories.
- Fat provides 9 Kcal/gm.
- Its available as 10% & 20% emulsion providing 1.1 & 2 Kcal/ml.
- Thus 500 ml of 10% fat emulsion = 500 × 1.1 = 550 Kcal.
- 500 ml of 20% fat emulsion = 500 × 2 = 1000 Kcal.

Crystalline Amino Acids: As protein source.

- Proteins are not provided for calories but to provide nitrogen for protein catabolism.
- 6.25 gm of protein contain 1 gm of nitrogen.
- The basic solution of TPN contains final conc. of 3-5% amino acid
- Thus 500 ml of 10% AA = 4.63 gm of N+ or 28.9 gm of proteins

Electrolytes and mineral are provided for maintenance and to for acute loss, should include: Na+, K+, Ca++, Mg+, Cl-, Po4—

Trace elements given daily are:

- 0.8 mg Manganese.
- 1 mg Copper.
- 4 mg of Zinc.
- 10 mg Chromium.

Adequate Vitamin supplementation should be done intravenously. Following vitamins have to be given I.M. as they are unstable in hyperalimentation solution.

Vit. K = 10 mg IMI / Week.
Folic acid = 5 mg / week
Vit B12 = 1 mg / month

3 In 1 TPN solution: combine glucose fat AA and other additives in One bag for infusion over 24 hours.

Advantages:

- Decreased risk of infection Due to less manipulation/ Cost saving/ Time saving
- Using a glucose, and fat calorie source provides a more physiologic solution > reduced co2 production.
- In this solution up to 40% kcal may be given as fat.

EXAMPLE: ordering TPN for 70 kg man, 170 cm height

Step I: Calculate caloric and nitrogen needs.

BSA = 1.8
REE = 7.89 × BSA + 137 = 789×1.8-137= **1557 Kcal.**
20% increment: Final REE = 1867 Kcal.
Calculated caloric requirement = 1867 Kcal.
Nitrogen requirement: 70 × 1.3 gm protein = 91 gm protein.
91 gm / 6.25 = 14.5 gm of nitrogen.
Calculated nitrogen need = 14.65 gm NT.

Step II: Ordering solution for 24 hrs. administration.

- 800 ml of 50% dextrose. = 1360 Kcal
- 500 ml of 10% fat. = 550 Kcal
- 900 ml of 10% AA = 15.1 gm N+

Step II: Add electrolyte mineral vitamins.

The starting infusion rate should be 50-100 ml / hr depending to patients cardiovascular and renal status.
This rate gives 1200-2400 Kcal / day.
The increase should be 25-50 ml / hr. every day to allow kidney and pancreas to adjust to increased osmolality and glucose level.

SPECIFIC FORMULATIONS IN SPECIFIC DISESE STATE:

I: TPN in patients with Renal Failure:

- Patients in ARF not requiring dialysis require Concentrated TPN, (eg. Glucose-10%, Fat-20%, AA-10%), to reduce fluid load yet to provide adequate calories to prevent catabolism.
- Nitrogen conc. should be less.
- After regular dialysis is established protein content can be liberalized to provide 1-1.5 gm protein / kg / day.

II: In hepatic failure:

- Here ureagenesis is impaired with accumulation of toxic nitrogenous compounds eg. Ammonia
- Thus TPN is started with a reduced load of protein (0.7 gm/kg)
- Solution should contain more of branched chain AA and less of aromatic AA.
- Such solution appears to improve encephalopathy though it may not improve survival dictated by underlying liver failure.

III: In cardiac or respiratory failure.

- Fluid and Na+ restriction is indicated in CCF.
- In respiratory failure, a TPN solution may provide benefit, which contains higher percentage of calories as fat. (Fat has a lower RQ then carbohydrate; .07:1, thus less likely to lead to hypercapnia.)
- 40% of non-protein calories are given as fat if hypercapnia impairs respiratory functions.

EFFECTS OF TPN ON GUT FUNCTIONS:

ORGAN	**EFFECT OF TPN**
STOMACH	**Delayed gastric emptying. Increased acid secretion**
PANCREAS	**Decreased enzymes and bicarbonate**
SMALL BOWEL	**Increased Weight, DNA, Enzymes**
LIVER	**Increased Liver Chemistry. Steatosis, Cholestosis**
GALL BLADDER	**Increased incidence of ball stones**

MONITORING THE PATIENT ON TPN:

A: CLINICAL DATA TO BE CHECKED DAILY

1. Patient's sense of well being, symptoms suggesting fluid overload, high or low blood glucose.
2. Patient's strength as judged by graded activity, getting out of bed, walking stairs, climbing and weight measurement.
3. Vitals; Temp. BP, PR, RR.
4. Fluid balance: input vs. output.

5.Delivery equipment of TPN nutrition.

B: LABORATORY DATA TO BE MONITORED

Urine quantitation glucose	Four times daily
Blood Glucose, Na+, K+, Cl-, HCO3--, BUN	Daily until glucose infusion load & patient are stable.
S. albumin, Transferrin, LFT, S. creatinine, Ca++, PO4--, Mg++	Base line then twice weekly
Prothombin time	Base line then weekly

Nitrogen balance:N+ intake – (UUN + NUN).

UUN= Urine urea N+, NUN= Non urea and insensible losses.

C: INDIRECT CALORIMETERY:

To find out how the body is utilizing the caloric intake. It measures the respiratory quotient (RQ)

RQ > 1 Indirect Lipogenesis

RQ = 1 Carbohydrate Utilization

RQ= 0.74-0.85 Mixed fuel utilization.

RQ= 0.7 Fat utilization

COMPLICATIONS OF TPN

It can be broadly classified into 3 categories.

A: Mechanical.
B: Infectious.
C: Metabolic.

A: MECHANICAL COMPLICATIONS.

Arise either due to wrong placement of catheter or due to maintenance of venous access.

- Development of pneumo, hydro, hemo, or chylothorax.
- Injury to subclavian artery or brachial plexus.
- Malposition of catheter leading to arrhythmias.
- Air embolism or catheter embolism.
- Thrombophlebitis or thrombosis of SVC.
- Slipping of catheter, or hub detachment.

In order to avoid these complications following steps should be taken:

- *Catheter position must be confirmed by X-ray before hypertonic solution is infused.*
- *Minimal handling of the catheter*
- *Daily check arm of the patient for edema.*

B: INFECTION: Catheter sepsis is confirmed if;

- The catheter tip and blood cultures are positive for the same organism.
- Fever disappears/ decreases within 24 hrs of catheter removal.
- No other source of infection is identified.

One of the earliest sign of systemic sepsis is sudden development of glucose intolerance (with or without temp increase), in a pt. who previously has been maintained on TPN.
Sepsis is more likely with double or triple lumen tube.

METABOLIC COMPLICATIONS IN TPN

Nutrient Excess	Presentation
Glucose	Hyperglycemia, Polyuria (*)+polydipsia + Hyperosmolar non ketotic hyperglycemia
Amino acids	Hyperammonia in patients with liver disease, Azotemia in liver failure
Calcium	Hypercalcemia, Pancreatitis, renal stones
Vitamin D	Hypercalcemia, Osteopenia, long bone pains
NUTRIENT DEFICIENCY	
Copper	Neutropenia, Anaemia, Scorbutic bone lesions, decreased ceruloplasim, Microcytic anaemia.
Zinc	Nasolabial and perineal acrodermatitis, Alopecia, decreased cell function, decreased alkaline phosphatase.
Chromium	Glucose intolerance, Peripheral neuropathy.
Selenium	Myalgia, Cardiomyopathy, Decreased glutathion peroxidase.
Molybdenum	Amino acid intolerance, tachycardia, techypnoea, central scotoma, irritability, decreased uric acids.
Essential fatty acids	Eczymoid dermatitis, alopecia
Vitamin A (#)	Night blindness, Decreased dark field adaptation.
Biotin	Dermatitis, alopecia, hypotonia.
Thiamin	Wernick's encephalopathy

* Normal rate of glucose utilization in a normal adult is = 0.4-1.2 g/kg/hr.
# Requirement of Vit. E. is directly proportional to dietary fat.

Hypophosphatemia: Develops if phosphorus has not been added in amount adequate to meet the requirements for the metabolism of infused glucose and amino acids. The result is an extra vascular to intracellular shift of phosphate.

Signs and symptoms: paresthesia, confusion, convulsion and death.

Associated with Hypophosphatemia is a reduction in erythrocytic 2,3-diphosphoglycerate leads to increased affinity of Hb for oxygen hence, less O2 is released to peripheral tissue.

Early metabolic problem specially in elderly and debilitated patients including fluid overload producing CHF and glucose overload leading to stimulation of insulin secretion which causes intracellular shift of Phosphorus and potassium with resultant depletion of phosphorus and potassium leading to ***arrhythmias, cardiopulmonary function and neurological symptoms.***

To avoid these complications TPN should be started slowly and monitored carefully.

Late metabolic complications include ***cholestatic liver disease with bile sludging and gall stones***. The exact cause of liver disease is not understood but appears to be linked to the lack of enteral nutrition, the disease is less likely if some enteral feeding is continued.

Hyperosmolar non-ketotic hyperglycemia develops either if the hypertonic solutions are administered too rapidly or if the patient has impaired glucose tolerance. This is particularly common in latent diabetics and in patients following severe surgical stress or trauma.

Treatment of the condition consists of volume replacement, administration of insulin, electrolyte abnormality to be corrected.

COMPLICATIONS OF TPN (SUMMARY)

	Metabolic	Infectious	Mechanical
First 24 hrs.	Fluid overload Hyperglycemia Hypophosphatemia Hypokalemia		Cephalad displacement.
First 2 weeks	Cardio-pulm. Failure Hyper osmolar non-ketotic Hyperglycemia Electrolyte imbalance Acid-base imbalance	Catheter induced sepsis	Catheter extrusion Air embolism
After 3 months	Essential fatty acid def. Zn, Cu, Cr, Se, Mo, def. Iron def. Vit. Def. TPN induced liver disease. TPN induced metabolic bone Disease.	Catheter induced sepsis.	# or tear in catheter. Displacement of catheter hub with blood loss or air embolism

ONCOLOGY

The Cell Division Cycle

1. The General Strategy of the Cell Cycle.
   - For a typical mammalian cell, the cell cycle is divided into two major periods: mitosis, the process of nuclear division, and interphase, which comprises the time between successive mitosis. In early mitosis (i.e. prophase and prometaphase) the nuclear envelope breaks down, the contents of the nucleus condense into visible chromosomes, and the cell's microtubules reorganize to form the mitotic spindle. Then, the cell seems to pause at metaphase, in which the duplicated chromosomes are aligned on the mitotic spindle, poised for segregation. At this point, the cell "can decide" whether to stop cell division or not, however, past metaphase, there is no return and the process is

taken till two daughter cells form. Anaphase marks the beginning of chromosome segregation, which will be followed by telophase and eventually, by cytokinesis, the separation of the two cells by division of the plasma membrane. This marks the end of the mitotic period, also known as the M phase. The M phase may last only for ~ 1hr, the other ~23 hr the cell spends in interphase. Towards late interphase is when the DNA is replicated.

- The portion of interphase in which DNA replication occurs is known as the S phase (S=synthesis). Cells in S phase can be recognized by supplying them with 3H-thymidine, which only gets incorporated into DNA, or with bromo-deoxyuridine (BrdU), a T analog that can be recognized with a specific antibody. The interval between the completion of mitosis and the start of S phase is called G_1 phase (G=gap). During G_1 the cell monitors its environment and its own size, then, decides at the appropriate time to enter S phase. G_1 is by far the most variable cycle period timewise among different types of cells. Cells in G1, if they have not committed themselves to DNA replication, can enter G_0 (G zero), in which the cycle stalls with no S phase. G_0 can last from days to years and is typical of fully differentiated cells. After the S phase and before mitosis, cells are in G_2 phase. G1, S, G2 and M are the traditional subdivisions of the standard cell cycle.
- There is an independent cell cycle control system made up of proteins that are different from the effector proteins that directly perform mitosis, G_1, DNA replication, or G_2. Brakes that can stop the cycle at specific checkpoints (a.k.a restriction points) regulate the control system. At checkpoints, feedback signals conveying information about the effector processes, or extracellular signals, can delay progress of the control system itself, so as to prevent it from triggering the next effector process before the previous one is finished. The two major checkpoints occur at G_1, just before entry into S phase, and at G_2 shortly before mitosis. There is an additional checkpoint before the exit from mitosis that corresponds to the point of no return at metaphase. In yeast this checkpoint is call Start. This is also the point where cells enter G_0 if the conditions are appropriate.
- The G_2 checkpoint senses unreplicated DNA, which generates a signal that leads to cell cycle arrest, unless DNA replication is complete. Progression through the cycle is also stopped at the G_2 checkpoint in response to DNA damage, such as that resulting from irradiation.
- DNA damage arrests the cycle at G_1 too, which allows time for repair before going into the S phase. At G_1, damaged DNA induces the rapid synthesis of the p53 protein, which then signals cell cycle arrest. Mutations in the p53 gene are the most common genetic alterations in human cancers, illustrating the critical importance of cell cycle regulation in the life of multicellular organisms.
- The checkpoint at metaphase monitors the alignment of chromosomes on the mitotic spindle, thus ensuring that a complete set of chromosomes is distributed accurately to the daughter cells.
- The cell-cycle control system is based on two families of proteins: the cyclin-dependent protein kinases (Cdk) and the cyclins. Cyclins bind and activate Cdk's, which phosphorylate selected proteins on Ser/Thr residues thereby inducing downstream effector cell cycle processes. There are mitotic cyclins, which bind Cdk molecules during G_2 and are required for entry during mitosis, and G1 cyclins, which binds to other Cdk molecules during G_1 and are required for entry into S phase. The cyclic assembly, activation, and disassembly of cyclin-Cdk complexes are the pivotal events that drive the cell cycle.

2. Regulators of Cell Cycle Progression.

- MPF: a Dimer of Cdc2 and Cyclin. Experiments have led to the identification of the first cell cycle regulator, M phase-promoting factor (MPF). Further studies showed that MPF could also promote the G_2-to-M phase transition in mitotic cells.
- Temperature-sensitive mutants that were defective in cell cycle regulation were isolated from two species of yeasts, *S. serevisiae and S. pombe.* These were called cdc (for cell division cycle) mutants. They showed arrest at specific points in the cycle. For example, cdc28 mutant in *S. cerevisiae* was arrested at Start, and S. *pombe* cdc2 mutant was arrested at the G2-M transition. These two genes turned out to encode for the same protein kinase (called Cdc2), which was the first evidence for protein phosphorylation in cell cycle control. The human homologue was later isolated and shown to complement the yeast mutations, indicating the high level of conservation in the control mechanism across species.

G1 Cell Cycle Regulation in Oncogenesis and Macromolecular Delivery

Growth factor stimulation of a resting G0 cell to enter the early G1 phase of the cell cycle and transition across the G1 restriction point into the late G1 phase, followed by entrance into S phase and DNA synthesis, requires the coordinated efforts of multiple cyclin:Cdk complexes and an increased metabolism. Previous research has demonstrated the roles of tumor-suppressor genes in the regulation of cell cycle progression, specifically the G1 phase of the cell cycle. An important negative regulator of G1 cell cycle progression at the restriction point is pRB, the product of the retinoblastoma tumor-suppressor gene. pRB targets cellular transcription factors, such as members of the E2F family. E2F transcription factors are involved in driving the expression of genes involved in DNA synthesis after transition through the restriction point into late G1. Transition across the restriction point irrevocably commits a cell to continue through the rest of the cell cycle. This key growth regulatory checkpoint balances the appropriate requisite level of metabolism with growth factor stimulation.

Phosphorylation on 16 cyclin-dependent kinase (Cdk) consensus sites by G1 cyclin:Cdk complexes regulates pRB. In G0 cells, pRB is unphosphorylated and does not associate with E2F transcription factors, suggesting that this form is inactive. As cells progress into early G1, pRB becomes hypophosphorylated on Cdk sites and associates with E2Fs. At the restriction point, pRB becomes inactivated by hyperphosphorylation on Cdk sites and E2Fs are released. Due to continued Cdk activity, pRB remains hyperphosphorylated through S, G2, and M phases. Thus, in response to growth factor stimulation, pRB is differentially regulated by cyclin:Cdk complexes in early and late G1. Although the *RB* gene is genetically altered in a low percentage of human malignancies (<1 percent), the $p16^{INK4a}$, and cyclin D1, Cdk4, and Cdk6 proto-oncogenes are mutated in most, if not all, human malignancies.

Serum Tumor Markers

Monoclonal antibodies are used to detect serum antigens associated with specific malignancies. These tumor markers are most useful for monitoring response to therapy and detecting early relapse. With the exception of prostate-specific antigen (PSA), tumor markers do not have sufficient sensitivity or specificity for use in screening.

- Cancer antigen (CA) 27.29 is used to follow response to therapy in metastatic breast cancer. Carcinoembryonic antigen is used to detect relapse of colorectal cancer.
- CA 19-9 may be helpful in establishing the nature of pancreatic masses.
- CA 125 is useful for evaluating pelvic masses in postmenopausal women, monitoring response to therapy in women with ovarian cancer, and detecting recurrence of this malignancy.
- Alpha-fetoprotein (AFP), a marker for hepatocellular carcinoma.
- Beta subunit of human chorionic gonadotropin (b-hCG) is an integral part of the diagnosis and management of gestational trophoblastic disease.
- Combined AFP and b-hCG testing is an essential adjunct in the evaluation and treatment of nonseminomatous germ cell tumors, and in monitoring the response to therapy.
- PSA is used to screen for prostate cancer and to detect recurrence of the malignancy.

To date, no tumor marker has demonstrated a survival benefit in randomized controlled trials of screening in the general population. Nevertheless, tumor markers can play a crucial role in detecting disease and assessing response to therapy in selected groups of patients.

Conditions Associated with Elevated Tumor Marker Levels

Tumor marker	***Normal value***	***Primary tumor(s)***	***Additional associated malignancies***	***Benign conditions***	***Level wherebenign disease is unlikely***	***Sensitivity***
CA 27.29	<38 units per mL	Breast cancer	Colon, gastric, hepatic, lung, pancreatic, ovarian, and prostate	Breast, liver, and kidney disorders, ovarian	>100 units per mL	Elevated in 33% of early-stage breast cancers and

			cancers	cysts		67% of late-stage breast cancers
CEA[3,4]	<2.5 ng per mL in nonsmokers <5 ng per mL in smokers	Colorectal cancer	Breast, lung, gastric, pancreatic, bladder, medullary thyroid, head / neck, cervical, and hepatic cancers, lymphoma, melanoma	Cigarette smoking, peptic ulcer, IBD, pancreatitis, hypothyroidism, cirrhosis, biliary obstruction	>10 ng per mL	Elevated in less than 25% of early-stage colon cancers and 75% of late-stage colon cancers
CA 19-9[5]	<37 units per mL	Pancreatic and biliary tract cancers	Colon, esophageal, and hepatic cancers	Pancreatitis, biliary disease, cirrhosis	>1,000 units per mL	Elevated in 80% to 90% of pancreatic cancers and 60% to 70% of biliary tract cancers*
AFP[6]	<5.4 ng per mL	Hepatocellular carcinoma, nonseminomatous germ cell tumors	Gastric, biliary, and pancreatic cancers	Cirrhosis, viral hepatitis, pregnancy	>500 ng per mL	Elevated in 80% of hepatocellular carcinomasNonseminomatous germ cell tumors: see b-hCG below
b-hCG[7,8]	<5 mIU per mL	Nonseminomatous germ cell tumors, gestational trophoblastic Dis	Rarely, gastrointestinal cancers	Hypogonadal states, marijuana use	>30 mIU per mL[7]	AFP or b-hCG elevated in 85% of nonseminomatous germ cell tumors; elevated in only 20% of early-stage nonseminomatous germ cell tumors
CA 125[9-11]	<35 units per mL	Ovarian cancer	Endometrial, fallopian tube, breast, lung, esophageal, gastric, hepatic, and pancreatic cancers	Menstruation, pregnancy, fibroids, ovarian cysts, PID, cirrhosis, ascites, pleural / pericardial effusions, endometrios	>200 units per mL[11]	Elevated in about 85% of ovarian cancers; elevated in only 50% of early-stage ovarian cancers

				is		
PSA[12-14]	<4 ng /mL for screening Undetectable level after radical prostatectomy	Prostate cancer	None	Prostatitis, benign prostatic hypertrophy, prostatic trauma, after ejaculation	>10 ng per mL[12]	Elevated in more than 75 percent of organ-confined prostate cancers[14]
CA = cancer antigen; CEA = carcinoembryonic antigen; AFP = alpha-fetoprotein; b-hCG = beta subunit of human chorionic gonadotropin; PSA = prostate-specific antigen. **--The greatest possible sensitivity is 95 percent, given that 5% of the population have Lewis-null blood type and are unable to produce the antigen.* *Information from references 1 through 14.*						

Cancer Antigen 27.29

- Cancer antigen (CA) 27.29 is a monoclonal antibody to a glycoprotein (MUC1) that is present on the apical surface of normal epithelial cells. CA 27.29 is highly associated with breast cancer.
- CA 27.29 also can be found in patients with benign disorders of the breast, liver, and kidney, and in patients with ovarian cysts.
- However, CA 27.29 levels higher than 100 units per mL are rare in benign conditions.
- Because of superior sensitivity and specificity, CA 27.29 has supplanted CA 15-3 as the preferred tumor marker in breast cancer.
- The CA 27.29 level is elevated in approximately one third of women with early-stage breast cancer (stage I or II) and in two thirds of women with late-stage disease (stage III or IV).
- CA 27.29 lacks predictive value in the earliest stages of breast cancer and thus has no role in screening for or diagnosing the malignancy.

Carcinoembryonic Antigen

- Carcinoembryonic antigen (CEA), an oncofetal glycoprotein, is expressed in normal mucosal cells and overexpressed in adenocarcinoma, especially colorectal cancer.
- Benign conditions with higher CEA levels include cigarette smoking, peptic ulcer disease, inflammatory bowel disease, pancreatitis, hypothyroidism, biliary obstruction, and cirrhosis. Levels exceeding 10 ng per mL are rarely due to benign disease.
- Fewer than 25 percent of patients with disease confined to the colon have an elevated CEA level. Sensitivity increases with advancing tumor stage: CEA values are elevated in approximately 50 percent of patients with tumor extension to lymph nodes and 75 percent of patients with distant metastasis. The highest values (above 100 ng per mL) occur with metastasis, although poorly differentiated tumors are less likely to produce CEA.
- CEA is not useful in screening for colorectal cancer or in the diagnostic evaluation of an undefined illness.
- CEA levels typically return to normal within four to six weeks after successful surgical resection.
- The major role for CEA levels is in following patients for relapse after intended curative treatment of colorectal cancer.

Cancer Antigen 19-9

- Elevated levels of CA 19-9, an intracellular adhesion molecule, occur primarily in patients with pancreatic and biliary tract cancers.
- This tumor marker has a sensitivity and specificity of 80 to 90 percent for pancreatic cancer and a sensitivity of 60 to 70 percent for biliary tract cancer.
- Benign conditions such as cirrhosis, cholestasis, cholangitis, and pancreatitis also result in CA 19-9 elevations, although values are usually less than 1,000 units per mL.

- Patients with Lewis-null blood type do not produce CA 19-9. Thus, about 5 percent of persons are unable to produce this antigen.
- The antigen has no value in screening because its positive predictive value is < 1 %.

Alpha-Fetoprotein

- Alpha-fetoprotein is the major protein of fetal serum but falls to an undetectable level after birth.
- The primary malignancies associated with AFP elevations are hepatocellular carcinoma and nonseminomatous germ cell tumors.
- Other gastrointestinal cancers occasionally cause elevations of AFP, but rarely to greater than 1,000 ng per mL.
- Patients with cirrhosis or viral hepatitis may have abnormal AFP values, although usually less than 500 ng per mL.
- Pregnancy also is associated with elevated AFP levels, particularly if the pregnancy is complicated by a spinal cord defect or other abnormality.
- AFP levels are abnormal in 80 percent of patients with hepatocellular carcinoma.

Beta Subunit of Human Chorionic Gonadotropin

The beta subunit of human chorionic gonadotropin (b-hCG) normally is produced by the placenta. Elevated b-hCG levels most commonly are associated with pregnancy, germ cell tumors, and gestational trophoblastic disease. False-positive levels occur in hypogonadal states and with marijuana use.

AFP and b-hCG Levels in Germ Cell Tumors and Gestational Trophoblastic Disease		
Tumor	*AFP elevation*	*b-hCG elevation*
Seminoma and dysgerminoma	Never*	Occasional, minimal
Embryonal cell carcinoma	Yes	Yes
Choriocarcinoma	No	Yes
Yolk sac tumors	Yes	No
Teratoma	No	No
Gestational trophoblastic disease†	No	Yes

AFP = alpha-fetoprotein; b-hCG = beta subunit of human chorionic gonadotropin.
**--Any detectable AFP indicates the presence of a nonseminomatous component; in this situation, the malignancy should be treated as a nonseminomatous germ cell tumor.*
†--Gestational trophoblastic disease is not a germ cell tumor; rather, it is a rare gynecologic malignancy related to pregnancy.

Both AFP and b-hCG play crucial roles in the management of patients with nonseminomatous germ cell tumors. The AFP or b-hCG level is elevated in 85 percent of patients with these tumors, but in only 20 percent of patients with stage I disease. Hence, these markers have no role in screening.

In patients with extragonadal disease or metastasis at the time of diagnosis, highly elevated AFP or b-hCG values can be used in place of biopsy to establish a diagnosis of nonseminomatous germ cell tumor. AFP values in excess of 10,000 ng per mL or b-hCG levels above 50,000 mIU per mL at initial diagnosis portend a poor prognosis, with a five-year survival rate of 50 percent. Similarly staged patients with lower AFP and b-hCG levels have a cure rate higher than 90 percent.

Following AFP and b-hCG levels is imperative in monitoring response to treatment in patients who have nonseminomatous germ cell tumors. Patients with AFP and b-hCG levels that do not decline as expected after treatment have a significantly worse prognosis. AFP or b-hCG elevation is frequently the first evidence of germ cell tumor recurrence; a confirmed elevation should prompt reinstitution of therapy.

The b-hCG level is used to diagnose gestational trophoblastic disease, a rare neoplastic complication of pregnancy. The b-hCG value is followed to assess response to treatment and to detect relapse in a manner similar to that for germ cell tumor.

Cancer Antigen 125

CA 125 is a glycoprotein normally expressed in coelomic epithelium during fetal development. This epithelium lines body cavities and envelopes the ovaries.

Elevated CA 125 values most often are associated with epithelial ovarian cancer. CA 125 levels are elevated in about 85 percent of women with ovarian cancer, but in only 50 percent of those with stage I disease. Higher levels are associated with increasing bulk of disease and are highest in tumors with nonmucinous histology. Multiple benign disorders also are associated with CA 125 elevations, presumably by stimulation of the serosal surfaces.

Annual ultrasound examination and CA 125 screening have been advocated for women with hereditary ovarian cancer syndromes.

CA 125 has been used as an adjunct in the diagnosis of pelvic masses. In postmenopausal women with asymptomatic palpable pelvic masses, CA 125 levels higher than 65 units per mL have a positive predictive value of 98 percent for ovarian cancer. Because premenopausal women have more benign causes of elevated CA 125 levels, testing for the marker is less useful in this population.

Prostate-Specific Antigen

Prostate-specific antigen (PSA) is a glycoprotein produced by prostatic epithelium. The PSA level can be elevated in prostate cancer, prostatitis, benign prostatic hypertrophy, and prostatic trauma, as well as after ejaculation.

In men with prostatitis, PSA levels return to normal within eight weeks of symptom resolution. Waiting 48 hours after ejaculation to measure the PSA level has been recommended. Digital rectal examination does not elevate PSA levels above normal values. In men who have been taking finasteride (Proscar) for more than six months, reported PSA levels should be doubled to accurately reflect true values.

In prostate cancer, the positive predictive value of PSA levels greater than 4 ng per mL is 20 to 30 percent and rises to 50 percent when PSA levels exceed 10 ng per mL. Nevertheless, 20 to 30 percent of men with prostate cancer have PSA levels within normal ranges.

In patients with PSA values between 4 and 10 ng per mL, the PSA velocity and percentage of free PSA have been helpful in making clinical decisions. A velocity of 0.75 ng per mL per year is predictive of cancer. When less than 10 percent of PSA is unbound, the positive predictive value for prostate cancer is 55 percent, compared with 8 percent when more than 25 percent of PSA is unbound.

PSA levels predict the presence of metastatic disease. Patients with newly diagnosed prostate cancer and PSA levels below 20 ng per mL rarely have osseous metastasis (lower than 2 percent). In addition, CAT scanning is unnecessary in men with PSA levels below 25 ng per mL.

Cancer of Unknown Primary

Confusion exists about the value of tumor markers in a patient with cancer of unknown primary. Unfortunately, most tumor markers are too nonspecific for this purpose. However, with adenocarcinoma in older men, significant PSA elevations have sufficient specificity to make the diagnosis of prostate cancer.

In poorly differentiated tumors, AFP and b-hCG levels should be ordered. Marked elevations of these tumor markers signify the presence of an extragonadal germ cell tumor. In women with peritoneal carcinomatosis or malignant ascites, treatment for ovarian cancer is instituted if the CA 125 level is elevated.

Tumor Markers In Common Use

		Use of tumor marker			
Tumor marker	*Primary tumor(s)*	*Screening*	*Diagnosis*	*Follow-up after primary treatment*	*Monitoring of treatment response*
CA 27.29[1]	Breast cancer	No	No	Consider in patients at high risk for recurrence; obtain CA 27.29 level every 4 to 6 months.	Helpful
CEA[16]	Colorectal cancer	No	No	In patients at high risk for	Very helpful

				recurrence, obtain CEA level every 2 to 3 months for at least 2 years.	
CA 19-9[5]	Pancreatic cancer, biliary tract cancer	No	Selected pancreatic masses	No	Helpful
AFP[8,20,41]	Hepatocellular carcinoma, nonseminomatous germ cell tumor	No*	Poorly differentiated cancer of unknown primary; patients with cirrhosis and a liver mass	In patients treated for nonseminomatous germ cell tumor, obtain AFP and b-hCG levels every 1 to 2 months for 1 year, then quarterly for 1 year, and less frequently thereafter.	Essential in patients treated for nonseminomatous germ cell tumor; very helpful in patients treated for hepatocellular carcinoma
b-hCG[8,24,41]	Nonseminomatous germ cell tumor, gestational trophoblastic disease	No	Poorly differentiated cancer of unknown primary; gestational trophoblastic disease	Nonseminomatous germ cell tumor: In patients treated for gestational trophoblastic disease, obtain b-hCG level once a month for 6 to 12 months.	Essential in patients treated for nonseminomatous germ cell tumor or gestational trophoblastic disease
CA 125[26,27,41]	Ovarian cancer	No†	Adjunct for diagnosis of pelvic mass in postmenopausal women; malignant ascites in women with cancer of unknown primary	Obtain CA 125 level every 3 months for 2 years, then less frequently.	Very helpful
PSA[12,39-41]	Prostate cancer	Yes	Adenocarcinoma of unknown primary; widely positive bone scan and prostate mass	Obtain PSA level every 6 months for 5 years, then annually. Any detectable PSA after radical prostatectomy indicates recurrence. 3 consecutive PSA elevations after radiation therapy indicate recurrence.	Very helpful

CA = cancer antigen; CEA = carcinoembryonic antigen; AFP = alpha-fetoprotein; b-*hCG = beta subunit of human chorionic gonadotropin; PSA = prostate-specific antigen.*
**--Except in highly selected patients with nonalcoholic-induced cirrhosis.*
†*--Except in heritable ovarian cancer syndromes.*

Oncogene

An **oncogene** is a modified gene, or a set of nucleotides that codes for a protein, that increases the malignancy of a tumor cell. New research indicates that small RNAs 21-25 nucleotides in length called miRNAs can control expression of these genes by downregulating them.

The first oncogene was discovered in 1970 and was termed SRC (pronounced *SARK*). Src was in fact first discovered as an oncogene in a chicken retrovirus. Experiments performed by Dr G. Steve Martin of the University of California Berkeley demonstrated that the SRC was indeed the oncogene of the virus. In 1976 Drs. J. Michael Bishop and Harold E. Varmus of the University of California San Francisco demonstrated that oncogenes were defective proto-oncogenes, found in many organisms including humans. For this discovery Bishop and Varmus were awarded the Nobel Prize in 1989.

Proto-oncogene

A **proto-oncogene** is a normal gene that can become an oncogene, either after mutation or increased expression. Proto-oncogenes code for proteins that help to regulate cell growth and differentiation. Proto-oncogenes are often involved in signal transduction and execution of mitogenic signals, usually through its protein product. Upon *activation*, it (or its product) becomes a tumor inducing agent, an oncogene.

Activation

The proto-oncogene can become an oncogene by a relatively small modification of its original function. There are two basic activation types:

- A mutation within a proto-oncogene can cause a change in the protein structure, caused by
  - an increase in protein (enzyme) activity
  - a loss of regulation
  - the creation of a *hybrid protein*, through a chromosomal aberration during cell division. A distinct aberration in a dividing stem cell in the bone marrow leads to adult leukemia
- An increase in protein concentration, caused by
  - an increase of protein expression (through misregulation)
  - an increase of protein stability, prolonging its existence and thus its activity in the cell
  - a gene duplication, resulting in an increased amount of protein in the cell

Oncogene

Growth factors

Growth factors, or mitogens, are usually secreted by a few specialized cells to induce cell proliferation in paracrine, autocrine, or endocrine manner. If a cell that usually does *not* produce growth factors suddenly starts to do so (because it developed an oncogene), it will thereby induce its own uncontrolled proliferation (*autocrine loop*), as well as the proliferation of neighboring cells. In addition, abnormal growth of endocrine glands often cause ectopic production of growth hormones that have secondary effects on other parts of the body.

Protein kinases and related proteins

There are six known classes of protein kinases and related proteins that can become an oncogene:

- **Receptor tyrosine kinases** that become constitutively (permanently) active like the epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR).
- **Cytoplasmic tyrosine kinases** like the Src-family, Syk-ZAP-70 family and BTK family of tyrosine kinases.
- **Regulatory GTPases**, for example, the Ras protein.
- **Cytoplasmic Serine/Threonine kinases and their regulatory subunits**, for example, the Raf kinase, and cyclin-dependent kinases (through overexpression).
- **Adaptor proteins in signal transduction**.
- **Transcription factors**.

Important Oncogenes

Numerous genes have been identified as proto-oncogenes. Many of these genes are responsible for providing the positive signals that lead to cell division. Some proto-oncogenes work to regulate cell death. As stated in the introduction to this section, the defective versions of these genes, known as oncogenes, can cause a cell to divide in an unregulated manner. This growth can occur in the absence of normal pro-growth signals such as those provided by growth factors. A key feature of oncogene activity is that a single altered copy leads to unregulated growth. This is in contrast with tumor suppressor genes which must BOTH be defective to lead to abnormal cell division.

The proto-oncogenes that have been identified so far have many different functions in the cell. Despite the differences in their 0normal roles, these genes all contribute to unregulated cell division if they are present in a mutant (oncogenic) form. The mutant proteins often retain some of their capabilities but are no longer sensitive to the controls that regulate the normal form of the protein. Selected oncogenes that have been associated with numerous cancer types are described in more detail on the pages that follow. To learn about a particular gene, choose from the list below.

- HER-2/*neu* (*erb*B-2): a growth factor receptor.
- *ras*: a signal transduction molecule
- *myc*: a transcription factor
- *src*: a protein tyrosine kinase.
- *hTERT*: an enzyme that functions in DNA replication.

Bcl-2: a membrane associated protein that functions to prevent apoptosis.

UROLOGY

ANATOMY:

The Kidneys are paired, reddish brown, solid organ, measuring 10-12 cm. in vertical dimension, 5-7 cm. in transverse width and approximately 3 cm. in AP thickness.

In males the normal kidney weighs approx. 150 gm. While in females it is 135 gm.

The kidneys receive about 20% of total cardiac output.

At birth Kidneys are irregular in contour with multiple "fetal lobations", which disappear in first year of life. Some times a focal bulge persists in the mid-lateral contour of the kidney on either side referred to as "*DROMEDARY HUMP".* This occurs much more frequently on the left side.

The renal parenchyma is divided into *Cortex & medulla*. The medulla is not contiguous but consists of multiple conical segments, The *RENAL PYRAMIDS*, which points centrally into the renal sinus, where it is cupped by an individual minor calyx, thus the number of pyramids corresponds with the number of minor calyx. The renal cortex covers the pyramids not only peripherally but also extends between the pyramids to renal sinus forming "*renal columns of BERTIN".* Through these columns renal vessel enter and leave the kidney.

RENAL VESCULATURE:

Each kidney is supplied by an artery (a branch of aorta) and drains into a renal vein (to IVC). The renal vein lies most anterior and pelvis is most posterior, renal artery lies in between (VAP). The right renal artery passes behind the IVC, while the left renal vein is anterior to the aorta. Some times renal vein divides and sends one limb anterior and one limb posterior to the aorta forming "*RENAL COLLAR".*

The main renal artery divides into four or more segmental arteries. *The first and most consistent division is posterior branch*. The remaining anterior division branches into *apical, upper, middle and lower anterior segmental arteries. Each segmental artery is*

end artery.
Renal lymphatics: There are often 2 or more lymph nodes at the renal hilum, (first site of metastatis). From the left kidney lymphatic trunk then drain into Para-aortic nodes. From the right kidney, lymphatics drain into inter-aortocaval and para-caval nodes. Some lymphatics may cross over from right to left and drain primarily into Para-aortic nodes.

URETER:
In the adult length of Ureter is generally 24 to 30 cm. It is lined by Transitional epithelium. Beneath the epithelium is a layer of connecting tissue, the lamina propria. In a collapsed state ureteral mucosa lies in longitudinal folds. Mucosa is covered by inner longitudinal muscle and outer circular and oblique muscles. The adventitial layer contains extensive plexus of ureteral blood vessels and lymphatics.
The Ureter receives its blood supply by multiple feeding branches along its course. In the abdomen feeding vessels comes from, renal artery, gonadal artery, aorta and common iliac artery. In the pelvic cavity additional branches come from internal iliac artery or its branches, mainly the vesical and uterine and also from middle rectal and veginal.
The right Ureter is related to the terminal ileum, cecum, appendix, and ascending colon with their mesentery. The left Ureter is related to the descending colon and sigmoid colon along with their mesentery.
Within the female pelvis, Ureters are closely related to the uterine cervix and are ***crossed anteriorly by the uterine arteries.***

ADRENALS:
The adrenals are embriologically and functionally distinct from the kidneys, thus ***in cases of renal ectopia, the adrenals are found at its normal location.***
In the normal adults weighs approx. 35 gm. & measures 3-5 cm. in greatest dimension.
The right gland is pyramidal in shape while left one in crescentic and rests more medal to the upper pole. The right adrenal thus lie more superior than the left adrenal.
Each adrenal has two separate distinct elements; *CORTEX AND MEDULLA.* The central medulla consists of *chromaffin cells derived from the neural crest.* It is closely related to the sympathetic nervous system. The adrenal cortex is mesodermally derived and forms the bulk of the gland; 80-90%. Cortex consists of (GFR) *Zona glomerulosa,* which produces aldosterone in response to rennin angiotensin system; *Zona fasciculata and Zona reticularis,* which produce glucocorticoids and sex steroid respectively.
Vascular supply:
Each adrenal is supplied by three arteries and one vein: 1. Superior branches from inferior phrenic. 2. Middle branches from the aorta. 3: Inferior branches from the ipsilateral renal artery.
A single large vein exits from the adrenal hilum and drains into the IVC on the right side and renal vein on the left side.
The adrenal lymphatics drain into the para-aortic lymph nodes.
The adrenal cortex is believed to receive no innervations.

EMBRYOLOGY OF THE GENITOURINARY SYSTEM
The nephric system develops progressively from3 distinct entities:
PRONEPHROS:
- It is the earliest nephric stage and extends from 4^{th} to 14^{th} somites and consists of 6-10 pairs of tubules.
- It disappears completely by 4^{th} week.

MESONEPHROS:
- It is the principle excretory organ during early embryonic life (4-8 weeks).
- Though it gradually disintegrates, part of its duct system forms male reproductive organ.
- In mesonephros, primitive glomeruli are present.
- Its primary nephric duct is called mesonephric duct, and it opens distally into the cloaca.

METANEPHROS:
It originates both from mesonephric duct and intermediate mesoderm.

It forms the main kidney, while a ureteral bud (a branch of mesonephric duct) forms ureter, pelvis and collecting duct.
Main features of development are:
The 3 successive units of the system develop from the intermediate mesoderm.
The tubules of all levels appear as independent primordial and only secondarily unite with the duct system.
The nephric system is laid down as the duct of the pronephros and develops from the union of the ends of the anterior pronephric tubules.
The pronephric duct serves later on as mesonephric duct and gives rise to ureter.
The embryonic ureter is an outgrowth of the nephric duct, yet the kidney tubules differentiate from the adjacent metanephric blastema.

ANOMALIES OF THE NEPHRIC SYSTEM

Failure to ascend leads to ectopic kidney (1 in 1000). An ectopic kidney may be on the proper side but low (simple ectopia), or on the opposite side (crossed ectopia), with or without fusion.
Failure to rotate during ascent causes malrotated kidney.
Fusion of the paired metanephric masses leads to various anomalies; most common of which is horseshoe kidney.
The ureteral bud from the mesonephric duct may bifurcate, causing *bifid ureter.* An accessory ureteral but may develop from the mesonephric duct, thereby forming a *duplicated ureter.* Rarely such bud has a separate metanephric mass resulting in *supernumerary kidney.*
Lack of development of a ureteral bud results in a solitary kidney and a hemitrigone. *(Renal agenesis = 1: 1400)*
In the double ureteral buds, the main ureter bud, which is first to appear, drains upper moiety and is more caudal on the mesonephric duct, reaches the bladder first. It then moves upwards and laterally. The 2nd bud is more caudal in bladder. The double ureter always cross *(Weigert-Meyer Law).*

HORSESHOE KIDNEY

- The horseshoe kidney is the ***most common type of renal fusion anomaly*.**
- It consists of 2 distinct, functioning kidneys on each side of the midline, connected at the lower poles by an isthmus of functioning renal parenchyma or fibrous tissue.
- Horseshoe kidney occurs in from 1 in 800-1000 live births. It is twice as common in males.

Pathophysiology:

- The horseshoe kidney does not by itself produce symptoms.
- There are higher rates of hydronephrosis stone formation, infection.
- The most common associated finding in horseshoe kidney is ureteropelvic junction obstruction.
- It causes the majority of problems. Obstruction is due to the high insertion of the ureter into the renal pelvis. The crossing of the ureter over the isthmus may also contribute to obstruction.

Clinical:

- Nearly one-third of patients with a horseshoe kidney remain asymptomatic.
- Symptoms, when present, are usually due to obstruction, stones, or infection.
- ***In children urinary tract infection and in adults, pain is the most common presenting symptom***.
- *Rovsing's sign is abdominal pain, nausea, and vomiting with hyperextension of the spine*.

Relevant Anatomy:

- The kidneys may be lower than normal as the isthmus is tethered during renal ascent by the inferior mesenteric artery.
- The isthmus usually lies anterior to the great vessels at the level of the 3rd-5th lumbar vertebra.
- The vascular supply is variable and originates from the aorta, the iliac arteries, and the inferior mesenteric artery.
- ***The collecting system has a characteristic appearance on intravenous urogram due to an incomplete inward rotation of the renal pelvis, which faces anterior.***

Investigations:

An IVP is the best initial radiological study to determine anatomy and relative renal function.
CT scan or renal ultrasound is helpful to screen for the presence of stones, masses, or hydronephrosis.
Further studies are performed as indicated and tailored to the clinical situation. These include: ***diuresis renal scan to assess renal function.***
Medical therapy: The horseshoe kidney is susceptible to medical renal disease. If present are treated as indicated.
Surgical therapy: Surgical treatment is based on the disease process and standard surgical indications
e.g. ***Ureteropelvic junction obstruction, Kidney stones, Renal Tumors, Abdominal Aneurysmectomy.***
Prognosis

- The horseshoe kidney does not complicate pregnancy or delivery.
- Presence of the horseshoe kidney alone does not affect survival.
- The horseshoe kidney does have a higher propensity to become diseased. Survival is therefore dependent on the disease process that the horseshoe kidney may harbor.

RADIOLOGY OF THE URINARY TRACT

RADIOGRAPHY:

X-rays are electromagnetic waves with photon energies that fall between those of gamma rays and ultraviolet radiation in electromagnetic spectrum.
The basic radiological studies commonly used are: Plain KUB, IVP, RGU, AGP, MCU, RGU and Angiogram. These studies can be enhanced by digital radiographic subtraction.
1. PLAIN FILM:
Plain film provides soft tissue shadow of the kidney and gives a rough idea of size (Shrunken kidney in renal failure indicate medical rather than surgical cause), number and location of kidney.
It demonstrates the: foreign body, bones, abnormal calcifications (stone, calcified aneurysm/ hydatid cyst, calcified ovarian cyst and calcified lymph nodes). Renal stone in lateral view overlies the spine.

***2. INTRVENOUS PYELOGRAPHY (I*ntravenous urography):
In this procedure after a initial plain film, films are taken at timed interval after the IV injection of iodine containing contrast media, which is promptly excreted by the kidney.
It is commonly used for obstruction and to delineate lesions like; papillary necrosis, medullary sponge kidney, Tumours etc.
Contrast media are *ionic (Iodopyracet, Acetrizoate, **Diatrizoate**, Iothalmate and dimmer of iothalmic acid)* and *non-ionic (Metrizamide, Iopamidol, Iohexol and ioxalate).*
Non-ionic contrast media are safer in cases of history of allergy to iodinated compounds.
3. RETROGRADE UROGRAM: It is helpful in cases of unsatisfactory excretory urogram; history of adverse reaction to IV contrast media or other method of imaging is unavailable.
It may precipitate urinary tract infection.
4. ANTIGRADE PYELOGRAPHY:It is occasionally done when urinary tact imaging is necessary but excretory or retrograde urography has failed or is contraindicated, or when there is nephrostomy tube in place and delineation of upper tract is desired.
5. MICTURATING CYSTOURETHROGRAPHY / REATROGRADE URETHROGRAPHY:
Cystogram is obtained by instilling a radiographic contrast media in the bladder and obtain an x-ray film. This outlines the bladder. Then the patient is asked to micturate and voiding films are taken and this is called MCU.
The urethra can be imaged by obtaining an x-ray while retrograde injection of the contrast in urethra.
MCU is required in lesions of the posterior urethra (PU valves), RGU is more helpful for examining the anterior urethra.

SONOGRAPHY

BASIC PRINCIPLES:

- Sound frequency greater than 20 KHz in called ultrasound.
- The frequencies, commonly used in medical practice are between 3.5-10 MHz.

CLINICAL APPLICATION:

- Ultrasound is commonly used for the evaluation of bladder, prostate, kidney, testis and penis.
- In kidney it evaluates size, cortical thickness, echogenicity, cortico-medullary differentiation, mass lesion and cyst.
- In the bladder it helps in detecting stone, tumour bladder wall thickness and residual urine.
- Prostatic size, calculi and echogenicity can be determined with the help of USG.
- Stones appear as hyper echoic (white) while malignancy as hypo echoic (black) shadow.
- ***Higher the frequency, better is the resolution and poor penetration, thus for superficial examination (e.g. testis) higher frequency probes are used.***

COMPUTERIZED AXIAL TOMOGRAPHY

BASIC PRINCIPLE:

- In CT scan a thin x-ray film is passed through the patient, and absorbed in a linear array of solid-state or gas detector.
- Digital computers assemble and integrate the collected x-ray transmission data to reconstruct a cross sectional image (Tomogram).
- CT works on density difference. The unit of CT number is HU (Hounsfield unit). This relative density scale of numbers assigns a value of 0 for water, -1000 for air and +1000-2000 for bone.

MAGNETIC RESONANCE IMAGING

BASIC PRINCIPLES:

The nucleus of the H+ atom consists of a single proton. Any atom containing an odd number of proton and neutron has a nuclear property to spin. Normally the axis of spin of Hydrogen nuclei is randomly oriented. If the body is placed in a strong magnetic field the Hydrogen nuclei wobble like a spinning top around the line of Magnetic field.

If hydrogen nuclei are additionally stimulated by very short pulse of radio waves, they absorb the energy and invert their orientation.

Once the short radio wave is terminated the hydrogen nuclei return at various speed to their (low energy) state, emitting energy. This phenomenon is called nuclear magnetic resonance.

This emitting energy is collected and transformed with various computer programs into cross sectional area.

CLINICAL APPLICATION:

- MRI in urological diseases gives more or less same information as CT scan, but MR angiography, which does not require contrast media is useful in evaluating renal transplant vessels and renal vein, tumour, thrombus and renal artery stenosis.
- Contrast used in MRI is ***gadolinium***. It is contraindicated in cases of metallic prosthesis.

UROLOGICAL TRAUMA (KIDNEY AND URETER)

10% of all injuries involve genitourinary system.

Initial assessment includes: ABC (Airway, bleeding control, establishing circulation).

General examination Other than BP, Pulse etc. includes: specifically look for rib fracture (Mainly 9th to 12th), Pelvic Fracture, Other visceral injuries, Blood at urethral meatus, Perineal hematoma or contusion.

1.CATHETERIZATION AND ASSESSMENT OF INJURIY:

- ***Catheterization is contraindicated if blood is present at urethral meatus.***
- In these cases RGU should be done prior to catheterization.
- Urine is collected for microscopic and gross hematuria.
- IVP helps in staging and in evaluation of renal injuries.
- Arteriography helps in renal parenchymal and vascular injuries.
- ***CT scan is the investigation of choice.***
- Abdominal ultrasound can be used as a screening modality.

RENAL TRAUMA:

- Blunt trauma over abdomen, flank or back is the most common mechanism (80-85%).

CLASSIFIACTION:
MINOR RENAL TRAUMA:

- Accounts for 85% of all renal injuries.
- Renal contusion or bruising is the most common lesion.
- Other minor traumas are: subcapsular contusion and superficial cortical lacerations.

MAJOR RENAL TRAUMA:

- Accounts for 15% of all cases.
- This includes: deep cortico-medullary lacerations extending into the collecting system (causing extravasation of urine), Large retroperitoneal/ perinephric haematoma or shattered kidney.

VASCULAR INJURY:

- <1% of all trauma cases.
- There may be total avulsion of the artery or vain or partial avulsion of the segmental branches of these vessels.
- Renal artery thrombosis (Usually presents late).is another way of presentation.

Grade I & II are minor. Grade II, IV and V are major.

LATE FEATURES:
URINOMA:
Missed deep cortico-medullary laceration causes extarvasation and urinoma formation.
This leads to large peri nephric mass and eventually hydronephrosis or abscess.
HYDRONEPHROSIS:
Large perinephric hematoma or extravasation causes fibroses, which later on engulfs PUJ
Follow up IVP is indicated in all cases of major trauma.
AV FISTULA:
This occurs after penetrating injuries, but is not common.
RENO-VASCULAR HYPERTENSION:
Seen in <1% of cases.
Caused by either thrombosis of small vessel (All renal vessels are end artery), or by engulfment of vessel in posttraumatic fibrosis.

SYMPTOMS:

- Abdominal pain usually localized to one flank.
- Hematuria.
- Retroperitoneal bleed may cause peritonism, ileus, distention, Nausea and vomiting.
- *Degree of hematuria does not correlate to the degree of renal injury.*

SIGNS:

- *Patient may present in shock in massive bleed.*
- *Bruise, echymosis, lump, or lower rib fracture.*
- *Features of peritonitis.*

LABORATORY FINDINGS: *Microscopic or gross hematuria.*
X-RAY FINDING:
Indications for IVP:

- All patient with gross hematuria.
- All patients with microscopic hematuria with shock.
- Gross hematuria with normal IVP requires no additional test.
- Nonvisualiztion requires immediate CT scan.

IVP also functions as plain x-ray as far as Gas under diaphragm or bone fractures are to be seen
Arteriography defines vascular and major parenchymal damage, thrombus and avulsion.

TREATMENT:
EMERGENCY MEASURES: ABC
CONSERVATIVE MEASURES:

- As 85% of renal injuries are of minor grade, conservative measure is very important.

- This includes, IV fluids/ blood, antibiotics, bed rest, sedatives, regular urinalysis and strict vitals monitoring.

SURGICAL MEASURES:

- Persistent retroperitoneal bleed, Urinary extravasation, Evidence of non-viable renal parenchyma and renal pedicle injury are indications for immediate exploration.
- Nephrectomy, Partial nephrectomy and repair of laceration are the main surgical procedures done in cases of renal trauma.

TREATMENT OF COMLICATIONS:

- Retroperitoneal urinoma or perinephric abscess requires immediate surgical drainage.
- Malignant hypertension requires vascular surgery, endo-vascular dilatation or nephrectomy.
- Hydronephrosis in a functioning kidney requires repair and in non-functioning kidney nephrectomy can be done.

URETERAL INJURIES:

Ureteral injuries are rare, and may be caused by penetrating injuries, Rapid deceleration (Causes avulsion of ureter at UPJ), Iatrogenic e.g. hysterectomy, endoscopic basket manipulation of ureteral stone, devascularization of ureter in pelvic nodes dissection).

CLINICAL FINDING:

- In cases of accidental ligation of ureter there is: flank pain, fever, paralytic ileus, with nausea and vomiting.
- Bilateral ligation presents as aneuria.
- Ureterocutaneous, or ureteroveginal fistula may develop, usually within first 10 post op days.
- Mid ureter is most common site in penetrating injuries
- Acute peritonitis may develop if urine enters in peritoneal cavity.

