GIT

OESOPHAGUS

The oesophagus begins at the lower margin of the cricopharyngeous muscle and is approximately 25cm long.

It is composed of striated muscle in upper third, smooth muscle in the lower two thirds, and is lined throughout by squamous epithelium.

In the mediastinum, the oesophagus is closely related to the two trunks of the vagus nerve, the trachea, the aorta and the heart.

Barium swallow may show a slight constriction approximately 2cm above the diaphragm, below which is an area of dilatation known as the vestibule, or phrenic ampulla.

The oesophagus enters the stomach approximately 40-45 cm from the incisor teeth.

The barrier functions of the oesophagus depend on the upper cricopharyngeal and lower oesophageal sphincters, a zone of high pressure (15- 35 mmHg) extending over lowest 3-4cm of the esophagus; it has no anatomical counterpart.

The pH within the oesophagus is usually 5-7, unless there is reflux of acidic gastric contents. ***A pH of less than 4 is normally considered pathological; assessment is best made by continuous 24 hour pH monitoring.***

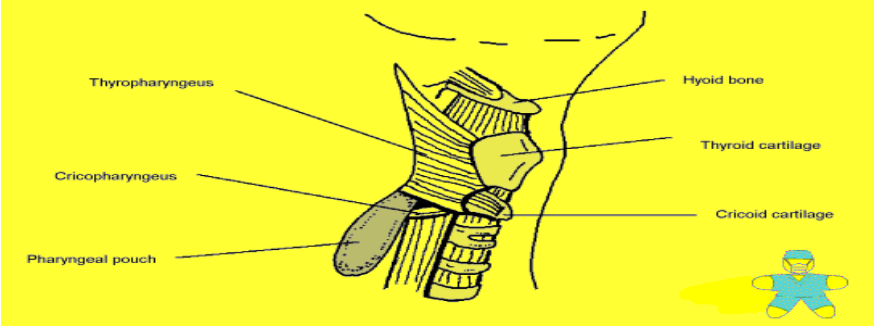
At the gastro-oesophageal junction, the transition from oesophageal to gastric mucosa is easily seen as an irregular circumferential line known as the ***ora serrata, gastric rosette, or Z-line***.

Esophageal Diverticula

Zenker's diverticulum occurs due to increased pressure in the oropharynx during swallowing against a closed upper esophageal sphincter.

Zenker diverticula are an acquired pulsion-type of diverticula that form in the posterior hypopharynx from a defect in the muscular wall, between the inferior pharyngeal constrictor muscle and the cricopharyngeal sphincter (Killian triangle).

Retention of undigested food in large diverticula occasionally results in ***regurgitation***, nocturnal cough, and aspiration pneumonia.



Imaging Studies:

On chest x-rays and CT scans, large diverticula of the esophagus and hypopharynx may also manifest as air or fluid-filled structures communicating with the esophagus.

Diagnosis of Zenker diverticulum is made best by barium swallow.

Medical Care: In many patients with mid esophageal and epiphrenic diverticula, dysphagia is related to underlying dysmotility; thus, treatment should be directed to the motility disorder when feasible e.g. ***it can be treated with pneumatic dilation, botulinum toxin injection into lower esophageal sphincter, or surgical Heller esophagomyotomy***.

Surgical Care: Treatment of Zenker diverticulum is surgical; Surgical options include ***diverticulectomy with cricopharyngeal myotomy***, diverticular suspension (diverticulopexy) with cricopharyngeal myotomy, and cricopharyngeal myotomy alone.

Surgical Treatment:

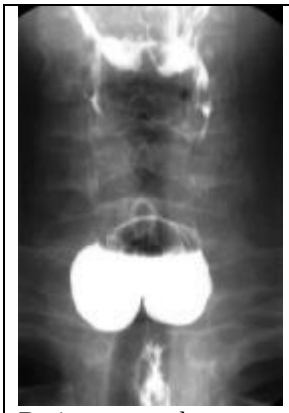
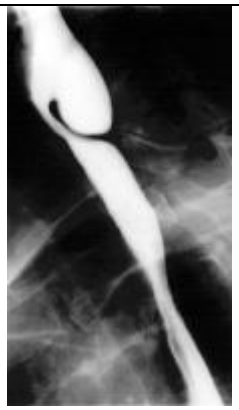
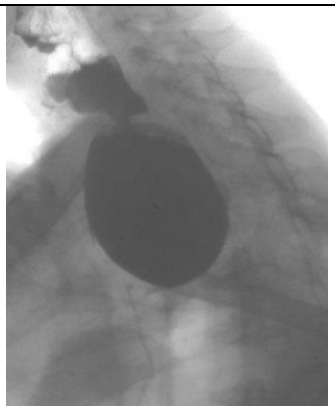
- Diverticulectomy & Dohlman's procedure

Diverticulectomy

- Fascia at anterior border of sternomastoid is divided
- Pouch is identified anterior to prevertebral fascia
- Pouch is then excised an defect closed
- Cricopharyngeal myotomy is performed to prevent recurrence
- Patient is fed via a nasogastric tube for a week postoperatively
- Complications include:
    - Recurrent laryngeal nerve palsy
    - Cervical emphysema
    - Mediastinitis
    - Cutaneous fistula

Dohlman's procedure

- Is an endoscopic procedure
- A double-lipped oesophagoscope is used
- Wall between the diverticulum and oesophageal wall is exposed
- Hypopharyngeal bar divided with diathermy or laser

 Barium esophagram, AP view, demonstrating a bilobed Zenker diverticulum	 Zenker diverticulum, lateral view	 Barium swallow show residual pool of contrast within the pouch

Gastroesophageal Reflux Disease

Pathophysiology:

- The lower esophageal sphincter (LES) must have normal length and pressure and a normal number of episodes of transient relaxation,.
- The gastroesophageal junction must be located in the abdomen so that the diaphragmatic crura can assist the action of the LES functioning as an extrinsic sphincter. The presence of a hiatus hernia disrupts this synergistic action and can promote reflux.
- Esophageal clearance must be able to neutralize the acid refluxed (mechanical clearance is by esophageal peristalsis; chemical clearance is due to saliva).
- The stomach must empty properly.

A functional (frequent transient LES relaxation) or mechanical problem of the LES (hypotensive LES) is the most common cause of GERD. Certain foods (coffee, alcohol), medications (calcium channel blockers, nitrates, β blockers), or hormones (progesterone) can decrease LES pressure. Obesity is a contributing factor.

History: *Typical symptoms include the following:*

- Heartburn/ Regurgitation/ Dysphagia:

Atypical symptoms include the following:

- Cough and/or wheezing/ Hoarseness/ Chest pain:

Imaging Studies:

1: Barium esophagogrm: It is particularly important for patients who experience dysphagia.

2: Esophagogastroduodenoscopy: It identifies the presence and severity of esophagitis and the possible presence of Barrett esophagus and also excludes the presence of other diseases that can present similarly, such as a peptic ulcer.

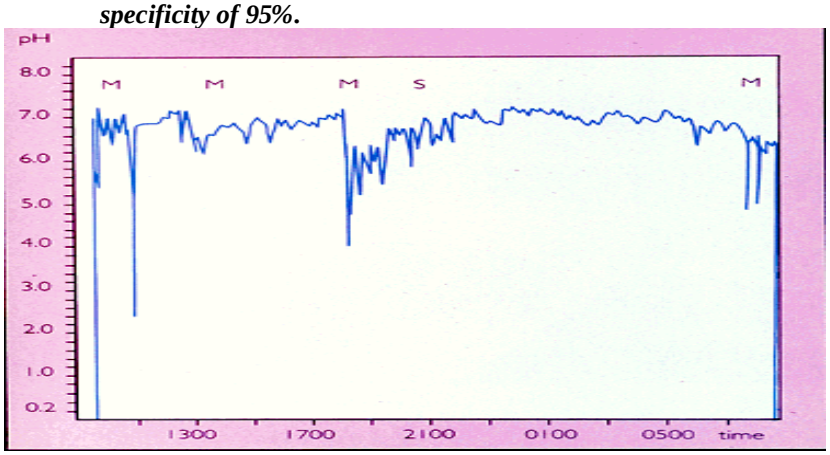
Other Tests:

3: Esophageal manometry

- This study defines the function of the LES and esophageal body (peristalsis).

4: Ambulatory 24-hour pH monitoring

- ***This test is the criterion standard for diagnosis of GERD, with a sensitivity of 96% and a specificity of 95%.***



5: Radionuclide measurement of gastric emptying

Medical Care:

Lifestyle modifications include the following:

- Lose weight (if overweight). Avoid alcohol, chocolate, citrus juice, and tomato-based products. Avoid large meals. Wait 3 hours after a meal before lying down.
- Elevate head of bed 8 inches.

Pharmacological therapy

- Antacids.
- Histamine-2 receptor antagonists.
- Proton pump inhibitors: used only when GERD has been objectively documented.
- Prokinetic agents:

Surgical Care:

Indications for fundoplication include the following:

- Patients with symptoms incompletely controlled by proton pump inhibitor.
- The presence of Barrett esophagus is an indication for surgery.
- Presence of extraesophageal manifestations of GERD may indicate the need for surgery. These include (1) respiratory manifestations (cough, wheezing, aspiration); (2) ear, nose, and throat manifestations (hoarseness, sore throat, otitis media); and (3) dental manifestations (enamel erosion).