LABORATORY FINDINGS:

- Microscopic hematuria is present in 90% of cases.
- Serum creatinine level usually remains normal except in bilateral injuries.

X-RAY:

- Diagnosis is made by IVP, showing extravasation.
- Plain film may show an area of increased density.
- In late cases there is hydronephrosis or non-functional kidney.
- Retrograde ureterography demonstrates the exact site of obstruction.

ULTRASOUND:

USG demonstrates hydroureter and collection due to extravasation.

TREATMENT:

- Immediate exploration and repair is indicated.
- If the injury is recognized late, proximal diversion by PCN or formal nephrostomy should be done.

For upper ureter, options available are:

- End to end primary uretero-ureteral anastomosis.
- Trans uretero-ureteral anastomosis.
- If there is extensive loss of ureteral tissue then: bowel interposition or auto transplantation.

For mid ureter:

- Primary uretero-ureteral or trans uretero-ureteral anastomosis.

For lower ureter:

- Reimplantation in bladder with psoas hitch (to decrease tension).
- Primary uretero-ureteral repair.
- A bladder tube flap can be used if the ureter is short (Boari flap).
- In the presence of extensive urinoma or pelvic infection trans uretero-ureteral anastomosis is preferred as this allows reconstruction in a clean area.

PELVI-URETERIC JUCNCTION OBSTRUCTION

UPJ obstruction is the most common cause of antenatal and neonatal hydronephrosis. UPJ obstruction presents with pain, hematuria, urosepsis, failure to thrive, or a palpable mass. Fifty percent of patients diagnosed with antenatal hydronephrosis will be found to have a UPJ obstruction on further work-up. .

Frequency:

UPJ obstruction is seen in 50% of patients diagnosed with antenatal hydronephrosis.

There is a male to female ratio of 2-3:1. *

In general, the left kidney is more commonly affected.

Etiology:

- Possible etiologies for UPJ obstruction include the following:
    - Intrinsic obstruction occur secondary to stenosis from scarring.
    - Ureteral hypoplasia may result in abnormal peristalsis through the UPJ.
    - Abnormal or a high insertion of the ureter into the renal pelvis.
    - Crossing lower pole renal vessel(s) or entrapment of the ureter by a vessel.
    - Rotation of the kidney, such as renal ectopy, and renal hyper-mobility.
- There is impaired drainage of urine from the kidney into the ureter, resulting in elevated intrarenal backpressure, dilation of the collecting system, and hydronephrosis.

Clinical:

- Neonates presenting with hydronephrosis should be placed on prophylactic antibiotics (amoxicillin 15 mg/kg) to prevent urinary tract infections.
- If renal sonography demonstrates hydronephrosis without reflux on VCUG, then a diuretic renal scan (MAG-3, DTPA, or DMSA) should be performed to quantify relative renal function and to define the extent of obstruction.
- Older children may present with urinary tract infections (UTI), a ***flank mass*** or intermittent flank pain secondary to a primary UPJ obstruction. Hematuria may also be a presenting sign if associated with infection.
- Adults can present with a variety of symptoms, including back and ***flank pain***, UTI, and/or pyelonephritis. Through a detailed history, the pain may be correlated with periods of increased fluid intake or ingestion of a food with diuretic properties ***(Dietl's crisis).***

INDICATIONS

- Dilation of the intrarenal collecting system or hydronephrosis does not necessarily imply obstruction.
- Renal pelvic dilation should be followed with serial imaging for changes in dilation, renal parenchymal thickness and/or the presence of scarring, and function.
- ***Surgical repair is indicated if there is a significant differential in serial imaging or if progressive deterioration of renal function occurs.***
- Similarly, in adults, repair is recommended if ureteral obstruction is demonstrated either on nuclear medicine renal scan or IVP.

Lab Studies:

All patients should be evaluated with a CBC, coagulation profile, electrolytes, and assessment of overall renal function with BUN and creatinine and urine culture.

Imaging Studies:

- In children, a renal ultrasound and voiding cysto-urethrogram are performed.
- ***IVP is used to evaluate patients with possible UPJ obstruction***, however, diuretic renograms is useful in advanced cases of obstruction with poor renal function.
- In children, a retrograde ureteropyelogram to define the entire ureter is sometimes performed just prior to surgical repair

Diagnostic Procedures:

- In those patients where the diagnosis of obstruction is equivocal, a Whitaker antegrade pressure-flow study may be performed.
- This test begins with the placement of a small diameter nephrostomy
- Dilute contrast medium is instilled and intrarenal collecting system pressure monitored.

- Perfusion is started at the rate of 10 ml / min. until steady state equilibrium of pressure is reached. Bladder is continuously drained with a catheter.
- At a flow rate of 10 ml/min, differential pressure (pelvic pressure – vesical pressure) ***below 13 cm of water is normal; 14-22 suggests mild obstruction, > 22 suggest moderate to severe obstruction.***
- While function cannot be assessed, relative resistance and pressure within the renal pelvis can be determined.

TREATMENT Medical therapy:

- In children, medical therapy is focused on maintaining sterile urine and assessment of renal function and the degree of hydronephrosis.
- Patients are typically followed with routine renal ultrasounds and nuclear medicine renograms if an incomplete obstruction is defined on imaging.

Surgical therapy:

- Surgical intervention to treat an obstructed ureteropelvic junction is warranted, especially with deterioration of renal function.
- The principles of surgical repair as initially described by Foley include the following:
    - Formation of a funnel
    - Dependent drainage
    - Water-tight anastomosis
    - Tension-free anastomosis
- ***In children, the procedure of choice is an Anderson-Hynes dismembered pyeloplasty.***
- The success of dismembered pyeloplasty is greater than 95%.
- Treatment alternatives include an ***antegrade or retrograde endopyelotomy***, which is an endoscopic incision performed through the obstructing segment.
- Success rates with the percutaneous and ureteroscopic endopyelotomy range from 80-90%.
- Traditional open or laparoscopic pyeloplasty is also indicated after failed endopyelotomy.
- The ***Foley Y-V plasty*** is useful for the high insertion variant.
- ***Spiral and vertical flaps, such as Culp and DeWeerd and Scardino and Prince***, are useful when a long-strictured segment of diseased ureter is encountered.
- ***Ureterocalicostomy***, anastomosis of the ureter to a lower pole renal calyx, is most often reserved for failed open pyeloplasty where there is no extrarenal pelvis.

COMPLICATIONS

- Urinary tract infection and pyelonephritis,
- Urinary extravasation and leakage,
- Recurrent UPJ obstruction or stricture formation.
- Specific complications from endopyelotomy include: Significant intra-operative bleeding if the endoscopic incision is made inadvertently into a major polar vessel, postoperative infection, and recurrence of obstruction.

VESICO URETERIC REFLUX

Vesico-ureteric reflux is retrograde passage of urine from the bladder into the ureter. Vesicoureteric reflux may be primary or secondary. Primary vesicoureteric reflux is common in childhood, and is believed to be due to a developmental deficiency in the muscle layer of the ureterotrigonal region. Other congenital causes of vesicoureteric reflux include complete ureteric duplication (reflux typically occurs into the ureter of the lower pole moiety), ectopic ureter, prune belly syndrome, and congenital periureteric diverticulum. Acquired causes include bladder wall oedema or fibrosis, prostatectomy, bladder neck incision, and ureteric reimplantation.

Vesicoureteric reflux may lead to renal damage by allowing reflux of infected urine from the bladder to the kidney, which results in pyelonephritis, or by allowing transmission of bladder voiding pressures to the kidneys, causing hydronephrosis and reflux nephropathy. Patients may present with pyelonephritis, cystitis or uraemic symptoms. Asymptomatic pyelonephritis may be discovered as an incidental finding on routine urinalysis.

The incidence of vesicoureteric reflux in healthy children is under 1%, but is 20 – 50% in children with urinary tract infection. The definitive test for the diagnosis of reflux is conventional contrast cystography. Films are taken during bladder filling, during voiding and after voiding.

Grading

Grades are as follows:

- Grade I reflux, contrast refluxes into the ureter only, opacifying part (IA) or all of the ureter. In the latter case, the ureter may be of normal calibre (IB) or dilated (IC).
- Grade II reflux, contrast reaches the renal pelvis, which is not dilated. Ureteric opacification may be incomplete (IIA), incomplete with focal dilatation (IIB), or complete (IIC).
- Grade III reflux, contrast reaches the renal pelvis, with mild dilatation of the ureter and pelvicaliceal system (IIIA), or moderate dilatation with early forniceal blunting (IIIC).
- Grade IV reflux, there is moderate pelviureteroectasis, with obliteration of the forniceal angles but preservation of the papillary impressions. The forniceal angles may be partially (IVA) or completely obliterated. In the latter case, the ureter may be tortuous (IVB) and there may be extensive pelviectasis (IVC).
- Grade V reflux, there is moderate to severe pelviureteroectasis, with near complete (VA) or complete obliteration of the papillary impressions. The latter may be associated with severe (VB) or extreme (VC) collecting system dilatation.

Reflux may also be demonstrated by voiding radionuclide cystography; it is sometimes detected by US . Vesicoureteric reflux may be unilateral, bilateral or intermittent. Children with lower grades of primary vesicoureteric reflux can often be successfully managed with medical treatment, with spontaneous resolution as they grow up. Other children may require surgery.

Clinical features

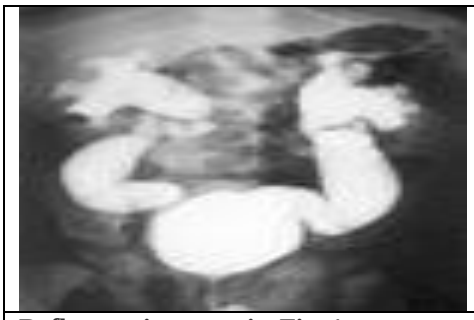
Clinical features are those of urinary tract infection. Suspicion should be raised after a single infection in boys or two in girls.

Other features include:

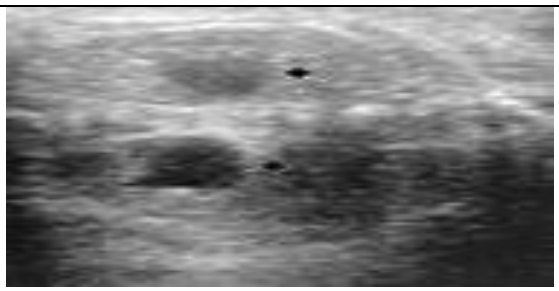
- Incontinence/ frequency/ dysuria/ abdominal pain

Investigation

- The diagnostic investigation is micturating cystography.
- DMSA or DTPA may be helpful to assess renal function and scarring.



Reflux, vesicoureteric, Fig. 1
Voiding cystourethrogram in a patient with severe bilateral vesicoureteral reflux.



Reflux, vesicoureteric, Fig. 2
Antenatal sonogram, showing bilateral pelvicaliectasis (arrow). Postnatal studies confirmed bilateral vesicoureteral reflux.

- micturating cystourography
- DMSA imaging
- DTPA imaging

Complications

Vesico-ureteric reflux can lead to scarring and destruction of the kidney.

Management

- Management is dependant on the grade of reflux, as follows:
- Grades I and II are managed conservatively, whilst attempting to prevent infection with improved hygiene, high fluid intake and regular voiding.
- Grades III and IV requires surgical management - ie correction of the underlying abnormality. This is by tunneling the ureter through the bladder wall.

Follow up depends on the renal function, and the degree of scarring of the kidneys. The presence of the latter requires long term follow up to monitor for hypertension.

Treatment

Nonoperative Management

When reflux is related to an underlying problem such as constipation, infrequent voiding, abnormal bladder activity, or blockages such as strictures or valves, the predisposing factor should be corrected first and the reflux then re-evaluated.

Mild-to-moderate degrees of reflux (grades 1 to 3) have a good chance of spontaneous resolution with age in over 80% of children. After a 1- to 2-year interval of treatment with antibiotics, reflux is reevaluated with VCUG and the kidneys with ultrasonography to be certain they are growing properly and no interval damage has occurred.

During the course of nonoperative management, any fever, unexplained illness, or urinary tract symptoms (burning, frequency, urgency, foul odor, bloody urine, or unusual urinary accidents) must be aggressively evaluated with urine analysis and urine culture to make certain that it is not a urinary infection. A breakthrough urinary infection, in spite of preventive antibiotics, is a dangerous situation indicating that there is not enough time for spontaneous resolution and that the next step should be surgical correction of reflux.

Surgical Correction

- Indications:
  - Breakthrough UTTs despite prophylactic antibiotics
  - Noncompliance with medical management
  - Severe grades of reflux - grade V or bilateral gradelV
  - New renal scars or deterioration of renal function as on serial USG or DMSA scan,
  - Reflux that persists in girls at full linear growth (at puberty)
  - Reflux associated with congenital abnormalities at UVJ (e.g. bladder diverticula),
  - All secondary reflux, which persist after correction of the primary cause e.g. fulguration of posterior urethral valves or management of uninhibited detrusor.
- Ureteroneocystostomy (ureteric reimplantation) with a tunnel length of S times the ureteral diameter.

Correction of reflux (called ureteral reimplantation or ureteroneocystostomy) is recommended for high rades of reflux, for reflux that fails to resolve on its own despite monitoring over several years, and for patients with breakthrough infections.

The traditional surgical approaches have high degrees of success and usually involve opening the bladder and creating a new, longer tunnel for the ureter to pass through the bladder wall. If the ureter is very wide due to high grade reflux, it is narrowed to make a successful flap valve with at least a 4:1 ratio of tunnel length to ureter width

Other alternative procedures to correct reflux are injection of bulking agent at the ureteral opening with scope and laparoscopic correction of reflux.

Micturating cystourography

A micturating cystourogram is used to investigate:

- recurrent urinary tract infections in children, or a single urinary tract in a young child
- disturbed bladder function in adults
- suspected vesico-ureteric reflux

- Bladder diverticula

The patient is catheterised and the bladder filled with contrast. The patient is then screened whilst voiding.

DMSA imaging

Static renal imaging provides ***morphological information*** on each kidney. It is most commonly performed using ***99m technetium labelled dimercaptosuccinic acid which becomes fixed in proximal renal tubular cells***. DMSA imaging enables assessment of:

- size and position of the kidneys
- differential function - expressed as a percentage of the total function. The upper limit of normal is 5% either side of 50%. A kidney functioning at 15% of more is still useful; one whose function is less than 7% is not.
- parenchymal defects - scars, cysts, tumours, ischaemic areas in renal hypertension
- morphological abnormalities such as duplex and horseshoe kidney

Imaging should not be performed too soon after a UTI as it will identify areas of transient ischaemia. Postponement for about three months is recommended.

DTPA imaging

Diethylenetriamine penta-acetic acid - DTPA - labelled with 99m technetium can be used to image the renal tract, and ***is useful for functional assessment***.

It is filtered the glomeruls and not reabsorbed.

Normal images

Sequential images are obtained at 5-20 second intervals over a period of 20-30 minutes. A renogram is constructed by plotting activity of the isotope against time in selected regions. Three phases are recognised:

- Vascular phase - a rapidly rising curve of activity due to arrival of isotope in the kidney from the bloodstream. It is usually of about 30 seconds duration.
- filtration phase - a more slowly rising curve denoting concentration of isotope as it passes into the collecting system
- Excretory phase - a declining curve denoting that isotope is no longer being delivered to the kidney but continues to pass down the ureter

Images in disease

Characteristic patterns include:

- Prolonged vascular phase in renal artery stenosis.
- Prolonged excretory phase in upper urinary tract obstruction. Administration of frusemide distinguishes a truly obstructed kidney from one that is hydronephrotic but not obstructed. In the latter, frusemide causes a diuresis with a rapid decline in activity.

RETROPERITONEAL FIBROSIS

- ✓ Fibrotic Plaque centered over L_4- L5 „ near sacral promontory and extending from renal hilum to sacral promontory and outer borders of Psoas.
- ✓ Prevalence 1 in 2 Lacs
- ✓ Male > Female 2 :1 (30 - 60 Years)

Causes: 2/3 Idiopathic (Ormond's Disease)

Known causes:

1) Drugs- Methysergide Methyldopa, LSD Other Ergots (eg. Bromocriptine) Phenacetin Amphetamines β- Blockers
2) Malignancies - Lymphomas, Sarcomas
3) Inflammatory conditions. IBD, Diverticulitis
4) Radiation

Presentation

Obstructive uropathy (Earliest + MC)

Diagnosis

IVPorRGP:

1. Medial pulling of ureters
2. Pipestem ureters CT/MRI: Delineate RP Fibrosis

RENAL TUBERCULOSIS

Genito-urinary Tuberculosis (GUTB) is caused by *Mycobacterium tuberculosis,* mainly through *hematogenous route.* It affects young adults and is more common in males.

PATHOGENESIS AND COURSE:

Severity of the infection depends upon, virulence of the organism and host resistance.

It is a slowly progressive disease and primary site is often asymptomatic. The disease starts near the glomerulous, causing caseous breakdown. The ureter undergoes fibrosis and tends to shorten and straighten leading to loss of sub mucosal tunneling in the bladder and forms golf hole ureteric opening.

Bladder involvement is always secondary to the **kidney**. Vesical irritative symptoms are main presenting feature. Tubercles are formed in the region of ureteric orifice and later on they coalesce and ulcerate. Healing is through fibrosis and contracture with the development of small bladder (thimble bladder).

Involvement of **prostate** is rare and is always hematogenous. Prostate may become fibrosed this causes decrease in semen volume.

Involvement of testis is always secondary to **epididymis**, which is involved through hematogenous route. Tail of epididymis is primary site of involvement, thus a tubercular scrotal fistula is posteriorly located.

CLINICAL PRESENTATION:

GUTB is considered in any of the following condition:

1. Chronic cystitis not responding to adequate antibiotic treatment.
2. Pyuria without bacteriuria.
3. Gross or microscopic hematuria.
4. A non-tender enlarged beaded epididymis.
5. Chronic discharging posteriorly placed discharging sinus.
6. A history of present or past tuberculosis elsewhere.

LABORATORY FINDINGS:

Urinalysis:	Persistent pyuria with sterile routine culture; ZN staining for acid-fast bacilli and LJ medium culture should be done, (takes around 4-6 weeks).
X-ray chest:	To rule out pulm. tuberculosis.
X-ray KUB:	May also show enlarged kidney / contracted kidney / calcification or features of perinephric abscess (e.g. obscured renal or psoas shadow).
IVP:	Moth eaten appearance of the involved ulcerated calices. Obliteration of one or more calyces. Abscess cavity (space occupying lesion), which may or may not Communicate with the collecting system. Ureteral strictures. Non-functioning kidney.
Cystoscopy:	Tubercles; ulcer, Cystitis, Golf hole ureter or contracted bladder.

COMPLICATIONS:

Renal:	Perinephric nephric abscess, intrarenal abscess, stone formation, CRF and aneuria.
Ureteral:	Scarring and stricture formation, hydronephrosis, Pyonephrosis, autonephrectomy, Vesico-ureteral reflux.
Vesical:	Contracted bladder, Vesico-ureteral reflux.
Genital:	Sterility due to epididymal block, Rupture of epididymal or testicular abscess leading to discharging scrotal sinus.

TREATMENT:

- Four drug ATT (INH, RCIN, P-zide, ethumbutol/streptomycin), is required in all.

- In cases of 1st line drug resistance, drug used are: PAS, Capreomycin, Cycloserine, Ethionamide, and Viomycin etc.
- More than 1 year course or may be even 2 years course is generally requires.
- If after 3 months, cultures are still positive and gross involvement of kidney is radiologically evident, Nephrectomy should be considered.
- If a vesical ulcer fails to respond on medical treatment, trans-urethral electro-coagulation may be done. Vesical instillation of chlorpectin (monoxychlorosene) also stimulates healing.
- In extremely contracted bladder augmentation cystoplasty is done,
- For epididymal involvement treatment is medical and if it fails to respond or abscess or discharging sinus develops epididymectomy should be done.
- Perinephric abscess often occurs when kidney is destroyed, abscess should be drained and nephrectomy should be done.
- For ureteral stricture, either endoscopic dilatation or surgery is required
- For distal ureteral strictures or severely refluxing Vesico-ureteric junction, uretero-neocystostomy should be done.
- **Safe drugs in cases of renal insufficiency are; R-cin & Pyrazinamide**

RENAL CELL CARCINOMA

- Renal cell carcinoma represents 2-3% of all cancers and 2% of all cancer deaths; 90-95% of neoplasms arising from the kidney.
- 9th most common male malignant tumor; 13th most common female malignant tumor.
- The tissue of origin for renal cell carcinoma is the proximal renal tubular epithelium. Renal cancer occurs in both a sporadic (nonhereditary) and a hereditary form.
- Familial and sporadic forms of renal cell carcinoma are associated with structural alterations of the short arm of chromosome 3 (3p).
- This condition occurs most commonly in the fourth to sixth decades of life.

Incidence/Prevalence:
30,000 new cases/year (1998 in USA); 11,600 deaths /year
Men: 9.6/100,000/ Women: 4.2/100,000
Predominant age: 5th and 6th decades
Predominant sex: Male > Female (2:1)
Synonyms: Hypernephroma/ Grawitz's tumor/ Hypernephroid cancer
Most of the carcinogens that cause renal cancer are unknown. Smoking, obesity, long-term use of phenacetin and acetaminophen, presence of kidney stones, and exposure to cadmium, thorotrast, petroleum products, and other industrial chemicals are important risk factors for developing renal cancer.
Whether polycystic kidney disease is associated with RCC remains controversial; however, acquired renal cystic disease, which typically occurs in patients with chronic renal failure on hemodialysis, is strongly associated with RCC.
The relationship between benign renal adenomas and RCC is controversial.

Hereditary syndromes associated with renal cell carcinoma are:
(1) von Hippel-Lindau (VHL) syndrome: VHL disease is transmitted in an autosomal dominant familial multiple-cancer syndrome, in which there is predisposition to a variety of neoplasms, including the following:

- Renal cell carcinoma with clear cell histology
- Pheochromocytoma
- Pancreatic cysts and islet cell tumors
- Retinal angiomas

- Central nervous system hemangioblastomas
- Endolymphatic sac tumors
- Epididymal cystadenomas

(2) hereditary papillary renal carcinoma (HPRC): an autosomal dominant inheritance pattern in which individuals who are affected develop bilateral, multifocal papillary renal carcinoma.
(3) familial renal oncocytoma (FRO): individuals can develop bilateral, multifocal oncocytoma or oncocytic neoplasms in the kidney; associated with Birt-Hogg-Dube syndrome (BHDS), a hereditary cutaneous syndrome.
(4) hereditary renal carcinoma (HRC).

History: The classic triad of flank pain, hematuria, and flank mass is infrequent (10%) and is indicative of advanced disease.

Most common presentations

- Hematuria (40%)/ Flank pain (40%)/ Palpable mass in the flank (25%)

Other signs and symptoms

- Weight loss (33%)/ Fever (20%)/ Hypertension (20%)/ Hypercalcemia (5%)/ Night sweats/ Malaise/ Varicocele, usually left sided, (2% of males)

Paraneoplastic syndromes, including hypercalcemia, erythrocytosis, and nonmetastatic hepatic dysfunction (Stauffer syndrome). Polyneuromyopathy, amyloidosis, anemia, fever, cachexia, weight loss, dermatomyositis, increased sedimentation rate, and hypertension also are associated with renal cell carcinoma.

Physical:

- Gross hematuria with vermiform clots suggests upper urinary tract bleeding.
- Hypertension, supraclavicular adenopathy, and abdominal mass with bruit.
- Approximately 30% of patients with renal carcinoma present with metastatic disease. Physical examination should include thorough evaluation for metastatic disease. Organs involved include:
    - Lung (75%)/ Soft tissues (36%)/ Bone (20%)/ Liver (18%)/ Cutaneous sites/ Central nervous system

Varicocele and findings of paraneoplastic syndrome raise clinical suspicion for this diagnosis.

Lab Studies:

- Laboratory studies in the evaluation of renal cell carcinoma should include a workup for paraneoplastic syndromes. Initial studies are as follows:
    - Urine analysis
    - CBC with differential count
    - Electrolytes
    - Renal profile
- Liver function test
- Calcium
- Erythrocyte sedimentation rate
- Prothrombin time
- Activated partial thromboplastin time

Imaging Studies:

- Contrast-enhanced CT scanning has become the imaging procedure of choice for diagnosis and staging of renal cell cancer. CT imaging can differentiate cystic masses from solid masses and supplies information about lymph nodes and renal vein and inferior vena cava involvement.
- Ultrasound examination provides excellent staging and diagnostic information. Ultrasound provides accurate anatomic detail of extrarenal extension of tumor, adrenal or lymph node involvement, and infiltration of adjacent viscera.
- Renal arteriography is used in cases where nephron sparing nephrectomy is planned.

- When inferior vena cava involvement is suspected, either inferior venacavography or MRI is used. MRI is currently the preferred imaging technique. Inferior vena cava involvement is important in planning the vascular aspect of the operative procedure.
- A bone scan is recommended for bony symptoms with elevated alkaline phosphatase.

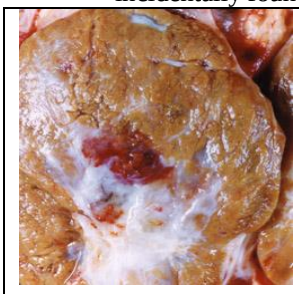
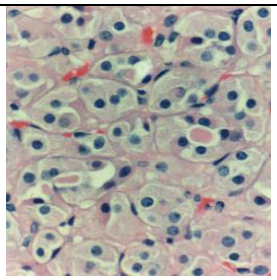
Histologic Findings (The Mainz Classification of Renal Cell Tumors): Renal cell carcinoma has 5 histological subtypes, as follows: clear cell (75%), chromophilic (15%), chromophobe (5%), oncocytoma (3%), and collecting duct (2%).

Renal Adenoma

- Small renal epithelial neoplasms are commonly and incidentally found during autopsies.
- Many investigators believe that these lesions lack the ability to progress to RCC and are benign. However, since the same lesions are not uncommonly associated with concomitant
- Microscopically, histopathologic features of both greatly overlap, and almost any histologic pattern described in RCC can be encountered in benign adenomas.
- Although it is acknowledged that many of these small renal neoplasms are probably benign, they should be considered potentially malignant, regardless of their size.

Renal Oncocytoma

- Renal oncocytoma (5% of the tumors); is derived from tubular epithelium). While most tumors are incidentally found, they can present as a mass or with hematuria.

	The mahogany appearance of the tumor contrast with the white fibrous scar in the center of the mast.		Eosinophilic tumor cells with large granular cytoplasm form small aggregates and tubules. Note the lack of mitotic activity and cytologic atypia.

- Histologically tumor cells exhibit large and finely granular cytoplasm, uniform round nuclei, clumped chromatin and small nucleoli.
- Conservative surgery is considered an adequate treatment since true oncocytomas are always benign.
- Renal oncocytoma has a characteristic central white fibrous scar.
- Although rare, necrosis may occur and Hemorrhage is common.
- Bilaterally or multicentricity are common.

Staging:

The Robson modification of the Flocks and Kadesky system:

- Stage I - Tumor confined within capsule of kidney
- Stage II - Tumor invading perinephric fat but still contained within the Gerota fascia
- Stage III - Tumor invading the renal vein or inferior vena cava (A), or regional lymph-node involvement (B), or both (C)
- Stage IV - Tumor invading adjacent viscera (excluding ipsilateral adrenal) or distant metastases

TREATMENT

The probability of cure is directly related to the stage or degree of tumor dissemination, so the approach is curative for early stage disease.

The treatment options for renal cell cancer are surgery, radiation therapy, chemotherapy, hormonal therapy, immunotherapy, or combinations of these.

Options for systemic therapy are limited, and no hormonal or chemotherapeutic regimen is accepted as a standard of care.

Renal cell carcinoma is an immunogenic tumor, and spontaneous regressions have been documented. Many immune modulators, such as interferon, IL-2, lymphokine-activated killer (LAK) cells plus IL-2, tumor-infiltrating lymphocytes, and nonmyeloablative allogeneic peripheral blood stem-cell transplantation have been tried.

Renal cell carcinoma is refractory to most chemotherapeutic agents because of multidrug resistance mediated by *p*-glycoprotein.

Surgical Care:

- Surgical resection remains the only known effective treatment for localized renal cell carcinoma, and it also is used for palliation in metastatic disease.
- *Radical nephrectomy*, which is the standard procedure today for treatment of localized renal carcinoma, involves complete removal of Gerota's fascia and its contents, including a resection of kidney, perirenal fat, and ipsilateral adrenal gland, with or without ipsilateral lymph node dissection.

Radiation therapy may be considered as the primary therapy for palliation in patients whose clinical condition precludes surgery.

Palliative radiation therapy is commonly used for local or symptomatic metastatic disease, such as painful osseous lesions and brain metastasis, to halt potential neurologic progression.

Wilms Tumor

Wilms tumor (WT) is the fifth most common pediatric malignancy and the most common renal tumor in children.

Incidence is approximately 0.8 cases per 100,000 persons.

Etiology: The tumor may arise in 3 clinical settings, (1) sporadic, (2) association with genetic syndromes, and (3) familial. The etiology essentially remains unknown.

Sporadic Wilms tumor

- Beckwith-Wiedemann syndrome (macroglossia, gigantism, and umbilical hernia)
- Hemihypertrophy
- Congenital aniridia
- WT, aniridia, genitourinary malformations, and mental retardation (WAGR syndrome)
- Denys-Drash syndrome (WT, pseudohermaphroditism, and glomerulopathy)
- Trisomy 18 mutation

Pathophysiology: The pathophysiology of WT is characterized by an abnormal proliferation of the metanephric blastema.

Clinical: The mean age at diagnosis is 3.5 years.

- The most common feature at presentation is an abdominal mass.
- Abdominal pain occurs in 30-40% of cases.
- Other signs and symptoms include hypertension, fever from tumor necrosis, hematuria, and anemia.

Major congenital anomalies include genitourinary anomalies (WAGR and Denys-Drash syndromes- 5%); ectopic, solitary, horseshoe kidney; hypospadias and cryptorchidism; hemihypertrophy & organomegaly (Beckwith-Wiedemann syndrome- 2%); aniridia (1%).

WORKUP

Lab Studies:

- Complete blood count
- Basic metabolic panel
- Coagulation abnormalities (acquired von Willebrand disease)

Imaging Studies:

Ultrasound

- Initial diagnosis of a renal or abdominal mass, possible renal vein or inferior vena cava (IVC) thrombus
- Information regarding liver and other kidney

Computed tomography scan

- Differential diagnosis of a kidney tumor versus adrenal tumor (neuroblastoma)
- Liver metastases
- Status of opposite kidney
- Lymph node assessment
- Status of chest with respect to metastases

Chest x-ray - As a baseline for pulmonary metastases

Bone scan - Necessary for children with clear cell sarcoma of the kidney

Magnetic resonance imaging

- Typically, these tumors appear inhomogeneous when using gadolinium-enhanced MRI, while the nephrogenic rests (which sometimes are precursors of WT) appear as homogeneous masses.

Histologic Findings: WT arises from the primitive embryonal renal tissue and contains epithelial, stromal, and blastemal elements.

Favorable histology (FH): 90% of cases. All 3 histological elements are present. The cure rate is close to 90%. Occasionally, foci of cartilaginous, adipose, or muscle tissue may appear (ie, teratoid WT).

Unfavorable histology (UH): 10% of the cases. Focal or diffuse anaplasia, clear cell carcinoma of the kidney (bone-metastasizing renal tumor of childhood), and rhabdoid tumor of the kidney are present.

Staging:

- Stage I: The tumor is limited to the kidney and is excised completely.
- Stage II: The tumor extends beyond the kidney but is excised completely. Capsular penetration, renal vein involvement, and renal sinus involvement also may be found. A biopsy of the tumor is performed, and local spillage occurs.
- Stage III: Residual intra-abdominal tumor (nonhematogenous) exists after the completion of surgery. Lymph node findings are positive, or peritoneal implants are found. The resected specimen has histologically positive margins, or the tumor has been spilled into the abdominal cavity.
- Stage IV: Hematogenous or lymph node metastasis has occurred outside the abdomen or pelvis.
- Stage V: Synchronous bilateral involvement has occurred. Each side is assigned a stage from I to III, and histology is based on biopsy findings.

TREATMENT

Surgical therapy: According to the NWTSG protocol, the first step in the treatment of WT is surgical staging followed by radical nephrectomy and regional lymph node dissection or sampling are performed (If the disease is unilateral).

If bilateral disease is diagnosed, nephrectomy is not performed but biopsy specimens are obtained.

If the tumor is unresectable, biopsies are performed and the nephrectomy is deferred until after chemotherapy, which will shrink the tumor in most cases.

Contiguous involvement of adjacent organs frequently is overdiagnosed.

With bilateral WT (5% of cases), surgical exploration, biopsies from both sides, and accurate surgical staging (including lymph node biopsy of both sides) are performed. This is followed by 6 weeks of chemotherapy that is appropriate to the stage and histology of the tumor. Then, reassessment is performed using imaging studies, followed by definitive surgery with (1) unilateral radical nephrectomy and partial nephrectomy on the contralateral side; (2) bilateral partial nephrectomy; and (3) unilateral nephrectomy only, if the response was complete on the opposite side. This approach dramatically reduces the renal failure rate following bilateral WT therapy.

Postoperative details: Postoperative chemotherapy and radiotherapy protocols are based on the surgical staging and follow the guidelines of the NWTSG.

 Stage I FH and UH or stage II FH

- Nephrectomy
- Postoperative vincristine and actinomycin D (18 wk)

 Stage II focal anaplasia or stage III FH and focal anaplasia

- Nephrectomy

- Abdominal radiation (1000 rad)
- Vincristine, actinomycin D, and doxorubicin (24 wk)

 Stage IV FH or focal anaplasia

- Nephrectomy
- Abdominal irradiation according to local stage
- Bilateral pulmonary irradiation (1200 rad) with Bactrim prophylaxis for *Pneumocystis carinii*
- Chemotherapy with vincristine, actinomycin D, and doxorubicin

 Stage II and stage IV diffuse anaplasia

- Nephrectomy
- Abdominal irradiation
- Whole lung irradiation for stage IV
- Chemotherapy for 24 months with vincristine, actinomycin D, doxorubicin, etoposide, and cyclophosphamide

PROGNOSIS: With the advent of multimodal therapy, the overall cure rate approaches 80-85%. Cases with diffuse anaplasia and stage III or IV that recur in spite of the complex therapy have a bad prognosis.

RENAL CALCULI

Epidemiology

Peak incidence 20-40 years; Males 3 times affected.
Stones commoner in women
Infectious stones (UTI common in women).
Cystinuria.
Hyper parathyroidism.
MC Calculi are calcium stones occurring in combination with either oxalates or phosphates.
4 most common types of stones -
Calcium containing stones [calcium oxalate (MC), calcium phosphate, mixed] - 70%. o Infection stones (struvite) - 15-20%
Uric acid stones - 5 -10%
Cystine stones - 1-5%

Model of formation of renal calculi (Super saturation and crystallization). PH for crystallization.

Uric acid and cystine calculi - acidic urine (PH < 6)
Struvite (MAP) and other phosphates - alkaline urine

Struvite stones (Stag horrf calculi)

Synonyms: infection stones, triple phosphate stones.

Women > men, perhaps because of their T susceptibility for UT1. Tend to grow in alkaline urine and tend to fill whole of the PCS. Composed of magnesium, ammonium & phosphate (MAP) Pathogenesis:
Two conditions must coexist for crystallization of struvite.

- Urine pH of 7.2 or above.
- Ammonia in the urine (produced from hydrolysis of urea by urease producing bacteria)
- Organisms that produce urease:
- Proteus mirabilis (MC)
  - Klebsiella
- Hemophilus influenza
- Staph aureus
- Corynebacterium sp.
  - Pseudomonas aeruginosa.
  - Urea plasma urealyticum.

- *One important organism that does not produce urease: E. colL*

Two urological conditions which contribute to the tendency to form struvite calculi:

- Foreign body in the urinary tract e.g. Foley's catheter.
- Neurogenic bladder

Most of the stag horn calculi are silent and cause progressive destruction of renal parenchyma. Management:

1. Complete stone removal— if not done, urea splitting bacteria may persist, leading to recurrence.
2. Treatment of a metabolic abnormality, if any.
3. Correction of any anatomic abnormalities contributing to stasis
4. Surgical management

- PCNL+ESWL— best treatment option, o
  Medical
- Antibiotics: Adjuncts to the surgical therapy, to prevent stone recurrences or growth.
- Acetohydroxaminic acid: irreversible inhibitor of urease.
- Diet: low calcium, low phosphorus diet.

Upto 50% of patients have stone recurrences or UTI over a 10 year follow up.

Uric acid Calculi (also called "jackstone")

5-10% of all stones.

Due to super saturation of urine with undissociated uric acid.

The pure uric acid calculi are the most common radiolucent urinary calculi

- May form staghorn calculi.
- May be familial or sporadic.

The familial variety is transmitted as autosomal dominant.

High levels are seen in patients with **Lesch- Nyhan -Syndrome** who have a deficiency or complete lack of enzyme hypoxanthine guanine phosphoribosyl transferase. This results in shunting of hypoxanthine to the xanthine-uric acid pathway, resulting in hyperuricemia and extreme hyperuricosuria. Treatment:

Cornerstone of treatment - diet, hydration and alkalization of urine.

- Low purine diet (low animal proteins). If urinary uric acid excretion is still > 100 mg/day, start Allopurinol 300-600mg/day. It inhibits conversion of hypoxanthine and xanthine to uric acid.
- Urine alkalinization to a pH of 6.5 - 7 with potassium citrate. Acetazolamide, a carbonic acid anhydrase, may be added if urine pH is still below 6.5.
  - ✓ Occur in patienis of cystinuria - an autosomal recessive disorder. It is a transepithelial transport defect that result in renal tubular reabsorption of four amino acids - cystine, arginine, lysine, and arginine.
  - ✓ Only cystine forms calculi, it has poor solubility within the range of normal urinary pH (PH < 7)
  - ✓ Less radiodense than the calcium oxalate ones. Typical "ground glass" appearance with a round smooth outline.
  - ✓ Typical benzene or hexagonal cystine crystals in urine.
  - ✓ Cyanide - nitroprusside - colorimetric test: shows a magenta ring at urine cystine levels > 75mg/l
  - ✓ Treatment goals:
    (1)Stone removal
    (2)To lower cystine concentration in urine below its solubility,

Low methionine diet

Alkalizatior. (Ph over 7.5)

Sodium bicarbonate & potassium citrate
Acetazolamide augments urinary bicarbonate excretion
Cystine complexing agents

- D- Penicillamine
- a mercaptopropionylglycine (MPG)

These bind cystine, forming a complex that is soluble in urine.

Xanthine

- ✓ Xanthinuria - an inborn error of metabolism; deficiency of xanthine oxidase. Autosomal recessive.
- ✓ Oxidation of hypoxanthine to xanthine and then to uric acid is blocked.
- ✓ Xanthine being less soluble, develops stones.
- ✓ Stones are smooth, brick red colored, round, radiolucent.
- ✓ Shows lamination on cross section.
- ✓ S. **Uric** acid is low (< 1.5 mg/dl). Serum and urine levels of xanthine & hypoxanthine are raised. Treatment
  - o High fluid intake - the most effective therapy.
  - o Allopurinol - paradoxically, by inhibiting residual xanthine oxidase, may inhibit the oxidation of hypoxanthine to xanthine, resulting in i crystallization.

Clinical features:

MC symptom is pain.

- ✓ Stone in upper ureter or renal pelvis →pain referred to testis
- ✓ Stone in mid ureter → referred along iliohypogastric nerve to iliac fossa, mimicking appendicitis
- ✓ Stone in lower ureter →referred along the ilioinguinal nerve to thigh, scrotum, and perineum.
- ✓ Stone approaching bladder -» bladder symptoms - frequency urgency dysuria e.t.c.
- ✓ Stone in the intramural ureter → strangury.

Investigations

Urine

PH

- Acid pH suggests uric acid lithiasis
- Alkaline pH is compatible with infectious lithiasis

M/E

- RBC's; Pus cells
- Crystalluria - to determine the stone composition

- Calcium oxalate monohydrate - dumbbell or hourglass
- Calcium oxalate dihydrate - enveloped or bipyradimol
- Calcium phosphate (apatite)- amorphous
- Bruihite - needle shaped
- Struvite - coffin lid
- Uric acid - multifaced, irregular plates or rosettes
- Cystine - Hexagonal or benzene ring

o Culture for urea splitting organisms.

Radiological evaluation

X ray KUB:

- o 90% radiopaque
- o Radiolucent Stones
- Pure uric acid stones (MC)
- Xanthine stones

- Matrix calculi
- Dihydroxyadenine
- Triamterene
- Indinavir

USG:

o A screening tool for hydronephrosis or stones within collecting system.

IVP:

o Early films (land 5 min) & Delayed films.
  o Promptness of contrast excretion
  o Any obstruction along urinary tract.

CT scan:

- Unenhanced spiral CT is the most sensitive investigation for a renal/ureteric calculus.
- **Retrograde pyeiogram (RGP)**

Better delineation of anatomy. Especially useful if distal ureter not visualized well.
It excludes unsuspected additional ureteric calculi and allows assessment of coexistent **ureteric disease** such as stricture, which may complicate the operative and post operative course, **gaittonucleidt evaluation**
DMSA (Dimercaptosuccinic acid) scan - Renal Morphology
DTP A (Diethylene Triaraine Pentacetlc Acid) to assess Perfusion -Effective renal plasma flow Function -Total and differential GFR **Metabolic workup**

Young patient.
Recurrent calculi
Multiple calculi
nephrocalcinosis

Management

Conservative: Features of stones likely to pass spontaneously-

- Single stone < 5 mm.
- Stone in lower third of ureter
- Ureter is undiluted
- E/O downward movement

5 different modalities of surgery available

- ESWL (extracorporeal shock wave lithotripsy)
- PCNL (percutaneous nephrolithotomy)
- RIRS (retrograde ureteroscopy intrarenal surgery)
- Laparoscopic stone surgery
- OSS (open stone surgery)
- The majority (80-85%) of 'simple' renal calculi are treated satisfactorily with ESWL.
- Rests are managed by PCNL/RIRS.
- OSS - the least common treatment modality now days.

ESWL:

High energy shock waves are produced outside the patient's body, which are focused on stones (renal or ureteric) with help of fluoroscopy or ultrasound, o The change in density between the soft renal tissue and hard stone causes a release of energy at the stone surface which causes "compression induced tensile cracking of stones". The stone fragments into small pieces and may pass down the ureter.

Factors involved in reducing the chances of stone free status

1. Stone burden - Multiple stones, stone > 2 cm, and staghorn calculi. ESWL is best suited for stone £ 2 cm in renal pelvis or calyces with no distal obstruction.
2. Reduced clearance - Lower calyceal location, marked HDN or scarring, calyceal diverticulum, horseshoe kidney.
3. Stone composition -

- Breakable - Uric acid, struvite, Ca oxalate dihydrate
- Difficult - Cystine, calcium oxalate monohydrate, hydroxyapatite/Brushite.

Complications

1. Acute injury to the renal parenchyma leading to hematuria and edema around the kidney.
2. Chronic renal injury leading to long term adverse effects
   a. Accelerated rise in the systemic blood pressure.
   b. Decrease in renal function.
   c. Increase in rale of stone recurrence.
3. Lung parenchymal injury, if exposed.
4. Extrasystoles
5. Infection - release of bacteria in fragment
6. Steinstrase ("street of tones")

Contraindications

Absolute	Relative
• **Pregnancy (most important)**	• Children (injury to lung parenchyma)
• Bleeding diathesis	• UTI
• Unrelieved distal obstruction	• Cardiac pacemaker
	▪ S. Creatinine > 3 mg/dl
	▪ Severe orthopedic deformity
	▪ Uncontrolled hypertension

PCNL (percutaneous nephrolithotmy)

Indications

1. Obstructive uropathy (contraindication for ESWL)
2. Large stone volume; stag horn
3. Other modalities failure - e.g. ureteroscopic failures; ESWL failure
4. Stone location - Lower pole calyces
5. Stone composition - Calcium oxalate monohydrate, brushite e.t.c. not amenable to ESWL

Complications

Injury to other viscera - Colon, pleura, spleen
Bleeding, urinary extravalation Retained fragments
Sepsis

Ureteroscopy

Indications

1. All lower ureteric calculi
2. Upper ureteric calculi of ESWL failure
3. Suspicion of Urothelial tumor - filling effect, Brush cytology
4. Ureteric dilatations; DJ stents
5. Retrieval of foreign body

Complications

Iatrogenic injuries

Intracorporeal lithotripsy

Techniques

1. Electro hydrolytic lithotripter (EHL)
   i. Narrow safety margin, may damage ureteral mucosa
   ii. Suitable for bladder calculi.
   iii. Successfully fragments 90% of all calculi.
   iv. Least expensive.
2. Ultrasonic lithotripter
3. Ballistic lithotripter
4. Laser lithotripter (Holmium: YAG laser)
   i. Ho:YAG is the best laser source for intracorporeal lithotripsy.
   ii. Most effective and versatile.
   iii. Good safety margin
   iv. Fragments all stones regardless of composition.
   v. It can cut through the metal. So, caution must be exercised while using a basket.
   vi. Potential side effects: production of cyanide when uric acid stones are treated. This has been reported in vitro. The clinical experience has suggested no significant cyanide toxicity.
   vii. Major disadvantage: initial high cost of the device and the laser fibers.

Open stone surgery-

Indications

- Whole of pelvicalyceal system packed with a stag horn calculus.
- Morbid obesity - these patients are poor candidates for ESWL/PCNL
- Anatomic abnormality requiring open operative intervention, e.g. PUJO.
- Nonfunctioning kidney with stone (nephrectomy)

Treatment decisions by stone burden

Upto 2 cm — ESWL, unless factors of stone composition, location or renal anatomy shift the balance towards more invasive modalities (PCNL/RIRS).

>2cm—PCNL

Stag horn stones - Treatment of choice: combined approach— PCNL + ESWL.Primary (initial) approach is PCNL, followed by ESWL, as an adjunct to minimize the number of repeat PCNL accesses.

OSS recommended in unusual circumstances where a stag horn calculus is not expected to be removed by a reasonable number of PCNL and or ESWL.

Treatment decisions by stone composition:

Stones too hard to be fragmented by ESWL (in decreasing order)

Brushite

Cystine

Calcium oxalate monohydrate

Hydioxyapatite

These are best managed by PCNL.

Treatment decisions by renal anatomy:

Congenital anomalies

- PUJ obstruction
- Horseshoe kidneys
- Other ectopic or fusional anomalies
- Calyceal diverticula

These hinder stone clearance after ESWL. PCNL — preferred modality.

2. Lower pole stones - PCNL

Treatment decisions by clinical factors:

i. UTI — ESWL is performed only if urine is sterile and no distal obstruction
ii. Morbid obesity — focusing by ESWL difficult. PCNL also difficult. URS — if stone burden is small, otherwise OSS.
iii. Uncorrected coagulopathy — ESWL & PCNL are contraindicated. RIRS using Holmium:YAG laser is preferred.
iv. Other conditions:
   a. Children
   b. Elderly
   c. Impaired renal function

   In these conditions, adverse effects of shock waves may occur.

Ureteric calculi

Treatment modalities

- ESWL with or without stone manipulation
- Ureteroscopy
- PCNL

Open stone surgery. Proximal and mid ureteral stones

❖ *< 1 cm*

1. ESWL- primary approach
2. Ureteroscopy is preferred in
   - Failed ESWL
   - Distal obstruction
   - Impacted stones

❖ > 1 cm

- Ureteroscopy primary approach
- PCNL for large proximal stones or impacted calculi that have Failed other modes

Distal ureteral stones

❖ < 1 cm

- ESWL & Ureteroscopy equally successful.
- Ureteroscopy primary approach

❖ > 1 cm

- Ureteroscopy

PROSTATE:

PROSTATITIS

Classification: 1. Acute bacterial prostatitis, 2. Chronic bacterial prostatitis, 3. Nonbacterial prostatitis, 4. Prostatodynia

ACUTE BACTERIAL PROSTATIS (ABP):

Characterized by; Fever, chills, low back and perineal pain, Myalgia and varying degree of irritative and bladder outlet obstruction features. Rectal examination reveals hot and tender prostate.

Caused by *E. Coli* (commonest), *Proteus, Klebsiella, Enterobactor, Pseudomonas, Serratia* and other less common gr.-ve organism. (Most inf. Is caused by single pathogen)

TREATMENT: Antibiotics and symptomatic (analgesics) treatment.

Septran (TMP-SMX): Should be given for 30 days to prevent CBP, Ciprofloxacin, Norfloxacin, Ofloxacin or ampicillin with gentamicin (IV). ***Urethral instrumentation should be avoided in acute phase.***

PROSTATIC ABSCESS: Coliform (mainly E. coli) is the main causative organism (>70%). Presentation is like acute prostatitis, which fails to respond to antibiotics, ***(commonest presenting symptom is acute urinary retention and fever > 35%)***. On PR examination prostate is tender with an area of fluctuation. Main diagnostic tools are TRUS and CT scan. Treatment is: drainage under antibiotic cover. Drainage is done by transurethral route, percutaneous aspiration, or perineal incision.

CHRONIC BACTERIAL PROSTATITIS (CBP):

It may evolve from ABP, but many men with CPB have no prior history of ABP. It mainly presents with irritative voiding symptoms. Postejaculatory pain or hemospermia may be found. ***Hallmark of CBP is recurrent UTI, caused by same pathogen***. Prostatic exprassates show excessive WBC and fat laden macrophages and fewer bacteria.

Treatment is mainly medical: Antibiotic therapy, Septran (for 4 to 16 weeks), Carbenicillin, erythromycin, minocyclin, Doxycyclin and cephalexin. Fluoroqunolone: ciprofloxacin, norfloxacin and ofloxacin are also effective. Those who do not respond to medical therapy are candidate for surgical therapy (TURP).

NONBACTERIAL PROSTATITIS (Abacterial prostatitis, Prostatosis):

It is an inflammatory condition of unknown cause. Usually presents with irritative voiding symptom and pain / discomfort in pelvis, suprapubic region genitals, perineal or postejaculatory. *In NBP culture is negative despite the presence of excessive leukocytes and macrophages.*

Exact causative organism is not known but Staphylococcus epidermidis, Ureaplasma urealyticum, Mycoplasma and ***Chlamydia tracomatis*** are probable pathigen.

As the causative organism is not known, when culture is negative an empirical trial of tetracycline, erythromycin, minocyclin or doxycyclin is given.

PROSTATODYNIA (PD):

Patient with PD has symptoms of prostatitis but no H/O UTI, culture is negative and typically normal Prostatic secretion. A typical patient of prostatodynia is young or middle aged with variable sign and symptom of urinary flow, irritative voiding and pain.

It is diagnosed by normal urine findings, normal EPS, sterile culture but abnormal urodynamic study (Decreased UFR, decreased relaxation of the sphincter, increased urethral pressure).

Treatment includes: Sitz bath, alpha-1 blockers, sedative and analgesics.

Summary

Syndrome	**H/O UTI**	**PR: prost abnormal**	**EPS: WBC excessive**	**EPS: +ve culture**	**Common causative agent**	**Antibiotic response**	**Urinary flow rate**
ABP	+	+	+	+	Coliform	+	+
CBP	+	±	+	+	Coliform	+	±
NBP	-	±	+	-	None ?Chlamydia ?Ureaplas.	±	±
Prostatodynia	-	-	-	-	None	-	+

BENIGN HYPERPLASIA OF PROSTATE:

Mc Neal's 4 zones

1. Peripheral zone
2. Transitional zone(periurethral zone)
3. Central zone
4. Anterior fibro muscular stromal

BHP typically affects transitional zone.

Symptoms:

A- Irritative symptoms

1: Frequency, urgency, nocturia, urge incontinence, nocturnal enuresis.
B- Bladder outlet obstruction
1. Poor flow
2. Hesitancy in initiating urine
3. Intermittency (double voiding)
4. Sense of incomplete emptying
5. Inability to terminate micturition abruptly with post micturition dribbling.

Most common benign tumour in men. Seen in 50% between 50-60 years and 90% in ninth decade.
Pathology: Characterized by adenosis, epitheliosis and stromal proliferations**. *It mainly involves the central part and lateral part gets compressed***. With enlarging prostate middle lobe develops, which projects into the base of bladder.
Secondary effects: The urethra gets compressed laterally and is elongated causing bladder outlet obstruction e.g. trabaculation/ secculation/ diverticuli. Later on there may be stone formation or Vesico-ureteral reflux.
Clinical presentation: Frequency is the earliest symptom, which initially is only nocturnal. Bladder symptoms are divided in irritative symptoms (e.g. Frequency, urgency, urge incontinence, nocturia) or obstructive symptoms (e.g. hesitancy, thin stream of urine, terminal dribbling and retention). Other features are recurrent UTI (due to increased residual urine) hematuria, or renal failure due to backpressure changes.
Examination may reveal bladder lump and on PR examination enlarged prostate (feature on BPH are: non nodular enlarged prostate with firm consistency, prominent median sulcus) In clinical examination one should always exclude presence of CRF e.g. evidence of weight loss or edema, anaemia, tenderness at renal angle and low urine output.
It is important to examine nervous system also to exclude the presence of neurogenic bladder.
Investigations: Complete hemogram and urinalysis, blood urea and serum creatinine. ***USG is the investigation of choice***. PSA (prostate specific antigen) is helpful in excluding carcinoma. It is a glycoprotein (mol.wt: 33,000), its normal value is 0- 4 ng/dl.
Urodynamic study (uroflowmetry, cystometrogram, and urethral pressure profile) is also helpful. A value of <10 ml/sec in UFR is suggestive of obstruction. Cystometrogram is helpful in differentiating between BPH and neurogenic bladder (indicated when patient presents with mainly irritative symptoms).

Uroflowmetry (Flow studies)	**Pressure studies (cystometry)**
i.Qmax >15ml/s normal	Differentiates between low Qmax secondary to obstruction and a neurogenic bladder.
ii. 10-15 ml/s-equivocal	Voiding Pressure >
iii.<10 ml/s suggestive of obstruction.	I. (N) < 60 cm H_20 voided.
Flow rate measurements are inaccurate if the volume is less than 150ml	II. Equivocal -60-80 III > 80 signifies outlet obstruction

AUA Symptom score
- Mild-0-7
- Moderate-8-19
- Severe-20-35
  - For mild symptoms, "Wait and watch" is recommended.
  - For moderate & severe symptoms, intervention is required.

Treatment: 1: Medical: By A) Androgen deprivation with LHRH agonists; Progestational compounds; Antiandrogens (cyproterone acetate, flutamide); 5 alpha reductase inhibitor (finastride: it prevents conversion of testosterone to dihydrotestosterone).
B) alpha 1 blockers prazocine, terazocin (long acting).

2: Surgical: Open prostatectomy (suprapubic- *Freyer's*, transpubic- *Millin's*, perineal- *Young's*) and Trans urethral prostatectomy. 2 main complications of TURP are; Dilutional hyponatremia (when distilled water is used for irrigation) and hyperammonical state (with glycein).

Absolute Indications for surgery

1. Bladder decompensation with overflow incontinence
2. Hydronephrosis

AGENT	ACTION MECHANISM	SIDE EFFECTS
GnRH analogue: Leuporalide, Goserelin, nefralin	Blocks pituitary LH secretion, Decreases level of T & DHT.	Loss of libido, hot flashes, gnaecomastia
Antiandrogen: Flutamide, Kasadex, Nilutamide	Blocks nuclear androgen receptor. *Does not decrease level of T or DHT.*	Impotency, Diarrhoea, Gynaecomastia.
5-alpha reductase inhibitor: Finastride(proscar), Epristride.	Blocks conversion of T to DHT. Dose not decrease level of T.	Headache, No impotency, Minimal loss of libido.
Combined agents: Progestational, antiandrogenic and gonadotripic effects; cyproterone acetate, magestrol acetate	Blocks LH release and nuclear androgen receptor.	Impotency, loss of libido (100%)
Aromatase inhibitors: testolactone, atamestane.	Blocks peripheral conversion of T to estrogen	Occasional headache. No impotency or loss of libido.
Alpha 1 sympathetic blockers: terazocine, prazocine	Relaxes bladder neck.	Postural hypotension

CARCINOMA OF THE PROSTATE.

Commonest malignant condition in men over 65 years. It usually originates from ***lateral lobes (Lowsley) / peripheral zone (Mcneal).*** *Porsterior lobe 70%, central lobe – 15-20%, Transitional lobe – 10-15%. Histologically commonest type is Adenocarcinoma.*

Spread: Local: initially capsule and the denonvillier's fascia prevents its spread. Later on there is spread to SV, ureter, bladder base, urethra or rectum.

Hematogenous: Ca prostate spreads to bones through periprostatic venous plexus. *Prostate is the most common site of origin to bone mets.* Secondary is mostly to Pelvic bone, lower vertebra, Femur, ribs and skull. Other than bones, breast, kidney, lungs or thyroid may be secondarily involved.

Lymphatic: to internal iliac nodes, external iliac nodes, and later on to retroperitoneal node, mediastinal and supraclavicular node.

Common presenting symptoms are: Features of bladder outlet obstruction, retention, haematuria or incontinence. This may be an incidental finding found by raised PSA, palpable nodule in PR examination, *histologically detected Ca in TURP chips*. Occasionally bone mets. (Pain, neurological symptoms due to cord compression, or pathological fracture) may be a presenting symptom.

PR examination reveals hard irregular enlarged prostate with loss of median sulcus.

Diagnosis *is confirmed by ultrasound guided needle biopsy of mass lesion* (Carcinoma appear as hypoechoic lesion in USG).

Other important investigations are complete hemogram, LFT, acid phosphatase (raised in 70% cases of bone mets), PSA (other then diagnosis it is also helpful in detecting recurrence after radical prostatectmy), x-ray chest and pelvis (to rule out mets, *bone secondary in Ca prostate is sclerotic*: D/D; pegets disease), CT scan (to see the extent of disease in advanced cases) MRI (to locate the neuro-vasculer bundle, if nerve sparing prostatectomy is to be done), Bone scan (Technitiun 99-m labeled methylene diphosphonate is used).

Treatment:

A: Surgery: radical prostatectomy or TURP to relieve outflow obstruction. Complications of surgery include: Haemorrhage, injury to obturator nerve, ureter, or rectum, incontinence and impotency.

B: Radiation Therapy: A: External beam radiotherapy of 6800-7000 rads to prostate and 4500-5000 rads to pelvic nodes. B: Intrestitial implants: I 125 is used to deliver high dose (10,000 to 17,000 rads) to prostate without damaging surrounding tissue. Complications of radiothery are: Inestinal sequelae (rectal bleed, tenesmus, mucous discharge, diarrhoea, fecal incontinence, intestinal obstruction, and rectal stricture), Urological (frequency, dysuria, cystitis, hematuria, and urethral stricture, and recto-vesical fistula) and other rare complications like; impotency, pedal edema.
C: Hormone manipulation:
1: Estrogen: DES has comparable efficacy with orchidectomy, but complication rate is higher.
2: Orchidectomy.
3: LHRH agonist: Complications are like DES e.g. hot flashes, gynacomastia etc.
4: Antiandrogens.Inhibitors of androgen synthesis includes aminoglutethimide, ketokonazole and spironolactone. Ketoconazole is a P450 inhibitor, which inhibits both adrenal and testicular androgen synthesis. Side effects are severe; GI intolerance, hepatotoxicity, gynacomastia and hypocalcemia. It is rapid acting and is useful in bone pains or impending spinal cord compression.
D: Chemotherapy: It is a relatively chemoresistant tumour. Some agents (e.g. adramycin, 5-FU) have shown some effects (about 10% objective response). *Suramin, by blocking growth factors (Beta FGF, EGF), direct cytotoxicity and adrenocorticolytic activity has shown 40 % response rate.*
E: Palliative therapy: Painful Bone mets are managed with RT (2000-3000 rads). *Strontium 89 (a beta emoting compound) has a affinity for new bone activity and is effective in bone secondary.* TURP is done to relieve outflow obstruction.

BLADDER NECK CONTRACTURE
May be congenital, seen in children (Marion's disease: due to congenital bladder neck hypertrophy), or acquired (fibrotic prostate or following TURP)
Treatment:

- Medical: Alpha 1 blocker.
- Surgical: A; Dilatation, B; Transurethral incision of bladder neck; C; Sphincteroplasty (Bonin's operation): a kind of V-Y plasty of bladder neck.

PROSTATIC CALCULI

- Endogenous calculi are composed mainly of calcium phosphate.
- Often, they are asymptomatic but may present as prostatitis or retention.
- Treatment of symptomatic stones: TURP (not very effective because most of the stones are peripherally located), or retropubic prostatolithotomy.

CORPORA AMYLACEAE is amorphous debris, always pigmented desqumated epithelium in Prostatic duct and forerunner or Prostatic calculi.

SEXUALLY TRANSMITTED DISEASES
GONOCOCCAL URETHRITIS:
Caused by *Nisseria gonorrhoea,* a gram negative diplococci located within neutrophils. Incubation period is 3-10 days. Presents with urethral discharge and dysuria. Discharge is yellow or brown. Without treatment urethritis persists for 3-7 weeks. A calcium alginate swab is used. Intracellular diplococci are diagnostic (diagnosis is equivocal if diplococci are extracellular or intrcellular but atypical).
Complications: Periurethritis ____→ Abscess / fistula.
|____->Fibrosis / stricture.
Prostatitis, Epididymitis (may lead to testicular atrophy), proctitis, arthritis, tenosynovitis.
Treatment:

Type of infection	**Recommended Regimen**	**Alternative Regimen**
Uncomplicated urethral, cervical or	**Ceftrioxone 125 mg IMI + Doxycycline 100 mg BD for 7 days**	1. Cefixime 400 mg stat 2. 2. Ciproflloxacin 500 mg

rectal infection		stat 3. Ofloxacin 400 stat All regimen followed by: Doxycycline 100 mg BD for 7 days
Epididymitis	Ceftrioxone 125 mg IMI + Doxycycline 100 mg BD for 10 days	Ofloxacin 300 BD for 10 days

NONGONOCOCCAL URETHRITIS:

Commonly caused by ***Clamydia trachomatis*.** Its an obligate intracellular parasite. It has 15 serotypes. Serotype A-C caus hyperendemic trachoma. Serotype D-K cause GU infection, and type L1-L3 cause Lymphogranuloma venerum. Another cause is *ureaplasma urealyticum*

Presentation: Incubation period is 7-21 days, and presents with dysuria and urethral discharge (often scant but may be thick or purulent). Sometimes only complain in urethral itching.

Diagnosis: Diagnosis of NGU requires demonstration of urethritis and exclusion of infection with N. gonorrhgoea. Gram stain of urethral discharge (swab) showing > 4 polymorphonuclear leukocytes / HPF or >15 PMNs in 5 random fields suggests urethritis.

Because C. trachomatis is an intracellular parasite, the best specime is endourethral swab (Dacron-tipped swab is used), and not urethral exudates or urine, taken from 2-4 cm. inside the urethra

Treatment:

Initial Rx of diagnosed urethritis	Doxycycline 100 mg BD for 7 days; Erythromycin base 500 mg QID for 7 days; Erythromycin ethylsuccinate 800 mg QID for 7 days; Sexual partner should be treated with same regimen.
Rx of persistent or recurrent cases	Enquire about the compliance and re-exposure. Confirm urethritis. Rule out T. vaginalis. If no specific cause is found: treat with erythromycin for 14 days.

REITER'S SYNDROME: Consists of urethritis, conjunctivitis, arthritis, and mucocutaneous lesions. Preceding or concurrent infection with C trachomatis is seen in >80% of cases. Increased frequency is seen with HLA-B27 serotype.

TRICHMONIASIS:

It is caused by Trichomonas vaginalis. Most of the male cases of trichomoniasis are asymptomatic. It is treated with metronidazole 2gm stat or 500 mg BD for 7 days.

PRIMARY SYPHILIS:

Causative organism is Treponema pallidum, a spirochete. After an incubation period of 2-4 weeks patient presents with a painless penile sore (Chancre), which begins as a hyperemic or erythematous lesion. It may break down to form a painless, indurated punched out hard lesion. Without treatment, the lesion slowly heals spontaneously.

Lab studies: Spirochete may be seen on dark field examination of the scraping of the base of chancre or by fluorescent antibody test. When dark field examination is not available, a nontreponemal (VDRL, RPR-rapid plasma reagin) or a treponemal test (FTA-ABS: fluorescent trponemal antibody absorbed), microhemagglutination assey for antibody to T. pallidum (MHA-TP) serological tests are used. The serological test may remain negative for 1-3 weeks after the appearance of chancre. Non-treponemal test usually indicate disease activity.

Prevention: Benzathine penicillin G 2.4 mU IM to be given if exposure has occurred.

Treatment: All patients with early syphilis (primary, secondary or latent of <1year duration) should receive 2.4 mU, benzathine penicillin G, IM as single dose.

In documented penicillin allergy. Doxycycline 100 mg BD for 14 days, or tetracycline hydrochloride 500 mg QID for 14 days.

CHANCROID:
It is caused by Haemophilus ducreyi, and it ***is a well established factor for HIV transmission***.
Presentation: first lesion of chancroid is a papule, which appear few days after the exposure. One or more, deep, painful, soft, ulcers with flat ragged erythematous border and extending into the dermis or subcytaneous tissue may apper, with purulent discharge.
Untreated ulcer enlarge, rupture and coalesce with each other. It may cause genital elephantiasis.
Lab finding: Gram stained smear reveals Gr. –ve coccobacilli (50%). Biopsy is also diagnostic.

Treatment:

Specific Rx	Azithromycin 1 gm stat Erythromycin 500 mg QID for 7 days. Ceftrioxone 250 mg intramuscularly stat (HIV testing is recommended initially and at 3 months if initial report is negative).
General Rx	Washing the genitalia frequently with soap and immediately after intercourse.
Rx of complications	If super-infection is present: Penicillin or carbenicillin should be added.

LYMPHOGRANULOMA VANEREUM:
Caused by Chlymadia trachomatis immunotype L1, 2 and L3. A papule or a pustule appears 5-21 days after exposure. It is usually transient and followed by unilateral painful nodes, which become fluctuant. At this stage of bubo formation constitutional symptoms are common. (e.g. chills, fever, headache, joint pains, nausea, and skin rashes). Later on there may be formation of rectal stricture.
Lab findings: Proteins (globulins) are elevated. Culture of Chlamydia from inguinal node aspirate is most specific. Serological tests, like compliment fixation test and microimmunofluorescent test are helpful.
Complications: Rupture of nodes may lead to draining sinuses. Chronic lymphatic obstruction may cause elephantiasis. Rectal stricture is also a late complication.

Treatment:

Specific measures	Doxycyclin is the drug of choice; 100 mg BD for 3 weeks.

GRANULOMA INGINALE:
Infective agent is Calymmatobacterium grnulomatis (related to Klebsiella pneumoniae).
Incubation period is 2-3 momths. It causes chronic infection of the skin and subcutaneous tissue of genitalia, perineum and inguinal region.
It starts with a papule, which forms a firm, indurated nontender ulcer that protrudes above the skin level. Inguinal swelling is pseudobubo (it is subcutaneous ganulomatous process rather than enlarged nodes. If untreated it enlarges or erodes through the skin.
Lab finding: Identification of the Donovan bodies (bipolar staining rods) within the monocytes in crush preparation makes the diagnosis. Giemsa's stain, wright's stain or Leishman's stain can be used. *No reliable culture is available for C. granulomatis.*
Treatment:
Tetracycline 500 mg QID or Septran DS BD till the lesions are healed. Gentamicin and chloremphenicol are also effective.

GENITAL HERPES INFECTION:
Herpes simplex virus is a double stranded DNA virus that may cause persistent or latent infection. Most of the genital herpes is due to type 2 virus (type 1 virus is seen in 10-25% of cases).
50-75% of type 2 virus infections are asymptomatic. The incubation period is 10-21 days. Vesicles grouped on a erythematous base, *not following a neural distribution*, is pathognomic of genital herpes. Lesions are

tender. Mildly tender, non-fixed, bilateral lymphadenopathy is also seen. In 2% of cases, involvement of autonomic nervous system may result in retention.
Lab findings: Isolation of virus by culture is most sensitive test. Tzanck or Papanicolaou smears may be used to demonstrate intra-nuclear inclusion.
Treatment:
Acylovir (acts on viral thiymidine kinase as guanine analogue) 200 mg 5 times per day for 7-10 days.

URINARY BLADDER
ECTOPIA VESICAE
This is due to incomplete development of lower anterior abdominal wall associated with incomplete development of ant. wall of bladder. This is more common in males (4:1). Incidence is 1 in 50,000. The bladder mucosa is exposed and muco - cutaneous junction is well defined. It is often associated with inguinal and/or umbilical hernia. In males there is complete Epispadias. Prostate or seminal vesicles are rudimentary or absent. *Testis is normally developed and present at normal location.*
In females clitoris is cleft and labia majora is separated anteriorly. In both sexes there is separation of pubic symphysis. The exposed mucous memb. may undergo metaplastic changes, with development of Adenocarcinoma.
Tretment Options:
1) Diversion of urine in colon or rectum.
2) Excision of bladder and ileal conduit.
3) Repair consisting of reconstruction of bladder, creating a new symphysis after iliac bone osteotomy and recounstructed urethra is placed behind the pubis.

PSEUDOEXTROPHY: The presence of musculoskeletal defect of extrophy with no major defect in urinary tract.

URINARY RETENTION
ACUTE: In males it is ***commonly caused by BPH***, Urethral stricture, Phimosis or meatal stenosis/ scabbing and rarely by stones. In females, causes are retroverted gravid uterus, Stone or psychological.
On examination bladder lump is present. It is important to examine lower limb reflexes and anal tone to rule out neurogenic bladder. Prostatic/ meatal size must be evaluated.
After excluding the history of trauma (if present get a RGU done before catheterization), retention should be relieved by catheterization. If catheterization fails (usually due to stricture and rarely due to BPH), retention is relieved either by suprapubic puncture cystostomy or suprapubic cystostomy (SPC-Riche's technique).
CHRONIC: Usually it is painless. Overflow incontinence may be present. Neurogenic bladder must be ruled out. In these cases short course of decompression by catheterization must be tried before doing definitive surgery (except in Neuro. bladder).
OTHER CAUSES: Retention may be caused by certain drugs (e.g. Antihistaminic, INH, Anticholenergic, Tricyclic Antidepressants and antihypertensive), post operatively either due to Spinal anaesth., or local muscular spasm.

NEUROGENIC BLADDER:
Lesion Above D-10: (Upper motor neuron bladder). Detrusor contractions are present but ineffective as they are associated with sphincter spasm also. Because of high pressure upper tract show deterioration in function. Later on bladder capacity decreases.
Lesion at D10-L2: Essentially an upper motor neuron bladder but loss of sympathetic afferents and sensory efferent from the bladder.
Lesion at S2-S4: (Lower motor neuron bladder). Sensation is usually intact (T11-12), but bladder contraction is poor. Patient may empty his bladder with abdominal straining. If motor nerves are intact, sphinteric in-coordination is present. LMN bladder is of large capacity and reflux is common. CIC is used to keep the bladder empty.
URODYNAMIC STUDY
FLOW RATE: Normal flow rate from a full bladder is 20-25 ml/sec in males and 25-30 ml/sec in females. A flow rate of <10 is considered evidence of obstruction.

CYSTOMETRY: Performed by artificially simulating bladder filling and emptying while obtaining pressure and other measurements. It is helpful in assessing bladder capacity, accommodation, sensation, contractility, voluntary control, and response to drug.

SPHINCTERIC FUNCTION: Is evaluated by recording electromyographic activity of the voluntary component of the sphincter, or by recording the intraurethtral pressure of the sphincteric unit.

INCONTINANCE

Causes of Incontinence: In males most common cause is outlet obstruction (BPH) and overflow incont. In female most common cause is stress incontinence.

Other causes are discussed in symptomatology.

Treatment: Aim is to keep the patient dry, odourless, decrease skin excoriation, protect from UTI and *Bqck-pressure*. Indwelling catheter is not a good option, if need be then SPC should be done. External sphincteric weekness can be treated by gracilis sling or electrical stimulation.

In lower motor type of bladder intermittent catheterization is helpful. In upper motor (spastic type of bladder) it is important to keep the intra-vesical pressure low by drugs (anti-cholenergics to decrease bladder tone/ anti-adrenergics to lessen sphicteric tone), Sphicterotomy or by urinary diversion.

For stress incontinence Marshall Marchetti (suprapubic approach), where paraurethral tissue is hitched to retropubic ligaments or Edward Williams operation (retropubic approach) is helpful.

TREATMENT OPTIONS

DRUGS	To increase bladder neck strength.: Adrenergic agonist
	To decrease strength of bladder neck: Adrenergic blockers
	Mixed action on bladder neck and CNS: Tricyclic drugs
Intermittent self Catheterization (CIC)	
Device for collection or control	Condom catheter Indwelling catheter Penile clamps
Outlet surgery	Prostatectomy Bladder neck incision (widening) Sphincterotomy Artificial sphincter
Bladder Augmentation	Ileocystoplasty Caecocystoplasty
Urinary diversion	
Bladder neck elevation	Marshall Marchetti op. Edwards Williams' op. Levatorplasty

Nocturnal enuresis: It can be primary or secondary. Usually no organic lesion is found though bladder may be unstable.

Treatment consists of Pharmacotherapy (imipramine) & Behaviour modification (bladder training, responsibility reinforcement, conditioning therapy).

DIVERTICULUM OF THE BLADDER:

The normal intra-vesical pressure at micturation is 35 cm of water but in outlet obstruction pressure as high as 100 cm is seen leading to trabeculation and protusion of bladder mucosa between muscle layers.

TYPES: ***1) Congenital***: Consists of all layers of bladder wall. Usual sit is at the dome, which represent persistent lower part of urachus. This may become a seat of infection or stone.

2) Pulsion diverticulum: Seen in outlet obstruction. Commonest site is near the ureteric orifice, thus may cause ureteric obstruction.

COMPLICATIONS: Recurrent infections, Squamous metaplasia (15%) and even Carcioma, Stone formation in diverticulum and back-pressure changes due to ureteric obstruction.

PRESENTATION: Presenting symptoms are of lower urinary tract obstruction, recurrent infection, stone, hematuria or hydronephrosis.

DIAGNOSIS: Cystoscopy, IVP (to see the condition of the upper tract), MCU and USG.
TREATMENT: If the pouch has a narrow neck, is a seat of infection, stone, malignancy etc. then it requires treatment. Small diverticulum heals only by bladder drainage or relieving the outlet obstruction. Large diverticulum requires excision.

3) Traction diverticulum: A portion of the bladder protruding through the inguinal or femoral hernial orifices forming a wall of hernia (Sliding hernia).

URINARY FISTULAS

CONGENITAL: Ectopia Vesicae, Patent Urachus or in association with imperforate anus
TRAUMATIC: Penetrating wound, injury or avascular necrosis caused by surgery or RT.
VESICOVEGINAL FISTULA: Obstetrical cause (neglected labour), Gynaecological cause (total hysterectomy), Radiotherapeutic cause, malignant infiltration (Ca. Cx)
PRESENTATION: Continuous day and night urinary leak from vagina and skin excoriation. Fistulous opening is more clearly seen from the vaginal side. To differentiate between VVF and Uretero veginal fistula, methylene blue is injected in the bladder a swab is placed in the vagina. Blue coloring of the swab suggests VVF.
INVESTIGATIONS: Cystoscopy, IVP, MCU
TREATMENT: Surgical closure of fistula by abdominal or veginal route (Martius flap: Fat of labia majora is used for interposition after repair.

BLADDER TRAUMA

Bladder trauma is usually seen in blunt injury (15% of pelvic fracture). Iatrogenic injury is seen in Gynaecological operations, hernia repair, TURP or rectal surgery.
When the bladder is full, direct blow results to intraperitoneal bladder injury (20%) – More common in males. Injury associated with pelvic fracture fragments result in extraperitoneal rupture (80%).
First investigation is Cystogram/RGU and it should always be done before attempting to catheterize. Plain X-ray demonstrates pelvic fracture and lower abdominal haziness due to urine or clots. IVP should be done to rule out injuries to kidney or ureter. Cystoscopy is usually not helpful since bleeding and clots obscure visualization.
COMPLICATIONS: Pelvic abscess, Peritonitis, Partial incontinence.
TREATMENT: Extrapritoneal rupture; repair of the rupture (repair is done intravesically), indwelling catheter & SPC. In intraperitoneal rupture repair is done intraperitoneally.

INJURIES TO THE URETHRA

It may be bulbous/ membranous urethra rupture or complete/ incomplete; total/ partial.
***Rupture of bulbous urethra*:** Seen in perineal injuries. Presents with urethral hemorrhage, perineal haematoma and retention of urine. Patient is advised not to pass urine. If voiding has occurred a local swelling may be noted. Perineum is tender with a mass. P/R reveals a normal prostate. RGU is investigation of choice.
Treatment: If no extravasation is noted then, gentle catheterization may be tried. Otherwise a SPC is performed (immediate repair may be tried but the procedure is difficult and incidence of later on stricture is high). In cases of minor leak repeat dye study is performed after 7 days, in extensive injury one should wait for 3 weeks. If extensive extravasation is present then drainage of extravasated urine from perineum should be performed at the first surgery otherwise infection / abscess may follow. Later on open urethroplasty with end to end anastomosis or Internal urethrotomy may be ferpormed.
Injuries to membranous urethra: Commonly seen in association with fracture pelvis. The prostate is displaced superiorly (Due to rupture of puboprostatic ligament) and a hematoma forms at periprostatic and perivesical space.
Most important sign of urethral injury is blood at meatus. Patient presents with urinary retention, suprapubic fullness, perineal hematoma and floating prostate on P/R.
Complications: Stricture, incontinence, impotency.
Treatment: Immediate temporary measure is SPC. Primary repair by rail-roading may be done but chances of stricture formation is very high. A second stage (after 3 months of primary surgery) retrupubic urethroplasty may be performed. In cases of incomplete rupture sndoscopic urethrotomy is curative.

INJURY TO THE PENIS:

Penile fracture may be caused by excessive bending / trauma to the erect penis. **There is rupture of Tunica albugenia**. Presentation is penile pain and hematoma. This may be treated by immediate surgery and repair of tunical laceration with drainage of hematoma.

CYSTITIS

Common causes are 1) Incomplete emptying (e.g. BPH, urethral stricture, phimosis, bladder diverticulum and neurogenic bladder). 2) Stone or foreign body in the bladder. 3) Lowered general resistance e.g. malnutrition.

Infection may reach the bladder by ascending route (commonest organism is E. coli), Descending from kidney, Hematogenous or Lymphogenous (from Tubes, vagina or intestine).

Presenting features are Frequency, dysuria, pain, pyuria and hematuria.

Treatment consists of Culture sensitivity and antibiotics accordingly.

INTERSTITIAL CYSTITIS (Hunner's ulcer or elusive ulcer): This condition is mainly seen in women. It is characterized by Paracystitis and fibrosis of bladder musculature leading to decreased bladder capacity. Inflammation is seen in all layers of bladder wall. Presentation is mainly because of bladder inflammation (Dysuria, hematuria) or due to decreased bladder capacity (Frequency). Pain relieves by act of micturation.

Cystoscopy is diagnostic.

BLADDER NEOPLASM

It is second most common tumor of urinary tract. Average age is 65 years. 85% of the Ca. Bladder are localized. Male : Female ratio is 3:1. Bladder cancer promoters are cigarette smoking, alpha and beta naphthylamine, benzidine, 4-aminobiphenyl, artificial sweeteners and cyclophosphamide.

***Pathology*:** Normal urothelium is composed of 3-7 layers of tr. cell epi.

Papilloma (2%): A fine papillary tumour with a fine fibro-vascular stalk supporting an epithelial layer of normal tr. cell with normal polarity. Papilloma is has a good prognosis.

Transitional Cell Carcinoma: (90%). Commonly appear as exophytic papillary lesion.

CIS is recognized as flat nonpapillary anaplastic epithelium. Urothelium lacks normal polarity and cells have larger nucleoli. It may occur as focal or diffuse independent lesion or may be seen with other exophytic lesion.

Nontransitional cell tumours:

1) Adenocarcinoma: <2% of bladder Tm. Primary adenocarcinoma is preceded by Cystitis glandularis or metaplasia. Primary Adeno Ca. is seen at the floor but those associated with persistent urachus occur at the dome. It is also seen with Extrophy bladder. Overall prognosis is poorer in Adeno Ca. than TCC.
2) Squamous cell carcinoma: 5-10% of all bladder cancer. It is associated with chronic infection, vesical calculi, chronic catheter use or Schistosomiasis. Prognosis is poorer than TCC.
3) Undifferentiated carcinoma: (<2%)
4) Mixed Carcinoma: Combination of transitional, glandular, squamous or undifferentiated pattern. Most are large and infiltrating at the time of diagnosis.

The common metastatic tumour to the bladder include, in order of frequency *melanoma,* lymphoma, stomach, breast, kidney and lung.

Presentation: Hematuria is the most common symptom (85-95%). Irritative voiding symptoms (frequency, urgency and dysuria) may be present. Metastasis may present with bone pain, flank pain from retroperitoneal spread or ureteral obstruction.

Lab Findings:

1) Urinary cytology and flow cytometry: Exfoliated cells from normal and neoplastic epithelium can readily be identified. High grade and infiltrating carcinoma and CIS are easily detected but low grade malignancy may be missed.
2) Cell surface antigen: Blood group and related antigen (ABH, T and Lewis) are carbohydrate and certain structure detected on cell surface of RBC,some epithelial cells and secretion. Invasive and in situ carcinoma and superficial cancer showing progression to higher grade show loss of cell surface antigen.

Imaging: Although the presence of bladder tumour is confirmed by Cystoscopy but spread, extravesical extension and condition of the upper tract is determined by CT scan. USG can be used as a screening

modality. Advantages of MRI over CT are that, contrast is not needed and neurovascular bundle is more clearly delineated.
Cystoscopy: Diagnosis is confirmed by Cystoscopy. Primary resection of the tumour / biopsy can be performed simultaneously.

Treatment options for Bladder Cancer:

STAGE	**INITIAL TREATMENT OPTION**
TIS	Complete TUR + Intravesical BCG
Ta (Single, low grade, non-recurrent)	Complete TUR
Ta (Large, multiple, high grade, recurrent)	TUR + Intravesical Chemo / Immunotherapy
T1	TUR + Intravesical Chemo / Immunotherapy
T2-T4	1.Radical Cystectomy 2.Neoadjuvant chemotherapy+Radical Cystectomy 3. Radical Cystectomy + adjuvant chemotherapy 4. Neoadjuvant chemotherapy + Concomitant CT & RT
Any T, N+, M+	Systemic chemotherapy + Selective Surgery or RT

A: *Intrvesical Chemotherpy:*

1) Mitomycin C: Response rate is 40-80%. Side effects are irritative bladder symptoms and rash on palms and genitalia.
2) Thiotepa: Produces 55% response rate. Side effects are myelosupression.
3) Doxorubicin: Produces response rate of 40%. Systemic side effects are rare but cystitis is not uncommon.
4) BCG: Bacillus Calmette-Guerin is an attenuated strain of *Mycobacterium bovis.* Mucosal ulceration and granuloma formation is common. Main mechanism of action is immunological. BCG is most effective for CIS. Side effects are rare, but dysuria, hemorrhagic cystitis and Systemic infection are known. Systemic infection is treated with INH and R-Cin. Contraindications of intravesical BCG therapy are H/O traumatic catheterization and immuno-compromized patients.

B: *Surgery:*
1) Transurethral resection or laser vaporization:
2) Partial cystectomy: Patients with T1-T3 tumours, localized along the posterior lateral wall or dome are candidates for partial cystectomy. 2cm. tumour free margin should be left. Tumour implantation at wound may be minimized with short course of Radiotherapy (1000 to 1600 rads) or by intravesical chemotherapy, pre-opratively.
3) Radical Cystectomy: This implies removal of Bladder with its peritoneal attachments, prostate and seminal vesicles in malesu and in women removal of uterus, cervix, anterior veginal vault, urethra and ovaries.
4) Radiotherapy: External beam radiotherapy (5000 to 7000 cGy) for infiltrating Ca.
5) Chemotherapy: It is used for systemic control. Single most active agent is cysplatin. Other effective agents are methotrexate, vinblastin, cyclophosphamide and 5FU. Combination regimens are MVAC, CMV, CISCA.

VESICAL STONES
Etiology: Bladder outlet obstruction remains the most common cause of bladder calculi in adults. Crystals are formed in this static urine; therefore, larger calculi develop.
Other etiologic factors are spinal cord injuries, bladder inflammation secondary to external beam radiation or foreign bodies that act as a nidus for stone formation
Clinical: Suprapubic pain, dysuria, intermittency, terminal gross hematuria, frequency, hesitancy, and nocturia. Another common symptom is sudden termination of voiding with some degree of associated pain, initiated by the stone impacting the bladder neck.
WORKUP:

Urinalysis: Bladder calculi can be associated with positive testing for nitrite, leukocyte esterase, and blood. Microscopic crystals usually are consistent with the composition of the stone. Urine culture/sensitivity document and direct treatment of infections.

Urography of the kidneys, ureters, bladder: The initial test of choice remains the plain radiograph (KUB). It demonstrates the presence of radiopaque stones.

Intravenous pyelogram: These tests demonstrate the stone as a filling defect in the bladder.

If the filling defect moves when the patient is repositioned, presence of a stone is highly likely (differential diagnosis includes clot, fungal ball, and papillary urothelial carcinoma on a stalk).

Nonmobile filling defects could be calculi attached to the bladder wall via a stitch or in a diverticulum (differential diagnosis includes urothelial carcinoma, clot, and calculus).

Ultrasonography: Shows a classic hyperechoic object with posterior shadowing, & identifies both radiolucent and radiopaque stones.

Computed tomography & MRI

Cystoscopy remains the most commonly used test to confirm the presence of bladder stones and plan treatment.

TREATMENT

Surgical therapy: Currently, 3 different surgical approaches to this problem exist.

Unlike renal and most ureteral calculi, ESWL has shown little efficacy in most centers. Second approach in adults is transurethral cystolitholapaxy. If indicated at the completion of lithotripsy, transurethral resection of the prostate (TURP) or transurethral incision of the prostate (TUIP) can be accomplished. The third approach, open suprapubic cystostomy to remove the stone(s) intact can be employed with larger and harder stones.

THE MALE URETHRA

MEATAL STENOSIS

External urinary meatus is the narrowest part of male urethra. It may be a seat of congenital stenosis, or become stenosed after infection/scabbing or trauma. Meatus may become pinhole and it may lead to chronic retention/ enuresis/ or back pressure changes.

Intervention is indicated whenever there is symptom, retention or cystoscopy is to be done and it cannot be passed through it. Treatment is meatotomy.

CONGENITAL ANOMALIES OF URETHRA

URETHRAL STTICTURE: Fossa navicularis and membranous urethra are the 2 most common sites MCU and IVP are important investigations. RGU is also helpful in defining the extent of stricture. Urethrocystoscopy should be performed in all the cases and therapeutic internal urethrotomy is performed at the same sitting.

POSTERIOR URETHRAL VALVE: This is most common obstructive urethral lesion in male child. It occurs only male child and is present at the distal prostatic urethra. Presentation is varying degree of obstructive features and failure to thrive.

Lab finding: Azotemia and uremia should be detected and treated.

X-ray: MCU (Micturating custourethragram or voiding cystourethragram) is the best investion. Large amount of residual urine is found at initial catheterization. MCU shows obstruction at posterior urethra and VUR.

USG: Detects large volume bladder with trabaculation, hydroureter and hydronephrosis. It may show dilated posterior urethra. and can be used, in-utero, to detect urethral valves.

Cystoscopy: The valves are difficult to see at cystoscopy, because irrigating fluid sweeps them into open position.

Treatment: Cystoscopic fugulration is the treatment of choice. If in a newborn, Bladder is excessively dilated with complete atony and presence of hydrouretronephrosis, first stage diversion may be done by vesicostomy or uretrostomy.

HYPOSPADIAS:

The urethral meatus opens on the ventral side of the penis just proximal to the tip of the glans penis. Incidence is 1 in 300 cases.

CLASSIFICATION: 1) Glandular: Opens on the proximal glans penis. 2) Coronal: Opens at coronal sulcus. 3) Penile shaft: 4) Penoscrotal: 5) Perineal

PRESENTATAION: Penis has a ventral curvature (Chordee), Prepuce is deficient ventraly and it is hooded on dorsal side. Meatus is usually narrow (requiring meatotomy). Penoscrotal and perineal hypospadis is usually associated with undescended testis.

In perineal hypospadias scrotum is bifid, a buccal mucosa keratotyping should be done for sex determination. IVP is also indidated to detect additional congenital anomalies.

TREATMENT: Age of treatment is just before the child attains school going age (2-3 years). First step is correction of chordee, and exteriorization of distal tract. Later on Prepuce, or penile skin is used to reconstruct distal urethra.

URETHRAL STRICTURE

AETIOLOGY: Congenital, Inflammatory (gonorrheal, TB), Instrumental/ Traumatic (catheter induced, after TURP), Post-operative (prostatectomy, amputation of penis).

POSTGONORRHEAL: May occur at Bulb (70%), penoscrotal junction or in spongy urethra. Patient is generally young and gives history of progressive decrease in caliber of urine. Diagnosis is made by urethrocystoscopy. MCU/RGU helps in determining the length of stricture.Treatment is Internal urethrotomy.

INSTRUMENTAL TREATMENT: Instrumental dilatation can be done with *Gum-elastic bougies, Filiform bougie, Filiform bougie with followers, Lister's metal bougie.*

SURGICAL TREATMENT:

1. *EXTERNAL URETHROTOMY.*
2. *INTERNAL URETHROTOMY.*
3. *URETHROPLASTY:* A: Resection and end to end anastomosis. (Anterior urethral stricture with <2 cm. in size) B: Johanson's urethroplasty: The stricture is layed open in first stage. Then after 3-4 months urethra is reconstructed by adjacent skin. C: For reconstruction of urethra either perineal skin flap (Blandy), or a scrotal tunnel (Turner-Warwick) or an island flap technique can be used (Orandi).

PRIAPISM

Priapism is painful prolonged erection. It is idiopathic in 60% of cases and in remaining 40% it is caused by diseases (*Sickle cell disease*, Leukemia, pelvic tumour & pelvic infection), Penile trauma, Spinal cord tumour or medications.

The corpora cavernosa is tense and rigid while spongiosum is flaccid. There is buildup of highly viscous, poorly oxygenated venous blood, which if continues for days may lead to interstitial edema & fibrosis of corpora cavernosa and impotency.

Treatment: 1) Ketamine hydrochloride IM or IV is effective in 50% of cases. 2) Epidural or spinal anaesthesia can also be used. 3) With the use of large bore needle sludged blood is removed from cavernosa. 4) Intracavernosal irrigation of adrenergin drugs. 5) Creating a shunt between glans and cavernosa by Travenol needle (Winter's technique). 6)Creating a shunt by anastomosing Superficial dorsal vein to cavernosa.(Berry's technique). 7) Other shunts described are, Spongeosum to cavernosa by perineal anastomosis ans sephanous vein to cavernosa.

PEYRONIES DISEASE

This is also called plastic induration of penis and characterized by Painful erection, curvature of penis and poor erection distal to plaque. There is palpable dense fibrous plaque of varying size involving the tunica albugina. Spontaneous remission occur in 50% of cases. In other cases p-aminobenzoic acid powder or vit. E tablets are given. Excision of plaque with dermal graft or tunica veginalis graft is also done.

PHIMOSIS

Phimosis is a condition where foreskin cannot be retracted over the glans. Other than congenital cause, it may be caused by poor local hygiene and chronic infection. Calculi and squamous cell Ca. may develop under the foreskin. Treatment is circumcision.

PARAHIMOSIS

The foreskin once retracted cannot be replaced in the normal position. It is seen after forceful retraction of phimosed prepuce and after catheterization where foreskin is not pulled over the glans. Later on there is

formation of tight constriction ring, which further increases glans edema. Treatment is hylase injection in prepuce to decrease edema then try for reduction. In late stages circumcision should be done.

PENILE CARCINOMA

PREMALIGNANT CUTANEOUS LESION: Cutaneous horn, Leukoplakia, Viral infections like *Condyloma acuminate (caused by HPV and associated with SCC), Bowenoid papulosis, Kaposi's sarcoma (Occur as elevated painful bleeding papule).*

SQUAMOUS CELL CARCINOMA

This constitutes <1% of all malignancy. Incidence is 1-2 / lac. Mean age of presentation is 55-58years. SCC may be exophytic or flat. Metastasis is earlier in flat or ulcerative lesion. Buck's fascia acts as temporary barrier. Earliest metastasis is to the inguinal nodes. The prepuce and glans drains to superficial inginal nodes (superficial to fascia lata), While glans drains to deep inguinal lymph nodes. *Penile carcinoma is most frequent on the glans,* prepuce and coronal sulcus. Diagnosis is made by excisional biopsy. The strongest prognostic indicator for survival is nodal mets.

STAGING: **Jackson's classifiaction**

- Stage I: Tumor confine to glans prepuce or both
- Stage II: Tumour extending to shaft of penis.
- Stage III: Tumour with inguinal metastasis, which is operable.
- Stage IV: Tumours involving adjacent structures or inoperable ing. Mets, or Distant mets.

TREATMENT:

1) Surgery: Options are Circumcision (recurrence is common), ***Partial amputation*** (2 cm. margin should be included), ***Total amputation*** with perineal urethrostomy.
2) Radiation Therapy (6000 rads)

Stage Tis, Ta, T1: Treatment is local surgery and regular follow up for 2 years for inguinal nodes. In cases of glans lesion inguinal block dissection should be done.
Stage T2, T3: Local surgery + Inguinal nodal dissection
Any T + N1-3: Local surgery + Bilateral node dissection.
Any T, any N + M1 or T4: Only palliative measures.

THE TESTIS AND THE SCROTUM

UNDESCENDED TESTIS: The testis is arrested in some part of its descent to scrotum.

ECTOPIC TESTIS: Testis is abnormally placed outside this path.

CRYPTORCHIDISM:

Incidence: Preterm infants-30%. Full-term infants- 3.5%. At 1 years- 0.8%. Adults-0.8%.

Classification*:* Abdominal location, Canalicular (placed in the inguinal canal), Ectopic.

Diagnosis*:* A short course of hCG is used to differentiate between anorchia or nonpalpable testis. High levels of basal gonadotrophins suggests anorchia.

USG is helpful if the testis is in the inguinal canal.

CT Scan and MRI are useful in cases of impalpable testis.

Laparoscopy has now become the investigation of choice. A blind ending testicular vessel signifies that testis is absent. It also helps in deciding about immediate surgery or Clip the testicular vessel (if cord is short), and second stage orchidopexy.

Complications: Malignancy (Seminoma followed by embryonal cell carcinoma are the 2 most common malignancy), More susceptible to trauma, associated inguinal hernia, torsion, Atrophy and infertility.

Cryptorchidism is also seen in association with Klinefilter syndrome, Noonan syndrome and Pader-Wili syndrome.

Tretment: Is Surgical. Testis is brought down to the scrotum and fixed in the dartos pouch, or by narrowing the neck of scrotum or is passed through the scrotal septum (Ombredanne's operation).

TORSION OF THE TESTIS

This is commonly seen in young boy who gives history of sudden severe pain in one of the scrotum and development of edema. Predisposing causes are Inversion of testis (most common), Cryptorchidism, high investment of tunica veginalis. The initiating factor is spasm of cremaster which inserts obliquely in the cord.

- ✓ MC age group 10 - 25 years. Peak in adolescence.

- ✓ Normal fully descended testis is well anchored and so prevents torsion.
- ✓ Torsion Occurs within the space of the tunica vaginalis, which is highly invested, resulting in lack of normal fixation of testis to the scrotal wall.

Predisposing Causes

1) High investment of the tunica vaginalis

Causes the testis to hang within the tunica like a clapper in a bell

Main D/D is Epididymoorchitis. If the scrotum is lifted onto the pubis, pain due to orchitis is relieved but if due to torsion it gets worsened (Prehn's sign). In early stages epididymis may be felt anterior to the testis. Diagnosis is confirmed by coloured Doppler study. Most accurate investigation is 99m Tc pertechnetate scan.

Treatment is immediate exploration derotation and fixation of the testis. Results are good if the surgery is done within 6 hours and orchidectomy if done after 48 hours.

VARICOCELE

Varicocele is dilation of the pampiniform plexus. Left side is more commonly affected. Isolated right sided varicocele, sudden appearance of varicocele or persistence of dilated veins in supine position should be investigated further to role out RCC.

- ✓ Dilated & tortuous veins of pampiniform plexus
- ✓ Marked left sided predominance (90%)
- ✓ These veins drain the testis & the epididymis
- ✓ Merge together and at the deep ring, form 1 or 2 testicular veins
- ✓ (L) Testicular vein empties into (L) renal vein; (R) into the IVC.
- ✓ Drainage of (L) renal vein into the IVC is 8 - 10 cm cranial to the insertion of (R) internal spermatic vein into IVC.
- ✓ Alternative (collateral) venous return - Cremasteric veins which drain mainly into the inferior epigastric.

Etiology

1) MC cause - incomplete valves of the internal spermatic vein
2) Increased venous pressure in the left renal vein ('nutcracker' phenomenon - caused by compression of the lt. renal vein between the aorta and SM A)

Grades

- HI - Large, visible through the scrotal skin
- II - Moderate, easily palpable without valsava
- I - Small, palpable only with valsava Suspicious varicoceles
- Rt. Sided varicoceles - RCC, retroperitoneal tumors
- Rapidly evolving varicocele o Varicocele in elderly
- Varicocele that does not decompress in supine position

Presenting features are pain and infertility. On examination it is felt like a bag of worms.

Indications for surgery

- ✓ Infertility
- ✓ Poor testicular growth in the adolescent
- ✓ Defective sperm count or motility
- ✓ Significant discomfort
- ✓ Recruitment to police or armed forces

Treatment is surgical and consists of ligation of vein by scrotal, low inguinal or high inguinal routes.

Surgical procedures	Recurrence	Post OP Hydrocele
Open inguinal / sub inguinal	15%	3-9%

Laparoscopic	15%	3-9%
Retroperitoneal (Palomas)	10%	7%
Embolization	10-25%	None
Microscopic inguinal / sub inguinal	1-3%	< 1%

FOURNIER'S GANGRENE

Fournier gangrene is a necrotizing fasciitis involving the soft tissues of the male genitalia.

Pathophysiology: Necrosis of the superficial and deep fascial planes, Fibrinoid coagulation of the nutrient arterioles, Polymorphonuclear cell infiltration, Microorganisms identified within the involved tissues. Common causative organisms include: Streptococcal spp, Staphylococcal spp, Enterobacteriaceae spp, Anaerobic organisms & Fungi

Clinical: Fever and lethargy may be present for 2-7 days. Intense genital pain and tenderness that is usually associated with edema with progressive erythema of the overlying skin . Dusky appearance of the overlying skin; subcutaneous crepitance

Obvious gangrene of a portion of the genitalia; purulent drainage from wounds

Investigations

Blood tests

To assess the immunologic stress induced by the infectious process. Blood cultures should be drawn to assess the presence of septicemia.

Plain film radiography

Initial imaging study should be a plain radiograph that may show moderate to large amounts of soft tissue gas or foreign bodies. Demonstration of soft tissue gas or detection of subcutaneous crepitance is an absolute indication for surgical exploration.

Ultrasonography

This can be utilized to detect fluid or gas within the soft tissues. In addition, US can assess the blood flow to the testis if testicular torsion is in the differential diagnosis.

TREATMENT

Medical therapy: Treatment involves the institution of broad-spectrum antibiotics. The antibiotic spectrum should cover Staphylococcus, Streptococcus, the *Enterobacteriaceae* and anaerobes. If initial tissue stains (KOH) show fungi, add Amphotericin B.

Surgical therapy: All necrotic tissue must be excised. The skin should be opened widely to expose the full extent of the underlying fascial and subcutaneous tissue necrosis. Suprapubic cystostomy is utilized when urethral drainage of the bladder is not possible. Appearance of, healthy granulation tissue signifies the time to proceed to reconstruction.

Options for reconstruction

1. Primary closure of the skin, if possible
2. Local skin flap coverage
3. Split thickness skin grafts
4. Muscular flaps, which are used to fill a cavity (eg, ischiorectal space)

HYDROCELE

An accumulation of fluid within the tunica vaginalis

Communicating Hydrocele - (Congenital hydrocele)

- ✓ Due to persistence of processus vaginalis, most resolve during first 2 years of life. Surgery indicated after 2 years (Herniotomy).

Hydrocele of the cord

Segmental closure of the processus, which leaves a loculated hydrocele of the cord that may or may not communicate with the peritoneal cavity

Treatment - Inguinal exploration and high ligation of a patent processus vaginalis at the deep ring or deroofing of an encysted hydrocele

Infantile Hydrocele

Does not necessarily appear in infants

The tunica and processus vaginalis are distended to the inguinal ring but there is no connection.

Hydrocele of the Canal of Nuck

Condition similar to the hydrocele of the cord. Occurs in females

Primary vaginal Hydrocele

MC in middle or later life/ Translucent/ One can get over the swelling/ Painless

Treatment

Small Hydrocele - Minimal dissection techniques

Sharma Jhawar's tech

Window operation

Medium Hydrocele

Jobuylay's procedure (Eversion of sac, Most common)

Large hydrocele

Excision of sac

Lord's operation

Secondary Hydrocele

- ✓ Causes
  - MC - Acute or chronic epididimo - orchitis
  - Testicular tumors
  - Torsion
- ✓ Usually lax and of moderate size
- ✓ Underlying testis is palpable
- ✓ Subsides when the primary lesion resolves

TESTICULAR TUMOUR

99% of the testicular tumour are malignant and constitute 1-2% of malignant tumours of males. Undescended testis is a very important predisposing factor. It is more common on the right side.

TYPES: (Classified into germ cell tumour (Seminoma) & non germ cell tumour)

1: S*eminoma:* (40%), Commonest between 35-40 years. Histologically consists of round cells with clear cytoplasm and acidophilic nucleoli, arranged in sheets. Tumour is firm and smooth. Metastasis occurs through lymphatics to para-aortic lymph nodes. Blood born mets are rare.

2: *Teratoma:* (32%), Arise in rete testis from totipotent stem cells and contains elements of ectoderm, endoderm and mesoderm. Surface is irregular. It has been classified into:

A: Differentiated Teratoma: (1%) It is a true benign tumour consisting of cartilage muscle bone and glandular elements.

B: Tetratocarcinoma (Malignant teratoma intermediate): (30%), Contains some definitely malignant and undifferentiated tissue. Depending on the severity, it has been divided in type A & B.

C: Embryonal carcinoma (Malignant teratoma anaplastic): (15%), Composed of undifferentiated cells of embryonal nature. AFP is always raised. It is a radiosensitive tumour.

D: Choriocarcinoma (Malignant teratome trophoblastic): (1%), Contains syncitial mass. Produces bHCG. Hematogenous spred is very common.

3: *Interstitial cell tumours:* Leydig cell tumour (causes musulanization) and sertoli cell tumour (causes feminazation).

PRESENTATION: Patient presents with a nodule or painless testicular enlargement. 10% of patient may present with pain (epididymitis or hemorrhage). In 10% presentation is due to metastasis (suraclavicular node, cough and dyspnoea, bone pains or limb edema. Gynecomastia (5%) is due to increased bHCG). Secondary hydrocele is seen in 10%.

INVESTIGATIONS:

1: X ray chest.

2: Ultrasonography.

3: Tumour markers:

	Seminoma	Teratoma	Teartocarcinoma	Embryonal	**Choriocarcinoma**
hCG (%)	**7-10%**	25	57	60	**100**

AFP (%)	**0**	38	64	70	**0**

4: CT Scan abdomen.
5: IVP.
6: Lymphangiography.
7: Gallium scan.

STAGING:

Stage I: Lesion in testis only	UICC/ AJCC Classification
Stage II: Nodal involvement below diaphragm only A: < 2 cm in size B: 2 – 5 cm in size C: > 5 cm in size	T1: confined to testis. T2: beyond tunica. T3: Invasion of rete testis or epididymis. T4a: Invasion of cord. T4b: Invasion of scrotum.
Stage III: Nodes above diaphragm	
Stage IV: Pulm. Or Hepatic mets	

The commonest tumour in children is Yolk sac tumour.

TREATMENT:

Seminoma: Orchidectomy through inguinal route followed by:

Stage I, II (A, B +)
↓
Abdominal radiotherapy (2500-3500 rads)
↓
Follow up

Stage II B (+), II C, III
↓
Chemo (BEP)- 4 cycles
↓ ↓
Stable/regress Relapse/growth
↓ ↓
Follow up RPLND
Chemo
RT

THYROID

GROSS ANATOMY

The thyroid extends from the level of the fifth cervical vertebra down to the first thoracic. The gland varies from an H to a U shape and is formed by 2 elongated lateral lobes connected by a median isthmus (with an height of 12-15 mm) overlying the second to fourth tracheal rings. Each lobe is 50-60 mm long. Thyroid weight averages 25-30 g in adults.

Under the middle layer of deep cervical fascia, the thyroid has an inner true capsule. Extensions of this capsule within the substance of the gland form numerous septae, which divide it into lobes and lobules. The lobules are composed of follicles.

Epithelial cells are of 2 types: principal cells (ie, follicular) and parafollicular cells (ie, C, clear, light cells). Principal cells are responsible for formation of the colloid (iodothyroglobulin), whereas parafollicular cells produce the hormone calcitonin, a protein central to calcium homeostasis. Parafollicular cells lie adjacent to the follicles within the basal lamina.

Blood Supply: The thyroid gland has an abundant blood supply with normal flow rate of 5 ml/g/ min. Although the thyroid represents about 0.4% of body weight it accounts for 2% of total blood flow. This abundant blood supply is provided from the four major thyroid arteries. ***The superior pair arise from the external carotid*** and reach the upper poles of the thyroid, where they break into a number of branches and enter the substance of the gland. ***The inferior pair spring from the thyrocervical trunk of the subclavian arteries*** and enter the lower poles from behind. Frequently, a fifth artery, ***the thyreoidea ima, from the arch of the aorta, enters the thyroid in the midline (3%)***. The branching of the large arteries takes place on the surface of the gland, where they form a network. Only after much branching are small arteries sent deep into the gland. These penetrating vessels arborize among the follicles, finally sending a follicular artery to each follicle. This, in turn, breaks up into the rich capillary network surrounding the follicle.

The veins emerge from the interior of the gland and form a plexus of vessels under the capsule. These drain into the internal jugular, the brachiocephalic, and occasionally the anterior jugular veins.