Complications:

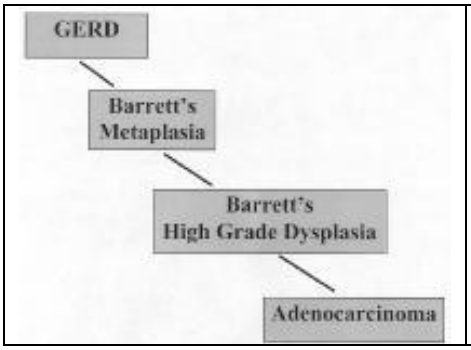
Esophagitis: The squamous epithelium responds to acid by summoning lymphocytes and neutrophils to the sub-epithelial layers. The resulting mucosal damage and loss of the surface squamous cells then promotes frank ulceration, fibrosis and stricture formation.

Barrett's esophagus: The alterations in the lower esophagus, caused by chronic regurgitation of gastric contents, are now recognized to predispose to the development of an adenocarcinoma of the lower esophagus. This risk of malignancy is related to the tendency of the squamous mucosa of the esophagus to be replaced by migrating columnar cells from the upper stomach (cardia). The gastric-type mucosa, placed

under considerable stress in its new environment, responds by developing numerous goblet cells, acquiring the characteristics of intestinal tissue, the so called intestinal metaplasia. It is commonly called Barrett's epithelium and has the propensity, over several years, to evolve into a true dysplasia and, eventually, to an adenocarcinoma.

The risk of developing Barrett's esophagus is related to the history of regular symptoms of gastro-esophageal reflux, the advancing age (> age 50) and the presence of inflammation of the squamous epithelium related to acid reflux. Risk of malignancy due to intestinal metaplasia of the columnar lined lower esophagus is 30 to 125 times that in the esophagus without the Barrett's changes. When dysplasia does develop, resection of the lower esophagus and a gastric pull-up or jejunal interposition is indicated.

Non-surgical eradication of Barrett's Esophagus: Laser ablation of the unwanted columnar intestinal metaplasia can be accomplished in 60-80 %.



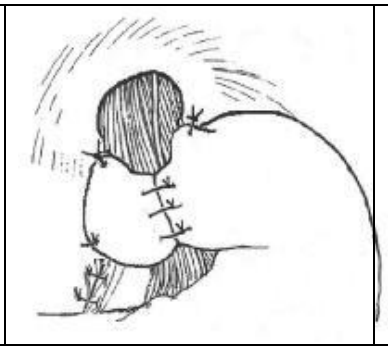


Fig1: Gastroesophageal reflux disease/Barrett esophagus/adenocarcinoma sequence

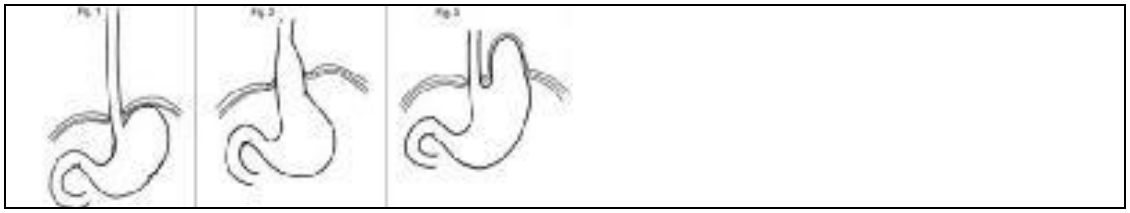
Fig2: Laparoscopic Nissen fundoplication

Hiatal hernia

Types:

- Sliding hiatal hernia (99%)
- Paraesophageal hernia (1%)
- congenitally short esophagus (not a true hernia)

Associated with: diverticulosis (25%); Gallstones (18%); esophagitis (25%); Duodenal ulcer (20%) ***(Saint's triad: Hiatus hernia + diverticulosis + Gall stones)***



Sliding hiatal hernia

"Axial hernia," "concentric hernia": 99%

- Portion of peritoneal sac forms part of wall of hernia, gastroesophageal junction and a portion of the stomach are above the diaphragm.
- incidence: increases with age
- etiology: rupture of phrenicoesophageal membrane due to repetitive stretching.

Findings:

- UGI: Epiphrenic bulge/ distance between B ring and hiatal margin > 2cm/ tortuous esophagus/ gastroesophageal reflux/ 6 thick gastric folds within suprahiatal pouch
- CT: Dehiscence of diaphragmtic crura > 15 mm/ pseudomass within/above distal esophagus/ fat (omemtum) surrounding distal esophagus

Paraesophageal hiatal hernia

"Rolling hiatal hernia," "parahiatal hernia"

- 1% of hiatal hernias. portion of stomach superiorly displaced into the thorax with the esophagogastric junction remaining in the subdiaphragmatic position

Findings:

- The gastroesophageal junction is in the normal location, but a portion of the stomach is adjacent to the esophagus i.e. cardia in normal position
- herniation of portion of the stomach anterior to esophagus
- frequently nonreducible, may be associated with gastric ulcer of lesser curvature at level of diaphragmatic hiatus

Symptoms and Signs

Most patients are asymptomatic, but chest pain can occur. GERD occurs in few patients. A paraesophageal hiatus hernia is generally asymptomatic but, may incarcerate and strangulate. Occult or massive GI hemorrhage may occur with either type.

Diagnosis and Treatment

- X-rays usually readily show hiatus hernia.
- **A barium study helps distinguish a sliding from a paraesophageal hernia.**
- Typical findings include an outpouching of barium at the lower end of the esophagus, a wide hiatus through which gastric folds are seen in continuum with those in the stomach, and, occasionally, free reflux of barium.

Endoscopy

- Hiatal hernia is diagnosed easily using upper gastrointestinal endoscopy.
- A hiatal hernia is confirmed when the endoscope is about to enter the stomach or on retrograde view once inside the stomach.
- Endoscopy also permits biopsy of any abnormal or suspicious area.

Treatment:

Self-care action plan

- Modifying lifestyle factors/ Neutralizing acid or inhibiting acid production/ Enhancing esophageal and gastric motility

Surgery: Surgery is necessary only in the minority of patients with complications of GERD despite aggressive treatment with proton pump inhibitors (PPIs). The rolling hernia may strangulate and frequently is operated on prophylactically to prevent this.

Nissen fundoplication

- This procedure involves a 360° fundic wrap around the gastroesophageal junction. The diaphragmatic hiatus also is repaired.
- It can be performed laparoscopically. Postoperative complications are dysphagia and gas bloating.
- The ***Toupet procedure*** is a variant of the Nissen wrap and involves a 180° wrap in an attempt to lessen the likelihood of postoperative dysphagia.

Belsey (mark IV) fundoplication: This operation involves a 270° wrap.

It also is preferred when minimal esophageal dysmotility is suspected. To complete this operation, the left and right crura of the diaphragm are approximated.

Hill repair: In this procedure, the cardia of the stomach is anchored to the posterior abdominal areas, such as the medial arcuate ligament. This also has the effect of augmenting the angle of His and thus strengthening the antireflux mechanism.

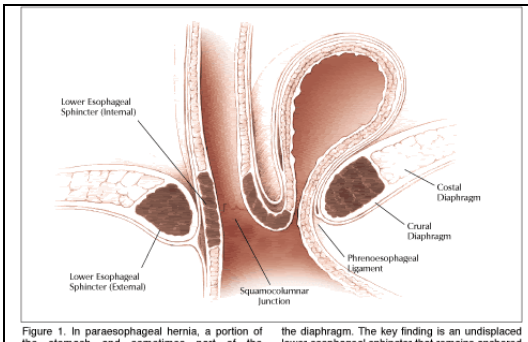


Figure 1. In paraesophageal hernia, a portion of the stomach—and sometimes part of the peritoneal sac containing the spleen or colon—migrates into the chest cavity through the esophageal hiatus (as shown here) or a defect in the diaphragm. The key finding is an undisplaced lower esophageal sphincter that remains anchored to the diaphragm by the phrenoesophageal ligament. (Adapted from Mittal, Am J Med 103:33S, 1997)

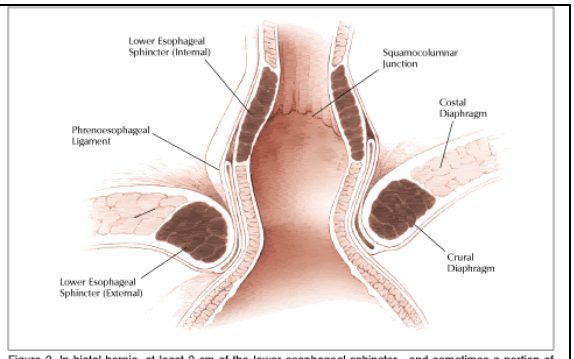


Figure 2. In hiatal hernia, at least 2 cm of the lower esophageal sphincter—and sometimes a portion of the stomach—is displaced above the diaphragmatic hiatus. The cause may involve a weakened phrenoesophageal ligament. (Adapted from Mittal, Am J Med 103:33S, 1997)

Boerhaave Syndrome:

Boerhaave syndrome is a spontaneous transmural perforation of the esophagus resulting from a sudden rise in intraluminal pressure caused by an uncoordinated act of forceful vomiting against a closed cricopharyngeal sphincter.