Innervation

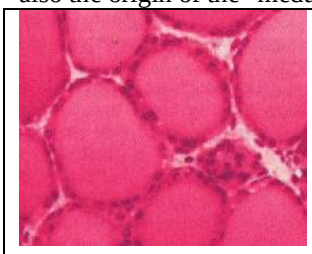
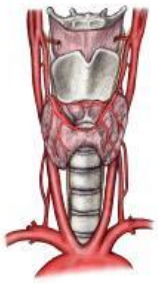
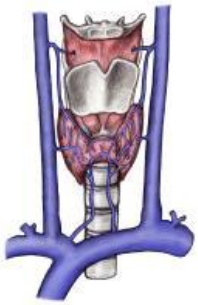
The gland receives fibers from both sympathetic and parasympathetic divisions of the autonomic nervous system. The sympathetic fibers are derived from the cervical ganglia and enter the gland along the blood vessels. The parasympathetic fibers are derived from the vagus and reach the gland by branches of the laryngeal nerves.

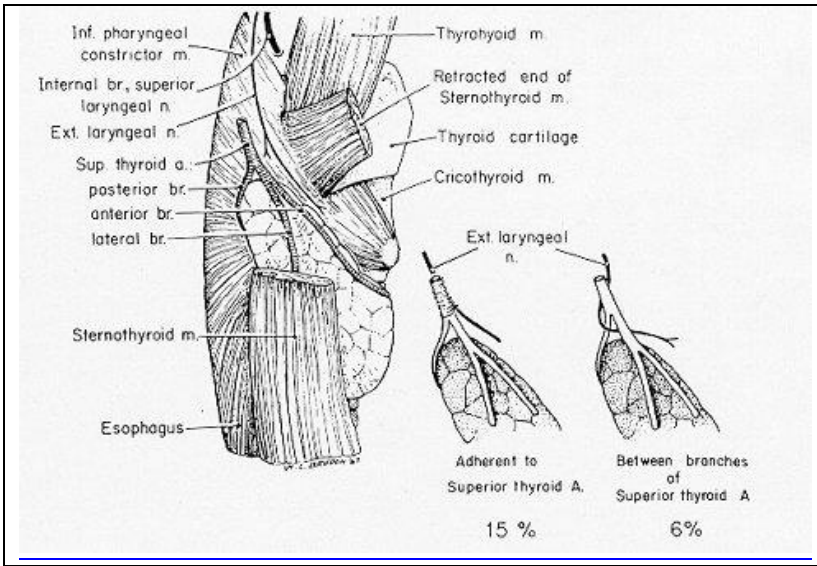
Lymphatics: A rich plexus of lymph vessels is in close approximation to the individual follicles, but no unique role in thyroid function has been assigned to this system.

The Secretory Unit - The Follicle

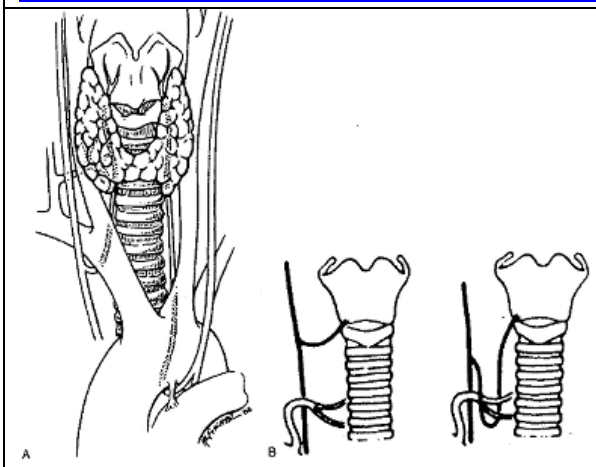
The adult thyroid is composed of follicles, or acini. The cells of the follicles are the makers of hormone; the lumina are the storage depots. The average diameter is 300 microns. Under chronic TSH stimulation such as occurs with iodide deficiency, the height increases, and the term columnar is applied. Such stimulation, which increases colloid resorption, also leads to a reduction in size the follicular lumen. As a result, the height of the epithelium is often inversely proportional to the diameter of the lumen of the follicle.

In addition to the acinar cells, there are individual cells or small groups of cells that are seen not to extend to the follicular lumen and which may appear as clusters between follicles. These light cells, or C-cells, are a distinct category probably derived from the neural crest via the ultimobranchial body. C-cells secrete calcitonin ("thyrocalcitonin") in response to an increase in serum calcium. Calcitonin acts primarily by suppressing resorption of calcium from bone and therefore lowers plasma free Ca++ levels. The C-cells are also the origin of the "medullary" thyroid cancers.

		
Histology of the thyroid gland shows the structural units of the gland and follicles, consisting of a layer of simple epithelium enclosing a colloid-filled cavity.	Distribution of thyroid arteries with associated laryngeal nerve, anterior view.	Distribution of thyroid veins



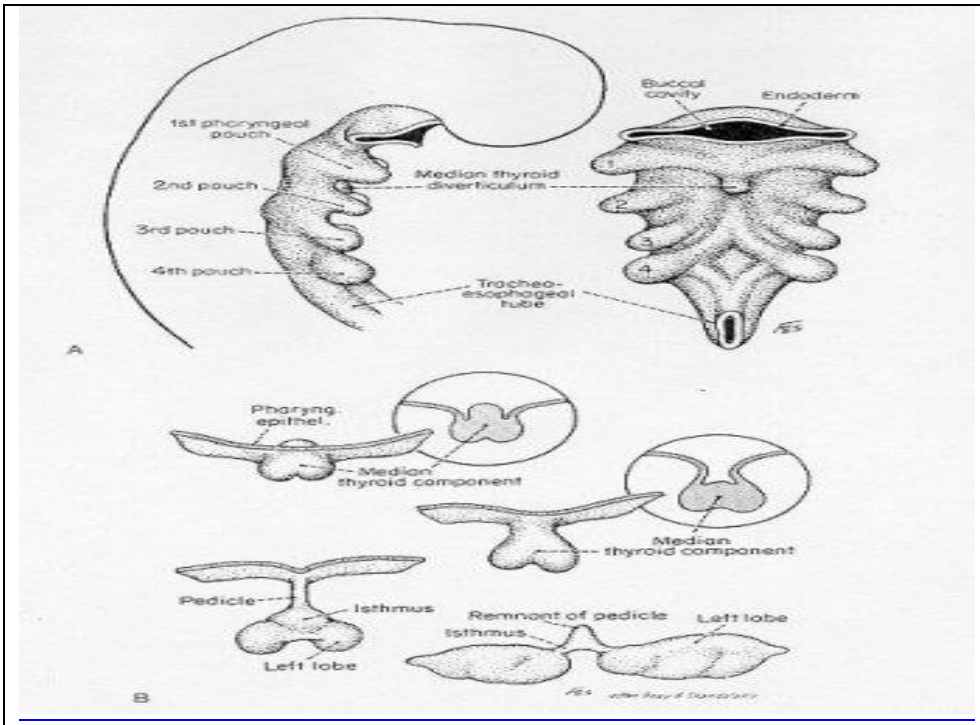
Proximity of the external branch of the superior laryngeal nerve to the superior thyroid vessels is clearly shown.



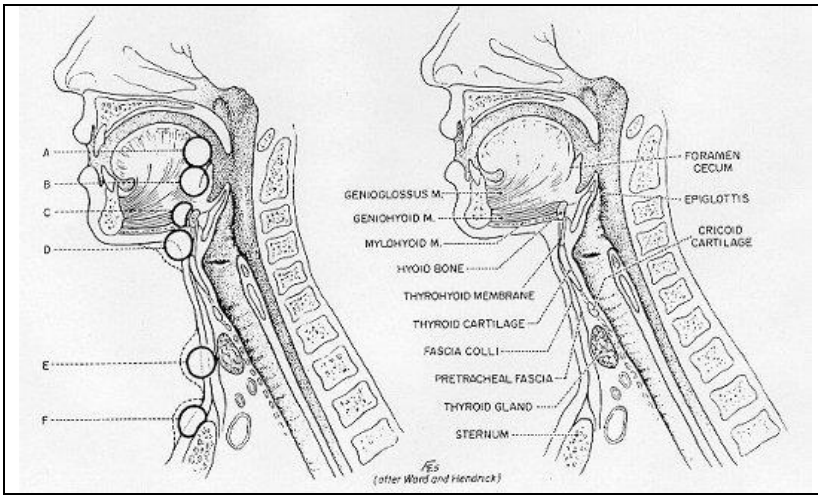
A) Normal anatomy of the recurrent laryngeal nerve. Note that on the right side the recurrent laryngeal nerve hooks around behind the subclavian artery, while on the left side this nerve passes around behind the aortic arch before ascending in the neck. B) When there is a vascular anomaly of the right subclavian artery, the recurrent laryngeal nerve no longer "recurs" around this artery but proceeds from the vagus nerve in a more transverse direction to the larynx. In such a situation, the nerve is much more likely to be damaged during operation unless care is taken to visualize its course in the neck.

THYROID ANOMALIES

The thyroid is embryologically an offshoot of the primitive alimentary tract, from which it later becomes separated. A median anlage arises from the pharyngeal floor in the region of the foramen cecum of the tongue. The main body of the thyroid descends into the neck from this origin and is joined by a pair of lateral components originating from the ultimobranchial bodies of the fourth and fifth branchial pouches. It is from these lateral components that the C cells enter the thyroid lobes.



The median thyroid anlage may rarely fail to develop, causing athyreosis, that is, absence of the thyroid gland, or it may differentiate in locations other than the isthmus and lateral lobes. The most common of these is as the pyramidal lobe, which has been reported in as many as 80 percent of patients. Other variations involving the median thyroid anlage represent an arrest in the usual descent of part or all of the thyroid-forming material. These variations include the development of a lingual thyroid, suprahyoid and infrahyoid thyroid tissue, and persistence of the thyroglossal duct as a sinus tract or cyst.



Developmental abnormalities of the thyroid gland in humans. Location of thyroglossal cysts. (A). In front of the foramen cecum. (B). At the foramen cecum. (C). Suprahyoid. (D). Infrahyoid. (E). Area of the thyroid gland. (F). Suprasternal.

A thyroglossal duct cyst is the most common of the clinically important anomalies of thyroid development.

Thyroglossal Duct Cysts

Both cysts and sinus tracts can develop along the course of the thyroglossal duct. Normally the thyroglossal duct becomes obliterated early in embryonic life, but occasionally it may persist as a cyst or a draining sinus tract. Cysts often become infected and may rupture spontaneously. Removal of the cyst or sinus

usually requires excision of the central part of the hyoid bone and dissection of the tract to the base of the tongue (the Sistrunk operation), if recurrence is to be minimized.

Lateral Aberrant Thyroid Rests

True lateral aberrant thyroid tissue is rare since the lateral anlages are normally incorporated into the expanding lateral lobes of the median thyroid anlage. Thus, a mass of thyroid in the lateral neck, which used to be called lateral aberrant thyroid, almost always represents well-differentiated, metastatic thyroid cancer within a cervical lymph node rather than an embryonic rest. It should be treated as a metastasis from a papillary thyroid cancer.

Thyroid Physiology and Function Testing

TRH/TSH

Thyroid Releasing Hormone ***(TRH) is a peptide hormone*** synthesized in the hypothalamus and passed through the hypophyseal portal venous system. ***In the anterior pituitary, TRH stimulates synthesis and release of Thyrotropin (TSH).*** TSH in turn acts on the thyroid glad to stimulate thyroid gland growth and thyroid hormone synthesis***. The release of TSH is inhibited at the pituitary by elevated circulating levels of thyroxine (T4) that is ccnverted by intrapituitary type II deiodinase to triidothyronine (T3).***

Thyroid Hormone Synthesis

There are 4 basic steps involved in thyroid hormone synthesis which include:

- **Iodide trapping** - iodide is actively transported into the thyroid gland
- **Organification** - the ***enzyme thyroid peroxidase using tyrosine and iodide as substrates, forms inactive iodotyrosines: 3--monoiodotyrosine (MIT) and 3,5-Diidotyrosine (DIT)***. ***The tyrosine residues MIT and DIT are incorporated into the soluble protein thyroglobulin which is stored as colloid in the follicular lumen***.
- **Coupling** - *the enzyme thyroid peroxidase catalyzed the coupling of MIT + DIT to form triidothyronine (T3) and the coupling of DIT + DIT to form thyroxine (T4).*
- **Proteolysis or release** - *proteolysis of thyroglobulin produces the active hormones T4 and T3, which are then secreted into the blood.*

Approximately 90% of the released thyroid hormone is in the form of T4, and 10% in the form of T3. The great majority of T3 (80-90%) is produced by the peripheral conversion of T4. The metabolic activity of thyroid hormone is determined by the amount of free T3 and free ***T4. Thyroxine (T4) is very highly protein bound to thyroid binding globulin in plasma (99.95% bound, about 0.05% free)***. Therefore, a rough estimate of the total T4 can be approximated by the amount of bound thyroxine.

Tri-iodothyronine (T3) is produced by the peripheral deiodination of T4. ***T3 is much more potent than T4. About 99.5% of circulating T3 is bound (0.5% free)***. ***Reverse T3 is also produced by the deiodination of T4, but only when there is excess circulating thyroid hormone (hyperthyroid states). Reverse T3 is not physiologically active, so its production helps to prevent excess catabolism***. Levels of reverse T3 are also elevated during periods of severe illness. Elevated levels of reverse T3 are also present during *periods of severe nonthyroidal illness such as sepsis, congestive heart failure or burns.* Since reverse T3 is not physiologically active, the conversion of T4 to T3 instead of the more active T3 is a metabolic compensation to prevent excess catabolism.

Thyroid Hormone Transport/TBG

More than 99% of thyroid hormone is carried in circulation firmly bound to three major binding proteins: ***thyroid binding globulin (TBG), transthyretin (TTR, formerly called thyroxine binding pre-albumin - TBPA) and albumin***. TBG is the primary serum binding protein because of its higher affinity for T4. *Under normal conditions, 75% of T4 is bound to TBG, 10-15% to TTR, and 5-15% to albumin*. ***When bound, T4 is not physiologically active but provides a storage pool of thyroid hormone which can last 2-3 months (mean half-life of T4=6.7 days in adults***).

TBG is synthesized by the liver under the influence of estrogen. An increase in TBG concentration in response to higher estrogen levels may result in higher measured total T4 concentration. However, the amount of free T4 concentration remains constant and the patient remains clinically euthyroid.

Conditions associated with increased levels of TBG:

- Estrogen Effects - pregnancy, oral contraceptives
- Infectious Hepatitis
- Biliary Cirrhosis
- Genetic Determination

In contrast, factors that cause a decrease in TBG concentration or lower affinity for T4 binding to TBG may result in low measured total T4 concentration without affecting free T4 levels.

Conditions associated with decreased binding of T4 by TBG:

- Androgens and Anabolic Steroids
- Large doses of Glucocorticoids
- Nephrotic Syndrome
- Major Systemic Nonthyroidal Illness
- Active Acromegaly
- Chronic Liver Disease
- Drugs - dilantin, tegretol
- Genetic Determination

Thyroid Function Tests

Total serum thyroxine (T4)

This includes both bound and free T4 concentration. Under most conditions with normal TBG concentrations, the total T4 level reflects the functional state of the thyroid. However, changes in binding proteins as described above, may alter total T4 concentration without affecting the unbound free T4 level. In these circumstances, calculating the free thyroxine index (FT4I) or obtaining a direct free T4 or free T3 level would provide a more accurate estimate of the patients true thyroid status.

T3 resin uptake (T3RU)

This test has been renamed ***thyroid hormone binding index (THBI) or thyroid hormone binding ratio (THBR),*** although most clinicians are still more familiar with the use of the term T3RU. It is important not to confuse T3RU with the serum total T3 by radioimmunoassay (total T3-RIA) that measures the total serum triidothyronine (T3) concentration. ***The T3 Resin uptake test measures the amount of unsaturated binding sites on the thyroid hormone transport proteins***. A proportion of the labeled T3 will bind to available sites on the serum TBG; any excess will bind to the resin. ***Resin uptake is inversely proportional to the number of vacant binding sites, and therefore inversely proportional to the total TBG.***

In thyrotoxicosis, there are fewer vacant binding sites available on thyroxine binding globulin due to the high circulating levels of thyroid hormone. This means less radioactive T3 will be able to bind to TBG and more will bind to the resin. *Hence, resin uptake is higher in hyperthyroid patients than it is in normals. The converse is true in hypothyroid states. In high TBG states, like pregnancy or estrogen therapy, the T3RU will be low. However the physiologically active free thyroxine level will still be normal***.**

Free thyroxine Index (FT4I)

FT4I is a reflection of the amount of free hormone (free T4) in most situations. It is a calculated value and corrects for changes in TBG concentrations by using the following formula:

- ***FTI = (Total T4) X (T3 Resin Uptake / T 3RU control).***

Mean normal T3RU for the particular assay (i.e. ***normal range 25-35% mean normal is 30%)***

With extreme changes in TBG concentrations, acute medical illness, heparin therapy or low protein states secondary to nephrotic syndrome, the FT4I may not accurately reflect the amount of free T4 concentrations.

Free T4 and T3

More direct methods are now available for measuring free T4 and T3 levels. These tests have replaced the FT4I and FT3I in many centers. In reality, most methods of measuring "free T4" provide only indirect estimates of true levels of circulating free hormone and its accuracy may be affected by severe TBG changes or alterations in binding protein affinity. The gold standard for obtaining a true free T4 concentration is by direct equilibrium dialysis but is limited by cost and availability.

TSH

The development of new sensitive ***immunoradiometric (IRMA) assays*** to measure serum thyroid hormone (TSH, thyrotropin) has been a valuable tool in the diagnosis and management of thyroid diseases. ***The expected normal range for TSH is 0.5-5.0 mU/L. Older insensitive TSH-RIA assays could only measure concentrations as low as 0.5 mU/L.*** With the new sensitive TSH assays, TSH concentrations as low as 0.001 mU/L. With the new sensitive TSH assays, TSH concentrations as low as 0.001 mU/L can be detected.

Measuring the serum TSH has become the screen test of choice for thyroid disease. Primary hypothyroidism produces elevated TSH levels whereas patients with primary hyperthyroidism (i.e. Graves) should have undetectable TSH values. This relationship is true only in individuals with an intact hypothalamic-pituitary-thyroid axis. Patients who present with a normal or detectable TSH level and elevated thyroid hormone concentrations require further evaluation to exclude central causes of hyperthyroidism.

TRH test

The administration of thyrotropin releasing hormone (TRH) causes a rise in TSH concentration in normal subjects (TSH = 2-30 MU/L.) An exaggerated response occurs in primary hypothyroid subjects (TSH often > 30 mU/L, depending on the baseline TSH elevation.) Hyperthyroid patients have a mild or absent TSH response (TSH < 2 m U/L) since the suppressed TSH cannot be stimulated by exogenous TRH. The introduction of sensitive TSH assays that can detect low suppressed TSH levels, identifying patients with primary hyperthyroidism, has virtually made the TRH stimulation test obsolete.

Iodine

Plasma iodine in the form of iodide is concentrated (trapped) in the thyroid cells by an energy requiring active transport mechanism where it is incorporated into T3 (triiodothyronine) and T4 (thyroxine) via organification (Therefore, iodine measures both trapping and organification by the thyroid gland). These active hormones are stored in follicles as thyroglobulin.

The normal distribution of iodine, and therefore its radiotracer isotopes, is in the thyroid, salivary glands, gastric mucosa, small and large bowel, urinary bladder, liver, and breast (esp. during lactation; see below). Iodine undergoes both renal (up to 75% in 24 hours) and GI excretion.

The normal daily dietary intake of iodine is about 500 ug. The amount of iodine in a typical uptake dose (10 uCi) is about 8 nanograms. This is significantly less than the amount of iodine in I.V. contrast- which, assuming a 40% content of iodine, contains about 40 grams of iodine in 100 ml.

Iodine Deficiency Goiter

Iodine deficiency goiters are the result of chronic TSH stimulation. Patients have elevated TSH levels and low serum T4 (due to lack of iodine for hormone synthesis). RAIU is increased due to the glands need for iodine.

Jod-Basedow phenomenon ***(iodine induced hyperthyroidism): Refers to the excessive amounts of T4 synthesized and released in an iodine deficient patient upon resumption of dietary iodine intake or administration of IV contrast. It is most commonly observed in patients over the age of 50 years with long-standing MNG***. It can also occur in patients taking iodine containing medications such as SSKI drops or amiodarone.

Fetal and Neonatal Thyroid Function

Iodine and Technetium both cross the placenta and will be concentrated in the fetal thyroid. The fetal thyroid does not concentrate iodine during the first 12 weeks of gestation; beyond this point, iodine uptake increases progressively until term. There is probably only minimal transfer of maternal TSH, T4 and T3 across the placenta. However, ***Iodine, Thionamides, and TRH can cross the placenta without difficulty***.

Following delivery there is an abrupt increase in serum TSH and thyroid uptake of iodine is elevated from 10 hours to 2 days post-delivery. TSH levels and uptake return to normal levels within a few days. Both Iodine and Technetium are secreted in the breast milk of lactating women, so nursing should be delayed for 48-72 hours following Tc99m, and for 2-3 weeks following I-131 imaging- essentially this translates to discontinuance of breast feeding. We recommend that women who are breast feeding permanently discontinue breast feeding if they are to undergo I-131 therapy.

Goitre

- Goitre is a non-specific term describing enlargement of the thyroid gland

- Does not imply the presence of any specific pathology
- Goitres can be either diffuse or multi-nodular

Causes of diffuse goitres

- Simple goiter: Patient euthyroid
  - Due to compensatory hypertrophy resulting from
    - Iodine deficient diet
    - Congenital enzyme defect in thyroxine synthesis
    - Increased physiological demands
- Smooth toxic goiter: Patient hyperthyroid (= Graves disease)
- Other smooth goitres
  - Thyroiditis
  - Lymphoma
  - Thyroid amyloidosis

Causes of multinodular goitres

- Usually a simple goitre that has progressed to nodularity

Examination	**Function**	**Causes**
Diffuse goitre	Euthyroid	Physiological goitre or autoimmune thyroiditis
Diffuse goitre	Hyperthyroid	Primary hyperthyroidism
Multinodular goitre	Euthyroid	Multinodular goitre
Multinodular goitre	Hyperthyroid	Toxic nodular goitre (rare)
Solitary nodule	Euthyroid	Thyroid cyst or tumour
Solitary nodule	Hyperthyroid	Functioning adenoma

GOITER

The normal adult thyroid gland weighs 10-25 g and has 2 lobes connected by an isthmus. Nearly 50% of thyroid glands exhibit a pyramidal lobe arising from the. A goiter is an enlarged thyroid gland, and it may be diffuse or nodular.

Pathophysiology: The thyroid gland is controlled by thyrotropin (TSH), secreted from the pituitary gland, which, in turn, is influenced by the thyrotropin-releasing hormone (TRH) from the hypothalamus. A deficiency in thyroid hormone synthesis or intake leads to increased TSH production. Increased TSH causes increased cellularity and hyperplasia of the thyroid gland in an attempt to normalize thyroid hormone levels. If this process is sustained, a goiter is established. Causes of thyroid hormone deficiency include inborn errors of thyroid hormone synthesis, iodine deficiency, and goitrogens.

Goiter may result from a number of TSH receptor agonists. TSH receptor stimulators include TSH receptor antibodies, pituitary resistance to thyroid hormone, adenomas of the hypothalamus or pituitary gland, and tumors producing hCG

Sex: The female-to-male ratio is 4:1.

CLINICAL: Incidental swelling in the neck or compression causing dysphagia, dyspnea, stridor, plethora or hoarseness. Pain due to hemorrhage, inflammation, necrosis, or malignant transformation. Signs and symptoms of hyperthyroidism or hypothyroidism

- The pyramidal lobe often is enlarged in Graves disease.
- A firm rubbery thyroid gland suggests Hashimoto thyroiditis, and a hard thyroid gland suggests malignancy or Reidel struma.
- Multiple nodules may suggest a multinodular goiter or Hashimoto thyroiditis. A solitary hard nodule suggests malignancy, whereas a solitary firm nodule may be a thyroid cyst.
- ***Diffuse thyroid tenderness suggests subacute thyroiditis***, and local thyroid tenderness suggests intranodal hemorrhage or necrosis.
- Cervical lymph glands are palpated for signs of metastatic thyroid cancer.
- Auscultation of a soft bruit over the inferior thyroidal artery may be preresnt in a toxic goiter.
- Goiters are described in a variety of ways, including the following:

  - Toxic goiter: A goiter that is associated with hyperthyroidism is described as a toxic goiter. Examples of toxic goiters include diffuse toxic goiter (Graves disease), toxic multinodular goiter, and toxic adenoma (Plummer disease.)
  - Nontoxic goiter: A goiter without hyperthyroidism or hypothyroidism is described as a nontoxic goiter. It may be diffuse or multinodular, but a diffuse goiter often evolves into a nodular goiter. Examination of the thyroid may not reveal small or posterior nodules. Examples of nontoxic goiters include chronic lymphocytic thyroiditis (Hashimoto disease), goiter identified in early Graves disease, endemic goiter, sporadic goiter, congenital goiter, and physiologic goiter that occurs during puberty.
- The **Pemberton maneuver** raises a goiter into the thoracic inlet by having the patient elevate the arms. This may cause shortness of breath, stridor, or distention of neck veins.

Causes: The different etiologic mechanisms that can cause a goiter include the following:

- Iodine deficiency
- Autoimmune thyroiditis: Hashimoto or postpartum thyroiditis
- Excess iodine (Wolff-Chaikoff effect) or lithium ingestion, which decrease release of thyroid hormone
- Goitrogens
- Stimulation of TSH receptors by TSH from pituitary tumors, pituitary thyroid hormone resistance, gonadotropins, and/or thyroid-stimulating immunoglobulins
- Inborn errors of metabolism causing defects in biosynthesis of thyroid hormones
- Exposure to radiation
- Deposition diseases
- Thyroid hormone resistance
- Subacute thyroiditis (de Quervain thyroiditis)
- Silent thyroiditis
- Riedel thyroiditis
- Infectious agents
  - Acute suppurative: bacterial
  - Chronic: mycobacteria, fungal, and parasitic
- Granulomatous disease
- Thyroid malignancy

Lab Studies:

- ***Initial screening should include TSH***. Further laboratory testing is based on presentation and results of screening studies and may include thyroid antibodies (antithyroid peroxidase formerly the antimicrosomal antibodies and antithyroglobulin), thyroglobulin, sedimentation rate and calcitonin in a high risk individual for medullary carcinoma of the thyroid.

Imaging Studies:

Ultrasound: Localize nodules for ultrasound-guided biopsy.

Roentgenography

- Roentgenography is used to visualize calcifications within a goiter and tracheal deviation by retrosternal goiter.

Spirometry: useful in determining the functional significance of compressive goiters.

Perchlorate discharge test is used in individuals with inborn errors of thyroid hormone synthesis.

Histologic Findings: Simple nontoxic goiters show hyperplasia, colloid accumulation, and nodularity. Nodular hyperplasia is commonly seen in multinodular goiter. Cytologic findings include benign appearing follicular cells, abundant colloid, macrophages, and, sometimes, Hürthle cells. Inflammatory disorders of the thyroid, such as chronic lymphocytic (Hashimoto) thyroiditis, contain a mixed population of lymphocytes mixed with benign appearing follicular cells. Malignant nodules may be follicular cell in origin, ie, papillary (most common), follicular, Hürthle cell, or anaplastic. They also may be from parafollicular cells, medullary carcinoma or lymphoma, or other categories.

TREATMENT

Medical Care:

- The size of a benign euthyroid goiter may be reduced with levothyroxine suppressive therapy. The patient is monitored to keep serum TSH in a low but detectable range to avoid hyperthyroidism, cardiac arrhythmias and osteoporosis. Treatment of hypothyroidism or hyperthyroidism often reduces the size of a goiter.
- Thyroid hormone replacement is often required following surgical and radiation treatment of a goiter.
- Medical therapy of autonomous nodules with thyroid hormone is not indicated.

Surgical Care: Surgery is reserved for the following situations:

- Large goiters with compression
- Malignancy
- When other forms of therapy are not practical or ineffective

Partial thyroidectomy may be used as a first-line procedure for patients with a high probability of cancer. It is reserved mostly if the result of a fine-needle aspiration is suspicious or if the patient/physician prefers it.
Total thyroidectomy is performed for malignant goiters.

Diffuse Toxic Goiter

Diffuse toxic goiter is the major manifestation of Graves disease. Other features are ophthalmopathy, dermopathy, and acropachy.

Pathophysiology: Graves disease is an autoimmune disease caused by the presence of thyroid-stimulating immunoglobulins (TSIs) in the plasma. TSIs are antibodies to the thyroid-stimulating hormone (TSH) receptor, ie, thyrotrophin receptor antibody (TRAb). Two types of these antibodies exist, the thyroid-stimulating antibody (TSAb) and the TSH-binding inhibitor (TBI). TRAb constitutes immunoglobulins of diverse potential and clinical expression.

More than one antibody can be present in the blood of a patient. TSIs stimulate TSH receptors and cause excessive secretion of thyroxine (T4) and triiodothyronine (T3). Grossly, the thyroid gland in Graves disease is diffusely enlarged, soft, and vascular. Histologic section reveals stromal hypertrophy and hyperplasia.

Sex: The female-to-male ratio ranges from 5:1 to 10:1.

CLINICAL

The typical manifestations include the following:
Nervousness, Sweating, Heat intolerance, Palpitations, Fatigue, Weight loss, Menstrual irregularities, Muscle weakness (proximal muscles)

Physical: Signs found on physical examination include the following:
Diffuse goiter (97% of young patients), CNS - Nervousness, emotional lability, and fine tremor of hands, Cardiovascular - Tachycardia, atrial fibrillation, wide pulse pressure, Gastrointestinal - Gastrointestinal hypermotility, Muscle - Proximal muscle weakness, muscle atrophy, hyperreflexia, Skin - Warm, moist, smooth skin; onycholysis; fine hair; hair loss; excessive sweat, Metabolic - Weight loss and occasionally weight gain if increased appetite leads to food intake that exceeds the hypermetabolic requirements, ***Signs specific to Graves disease*** –

- Diffuse symmetrical thyroid enlargement
- Infiltrative ophthalmopathy - Occurs in 20-40% of cases; often bilateral, but unilateral in 5-14% of cases
- Lid lag with upper lid retraction and stare (Lid lag alone can be observed in any thyrotoxic state as a result of increased adrenergic tone of levator palpebrae.)
- Dermopathy and acropachy - pretibial myxedema rash or patch (might be nodular or polypoid, typically nonpitting, and can be accompanied by digital clubbing

Lab Studies:

Total T4

- Level elevated above 12.5 mg/dL (normal range [N] = 4.5-10.9) is sensitive with low specificity. Drugs that may alter T4 laboratory results include anabolic steroids, androgens, estrogens, heparin, iodine, phenytoin, rifampin, salicylates, and thyroxine/triiodothyronine.

Free T4

- Free T4 is one of the most common tests performed because of the limitation of total T4, particularly in patients taking medication that affects TBG levels.

T3 - The level is elevated above 200 ng/mL (N = 60-181;). This is a total T3 assay that frequently is replaced by free T3 (N = 2.2-4.0). T3 should be measured in cases with T4 levels that fall within the reference range (T3 thyrotoxicosis).

Radioactive iodine uptake, most commonly performed 24 hours after administration of radioactive iodine

- ***Radioactive iodine uptake (RIU) is high in Graves disease, high or normal in toxic multinodular goiter, and low in thyroiditis.***

Imaging Studies:

- Thyroid scan using radioiodine (ie, I-123) - Diffuse in Graves disease, focal in toxic nodule (This study is not needed if the diagnosis of Graves thyrotoxicosis is well established by clinical criteria and very high RIU.)

Histologic Findings: Grossly, the thyroid gland in Graves disease is diffusely enlarged. Histology section reveals stromal hypertrophy and lymphocytic infiltration.

TREATMENT

Medical Care: Three therapeutic options are available for patients with Graves disease—(1) radioactive iodine, (2) antithyroid drugs, and (3) subtotal thyroidectomy

Antithyroid drugs

- Antithyroid drugs are reversible, effective in most patients, and generally safe. It is recommended treatment for patients who cannot use radioactive iodine.
- Four to 8 weeks may be required for the patient to become euthyroid, and the medication often is used for 1-2 years.

Radioiodine (I-131)

- ***Radioiodine is the agent of choice because it is selectively taken up by the thyroid gland.***
- The usual dose is 5-6 microcurie (mCi), which releases 7000-10,000 rads (70-100 grays [Gy]) to the thyroid cells.
- ***Radioiodine is contraindicated in pregnancy and used with caution in women of childbearing age.***
- Radioiodine must not be used in a patient with thyroid storm/crisis until medications have brought the crisis under control.
- Its latent period lasts about 3 weeks to 3 months. Thus, beta-blockers are used adjunctively to suppress symptoms. Risk of hypothyroidism is another concern.
- Hypothyroidism occurs in more than 50% of patients during the first year and occurs in 2-3% each year thereafter.
- Risk of worsening ophthalmopathy can be reduced by pretreatment with glucocorticoid 2 weeks before administration of radioiodine.

Pregnancy

- Propylthiouracil is the drug of choice for patients who are pregnant. A lower dosage is recommended (< 100 mg tid) and should be withdrawn before delivery.

Surgical Care: Surgery is recommended for patients who refuse radioiodine therapy and for whom medication is not appropriate. ***Subtotal thyroidectomy is performed under general anesthesia. About 5-7 g of thyroid tissue is left behind***.

The risks include the following:

Hemorrhage (0-1.3%), Injury to recurrent laryngeal nerve (0-4.5%), Hypocalcemia (0-0.6%), Recurrent hyperthyroidism (1.3-17.8%), Hypothyroidism (21% at 1 y; as high as 36.3% at 5 y)

Preoperative preparation involves the use of iodine for about 10 days prior to surgery to make the goiter less vascular, which reduces the risk of precipitating thyroid crisis. Propranolol is administered for at least 48 hours before surgery. The patient must be clinically controlled and have a heart rate less than 100 beats per minute. Propylthiouracil (PTU) or methimazole also may be used to prepare the patient for surgery.

Hypothyroidism

Hypothyroidism results from failure to maintain adequate tissue levels of thyroid hormone. Hypothyroidism is divided into primary hypothyroidism, failure of the thyroid gland to produce hormones; secondary hypothyroidism where the thyroid gland is normal and the pituitary fails to secrete adequate thyrotropin (TSH); and tertiary hypothyroidism, failure to secrete thyrotropin releasing-hormone (TRH).

Cretinism refers to congenital hypothyroidism, and myxedema coma refers to the most severe form of hypothyroidism..

CLINICAL

Frequently found symptoms include the following:

Fatigue, Loss of energy, Muscle and/or joint pain or weakness in extremities, Lethargy, Sleepiness, Depression, Emotional lability, Forgetfulness, impaired memory, Inability to concentrate, Mental impairment, Blurred vision, Decreased hearing, Fullness in the throat, Cold intolerance, Dry skin, Hair loss, Hoarseness, Decreased perspiration, Weight gain, Decreased appetite, Constipation, Menstrual disturbances, Impaired fertility, Arthralgias, Paresthesia and nerve entrapment syndromes.

Symptoms more specific to Hashimoto's thyroiditis include the following:

Feeling of fullness in the throat, Painless thyroid enlargement, Exhaustion, Neck pain, sore throat, Low-grade fever, Subacute thyroiditis

Signs include the following:

Hypothermia, Weight gain, Dull facial expression, Coarse facial features, Periorbital puffiness, Slow movements, Slow speech, Hoarseness, Macroglossia, Goiter, Bradycardia, Pericardial effusion, Decreased systolic blood pressure, Increased systolic / diastolic pressure, Pallor, Loss of scalp, axillary and/or pubic hair, Neurologic: (Hyporeflexia with delayed relaxation phase, ataxia, other gait disturbances), Coarse and brittle hair, Dry skin, Nonpitting edema (myxedema), Pitting edema of the lower extremities, Abdominal distension, Jaundice, Constipation.

- Medical conditions associated with hypothyroidism include anemia, dilutional hyponatremia, and hyperlipidemia.
- Additional signs specific to different causes of hypothyroidism, such as diffuse or nodular goiter or pituitary tumor, can occur.

Causes: The 2 most common are autoimmune thyroid disease and previous treatment of hyperthyroidism.

- ***The most frequent cause of acquired hypothyroidism is autoimmune thyroiditis (Hashimoto disease).***
- Use of radioactive iodine for Graves disease and nontoxic goiter.
- A transient form of hypothyroidism can occur in the postpartum period or result from subacute thyroiditis or silent thyroiditis.

Lab Studies:

The sensitive TSH assay is the most useful test to screen for and confirm the diagnosis of hypothyroidism. Additional tests of free T4, total T4, T3 resin uptake, thyroid autoantibodies (antimicrosomal or antithyroid peroxidase [anti-TPO]), and antithyroglobulin (anti-Tg) may be helpful to determine the etiology.

A free T4 test is recommended over a total T4 test.

The TSH is not useful in patients with pituitary or hypo thalamic failure and secondary hypothyroidism. In these patients the TSH will be low in the face of low free T4 and low free T3. Since isolated pituitary loss of TSH is very rare, there will usually be other signs and symptoms to support the diagnosis of pituitary failure and secondary hypothyroidism.

Imaging Studies:

Radioactive iodine uptake (RAIU) and thyroid scanning can aid in assessing the anatomy of and function of the thyroid. In addition, scanning may identify cold or hot nodules. Nevertheless, RAIU and scans are not useful in hypothyroidism because these tests require some level of endogenous function in the hypofunctioning gland to provide information.

Ultrasound of the neck and thyroid can be used to detect nodules and infiltrative disease.

TREATMENT

Medical Care: Treatment consists of replacing the deficient hormone with synthetic T4, T3, or desiccated thyroid extracts. Low doses are used initially, 50 mcg of T4 or 0.5 grain (gr) (30 milligrains [mgr]) of desiccated thyroid. The dose can be increased every 1-2 month by 25-50 mcg of T4 or 0.5 gr of desiccated thyroid based on clinical response and laboratory values documenting normalization of TSH (in primary

hypothyroidism). End-points in treatment are clinical improvement, normalization of T4 and T3, or TSH in the normal range (in primary hypothyroidism).
Surgical Care: Surgery is needed rarely in hypothyroid patients and is more common in treatment of hyperthyroidism. It is indicated for huge goiters that compromise tracheoesophageal function.

THYROIDITIS
The broad category of thyroiditis includes the following inflammatory diseases of the thyroid gland:
(1) **Acute suppurative thyroiditis,** which is due to bacterial infection. Most cases of acute thyroiditis involve the left lobe and are associated with both a developmental abnormality of thyroid migration and persistence of a pyriform sinus from the pharynx to the thyroid capsule. The usual organisms responsible are *Staphylococcus aureus*, *Streptococcus hemolyticus*, and *Pneumococcus*. Other aerobic or anaerobic bacteria also may be involved. Patients with acute thyroiditis generally maintain normal thyroid function.
(2) **Subacute thyroiditis**, which results from a viral infection of the gland e.g. mumps, measles, influenza, infectious mononucleosis, adenoviral or Coxsackievirus infections etc. ***The disease is more common in individuals with the HLA-Bw35 antigen.*** Patients with subacute thyroiditis may be hyperthyroid for a brief time but usually regain normal thyroid function. ***Subacute disease includes granulomatous (painful or de Quervain thyroiditis) and lymphocytic (painless) thyroiditis. Neck tenderness and swelling may occur.*** Occasionally, the initial symptoms are those of hyperthyroidism. Systemic symptoms such as weakness, fatigue, malaise, and fever are usually low-grade.
(3) **Chronic thyroiditis** which is usually autoimmune in nature is the most common in childhood. Because chronic thyroiditis in children usually is due to an autoimmune process, it is HLA-associated, similar to other autoimmune endocrine diseases. In histologic disease picture ***lymphocytic thyroid infiltration is the hallmark***. Follicular thyroid cells may be small or hyperplastic. The degree of fibrosis also varies considerably among patients. ***Autoantibodies to thyroid peroxidase and, frequently, autoantibodies to thyroglobulin are present in the blood.*** The disease is also more common in type 1 diabetes and children with Down or Turner syndromes. Patients with autoimmune thyroiditis frequently become hypothyroid and require life-long treatment. The male-to-female ratio for autoimmune thyroiditis is 1: in adults and 1:2 for children. The specific alleles vary between the atrophic and goitrous forms of the disease.
Chronic autoimmune thyroiditis is observed in the following 3 patterns:

- A patient with a goiter that is usually diffuse and nontender (Hashimoto's): The thyroid gland is frequently 2-3 times its normal size and may be larger. The patient, parent, or physician may discover the goiter.
- A patient with symptoms of hypothyroidism (Atrophic)
- A patient has symptoms of hyperthyroidism

Antithyroid peroxidase (antithyrocellular, antimicrosomal) antibody levels elevated above the normal range are the most sensitive indicator of thyroid autoimmunity
Radioactive iodine thyroid scanning test is unnecessary for chronic thyroiditis because the results can be misleading and may show increased uptake consistent with Graves disease, a multinodular goiter, or a hypofunctioning or hyperfunctioning nodule.

THYROID CANCER

- Most common endocrine tumour.
- F>M
- Prevalence of thyroid cancer in solitary and multinodular goiter is 10-20%.
- After radiation 30% of thyroid nodule are malignant.

PATHOLOGY:

- Most malignancies are epithelial in origin and are carcinomas.
- Diagnosis of malignancy depends on vascular and capsular invasion rather than on histological appearance.

CLASSIFICATION:
I: Well Differentiated
1: Papillary/ mixed papillary – follicular.
A: Good prognosis variants.

Micropapillary
Encapsulated.
Solid.
Follicular.
B: Poor prognosis variants.
Tall cells.
Columnar.
Diffuse sclerosing.
Insular.
2: Follicular:
Hurthle cell.

II: Carcinoma of C cell: Medullary.
III: Undifferentiated / Anaplastic.
IV: Others: Sarcoma/ lymphoma/ Mets.

- It is important to examine junction of carcinoma with the surrounding tissue to determine capsular invasion.
- Multifocality is seen in 80% of papillary carcinoma.
- Lymph node metastasis I not a poor prognostic sign in most of the thyroid carcinomas. It is poor prognostic in medullary thyroid carcinoma.

PAPILLARY CARCINOMA: 75%

- Peak onset ages 30 through 50
- Females more common than males by 3 to 1 ratio
- Prognosis directly related to tumor size [less than 1.5 cm good prognosis]
- Accounts for 85% of thyroid cancers due to radiation exposure
- Spread to lymph nodes of the neck present in more than 50% of cases
- Distant spread (to lungs or bones) is very uncommon
- Overall cure rate very high (near 100% for small lesions in young patients)
- Characterized by infiltrative pattern, multicentricity and regional node spread.
- Nuclear membrane has ground glass appearance (Orphan Annie appearance).
- Mixed follicular and papillary variant is classified as papillary type.
- Even if occult papillary cancer metastasize to local nodes, prognosis is still excellent. Extrathyroid extension and distant metastasis worsens the prognosis.

FOLLICULAR CARCINOMA:

- Peak onset ages 40 through 60
- Females more common than males by 3 to 1 ratio
- Prognosis directly related to tumor size [less than 1.0 cm good prognosis]
- Rarely associated with radiation exposure
- Spread to lymph nodes is uncommon (~10%)
- Invasion into vascular structures (veins and arteries) within the thyroid gland is common
- Distant spread (to lungs or bones) is uncommon, but more common than with papillary cancer
- Overall cure rate high (near 95% for small lesions in young patients), decreases with advanced age
- Follicular adenoma and carcinoma have same uniform pattern. Detection of papilla/ Orphan Annie nucleus/ Psammoma bodies are not consistent with follicular carcinoma.
- Distinction of carcinoma and adenoma is based on capsular and vascular invasion, thus its differentiation is not possible by FNAC.
- Good prognostic features are: Small size (< 4cm), persons younger than 50 yrs, localized tumours without marked vascular invasion.
- Hurthle cell: It is derived from follicular cells.
- Hurthle cell neoplasm is composed of sheets of cells.
- Chances of Hurthle cell adenoma having malignancy is 1.5-2.5%.

MEDULLARY THYROID CARCINOMA: 5%

- It can be associated with other endocrine tumors – MEN II A and B
- F> M. (except for inherited cancers). Commonest in 5^{th} – 6^{th} decades.
- Regional metastases (spread to neck lymph nodes) occurs early in the disease
- Spread to distant organs (metastasis) occurs late and can be to the liver, bone, brain, and adrenal medulla
- Not associated with radiation exposure
- Usually originates in the upper central lobe of the thyroid
- Poor prognostic factors include age >50, male, distant spread (metastases), and when seen in patients with other endocrine tumors due to MEN II-B syndrome.
- Residual disease (following surgery) or recurrence can be detected by measuring calcitonin (a hormone that should be measured every 4 months for the first few years and then every 6 months for ever).
- 20% of patients acquire this through autosomal dominant inherited pattern.
- Germ line abnormality of chromosome 10 (pericentrometric region) is related to 3 different familial pattern (MEN II a, MEN II b, and non MEN medullayr carcinoma).
- MTC is screened by Pantagastin stimulated or calcium stimulated plasma level of calcitonin.
- Metastasis is through lymphatics and blood vessels.
- Prognosis is worse in: Older patients, MEN II b, large tumour size, Lymph node mets and distant metastasis.

ANAPLASTIC CARCINOMA: $\leq$ 5% OF ALL MALIGNANCIES.

- Peak onset age 65 and older
- Very rare in young patients
- Males more common than females by 2 to 1 ratio
- Typically presents as rapidly growing neck mass
- Can occur many years after radiation exposure
- Spread to lymph nodes of the neck present in more than 90% of cases
- Distant spread (to lungs or bones) is very common even when first diagnosed
- Overall cure rate very low
- Typically requires a very aggressive treatment plan with surgery, radiation and sometimes even chemotherapy.
- **Often requires the patient to get a tracheostomy to maintain their airway.**
- All tumours of anaplastic type is placed in type IV.
- Prognosis is poor with median survival of 7 months.

ETIOLOGY:

1: Radiation: Increases risk of papillary carcinoma.
Risk is dose dependent.
Risk is linear from 300 to 1200 cGy. > 1200 cGy risk declines.
Risk factors includes: Sex (F>M), Age (Younger the patients at the time of exposure greater the risk).
2: Iodine: Follicular carcinoma is more common in iodine deficient goitrous area and papillary carcinoam is more common in areas of iodinated salts or high iodine diet.
3: Goitres: Prolonged exposure of thyroid gland to TSH stimulation causes high rate of thyroid malignancy.
4: familial: Pericentromere region of chromosome 10 associated with MEN II a, MEN II b and familial MTC.
5: Oncogenes: Mutation of 3 RAS genes (K-Ras, H-Ras and N-Ras) have been identified in many human tumours.

DIGNOSIS:

LabTest:

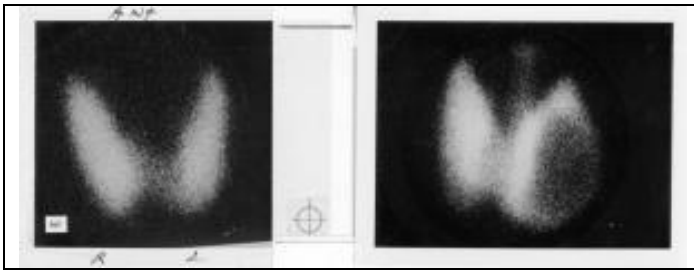
- Most patients of malignant thyroid nodule are euthyroid.
- If the patient has elevated T3 and T4 with low TSH then thyroid scan is indicated to determine hot, warm or cold nodule.
- Serum level of thyroglobulin may be used as tumour markers for well defferentiated carcinoma (its level is normal or low in anaplastic and medullary tumours) and nodal disease of thyroid secondary to previous neck irradiation.

Thyroid gland suppression:

Thyroid nodule can be suppressed by administering exogenous thyroid hormones. Suppression can be used for a small nodule with benign appearance. For malignant cytology, surgery without suppression is done. For unchanged or increasing nodule during suppression repeat cytology and excision should be done.

Radionuclide Imaging:

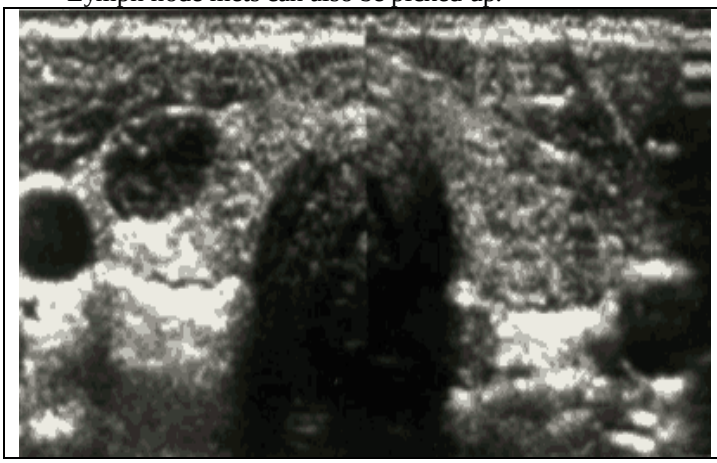
- I 123 does not have the high Beta emission of I 131 Beta emission useful therapeutically, it does not help in diagnostic information and adds to patient's radiation dose.
- I 131 uptake study is indicated for metastatic work up.
- Roughly a thyroid nodule is cold in 85% warm in10% and cold in 5.5%.
- Cold nodule is more likely to be malignant (10 – 20%) than warm (1.5%) or hot (0.2%) nodule.
- MTC recurrence of metastasis is imaged by using Thallium 99m Tc scintigraphy (Thallium is taken up by both thyroid and MTC while Tc is taken up only by thyroid). A substraction scan gives the picture.



Scintiscans of thyroid. The scan on the left is normal. A typical scan of a "cold" thyroid nodule failing to accumulate iodide isotope is shown on the right. Incidentally, a pyramidal lobe is also seen on this scan, which might suggest the presence of Hashimoto's Thyroiditis.

Ultrasound:

- It classifies nodules as solid, mixed or cystic lesions. 20% of solid, 12% of mixed and 7% of cystic lesions are malignant.
- USG can not differentiate between a malignant from a benign lesions (Halo sign: a thin sonolucent rim commonly seen in benign lesion is also found in well differentiated carcinoma).
- Lymph node mets can also be picked up.

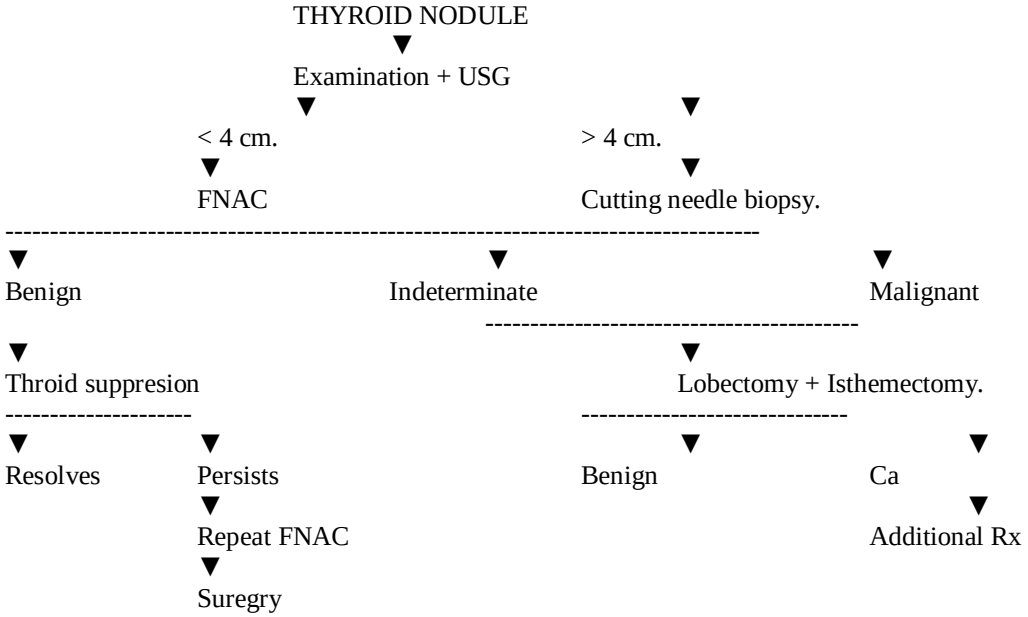


Ultrasooigraphic examination by transverse image of the thyroid containing a solid nodule in the right lobe and a homogeneous appearance of the left lobe. The structure peripheral to the nodule is the internal jugular vein

Biopsy: FNAC is most valuable aid in diagnosis.

- FNAC can not differentiate between follicular neoplasm from adenoma.
- For a larger lesion where there is concern about lymphoma or anaplastic carcinoma, is better assisted by cutting needle biopsy. A lymphoma in FNAC may give diagnosis of thyroiditis.

STANDARD WORKUP:



TREATMENT:

Thyroid nodule: Surgical approach.

Thyroid lobectomy with isthemectomy is the procedure of choice.

Well differentiated carcinoma:

- Subtotal resection is done for lesions < 1cm and age < 45.
- Near total resection is done for lesions that are large and in older patients
- Total thyroidectomy is done for bilateral tumours or multifocal tumours or tumour where I 131 is facilitated
- Indications for total thyroidectomy are: Large lesions > 2 cms, Older patients and poor prognosis variants of follocular.
- Most of the Hurthle cell nodulesare benign and only lobectomy is required. For pathologically proved Hurthle cell cancer total or near total thyroidectomy is done.

POST OPERATIVE:

- For well differentiated carcinoma, exogenous thyroid hormone to suppress TSH level can decrease the recurrence rate of radiation induced thyroid cancer.
- Post op ablative dose of I 131(30 mCi) is given in older patients (age> 45), Multiple lesions, locally invasive tumours, size > 2.5 cm and patients with local or distant mets.

MEDULLARY CARCINOMA THYROID.

- Treatment is total thyroidectomy with central node dissection.

ANAPLASTIC THYROID CANCER:

- It has poorer prognosis.
- It tumour is unresectable larger cutting needle biopsy is done to confirm the diagnosis. Radiotherapy alone is not useful so combination of RT (5760 rads) and Doxorubicin (as radiosensitizer) is used.

Malignant Lymphomas: < 5% of primary thyroid neoplasms

- lymphomas usually appear as rapidly enlarging masses and local symptoms are common. Many patients note pain, hoarseness, dysphagia, and dyspnea or stridor.

- The mean age at occurrence is 62 years.
- Two to three times more common in women than in men.
- The co-occurrence of pathologic lymphocytic thyroiditis has ranged from 30 to 87%.
- The clinical appearance must be carefully considered in accepting a diagnosis by fine needle aspiration of thyroiditis only or thyroiditis with lymphoma. An excisional or large needle biopsy may be necessary to make the correct diagnosis.
- The majority of thyroid lymphomas are diffuse, large-cell lymphomas (formerly classified as diffuse histiocytic or reticulum cell lymphomas), diffuse mixed small and large cell lymphomas (formerly called diffuse mixed lymphocytic-histiocytic), or diffuse small cleaved-cell lymphomas (formerly classified as diffuse poorly differentiated lymphocytic).

Metastatic Carcinomas to the Thyroid

Melanomas, breast tumors, pulmonary tumors, gastric, pancreatic, and intestinal carcinomas, renal carcinomas, lymphomas, carcinomas of the cervix, and tumors of the head and neck may metastasize to the thyroid.

COMPLICATIONS OF THYROIDECTOMY

Seven complications classically have been associated with thyroidectomy: (1) hypothyroidism. (2) thyroid storm, which is related to the patient's thyrotoxicosis. (3) wound infection. (4) wound hemorrhage with hematoma formation. (5) recurrent laryngeal nerve injury. (6) hypoparathyroidism. And (7) tracheomalacia.

Hypothyroidism

Following total or near-total thyroidectomy patients must take thyroid hormone replacement for life or they will suffer severe symptoms and signs of myxedema (including tiredness, weakness, depression, psychosis, mental retardation, coma and even death). Following lobectomy for benign conditions many patients are treated with l-thyroxine therapy as well for two reasons – to keep thyroid function normal and also since a low TSH level is thought to prevent the recurrence of other benign thyroid masses.

Thyroid Storm

Thyroid storm occurs in patients with preexisting thyrotoxicosis who either have not been treated at all or have been treated incompletely. In the past, before adequate preparation with antithyroid drugs, surgical treatment was the most common precipitating factor.

When thyroid storm is related to surgical treatment, the manifestations usually develop during the operative procedure or in the recovery room. The patient becomes markedly *hyperthermic, with profuse sweating and tachycardia. Nausea, vomiting, and abdominal pain are common*. Initial tremor and restlessness may progress to delirium with eventual coma.

Treatment is directed toward inhibiting the production of thyroid hormone and antagonizing the effects of thyroid hormone (Table). Sodium or potassium iodide or ipodate should be administered intravenously after an antithyroid drug, PTU (preferably) or methimazole has been started. Oxygen should be given, and glucose may be administered intravenously as therapy for the hypermetabolic state. Fluid and electrolytes must be maintained in view of the losses. Propranolol is given to antagonize b-adrenergic effects. Large doses of propranolol may be needed in toxic patients to control tachycardia, for thyroid storm has been reported to occur postoperatively in patients receiving 40 mg propranolol every 6 hours preoperatively. In severe cases, cortisol is administered to eliminate the possibility of a relative adrenal cortical insufficiency state and to suppress T4 to T3 conversion.

Treatment of Thyroid Storm	
Treatment	Dose or Description
Propranolol	60-80 mg q6h PO, or 1-3 mg IV, slowly, q4h
Hydrocortisone	100-500 mg IV ql2h
Sodium iodide or	I g in 1 L of saline ql2h
SSKIa	5 drops tid PO
Lugol's solution	5 drops tid PO
Ipodate	0.5 g PO daily or 3.0 g PO every 2-3 days
Supportive measures	Mild sedation, fluid replacement, oxygen, vitamins, cooling, and antibiotics, as needed

Propylthiouracil or	100-200 mg q4h PO
Methimazole	10-20 mg q4h PO
Abbreviation tz SSKI, saturated solution Or potassium iodide.	

Wound Infection

An infection in the wound is not common and occurs less frequently than 1 percent. Treatment requires antibiotics for cellulitis and drainage for an infected seroma or hematoma.

Wound Hemorrhage

Wound hemorrhage is a problem of the early postoperative period, usually within the first 12 hours. Hemorrhage in the neck is a significant problem since a small amount of blood that forms a hematoma deep to the strap muscles might be sufficient to obstruct the airway and result in respiratory death. The patients are rarely in shock. The initial manifestations are swelling of the neck and bulging of the wound; these conditions demand immediate attention. *Treatment consists of opening the incision, evacuating the clot, and securing the bleeding vessel*.

Recurrent Laryngeal Nerve Injury

Damage to the recurrent laryngeal nerve can be unilateral or bilateral and temporary or permanent. Injury occurs more commonly when thyroidectomy is being performed for malignant disease. Total thyroidectomy results in a greater incidence of recurrent laryngeal nerve injuries than does a lesser procedure. *A unilateral recurrent laryngeal nerve injury produces a loss of abduction of the ipsilateral vocal cord, which assumes a median or paramedian position. This injury is usually suggested by a huskiness or hoarseness of the speaking voice,* but with the passage of time the flaccidity is often replaced by spasticity. If the injury is related to trauma but the nerve is not divided, function should return usually within 3 to 6 months and invariably within 9 months.

Bilateral recurrent nerve injury is much more serious than unilateral injury. Many patients require immediate tracheostomy.

Asymptomatic paralysis of a vocal cord does not require correction. If the airway is adequate, no attempts to perform corrective procedures upon the paralyzed cord or cords are usually undertaken until 6 to 12 months have elapsed from the time of injury in order to permit spontaneous return of cord function.

Injury to the external branch of the superior laryngeal nerve results in a limitation of the force of projection of one's voice and impairs a singer's high tones.

Hypoparathyroidism

Overt manifestations of hypocalcemia occur in a minority of patients after thyroidectomy. This syndrome is usually temporary and is related to dissection in the region of the parathyroid glands. To prevent permanent hypoparathyroidism, it is probably necessary to leave only one gland in situ with an adequate blood supply or to autotransplant one parathyroid gland successfully.

The clinical manifestations of hypoparathyroidism usually occur within the first few days after operation and almost invariably within the first week. The initial symptoms are *circumoral numbness, tingling, and intense anxiety. The Chvostek sign appears early, followed by Trousseau's sign and carpopedal spasm*. As the disease progresses, muscle cramps and frank tetany develop. The greatest danger is from convulsions and respiratory stridor, which can occur with severe hypocalcemia and have occasionally resulted in hypoxia and even death, especially in children. Prolonged hypoparathyroidism may cause cataracts, convulsive episodes, and psychoses.

The diagnostic findings consist of reduced serum calcium and increased serum phosphorus levels. The serum concentration of parathyroid hormone is low or absent.

Tracheomalacia

Tracheomalacia, a softening of the tracheal rings due to pressure necrosis of the cartilaginous tracheal rings from a large goiter. If it is present, dangerous consequences can result after removal of the thyroid, for collapse or narrowing of the trachea would occur with inspiration, resulting in respiratory embarrassment. Although tracheal resection may be performed in some cases, the treatment of choice for this complication

is endotracheal intubation. Usually this procedure leads to fixation of the trachea, and with time the endotracheal tube can be removed. In severe cases a tracheostomy is necessary.

PARATHYROID GLANDS

- Usually, 4 parathyroid glands are situated posterior to the thyroid gland.
- A small number of patients have 3, 5, or occasionally, more glands (10-15%).
- The inferior glands are derived from the third pharyngeal pouch.
- The superior glands are derived from the fourth pharyngeal pouch.

The parathyroid glands secrete **parathyroid hormone** (**PTH**) a polypeptide of 84 amino acids. ***PTH increases the concentration of Ca^{2+} in the blood*** in three ways.

- Release of Ca^{2+} from the huge reservoir in the bones. (99% of the calcium in the body is incorporated in our bones.)
- Reabsorption of Ca^{2+} from the fluid in the tubules in the kidneys
- Absorption of Ca^{2+} from the contents of the intestine (this action is mediated by **calcitriol**, the active form of **vitamin D**.)

PTH also regulates the level of phosphate. PTH reduces the efficiency for phosphate resorption in the proximal tubules causing a drop in the phosphate concentration.

Control of the Parathyroids: the calcium receptor

The cells of the parathyroid glands have surface G-protein-coupled receptors that bind Ca^{2+}. Binding of Ca^{2+} to this receptor **depresses** the secretion of PTH and thus leads to a lowering of the concentration of Ca^{2+} in the blood.

2 classes of inherited disorders involving mutant genes encoding the Ca^{2+} receptor occur:

loss-of-function mutations with the mutant receptor always "off". Patients with this disorder have high levels of Ca^{2+} in their blood and excrete small amounts of Ca^{2+} in their urine. This causes **hyper**parathyroidism.

gain-of-function mutations with the mutant receptor always "on" (as though it had bound Ca^{2+}). People with this disorder have low levels of Ca^{2+} in their blood and excrete large amounts of Ca^{2+} in their urine. This causes **hypo**parathyroidism.

PRIMARY HYPERPARATHYROIDISM

overproduction of PTH resulting in abnormal calcium homeostasis.

Etiology

In approximately 85% of cases it is caused by a single adenoma.

In 15% of cases, multiple glands are involved (either multiple adenomas or hyperplasia).

Rarely, primary hyperparathyroidism is caused by parathyroid carcinoma (<1%).

Familial cases can occur as part of

- Multiple endocrine neoplasia syndromes (MEN 1 or MEN 2a),
- Hyperparathyroid-jaw tumor (HPT-JT) syndrome,
- Familial isolated hyperparathyroidism (FIHPT).
- Familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism

Pathophysiology

Chronic excessive resorption of calcium from bone caused can result in osteopenia.

In severe cases, this may result in osteitis fibrosa cystica, which is characterized by subperiosteal resorption of the distal phalanges, tapering of the distal clavicles, salt-and-pepper appearance of the skull, and brown tumors of the long bones.

Chronically increased excretion of calcium in the urine can cause renal stones.

Clinical presentation

At least one half of patients with hyperparathyroidism are asymptomatic.

"Painful bones (and tenderness), renal stones (nephrolithiasis), abdominal groans (abdominal pain), and psychic moans (changes in mental status)."

Renal: Thirst/ Polydipsia/ Polyuria

Gastrointestinal: Abdominal distress/ Constipation/ Vomiting/ Anorexia/ Weight loss

Skeletal and neuromuscular: Bone pain/ tenderness, muscle fatigue, weakness/ Spontaneous fractures

Mental: Anxiety/ Depression/ Psychosis/ Apathy/ Fatigue

Common Symptoms are bone pain, pathologic fractures, and nephrolithiasis.

Symptoms related to hypercalcemia may include muscle weakness, volume depletion, polyuria and polydipsia, neuropsychiatric symptoms, peptic ulcer, and pancreatitis.

Differential diagnosis

The causes of hypercalcemia that result in a concomitantly elevated PTH level are

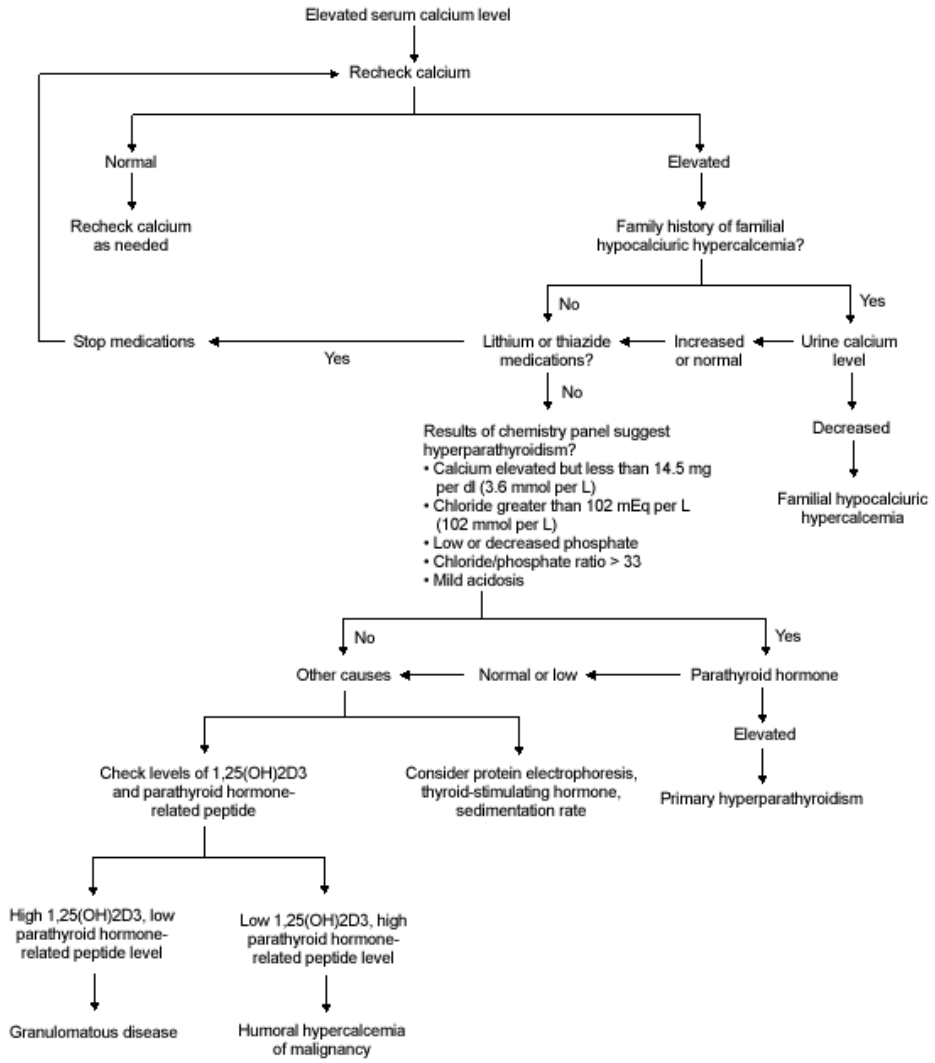
- familial benign (hypocalciuric) hypercalcemia (FHH)
- lithium-induced hypercalcemia, and
- Tertiary hyperparathyroidism.

A subset of patients has calcium levels within the reference range with elevated PTH, which is called ***normocalcemic hyperparathyroidism***. Then all potential causes of secondary hyperparathyroidism (eg, low calcium intake, GI disorders, renal insufficiency, vitamin D deficiency, hypercalciuria of renal origin) should be excluded.

Secondary and tertiary hyperparathyroidism are typically diagnosed on the basis of their clinical context.

Cancer-induced hypercalcemia is usually associated with a low PTH level but possibly a high PTH-related peptide level.

Workup:



Algorithm for diagnostic evaluation of hypercalcemia. ($1,25(OH)_2D_3$=1,25-dihydroxyvitamin D_3)

Laboratory studies

Total serum calcium and albumin levels or ionized calcium levels should be measured. ***Hypercalcemia should be documented on more than one occasion before a diagnostic workup is undertaken.***

Ratio of chloride to phosphate greater than 33 is suggestive of hyperparathyroidism.

Testing of the intact PTH level is the core of the diagnosis. An elevated intact PTH level with elevated ionized serum calcium level is diagnostic of primary hyperparathyroidism.

Imaging studies

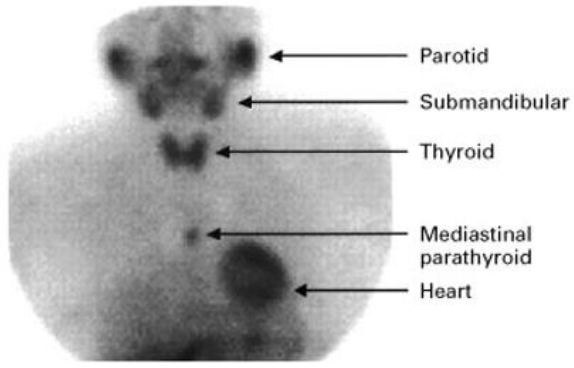
In recurrent or persistent hyperparathyroidism after a previous surgical exploration, an imaging test to localize involved glands is indicated. (***Tc 99 sestamibi scanning***)

It also has a sensitivity of greater than 90% in the case of solitary adenomas.

When combined with single-photon emission computed tomography scanning, it can be used effectively to localize ectopic and usual parathyroid adenomas and, therefore, is the imaging study of choice **(SPECT).**

Procedures

Bilateral internal jugular vein sampling is used to help localize ectopic parathyroid adenomas is reserved for selected patients.



Anterior Planar Image of the Neck and Chest of a Patient with Primary Hyperparathyroidism Obtained with Technetium-99m Sestamibi, Showing a Parathyroid Adenoma in the Mediastinum.

Treatment: Medical care

The diet in primary hyperparathyroidism should include 1200-1500 mg of calcium / day & 400 IU of vitamin D.

Estrogen therapy in postmenopausal women has been shown to cause a small reduction in serum calcium and increases in BMD, with stable PTH.

Mainly medical therapy is limited to the treatment of hypercalcemia itself.

In the acute setting, this can be accomplished by the use of intravascular volume expansion with sodium chloride and loop diuretics such as furosemide once the intravascular volume is restored. In rare cases, hypercalcemia has been treated with bisphosphonate therapy as a temporary measure prior to surgical treatment.

Surgical care

Indications

Symptomatic hyperparathyroidism with abnormal glands.

The indications for surgery as per National Institutes of Health (NIH)- 2002 guidelines: 1.0 mg/dL above the upper limit of the reference range for serum calcium

- 24-hour urinary calcium excretion greater than 400 mg
- A 30% reduction in creatinine clearance
- Bone mineral density T-score below -2.5 at any site
- Age less than 50 years

For asymptomatic patients who do not undergo surgery,: *serum calcium and creatinine levels every 6 months and annual bone mineral density (all 3 sites).*

Choice of surgical treatment

In the case of 4-gland hyperplasia, a 3.5-gland (subtotal) parathyroidectomy is performed. Approximately 50-70 mg of normal-appearing tissue is left behind. A nonabsorbable suture is left as a tag to identify the gland if reoperation is done. Approximately 85% of cases of primary hyperparathyroidism are caused by a single adenoma. With either sestamibi scanning or ultrasonography, an abnormal parathyroid may be detected preoperatively in 70-80% of cases. Some centers use the intraoperative PTH assay. Because the plasma half-life of PTH is only approximately 4 minutes, the level falls quickly after resection. If the level fails to fall ***(>50% in 10 mins)*** after resection of the identified abnormal gland, the procedure is extended to allow for further exploration.

For familial disease, such as MEN 1, total parathyroidectomy is performed with autotransplantation to the forearm and cryopreservation of some parathyroid tissue.

Hypocalcemia after parathyroid surgery may be due to hungry bone syndrome where calcium and phosphorus are rapidly deposited in the bone.

SECONDARY HYPERPARATHYROIDISM

Secondary hyperparathyroidism is the overproduction of PTH secondary to a chronic abnormal stimulus for its production. E.g. chronic renal failure or vitamin D deficiency.

Etiology: In renal failure, overproduction of PTH is due to:

- *hypocalcemia, impaired 1,25-dihydroxyvitamin D production by the diseased kidneys, and hyperphosphatemia.*
- Hyperphosphatemia cause multigland hyperplasia, resulting in increased PTH production.

Pathophysiology

In most patients on dialysis, the primary bone disease is osteitis fibrosa cystica, a disease of increased bone resorption caused by elevated PTH levels. Skeletal lesions include subperiosteal bone erosions, usually observed best in the distal phalanges. Likewise, the skull has a classic salt-and-pepper or ground-glass appearance.

Clinical presentation

The clinical presentation is often that of renal failure. In patients with secondary hyperparathyroidism due to vitamin D deficiency, the symptoms are mainly due to the vitamin deficiency (eg, osteomalacia with increased fracture risk, myopathy [rarely]). In advanced cases of secondary hyperparathyroidism, some patients may have bone pain.

Workup

All patients with renal failure should be monitored regularly with serum calcium, phosphorous, and PTH levels.

Patients with secondary hyperparathyroidism usually have a low-normal calcium and elevated PTH.

Imaging studies

To assess the bone disease, hand radiographs may show characteristic subperiosteal erosions. Imaging of the parathyroid glands is not indicated unless primary hyperparathyroidism is suggested.

Treatment

Unlike primary hyperparathyroidism, medical management is the mainstay of treatment for secondary hyperparathyroidism.

Treatment with calcitriol and calcium can either prevent or minimize secondary hyperparathyroidism. Control of the serum phosphate levels with a low-phosphate diet and phosphate-binding agents is essential.

Patients with dialysis-dependent chronic renal failure require calcitriol, oral calcium supplementation, calcium in the dialysate, aluminum-free phosphate binders, and cinacalcet to maintain levels of serum calcium and phosphate within normal ranges. **Surgical care**

Indications include bone pain or fracture, pruritus, and calciphylaxis.

TERTIARY HYPERPARATHYROIDISM

It is secondary to long-standing secondary hyperparathyroidism.

Tertiary disease is characterized by the development of autonomous hypersecretion of PTH causing hypercalcemia.

Pathophysiology
Tertiary hyperparathyroidism is observed most commonly in patients with chronic secondary hyperparathyroidism and often after renal transplantation. The hypertrophied parathyroid glands fail to return to normal and continue to oversecrete PTH, despite serum calcium levels that are within the reference range or even elevated. In these cases, the hypertrophied glands become autonomic and cause hypercalcemia, even after withdrawal of calcium and calcitriol therapy. This type of tertiary disease is particularly dangerous because due ti high phosphate levels. If the calcium value multiplied by the phosphate value yields a high product, diffuse calcinosis may occur.

Clinical presentation
Persistent hyperparathyroidism after renal transplantation or new hypercalcemia in the setting of chronic secondary hyperparathyroidism.
Treatment
Total parathyroidectomy with autotransplantation or subtotal parathyroidectomy is indicated
Familial benign (hypocalciuric) hypercalcemia
FHH is caused by a loss-of-function mutation of one allele of the gene for the calcium-sensing receptor (*CaR*). It causes hypercalcemia, hypophosphatemia, and hypermagnesemia. The PTH level is usually within the reference range or is mildly elevated. It can be distinguished from primary hyperparathyroidism by low 24-hour urinary calcium excretion. ***Persons with FHH are asymptomatic. Parathyroidectomy is not indicated.***
Hypercalcemia of malignancy
This disorder is usually caused by tumor release of a hormone called PTH-related peptide. Less commonly, hypercalcemia of malignancy is caused by local osteolytic lesions and, rarely, by overproduction of 1,25-dihydroxyvitamin D.
Calciphylaxis
Calciphylaxis, also known as ***uremic gangrene syndrome,*** is observed in patients with renal failure and secondary or tertiary hyperparathyroidism. *It is characterized by ischemic necrosis of the skin due to calcium phosphate crystal deposition and subsequent inflammation in small-to-medium–sized vessels.* The disease is often fatal. In many cases, total parathyroidectomy appears to reverse the course of the disease.

Hypoparathyroidism
It is a condition of parathyroid hormone (PTH) deficiency.
Primary hypoparathyroidism is a state of inadequate PTH activity. In the absence of PTH activity, the ionized calcium concentration in the extracellular fluid falls below normal.
Secondary hypoparathyroidism is a physiologic state in which PTH levels are low in response to a primary process that causes hypercalcemia.
Pathophysiology:
Ionized calcium in the ECF is in equilibrium with ionized calcium in storage pools such as bone, proteins in the circulation, and within the intracellular fluid.
In parathyroid cells, the extracellular calcium-sensing receptor regulates the secretion of PTH. Inactivating mutations of the extracellular calcium-sensing receptor lead to hypercalcemia, as observed in familial hypocalciuric hypercalcemia (heterozygous mutation) and neonatal severe hyperparathyroidism (homozygous mutation).
In the absence of PTH, bone resorption, phosphaturic effect, renal distal tubular calcium reabsorption, and 1,25-dihydroxy vitamin D–mediated dietary calcium absorption cannot occur. Therefore, the consequence of PTH deficiency is hypocalcemia.

CLINICAL
History: hypocalcemia presenting as neuromuscular irritability, including the following:
- Paresthesias (involving fingertips, toes, perioral area)
- Hyperirritability
- Fatigue
- Anxiety

- Mood swings and/or personality disturbances
- Seizures (especially in patients with epilepsy)
- Hoarseness (due to laryngospasm)
- Wheezing and dyspnea (due to bronchospasm)
- Muscle cramps, diaphoresis, and biliary colic
- Hypomagnesemia, hypokalemia, and alkalosis (eg, hyperventilation), which worsen signs and symptoms of hypocalcemia

Examination: The clinical manifestation of hypoparathyroidism is hypocalcemia.

Neurologic effects

- Hyperreflexia (Positive Chvostek or Trousseau sign)
- Tetany
- Seizures
- Altered level of consciousness

Chvostek sign: Facial twitching, especially around the mouth, is induced by gently tapping the ipsilateral facial nerve as it courses just anterior to the ear.

Trousseau sign: Carpal spasm is induced by inflating a blood pressure cuff around the arm to a pressure 20 mm Hg above obliteration of the radial pulse for 3-5 minutes.

Extra pyramidal choreoathetoid syndromes in patients with basal ganglia calcifications.

Causes:

Iatrogenic causes

The most common cause of hypoparathyroidism is excision of all 4 parathyroid glands.

Congenital causes

- Parathyroid aplasia
- DiGeorge syndrome (dysgenesis of thymus and parathyroid glands)

Infiltration or destruction

- Sarcoidosis
- Wilson disease
- Hemochromatosis
- Metastatic carcinoma
- Infarction
- Radiation

Suppression of the parathyroid gland

- Hypomagnesemia - May be caused by pancreatitis, aminoglycosides, pentamidine, loop diuretics, cisplatin, and amphotericin B
- Hypermagnesemia
- Drugs - Include aluminum, asparagine, doxorubicin, cytosine, arabinoside, cimetidine

Idiopathic ***Autoimmune causes***

Likely an autoimmune disorder; can occur in conjunction with other endocrine anomalies

- Early onset - Autoimmune polyglandular syndrome type 1 (HAM syndrome)
- Late onset - Kenny syndrome

Hypoparathyroidism also can be sporadic.

Lab Studies:

Parathyroid hormone

- Primary hypoparathyroidism is low concentration of PTH with a concomitant low calcium level.
- In pseudohypoparathyroidism, the serum PTH concentration is elevated as a result of resistance to PTH caused by mutations in the PTH receptor system.
- In secondary hypoparathyroidism, the serum PTH concentration is low and the serum calcium concentration is elevated.

Calcium

- The calcium ion is highly bound to protein. A total calcium level cannot be interpreted without a total protein or albumin level.
- Hypoalbuminemia causes a drop in total calcium concentration, but the ionized fraction may be within the reference range. Elevated protein states, such as multiple myeloma and paraproteinemias, may cause an elevation of the total calcium concentration, but the ionized fraction may be within the reference range.
- Conversely, in the presence of albumin or protein excess, low ionized calcium levels with reference range levels of total calcium are possible. Likewise, if the patient is hypoalbuminemic, high ionized calcium levels with a reference range level of total calcium are possible.
- Measurement of ionized calcium concentration in the plasma is ideal.

Measurement of 25-hydroxy vitamin D: This measurement is important to exclude vitamin D deficiency as a cause of hypocalcemia.
Serum magnesium: Hypomagnesemia may cause PTH deficiency and subsequent hypocalcemia. Exclude it in any patient with primary hypoparathyroidism.
Serum phosphorus: PTH is a phosphaturic hormone. In its absence, phosphorus levels in the blood rise.

TREATMENT

PTH is used in the treatment of osteoporosis.
Its use for patients with hypoparathyroidism is not approved by the Food and Drug Administration.
Currently, treatment of patients with hypoparathyroidism involves correcting the hypocalcemia by administering calcium and vitamin D.

Surgical Care:

Patients undergoing parathyroidectomy for parathyroid hyperplasia are at high risk of developing permanent primary hypoparathyroidism.
Patients may be treated with an autotransplant of a segment of parathyroid gland to prevent hypoparathyroidism.

ADRENAL

PHEOCHROMOCYTOMA

- Pheochromocytoma is a catecholamine-secreting tumor derived from chromaffin cells.
- Tumors arising outside the adrenal are termed extra-adrenal pheochromocytomas/ paragangliomas.
- The clinical manifestations of pheochromocytoma result from excessive catecholamine secretion by the tumor.
- Catecholamines typically secreted, either intermittently or continuously, include norepinephrine and epinephrine but rarely dopamine.
- Unlike the healthy adrenal medulla, pheochromocytomas are not innervated, and catecholamine release is not precipitated by neural stimulation.
- Most pheochromocytomas contain norepinephrine predominantly, in comparison with the normal adrenal medulla, which is comprised of roughly 85% epinephrine.
- Familial pheochromocytomas are exception as they secrete mainly epinephrine.

Pheochromocytomas may occur in certain familial syndromes, including multiple endocrine neoplasia (MEN) 2A and 2B, neurofibromatosis, and von Hippel-Lindau (VHL) disease, sturge weber syndrome & tuberus sclerosis.

Sex: Pheochromocytomas occur with equal frequency in males and females.

Age: Pheochromocytoma may occur at any age. The peak incidence, however, is between the third and the fifth decades.

CLINICAL

4 cardinal symptoms of pheochromocytoma are, headaches, palpitations, and diaphoresis in association with severe hypertension.

Symptoms

- Headache
- Diaphoresis
- Palpitations
- Tremor
- Nausea
- Weakness
- Anxiety, sense of doom
- Epigastric pain
- Flank pain
- Constipation
- Weight loss

Pheochromocytoma occur in certain familial syndromes. These include MEN 2A and 2B, neurofibromatosis (Von Recklinghausen disease), and VHL disease. Neurofibromatosis has a 1% incidence of pheochromocytoma. The VHL syndrome is associated with pheochromocytomas, cerebellar hemangioblastomas, and RCC

- MEN 2A (Sipple syndrome) is comprised of medullary thyroid carcinoma, hyperparathyroidism, pheochromocytoma, and Hirschsprung disease. > 95% of cases of MEN 2A are associated with mutations in the Ret proto-oncogene affecting 1 of 5 codons in exons 10.
- Medullary thyroid carcinoma, pheochromocytoma, mucosal neurofibromatosis, intestinal ganglioneuromatosis, Hirschsprung disease, and a marfanoid body habitus characterize MEN 2B.
- Other neuroectodermal disorders associated with pheochromocytoma include tuberous sclerosis (Bourneville disease, Epiloia) and Sturge-Weber syndrome.

Examination: The clinical signs associated with pheochromocytoma include hypertension (which may be paroxysmal in 50% of cases), postural hypotension, retinopathy, fever, pallor, tremor, cafe au lait spots, or neurofibromas.

Clinical signs

- Hypertension (paroxysmal in 50% of cases)
- Postural hypotension - Resulting from volume contraction
- Hypertensive retinopathy
- Weight loss
- Pallor
- Fever
- Tremor
- Neurofibromas
- Cafe au lait spots: These are patches of cutaneous pigmentation, which vary in size from 1-10 mm and occur any place on the body. Characteristic locations include the axillae and intertriginous areas (groin). Their color varies from light to dark brown, hence the name cafe au lait.
- Tachyarrhythmias
- Pulmonary edema
- Cardiomyopathy
- Ileus

Laboratory features

- Hyperglycemia
- Hypercalcemia
- Erythrocytosis

Lab Studies:

- A 24-hour urine collection for creatinine, total catecholamines, vanillylmandelic acid (VMA), and metanephrines. Metanephrines are considered the most sensitive and specific test for pheochromocytoma, while VMA is the least specific test

Imaging Studies:

- Over 90% of pheochromocytomas are located within the adrenal glands and 98% within the abdomen. Extra-adrenal pheochromocytomas develop in paraganglion chromaffin tissue of the sympathetic nervous system. Common locations for extra-adrenal pheochromocytomas include organ of Zuckerkandl (close to origin of the inferior mesenteric artery), bladder wall, heart, mediastinum, and carotid and glomus jugulare bodies.
- MRI has a sensitivity of 100% in detecting adrenal pheochromocytomas, does not necessitate contrast, and does not expose the patient to ionizing radiation. MRI also is superior to computed tomography (CT) scanning in detecting extra-adrenal pheochromocytomas.
- CT scans of the abdomen have an accuracy of 85-95% in detecting adrenal masses with a spatial resolution of 1 cm or greater.
- A scan with iodine-131 (^{131}I)–labeled metaiodobenzylguanidine (MIBG) is reserved for cases when a pheochromocytoma is confirmed biochemically but CT scan or MRI fail to visualize a tumor. The molecular structure of iodine-123 (^{123}I) MIBG resembles norepinephrine and concentrates within adrenal or extra-adrenal pheochromocytomas. This isotope has a short half-life and is very expensive.

Procedures: rarely indicated due to the high sensitivity of MRI and CT scanning.

- Selective venous sampling seldom is performed to localize pheochromocytomas but occasionally has been utilized to detect extra-adrenal pheochromocytomas.
- Arteriography rarely is indicated and provides little additional information compared to an MRI or CT scan.

Histologic Findings: Pheochromocytomas vary in size from 2 g to 3 kg but on average weigh 100 g. These tumors are well encapsulated, highly vascular, and appear reddish brown on cut section.

Histologically, the tumor cells are arranged in balls and clusters separated by endothelial-lined spaces; this classic pattern characteristic of pheochromocytoma is termed zellballen.

Staging: Approximately 10% of pheochromocytomas are malignant.
Direct invasion of surrounding tissue or the presence of metastases determines malignancy.

TREATMENT

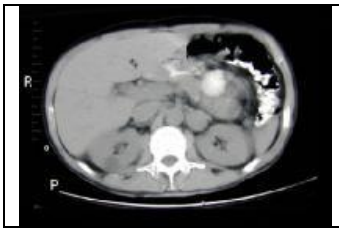
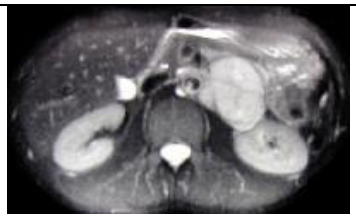
Surgical resection of the tumor is the treatment of choice and usually results in cure of the hypertension.
Careful treatment with alpha- and beta-blockers is required preoperatively to control blood pressure and prevent intraoperative hypertensive crises.

- Start alpha blockade with phenoxybenzamine 7-10 days preoperatively to allow for expansion of blood volume.
- Initiate a beta-blocker only after adequate alpha blockade. If beta blockade is started prematurely, unopposed alpha stimulation could precipitate a hypertensive crisis.
- Administer the last doses of oral alpha- and beta-blockers on the morning of surgery.

Surgical Care:

- An anterior midline abdominal approach was utilized in the past; however, now laparoscopic adrenalectomy is the preferred procedure for small to moderate lesions.

The 5-year survival rate for people with nonmalignant pheochromocytoma is greater than 95%. In malignant pheochromocytomas, the 5-year survival rate is less than 50%.

	Abdominal CT demonstrating left suprarenal mass of soft tissue attenuation representing a paraganglioma		Axial T2-weighted MRI scan showing large left suprarenal mass of high T2 signal intensity representing a pheochromocytoma

Malignant metastatic pheochromocytoma should be treated with α- and β-blockers and with metyrosine. The latter drug inhibits tyrosine hydroxylase, which catalyzes the first transformation in catecholamine biosynthesis. Thus, levels of VMA and BP fall. BP can be controlled even though the tumor growth continues and will eventually cause death. Combination chemotherapy using cyclophosphamide, vincristine, and dacarbazine is the best treatment for metastases. Experimentally, ^{131}I-MIBG has been used to treat large metastases. Radiotherapy may reduce bone pain but is generally ineffective.

Hyperaldosteronism

- Primary aldosteronism, also termed Conn syndrome
- It is clinically characterized by hypertension and hypokalemia.
- The cause of primary aldosteronism is an adrenal adenoma in 80% and adrenal gland hyperplasia in 20%. Adrenal carcinoma is an extremely rare cause
- In 75-90% of patients with a solitary aldosterone-producing tumor.

Pathophysiology: Aldosterone promotes the excessive preservation of sodium at the expense of potassium loss. Sodium retention promotes water retention, hypertension, and a suppression of renin production. Excessive potassium loss causes hypokalemic alkalosis, which may be associated with complications including muscular weakness, tetany, and abnormal electrocardiographic findings.
The diagnosis of primary aldosteronism is based on the typical biochemical findings of ***hypokalemia, hypernatremia, depletion of magnesium, elevated bicarbonate levels, low plasma pH, and elevated aldosterone levels in both the serum and urine***.
The demonstration of suppressed renin levels is vital to the diagnosis. A sodium chloride suppression test can be used that involves administration of large amounts of sodium chloride over 3-5 days, which causes hypokalemia in 80-90% of patients with primary aldosteronism. This response is associated with muscle weakness, cardiac arrhythmia, carbohydrate intolerance, and nephrogenic diabetes insipidus. Hypertension associated with primary aldosteronism is usually benign, malignant hypertension is rare.
Sex: The male-to-female ratio is 1:2.
Age: Primary aldosteronism occurs in patients aged 30-50 years.

Clinical Details: Primary aldosteronism is characterized by:

- Moderate-to-severe hypertension without edema.
- Biochemically, the condition is associated with hypokalemia, metabolic alkalosis, and hyperaldosteronism not appropriately suppressed during volume expansion and depression of plasma renin activity.
- With hypokalemic alkalosis, muscular weakness, polydipsia, polyuria, nocturia, paresthesia, tetany, headaches, and abnormal electrocardiographic features may develop.
- Other associated reported abnormalities include subarachnoid hemorrhage, postural hypotension, and bradycardia.

Preferred Examination: The workup starts with appropriate biochemical analysis, after which thin-collimation CT is performed. If CT findings are equivocal, radionuclide studies and MRI should be performed.

Limitations of Techniques: Adrenal hypersecreting glands may appear to be normal in size. The adrenal glands also vary in size and weight as a result of illness or stress. This size discrepancy is a particular problem with APAs because they are often small and difficult to detect. With the use of current scanners, the sensitivity is 82-88%.

MRI

APAs are isointense or hypointense relative to the liver on T1-weighted images and slightly hyperintense on T2-weighted images.

A sensitivity of 70-100% and a specificity of 64-100% have been reported in the detection of APAs with MRI.

ULTRASOUND

Sonograms may reveal a significantly sized APA, but because APAs tend to be small, the overall sensitivity of sonography is poor.

NUCLEAR MEDICINE

Findings: Iodine 131-6-β-iodomethylnorcholesterol (NP-59) is a cholesterol analog that binds to low-density lipoprotein receptors of the adrenal cortex and is the primary radionuclide used to image the adrenal cortex. Imaging is usually performed after dexamethasone suppression to reduce high background tracer uptake by the zona fasciculata. The normal glands (which show uptake of the radionuclide) are identified on day 5 or thereafter. Bilateral early depiction of the glands (before day 5) implies adrenal hyperplasia, whereas unilateral early depiction implies an APA.

ANGIOGRAPHY

Because APAs are small and not usually vascular, selective adrenal angiography is seldom helpful. However, adrenal phlebography has a useful role in the investigation of APA because the splaying of veins around APAs can help in identifying even small tumors. If contrast medium is refluxed into the veins of the APA, a wheel-spoke pattern is seen in the intratumoral veins.

The most useful technique in the investigation of primary aldosteronism is adrenal venous sampling.

INTERVENTION

Although primary aldosteronism accounts for 0.05-2% of cases of hypertension in the general population, recognition of the disease is important because patients readily respond to the removal of the adrenal gland tumor.

In 75-90% of patients with a solitary APA, surgical adrenalectomy corrects hypertension and hypokalemia.

In idiopathic hyperaldosteronism associated with bilateral adrenal hyperplasia; surgery rarely cures hypertension.

Patients with idiopathic hyperaldosteronism are usually treated medically; therefore, differentiating primary aldosteronism caused by APAs from idiopathic hyperaldosteronism is essential.

Adrenal Carcinoma

Adrenocortical masses are common; autopsy studies show that approximately 5-15% of the general adult population may have adrenal incidentalomas. Adrenal incidentalomas are biochemically and clinically asymptomatic adrenal masses found incidentally as a result of unrelated imaging such as abdominal CT or MRI scans. Only a small number of adrenal tumors are functional and an even smaller number (about 1%) are malignant.

- All nonfunctional adrenal tumors larger than or equal to 6 cm should be removed because of the significant potential cancer risk.
- Nonfunctional adrenal tumors (<3 cm) have a very low probability of being adrenal cancer; therefore, they can be removed safely.
- The management strategy for adrenal masses larger than 3-6 cm is disputed.

These criteria do not apply to children, who generally have smaller ACs.
Incidence rate of malignancy is small (<0.03%) in all adrenal incidentalomas that are 1.5-6 cm. However, this rate increases considerably with tumors larger than 6 cm (up to 15%).

Classifying adrenal tumors
Adrenal tumors are classified in several ways.

- Functional and nonfunctional,
    - Older reports suggest that approximately 50-80% of ACs are functional, and patients mainly present with Cushing syndrome.
    - More recent reports suggest that nonfunctional ACs may be more common than previously suggested.
    - Virtually all feminizing adrenal tumors in men are malignant.
- Sporadic and syndromic variants.

    The syndromic variants occur with Gardner, Beckwith-Wiedemann (associated with hemihypertrophy), and Li-Fraumeni syndromes.
- On the cellular origin of the neoplasm.
    - Primary adrenocortical carcinomas
    - Primary adrenal lymphomas
    - Soft-tissue sarcomas of the adrenal
    - Malignant pheochromocytomas
    - Secondary metastatic adrenal tumors (common primaries are the breast, kidney, lung, ovary, melanoma, leukemia, lymphoma).

Pathophysiology: The role of tumor suppressor gene mutations is suggested by their association with Li-Fraumeni syndrome, which is characterized by inactivating germline mutations of the *TP53* gene (a vital tumor suppressor gene or antioncogene) on chromosome 17. This syndrome also is associated with a predisposition to other malignancies, including breast carcinoma, leukemias, osteosarcomas, and soft-tissue sarcomas.
A few reports describe an association between AC and familial adenomatous polyposis, which also is due to a germline inactivating mutation of a tumor suppressor gene (in this case, the adenomatous polyposis coli gene, *APC*).
Incidence: The incidence is approximately 0.6-1.67 cases per million persons per year.
Race: AC has no specific racial predilection.
Sex: The female-to-male ratio is 2.5-3:1. Male patients tend to be older and have a worse overall prognosis than female patients.
Age: AC occurs in 2 major peaks:

- In the first decade of life and again in the fourth to fifth decades.
- Approximately 75% of the children with AC are younger than 5 years.
- Functional tumors also are more common in children, while nonfunctional tumors are more common in adults.

History: Most patients with AC present with advanced disease that is characterized by multiple abdominal or extra-abdominal metastatic masses (stage IV disease)
Nonfunctional variants

- These typically present with fever, weight loss, abdominal pain and tenderness, back pain, abdominal fullness, or symptoms related to metastases.
- In other cases, mass is found incidentally, during radiological imaging.

Endocrine syndromes

- Approximately 30-40% of patients present with the typical features of Cushing syndrome, while 20-30% present with virilization syndromes.
- *In children, however, virilization (in girls) or precocious puberty (in boys) is the most common endocrine presentation of a functional AC.*
- Other modes of presentation include profound weakness, hypertension, and/or ileus from hypokalemia related to hyperaldosteronism and hypoglycemia.

Physical:

- Patients may present with features of Cushing syndrome, including truncal obesity, striae, severe acne, malar flushing, supraclavicular and dorsocervical fat pads, Conn syndrome (hypertension with weakness and ileus resulting from hypokalemia), virilization in girls, or precocity and feminization (rarely) in boys.
- In nonfunctional tumors, the major finding is an abdominal mass, in a flank.

Lab Studies:

- The best screening tests for Cushing syndrome are the standard 1-mg dexamethasone suppression test and the 24-hour urinary cortisol excretion test.
- Screen for hyperaldosteronism by using simultaneous aldosterone and renin levels to compute aldosterone-to-renin ratios.
- Screen for virilization syndromes using serum adrenal androgens (androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate), serum testosterone, and 24-hour urinary 17 ketosteroids.
- Plasma estradiol and/or estrone tests can help screen for feminization syndromes.
- The evaluation of adrenal masses also must include screening for possible pheochromocytoma, including, at a minimum, a 24-hour urinary estimation of catecholamines (epinephrine, norepinephrine, dopamine) and metabolites (particularly metanephrines and normetanephrines).

Imaging Studies:

CT scans and MRI

- Adrenal CT scans and MRI are the imaging studies of choice. The typical case is characterized by a large unilateral adrenal mass with irregular edges. The presence of contiguous adenopathy serves as corroborating evidence.

Ultrasonography

- This test has less sensitivity in detecting adrenal tumors
- It has particular utility, in the follow-up of previously detected incidentalomas.

Other Tests:

Because the histologic analysis of these masses may be unreliable, fine and/or core tissue needle aspiration biopsies (percutaneous route) generally are not recommended.

Histological Findings: macroscopic features suggesting malignancy include a weight > 500 g, presence of areas of calcification or necrosis, and a grossly lobulated appearance.

Distinction between adrenocortical and adrenomedullary tumors

These have distinctive histologic appearances and immunohistochemical staining patterns. While adrenomedullary tumors stain positive for neuroendocrine markers (eg, synaptophysin, neuron-specific enolase, chromogranin A), adrenocortical cells stain positive for D11. ACs virtually always are unilateral.

Staging: Staging for adrenal carcinoma according to Sullivan and colleagues

Tumor criteria

- TI - Tumor diameter smaller than or equal to 5 cm with no local invasion
- T2 - Tumor diameter larger than 5 cm with no local invasion
- TI - Tumor of any size with local extension but not involving adjacent organs
- T4 - Tumor of any size with local invasion of adjacent organs

Lymph node criteria

- NO - No regional lymph node involvement
- NI - Positive regional nodes

Metastasis criteria

- MO - No distant metastasis
- MI - Distant metastasis

Stages

- Stage 1 - TI, NO, MO
- Stage 2 - T2, NO, MO
- Stage 3 - TI or T2, NI, MO
- Stage 4 - Any T, any N + M1 or T3, NI or T4

TREATMENT: Medical Care:

Mitotane

- It is a relatively specific to adrenocortical cytotoxin.
- At best, only 20-25% of patients respond to mitotane. Therapy may be required for at least 3 months before deciding the response of mitotane
- Mitotane apparently causes adrenal inhibition without cellular destruction. The

Suramin: Although a few reports suggest the potential utility of suramin as an additional chemotherapeutic agent in the treatment of AC, this drug is not recommended for AC.

Gossypol

- Gossypol also has been tried for metastatic adrenal cancer
- It was originally developed as a spermatotoxin and was derived from cottonseed oil. It has been used widely in China as a male contraceptive with few adverse effects. While the exact mechanism for its action is unclear, it is known to cause selective mitochondrial destruction by the uncoupling of oxidative phosphorylation.

Cisplatin-based chemotherapy

- In cases where mitotane fails, chemotherapeutic regimens containing cisplatin alone or in combination often are used.
- Cyclophosphamide, Adriamycin, and cisplatin (CAP), 5-fluoro uracil, Adriamycin, and cisplatin (FAP), and cisplatin with VP-16 have been tried.

Surgical Care:

- When feasible, total resection remains the management modality of choice for the definitive management of AC. It also remains the only potentially curative therapeutic modality.

Cushing syndrome

Cushing's Syndrome is due to excessive levels of glucocorticoids causing non-specific symptoms such as obesity, muscle weakness and depression

PATHOPHYSIOLOGY & ETIOLOGY

The glucocorticoid cortisol is secreted from the **zona fasciculata** and reticularis of the adrenal gland under the stimulus of adrenocorticotropin (ACTH) from the pituitary gland. ACTH in turn is secreted in response to corticotropin releasing hormone (CRH) and vasopressin from the hypothalamus. Cortisol exerts negative feedback control on both CRH and vasopressin in the hypothalamus, and ACTH in the pituitary. In normal individuals, cortisol is secreted in a circadian rhythm. It is the loss of this circadian rhythm, together with loss of the normal feedback mechanism of the hypothalamo-pituitary-adrenal (HPA) axis, which results in chronic exposure to excessive circulating cortisol levels and that gives Cushing's syndrome.

The etiology of Cushing's syndrome can broadly be divided into two categories; ACTH-dependent and ACTH-independent (Table). Of the ACTH-dependent forms, pituitary-dependent Cushing's syndrome, Cushing's disease, is the most common, accounting for 60-80% of all cases.

Ectopic sources of ACTH derive from multiple tumor types, the most frequent being small-cell lung carcinoma.

Excessive autonomous cortisol secretion can occur from an adrenal adenoma or carcinoma.

In addition, rarer forms of Cushing's syndrome include ectopic CRH production, macronodular adrenal hyperplasia, adrenal hyperplasia secondary to abnormal hormone receptor expression.

Table 1. Etiology of Cushing's syndrome

ACTH-dependent	**ACTH-independent**
Pituitary-dependent Cushing's syndrome (Cushing's disease)	Adrenal adenoma
Ectopic ACTH syndrome	Adrenal carcinoma
Ectopic CRH syndrome	Macronodular adrenal hyperplasia (partially ACTH dependent)
Exogenous ACTH administration	Pigmented micronodular adrenal hyperplasia
	Adrenal hyperplasia secondary to abnormal hormone receptor expression/function

CLINICAL FEATURES

The classical impression of the disease are:

gross obesity of the trunk with wasting of the limbs, facial rounding and plethora, hirsutism with frontal balding, muscle weakness, spontaneous bruising, vertebral fractures, hypertension and diabetes mellitus.

Other symptoms include lethargy, depression, acne, easy bruising, loss of libido and menstrual irregularity.

The signs are : myopathy, thin skin and easy bruising.

Severe hirsutism and virilisation strongly suggest an adrenal carcinoma.

BIOCHEMICAL CONFIRMATION:

Circadian rhythm assessment

Loss of the normal circadian rhythm of cortisol secretion in Cushing's syndrome, with elevated nocturnal levels.

At the NIH in the United States, an awake midnight cortisol of greater than 207 nmol/l was claimed to show 94% sensitivity and 100% specificity for the differentiation of Cushing's syndrome from pseudo-Cushing's states.

Urinary free cortisol

Measurement of urinary free cortisol (UFC) is a non-invasive test and is widely used. Under normal conditions, 10% of plasma cortisol is 'free' or unbound and physiologically active. Unbound cortisol is filtered by the kidney, with the majority being reabsorbed in the tubules, and the remainder excreted unchanged.

UFC measurement have a sensitivity of 95% for the diagnosis.

Low-dose dexamethasone suppression test

In normal individuals administration of an exogenous glucocorticoid results in suppression of the HPA axis, whilst patients with Cushing's syndrome are resistant, at least partially, to negative feedback.

Dexamethasone is a synthetic glucocorticoid that is 30 times more potent than cortisol.

TREATMENT OF CUSHING'S SYNDROME

Surgical Management

Transphenoidal surgery

Transsphenoidal surgery is widely regarded as the treatment of choice for Cushing's disease. The overall remission rate in various large series is in the order of 70-75%, although higher rates of approximately 90% can be achieved with microadenomas **Adrenalectomy**

Adrenalectomy is the definitive treatment for all cases ACTH-independent Cushing's syndrome. This is either unilateral in the case of an adrenal adenoma or carcinoma, or bilateral in cases of bilateral hyperplasia. In adrenal adenomas cure following surgery in skilled hands is 100%. Bilateral adrenalectomy is also an important therapeutic option in patients with ACTH-dependent Cushing's syndrome not cured by other techniques. However, the development of Nelson's syndrome in patients with ACTH-secreting pituitary adenomas occurs in between 8% and 38% of cases.

Patients undergoing bilateral adrenalectomy will require lifelong mineralocorticoid and glucocorticoid replacement.

Surgery for the ectopic ACTH syndrome
If the ectopic ACTH-secreting tumor is benign and amenable to surgical excision, such as in a lobectomy for a bronchial carcinoid tumor, the chance of cure of Cushing's syndrome is high. However, if significant metastatic disease is present, surgery is unlikely to be of benefit.

ADDISON'S DISEASE (adrenal insufficiency, hypocortisolism)
Addison's disease is characterized by weight loss, muscle weakness, fatigue, low blood pressure, and sometimes darkening of the skin in both exposed and nonexposed parts.
Addison's disease occurs when the adrenal glands do not produce enough of the hormone cortisol and, in some cases, the hormone aldosterone.
Causes
The problem may be due to a disorder of the adrenal glands themselves (primary adrenal insufficiency) or to inadequate secretion of ACTH by the pituitary gland (secondary adrenal insufficiency).
Primary Adrenal Insufficiency

- Addison's disease affects about 1 in 100,000 people.
- Most cases are caused by the gradual destruction of the adrenal cortex immune system.
- About 70 percent of reported cases of Addison's disease are autoimmune.
- Adrenal insufficiency occurs when at least 90 percent of the adrenal cortex has been destroyed.
- As a result, often both glucocorticoid (cortisol) and mineralocorticoid (aldostertone) hormones are lacking.
- Sometimes only the adrenal gland is affected, as in idiopathic adrenal insufficiency; sometimes other glands also are affected, as in the polyendocrine deficiency syndrome.