More than 90% of these perforations occur in the left posterolateral wall of the lower third of the esophagus.

The syndrome can also occur after other spontaneous Valsalva-like maneuvers, such as childbirth, coughing, straining during a bowel movement, or heavy lifting. Nonspontaneous causes include iatrogenic perforation associated with endoscopy, ingestion of a caustic substance, and blunt trauma to the neck and chest.

After repeated episodes of retching and vomiting patient feels a sudden onset of severe chest pain in the lower thorax and upper abdomen. The pain typically radiates to the back or left shoulder as a result of the intense inflammatory response to the saliva and gastric contents entering the mediastinum. Other symptoms are neck pain, dysphagia, odynophagia, respiratory distress, and fever.

On physical examination, nonspecific findings may be present: tachycardia, diaphoresis, fever, hypotension, and generalized abdominal tenderness with guarding and rebound.

The diagnosis is established by means of water-soluble contrast esophagraphy to reveal the location and extent of extravasation. Endoscopy has a limited role, as small tears are difficult to visualize on this study. In addition, the insufflation of air required for the procedure can result in the extension of the perforation.

Prompt diagnosis and early surgical intervention is crucial. Management includes strict adherence to giving the patient nothing by mouth, administration of broad-spectrum antibiotics, fluid resuscitation, nasogastric decompression, and early consultation with a surgeon. Depending on the location of the tear, a chest or abdominal approach to repair the perforation is performed, and parenteral nutrition is required.

The pathophysiology of Boerhaave's syndrome closely resembles that of ***Mallory-Weiss syndrome, which is characterized by upper gastrointestinal bleeding due to a mucosal tear at the esophago-gastric junction.*** Forceful vomiting may lead to either disease, but in Boerhaave's syndrome, the tear extends through all layers of the esophageal wall.

Early recognition followed by prompt surgery remains the treatment of choice for this life-threatening thoracic emergency. Since the perforation is usually on the left side of the lower esophagus, the lesion can be visualized through a left-sided thoracotomy. After the esophageal tear is identified, it should be closed and then reinforced with a patch of adjacent tissue. External drainage of the chest completes the procedure.

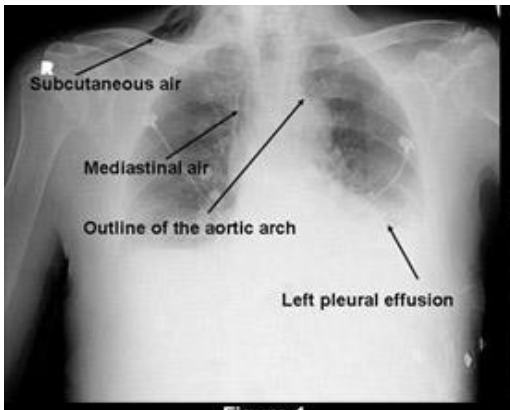


Figure 1

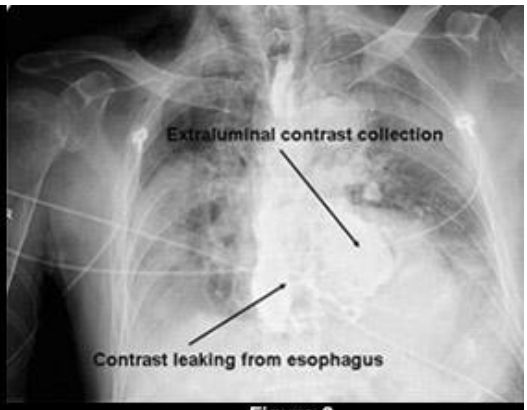


Figure 2

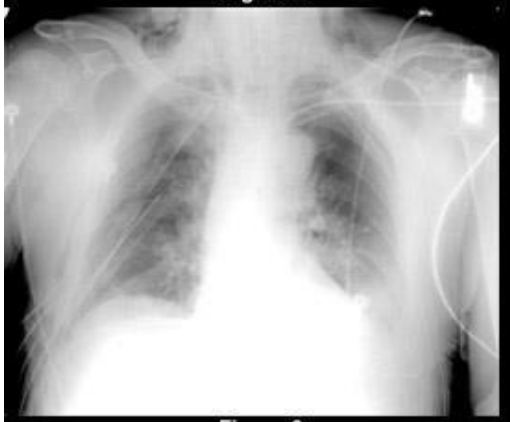


Figure 3

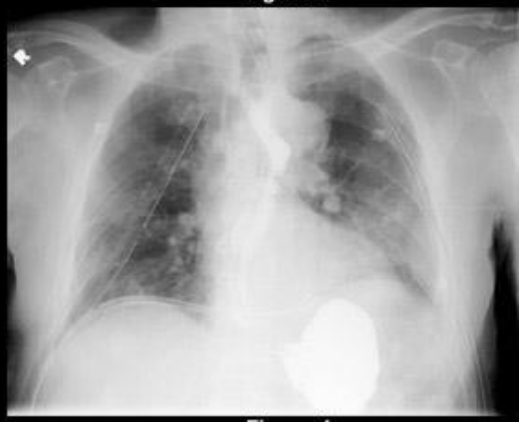
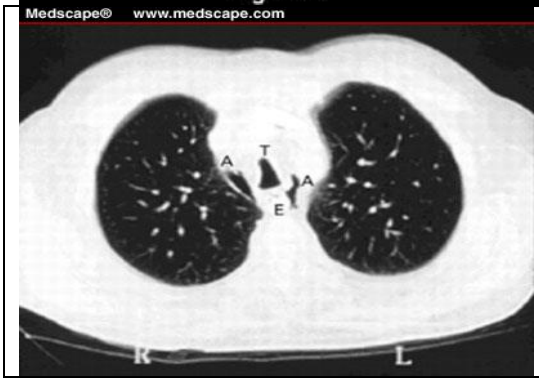


Figure 4



Computed tomography of the chest through the superior mediastinum with the use of intravenous and oral contrast medium showed air (A) in the mediastinum adjacent to the esophagus (E) and the trachea (T), indicating the occurrence of spontaneous esophageal rupture (Boerhaave's syndrome).

RINGS AND WEBS

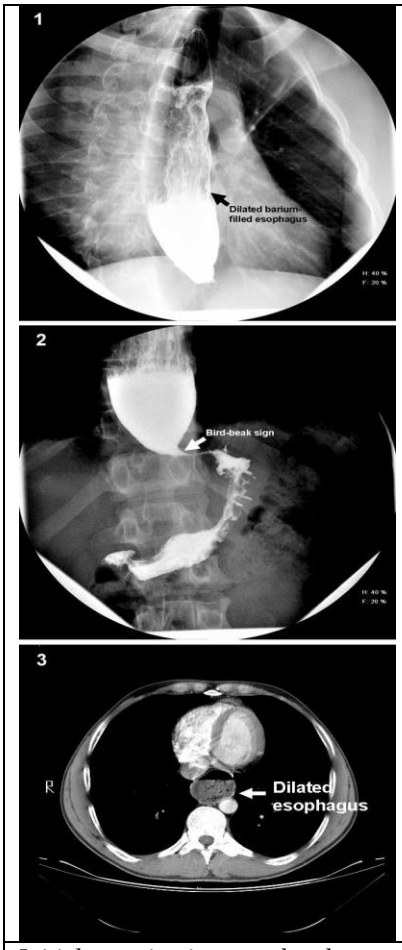
Oesophageal webs are thin membranes of connective tissue covered by normal squamous epithelium, usually situated in the upper third and are frequently asymmetrical. The association of a cervical oesophageal web and iron deficiency anaemia is known as the Paterson-Brown-Kelly (or Plummer-Vinson) syndrome and occurs most often in middle-aged women.. These webs regress spontaneously with treatment of the anaemia and, the syndrome is associated with an increased incidence of post-cricoid carcinoma.

Two types of oesophageal ring have been described. The Schatzki ring is a symmetrical, submucosal, fibrous thickening, measuring 1-3mm in thickness and occurs at the squamo-columnar junction at the lower end of the oesophagus. The ring can be seen endoscopically above the diaphragmatic indentation.

The other type of ring occurs just cephalad to the site of the Schatzki ring, at the junction of the distal oesophagus and the uppermost part of the lower oesophageal sphincter and is thought to be muscular.

Manometrically, this corresponds to a high pressure zone and is frequently associated with oesophageal motor disorders and diffuse oesophageal spasm.

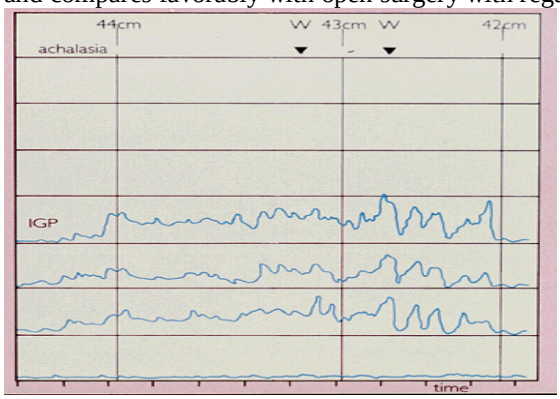
ACHALASIA OF THE CARDIA



In 1672, Sir Thomas Willis first described this condition.
The term achalasia cardia was coined in 1929 to signify a disorder of esophageal motility characterized by decreased or absent peristalsis of the esophageal body, increased pressure in the esophagus, and impaired relaxation of the lower esophageal sphincter.
The condition can be divided into primary and secondary forms.
Primary achalasia is due to loss of ganglion cells in the myenteric plexus of Auerbach and is more common than secondary achalasia, which may be due to malignancy, diabetes, or Chagas disease (*Trypanosoma cruzi*).
The most common age range at presentation is 25-60 years, with no predilection for sex. Patients with this condition have an increased incidence of malignancy; approximately 5% developing squamous cell carcinoma, usually in the mid-esophagus.
Dysphagia is the cardinal symptom. Regurgitation, weight loss, and chest pain or discomfort are other symptoms.
(Patients with achalasia may have chronic aspiration pneumonia involving *Mycobacterium fortuitum-chelonei*.)

Initial examination may be chest radiography, which often demonstrates a homogeneous, usually right-sided, paramediastinal soft-tissue opacity. Other findings may include mediastinal widening, air-fluid levels, absence of a gastric air bubble (due to a water-seal effect), and complications such as aspiration pneumonia or lung abscess.
Fluoroscopic barium swallow demonstrates failure of the contrast agent to enter the stomach when the patient is in the recumbent position, nonpropulsive tertiary esophageal contractions, various degrees of dilatation, and the bird-beak sign (ie, abrupt, smooth tapering of the distal esophagus).
CT findings are nonspecific and insensitive, with esophageal dilatation usually present. Symmetric wall thickening helps to distinguish achalasia from pseudoachalasia of malignancy, in which mucosal irregularity or mass effect at the cardia is usually present.
Esophageal manometry is considered the diagnostic criterion standard. Findings include increased LES pressure and incomplete relaxation, as well as abnormal esophageal peristalsis.
Endoscopy can yield biopsy samples to exclude malignancy and permit direct visualization of esophagitis or ulcers.
In addition, therapeutic interventions, including pneumatic balloon dilation (which is 70% effective with 5% perforation rate) and botulinum toxin injection (though only 30% of patients have continued relief at 1-year follow-up), may be performed during the procedure.
Heller myotomy done with a laparoscopic technique usually results in progressive improvement

and compares favorably with open surgery with regard to relief of dysphagia and GERD.



Medical therapies with various drugs, including calcium channel blockers and nitrates, are effective in a few patients and may be tried in patients with contraindications to pneumatic dilation or surgery.

Esophageal Atresia and Tracheoesophageal Fistula

Esophageal atresia with tracheoesophageal fistula occurs in one of 3,000 to 5,000 births. **Embryology**

The esophagus and trachea derive from the primitive foregut. During the fourth and fifth weeks of embryologic development, the trachea forms as a ventral diverticulum from the primitive pharynx (caudal part of the foregut). A tracheoesophageal septum develops at the site where the longitudinal tracheoesophageal folds fuse together. This septum divides the foregut into a ventral portion, the laryngotracheal tube and a dorsal portion (the esophagus). Esophageal atresia results if the tracheoesophageal septum is deviated posteriorly. This deviation causes incomplete separation of the esophagus from the laryngotracheal tube and results in a concurrent tracheoesophageal fistula. Esophageal atresia as an isolated congenital anomaly may occur, rarely. In these cases, the atresia is attributable to failure of the recanalization of the esophagus during the eighth week of development and is not associated with tracheoesophageal fistula.

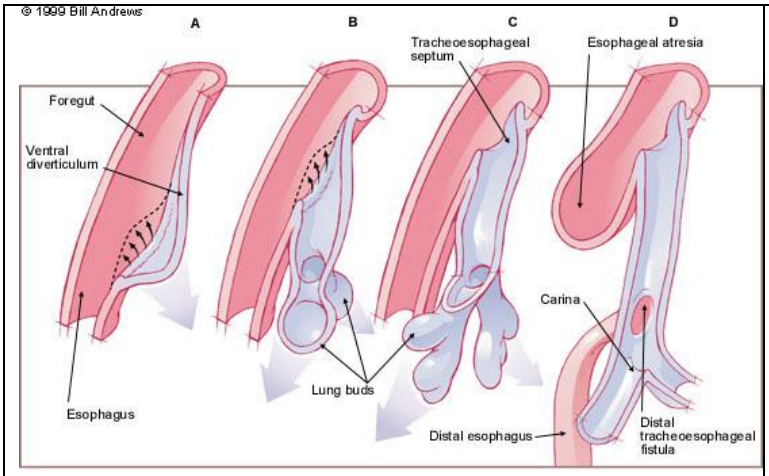
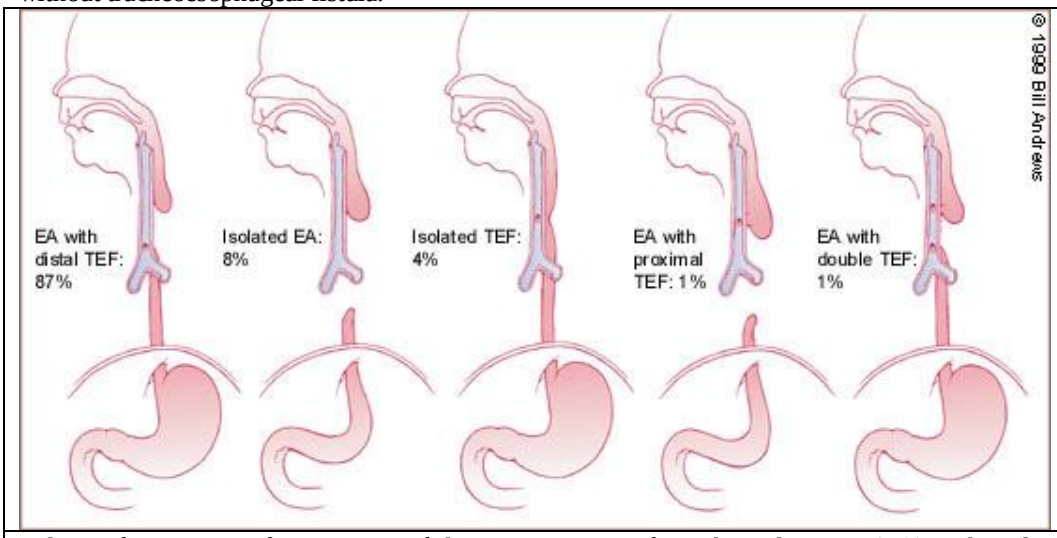


FIGURE. Successive stages in the development of the tracheoesophageal septum during embryologic development. **(A)** The laryngotracheal diverticulum forms as a ventral outpouching from the caudal part of the primitive pharynx. **(B)** Longitudinal tracheoesophageal folds begin to fuse toward the midline to eventually form the tracheoesophageal septum. **(C)** The tracheoesophageal septum has completely formed. **(D)** If the tracheoesophageal septum deviates posteriorly, esophageal atresia with a tracheoesophageal fistula develops.

Pathology

Many anatomic variations of esophageal atresia with or without tracheoesophageal fistula have been described *(Figure*). The most common variant of this anomaly consists of a blind esophageal pouch with a fistula between the trachea and the distal esophagus, which is estimated to occur 84 percent of the time. The fistula often enters the trachea close to the carina. The second most common anomaly is pure atresia without tracheoesophageal fistula.



Relative frequencies of occurrence of the various types of esophageal atresia (EA) with and without tracheoesophageal fistula (TEF).

Associated Defects

Associated congenital anomalies are discovered in approximately 50%. The acronym VATER, or VACTERL (**v**ertebral defect, **a**norectal malformation, **c**ardiac defect, **t**racheo**e**sophageal fistula, **r**enal anomaly, **r**adial dysplasia and **l**imb defects), has been used to describe the condition of multiple anomalies in these infants.

Clinical Presentation and Diagnosis

The first sign of esophageal atresia in the fetus may be ***polyhydramnios in the mother.*** Classically, the neonate with esophageal atresia presents with copious, fine, white, frothy bubbles of mucus in the mouth and, sometimes, the nose. The infant may have rattling respirations and episodes of coughing, choking and cyanosis. These episodes may be exaggerated during feeding.

Management and Treatment

Measures should be taken to reduce the risk of aspiration. The oral pharynx should be cleared, and an 8 French sump tube placed to allow for continuous suctioning of the upper pouch. The infant's head should be elevated. Intravenous fluids (10 percent dextrose in water) should be started. Oxygen therapy is used as needed to maintain normal oxygen saturation. In infants with respiratory failure, endotracheal intubation should be performed. Bag-mask ventilation is not appropriate since it may cause acute gastric distention requiring emergency gastrostomy.