Polyendocrine Deficiency Syndrome
The polyendocrine deficiency syndrome is classified into two separate forms, referred to as type I and type II.
Type I occurs in children, and adrenal insufficiency may be accompanied by

- underactive parathyroid glands
- slow sexual development
- pernicious anemia
- chronic candida infections
- chronic active hepatitis
- hair loss (in very rare cases)

Type II, often called Schmidt's syndrome, afflicts young adults. Features of type II are:

- an underactive thyroid gland
- slow sexual development
- diabetes
- vitiligo
- loss of pigment on areas of the skin

Tuberculosis
Tuberculosis (TB), accounts for about 20 percent of cases of primary adrenal insufficiency in developed countries.

Other Causes

- chronic infection, mainly fungal infections
- cancer cells spreading from other parts of the body to the adrenal glands
- amyloidosis
- surgical removal of the adrenal glands

Secondary Adrenal Insufficiency
This form of adrenal insufficiency is more common than primary adrenal insufficiency. Without ACTH to stimulate the adrenals, the adrenal glands' production of cortisol drops, but not aldosterone.

A temporary form of secondary adrenal insufficiency may occur when a person who has been receiving a glucocorticoid hormone
Glucocorticoid hormones block the release of both corticotropin-releasing hormone (CRH) and ACTH. Normally, CRH instructs the pituitary gland to release ACTH. If CRH levels drop, the pituitary is not stimulated to release ACTH, and the adrenals then fail to secrete sufficient levels of cortisol.
Less commonly, adrenal insufficiency occurs when the pituitary gland either decreases in size or stops producing ACTH. These events can result from

- tumors or infections of the area
- loss of blood flow to the pituitary
- radiation for the treatment of pituitary tumors
- surgical removal of parts of the hypothalamus
- surgical removal of the pituitary gland

Symptoms: The symptoms of adrenal insufficiency usually begin gradually.

- chronic, worsening fatigue
- muscle weakness
- loss of appetite
- weight loss

About 50 percent of the time, one will notice

- nausea
- vomiting
- diarrhea

Other symptoms include

- low blood pressure that falls further when standing, causing dizziness or fainting
- skin changes in Addison's disease, with areas of hyperpigmentation, or dark tanning, covering exposed and nonexposed parts of the body; this darkening of the skin is most visible on scars; skin folds; pressure points such as the elbows, knees, knuckles, and toes; lips; and mucous membranes
- Addison's disease can cause irritability and depression.
- Hypoglycemia, or low blood glucose, is more severe in children than in adults.
- In women, menstrual periods may become irregular or stop.
- Because the symptoms progress slowly, they are usually ignored until a stressful event like an illness or an accident causes them to become worse. This is called an addisonian crisis, or acute adrenal insufficiency. In about 25 percent of patients, symptoms first appear during an addisonian crisis.

Symptoms of an addisonian crisis include

- sudden penetrating pain in the lower back, abdomen, or legs
- severe vomiting and diarrhea
- dehydration
- low blood pressure
- loss of consciousness

Diagnosis
ACTH Stimulation Test
This is the most specific test for diagnosing Addison's disease. In this test, blood cortisol, urine cortisol, or both are measured before and after a synthetic form of ACTH is given, and measurement of cortisol in blood is repeated 30 to 60 minutes after an intravenous ACTH injection. The normal response after an injection of ACTH is a rise in blood and urine cortisol levels. Patients with either form of adrenal insufficiency respond poorly or do not respond at all.

CRH Stimulation Test

When the response to the short ACTH test is abnormal, a "long" CRH stimulation test is required to determine the cause of adrenal insufficiency. In this test, synthetic CRH is injected intravenously and blood cortisol is measured before and 30, 60, 90, and 120 minutes after the injection. Patients with primary adrenal insufficiency have high ACTHs but do not produce cortisol. Patients with secondary adrenal insufficiency have deficient cortisol responses but absent or delayed ACTH responses. Absent ACTH response points to the pituitary as the cause; a delayed ACTH response points to the hypothalamus as the cause.

Addisonian crisis must be teeated with injections of salt, fluids, and glucocorticoid hormones immediately.

Treatment

Cortisol is replaced orally with hydrocortisone tablets, a synthetic glucocorticoid, taken once or twice a day.

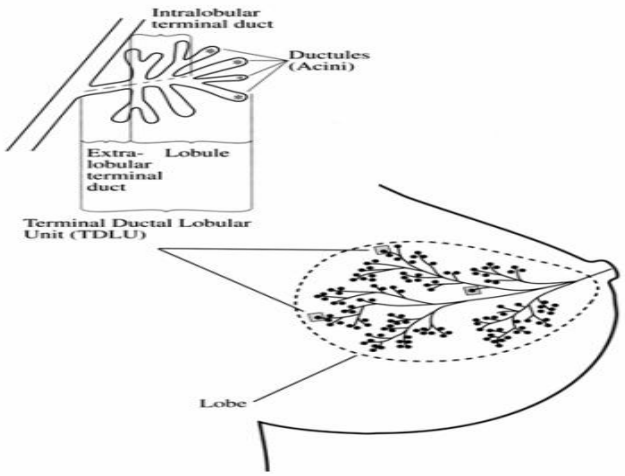
If aldosterone is also deficient, it is replaced with oral doses of fludrocortisone acetate. Patients with secondary adrenal insufficiency do not require aldosterone replacement therapy.

BREAST

Breast anatomy and physiology

The breast is located on the chest between the pectoralis muscle, i.e. the superficial fascia and the subcutaneous tissue. The breast rests on a rich vascular and lymphatic network within the pectoralis fascia representing the retromammary space, which is positioned between the deep pectoralis fascia and the superficial pectoralis fascia.

The breast consists of 15 to 25 lobes, each of which is drained by a collecting duct terminating in the nipple. The collecting duct has several branches, which end in a terminal ductal-lobular unit (TDLU), the basic functional unit of the breast. The TDLU is composed of a small segment of terminal duct and a cluster of ductules (acini), which are the actual secretory units. Microscopically, the duct system is lined by an inner epithelial cell layer along the luminal side and the outer layer of myoepithelial cells. These two layers are further surrounded by a layer of basal lamina. A small part of the ducts at the nipple is lined by squamous epithelium.



Anatomy of the human breast, a lobe and a TDLU. (Tabár 1998.)

At menarche, the main events include development and growth of ductal and lobular units. At pregnancy, a remarkable rise of hormone levels induces growth and secretory activity of the breast. Postmenopausally, the breast undergoes involution.

BREAST ANATOMY

Breast tissue extends from below the clavicle to the sixth or seventh rib, and from the sternum to the axilla. Montgomery's glands, located around the edge of the areola, release a fatty substance that protects the nipples during nursing.

Each breast contains several milk glands with ducts that carry milk to the nipples. About 15 to 20 ducts come together near the areola to form reservoirs of milk.

The breast is made up of fatty tissue and glandular milk-producing tissues. With the onset of menopause, relative amount of fatty tissue increases and glandular tissue diminishes.

The soft tissues of the breast are supported by the suspensory ligaments of Cooper, throughout the breast tissue parenchyma from the deep fascia beneath the breast and attach to the dermis of the skin. Breast ptosis withage is due to lax ligaments.

The blood of the breast is derived from:

Perforating branches of the internal mammary artery/ the lateral thoracic artery/ the thoracodorsal artery/ intercostal artery perforator and the thoracoacromial artery.

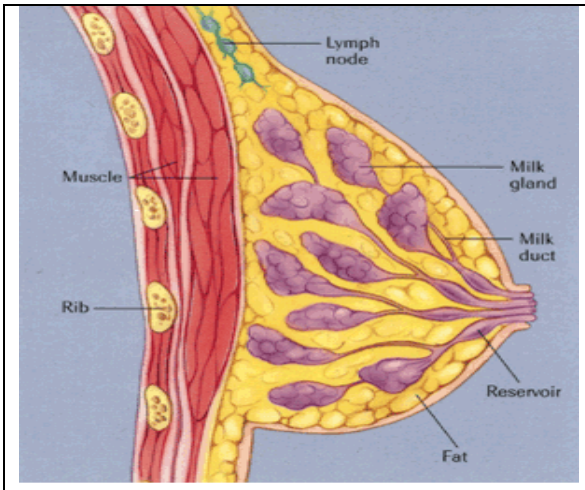
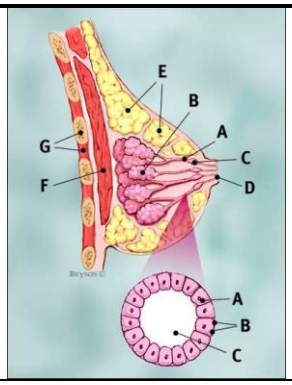
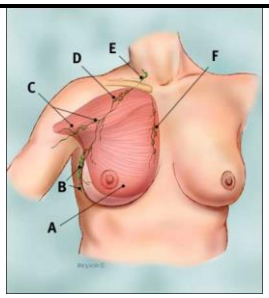


Image made available by a generous grant from Bristol-Myers Squibb

Sensory innervation of the breast is dermatomal in nature, mainly derived from the anterolateral and anteromedial branches of thoracic intercostal nerves T3-T5. Supraclavicular nerves from the lower fibers of the cervical plexus also provide innervation to the upper and lateral portions of the breast. Some believe that sensation to the nipple is derived from the lateral cutaneous branch of T4.
The breast lies over the musculature that encases the chest wall. The muscles involved include the pectoralis major, serratus anterior, external oblique, and rectus abdominus fascia.



Breast profile:
A ducts
B lobules
C dilated section of duct
D nipple
E fat
F pec major muscle
G chest wall/rib cage
Enlargement:
A normal duct cells
B basement membrane
C lumen



Axillary Lymph Nodes
A pectoralis major **B** axillary lymph nodes: levels I
C levels II
D levels III
E supraclavicular lymph nodes
F internal mammary nodes

The Lobules: The lobules, also called the lobular units, are responsible for the production of milk.
The Ductal System: The milk is collected by distal lactiferous ducts or acini which merge into minor and then major lactiferous ducts. In most instances, these empty into the major duct or sinus which ends in the nipple. The ductal system has a ductal epithelium surrounded by a myo-epithelium. This ductal epithelium is responsible for the propulsion of milk through the ductal system as it has contractile capabilities. This ductal system is sealed and surrounded by an uninterrupted basement membrane.
The Stroma: This interlobular tissue, also referred to as connective tissue, contains capillaries and other specialized cells.
Cooper's Ligaments: These are dense strands of fascia found throughout the entire breast which end on the skin itself.
The Basement Membrane of the Ductal System: It is essential to visualize the basement membrane in the microscopic analysis of a malignant breast tumor. This will assist in the assessment as to whether a tumor is "in situ" (has not grown through the basement membrane) or "invasive" (has grown through the basement membrane).

BENIGN BREAST LESIONS:

Most benign lesions can actually be regarded as aberrations of normal processes. The most common benign disorder, fibrocystic change, affects 40–50% of premenopausal women. It is a unified term for several proliferative, but nonneoplastic parenchymal alterations, which are usually bilateral and multifocal. The histologic pattern in each case is varying and may include pure fibrocystic lesions (duct ectasia, cysts, fibrosis, adenosis, ductal epithelial proliferation), focal fibrosis, ductal and lobular epithelial hyperplasia (also atypical) and microcystic and fibrous mastopathy due to involutional change.

I. Fibrocystic change A. Cyst B. Ductal hyperplasia with and without atypia C. Adenosis D. Fibrosis	III. Fibroepithelial tumors A. Fibroadenoma B. Phyllodes tumor
II. Mammary ductal ectasia	IV. Nipple diseases A. Paget's disease B. Chronic dermatitis C. Nipple adenoma (papilloma, papillomatosis)
III. Benign papillary neoplasm and changes A. Papilloma B. Radial scar	V. Others changes A. Fat necrosis

I. FIBROCYSTIC CHANGE

One of the most common benign conditions (affects > 50 percent of women having palpably irregular breasts, cyclic pain, and tenderness). At the time of increased estrogenic stimulation epithelial cells proliferate in the ducts (ductal hyperplasia) and lobules (adenosis). With decreased estrogen levels, the epithelium involutes, the ducts become cystic, and the lobules and stroma increase fibrous tissue (sclerosing adenosis and stromal fibrosis, respectively).

Fibrocystic change occurs in the following three major elements through the mediation of estrogen and progesterone receptors:

1. Ducts: ductal hyperplasia and cyst formation
2. Lobules: adenosis (lobular hyperplasia) and sclerosing adenosis
3. Stroma: fibrosis

The original study by Dupont and Page (1985) has classified and specifying epithelial proliferations into those with and without atypia.

Proliferative Lesions and their Relative Risks for Developing Invasive Breast Cancer*	
Nonproliferative changes: 70% Relative Risk = 1.0	Adenosis Cysts and apocrine change Ductal ectasia Mild epithelial hyperplasia of usual type
Proliferative disease without atypia: 26% Relative Risk = 1.5-2.0	Hyperplasia of usual type, moderate or florid Papilloma Sclerosing adenosis
Proliferative disease with atypia: 4% Relative Risk = 4-5	Atypical ductal hyperplasia Atypical lobular hyperplasia

A. Cysts

Cysts are the most common breast masses in women aged 40 to 50 years.

Cysts are fluid-filled spaces that originate from the terminal ductal lobular unit or from an obstructed ectatic duct. They are frequently multiple and bilateral.

B. Epithelial Hyperplasia With and Without Atypia

Epithelial hyperplasia is divided into ductal and lobular types. In general, lobules include acini and terminal ductules, whereas ducts comprise of interlobular ducts and beyond.

The morphologic hallmarks of ductal hyperplasia is increased cellularity and altered architectures, most commonly with

1. Papillary formation.
2. Sieve-like, cribriform, back to back pattern.
3. Solid filling of ductal lumens.

These ductal hyperplasias have also been referred as epitheliosis and papillomatosis. In ductal hyperplasia, both epithelial and myoepithelial cells. Based on the architecture, ductal hyperplasia is graded as mild, and moderate (or florid- solid pattern predominates).

In the presence of architectural and nuclear atypicality, the ductal hyperplasia is designated as atypical ductal or lobular hyperplasia.

It is common for ductal and atypical ductal hyperplasias to undergo focal stromal fibrosis, elastosis, and hyalinization producing stellate shaped, indurated lesions, the radial scar.

Atypical lobular hyperplasia is characterized by partial expansion of the lobules and the atypical cells are loosely cohesive. In lobular carcinoma in situ, the lobules are expanded and solidly filled by atypical cells. The myoepithelial cells are absent, except a few in the periphery of the lobules.

C. Adenosis

Adenosis refers to a spectrum of changes within the lobules beginning from the hyperplasia to the subsequent fibrosis and calcifications. In the early stage of adenosis, the lobules are enlarged with an increased number of acini. Later, myoepithelial proliferation and stromal fibrosis cause distortion of the individual acini, the so called sclerosing adenosis. Within the acini, laminated, purple, psammoma bodies often occur. With further stromal fibrosis and atrophy, the acini become few in number and the lobules become small.

Microglandular adenosis is typically seen in postmenopausal women. Clusters of round glandular profiles occur in the adipose tissue.

D. Fibrosis (Fibrous Mastopathy)

Fibrosis or fibrous mastopathy is an increase of fibrous connective tissue, which is usually hypo- to acellular. The lobules in particular are reduced in number and in size. Focal fibrosis may present as a palpable mass or as an impalpable mammographic abnormality. A variant of fibrosis occurs in some women with a long history of insulin-dependent diabetes mellitus, referred to as ***diabetic fibrous breast disease***.

II. MAMMARY DUCT ECTASIA

Duct ectasia is a nonspecific dilatation of the major subareolar ducts with occasional involvement of the smaller ducts, unrelated to fibrocystic change.

Microscopically, the dilated ducts contain foamy macrophages mixed with lipid material, cholesterol clefts and eosinophilic debris. The material within the ducts often calcifies. Infiltration of lymphocytes, plasma cells, and histiocytes occurs in the periductal tissue. With time, fibrosis increases in amount. Thus terms, such as plasma cell mastitis, obliterative mastitis and comedomastitis, were used.

III. BENIGN PAPILLARY NEOPLASM AND CHANGES

A. Intraductal papilloma

Intraductal papilloma usually occurs within a major duct in the subareolar region. When a similar papilloma occurs in the nipple, the term ***nipple adenoma or papillomatosis*** is used. ***The clinical presentation is bloody, or serous nipple discharge***. Multiple papillomas are associated with an increased risk for recurrence and subsequent development of breast carcinoma.

Secondary changes occur often in the form of hemorrhage, infarct, fibrosis and hyalinization. The damaged epithelium and hyalinized stroma may also deposit calcium.

B. Radial Scar

Radial scar is a benign lesion also known as infiltrating epitheliosis, nonencapsulated sclerosing lesion, indurative mastopathy, scleroelastic lesion, sclerosing papillary proliferation, benign sclerosing ductal hyperplasia, and radial sclerosing lesion.

Most radial scars are spiculated masses or areas of architectural distortion, often with multiple long spicules and central areas of lucency.

Radial scar occurs in the background of benign ductal hyperplasia, intraductal papilloma and/or sclerosing adenosis, in which fibrous stromal undergoes fibrosis and elastosis.

III. FIBROEPITHELIAL TUMORS

A. Fibroadenoma

Fibroadenoma is the most common benign breast tumors seen in women under the age of 35 years. The peak age of incidence is in the third decade.

Most fibroadenomas are 2-3 cm in size, but may reach to 6-7 cm, the so called giant fibroadenomas. They are well-circumscribed, but not encapsulated. Cut surfaces have a lobulated, grey-white myxoid, semitransparent to dense fibrous appearance. About 10-20% of fibroadenomas are multiple and bilateral and may increase in size during pregnancy and undergo infarct following childbirth.

Fibroadenomas consist of epithelial and fibrous components. Branching and budding ducts are surrounded by fibrous tissue. The pericanalicular fibroadenoma maintains round and oval dilated ductal spaces. Whereas in the intracanalicular type, the ductal lumens are compressed by polypoid fibrous stroma creating slit-like irregular spaces. The fibrous stroma varies from myxoid and hypocellular to fibrous and moderately cellular. Rare mitotic figures may occur, but nuclear atypia is absent or minimal, allowing separation from phyllodes tumor.

Involution is common with increasing age of the lesion. In old fibroadenomas, the ductal epithelium becomes atrophic as to disappear completely. The giant fibroadenoma is simply a fibroadenoma that has reached a large size. Microscopically these are the same as other fibroadenoma, the cellularity can be high.

B. Cystosarcoma Phyllodes or Phyllodes Tumor.

The phyllodes tumor has a lobulated, leaf-like appearance and varies in size from 1 cm to greater than 15 cm.

Clinical Presentation: These tumors can be of any size but are usually diagnosed as a large, rapidly growing, bulky breast tumor (over 5 cm in size). They can occur at any age but is seen mostly in women in their fifties.

Mammographic Presentation: Same as fibroadenoma.

Diagnosis: The histological diagnosis is made by excisional biopsy. Most of these tumors are usually benign. However, a few can be malignant.

Treatment: The treatment of these tumors is surgical. As they have a significant rate of local recurrence, surgical local control is essential. For small benign cystosarcoma phyllodes, a wide local excision can be performed with life long monitoring. For large tumors or malignant / borderline tumors, a total mastectomy is the procedure of choice. No axillary lymphadenectomy is performed as the rate of axillary metastasis is less than 0.9%. The majority of phyllodes tumors are local problems and do not metastasize. Less than 20% of phyllodes tumors metastasize by vascular spread, most commonly to the lung, pleura, and bone.

IV. NIPPLE DISEASES

Women with eczematous, erosive, pruritic changes of the nipple should be biopsied promptly to distinguish among chronic dermatitis, Paget's disease of the nipple, and nipple adenoma (papilloma, papillomatosis).

A. Paget's Disease

Paget's disease results from an intraductal spread of malignant cells to involve the nipple. About 1-2% of breast cancer patients present with Paget's disease. 50-60% of women have a palpable mass. Of these 90% have underlying infiltrating ductal carcinoma.10-28% have no clinical lesion.

The diagnosis is made by finding large cells with pale, vacuolated cytoplasm, round to oval large nuclei, prominent nucleoli migrating through the epidermis. Paget's cells are positive with mucicarmine stain, and express CEA, epithelial membrane antigen, milk fat globule by immunohistochemistry. ***Paget's disease is not associate with lobular carcinoma***. The underlying DCIS is usually comedo or solid type, and the invasive carcinoma poorly differentiated. Prognosis depends on the behavior and extent of the underlying carcinoma.

B. Nipple adenoma or papillomatosis

It is a ductal hyperplasia of the lactiferous ducts, sometimes protruding onto the nipple surface to manifest as a granular or ulcerated lesion. Typical patients are 40-50 years of age.

Nipple adenoma should be distinguished from subareolar sclerosing papillomatosis which occurs deeper in the breast tissue. Histologic appearance of both lesions is similar.

C. Chronic Dermatitis

It is characterized by hyperkeratosis, spongiosis, hyperplasia of the epidermis and chronic inflammation of the underlying dermis

V. OTHER CHANGES

Fat Necrosis

Fat necrosis may mimic carcinoma with a mass, pain, or skin retraction. It is associated with trauma, surgical intervention, and radiotherapy. The excised lesion has a slightly firm consistency in the periphery and golden brown color, soft, sometimes liquified, material in the center.

Histologically fat necrosis is characterized by irregular empty spaces, which are lined by foamy histiocytes foamy histiocytes.

BREAST CANCER

RISK FACTORS:

1: 20%decrease in risk for each year that menarche is delayed.
2: Risk is delayed by early menopause.
3: First late pregnancy (after 30 yrs) have 2-5 folds increased risk.
4: Nulliparous women have greater risk.
5: Increased risk with long term users of oral contraceptives.
6: Environmental: American> Japanese.
7: Dietary: Increased risk with fat.
8: Irradiation: Increased risk.

The Genetics of Breast Cancer

Most cases of breast cancer, about 90%, are thought to be the result of sporadic, somatic mutations in the breast tissue itself. The other 10% are associated with germline, or inherited mutations. Both BRCA1 and BRCA2 mutations confer increased risk for breast and ovarian cancer as well as for other cancers. They are tumor suppressor genes, and when mutations alter or inactivate this function, cancer is more likely to develop. The mode of inheritance is autosomal dominant

Effects of Mutations in BRCA1 and BRCA2

	BRCA1	BRCA2	Bkgrd Risk
Chromosome	**17**	**13**	
Year Discovered	1990	1994	
Year Isolated	1994	1995	
Mutations	100	100	
Breast cancer	56-85%	56-85%	10-12%
Ovarian cancer	**26-85%**	**< 10%**	1%
Male Breast cancer	**no**	**yes**	
Other cancers	**prostate**	**colon**	

HEREDITARY SYNDROMES

Li Fraumani Syndrome: Sarcomas (Soft tissue and bone), Brain tumours, Leukemia, Adrenocortical carcinoma.

Cowden Syndrome: Facial trichilemmomas, papillomatosis of lips and oral mucosa, acral keratosis, GI polyps and uterine leiomyomas.

Muir Syndrome: Basal cell carcinoma, benign and malignant GI tumours.

PAGET'S DISEASE (PD) OF THE BREAST is rare, with a reported incidence of 0.5-2% of patients with breast cancer. The characteristic changes are erythema and eczematous changes of the nipple. Ulceration, crusting and serous or bloody discharge characterize more advanced cases. Exfoliative cytology with demonstration of Paget's cells is useful, but a negative finding does not exclude PD. Surgical biopsy is the diagnostic standard.

The ***epidermotropic theory*** holds that Paget's cells are ductal carcinoma cells that have migrated from the underlying breast parenchyma. According to the ***in situ transformation theory***, the Paget's cells arise as malignant cells in the nipple epidermis independent from any other pathologic process within the breast parenchyma.

Paget's cells express heregulin receptors, including HER2/Neu, which exert a chemotactic effect resulting in migration into the epidermis. ***Fifty to sixty percent of patients have a palpable tumor in the breast. An invasive carcinoma was detected in 75-90%.***

Microscopically, the characteristic feature is the presence of adenocarcinoma cells (Paget's cells) in the keratinizing epithelium of the epidermis. These cells occur singly in superficial epidermal layers. They are more likely to form clusters in the basal portions of the epidermis. Isolated Paget's cells appear to lie in vacuoles. The cytoplasm is pale or clear, and it may contain mucin secretion vacuoles. Nuclei tend to have prominent nucleoli.

The most common differential diagnoses are malignant melanoma, squamous or basal cell Ca.

The extramammary forms of PD occur predominantly as vulvar or perianal disease. Primary vulvar PD is a localized carcinoma of sweat duct origin. The extravulvar form presents in the perianal areas as metastatic disease from sites that may include the rectum or urinary bladder

PD of the breast often is estrogen- and progesterone-receptor negative.

The prognosis of patients is determined by the extent of the associated carcinoma.

Treatment is mastectomy. Some patients without a palpable mass may be candidates for breast-conservation therapy.

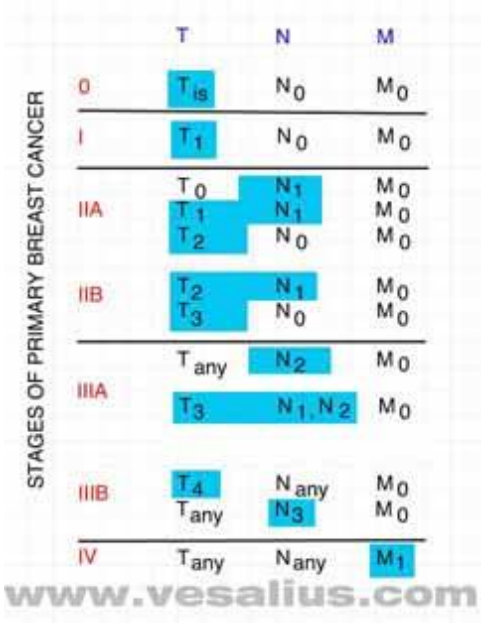
Breast Cancer – Staging: TMN Universal Classification for Breast Cancer		
T0: no evidence of primary tumor **Tis**: carcinoma in situ **T1**: < 2cm **T1a**: <0.5cm **T1b**: 0.5-1cm **T1c**: 1-2cm **T2**: 2-5cm **T3**: >5cm **T4**: any size, extension to skin or chest	**N0**: no regional lymph node metastasis **N1**: cancer in movable nodes, same side **N2**: cancer in fixed nodes **N3**: cancer in internal mammary nodes, same side (including supraclavicular nodes, same side)	**M0**: no metastasis **M1**: distant metastasis

wall (excluding pectoralis muscle) **T4a**: extension to chest wall **T4b**: skin edema, ulceration or satellite nodules **T4c**: both a and b **T4d**: inflammatory carcinoma		

Thanks to early detection through **breast self-examination, yearly doctor examination and mammography**, up to half the breast cancers now detected are DCIS. Treatment for DCIS may be **lumpectomy** plus **radiation (breast conserving therapy)** or **total mastectomy**. If the DCIS is **multi-focal** (multiple sites within one quadrant) or **multi-centric** (in more than one quadrant), it may mitigate for total mastectomy. Tamoxifen may also be added.

STAGE GROUPING FOR BREAST CANCER

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II A	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1,N2	M0
Stage IIIB	T4	any N	M0
	any T	N3	M0
Stage IV	any T	any N	M1



Stage 0 is very early cancer at a pre-invasive level called **carcinoma in situ**. It most often originates in the ducts **(ductal carcinoma in situ, DCIS)** and less commonly in the glandular lobules **(lobular carcinoma in situ, LCIS).**

The former by definition has not spread, is usually detected early by mammography and is highly curable. The latter is also called **lobular neoplasia** and is not technically considered a cancer, but it is associated with a high incidence (25% in 25 years from diagnosis) of invasive cancer developing in either breast. DCIS is often difficult to differentiate microscopically from LCIS, and a second expert opinion is sometimes beneficial.

After LCIS has been diagnosed by excisional biopsy, treatment may consist of **close surveillance alone.** Although there is a significantly increased risk of developing a subsequent infiltrating cancer in either breast, the majority of women (75%) will not. The other option is **prophylactic bilateral total mastectomy.** Tamoxifen, has been shown to greatly reduce (40%) the risk of recurrent cancer.

Stage I cancer is an invasive (usually ductal) cancer less than 2 cm in size with no nodal or distant spread, i.e. localized to the breast. Stage I disease is also highly curable.
The **treatment of stage I disease** is either **breast-conserving therapy** or **modified radical mastectomy**. Breast conserving therapy includes removal of the tumor with a safe margin of normal tissue around it **(lumpectomy, segmentectomy or quadrantectomy)**, axillary sampling and adjuvant radiotherapy after the surgical wound has healed (2-3 weeks). Modified radical mastectomy eliminates the need for radiation. **Tamoxifen** is added to many treatment regimens if the tumor is **ER/PR positive** because of its potential to reduce recurrence. If nodal metastasis is found on axillary sampling, it changes the stage from a clinical stage I to a pathological stage II.

Stage II is the presence of a small tumor (<2 cm) with isolated nodal metastasis, a moderate size (2-5 cm) tumor with or without scattered nodal metastasis, or the presence of a large tumor (>5cm) without nodal metastasis. Stage II is divided into A and B depending on the combination of features.
The treatment options for stage II disease are similar to those for stage I, with the combination of **local** (surgery, radiotherapy) and **systemic** (chemotherapy, hormonal therapy). The choices are based on the character and extent of a particular patient's disease within the confines of the stage II parameters. A large tumor, for example may mitigate for mastectomy; multiple involved lymph nodes may mitigate for more radical chemotherapy.

Stage III is disease that is spread beyond the breast. The three features that, by themselves, establish stage III are:
• **Matted, fixed axillary nodal metastasis (N2)** or
• involvement of the **chest wall or the skin (T4)** by tumor, or
• the presence of **internal mammary (N3)** lymph node metastasis.
These features may be combined with any other T or N category. A large (T3/>5 cm) tumor with mobile nodal metastasis (N1), also is a stage III. Stage III is also divided into A and B. Stage IIIB is either an extensive tumor or internal mammary node involvement with any combination of the other features.
Treatment of stage IIIA usually includes modified radical or radical mastectomy in combination with radiation, chemotherapy and possibly hormonal therapy. The chemotherapy may also be given preoperatively **(neo-adjuvant)** to reduce the extent of disease. Radical chemotherapy may also be indicated. Stage IIIB disease usually involves diagnosis by biopsy with systemic therapy playing the primary treatment role. Surgery may be done later to try and gain local control. **Inflammatory** breast cancer (T4d) is a grave, special case not classified by stage, but is also treated in this way.

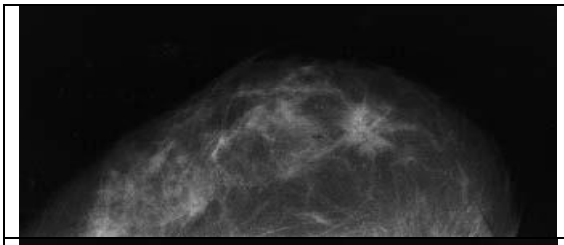
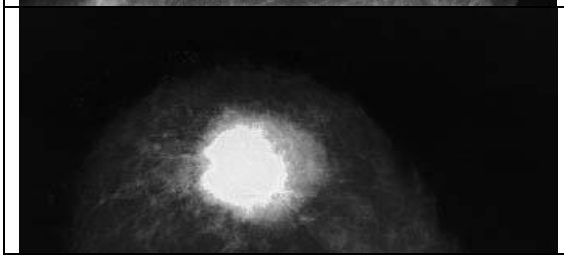
Stage IV is distant **metastasis** (including supraclavicular lymph nodes on the same side as the primary tumor).
Breast cancer most commonly spreads to **bone, lungs, brain** and **liver**. Diagnosis of metastasis may be made by bone scan, brain scan, X-ray, abdominal CT and lab tests. Stage IV disease is treated systemically with the goal of retarding the progress of the disease. Mastectomy may be used for local control.

Breast imaging modalities
MAMMOGRAPHY: Mammography refers to breast imaging with the use of x-rays. The x-ray images are produced by the attenuation (absorption) and scattering of the x-ray beam by the various breast tissues before the beam reaches and exposes the film.

DEFINITION OF MAMMOGRAPHIC LESIONS
The sensitivity of mammography is initially determined by the relative background composition of the breast parenchyma. The denser the breast the less sensitive it is to the detection of small masses. The

mammograms are initially evaluated for the presence of masses, architectural distortion, asymmetric parenchyma, calcifications and skin changes.
Mammographicaly a ***mass*** is defined as a space occupying lesion seen in two different projections, with ***density*** defined as a collection seen in only one view. A mass is then further characterized by it's shape, margins, density, size, orientation and presence of associated calcifications.

Shape is a generally nonspecific characteristic, both benign and malignant masses tend to develop in one spot and grow circumferentially. An irregular shape is more concerning as its suggests indistinct or irregular margins. Some skins lesions, warts and seborreic keratoses, have typical appearances due to the variegated surfaces and occasionally radiolucent/air halo. Some intramammary nodes have a typical reniform configuration with a fatty notch.
Margin or contour analysis characterizes the transition zone from mass to surrounding parenchyma or fatty tissue. The significance arises from the tendency of invasive carcinoma to infiltrate adjacent tissue and have indistinct, microlobulated or frankly spiculated margins.
Well circumscribed or sharply marginated masses, either with or without a radiolucent halo, are probably benign. If all margins remain sharply circumscribed on magnification views , and there is no associated suspicious calcification, 98% to 99% will be benign with a differential of fibroadenoma, cyst or intramammary lumph node
Circumscribed masses with irregular or microlobulated margins on magnification views should be considered suspicious and biopsy suggested.

	Similarly if the margins remain indistinct or ill-defined on additional special views the lesion must be considered suspicious and biopsy considered.
	

Masses with spiculated margins are suggestive of malignancy. With cancer, the spicules represent finger-like projections of the malignant cells. Other spiculated densities may represent radial scar/sclerosising adenosis but are still suspicious and can be associated with tubular carcinoma. A spiculated density may also be secondary to a post operative scar.
Density describes the relative attenuation of a breast lesion compared to the normal fibroglandular tissue of the breast. ***Cancer is frequently, but not always higher in density*** than surrounding parenchyma, and can be isodense or rarely lower in density. Fat containing/radiolucent masses most frequently represent oil cysts, lipoma, galactocele, hamartoma or fibrolipoma, and are considered benign,
Calcifications can occur in the breast from many causes and be associated with both benign and malignant conditions. The pattern of distribution may also be helpful in evaluating the calcifications, with clustered, segmental and fine linear or branching patterns being more suspicious.

MAMMOGRAPHIC LESIONS: TYPICALLY BENIGN
Skin calcifications are typically small round to oval with lucent centers.
Vascular calcification is similar to elsewhere in the body and forms contiguous or interrupted dense paired tubular lines.

Coarse or popcorn like calcification *can be seen in an involuting fibroadenoma.*
The large rod shaped calcification of secratory disease/plasma cell mastitis are usually over 1mm in diameter, may have lucent centers and occasionally branch.
Small, dense rounded calcifications are usually considered benign and related to involution.
Milk of calcium is benign and represents calcium precipitate in small cysts.
Eggshell calcifications are benign
Small amorphous, indistinct, hazy rounded and flake like calcifications may be associated with both benign and malignant process and are of intermediate concern.

MAMMOGRAPHIC LESIONS: HIGH PROBABILITY OF MALIGNANCY
Pleomorphic or heterogeneous (granular) fine linear and/or branching calcifications.
Ultrasonography
B-mode ultrasonography
The main indications of breast US have been differentiation between cystic and solid lesions, evaluation of a palpable lesion in a mammographically dense breast (for example young, pregnant or lactating patient), evaluation of a lesion detected at mammography or mammographic asymmetry, detection of an abscess in an infectious breast, evaluation after breast cancer treatment and breast augmentation, evaluation of axillary lymph nodes and guidance for interventional procedures
Ultrasound can detect mammographically occult cancers, but it is generally accepted that US is not suitable for screening. Microcalcifications with no associate mass are not usually reliably detectable at US.
Currently, most solid breast lesions undergo a diagnostic or preoperative needle biopsy.

Magnetic resonance imaging
MR imaging has proved to be the most sensitive method for the detection of invasive breast cancer. The detection is based on lesion enhancement after contrast agent administration.
Diagnostic criteria
The diagnostic criteria consist of both lesion morphology and enhancement kinetics. The morphologic criteria are comparable to those used at mammography. Well-defined margins indicate benignity, while ill-defined or spiculated lesions are suggestive of malignancy. Internal septations, if seen, are specific for fibroadenomas.
Enhancement in benign lesions is homogeneous and proceeds centrifugally. Benign lesions also usually enhance less and do so more slowly than malignant lesions. In malignant lesions enhancement is often inhomogeneous or rim-like and tends to proceed centripetally. Enhancement kinetics can also be analyzed by the shape of time-signal intensity curve: a continuous increase in signal intensity is considered a benign finding, a rapid increase followed by a washout phenomenon is considered malignant.

Other imaging modalities
Computed tomography has not been recommended for breast imaging, mainly because of high radiation dose. It has been successfully used in regional staging of small breast cancer before breast conserving surgery.
Electrical impedance scanning is a new technique, which is based upon the principle that malignant cells exhibit altered local dielectric properties and show measurably higher conductivity values.

Image-guided needle biopsies
Fine-needle aspiration biopsy
Fine-needle aspiration biopsy, usually performed with a 20–25 gauge needle, is a widely used method for further evaluation of breast lesions other than microcalcifications. In qualified hands it decreases the need for surgical biopsies. The reported overall accuracy is from 81% to 98%. Lesions liable to misinterpretation include phyllodes tumor, lobular and tubular carcinomas.

Core needle biopsy
Histologic examination is more likely than a cytologic examination to give a definitive diagnosis of a breast lesion. It is the only non-operative method that differentiates between an invasive and noninvasive tumor, and it has therefore become the preferred biopsy method. The reported sensitivities range from 89% to

100%, and the specificities from 96% to 100% Surgery is needed in case of atypical ductal hyperplasia or phyllodes tumor, radial scar, papillary lesions, atypical lobular hyperplasia and LCIS as well as in cases with suspicious microcalcifications despite a benign diagnosis at core biopsy

Guiding methods

The oldest and previously the most common guiding method is palpation, which is no longer preferred. US has emerged as the optimal guidance technique for percutaneous biopsies. The advantages of US over stereotactic x-ray guidance include real-time monitoring, the lack of ionizing radiation, the almost unlimited applicability to the lesion, the ability to use the shortest route to the lesion, the possibility of multidirectional sampling (FNAB) and the availability of the equipment. Mammographic stereotactic guidance is used for lesions not seen well at US, microcalcifications with no associated mass as the most important type

DCIS - Ductal Carcinoma In Situ

Malignant cells proliferate within the pre-existing ductal structures and basement membranes to replace benign lining cells located within the ducts proximally and the lobules distally.

Gross Pathology of DCIS: By gross examination, most lesions of DCIS do not present with a distinct appearance. The background breast tissue may be fatty or fibrous, and slightly firm on palpation. Only extensive comedo type of DCIS depicts visible abnormality. The involved area has a granular character. By squeezing the area, necrotic material exudes from the ducts.

Classification of DCIS

Classification of DCIS is based on the microscopic characters of
1. architecture (growth pattern)
2. nuclear features

Classification of DCIS by the Predominant Architecture

1. Papillary/micropapillary type
- Multiple isolated papillary projections, most of which lack fibrovascular stalks
- Papillae become fused to form Roman bridges and arches giving the impression of rigidity

2. Cribriform type
- Tumor cells are arranged in a sieve-like pattern, multiple small round glands growing in a larger gland or duct. These glands are confluent without fibrous walls.
- Most tumor cells have low nuclear grade

3. Solid type
- Tumor cells fill the ducts and ductules as solid sheets
- Nuclear grade is predominantly intermediate or high grade. Necrosis is usually focal

4. Comedo type
- Central necrosis of the involved ducts is a prominent feature
- Calcification occurs within the necrosis
- High nuclear grade in most tumors.

Prognosis of DCIS (by pathological analysis)

1. Nuclear grade is more important than architecture (growth) pattern
2. Status of surgical margin
3. Lesion size

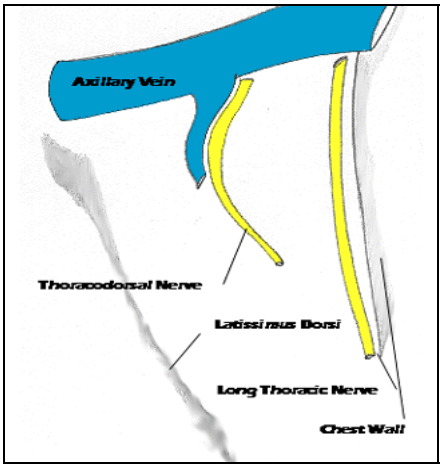
MASTECTOMY: Definitions of Standard Mastectomy Types

Modified Radical Mastectomy (or Total Mastectomy with formal ipsilateral axillary dissection): This surgical procedure removes the entire breast parenchyma including the nipple-areolar complex. The pectoralis muscles (minor and major) are left intact unless part of it needs to be resected to obtain clear margins. An ipsilateral axillary dissection is included.

Simple Mastectomy (or Total Mastectomy): This includes removal of entire breast parenchyma including the nipple-areolar complex. The pectoralis muscles (minor and major) are left intact unless part of it needs to be resected to obtain clear margins. No axillary dissection is included.
Simple Mastectomy with Sentinel Lymphadenectomy: This surgical procedure removes the entire breast parenchyma including the nipple-areolar complex. The pectoralis muscles (minor and major) are left intact unless part of it needs to be resected to obtain clear margins. An ipsilateral sentinel lymphadenectomy is included.
Subcutaneous Mastectomy: The entire breast parenchyma is resected while preserving the nipple-areolar complex and its vascular viability. No axillary dissection is performed.
Skin Sparing Total Mastectomy (or reconstruction ready Mastectomy): This is the equivalent of a total mastectomy (with or without axillary dissection). The skin flaps however are designed to be long and the skin resection is minimal. The actual resection site for the mastectomy is a round incision. This mastectomy is used for immediate reconstruction with breast implants (Becker or standard).

Technical Steps for THE TOTAL MASTECTOMY
The upper skin flap is extended to the clavicula. The lower skin flap is then developed using the electrocautery. It is extended to the aponeurosis recti. Laterally the dissection is extended to the edge of the latissimus dorsi muscle. Starting at its medial aspect, the skin flaps are retracted and the breast meticulously dissected from the pectoralis major muscle. Perforator vessels can be electrocoagulated with the electrocautery. The dissection is extended to the lateral aspect of the pectoralis major muscle.
The Axillary dissection can be performed either as a standard axillary lymphadenectomy or as a Sentinel lymphadenectomy.
Complications
***Injury to the Intercostobrachial (Sensory) Nerve*:** It will result in a permanent numbness in the lateral aspect of the axillary and the inferior aspect of the arm.
***Injury to the Long Thoracic (Motor) Nerve*:** Seen in 10% of all cases. It will result in a palsy of the Serratus anterior muscle and clinically will create a classical winged scapula.
***Injury to the Thoracodorsal Nerve*:** Leads to palsy of the latissimus dorsi muscle.
***Lymphedema*:** This is a complication which occurs less frequently with the standard axillary dissections. However, it is commonly seen when an axillary dissection is combined with axillary radiation.
Seroma:
Redundant Axillary Fat Pad:

STANDARD AXILLARY LYMPHADENECTOMY
In 1997, a standard axillary lymphadenectomy or an axillary dissection is an integral part of the staging protocol of patients diagnosed with invasive breast carcinoma. Recently, a less invasive version, lymphadenectomy, the axillary sentinel lymphadenectomy, has emerged as a potential replacement for this technique.



1. The Long Thoracic Nerve runs along the chest wall. It innervates the Serratus Anterior muscle. The best access to this nerve is located at the junction of the chest wall and below and posterior to the axillary vein. The lymph node bearing tissue should be retracted medially.
2. The Thoraco-Dorsal Nerve runs parallel to the subscapular vein for two to three centimeters and then, dives posteriorly. It innervates the Latissimus Dorsi muscle.
3. The Intercostal Brachial Nerve is not always identified with accuracy. It is a sensory neural bundle for the inferior aspect of the arm. It is found under the axillary vein and usually runs parallel to it.

Technical Notes

1. Number of Resected Lymph Nodes: The average number of axillary lymph nodes resected is between 15 to 25.

2. Postoperative Drainage: The Drains are left in place on the average of 5-6 days.

3. Numbness at inferior aspect of Arm: In the majority of cases the intercostal brachial nerve and its branches, are frequently severed.

4. Axillary Specimen Handling: The surgeon should always orient the specimen with silk sutures indicating LEVEL I and LEVEL III before sending it to the pathologist.

Axillary Sentinel Lymphadenectomy for Breast Cancer

The theory behind this technique is, when a sentinel axillary lymph node (or first node in the lymphatic drainage path) can be identified, it correlates with the status of the rest of the lymph nodes of the axilla. An axillary lymph node can be identified in 92% of the patients with breast cancer using combined dye and scintigraphic mapping techniques. In addition, a sentinel lymph node will be found positive (with metastatic tumor) in all patients with axillary invasion, and a negative sentinel lymph node equates to an axilla negative for tumor invasion. One of the positive aspects of a sentinel lymphadenectomy is that it will eliminate most of the morbidity associated with standard axillary dissection.

The Technique

There are two methods to identify an axillary sentinel lymph node. ***1) Vital Blue dye technique and 2) Filtered technetium-lable sulfur colloid (scintigraphy).***

Indications

All patients requiring an axillary dissection for staging purposes. This includes patients requiring a lumpectomy with axillary dissection followed by radiation treatment or a patient requiring a standard modified radical mastectomy (Stage I, II and III).

Patients with medial lesions of the breast should be excluded as well as patients whose lesions cannot be accurately diagnosed.

Performing the Lumpectomy or Total Mastectomy

The total mastectomy or the lumpectomy should be then performed.

CONTRAINDICATIONS FOR BREAST CONSERVATIVE SURGERY:

Pregnancy/ Multicentric tumour/ Previous irradiation/ Collagen vascular disease/ tumour > 4 cm in size/ N1 stage.

Breast Reconstruction After Mastectomy

Common breast reconstruction techniques include synthetic implants and autologous tissue flaps (including the latissimus dorsi flap and the transverse rectus abdominis myocutaneous flap). Procedures may be implemented immediately following mastectomy or can be deferred until after adjuvant therapy is completed.

Techniques of Reconstruction

Implant Reconstruction

An implant consists of a silicone shell that contains saline or silicone gel and is available in a variety of shapes and sizes. To replace missing breast volume, tissue expanders are inserted submuscularly after the mastectomy. The expander is placed deep in relation to the pectoralis major and serratus anterior. Initially, a minimally inflated tissue expander is placed; then it is slowly inflated over a period of weeks, allowing the overlying tissues to stretch. After total expansion is achieved and the tissues have been allowed to stretch (usually over a period of four to six months), the expander is replaced with a permanent implant

Autologous Tissue Flaps

Of several autologous flap options, the most common are the ***latissimus dorsi flap and the TRAM flap.***

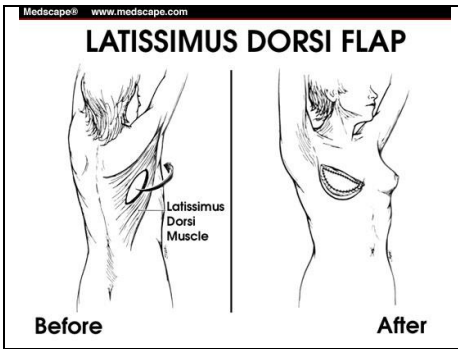
The *latissimus dorsi flap* utilizes the back muscle with its overlying tissue and skin, rotated around to the mastectomy defect. The latissimus dorsi flap is appropriate for replacing small- to moderate-sized breasts; candidates include women who smoke, have extensive abdominal scarring, or are morbidly obese. The

disadvantages: This surgery requires an additional scar on the patient's back and occasionally diminishes overhead strength.

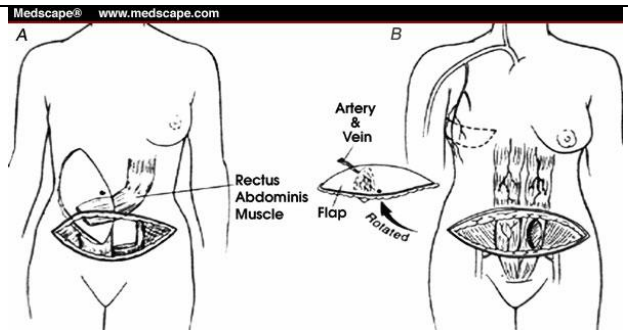
The *transverse rectus abdominis myocutaneous (TRAM) flap* is currently considered the gold standard of breast reconstruction. This autologous tissue transfer is well suited for immediate reconstruction. ***The conventional TRAM flap or pedicle flap is supplied superiorly by the superior epigastric artery and vein***. The flap is elevated from an inferior to a superior position, leaving the top portion of the muscle and the superior pedicle intact.

Free TRAM: In this procedure, the inferior blood supply, the deep inferior epigastric vessels, and the superior pedicle are divided, then the entire flap is brought up to the mastectomy site. Fine suturing is used to reattach or anastomose the inferior epigastric vessels microscopically into the recipient vessels -- in most cases, the thoracodorsal vessels.

The *gluteal free flap* is another option for autologous breast reconstruction. This technique may appeal to many women with excess tissue in their buttocks; however, it is used rarely because of the technical complexity of the flap. It also creates a significant donor defect for many women.



A typical latissimus dorsi flap procedure, in which autologous tissue is rotated to the mastectomy defect.



A conventional transverse rectus abdominis myocutaneous (TRAM) flap procedure (A) and a free TRAM procedure (B), which improves blood supply to the flap.

SALIVARY GLAND

A. **Parotid Gland**

1. Located on side of face, anterior to mastoid tip and external auditory canal, inferior to zygomatic arch, and superior to the lower border of the angle of the mandible. Anteriorly, it overlaps the masseter muscle.
2. Stenson's duct enters oral cavity through buccal mucosa opposite upper 2nd molar.
3. Parasympathetic secretory afferents to the parotid leave the inferior salivary nucleus with the glossopharyngeal nerve and travel via Jacobson's plexus in the middle ear to synapse in the otic ganglion. Post-synaptic fibers are distributed to the parotid by the auriculotemporal nerve.
4. Facial nerve passes through this gland.

B. **Submandibular Gland**

1. Beneath floor of the mouth, inferior to mylohyoid muscles and superior to digastric muscle.
2. Marginal mandibular branch of the facial nerve travels in the fascia on the lateral surface of this gland.
3. Parasympathetic secretory afferents to the submandibular gland arise from the superior salivatory nucleus, and leave the brainstem in the facial nerve. They exit the facial nerve at the geniculate ganglion and travel via the chorda tympani to the lingual nerve. Fibers synapse in the submandibular ganglion, and post-synaptic fibers then enter the gland.
4. The lingual and hypoglossal nerves lie deep to this gland.
5. Wharton's duct enters the floor of the mouth near the lingual frenula.

C. **Sublingual Glands** - located below the mucous membrane of the floor of the mouth, adjacent to mandible and mylohyoid muscle. Ten to twelve small caliber ducts drain the gland, some emptying into the submandibular duct, and others draining directly into the floor of the mouth.

D. **Minor Salivary Glands** - small collections of salivary gland tissues are scattered throughout the oral mucosa, and can also be seen in the pharynx, supraglottis, nose and sinuses.

Parotid Gland:

- Parotid gland appears on the 4th week of gestational life from the epithelium of the oro-pharynx.
- Agenesis of the parotid glands is rare; may be associated with other facial abnormalities.
- Cyst arising from the first branchial cleft may be located within the parotid gland
- Largest of the salivary glands and it overlaps the masseter muscle.
- VIIth Nr. passes through and divides the gland into a superficial and deep lobe
- The deep surface of the gland lies alongside the back of the throat, near the tonsils
- Stenson's duct enters oral cavity through buccal mucosa opposite upper 2nd molar.
- Parasympathetic secretory afferents to the parotid leave the inferior salivary nucleus with the glossopharyngeal nerve and travel via Jacobson's plexus in the middle ear to synapse in the otic ganglion. Post-synaptic fibers are distributed to the parotid by the auriculotemporal nerve.

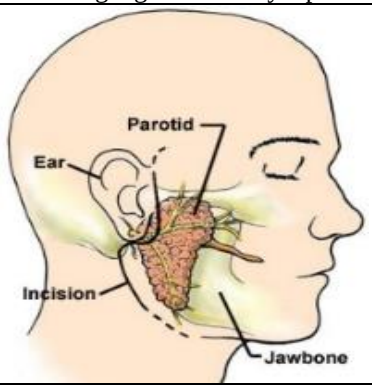


Figure 1 - The superficial lobe of the parotid gland lies outside the mandible (jawbone) while the deep lobe wraps around the back angle of the mandible. The most common incision is represented by the continuous line and possible extensions are indicated by the dotted lines.

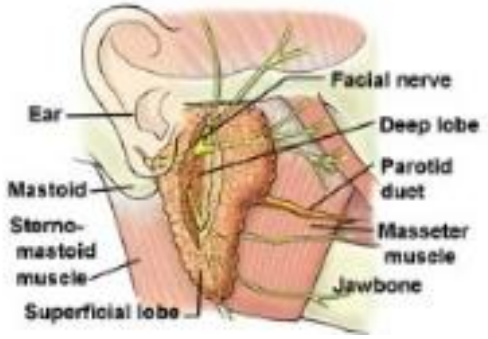


Figure 2 - The parotid lies on the masseter muscle. It lies in front of the sternomastoid muscle. The facial nerve divides the parotid gland into superficial and deep lobes.

Submandibular Gland

- Beneath floor of the mouth, inferior to mylohyoid muscles and superior to digastric muscle.

- Marginal mandibular branch of the facial nerve travels in the fascia on the lateral surface of this gland.
- Parasympathetic secretory afferents to the submandibular gland arise from the superior salivatory nucleus, and leave the brainstem in the facial nerve. They exit the facial nerve at the geniculate ganglion and travel via the chorda tympani to the lingual nerve. Fibers synapse in the submandibular ganglion, and post-synaptic fibers then enter the gland.
- The lingual and hypoglossal nerves lie deep to this gland.
- Wharton's duct enters the floor of the mouth near the lingual frenula.

Sublingual Glands - located below the mucous membrane of the floor of the mouth, adjacent to mandible and mylohyoid muscle. Ten to twelve small caliber ducts drain the gland, some emptying into the submandibular duct and others draining directly into the floor of the mouth.
Minor Salivary Glands - small collections of salivary gland tissues are scattered throughout the oral mucosa, and can also be seen in the pharynx, supraglottis, nose and sinuses. Minor glands are muco-serous only Ebner gland (posterior lingual gland) like parotid, is pure serous.

TRAUMA:
A: Laceration: Parenchymal damage only – usually heals by itself.
Injury to Stenson's duct – should be repaired over a small catheter.
Injury to facial nerve – should be repaired within 72 hours.

- *Injury to Stenson's duct may cause chronic salivary fistula.*
- *Acute obstruction or ligation of parotid duct causes complete atrophy of the gland*.

B: Any foreign body should be removed.

SIALOADINITIS:
- In viral infection Mumps is the most common infection. Its treatment is symptomatic.
- Low grade bacterial infection of salivary gland is usually self limiting.
- Stenson's duct obstruction by Stone/stricture also causes intermittent painful swelling → Sialogram should be done → obstruction should be relieved by →

1. Transorally (if the stone is near the duct end).
2. By external incision (If the stone is deep).
3. Parotidectomy (If multiple stone / stricture is present).

ACUTE SUPPURATIVE PAROTITIS:
- Characterized by presence of pus and seen in debilitated/ dehydrated/ or in patients with poor oral hygiene.
- Commonest causing organism is Staph. aureus.
- Initial treatment is proper hydration/ antibiotics/ improving oral hygiene.
- If abscess develops then it is drained by giving a J shaped incision (see 1st diagram).
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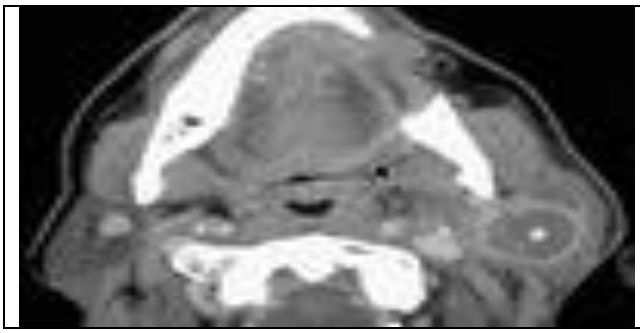
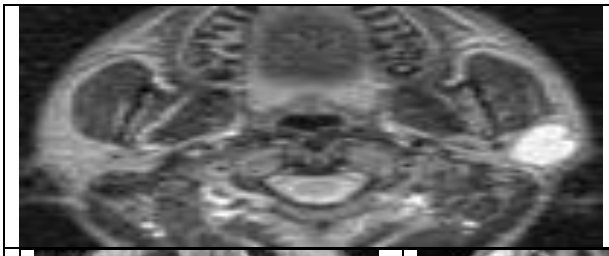
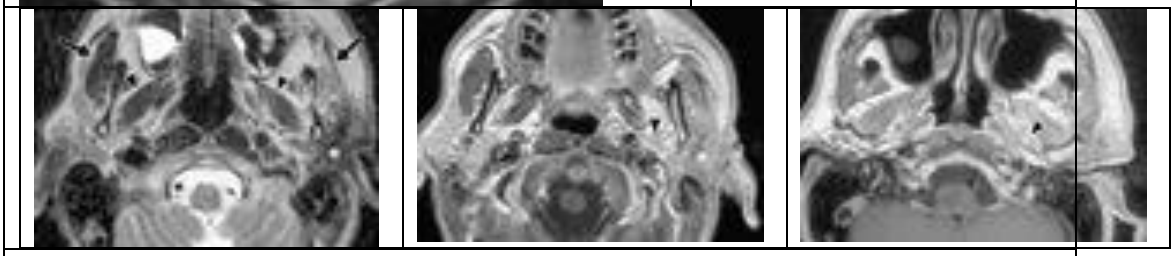


Parotid gland, Fig. 1
Axial contrast-enhanced CT images of parotid glands. Increased attenuation of left parotid gland due to sialadenitis, with intraglandular abcedation (asterisk). Note associated cellulitis of parapharyngeal space (arrowhead).



Parotid gland, Fig. 2
Axial T2-weighted spin-echo image of parotid glands. Lobulated soft tissue mass with high signal intensity, in the superficial part of the left gland. Pleomorphic adenoma.



Parotid gland, Fig. 3: Axial T2-weighted (a) and gadolinium-enhanced T1-weighted spin-echo images (b 1 cm caudal to c) of a patient with a history of left facial nerve paralysis for several months. Ill-defined soft tissue mass in the left parotid gland (asterisk); by perineural tumour spread along the auriculotemporal nerve (arrowhead, b-c), the neoplasm reaches the main stem of the mandibular nerve, causing denervation muscle atrophy of the masticator muscles (compare masseter muscles (arrows) and lateral pterygoid muscles (arrowheads, a).

SALIVARY GLAND TUMORS

- Tumors of the salivary glands are grouped into epithelial, nonepithelial, and metastatic categories. Benign epithelial tumors include pleomorphic adenoma (80%), Warthin tumor, monomorphic adenoma, intraductal papilloma, oncocytoma etc.
- Benign nonepithelial tumors (mesenchymal origin) include lipoma, hemangioma, lymphangioma (cystic hygroma), and neural sheath tumors.
- Pleomorphic adenomas make up 70% of parotid gland tumors and 50% of submandibular gland tumors.
- Of minor SGTs, 50% are malignant.
- *Mucoepidermoid cancer is the most common parotid malignancy.*
- Overall, *adenoid cystic carcinoma is the most common malignant tumor of all minor salivary glands* and, specifically, the submandibular gland

BENIGN EPITHELIAL TUMORS

1. Pleomorphic adenoma

- Commonly located at the tail of the parotid.
- Lesions arising from the deep lobe develop primarily within the parapharyngeal space and present late with symptoms related to pharyngeal compression
- It consists of epithelial and connective tissue. It is round, smooth, and freely mobile.
- The term pleomorphic adenoma describes its multiples histological components, including myxoid, mucoid, chondroid, and other element.
- Malignant mixed tumour has a tendency for perineural and perivascular invasion and significant cellular atypia
- It has a thin, delicate capsule with occasional *projections into the surrounding parotid tissue*, so obtaining clean margins is mandatory to minimize recurrence.
- If the parotid is the gland involved, *superficial parotidectomy* with standard facial nerve dissection and preservation is the procedure of choice.

2. Warthin tumor (ie, papillary cystadenoma lymphomatosum, cystic papillary adenoma, adenolymphoma)

- It is the second most common benign tumour of the parotid gland.
- In gross appearance, it is a smooth, soft parotid mass.
- It is well encapsulated and contains multiple cysts.
- Histologically, it has a heavy lymphoid stroma and aciniform epithelial cells lining the cystic areas with papillary projections.
- Malignant transformation has not been observed. The recurrence rate is 5%.
- The Warthin tumor tends to be bilateral (10% of cases)

3. Lymphoepithelial hyperplasia (Mikulicz disease)

- Manifest as a diffuse enlargement of the parotid gland, or it may manifest as a discrete mass.
- Histologically, the lesion is composed of a diffused, well-organized lymphoid tissue and lymphocytic interstitial infiltrate.
- More frequent in females, with peak incidence in the fourth and fifth decades.
- Growth of this tumor is slowly progressive, and it gives rise to pain around the ear or the retromandibular area.

4. Intraductal papilloma

Intraductal papilloma is a small, smooth lesion that is found in the submucosal layer. Microscopically, it consists of a cystically dilated duct partially lined with a cuboidal epithelium with complex anatomizing papillary fronds filling the cystic area.

5. Oxyphil adenoma (oncocytoma)

Oncocytomas of the salivary glands are very uncommon.

Such neoplasms occur in women, after fifth decade (female-to-male ratio of 2:1), and the superficial lobe of the parotid is commonly involved.

BENIGN NONEPITHELIAL TUMORS

Hemangiomas

Two forms, capillary and cavernous, develop in the major salivary glands. The capillary type is the most prevalent tumor in the first year of life. Capillary hemangiomas are rapidly growing, lack a capsule and are formed by purple, spongy, lobular masses that infiltrate salivary gland tissue. Observation is recommended in children.

Cavernous hemangiomas, which present in an older age group, rarely show spontaneous regression. Recurrent ulceration or bleeding may require conservative surgical resection.

Lymphangioma (cystic hygroma)

They manifest as painless masses that may involve parotid, submandibular, or both. Diagnosis is made based on clinical findings. Surgical excision with preservation of the vital structures is the treatment of choice.

Lipoma

These tumors manifest as soft, mobile, painful masses and peak in the fifth and sixth decades, with a male-to-female ratio of 10:1. They are slow-growing tumors with an average diameter of 3 cm. Treatment is surgical excision.

Metastatic disease of the parotid gland

Melanoma (46%), squamous cell carcinoma (37%), and a variety of tumors (17%) are included in this category.

MALIGNANT TUMOURS:

Mucoepidermoid carcinoma, Adenoid cystic carcinoma, Adenocarcinoma, Malignant mixed tumour, Acinic cell carcinoma, epidermoid carcinoma.

Acinic cell carcinoma:

It is a rare, low grade malignancy commonly seen in parotid. Infrequently invade the facial nerve and are late to metastasize (to lung).

Mucoepidermoid carcinoma:

Most common Major salivary gland tumour

It can be of low grade or high grade type. High grade version is locally aggressive and prone for invasion of nerves and vessels and to early metastasis (to regional nodes).
Treatment of high grade type is generous primary excision with regional node dissection followed by radiotherapy.

Adenocarcinoma:
It is more common in minor salivary glands than parotid. It again has a low grade and high grade type and high grade has a very poor prognosis.

Adenoid cystic carcinoma:
It makes up one fourth of malignant salivary gland tumours. Lung is most common metastatic site but it is known for its prolonged natural history (eg. Pt. may live for 10-15 years even after lung metastasis). When visceral or bone metastasis occurs prognosis is poor. Adenoid cystic carcinoma invades nerve tissue. Treatment is wide surgical excision with radiation therapy.

Clinical:

- SGTs manifest as a painless mass on the face (parotid), the angle of the jaw (parotid tail, submandibular), neck (submandibular), or a swelling at the floor of mouth (sublingual).
- New onset of pain, rapid growth of the mass, facial nerve weakness, paresthesias, and hoarseness of the voice are indicators of possible underlying malignancy.
- Trismus usually represents invasion to the masseter or pterygoid muscles. Skin involvement and fixation to the mastoid tip are also signs of malignancy.

Etiology: An associated long-standing history of smoking and a strong family history may be risk factors. SGTs are indolent, painless, and well-circumscribed tumors.

TREATMENT:

Medical therapy: Inflammatory, infectious masses (eg, reactive, fungal), and lymphoma should be treated medically.
Salivary gland excision is also sometimes done for symptomatic, recurrent chronic gland infection, refractory to conservative treatments.

Surgical therapy:
Standard in the management of SGTs is surgical therapy.
Treatment of the benign neoplasm is complete surgical excision of the affected gland -Superficial parotidectomy with nerve preservation. Tumor spillage of a pleomorphic adenoma is undesirable because it can lead to tumor recurrence and should be avoided.
Excision of the tumor with clear margins is the aim for malignant tumours. No adjuvant chemotherapy is required.

PLASTIC SURGERY

WOUND HEALING: Normal wound healing comprises a combination of regeneration and repair. Three mechanisms are involved:

- ***epithelialization,***
- ***wound contraction, and***
- ***extracellular matrix synthesis***.

During repair, a complex chain of events eventually leads to the formation of a scar. The process requires: phagocytosis, chemotaxis, mitogenesis, and the synthesis of collagen and extracellular matrix components. In certain circumstances, the cellular processes that contribute to repair become unregulated, leading to excessive scarring in the form of hypertrophic scars and keloids.

TYPES OF HEALING:

There are four general types of wound healing:

1. Primary,
2. Delayed primary,
3. Secondary,
4. Healing that occurs in partial-thickness wounds.

Primary Healing: when wound is closed within hours of its creation.

- The wound edges are reapproximated directly using sutures or by some other mechanical means.
- Collagen metabolism provides long-term strength to the wound when normal synthesis, deposition, and cross-linking of the collagen occur.
- Matrix metalloproteinase enzymes regulate collagen and extracellular matrix degradation and allow for remodeling of the wound, leaving a relatively narrow scar.
- Epithelialization provides coverage of the wound surface and acts as a barrier from bacterial invasion.

*Delayed Primary Healing: C*ontaminated wound is left open to prevent wound infection.

- The skin and subcutaneous tissues are left unopposed and closure is performed after the normal host defenses are allowed to debride the wound.
- After 3 to 4 days, local phagocytic cell recruitment into the wound has occurred and angiogenesis has begun.
- Inflammatory cells are present that destroy contaminating bacteria.
- The wound edges are approximated following a delay of several days.
- Collagen metabolism is undisturbed and tensile strength develops as if closure had been immediate.

Secondary Healing: an open full-thickness wound is allowed to close by both wound contraction and epithelialization.

- The wound decreases in size by contraction. (myofibroblast is thought to play a key role). The cells appear in the wound on approximately the 3rd day after wounding and increase in number to a maximal level between 10th and 21st day.
- They disappear as contraction is completed.

Healing of Partial-Thickness Wounds

- Partial-thickness wounds, which involve the epithelium and the superficial portion of the dermis, heal mainly by epithelialization.
- Epithelial cells within the dermal appendages, hair follicles, and sebaceous glands replicate to cover the exposed dermis.
- There is minimal collagen deposition and an absence of wound contraction.

OVERVIEW: The process of wound healing occurs as a sequential cascade of phagocytosis, chemotaxis, mitogenesis, collagen synthesis, and the synthesis of other matrix components.

Tissue Injury

- Tissue injury initiates the process of bleeding, coagulation, inflammation, cell replication, angiogenesis, epithelialization, and matrix synthesis.
- Tissue injury is characterized by microvascular injury and therefore extravasation of blood into the wound.
- Injured vessels constrict rapidly and the coagulation cascade is activated in order to limit the blood loss.
- Vasoactive amines and other mediators are released by inflammatory cells, which contribute to the leak of plasma and proteins into the wound and allow effector cells to enter.

Coagulation

- Coagulation leads to hemostasis. Platelets trapped in the clot are essential for hemostasis as well as for a normal inflammatory response. The alpha granules of the platelets contain growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-b), and platelet factor IV. These proteins initiate the wound-healing cascade by attracting and activating fibroblasts, endothelial cells, and macrophages. The platelets also contain dense bodies that store vasoactive amines, e.g. serotonin, that increase microvascular permeability.
- The end product of both the intrinsic and extrinsic coagulation pathways is fibrin.
- Fibrin is essential to early wound healing because it provides the matrix.

Early Inflammation

- The next phase of healing, inflammation, begins with the activation of complement and the initiation of the classical molecular cascade, which leads to infiltration of the wound with granulocytes within 24 to 48 hours of injury.
- the granulocytes begin to adhere to the endothelial cells in the adjacent blood vessels by a process called margination, and begin to actively move through the vessel wall, a process known as diapedesis.
- The major function of granulocytes is to remove bacteria and foreign debris from the wound, thereby helping to prevent infection.

Late Inflammation

- Macrophages are the most important cells present in the healing wound and appear to act as the key regulatory cells for repair.
- Circulating monocytes and tissue macrophages, when depleted, cause severe alterations in wound healing with poor debridement, delayed fibroblast proliferation, inadequate angiogenesis, and poor fibrosis.
- Once the circulating monocyte passes through the blood vessel wall and into the wound, it is considered a wound macrophage.
- Between 48 and 72 hours after wounding, macrophages represent the predominant cell type within the wound.
- The macrophage functions as a phagocytic cell as well as being the primary producer of growth factors responsible for both the production and proliferation of the extracellular matrix (ECM) by

fibroblasts, proliferation of smooth muscle cells, and proliferation of endothelial cells resulting in angiogenesis.

- The lymphocyte is the last cell to enter the wound during the inflammatory phase (>72 hours after wounding).

Fibroblast Migration/Collagen Synthesis

- Successful healing requires the migration of mesenchymal cells into the wound. Stimulated by growth factors, fibroblasts migrate into the wound through the ECM.
- By 7 days, they are the predominant cell type in the wound.
- At 5 to 7 days after wounding, the fibroblasts begin synthesizing collagen, which increases in a linear fashion for 2 to 3 weeks.
- Collagens provide strength and integrity for all tissues.
    - Type I collagen is the major structural component of bones, skin, and tendons.
    - Type II collagen is found predominantly in cartilage.
    - Type III collagen is found in association with type I collagen in varying ratios depending on the type of tissue.
    - Type IV collagen is found in the basement membrane.
    - Type V collagen is found in the cornea.

Angiogenesis

- Angiogenesis is the process of forming new blood vessels and is ongoing throughout the previously mentioned phases of wound healing.
- Platelets enter the wound in the earliest phase of repair and secrete, among others things, TGF-b, which indirectly promotes angiogenesis and attracts macrophages.
- The platelets also secrete PDGF, which attracts macrophages and granulocytes and promotes angiogenesis.

Epithelialization

Mitosis of epithelial cells begins 48 to 72 hours after injury.

The rate of epithelial coverage is increased if the wound does not need debridement, if the basal lamina is intact, and if the wound is kept moist.

Several growth factors modulate epithelialization. E.g. Epidermal growth factor (EGF), basic FGF and keratinocyte growth factor (KGF).

Remodeling Phase

Collagen synthesis and breakdown equilibrate to a steady state approximately 21 days after wounding.

There is ongoing collagen synthesis and collagen breakdown as the ECM is continually remodeled.

Collagen degradation is achieved by specific matrix metalloproteinases

Fibronectins are matrix molecules that are involved in wound contraction, cell-cell and cell-matrix interaction, cell migration, collagen matrix deposition, and epithelialization. They act as a scaffold for collagen deposition.

ABNORMALITY:

Excessive Wound Healing

- Hypertrophic scars and keloids are forms of excessive healing.
- Hypertrophic scars are defined as those that remain within the borders of the original scar, whereas keloids extend beyond the original scar margins.
- Wounds that cross skin tension lines, in thick skin or in susceptible locations such as the earlobe, presternal, and deltoid regions, are more prone to abnormal healing.
- Hypertrophic scars generally begin to develop in the weeks after injury, whereas keloids can develop up to 1 year later.
- Histologically, mucinous ground substance is present in large amounts in keloids, but fibroblast density is less than in hypertrophic scars.

The nonsurgical management of keloids:

1. Physical: Examples of physical forms of treatment include radiotherapy, ultrasound, cryotherapy, pressure, and laser.
2. Pharmacologic: intralesional steroids

Cleft Lip Palate

1. Epidemiology

- Cleft lip and palate represents the second most frequently occurring congenital deformity (after clubfoot deformity).
- 1/700 overall incidence for facial clefting.
- Clefting more common in Asians (1/400) and less common in African American (1/2000)
- Clefts can be unilateral or bilateral; Left side more common for unilateral
- Syndromic clefting accounts for 50-60% pts Cleft lip, cleft palate or both affects approximately 1 in 750.

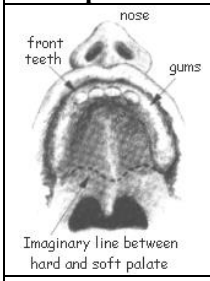
Embryology

- Weeks 5 & 6: Maxillary processes grow medially & fuse with frontonasal process
  a. Failure here > cleft lip +/- primary (anterior) palate
- Weeks 7 & 8: Tongue descent, migration & fusion of palatal shelves
  a. Failure here > cleft secondary (posterior) palate (Pierre-Robin, & other)

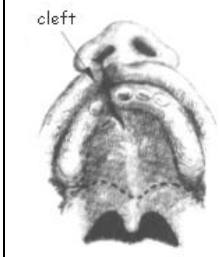
Anatomy

- The palatine processes of the maxilla and horizontal lamina of the palatine bones form the hard palate.
  - Its blood supply is mainly from the greater palatine artery.
  - The nerve supply is via the anterior palatine and nasopalatine nerves.
- The soft palate is a fibromuscular shelf made up of several muscles attached like a sling to the posterior portion of the hard palate.
  - It closes off the nasopharynx by tensing and elevating, thereby contacting Passavants ridge posteriorly.
  - The soft palate consists of the tensor veli palatini, the levator veli palatini, the musculus uvulae, the palatoglossus, and palatopharyngeus muscles.
  - CN V supplies the tensor veli palatini, while CN IX and CN X innervate the others.
  - The levator veli palatini is the primary elevator of the palate.

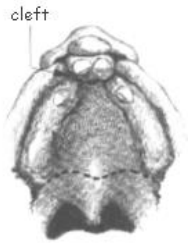
Examples of Unilateral and Bilateral Cleft Lip



Normal roof of mouth

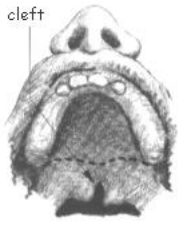


One-sided cleft lip

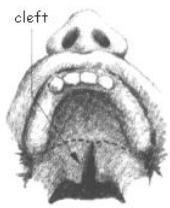


Two-sided cleft lip

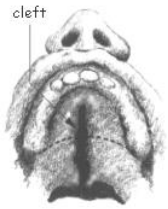
Examples of cleft palate



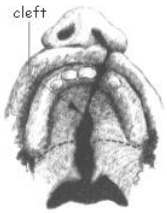
Cleft of back of soft palate



Complete cleft of soft



Cleft of soft and hard palates

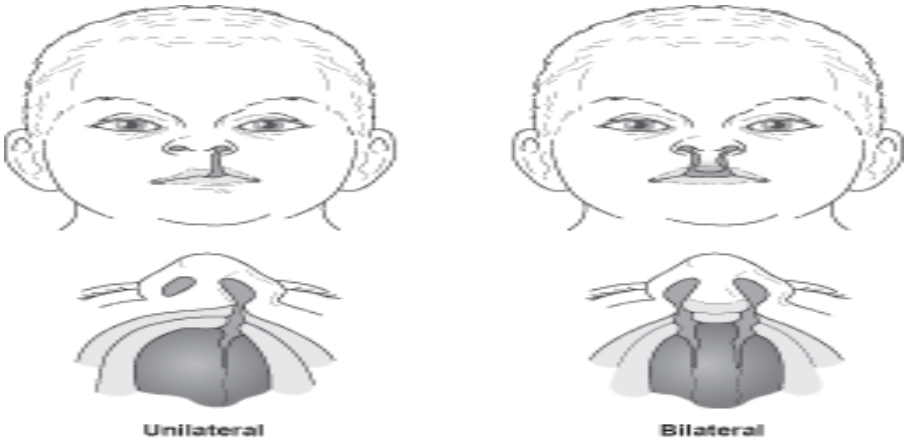


Complete cleft

	palate		of lip and palate

2. Etiologies

- Teratogens: ethanol (FAS), anti-convulsants, steroids, chemo, excess Vita A
- Maternal / intra-uterine conditions: infant of diabetic mom, amniotic bands
- Chromosomal abnormalities, monogenic causes (AR, AD, XL)
- Unknown



Cleft lip and palate

Genetics

- Nonsyndromic inheritance of facial clefting is multifactorial.
- Familial inheritance of both cleft lip and palate occurs with varying frequency, depending on whether a parent or sibling is affected.
    - For cleft lip with or without cleft palate, the risk rate for future offspring is 2% with only one parent affected, 4% with only one sibling affected, 9% with two siblings affected, and 10-17% with one parent and one sibling affected.
    - For cleft palate alone, the risk rate for future offspring is 7% with only one parent affected, 2% with only one sibling affected, 1% with two siblings affected, and 17% with one parent and one sibling affected.
- Chromosome aberrations such as trisomy D and E have increased incidence of clefts.
- More than 200 recognized syndromes may include a facial cleft as a manifestation.
    - Common syndromes with cleft palates include Apert's, Stickler's and Treacher Collins. Van der Woude's and Waardenberg's syndromes are associated with cleft lip with or without cleft palate.

3. Diagnosis -- Newborn Physical Exam

- Inspect lip & oropharynx
- Palpate palate with gloved finger (submucous cleft is not visible, but can be felt in bony palate underlying mucous membrane. This diagnosis is often missed until later childhood when speech problems arise.

4. Newborn Feeding

- Isolated cleft lip rarely causes feeding problems
- Cleft lip & palate or palate alone may require special nipples, occluders.

5. Surgical Treatment

- Cleft lip: "Rule of Tens" -- ten weeks, ten pounds, hemoglobin of 10
- Cleft palate: around 1 year, before speech develops
    a. Subsequent surgical revisions required as child grows

b. Palatal repair- repaired at approximately 9-12 months
c. Secondary repair- if needed- repaired at approximately 4-6 years
d. Alveolar cleft- repaired at 8-10 years
e. Final repair- if needed repaired at 14-16 years

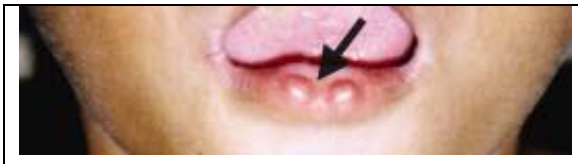
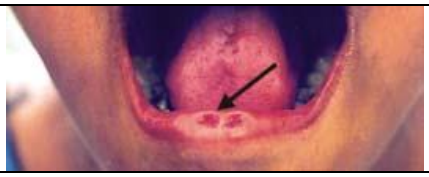
6. Associated Problems in Childhood

- ENT problems: often requires ear tubes
    a. Hearing loss (cleft palate): Cleft palate is very often associated with eustachian tube dysfunction due to an abnormal insertion of the levator and tensor veli palatini muscles into the posterior margin of the hard palate. In addition to middle ear effusion, the patients also appear to have an increased incidence of cholesteatoma (7%).
    b. Indications for myringotomy and tube insertion include a significant conductive hearing loss or persistent middle ear effusion, recurrent otitis media, or tympanic membrane retraction.
- Speech problems, often speech therapy (cleft palate): It is estimated that 75% of patients have velopharyngeal competence following primary cleft palate surgery, and this can be increased to 90-95% with directed secondary procedures.
- Dental problems, usually orthodontics
- Multi-disciplinary cranio-facial teams address child's multiple needs
- **Airway problems:** may arise in children with cleft palates, especially those with concomitant structural or functional anomalies. eg, Pierre-Robin sequence is the combination of micrognathia, cleft palate, and glossoptosis.

Van der Woude Syndrome (VWS)

About three percent of people with a cleft have VWS. VWS is inherited in an autosomal dominant pattern. Features of VWS include:

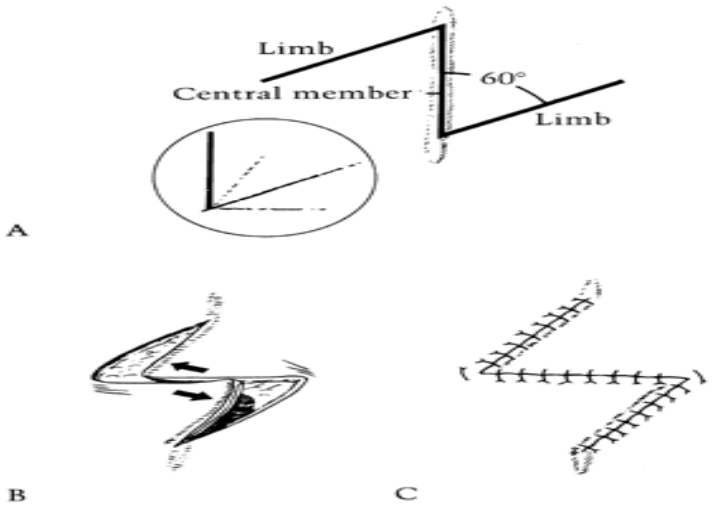
- Mounds or depressions (pits) on the lower lip
- Cleft lip, with or without cleft palate
- Cleft palate alone
- Missing teeth

	
Lip mounds in patient of Van der Woude Syndrome	Lip pits in patient with Van der Woude Syndrome

PRINCIPLE OF PLASTIC SUREGRY:

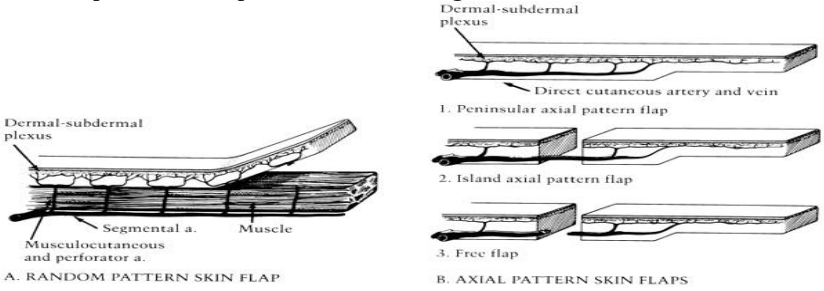
Geometric Principle of the Z-Plasty

- The Z-plasty is an ingenious principle that can be applied to revise and redirect existing scars or to provide additional length in the setting of scar contractor.
- The Z-plasty involves the transposition of two triangular flaps.
- The limbs of the Z must be equal in length to the central limb but can extend at varying angles (from 30–90 degrees) depending on the desired gain in length.
- The classic Z-plasty has an angle of 60 degrees and provides a 75% gain in length of the central limb by recruiting lateral tissue.



SKIN FLAPS:

- Unlike a graft, a flap has its own blood supply.
- Flaps are usually needed for covering recipient beds that have poor vascularity; reconstructing the full thickness of the eyelids, lips, ears, nose, and cheeks; and padding body prominences (i.e., for bulk and contour).
- A skin flap consists of skin and subcutaneous tissue that are transferred from one part of the body to another with a vascular pedicle or attachment to the body being maintained for nourishment.
- If the flap is pedicled, it is important that the pattern is cut to include the base of the flap and that it is made a little longer and wider than needed.
- The pattern is then tried again, being certain each time that it is shifted so that the base is held in a fixed position and not allowed to shift with the flap.
- The final pattern must be larger than needed, particularly its length, to avoid undue tension and kinking.
- Planning a transposition or rotation flap requires special attention to ensure that the most distal part of the flap is of sufficient length.



RANDOM & AXIAL FLAPS

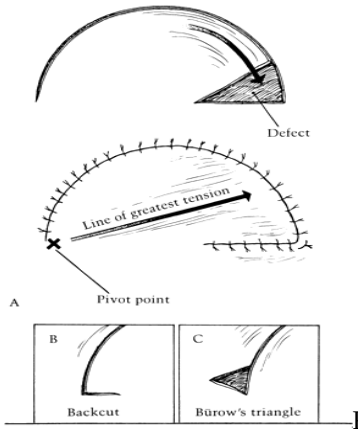
Local skin flaps are of two types:

- Flaps that rotate about a pivot point (rotation, transposition, interpolation flaps)
- Advancement flaps (single-pedicle advancement, V-Y advancement, Y-V advancement, and bipedicle advancement flaps).

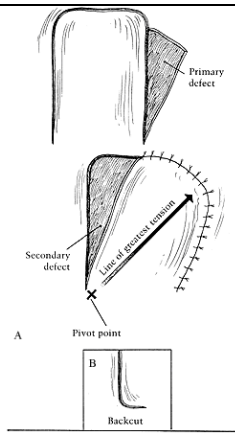
Flaps Rotating About a Pivot Point

- Rotation, transposition, and interpolation flaps have in common a pivot point and an arc through which the flap is rotated.
- The radius of this arc is the line of greatest tension of the flap.

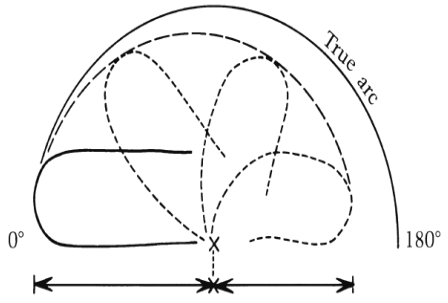
- The rotation flap is a semicircular flap of skin and subcutaneous tissue that rotates about a pivot point into the defect to be closed.
- A flap that is too tight along its radius can be released by making a short back-cut from the pivot point along the base of the flap.
- A triangle of skin (Burow's triangle) can be removed from the area adjacent to the pivot point of the flap to aid its advancement and rotation.
- The transposition flap is a rectangle or square of skin and subcutaneous tissue that also is rotated about a pivot point into an immediately adjacent defect.
- Bilobed flap: The key to a successful bilobed flap is an area of loose skin to permit direct closure of the secondary flap defect.



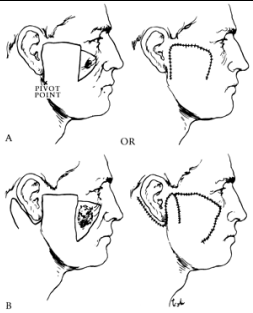
Rotation flaps



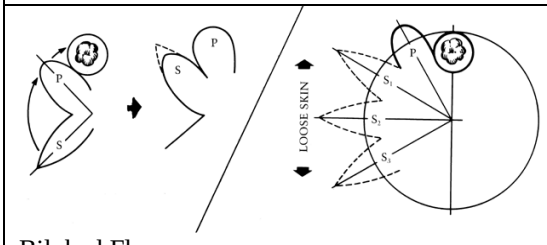
Transposition flaps



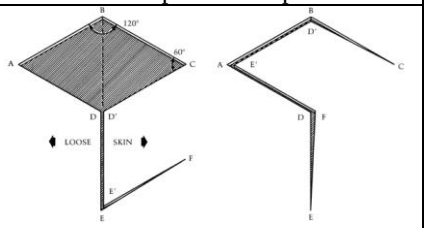
- Rotational flap



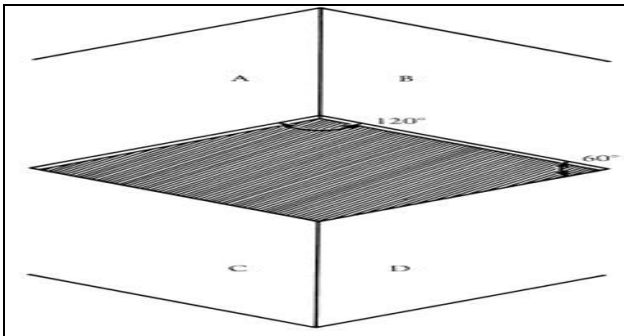
- Transposition flap



Bilobed Flap



Limberg flap

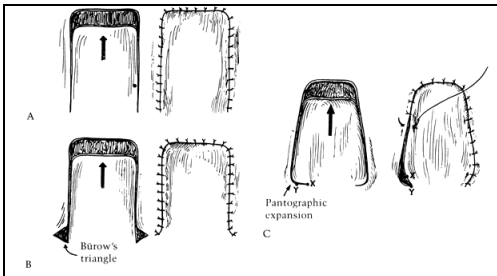


Four Limberg flap

- The Limberg flap is another transposition flap. This flap, like the bilobed flap and the Z-plasty, depends on the looseness of adjacent skin.
- A Limberg flap is suitable only for closure of rhomboid defects with angles of 60 and 120 degrees.
- With the Limberg flap, the sides are of the same length as the short axis of the rhomboid defect.

Advancement Flaps

- All advancement flaps are moved directly forward into a defect without any rotation or lateral movement.
- Modifications are the single-pedicle advancement, the V-Y advancement, and the bipedicle advancement flaps.
- The single-pedicle advancement flap is a rectangular or square flap of skin and subcutaneous tissue that is stretched forward.
- Advancement is accomplished by taking advantage of the elasticity of the skin and by excising Burow's triangles lateral to the flap.



Advancement

V-Y advancement

- This V-Y technique can be used to lengthen such structures as the nasal columella, eliminate minor notches of the lip, and, in certain instances, close the donor site of a skin flap.

SKIN GRAFTING

Skin grafts are divided into 2 major categories: ***full-thickness skin grafts (FTSGs) and split-thickness skin grafts (STSGs). STSGs may be subdivided into thin (0.008- to 0.012-mm), medium (0.012- to 0.018-mm), and thick (0.018- to 0.030-mm) grafts.***

STSGs are most commonly used when:

- Cosmesis is not a primary concern or when the defect to be corrected is of a substantial size that precludes the use of an FTSG.
- Coverage of chronic unhealing cutaneous ulcers, temporary coverage to allow observation of possible tumor recurrence, surgical correction of depigmenting disorders with the use of suction blister grafts to line cavities such as the orbit, and coverage of burn areas to accelerate wound healing and to reduce fluid loss.

The use of FTSGs is indicated:

- In defects in which the adjacent tissues are immobile or scarce.

- If that adjacent tissue has premalignant or malignant lesions and precludes the use of a flap.
- Specific locations for FTSGs include the nasal tip, helical rim, forehead, eyelids, medial canthus, concha, and digits.
- Other indications for the use of FTSG include punch grafting for hair transplantation and minigrafting (punch grafting) for the surgical correction of depigmenting conditions.

Contraindications: Contraindications to the use of STSGs include the need to place the graft in areas where good cosmesis or durability is essential or where significant wound contraction could compromise function.
The use of FTSGs is contraindicated when the recipient bed, due to lack of reasonable vascular supply, cannot sustain the graft. Using an FTSG on avascular tissues, such as exposed bone or cartilage, most often leads to graft necrosis.
Uncontrolled bleeding in the recipient bed is another contraindication to the placement of an FTSG because hematoma and/or seroma formation under the graft compromises graft survival.

Split-thickness skin grafts

An appropriate donor sites are anterior, lateral, or medial part of the thigh; the buttock; or the medial aspect of the arm. For larger defects, a large, flat donor surface is ideal for harvesting an STSG.

Full-thickness skin grafts

Common donor locations for FTSGs include areas of preauricular and postauricular, conchal bowl, supraclavicular, upper eyelid, nasolabial fold, axillary, antecubital, and inguinal fold skin.
Wound contracture is more common in STSGs than in FTSGs, and it can lead to cosmetic and functional problems.

SWELLINGS:

Dermoid Cyst

Dermoid cysts a solitary, or occasionally multiple, hamartomatous tumor. The tumor is covered by a thick dermislike wall that contains multiple sebaceous glands and almost all skin adnexa. Hairs and large amounts of fatty masses cover poorly to fully differentiated structures derived from the ectoderm.
In addition to the skin, dermoid cysts can be intracranial, intraspinal, or perispinal. Intra-abdominal cysts, such as cystic tumors of the ovary or omentum, occur as well.

Causes:

- Dermoid cysts are true hamartomas.
- Dermoid cysts occur when skin and skin structures become trapped during fetal development.
- Histogenetically, dermoid cysts are a result of the sequestration of skin along the lines of embryonic closure.

History:

- Dermoid cysts that are congenital and localized on the neck, head, or trunk are usually visible at birth.
- Intracranial, intraspinal, or intra-abdominal dermoid cysts may be suspected after specific or nonspecific neurologic or gynecologic symptoms occur.

Treatment: Surgical excision is the treatment of choice in any localization.

Lipoma

Lipomas are adipose tumors that are often located in the subcutaneous tissues of the head, neck, shoulders, and back. These slow-growing, nearly always benign, tumors usually present as nonpainful, round, mobile masses with a characteristic soft, doughy feel. Rarely, lipomas can be associated with syndromes such as hereditary multiple lipomatosis, adiposis dolorosa, Gardner's syndrome, and Madelung's disease. **Hereditary multiple lipomatosis**, an autosomal dominant condition is found most frequently in men, is characterized by widespread symmetric lipomas appearing most often over the extremities and trunk. **Gardner's syndrome**, an autosomal dominant condition involving intestinal polyposis, cysts, and osteomas. **Madelung's disease**, or benign symmetric lipomatosis, refers to lipomatosis of the head, neck, shoulders, and proximal upper extremities. Persons with Madelung's disease, often men who consume alcohol, may present with the characteristic "horse collar" cervical appearance. **Dercum's disease**, or adiposis dolorosa, which is characterized by the presence of irregular painful lipomas most often found on

the trunk, shoulders, arms, forearms, and legs. Dercum's disease is five times more common in women, is often found in middle age, and has asthenia and psychic disturbances as other prominent features.
There are also variants such as angiolipomas, neomorphic lipomas, spindle cell lipomas, and adenolipomas. Most lipomas are best left alone, but rapidly growing or painful lipomas can be treated with excision of the tumor.

Hemangioma

A haemangioma is a benign (overgrowth of blood vessels in the skin. It is due to proliferating endothelial cells. Ten percent of babies develop one or more haemangiomas. Over 80% occur on the head and neck area. They can grow for up to 18 months before they start regressing. This regression is known as involution and can take as long as 3-10 years.

Haemangioma is compressible because it consists of multiple blood-filled vascular spaces. Other compressible swellings are lymphangiomas, aneurysms, pharyngeal pouch, saphena varix, varicocoele, pneumatocoele, laryngeocoele, tracheocoele and hernias.
The commonest site of a haemangioma is head and neck region.
It affects internal organs also like liver and spleen.
Different types of haemangioma are:
1. Capillary Haemangioma : Port wine stain, Strawberry angioma, Salmon patch, Spider naevi
2. Venous Haemangioma (Cavernous haemangioma)
3. Arterial Haemangioma (Circoid aneurysm)
The commonest complication of a haemangioma is Haemorrhage.

Types of haemangiomas

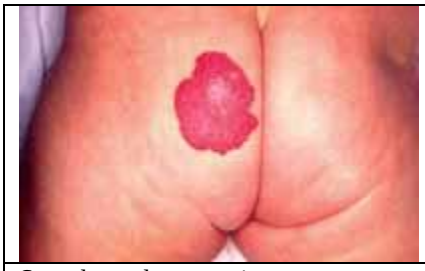
There are basically two main types of haemangiomas, capillary and cavernous. Capillary haemangiomas (superficial angiomatous naevi) affect the blood vessels in uppermost layers of the skin whilst cavernous haemangiomas (subcutaneous angiomatous naevi) are more deeply set in the dermis and subcutis. In some cases, both types of haemangiomas may occur together (mixed angiomatous naevi).

Capillary haemangioma

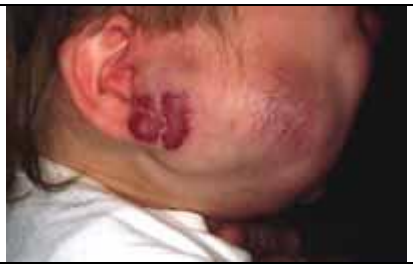
The capillary haemangioma or superficial angiomatous naevus is most commonly known as a strawberry haemangioma (strawberry birthmark, capillary naevus, haemangioma simplex). It is more common in premature babies and may appear when the baby is a few days or weeks old and rapidly grows over a few months. The eventual size varies from a tiny dot to several centimetres in diameter. Occasionally haemangiomas bleed or ulcerate, but this is rarely serious.

As most strawberry birthmarks disappear without any treatment by themselves over 5-7 years, treatment is rarely indicated.

If the birthmark grows over the eye, nose or mouth it could interfere with the breathing or feeding problems. Possible treatment includes oral steroids ***or laser therapy***. Interferon is no longer advised because it has been associated with the development of cerebral palsy in a few infants.



Strawberry haemangioma



Mixed capillary and cavernous haemangioma

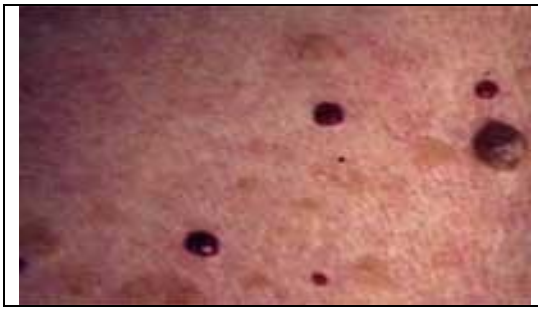
Cavernous haemangioma

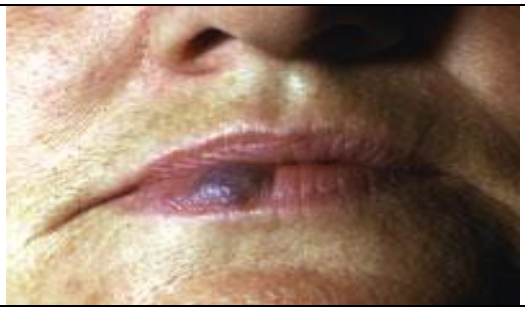
This type of birthmark is caused by overgrown blood vessels deep within the skin, resulting in a bluish swollen-up appearance. They may also grow and then get smaller, sometimes in conjunction with a strawberry mark.
The Kasabach-Merritt syndrome is also known as haemangioma-thrombocytopaenia syndrome. It is a rare complication of a rapidly growing cavernous haemangioma in the first few months of life. A defect of blood clotting (coagulopathy) is marked by anaemia, low platelet count and prolonged bleeding. The bleeding is thought to result from trapping and destruction of the platelets and depletion of circulating clotting factors. The coagulopathy is treated with special blood transfusions, and generally oral steroids to reduce the size of the haemangioma. The rapid growth of the haemangioma may also result in heart failure.

Other haemangiomas
The haemangiomas described below are all very rare conditons.

Type	Features
Verrucous haemangioma	Haemangiomas that also show an overgrowth and thickening of skin cells May be a single lesion or group occurring most often on the legs Do not resolve spontaneously and may need to be surgically excised
Eruptive neonatal haemangiomatosis	Multiple capillary haemangiomas present at birth or develop with first few weeks of life If only the skin is involved the disorder is called benign eruptive neonatal haemangiomatosis: these usually resolve spontaneously over time If lesions are also present on internal organs of the body (e.g. GI tract, lungs, brain, eyes) this is called disseminated eruptive neonatal haemangiomatosis: death generally occurs within the first few months of life A newborn with multiple haemangiomas present must be investigated thoroughly for haemangiomas on internal organs
Ulcero-mutilating haemangiomatosis	Rare disorder of multiple haemangiomas that form ulcers that lead to severe tissue damage
Acquired multiple haemangiomatosis	Large numbers of haemangiomas appear in childhood or adulthood on the skin and internal organs, particularly the skeleton, brain and liver Lesions persist indefinitely but are usually free of symptoms or complications

Haemangiomas arising in adults
Small capillary spots are called ***Campbell de Morgan lesions*** (also known as cherry angiomas), and appear most often around the midtrunk. They increase in number from about the age of 40. Their cause is unknown. They can be simply removed by diathermy or laser, but are usually left alone.
Angiomas are common on the face, particularly around the mouth. On the lip they are known as Venous Lakes, and are bluish in colour. No treatment is generally required.





Campbell de Morgan spots	Venous lake

Investigations

Haemangiomas are usually diagnosed clinically and no investigations are necessary. However, when there is uncertainty about the diagnosis or whether underlying tissues are affected, an ultrasound scan is often performed. Characteristically, a haemangioma has a firm lobular structure with vessels separating the lobules.

In more complicated cases it may be necessary to perform Magnetic Resonance Imaging (MRI) or angiography to help plan treatment.

Treatment of a cavernous haemangioma: Different lines of treatment are:

1. Injection of a sclerosant material (commonest material used is Ethanolamine oleate.)
2. Embolization injection (materials used are Gelfoam, alcohol foam & silicon particles)
3. Surgical excision
4. Laser radiation

CARCINOMA OF THE SKIN

Skin cancers are the most common forms of cancer.

Basal cell cancers account for nearly two thirds of skin cancer cases, while squamous cell cancers account for 10% of skin cancers.

RISK FACTORS

UV radiation, specifically 280-320 nm UV-B, is the most important risk factor for the development of skin cancer.

An increased risk is associated with geographic latitude; individuals who live closest to the equator have an increased risk for the development of skin cancer.

Less common risk factors include exposure to soot (scrotal SCCA in chimney sweeps noted by Sir Percivall Pott in 1775), tar, polycyclic aromatic hydrocarbons, arsenic pesticides, and pharmaceuticals.

Certain viral factors are also proposed to increase risk for the development of skin cancer (eg, human papilloma virus [HPV]).

Skin trauma (eg, burns, chronic ulcers) and ionizing radiation also contribute to skin cancer risk.

CLINICAL FEATURES

Presentation

- Erythematous, ulcerated, crusting lesion
- Area of persistent ulceration
- Hyperkeratotic patch
- Opaque nodule with or without ulceration
- Actinic keratosis (a premalignant condition that may develop into SCCA)

PATHOLOGY AND HISTOLOGIC VARIANTS

The current pathologic designations for premalignant and malignant skin lesions of squamous epithelial origin are squamous cell carcinoma-in-situ and SCCA.

Bowen disease of the skin and erythroplasia of Queyrat of the penis are clinical expressions of squamous cell carcinoma-in-situ.

Full-thickness involvement of the epidermis by cells with atypical and dysplastic features characterizes squamous cell carcinoma-in-situ.

Features include loss of orderly maturation as cells progress from basal to superficial layers; significant variability in nuclear size, shape, and staining between neighboring cells; mitoses at higher than expected levels; multinucleation; and dyskeratosis, hyperkeratosis, and parakeratosis.

Lesions with features that fall short of full-thickness involvement are characterized as actinic (solar) keratosis.

By definition, SCCA is a malignant squamous neoplasm in which the cells have penetrated the epithelial basement membrane and invaded the dermis for a variable distance.
Variants of SCCA are named according to their architectural features, including:
Spindle cell type/ adenoid type/ and verrucous type.
The spindle cell variant has large vesicular nuclei, indistinct cytoplasmic borders, and a spindled pattern, often resembling dermal sarcomas.
The adenoid (acantholytic) variant consists of nests of squamous cells with pseudoglandular formations secondary to central acantholysis.
Verrucous carcinomas are both exophytic and endophytic. The exophytic component displays papillomatosis, hyperkeratosis, and parakeratosis. The endophytic component manifests as acanthotic extensions of rete pegs with rounded appearance.

DIAGNOSIS

- Punch biopsy
- incisional biopsy
- Excisional biopsy

TREATMENT

High-risk tumors display the following characteristics:

- Size greater than 2 cm/ Depth greater than 4 mm/ Histology - Poorly differentiated/ Rapid growth/ Etiology - Burn, scar, and chronic ulcer/ Immunosuppressed patients/ Anatomic site - Scalp, nose, lip, eyelid, and ear (The ear is the primary site for aggressive tumor behavior.)/ Perineural invasion/ Recurrent lesions
    1. Surgical excision and primary closure occur under local anesthesia. The standard treatment includes 4- to 6-mm margins for 95% nonrecurrence rate.
    2. Mohs micrographic surgery offers better cure rates for lesions associated with high-risk factors. The surgery is performed using sequential excisions and histologic examination of the entire surgical margin. Subsequent excisions are performed only of the areas with persistent disease.
    3. Radiation is reserved for unusual cases.
    4. Topical chemotherapy with 5-fluorouracil may be useful for certain patients.

Risk factors for metastatic disease to regional lymph nodes include primary site tumor greater than 2 cm, depth greater than 6 mm, rapid growth, immunocompromised host state, anatomic site (eg, ear, temple, lip), and perineural invasion.
General guidelines for regional control include the following:

- Scalp, forehead, temple, and auricle may drain to paraparotid or intraparotid lymph nodes and to deep cervical nodes.
- Neck dissection is not usually indicated for patients with N0 necks. Monitor these patients, especially for the first 2 years. Rarely, prophylactic radiation to the neck is considered.
- Metastatic disease to the parotid region requires parotidectomy in conjunction with neck dissection.
- If cancer involves the skin or a scar from a previous excision or biopsy, include these areas in the surgical specimen.
- Preserve the facial nerve, unless the nerve is invaded directly by a tumor. If the nerve is resected, make every attempt to reconstruct the nerve using primary anastomosis, cable graft, or hypoglossal transfer.
- Patients who have distal metastatic disease do poorly. Combination surgery, radiation, and chemotherapy may benefit selected patients.

Head and Neck Cancer

Squamous cell carcinoma represents more than 90% of all head and neck cancers.

Pathophysiology

Squamous cell carcinoma is thought to arise from keratinizing or malpighian epithelial cells. The hallmark of squamous cell carcinoma is the presence of keratin or "keratin pearls" on histology. These are well-formed desmosome attachments and intracytoplasmic bundles of keratin tonofilaments.
Morphologically, it is variable and may appear as plaques, nodules, or verrucae.
These in turn may be scaly or ulcerated, white, red, or brown.
Verrucous carcinoma has a more favorable prognosis because of infrequent nodal and distant metastasis.

TNM clinical classification
T Primary tumor

- Tis Preinvasive cancer (carcinoma in situ)
- T0 No evidence of primary tumor
- T1 Tumor 2 cm or less in greatest dimension
- T2 Tumor more than 2 cm but not more than 4 cm
- T3 Tumor more than 4 cm
- T4 Tumor with extension to bone, muscle, skin, antrum, neck, etc
- Tx Minimum requirements to assess primary tumor cannot be met

N Regional lymph nodes

- N0 No evidence of regional lymph node involvement
- N1 Evidence of involvement of movable homolateral regional lymph nodes
- N2 Evidence of involvement of movable contralateral or bilateral regional lymph nodes
- N3 Evidence of involvement of fixed regional lymph nodes
- Nx Minimum requirements to assess the regional nodes cannot be met

M Distant metastases

- M0 No evidence of distant metastases
- M1 Evidence of distant metastases
- Mx Minimum requirements to assess the presence of distant metastases cannot be met

Staging

- Stage 1 T1 N0 M0
- Stage 2 T2 N0 M0
- Stage 3 T3 N0 N1 M0
- Stage 4 T1 T2 T3 T4 N1 M0 Any T N01N1 M0 Any T N2 N3 M0 Any N M1

RELEVANT ANATOMY
The oral cavity is defined as the area extending from the vermilion border of the lips to a plane between the junction of the hard and soft palate superiorly and the circumvallate papillae of the tongue inferiorly. This region includes the buccal mucosa, upper and lower alveolar ridges, floor of the mouth, retromolar trigone, hard palate, and anterior two thirds of the tongue. The lips are the most common site of malignancy in the oral cavity and account for 12% of all head and neck cancers, excluding nonmelanoma skin cancers. Squamous cell carcinoma is the most common histologic type, with 98% involving the lower lip. This predilection to the lower lip has been attributed to sun exposure. Next most common sites in order of frequency are the tongue, floor of the mouth, mandibular gingiva, buccal mucosa, hard palate, and maxillary gingiva.