If sepsis or pulmonary infection is suspected, broad-spectrum antibiotics should be administered. Before surgical correction, the infant must be evaluated thoroughly for other congenital anomalies. Gastrostomy for gastric decompression is reserved for use in patients with significant pneumonia or atelectasis, to prevent reflux of gastric contents through the fistula and into the trachea. Healthy infants without pulmonary complications or other major anomalies usually can undergo primary repair in the first few day

Esophageal Carcinoma

Incidence of esophageal carcinoma is less than 10 per 100,000 in the US but it is as high as 15-20 cases per 100,000 in most areas of China and over 150 per 100,000 in particularly high risks areas of China. Overall, of patients with esophageal carcinoma, a dismal 5 year survival rate is less than 10%. With surgical treatment, depending on the study and stage of the tumor, an approximate 20%, or less may survive 5 years.

Risk Factors

Cigarette smoking and alcohol drinking are the two major etiological factors of esophageal carcinomas. Incidences of heavy smoking and heavy drinking combined, increases the risk from 25 to100 folds.

Diets low in beta-carotene, vitamins A, C, B, magnesium, and zinc have been associated with cancer. Also, reduced consumption of fruits, vegetables, fresh meat, fresh fish and dairy products resulted in a 2 fold increased incidence of esophageal carcinoma. In addition, high level exposure to asbestos, ionizing radiation, and drinking exceptionally hot beverages (tea) has also been found to be positively correlated.

Predisposing Conditions:

- Tylosis
- Achalasia
- Barrett's Esophagus
- Caustic Injury
- Esophageal Diverticula
- Esophageal Webs

Anatomy

It receives arterial blood flow from three sources: inferior thyroid, esophageal branches from descending aorta, left gastric/celiac axisThe submucosa has a rich network of capillaries. Venous drainage is through three systems: the inferior thyroid, azygos/ hemiazygous venous system, and the left gastric vein.

The lymphatic drainage of the esophagus is conducted by a vast network of vessels originating in the mucosal plexus which communicates with a submucosal plexus. These two then coalesce with lymph channels of the muscularis layer. Because of the rich and complex lymphatic drainage, fluids from any part of the esophagus can travel to any other portion of the esophagus. ***Therefore, when resection of the tumor is carried out, ample distance from the actual tumor (10 cm) must also be resected***. The lymph channels eventually drain into a number of lymph nodes: internal jugular, cervical, supraclavicular, paratracheal, hilar, subcarinal, paraesophageal, para-aortic, paracardial, lesser curvature, left gastric, and celiac.

Normal Histology

The esophagus consists of three layers: mucosa, submucosa, and muscularis. The mucosa consists of epithelial lining containing nonkeratinizing, stratified squamous epithelium with a layer of basal and parabasal cells. Squamous cell carcinoma is derived from this layer. The sublayer, lamina propria, contains vessels, connective tissue, lymphatics, inflammatory cells and esophageal cardiac glands which are mucus secreting glands. Adenocarcinomas arise from these glands. Without the serosa covering, neoplasms that arise in the esophagus can spread unimpeded to other tissues

Squamous Cell Carcinoma (Epidermoid Carcinoma)

Squamous cell carcinoma has been the more common cell-type of esophageal cancers. However, in the last decade, the incidence of adenocarcinoma has increased an approximate 10% per year. It is no longer the leading form of esophageal cancer.

Afro-Americans are five times more likely to develop squamous cell carcinoma. Males are 4 to 6 times more likely than females.

Tumors of epidermoid carcinoma are located mainly in the thoracic esophagus. Approximately 60% are found in the middle third and about 30% in the distal third. Neoplasms can be of four major types:

1) Fungating-type: Predominantly intraluminal growth with surface ulceration and extreme friability. This type frequently invades mediastinal structures.

2) Ulcerating-type: Characterized by a flat based ulcer with slightly raised edges; hemorragic and friable and surrounding induration and erythema.

3) Infiltrating-type: A dense firm logitudinal and circumferential intramural growth pattern.

4) Polypoid: Intraluminal polypoid growth with a smooth surface on a narrow stalk. A five year survival of 70% is associated with the polypoid tumor compared to less than 15% five year survival for other types[15].

Adenocarcinoma

Adenocarcinoma has been the second most common cell type of esophageal cancer, but now is the leading cell type of this type of cancer. Adenocarcinoma, by definition, is a carcinoma derived from glandular

tissue or in which the tumor cells form recognizable glandular structures. This gland-like or gland-derived carcinoma arises from three sources: superficial and deep glands of the esophagus such as mucous glands, embryonic remnants of glandular epithelium, or metaplastic glandular epithelium. **It is a cancer limited mainly to the lower third of the esophagus and arises mainly from the premalignant condition, Barrett's esophagus. Patients presenting with adenocarcinoma are usually white males.**

Histologically, adenocarcinoma has distinctive small or large gland patterns. The cell lining of the glands have variable cytoplasmic differentiation. Unlike the mucin-secreting cells of origin, adenocarcinoma cytologically has a reduced cytoplasmic-nuclear ratio. A loss of cellular polarity demonstrates variable atypia and nuclear size, enlarged nucleoli and increased mitoses.

Barrett's Esophagus

Seven percent of the population suffers from symptomatic gastroesophageal reflux disease and 2-15% of those patients with chronic reflux disease develop Barrett's esophagus. It is a condition where ***metaplastic columnar epithelium replaces the distal squamous mucosa due to prolonged exposure of the distal esophageal mucosa to gastroesophageal reflux.***

Barrett's esophagus is of clinical importance because it is a premalignant lesion strictly associated with the development of adenocarcinoma. Adenocarcinoma occurs in patients with Barrett's esophagus 30-40 times greater than the rate of the general population. Between 59-86% of adenocarcinomas arise in Barrett's esophagus.

Symptoms of Esophageal Carcinoma

The most common symptoms are dysphagia and weight loss. Because of the elasticity of the esophagus, two-thirds of the lumen must be obstructed to produce dysphagia. Pain can be a symptom of this disease. It can come from the growth of the tumor, be related to swallowing, or be related to metastases into the surrounding esophageal lymph nodes. Less frequent symptoms are coughing or hoarseness. These are usually associated with tumors of the cervical esophagus.

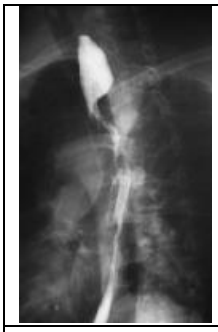
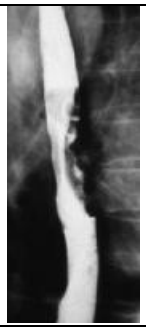
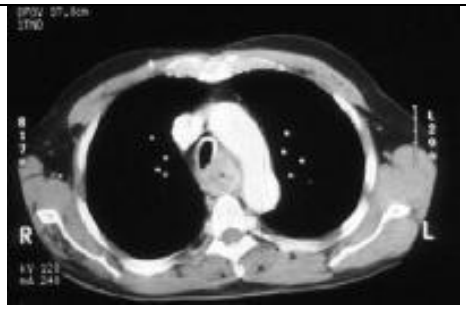
Symptoms of Esophageal Carcinoma

Dysphagia: 87-95/ Weight Loss: 42-71/ Vomiting or Regurgitation: 29-45/ Pain: 20-46/ Cough or Hoarseness: 7-26/ Cachexia: 6/ Dyspnea: 5

Diagnosis

Chest radiograph: The most common finding is an abnormal azygoesophageal recess. The next most frequent is widening of the mediastinum or posterior tracheal indentation. These findings may be seen on a computed tomography (CT) scan. ***A barium swallow is performed to determine the extent of the tumor and its location***. In addition, a CT scan or endoscopic ultrasound (EUS) can also identify the same factors that a contrast swallow can. The CT or EUS can determine the involvement of the mediastinal, perigastric, or celiac lymph nodes.

Flexible or rigid esophagoscopy is required to diagnose and determine the extent of longitudinal intramural tumor spread. The entire esophagus is visualized and tissue samples may be obtained for histological analysis. Biopsy and brush cytology may be performed. The accuracy of brush cytology alone is about 85-97% and biopsy alone ranging from 83-90%. The accuracy for the combination brush cytology and biopsy is 97-100%.

		
barium swallow demonstrating cancer stricture.	Barium swallow demonstrating a mass in the mid esophagus.	Chest CT scan showing invasion of the trachea by esophageal cancer.

Staging

Techniques in radiology, such as barium esophogram, CT, and magnetic resonance imaging (MRI) are often used as a basis for clinical staging. EUS is the method of choice to determine depth of tumor invasion and regional nodal disease and involvement of adjacent structures.

Table: TNM Classification of Esophageal Carcinomas

T: Primary Tumor

TO No evidence of a primary tumor

Tis Carcinoma-in-situ (High-grade dysplasia)

T1 The tumor invades the lamina propria, muscularis mucosae, or submucosa but does not breach the boundary between the submucosa and muscularis propria

T2 The tumor invades the muscularis propria but does not breach the boundary between the muscularis propria and periesophageal tissue

T3 The tumor invades the periesophageal tissue but does not invade adjacent structures

T4 The tumor invades adjacent structures

N: Regional Lymph Nodes

NO No regional lymph node metástasis

N1 Regional lymph node metastasis

M: Distant Metastasis

MO No distant metástasis

M1 Distant metastasis

Table 1.7: Stage Grouping for Esophageal Cancer

Stage O:	**Stage I:**	**Stage II:**	**Stage III:**	**Stage IV:**
TO NO Tis NO MO	T1 NO MO	IIA T2 NO MO T3 NO MO IIB T1 N1 MO T2 N1 MO	T3 N1 MO T4, any N, MO	Any T, any N, M1

Treatment

85 to 95% of patients have lymph node involvement at the time of surgical resection and with lymph node involvement, less than 10% survive five years. Palliation affords the patient the ability to swallow and perhaps resume a normal life. It has been found that the most used and useful approach is to use a combination of options.