Tumor site and lymphatic drainage

- Anterior tongue to subdigastric, submaxillary, or midjugular nodes
- Floor of mouth to subdigastric, submaxillary, or midjugular nodes
- Gingival to jugulodigastric, submaxillary, or midjugular nodes
- Buccal mucosa to submaxillary, preparotid, or jugular nodes
- Hard palate to submaxillary or jugulodigastric

TREATMENT

Several methods for treatment of cancer of the head and neck are acceptable, including surgery, radiotherapy, chemotherapy, and combinations of these.

Radiotherapy

- Nearly all patients with advanced disease require adjuvant radiotherapy, preoperatively or postoperatively. Radiation dosage in excess of 6000 cGy is recommended with a boost to areas of high risk.
- Indications for radiotherapy include a bulky tumor with significant risk of recurrence (T3 and T4), histologically positive margins, and perineural or perivascular invasion of tumor.
- For the neck, indications for radiotherapy include elective treatment of the N0 neck not treated surgically where risk of micrometastasis is high, gross residual tumor in the neck following neck dissection, multiple positive lymph nodes, and extranodal extension of tumor.

Chemotherapy

Bleomycin with or without electroporation has been used. Cisplatin is another chemotherapeutic drug of choice for head and neck cancers.

Surgical therapy

Surgical resection remains the criterion standard for treatment of head and neck cancer. Management of all but the earliest confirmed neck metastases is best achieved with surgical removal.

Neck dissection

Regardless of the site of the primary tumor, the presence of a single lymph node in either the ipsilateral or contralateral side of the neck reduces the 5-year survival rate by 50%.

Modified neck dissection is designed to preserve the spinal accessory nerve, the great auricular, and the sternocleidomastoid muscle. The jugular vein and submandibular gland also have been preserved.

In addition, successful results can be achieved through less than complete lymph node removal, selectively removing only those lymph node levels likely to be involved by metastases.

Classic radical neck dissection was described by Crile in 1901 and includes removal of all 5 levels of cervical lymph nodes en bloc down to the deep muscular fascia. This removal includes the sternocleidomastoid muscle, submandibular gland, jugular vein, and spinal accessory nerve. This operation remains the best procedure for definitive control of neck disease. Radical neck dissection can be combined with resection of the primary cancer and postoperative radiation therapy.

has pain and difficulty lifting his or her arm.

roduces a unique thymidine kinase. This viral enzyme preferentially phosphorylates the prodrug ganciclovir, a guanine nucleoside analogue, to produce a metabolite that, after cellular phosphorylation, is incorporated into replicating DNA, inhibiting DNA polymerase and ultimately killing the cell. This therapy is most effective in treating cancer cells growing in tissues where normal cells are not proliferating.

Many phase I and II trials are being pursued, and may ultimately provide nontoxic, tumor-specific, locally and regionally active, and biologically active injectable modalities that add therapeutic advantages to the existing treatment of head and neck cancers.

Basal cell carcinoma

There are four main clinical types of basal cell carcinoma: nodular, superficial, morpheaform, and pigmented.

Nodular basal cell carcinoma, the most common type, is a waxy, semitranslucent papule or nodule. The border is often pearly and rolled, and telangiectasias course over the surface of the lesion. Eventually, central ulcerations (rodent ulcers) develop.

Superficial basal cell carcinoma usually occurs as a slightly raised, pink or red, scaly, focally crusted plaque with a threadlike border.

Morpheaform basal cell carcinoma appears as an ivory plaque with overlying telangiectasias. This lesion may be more difficult to treat than other basal cell cancers.

Pigmented basal cell carcinoma is similar to the nodular and superficial variants but has brown or black pigmentation.It may be difficult to differentiate from melanoma.

MALIGNANT MELANOMA

Melanoma is a malignancy of pigment-producing cells (melanocytes) occurring in the skin, eyes, ears, GI tract, leptomeninges of the central nervous system (CNS), and oral and genital mucous membranes. Melanoma accounts for only 4% of all skin cancers.

Consider lesions exhibiting these features to be potential melanomas:

- Asymmetry
- Border notching
- Color variegation with black, brown, red, or white hue
- Diameter >6 mm

Types of Malignant Melanoma

There are four main types of melanoma

- Superficial spreading melanoma
- Nodular melanoma
- Lentigo Maligna melanoma (also sometimes called Hutchinson's melanotic freckle)
- Acral lentiginous melanoma

These four main types make up 90% of all diagnosed malignant melanoma.

Superficial spreading melanoma

This is the most common type of melanoma (65-70%). They are most common in middle aged people. To start with, they have a radial growth phase (grows in a horizontal plane, along, just above and below the dermo-epidermal junction) and is clinically macular or only slightly elevated. The melanoma will not become dangerously at risk of spreading until it begins to grow downwards into the deeper layers of skin and beyond. Most common on the trunk in men and women and on the legs in women

Nodular melanoma

About 1 in 4 melanomas (25%) are of this type. It is also found most often in middle aged people and ***in parts of the body only exposed to the sun.*** So it is most often found on the ***chest or back.*** Nodular melanomas are often very dark brownish black or black in colour. The depth of the lesion appears to correlate with the prognosis of the patient, and nodular melanoma is less often amenable to definitive treatment than is the superficial spreading variety.

Lentigo maligna melanoma

About 1 in 10 melanomas (10%) are this type. Lentigo MM is most common ***in elderly people.*** It appears in areas of skin that get a lot of sun exposure, so is ***commonest on the face.*** This type of melanoma grows very slowly, so it may be gradually getting bigger over several years. This lesion may grow for years as an in-situ tumor before developing the more aggressive vertical growth phase. In situ precursor lesion usually large (>3 cm diameter), existing for a minimum of 10-15 years, with dermal invasion characterized by development of dark brown-to-black macular pigmentation or raised blue-black nodules

Acral lentiginous melanoma

This type is most commonly found on the ***palms and soles or around the big toenail.*** It can also grow under the nails. It is much more common on the feet than on the hands.

Other types of melanoma

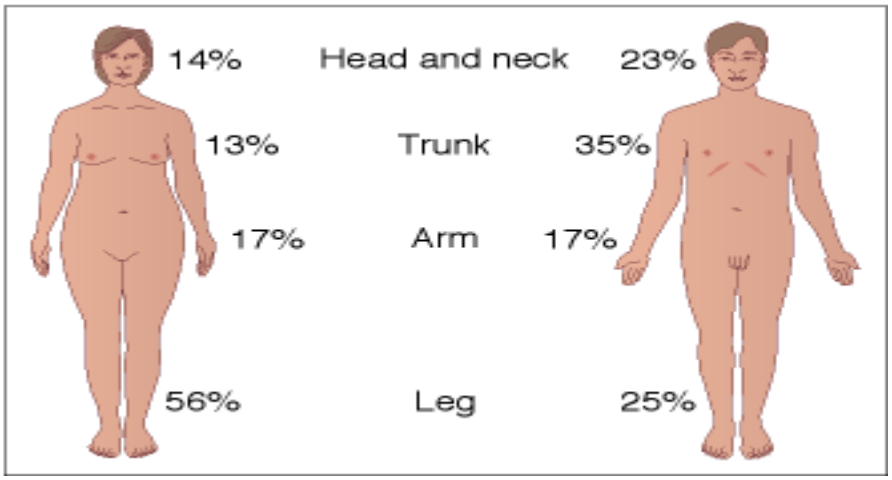
Melanoma can occur anywhere in the body, including in the internal organs. One area where melanoma does occur is eye. Rare melanoma variants (<2% of melanomas) include the following:

- Desmoplastic/neurotropic melanoma
- Mucosal (lentiginous) melanoma
- Malignant blue nevus
- Melanoma arising in a giant congenital nevus
- Melanoma of soft parts (clear cell sarcoma)

Amelanotic melanoma (<2% of melanomas) characteristics are as follows:

- Nonpigmented and appearing clinically as pink or flesh colored.
- Most commonly occurs in the setting of melanoma metastasis to the skin, presumably because of the inability of these poorly differentiated cancer cells to synthesize melanin pigment

The five year survival for tumours <0.75 mm is 95-99%, 0.76-1.49 mm is 80-90%, 1.5-3.99 mm is 60-75%, >4.0 mm is <50%.



Melanomas in men are most common on the back. In women, the commonest site is the legs.

- Two genodermatoses, ***xeroderma pigmentosum and familial atypical mole melanoma syndrome***, confer a 500-fold or greater relative risk of developing melanoma.
- arise from preexisting nevi; 1% of all cancers
- 30-40% mortality
- metastases: latent period of 2-20 years (most commonly 2-5 years)
    - lymphadenopathy
        - in 23% with level II + IV
        - in 75% with level V
    - bone (11-17%)
        - often initial manifestation of recurrence; poor prognosis
        - axial skeleton (80%); ribs (38%)
    - lungs (70% at autopsy)
        - ***most common site of relapse; most common cause of death***
    - liver (58% at autopsy): may be calcified, necrotic
    - spleen (1-5%): solid or cystic
    - bowel + mesentery (8%): mostly in small bowel
    - kidney (35%); adrenals (50%); subcutis

Clark staging:

- level I: all tumor cells above basement membrane (in situ)
- level II: tumor extends to papillary dermis
- level III: tumor extends to interface between papillary and reticular dermis
- level IV: tumor extends between bundles of collagen of reticular dermis
- level V: tumor invasion of sucutaneous tissue (87% metastases)

Breslow staging:

- thin: < 0.75 mm depth of invasion
- intermediate: 0.76 - 3.99 mm depth of invasion
- thick: > 4 mm depth of invasion

Malignant melanoma: gallium imaging
>50% sensitivity for primary and metastatic sites:

- 73% sensitivity if lesion is > 2 cm

- 17% sensitivity if < 2 cm

Surgical Care: Surgery is the primary mode of therapy for localized cutaneous melanoma.

Surgical margins for primary melanoma

- Surgical margins of 5 mm currently are recommended for melanoma in situ, and margins of 1 cm are recommended for melanomas up to 1 mm in depth (low-risk primaries).
- Randomized prospective studies show that 2-cm margins are appropriate for tumors in the intermediate-risk group (1-4 mm in Breslow depth), although 1-cm margins have been proposed for tumors of 1- to 2-mm thickness.
- Margins of at least 2 cm are recommended for cutaneous melanomas greater than 4 mm in thickness (high-risk primaries) to prevent potential local recurrence in or around the scar site.

Elective lymph node dissection

- Prophylactic lymph node dissection for primary cutaneous melanoma of intermediate thickness initially was believed to confer a survival advantage on patients with tumors 1-4 mm in depth. Subsequent clinical trials have shown no survival benefit for elective lymphadenectomy for melanomas of varying thicknesses on the extremities and marginal melanomas.

Sentinel lymph node biopsy/dissection

- Lymphatic mapping and sentinel node biopsy effectively have solved the dilemma of whether to perform regional lymphadenectomy (in absence of clinically palpable nodes) in patients with thicker melanomas ($\geq$1 mm in depth).
- The sentinel node is examined for the presence of micrometastasis on both routine histology and with immunohistochemistry; if present, a therapeutic completion lymph node dissection is performed.
- A negative sentinel node biopsy prevents the morbidity associated with an unnecessary lymphadenectomy, since the histology of the sentinel node is characteristic of the entire nodal basin.

Melanoma surgery

Resection margins

- Until recently history rather than controlled trials have dictated practice
- Handley (1907)
  - Hunterian Lecture based on one case.
  - Recommended 5 cm margin
- Butterworth and Klaude (1934)
  - Found microscopic lymphatic invasion to 3 cm
  - Recommended 5 cm resection margins
- Olson (1966)
  - Trial of resection 1 cm vs. 3 cm resection margins
  - Identical local recurrence rate but still recommended 5 cm margin !
- WHO Melanoma Group (1990)
  - Randomised controlled trial of 1 cm vs. 3 cm resection margins
  - Resection margins did not influence survival
- Generally accepted resection margins based on clinical appearance are:
  - Impalpable lesions - 1 cm margin
  - Palpable lesion - 2 cm margin
  - Nodular lesion -3 cm margin

Regional lymphadenectomy

- 20% clinically palpable nodes are histologically negative
- 20% palpably normal nodes have occult metastases
- Therapeutic lymph node dissection provides regional control and prognostic information
- No improvement in survival
- For tumours <0.75 mm thick - 90% cured by local excision alone

- For tumours >4.0 mm thick - 70% have distant metastases at presentation
- For these two groups lymphadenectomy provides no added survival benefit
- Lymphadenectomy for 'intermediate' thickness tumours controversial

Morbidity of lymphadenectomy

- Lymphoedema (26%)
- Seroma (23%)
- 'Functional deficit' (8%)
- Wound Infection (5%)
- Persistent pain (5%)

Adjuvant Therapy

- Patients at high risk of recurrence should be considered for systemic adjuvant therapy
- Patients include those with:
    - Primary tumour > 4 mm thick
    - Resectable positive locoregional lymph nodes
- No standard adjuvant therapy exists
- Interferon α2b has shown promising results
- Shown to increase disease-free and overall survival

Isolated limb perfusion

- Intra-arterial chemotherapy
- Commonly used agents - ***melphalan +/- TNF-alpha***
- Used with ***hyperoxygenation***
- Hyperthermia with a temperature of 41-42 °C
- Perfusion generally last about 1 hour
- Usually combined with lymphadenectomy

Indications

- Intransit metastases
- Irresectable local recurrence
- Adjuvant therapy for poor prognosis tumours
- Palliation to maintain limb function

VASCULAR DISEASES

Abdominal aortic aneurysms

- An AAA is an increase in aortic diameter by greater than 50% of normal (aortic diameter of greater than 3 cm diameter).
- More prevalent in elderly men. Male : female ratio is 4:1
- Risk factors – hypertension, peripheral vascular disease, family history (15-25%)
- Other causes of aortic aneurysms include:
    - Genetic: There is a familial tendency to aortic aneurysms. Connective tissue disorders such as Ehlers-Danlos syndrome and Marfan's syndrome.

- Post-traumatic:
- Arteritis, e.g.Takayasu disease, giant cell arteritis, and polychondritis.
- Congenital malformation of the aorta (aneurysms tend to develop just beyond the narrowing of a coarctation of the aorta).
- ***End-stage (tertiary) syphilis, which tends to affect the ascending aorta and arch of the aorta.***
- Mycotic: infective (immunodeficiency, IV drug abuse, valve surgery).

- Degenerative aneurysms account for more than 90% of all infrarenal AAAs.
- Most cases of AAA begin below the renal arteries and end above the iliac arteries.
- They generally are spindle shaped (fusiform)

Natural history

- In general, AAAs gradually enlarges (0.2-0.8 mm/y) and eventually rupture.
- 5 year risk of rupture:
  - 5.0 – 5.9 cm = 25%
  - 6.0 – 6.9 cm = 35%
  - More than 7 cm = 75%

Pathophysiology:

- The aortic wall contains smooth muscle, elastin, and collagen arranged in concentric layers.
- The number of medial elastin layers from the proximal thoracic aorta to the infrarenal aorta is markedly reduced, with medial thinning and intimal thickening.
- Elastin is the principal load-bearing element in the aorta. Elastin fragmentation and degeneration are observed in aneurysm walls.
- It is coupled with the histological changes of this matrix protein in aneurysms.

Clinical features: 75% are asymptomatic

- Possible symptoms include
  - Epigastric pain
  - Back pain
  - Malaise and weight loss (with inflammatory aneurysms)
- Rupture presents with
  - Sudden onset abdominal pain
  - Hypovolaemic shock
  - Pulsatile epigastric mass
- Rare presentations include
  - Distal embolic features: may cause livedo reticularis (blue toe syndrome)
  - Acute aortic occlusion: Occasionally, small AAAs thrombosis, producing acute claudication.
  - Aorto-caval fistula (symptoms include tachycardia, congestive heart failure (CHF), leg swelling, abdominal thrill, machinery-type abdominal bruit, renal failure, and peripheral ischemia).
  - Primary aorto-intestinal fistula (AAA may rupture ***into the fourth portion of the duodenum*** and present with a herald upper gastrointestinal bleed).

Indication for operation

- Rupture
- Symptomatic aneurysm; any size.
- Rapid expansion
- Asymptomatic > 6 cm – exact lower limit controversial.

Contraindications: COPD/ severe cardiac disease/ active infection/ and medical problems that preclude operative intervention. These patients may benefit best from endovascular stenting of the aneurysm. Severe life-threatening comorbidities include advanced cancer, end-stage lung disease, or cardiac disease.

Approach:

- Monitor patients if AAA is smaller than 4 cm with ultrasound every 6 months, offer surgical intervention if the aneurysm expands or becomes symptomatic.

- Patients with an AAA of 5-6 cm in diameter benefit from repair, especially if they have other contributing factors like hypertension, continued smoking, or COPD.
- For patients at higher risk, the threshold for repair may be 6-7 cm in diameter.

Pre-operative investigation

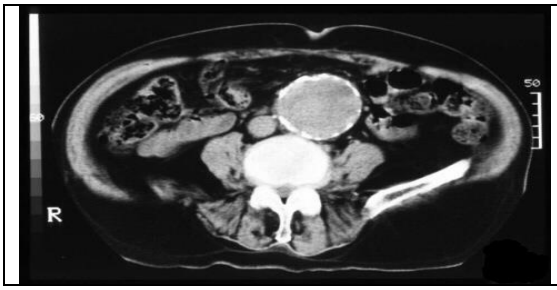
- Need to determine
  - Extent of aneurysm
  - Fitness for operation
- Ultrasound, conventional CT and more recently spiral CT
- Determines – aneurysm size, relation to renal arteries, involvement of iliac vessels
- ***Angiography: It is indicated only(not in all cases) when associated renal or visceral involvement, peripheral occlusive disease, or aneurysmal disease exists.***
- Most significant post op morbidity and mortality related to cardiac disease
- Cardiac revascularisation required in up to 10% of patients.

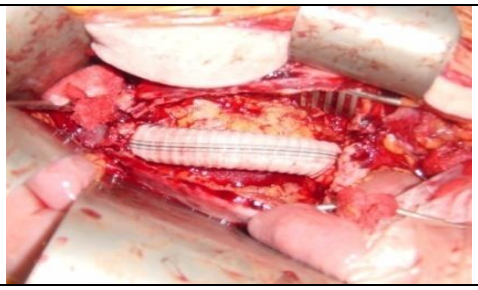
TREATMENT

Medical therapy: Smoking cessation/ aggressively control hypertension.

Surgical therapy: Operative approach is through the traditional open laparotomy approach or, by the placement of endovascular stents.

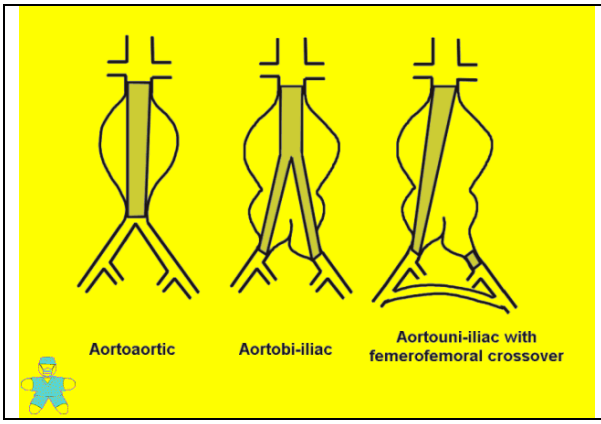
Prevention of distal embolization: The patient is heparinized prior to aortic cross clamping. ***If significant intraluminal debris, juxtarenal thrombus, or prior peripheral embolization exists, the distal arteries are clamped first,*** followed by aortic clamping.





Endovascular aneurysm repair

- Morbidity of conventional open aneurysm surgery related to:
  - Exposure of infra-renal aorta/ Cross clamping of aorta
- Endovascular repair achieved by transfemoral or transiliac placement of prosthetic graft
- Proximal and distal cuffs / stents anchor graft
- Exclude aneurysm from circulation
- Only ~40% of aneurysms suitable for this type of repair
- Major problem related to placement and leakage around stent



- Three main types of graft
  - Aorto-aortic
  - Bifurcated aorto-iliac
  - Aorto-uniiliac graft with femoro-femoral crossover and contralateral iliac occlusion

Complications

- Graft migration/ Endovascular leak/ Graft kinking/ Graft occlusion

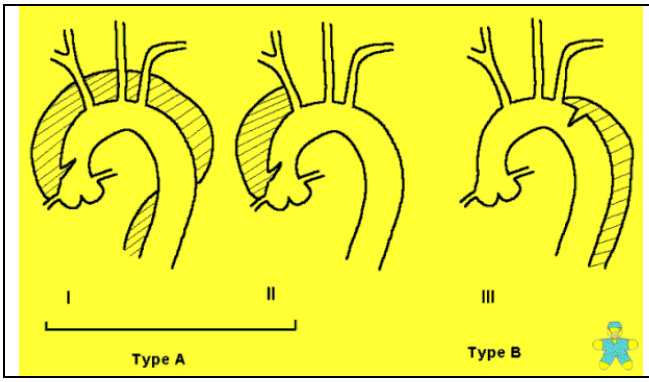
Aortic dissection

- **Commonest aortic emergency**
- Incidence is twice that of ruptured abdominal aortic aneurysm
- Most commonly seen between 50 and 70 years
- Associated with hypertension, Marfan's syndrome, bicuspid aortic valve

Pathology

- Intimal tear results in blood splitting the aortic media
- Rupture can occur back into the lumen or externally in pericardium/ mediastinum
- External rupture often results in fatal pericardial tamponade
- ***Commonest site of intimal tear is within 2-3 cm of aortic valve***
- Dissection can result in occlusion of aortic branches
- **Most commonly involved are renal, spinal, coronary or iliac arteries**

Classification



- Stanford - Type A and B depending on whether ascending or descending aorta involved
- DeBakey - Divided into Types I, II and III as above

Clinical features

- Usually presents with tearing chest pain radiating to back associated with collapse
- Examination may show
  - Reduced or absent peripheral pulsed
  - Soft early diastolic murmur
- Chest x-ray usually shows a widened mediastinum.
- If aortic branches occluded there may clinical evidence of
  - Acute renal failure
  - Paraplegia
  - Acute limb ischaemia
  - Cerebrovascular accident
  - Inferior myocardial infarction

Management

- All patients require urgent management of associated hypertension
- **Type A dissections <u>usually require</u> surgical intervention**
- Dissection excised and aorta replaced with graft
- Aortic valve is preserved if possible
- *<u>An evolving CVA or established renal failure are contraindications to surgery</u>*
- **Type B dissections <u>may be</u> treated without surgery**
- Requires fastidious blood pressure control

- Surgery should be considered if evidence of aortic expansion.
- Surgery for Type B dissections is associated with significant risk of paraplegia
- Without operation the prognosis for Type A dissections is poor
- 40% die within 24 hours and 80% die within 2 weeks

Popliteal artery aneurysms

- Defined as a popliteal artery diameter greater than 2 cm
- Account for 80% of all peripheral aneurysms
- 50% are bilateral. 50% are associated with an abdominal aortic aneurysm. 50% are asymptomatic
- Symptomatic aneurysms present with features of:
    - Compression of adjacent structures (veins or nerves)
    - Rupture
    - Limb iscahemia due to emboli or acute thrombosis
- **Treatment is by proximal and distal ligation**
- Revascularisation of the leg with a femoropopliteal bypass
- With a symptomatic popliteal aneurysm 20% patients will undergo an amputation

Arterial assessment
Clinical Assessment
Claudication

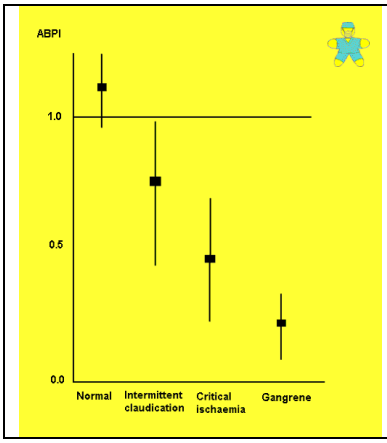
- Calf or thigh pain precipitated by exercise. Usually occurs after predictable distance. Relieved by rest
- Progression of symptoms is important - worsening or improvement
- Need to differentiate form spinal stenosis: Also cause exercise induced leg pain; Usually associated with neurological symptoms and relieved by spinal flexion
- Peripheral pulses can be present in patients with intermittent claudication

Critical limb ischaemia

- Characterised by rest pain
- Occurs when foot is elevated (e.g. in bed)
- Improved with foot dependent
- May be associated with ulceration or gangrene
- Foot pulses are invariably absent

Non-invasive testing of arterial patency
Hand-held doppler

- Reflection of an ultrasound wave off a stationary object does not change its frequency. Reflection off a moving object results in a change of frequency
- The change in frequency is proportional to velocity or blood flow
- Hand held 8 MHz doppler probe is used to assess arterial system
- Can be used to measure arterial pressures (at rest and after exercise).
- In normal individual lower limb pressures are greater than upper limb
- Ankle-brachial pressure index (ratio of best foot systolic to brachial systolic Pr)
-



- Normal >1.0
- Claudication 0.4 -0.7
- Critical Ischaemia 0.1-0.4

- In normal individuals pressures do not fall flowing exercise
- In claudicants the ABPI falls and recovery is delayed
- In diabetic lower limb pressures are falsely elevated due to calcification in the vessel wall

Toe pressures

- Provides accurate assessment of distal circulation
- Not influenced by calcification in pedal vessels
- Normal toe pressures are 90-100 mmHg
- Toe pressure less than 30 mmHg suggests critical limb ischaemia

Duplex ultrasound

- Combined pulsed doppler and real time B mode ultrasound
- Allows imaging of vessels and any stenotic lesion.
- Flow and pressure wave form can be also be assessed
- Duplex ultrasound has sensitivity of 80% and specificity of 90%.

Pulse generated run off

- Proximal occlusion often causes poor filling of crural vessels on arteriography
- Rapid cycling of a proximal cuff generates arterial pulse wave
- P GR allows functional testing of distal arterial patency

Magnetic resonance angiography: No contrast required.

Invasive vascular assessmen

Angiography

- Usually performed using digital subtraction techniques
- Femoral artery is commonest site of venous access.
- Potential complications include
    - Contrast-related: Anaphylactic reaction/ Toxic reactions. Deterioration in renal function
    - Technique-related: Haematoma/ Arterial spasm/ Sub-intimal dissection/ False aneurysm/ Arteriovenous fistula/ Embolisation/ Infection

CT angiography

- Required intravenous contrast and ionising radiation
- Spiral CT and reconstruction can provide detailed images
- Particularly useful for the assessment of aneurysmal disease

Acute limb ischaemia

- Effects of sudden arterial occlusion depends on state of collateral supply

Aetiology of acute limb ischaemia

Embolism

- Left atrium in patients in atrial fibrillation
- Mural thrombus after myocardial infarct
- Prosthetic and diseases heart valves

- Aneurysm or atheromatous stenosis
- Tumour, foreign body, paradoxical

Thrombosis
Trauma
Dissecting aneurysm
Raynaud's Syndrome

Clinical features of limb ischaemia

- Clinical diagnosis depends on the 6 'p' s
  - Pain/ Paraesthesia/ Pallor/ Pulselessness/ Paralysis/ Perishing with cold
- ***Objective sensory loss requires urgent treatment***
- Need to differentiate embolism from thrombosis
- Important clinical features include
  - Rapidity of onset of symptoms
  - Features of pre-existing chronic arterial disease
  - Potential source of embolus
  - State of pedal pulses in contralateral leg

Management of acute ischaemia

Initial

- Heparinise & analgesia. Treat associated cardiac disease
- Treatment options are:
  - Embolic disease - embolectomy or intra-arterial thrombolysis
  - Thrombotic disease - intra-arterial thrombolysis / angioplasty or bypass surgery

Emergency embolectomy: Can be performed under either general or local anaesthesia

- Transverse artereotomy performed over common femoral artery
- Fogarty balloon embolectomy catheters used to retrieve thrombus
- If embolectomy fails - on-table angiogram and consider
  - Bypass graft or intraoperative thrombolysis

Intra-arterial thrombolysis:

- Arteriogram and catheter advanced into thrombus. Streptokinase 5000u/hr + heparin 250u/hr
- Alternative thrombolytic agents are urokinase/ tissue plasminogen activator (tPA).
- Repeat arteriogram at 6 -12 hours
- Advance catheter and continue thrombolysis for 48 hours or until clot lysis.
- Angioplasty of chronic arterial stenosis may be necessary

Buerger Disease (Thromboangiitis Obliterans)

Thromboangiitis obliterans is a nonatherosclerotic, segmental, inflammatory, vasoocclusive disease that affects the ***small and medium-sized arteries and veins*** of the upper and lower extremities. It is strongly associated with heavy tobacco use.

Male-to-female ratio = 3:1and majority of patients are aged 20-45 years.

History: Because a firm diagnosis of thromboangiitis obliterans is difficult to establish, a number of different diagnostic criteria have been proposed:

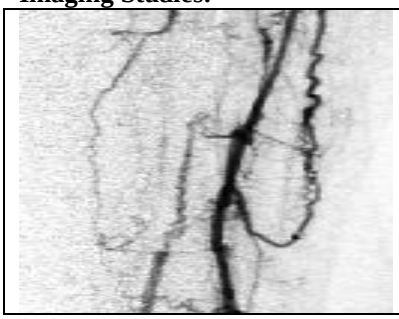
- Age younger than 45 years
- Current (or recent) history of tobacco use
- Presence of distal-extremity ischemia (indicated by claudication, pain at rest, ischemic ulcers, or gangrene) documented by noninvasive vascular testing
- Exclusion of autoimmune diseases, hypercoagulable states, and diabetes mellitus by laboratory tests
- Exclusion of a proximal source of emboli by echocardiography and arteriography
- Consistent arteriographic findings in the involved and noninvolved limbs

Patients also may present with claudication of the feet, legs, hands, or arms and often describe Raynaud phenomenon of sensitivity of the hands and fingers to cold.

Physical:

- The diseased hands and feet are usually cool and mildly edematous.
- Superficial thrombophlebitis is often migratory (in 50%). Paresthesias (numbness, tingling, burning, hypoesthesia) of the feet and hands.
- Impaired distal pulses in the presence of normal proximal pulses.

Imaging Studies:

	***Angiography/Arteriography:*** This lower extremity arteriogram of the peroneal and tibial arteries of a patient with Buerger disease demonstrates the classic findings of multiple small and medium-sized arterial occlusions with formation of compensatory **"corkscrew collaterals."**

Other Tests:

- An abnormal Allen test indicating distal arterial disease and establishing involvement of the upper extremities in addition to the lower extremities helps to differentiate thromboangiitis obliterans from atherosclerotic disease.

TREATMENT: Absolute discontinuation of tobacco use.

Treatment with intravenous ***iloprost*** (a prostaglandin analogue), has been shown to improve symptoms, accelerating resolution of distal extremity trophic changes.

Surgical Care: Given the diffuse segmental nature and that the disease affects primarily small and medium-sized arteries; surgical revascularization is usually not feasible.

Autologous vein bypass of coexistent large-vessel atherosclerotic stenoses should be considered in patients with severe ischemia who have an acceptable distal target vessel.

- Other proposed surgical treatments for thromboangiitis obliterans are:
  - Omental transfer
  - Sympathectomy
  - Spinal cord stimulator implantation
- Distal limb amputation for nonhealing ulcers, gangrene, or intractable pain may be required.

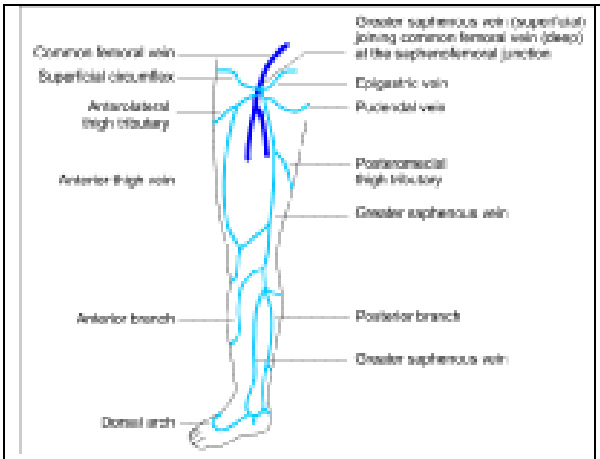
Varicose veins

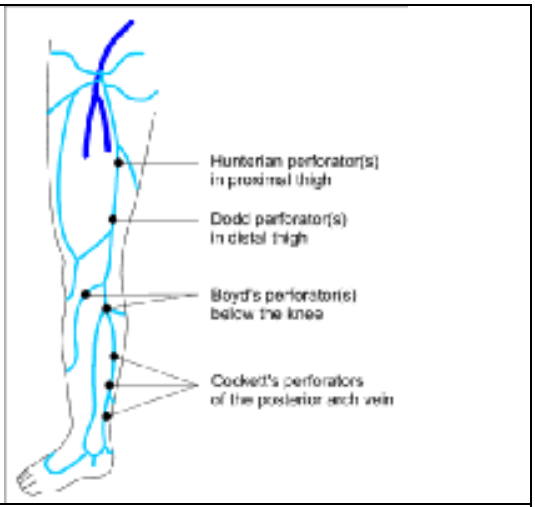
Varicose veins are veins that have dilated under the influence of increased venous pressure.

- Varicose veins affect: 20-25% of adult females.10-15% of adult males

Etiology:

- Intrinsic pathological conditions and extrinsic environmental factors combine to produce a wide spectrum of varicose disease.
- Most varicose disease is caused by elevated superficial venous pressures.
- Some people have an inborn weakness of vein walls.
- Reflux at the saphenofemoral junction (SFJ)
- Prolonged standing leads to increased hydrostatic pressures that can cause chronic venous distention and secondary valvular incompetence.
- If proximal junctional valves become incompetent, high pressure passes from the deep veins into superficial veins and the condition rapidly becomes irreversible.





Along its course, a variable number of perforating veins may connect the GSV to the deep system at the femoral, posterior tibial, gastrocnemius, and soleal veins. Between the ankle and the knee lie ***Cockett's perforators.*** Numerous superficial tributaries are there as it passes through the thigh like postero-medial and anterolateral thigh veins, and posterior accessory saphenous veins at the level of the canal of Hunter in the upper thigh. Just below the saphenofemoral junction, the GSV receives the lateral and medial femoral cutaneous branches, the external circumflex iliac vein, the superficial epigastric vein, and the internal pudendal vein The termination point of the GSV into the common femoral vein is called the saphenofemoral junction (SFJ).

History: Common symptoms include, leg heaviness, exercise intolerance, pain or tenderness along the course of a vein, pruritus, burning sensations, restless legs, night cramps, edema, skin changes, and paresthesias.

- ***Pain caused by venous insufficiency often is improved by walking in contrast to the pain of arterial insufficiency, which is worse with ambulation and elevation.***
- Acute varicose complications are variceal bleeding, dermatitis, thrombophlebitis, cellulitis, and ulceration.
- Poor correlation exists between symptoms and signs
- If history of DVT need preoperative investigation with duplex scanning

Examination

- Identify **distribution of varicose veins** - long saphenous vs short saphenous.
- Confirm with tourniquet testing and hand held-doppler probe (5 MHz)
- Indications for duplex scanning
    - Suspected short saphenous incompetence
    - Recurrent varicose veins
    - Complicated varicose veins (e.g. ulceration, lipodermatosclerosis)
    - History of deep venous thrombosis

Perthes maneuver: The Perthes maneuver is a traditional technique intended to distinguish antegrade flow from retrograde flow in superficial varices. Antegrade flow in a variceal system indicates that the system is a bypass pathway around a deep venous obstruction. This is critically important because if deep veins are not patent, superficial varices are an important pathway for venous return and must not be sclerosed or surgically removed.

If the Perthes maneuver is positive and the distal varices have become engorged, the patient is placed supine with the tourniquet in place and the leg is elevated (**Linton test**). If varices distal to the tourniquet fail to drain after a few seconds, deep venous obstruction must be suspected.

Trendelenburg test: The Trendelenburg test often can distinguish patients with superficial venous reflux from those with incompetent deep venous valves.

Indications for varicose vein surgery

- Most surgery is cosmetic or for minor symptoms
- Absolute indications for surgery :
    - Lipodermatosclerosis leading to venous ulceration
    - Recurrent superficial thrombophlebitis
    - Bleeding from ruptured varix

Contraindications: Venous outflow obstruction and during pregnancy.

LSV surgery

- Trendelenberg position with 20 - 30° head down
- Saphenofemoral junction (SFJ) found 2 cm below and lateral to pubic tubercle
- Essential to identify SFJ before performing flush ligation of the LSV
- Individually divide and ligate all tributaries of the LSV
    - ***Superficial circumflex iliac vein***
    - ***Superficial inferior epigastric vein***
    - ***Superficial and deep external pudendal vein***
- Check that femoral vein clear of direct branches for 1 cm above and below SFJ
- Stripping of LSV reduces risk of recurrence. Only strip to upper calf if needed.
- Stripping to ankle is associated with increased risk of saphenous neuralgia
- Post operative care: Elevate foot of bed for 12 hours. Varix stocking should be worn for at least 2 weeks

SSV surgery

- Patient prone with 20-30° head down
- Saphenopopliteal junction (SPJ) has very variable position
- Identify and preserve the sural nerve
- Need to identify the Sapheno-popliteal Junction
- Stripping associated with risk of sural nerve damage
- Subfascial ligation inadequate

Perforator surgery

- Perforator disease may be improved by superficial vein surgery
- Perforator surgery (e.g. Cockett's and Todd's procedure) associated with high morbidity
- Subfascial endoscopic perforator surgery (SEPS) recently described
- May have a role in addition to saphenous surgery in those with venous ulceration
- Sclerotherapy

Sclerotherapy "Varicose veins: sclerotherapy"

- Only suitable for below knee varicose veins
- Need to exclude SFJ or SPJ incompetence
- Main use is for persistent or recurrent varicose veins after adequate saphenous surgery
- Sclerosants
    - 5% Ethanolamine oleate/ 0.5% Sodium tetradecyl sulphate
- Needle placed in vein when full with patient standing
- Empty vein prior to injection
- Apply immediate compression and maintain for 4-6 weeks

Complications of sclerotherapy

- Extravasation causing pigmentation or ulceration
- Deep venous thrombosis

Other Modalities:

- **Endovenous laser:** Endovenous laser therapy is a thermal ablation technique that uses a laser fiber placed inside the vein to destroy the vascular endothelium.

- **Radiofrequency ablation:** Radiofrequency (RF) ablation is a thermal ablation technique. This tissue heating causes protein denaturation, collagenous contraction, and immediate closure of the vessel.
- **Ambulatory phlebectomy:** The stab-avulsion technique allows removal of short segments of varicose and reticular veins through tiny incisions.

Recurrent varicose veins "Varicose veins: recurrent"

- 15 - 25 % of varicose vein surgery is for recurrence

Reasons for recurrence

- Inaccurate clinical assessment
  - Confusion as to whether varicosities are in LSV or SSV distribution
- Inadequate primary surgery
  - 10% cases SFJ not correctly identified
  - 20% cases tributaries mistaken for LSV
  - Failure to strip LSV
- Injudicious use of sclerotherapy
  - 70% of SF incompetence treated with sclero-therapy will have recurrence
- Neovascularisation
  - With recurrent varicose vein need to image with duplex or varicography

COMPLICATIONS: ***Deep vein thrombosis and pulmonary embolism*** are the most serious complications. Other complications are dysesthesias from injury to the ***sural nerve or the saphenous nerve***, subcutaneous haematoma, infection and arterial injury.

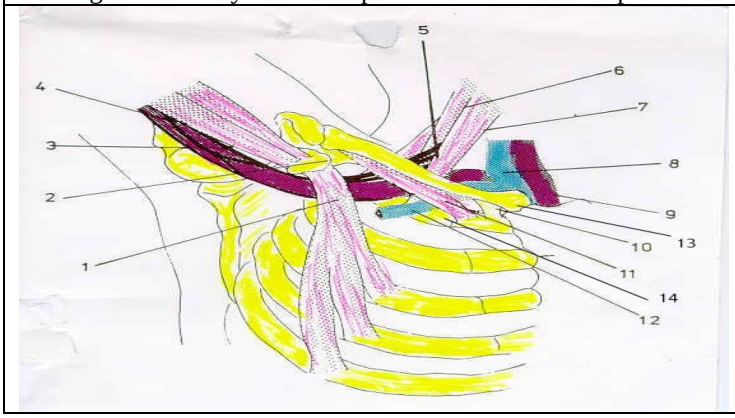
THORACIC OUTLET SYNDROME

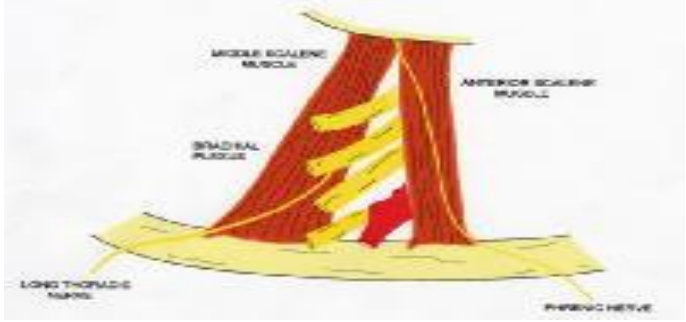
DEFINITIONS: Thoracic outlet syndrome is a disease of extrinsic compression of the artery, vein, or nerve at the thoracic outlet. The ***specific structures compressed are usually the nerves of the branchial plexus*** and occasionally the subclavian artery or subclavian vein. The compressing structures include the clavicle, the first rib, subclavian muscles, costoclavicular ligament and the anterior scalene.

Sir Astley Cooper first described axillary-subclavian artery symptoms due to compression from a cervical rib.

Thoracic outlet syndrome must be differentiated from symptomatic osteoarthritis of the cervical spine, tumors of the cervical spinal cord or nerve roots, periarthritis of the shoulder, and other cervicobrachial pain syndromes.

The predisposing factors are fibromuscular bands, bony protuberances and long or larger transverse processes, this together with the tendinous or cartilaginous muscular insertions are responsible for the compression of the neurovascular structures at the thoracic outlet.

Dynamic anatomical variations of tunnels have been postulated as possible etiologies for tunnel syndromes. This figure shows dynamic compression of the brachial plexus in the thoracic outlet.	
	1: Pectoralis minor muscle; 2: coracoid process; 3: median nerve; 4: subclavian artery; 5: brachial plexus; 6: medial scalene muscle; 7: anterior scalene muscle; 8: internal jugular vein; 9: common carotid artery; 10: costoclavicular ligament; 11: subclavious muscle; 12: subclavian vein; 13: Clavicle; 14: First Ribs.



Scalene triangle

SYMPTOMS

UPPER EXTEMITY	**ARTERIAL**	numbness of arms and hands
		tingling of arms and hands
		positional weakness of arms and hands
	VENOUS	swelling of fingers and hands
		heaviness of the upper extremity
	NERVES	upper extremity pain
		paresthesias of ulnar distribution
		weakness of the hands
		clumsiness of the hands
		coldness of the hands
		tiredness, heaviness and paresthesias on elevation of arms
SHOULDER AND NECK	~	pain - tightness
CHEST WALL	~	anginal chest pain
		inter-para scapular pain
HEAD	~	headaches
		funny feelings in face and ear
VERTEBRAL ARTERY	~	dizziness, lightheadness
		vertigo, syncope
		diplopia, dysarthria, dysphonia, dysphagia
		tinnitus, ear pain

Compression can be of different magnitude in each of these structures. For example, the subclavian vein can be the only compressed structure and this patient might have a thrombosis of the vein that was called in the past effort thrombosis, or a swelling of the fingers. The subclavian artery can also be compressed with symptoms of temporary, arterial, positional insufficiency of the upper extremity. When they are present for a long time, aneurysm and thrombosis of the subclavian artery may develop with distal embolization. Nerve compression of the brachial plexus is very common and is or not associated with venous or arterial compression.

Paget Schroetter Syndrome: This is the name given to the subclavian vein thrombosis (beneath the clavicle) which results in pain, swelling, blue discoloration, and congestion of the arm. It is commonly caused by compression of the vein between the clavicle and the first rib, and is considered one of the venous manifestations of TOS.

PHYSICAL EXAMINATION:

- Posture
- The White Hand Sign
- C7-C8-T1 Testing
- Sweating, Swelling

- ***SELMONOSKY TRIAD***
    - Tenderness in the supra clavicular area.
    - Hand paleness and/or paresthesias on elevation.
    - Adduction and abduction weakness of fingers 4 & 5. (C8 - T1 testing)
- ***The Adson sign*** *is the loss of radial pulse by rotating the head to the ipsilateral side and inspiring.*

INVESTIGATIONS: Imaging Studies:

Chest x-ray: Cervical ribs or rudimentary first ribs often can be identified with a CXR.

CT scan:

- CT scans with 3-dimensional reconstruction have become popular for evaluating the thoracic outlet.
- CT scan angiography and venography.

Standard MRI*:* Dynamic MRI with gadolinium infusion also provides detail of the thoracic outlet and may be helpful when evaluating for compression.

Angiography with dynamic positioning.

Venography with dynamic positioning.

Other Tests:

Electromyography (EMG) and nerve conduction studies are useful in the workup of patients suspected of having neurogenic TOS. ***A reduction in nerve conduction velocity <85 m/s of either ulnar or median nerves across the thoracic outlet corroborates the diagnosis of neurogenic TOS***.

INDICATIONS: Failure of conservative treatment in a patient with severe disability.

TREATMENT

Physical therapy: Postural exercises, stretching, abdominal breathing, and medications used to relieve muscular tension and pain are beneficial.

No satisfactory medical treatment for arterial TOS exists.

Surgical therapy:

- Arterial TOS requires prompt surgical intervention to treat or prevent acute thromboembolic events.
- Treatment for venous TOS-related effort thrombosis relies on anticoagulation and arm elevation leaves.

Venous thoracic outlet obstruction: Surgical treatment of venous TOS consists of releasing the extrinsic compression and restoring luminal patency. ***After thrombolysis, surgeons wait one month before decompressive treatment surgery is undertaken***. Surgical decompression of veins within the scalene triangle is achieved by anterior rib resection, anterior scalene release and in some cases clavicular resection.

Neurogenic/arterial thoracic outlet obstruction

Thoracic outlet decompression can be performed through an ***axillary, supraclavicular, or posterior approach.*** Thoracic outlet decompression may entail ***anterior and middle scalenectomy, first rib resection, or scalenectomy plus first rib resection***.

Vascular trauma

- Vascular trauma can result from either blunt or penetrating injury

Types of vascular injury

- Contusion/ Puncture/ Laceration/ Transection

Pathophysiology

- Haemorrhage is the prime consequence of vascular injury.
- Bleeding may be obvious, with visible arterial haemorrhage, or it may be concealed.
- Ischaemia results from an acute interruption of flow of blood to a limb or organ.
- Peripheral nerves are more sensitive to ischaemia, and prolonged neurological deficit may result from relatively short periods of tissue ischaemia.
- If arterial supply is restored to ischaemia tissue, the sudden release of inflammatory mediators, lactic acid, potassium and other intracellular material into the circulation can cause profound myocardial depression, generalised vasodilatation and initiate a systemic inflammatory response.

Clinical features

- Depends on site, mechanism and extent of injury
- Signs classically divided into 'hard' and 'soft' sign

Hard signs of vascular injury

- Pulsatile bleeding
- Expanding haematoma
- Absent distal pulses, cold, pale limb- Distal ischaemia.
- Audible Bruit or palpable thrill
- Active haemorrhage

The presence of hard signs of vascular injury mandates immediate operative intervention without prior investigation.

Soft signs of vascular injury

- Haematoma
- History of haemorrhage at site of accident
- Unexplained hypotension
- Peripheral nerve deficit
- Decreased pulse compared to the contralateral extremity
- Bony injury or in proximity penetrating wound

Softer signs require close observation and monitoring. If the ABI is higher than 0.9, close observation is advocated, but if the ABI is lower than 0.9, further evaluation is warranted.

Investigation

- Arteriography should be considered:
    - To confirm extent of injury in stable patient with equivocal signs
    - To exclude injury in patient without hard signs but strong suspicion of vascular injury

Diagnostic Adjuncts

Pulse Oximetry: A reduction in oximeter readings from one limb, as compared to another is suggestive of significant vascular injury.

***Doppler* Ultrasound**: The diagnosis of a significant (ie. requiring intervention) vascular injury has been shown to be related to the presence or absence of a palpable pulse. Similarly, a reduction in the ankle-brachial pressure index (ABPI) in the presence of a palpable pulse does not indicate the presence of a vascular injury requiring intervention. Doppler ultrasound is therefore adds little to careful clinical examination.

Duplex Ultrasound: Duplex imaging is a non-invasive examination combining B-mode and Doppler ultrasound. Duplex can detect intimal tears, thrombosis, false aneurysms and arteriovenous fistulae.

Angiography: Angiography remains the gold-standard investigation for the further investigation and delineation of vascular injury. Proximal control may be possible with an angioplasty catheter prior to transfer to the operating room.

Management

- The priorities of vascular injury are arrest of haemorrhage and restoration of normal circulation.
- Airway control and respiratory assessment take priority over management of the circulation.

Immediate Haemorrhage Control: by direct pressure or where haemorrhage is welling up from a deep knife or gunshot track, control may be temporarily achieved by passing a urinary catheter into the track as far as possible, inflating the balloon. If angiography is performed prior to surgery, it may be possible to obtain proximal control by passing an angioplasty balloon catheter into the proximal vessel and inflating the balloon.

Volume resuscitation: Prior to haemorrhage control, minimal fluids should be administered. Raising the blood pressure will increase haemorrhage from the vessel injury. No inotropes should be given to the hypovolaemic patient as this will effectively deplete myocardial tissue oxygen and increase myocardial work. Once haemorrhage control is achieved, aggressive volume resuscitation is done.

Operative Strategy

- The basic principle of vascular repair is to gain proximal and distal control of the relevant vessel before investigating the site of injury.
- Proximal control is best achieved through a separate incision away from the site of injury.
- Distal control similarly is best achieved via a second incision.
- Once proximal and distal control is achieved, the site of injury can be explored and control made closer to the injury site.
- Once the vessel injury is identified, the first step is debridement of devitalized tissue and definition of the edges of the wound.
- Next an assessment of inflow and outflow is made. If it is inadequate, a balloon (Fogarty) catheter is passed proximally and distally to extract any thrombus.
- Following extraction, heparinized saline is instilled proximally and distally to locally antcoagulate the vessel.
- Small, clean, transverse wounds to vessels that involve only part of the circumference can be repaired with a direct suture technique.
- A vein or synthetic patch may be required where there is a larger defect in the vessel wall where direct suturing may lead to narrowing of the vessel lumen.
- While vein grafts probably have a longer patency, the graft infection rates are the same for both vein and synthetic grafts, regardless of wound contamination.

Compartment syndrome

- Prolonged interruprion of blood flow to a limb leads to cellular ischaemia, activation of cellular and humoral inflammatory responses and alterations in vascular permeability. Subsequent reperfusion of the limb leads to generalised tissue oedema.
- When this occurs in a limited, enclosed space - such as the fascial compartments of the lower limb, the pressure in the compartment may rise above capillary and venous pressure and cause vascular stasis, cellular ischaemia and death.
- The pressure in the compartments is rarely above arterial pressure and distal pulses are preserved.
- If the patient is awake, there is intense, disproportionate pain in the limb, worsened by passive flexion of the muscle groups.
- **In measurement of compartment pressures values over 30mmHg are diagnostic of compartment syndrome**.
- Fasciotomy is best performed at the time of initial surgery, rather than as a subsequent procedure for a second episode of limb ischaemia.

Aims of surgery are to:

  - Control life-threatening haemorrhage
  - Prevent limb ischaemia
- If surgery is delayed **more than 6 hours**, revascularisation is unlikely to be successful

Vascular repair

- Usually performed after gaining proximal control and wound debridement
- Options include :
  - Simple suture of puncture hole or laceration
  - Vein patch angioplasty
  - Resection and end-to-end anastomosis
  - Interpositional graft
- ***Contralateral saphenous vein is the ideal Interpositional graft***
- Prosthetic graft material may be used if poor vein or bilateral limb trauma

Complications of vascular injury

- ***Thrombosis of the graft remains the most common complication of vascular injury.***
- Narrowing of the vessel with primary repair or kinking of the graft, may require revision of the repair.

"False aneurysm"

- Most commonly occurs following catheterisation of femoral artery
- Often presents with pain, bruising and a pulsatile swelling
- Diagnosis can be confirmed by doppler ultrasound
- Suturing of puncture site/ Vein patching may be required

Arteriovenous fistula

- Often presents several weeks after the injury
- Patient complains of a swollen limb with dilated superficial veins
- **Machinery type bruit** (continuous) often present throughout cardiac cycle
- Diagnosis can be confirmed by angiography
- Fistula can be divided an both the vein and artery sutured
- Flap of fascia can be interposed between vessels to reduce risk of recurrence.