Curative Treatment

Surgery

Only 50% of patients can undergo a curative resection. If a esophagectomy is indicated, there are three main types: A transhiatal esophagectomy without a thoracotomy, a "standard" (transthoracic) esophagectomy, or a en bloc esophagectomy are current methods.

Regardless of technique, because of the unusual lymphatic system of the esophagus, malignant cells can be found a number of centimeters away (8-10 cm) from the primary lesion. Therefore, when the esophagectomy is performed, a generous margin is included and lymph node dissection is carried out.

Transhiatal esophagectomy (THE)

The transhiatal esophagectomy with a cervical gastroesophageal anastomosis is the preference of some physicians. It is a highly debated technique because some believe it is not a typical "cancer" surgery. THE carries a low operative mortality of 2-6% and a low anastomotic leak rate of 5-7.9%.

There are instances where the transhiatal approach is not indicated. In addition to the contraindications of performing any esophagectomy, the contraindications include evidence through endoscopy of invasion of the tracheobronchial tree, invasion of the diaphragmatic hiatus and evidence through a cervical incision of the tumor being fixed to nearby structures such as the pericardium, aorta, and/or tracheobronchial tree is a major contraindication to THE. Transhiatal esophagectomy allows complete removal of the esophagus without a thoracotomy.

Transthoracic esophagectomy

The transthoracic esophagectomy is considered the "standard". Surgeons favor this approach over the THE because it allows a meticulous lymph node dissection, complete resection of tumor mass and adjacent tissue, and appropriate staging of the tumor which allows for a better chance of cure. Two of the main risks for this operation are a anastomotic leak and respiratory complications. Because of the relative location of the esophagus within the mediastinum, a left side thoracotomy is performed if the tumor in the distal third of the esophagus and a right side thoracotomy if it is in the middle and upper thirds.

Ivor Lewis Esophagectomy: This procedure was proposed by Ivor Lewis in 1946. It consists of a laparotomy to mobilize the stomach as the conduit. Then, the esophagus is resected through a right thoracotomy incision and an intrathoracic esophagogastric anastomosis is performed. The Ivor Lewis esophagectomy is chosen for patients that have tumors of esophageal cancer of the middle and lower third of the esophagus.

Total Thoracic Esophagectomy: This procedure also begins with a laparotomy as do all esophagectomies to mobilize the conduit of choice. The conduit, whether it be the stomach or the colon, is placed retrosternally and a cervical anastomosis is performed. A right thoracotomy is then made and the esophagus is resected.

En Bloc Esophagectomy

Because many patients present with metastases to regional lymph nodes as well as to the surrounding tissue and organs a more radical resection has been advocated; the en bloc esophagectomy. An envelope of normal tissue is removed along with the spleen, celiac nodes, posterior pericardium, azygous vein, thoracic duct, and adjacent diaphragm.

Thorascopic Esophagectomy

Because of their age or condition, some patients do not recover well from thoracotomy. The transhiatal approach is one alternative where thoracotomy is sparred, another newly developed approach is the thorascopic esophagectomy. This procedure is of interest because it is the only thoracotomy excluding technique that allows for a complete esophagectomy and a full lymphadenectomy.

Reconstruction After Esophagectomy

After a portion of the esophagus is removed or complete esophagectomy, a conduit must be established. The stomach, colon and jejunum have all been successfully used as an alternative channels, but ***the stomach appears to be the conduit of choice because of its ease in mobilization and tremendous vascular supply.*** The colon is used if the patient has undergone a partial or total gastrectomy previously or if metastases has spread to the stomach. Jejunal loops can also be used but their restricted mobility and possibly limited vascular supply limit the use of the jejunum as the conduit.

Anastomosis can be performed in the chest just below the arch of the aorta (intrathoracic anastomosis), or the rest of the esophagus can be resected and a cervical anastomosis can be performed in the neck.

Radiation Therapy

External Beam Radiation

External beam radiation therapy may be used alone in the treatment of esophageal carcinoma but is not considered curative. For curative attempts, chemotherapy and/ or surgery generally accompanies this technique. Used alone, there is a 5-10% 5 year survival. Radiation therapy is contraindicated in the presence of a fistula or likely fistula formation. Radiation shrinks the tumor and often leads to fistula formation when the tumor has spread to the trachea or bronchus.

make certain that local invasion has been adequately treated, the target includes a 5 cm margin on either side of the tumor. In addition to irradiating the tumor, lymph node stations are irradiated as well to treat possible metastatic disease. The supraclavicular and celiac lymph nodes are targets if the tumor is in either the upper or lower esophagus respectively.

In the chest, the critical structures to avoid as much as possible are the lung, heart, spinal cord and bone marrowLimits of the entire lung are 1750 cGy or 4500 cGy for one third of the lung. The heart's tolerance is 4000 cGy and 6000 cGy for the entire and one third of the heart, respectively. The spinal cord is probably the most critical structure to avoid when developing a radiation plan for the esophagus. Because the spinal cord lies just posterior to the esophagus, the prone position is the position of choice in order to take advantage of gravity to maximize the distance between the spinal cord and the esophagus. Radiation exposure to the spinal cord should rarely exceed 4000-4500 cGy. The bone marrow radiation threshold should not exceed 3000-4000. [132]

Therefore, because of the need to avoid specific sensitive structures in the chest, specific oblique fields must be used when administering the radiation.
The dosage of radiation used depends upon several factors. One is the choice of treatment. Treatment can be given in a hyperfractionation (small fractions 2-3 times a day), accelerated fractionation (normal-sized fractions given more than once a day), or conventionally (normal-sized fractions (180-250 rads) once a day). The range is between 5000 cGy in 20 treatments over 4 weeks to 6600 cGy in 33 treatments over 7 weeks. Definitive radiotherapy such as this commonly results in a median survival of less than 12 months and 5 year survival of less than 20%.

Intracavitary Radiation (Intraluminal Brachytherapy)

Intracavitary radiation is a technique that involves implanting a radiation source in or around the tumor. The radioactive source then delivers about 1000 cGy doses approximately 1-1.5 cm in diameter in or around the tumor. The tumor must therefore be quite small in order for this technique to work. It is used most often as a boost before or after external beam radiation therapy. Once external beam radiation therapy has shrunk the tumor to a desirable mass for intracavitary radiation, it is useful because it can deliver a cancercidal dose to cancerous cells without further radiating the spinal cord or lungs. Contraindications include stenosis, fistula, or deep ulceration.
In one study, high dose radiation boost therapy (HDRBT) of 12 Gy in 2 fractions for one week was implemented one week after the completion of 6 weeks of 60 Gy in 30 fractions over 6 weeks.

Chemotherapy

It is used more commonly in conjunction with radiation and/or surgery. Chemotherapy is used preoperatively alone or combined with radiation to treat micrometastases and to reduce the size of the tumor in order to improve resectability rates. Also, if surgery is not an option, it is used with radiation to palliate and possibly improve survival.
Chemotherapy is typically given in a combination of two or more chemotherapy drugs. The most prescribed drug is cisplatin. It has been most commonly combined with 5-fluorouracil (5-FU), vindesine, or bleomycin. Cisplatin and 5-FU is the most commonly prescribed combination in clinical trials. Cisplatin was used regularly in combination with bleomycin in the past; however, because of the pulmonary toxicity caused by bleomycin, trials have been discontinued. Chemotheraputic agents fall into five descriptive categories based on activities, source, and resultant toxicities:
1) Antibiotics include bleomycin, mitomycin, idarubicin and amonafide, deoxorubicin (Adriamycin) and methotrexate. The antibiotics' side effects include pulmonary toxicity such as fibrosis and decreased carbon monoxide diffusing capacity.
2) Antimetabolites include 5-fluorouracil, methotrexate, dichloromethotrexate, aminothidiazole, and trimetrexate. Toxicity to the gastrointestinal mucosa and bone marrow increases with the dosage.
3) Cisplatin and carboplatin are heavy metals whose dosage related and potentially reversible side effects include nephrotoxicity, ototoxicity, and peripheral neuropathy.
4) Plant alkaloids are vindesine, etoposide, taxol, and navelbine. They may cause myelosuppression, hypersensitivity reactions, cardiac arrhythmias.
5) Ifosphamide is in the alkylating agent group. Other general side effects of chemotherapy agents include nausea, vomiting, alopecia, stomatitis and diarrhea.

Palliative treatment

Palliation is appropriate when patients are too malnourished or debilitated to undergo surgery, have a tumor that is unresectable due to extensive invasion of vital structures, recurrence of resected or irradiated tumor, and/or due to metastases. Most of these patients have a complete or partial obstruction of the esophagus due to the tumor and swallowing is very painful or impossible. The goal of palliation is to use the least invasive means possible, limit hospitalization and relieve discomfort.
Dependent upon the life expectancy, relief is carried out by surgery, radiotherapy with or without chemotherapy, intubation, dilation, photodynamic therapy, and/or laser therapy.

Surgery

In most circumstances, esophageal cancer surgery is palliative by nature of its high probability of metastases at the time of surgical intervention. However surgery can be used as a means to relieve dysphagia while not attempting a curative resection. Two operations are performed; either an

esophagectomy or a bypass. In either, instance, the risk of the procedure should be less than the anticipated 5 year survival rate.

Esophagectomy

An esophagectomy is a surgical treatment in which the entire esophagus or a region of the esophagus is removed. As an alternative conduit, the stomach, colon or jejunum, may be used. This technique is preferable for low risk patients.

Bypass

A palliative bypass may be useful when a tumor is unresectable and severe dysphagia or tracheoesophageal fistula has occurred after radiochemotherapy. Tracheoesophageal fistula (TE) has a survival of weeks to months. Constant aspiration of food, liquids, and saliva cause an extremely unpleasant death. Bypass should be proposed for younger, healthier patients. The operative mortality is 11-40%. If the tumor is left in situ, a bypass can be performed by alternative routes: presternal, or retrosternal. The reterosternal route offers the most direct route to the neck. The operation consists of a retrosternal gastric bypass with either drainage or ligation of the lower esophagus.

Endothoracic Endoesophageal Pull-Through

The operation consists of stripping the esophagus of its mucosal layer and tumor and using the muscular tube of the esophagus as a sleeve inside which the stomach is pulled through. The operation is less risky than a bypass and achieves the same results. Normal swallowing and normal diet is achieved in almost 80% of the patients.

External Beam Radiation

There are a minority of patients that cannot undergo some type of surgery either because of weakened physical state or advancement of disease. In cases like these, radiation can offer a significant amount of relief. Dysphagia is satisfactorily relieved in approximately 80% of the patients that undergo radiation therapy. However, the relief achieved from radiotherapy is many times short lived. In half of patients, tumor regrowth may occur 6 months after radiation therapy has been completed.

Treatment schedules and dosages of external beam radiation are adjusted to the patient's tolerance. An approximate curative effort may be a total dose of 6000-6400 cGy in 180-200 cGy daily fractions, 5 days a week, for 6-7 weeks. On the other hand, pain relief may be more rapidly attained by increasing the daily dose to a total dosage of 4000-4500 cGy in 220-259 cGy daily fractions, 5 days a week.

Intracavitary Radiation

Intracavitary radiation has been shown to be an effective tool in the palliation of dysphagia. Intracavitary radiation involves placing a radioactive source in or around the tumor. This therapy is extremely desirable for debilitated patients that cannot undergo even non-invasive yet somewhat further debilitating procedures such as external beam radiotherapy or in patients who have had the maximum tolerable safe dose of external beam radiation. Dosages ranging from 10-20 Gy with length of relief of dysphagia increasing as the dosage increases. Doses of greater than 20 Gy will cause severe damage to the esophagus and this level should not be exceeded.

However, fractionating the dose may increase the tolerance and effectiveness.

Laser Therapy

This therapy is indicated when obstruction of the esophagus occurs and patients are unresectable. A neodymium:yttrium-aluminum-garnet (ND:YAG) laser is used for small obstructive tumors of the middle to lower thirds of the esophagus. Energy of the Nd-YAG laser applied through quartz fibers which is directed through the operating channel of the fiberoptic endoscope.

Photodynamic Therapy

The procedure is based on the principles that malignant tumor cells have a unique vascular and lymphatic system and that the photosensitizer used will absorb light and produce oxygen radicals. A photosensitizer such as, dihematoporphyrin ether, is given intravenously. After 2 or 3 days it is retained in the malignancies in a much higher concentration than in normal tissue of the body. Then, a low power laser system that produces red light, is delivered to the tumor by a flexible endoscope. The photosensitizer absorbs the red light and produces oxygen radicals which destroys the tumor. A red laser light wavelength of 620-630 nm is used. The power is in the range of 400-500 mW per centimeter of diffusing fiber and light doses of 300 joules per centimeter of diffuser tip is applied. Two to three days after PDT, esophagoscopy is repeated and

the necrotic tumor tissue is removed. PDT is usually repeated one month after the initial treatment and indefinitely if indicated.

Stents

The purpose of a stent is to bridge the obstruction in the esophagus with a rigid device that will allow for a re-establishment of luminal patency. The flexible self-expanding stent is made up of two layers of superalloy monofilament wire with a layer of silicon in between. The addition of the polymer in between the layers of mesh wire is a relatively new addition that extends the time the stent can be beneficial to the patient by preventing tumor overgrowth through the holes in the wire mesh.

Patients are placed under local or general anesthesia and the stricture is dilated to 42-45F using a flexible gastroscope and Savary bougies. The lesion is marked and insertion of the stent is carried out under fluoroscopic control. The procedure is very often successful, >90% and patients can begin the routine of eating normal foods. Patients complain of chest pain in almost 100% of the cases because of the stretching of the stricture. Also hematemesis and nausea are possible complications.

STOMACH

- **Mucous cells**: secrete **alkaline mucus** that protects the epithelium against acid.
- **Parietal cells**: secrete **hydrochloric acid**!
- **Chief cells**: secrete **pepsin**, a proteolytic enzyme
- **G cells**: secrete the hormone **gastrin**

There are differences in the distribution of these cell types among regions of the stomach: eg, parietal cells are abundant in the glands of the body, but absent in pyloric glands.

The stomach is lined by a layer of mucus, a gelatinous material composed of proteins, glycoproteins and mucopolysaccharides secreted by the surface epithelium and. The mucus appears to protect the gastric mucosa against surface injury by physical irritants, and to buffer gastric acid under basal conditions, although its effect in buffering stimulated acid secretion is negligible. ***The mucus layer is also important in allowing colonization by Helicobacter pylori.***

The vagus acts on parietal cells to stimulate acid production, and on G cells to stimulate gastrin release, in both cases via the action of acetylcholine. In addition, acetylcholine potentiates the parietal cell response to other secretagogues. Gastrin is also released directly by exposure to peptides and amino acids, and by antral distension.

BENIGN GASTRIC ULCER

The classical presentation of benign gastric ulcer with weight loss and indigestion made worse by eating though it is not often seen. Benign are commonest on the lesser curve away from acid-secreting epithelium.

Barium meal examination showing an ulcer crater with radiating mucosal folds reaching to its rim strongly suggests that the ulcer is benign. Histologically, the intact gastric mucosa extends to the margins of the ulcer crater, the base of the ulcer consisting mainly of granulation tissue. With chronicity, fibrosis may completely replace the gastric muscle, seen then only at the margins of the lesion.

Ulcers on the greater curve are more often malignant than ulcers elsewhere in the stomach, but a common benign variant is the sump ulcer, which occurs in the most dependent part of the stomach and is often associated with ingestion of anti-inflammatory drugs.

Juxtapyloric ulcers are invariably benign and can be considered with duodenal ulcers, which they resemble in clinical behaviour.

Complications of Gastric Ulcers

The major complications of gastric ulceration are bleeding and perforation; either may be the first manifestation of the ulcer. Erosion of a vessel in the base of an ulcer is a common cause of significant haemorrhage, and the endoscopic observation of a visible vessel indicates a significantly higher risk of rebleeding. ***Rarely, a bleeding vessel will be found in the proximal stomach with no apparent ulcer: the so-called Dieulafoy lesion.***

Perforation of a peptic ulcer usually presents as peritonitis and characteristic subphrenic gas, but a chronic ulcer may erode into adjacent structures thereby forming fistulae.

GASTRITIS

Gastritis - inflammation of the gastric mucosa - has 3 basic patterns - acute, chronic, and special'.

Acute Gastritis

Acute gastritis is often the result of toxic injury by drugs such as nonsteroidal anti-inflammatory agents or alcohol, and is frequently seen in the seriously ill patient.

The most important clinical feature is gastrointestinal haemorrhage, which may be both generalized and profuse.

Radiology is helpful only if a double contrast technique is used; it may then show small, shallow erosions in which a central pit of barium is surrounded by a lucent halo. Endoscopically, lesions appear as multiple haemorrhagic spots with small superficial erosions against a background of hyperaemia.

Acute gastritis can be broken down into the following additional categories: erosive (eg, hemorrhagic erosions, superficial erosions, deep erosions) and nonerosive (generally caused by *Helicobacter pylori*).

Acute gastritis has a number of causes, including certain drugs (Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen, and naproxen); alcohol; bacterial ***(*H pylori *gastritis typically starts in the antrum,*** causing intense inflammation, and over time, it may extend to involve the entire gastric mucosa. It is also responsible for as many as 80% of gastric ulcers and is associated with a transient increase in gastric acid secretion), viral (Cytomegalovirus can cause gastritis in immunocompromised, who have had a transplant, and even in immunocompetent. Gastric-fold thickening may be confined to the antrum), and fungal infections(*Candida albicans* and histoplasmosis. *C albicans* rarely involves the gastric mucosa); acute stress (shock); radiation; and direct trauma.

Other Tests:

For *H pylori*, the urea breath test uses 13C or 14C-labeled urea taken orally. The sensitivity and specificity of the urea breath test is greater than 90%.

TREATMENT: **Medical Care:**

Treatment is dependent on the pathology and cause of gastritis. No specific therapy is indicated. Discontinue use of drugs known to cause gastritis, eg, NSAIDs and alcohol.

Surgical Care: Surgical intervention is rarely needed for phlegmonous gastritis.

Chronic Gastritis

Chronic atrophic gastritis, **which usually spares the antrum*, is associated with parietal cell antibodies, reduced secretion of acid and intrinsic factor, and hence with pernicious anaemia and other autoimmune disorders.*** By contrast, ***in chronic gastritis associated with Helicobacter pylori infection, activity is maximal in the antrum, acid secretion is not much affected, and B12 malabsorption is not found.***

Special forms of Gastritis

Eosinophilic gastritis affects the distal stomach. Dyspepsia is common, and thickened antral folds may cause pyloric obstruction. Bleeding, protein-losing enteropathy, and eosinophilic ascites are also described. Other sites in the gastrointestinal tract may also be affected, and peripheral eosinophilia is usually present.

The diagnosis is generally made from gastric histology; the changes are most marked in the antrum, where there is submucosal oedema and a variable eosinophilic infiltrate.

Granulomatous gastritis is a diagnosis of exclusion. Macroscopically there may be ulceration, infiltration, and thickening of the mucosa responsible for pyloric narrowing, or changes resembling linitis plastica.

Giant-cell granulomas within the mucosa - with or without an associated gastritis - are seen histologically.

Menetrier's disease - giant hypertrophic gastritis - causes generalized (or less commonly localized) enlargement of the folds of the gastric body. Endoscopically, the giant folds are readily seen and may have a nodular or polypoid appearance. The surface is frequently congested or even ulcerated, but protein loss and hypoproteinaemia, which is characteristic of the condition, also occur without frank ulceration.

Deep biopsies reveals elongation and dilatation of the gastric pits. Some replacement of the acid-secreting glands by simple (and sometimes cystic) mucous glands is typical.

Gastritis, or even frank infarction, may result from ischaemic damage in patients with prolonged hypotension or with misplaced arterial chemotherapy for hepatic tumours; similar changes are associated with irradiation.

PORTAL HYPERTENSIVE GASTROPATHY

Portal hypertension is responsible for congestive gastropathy and watermelon stomach, which may otherwise be confused with gastritis. Gastric fundal varices also occur.

GASTRIC POLYPS

Gastric polyps may be hamartomatous and, regenerative or hyperplastic, or true neoplasms (adenomas). It is probably only the adenomathat have malignant potential, with a higher risk when multiple and diameter exceeds 2cm. Barium studies demonstrate apparently translucent filling defects, and at endoscopy, adenomatous polyps are more obviously distinct from surrounding mucosa than the commoner hyperplastic type.

Polyps in the duodenum are common in familial adenomatous polyposis, but unusual proximal to the ampulla of Vater.

GASTRIC CARCINOMA

Gastric cancer is the second most common cause of cancer-related death in the world.

The site of the lesion is classified based on the long axis of the stomach. Approximately 40% of cancers develop in the lower part, 40% in the middle part, 15% in the upper part, and 10% involve more than 1 part of the organ.

Gastric cancer afflicts slightly more men than women.

The median age at diagnosis is 65 years (range 40-70 y).

Risk factors	**Precursor states**
• Diet low in Vitamin C • Blood group A • Pernicious anaemia • Hypogammaglobulinaemia • Post gastrectomy	• *Helicobacter pylori* infection • Atrophic gastritis • Intestinal metaplasia • Gastric dysplasia • Gastric polyps

History: Early disease has no associated symptoms. Most symptoms of gastric cancer reflect advanced disease. Patients may complain of indigestion, nausea or vomiting, dysphagia, postprandial fullness, loss of appetite, and weight loss. Late complications include pathologic peritoneal and pleural effusions; obstruction of the gastric outlet, gastroesophageal junction, small bowel; intrahepatic jaundice caused by hepatomegaly; extrahepatic jaundice; and inanition resulting from starvation of tumor origin.

Physical: All physical signs are late events. Signs may include a palpable enlarged stomach with succussion splash; primary mass (rare); and enlarged liver, Virchow node's (ie, left supraclavicular), Sister Mary Joseph's node, and Blumer's shelf. Some patients have signs of weight loss. Other patients may have pallor from bleeding and anemia.

Causes: Several factors are implicated in the development of gastric cancer, including diet, *Helicobacter pylori* infection (*Helicobacter pylori* infection is associated with chronic atrophic gastritis, and patients with a history of prolonged gastritis have a 6-fold increase in their risk of developing gastric cancer), previous gastric surgery, pernicious anemia, adenomatous polyps, chronic atrophic gastritis, genetic factors, and previous radiation therapy.

Imaging Studies:

Esophagastroduodenoscopy: This procedure also is the primary method for obtaining a tissue diagnosis of suspicious lesions.

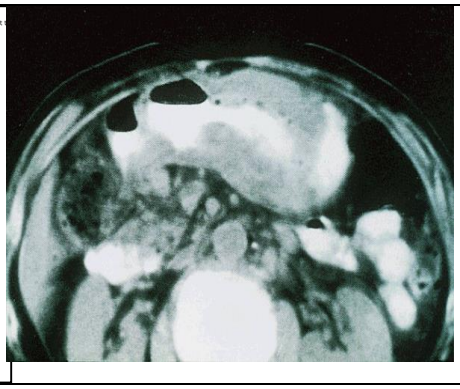
Double-contrast upper GI series: An upper gastrointestinal barium swallow detects large primary tumors but only occasionally detects their spread to the esophagus and duodenum (particularly if the tumor is small and submucosal).

Chest radiograph evaluates for metastatic lesions.

CT scan or MRI of the chest, abdomen, and pelvis

Endoscopic ultrasound

Histologic Findings: Adenocarcinoma of the stomach comprises between 90-95% of all gastric malignancies. The second most common malignancies are lymphomas. Leiomyosarcomas (2%), carcinoids (1%), adenoacanthomas (1%), and squamous cell carcinomas (1%) are the remaining histologies.



Staging of gastric carcinoma

- Requires a combination of preop investigations and intraoperative assessment
- OGD confirms diagnosis, site and extent of tumour
- ***Endoscopic ultrasound may allow assessment of intramural tumour penetration***
- CT will assess nodal spread and extent of metastatic disease
- ***Laparoscopy will identify peritoneal seedlings***
- Peritoneal lavage will identify free tumour cells

Birmingham Staging System

Clinicopathological system

Does not require detailed lymph node status

Stage 1 Disease confined to muscularis propria
Stage 2 Muscularis and serosal involvement
Stage 3 Gastric and nodal involvement
Stage 4a Residual disease
Stage 4b Metastatic disease

Staging: 1997 TNM classification system (AJCC) for staging gastric carcinoma.

Primary tumor	*Regional lymph nodes*	*Distant metastasis*
TX = primary tumor (T) cannot be assessed T0 = no evidence of primary tumor Tis = carcinoma in situ, intraepithelial tumor without invasion of lamina propria T1 = tumor invades lamina propria or submucosa T2 = tumor invades the muscularis propria or subserosa T3 = tumor penetrates serosa (ie, visceral peritoneum) without invasion of adjacent structures T4 = tumor invades adjacent structures	NX = regional lymph nodes (N) cannot be assessed N0 = no regional lymph node metastases N1 = metastasis in 1-6 regional lymph nodes N2 = metastasis in 7-15 regional lymph nodes N3 = metastasis in more than 15 regional lymph nodes	MX = distant metastasis (M) cannot be assessed M0 = no distant metastasis M1 = distant metastasis

TREATMENT:

- Surgery is the only prospective of cure
- Antral tumours may be suitable for a partial gastrectomy usually with Polya reconstruction
- Other tumours will need a total gastrectomy with oesophagojejunal anastomosis and Roux-en-Y biliary diversion

- A tumour is considered resectable if confined to stomach or N1 or N2 nodes involved
    - Nodes less than 3 cm from tumour = N1 nodes
    - Nodes greater than 3 cm from tumour = N2 nodes
        - If tumour and N1 nodes resected = D1 gastrectomy
        - If tumour and N2 nodes resected = D2 gastrectomy
- Evidence to support the use of D2 gastrectomy is incomplete & D2 gastrectomy associated with increased post-operative mortality
- Even in patients with incurable disease surgery may palliate symptoms
- Results from adjuvant chemotherapy post surgery are disappointing though Chemoradiotherapy may reduce relapse and improve survival

Surgical Care:

Type of surgery

- Total gastrectomy (if required for negative margins), an esophagastrectomy for tumors of the cardia and gastroesophageal junction, and a subtotal gastrectomy for tumors of the distal stomach.

Adjuvant therapy

- The pattern of failure prompted a number of investigations into adjuvant therapy. The rationale behind radiotherapy is to provide additional local-regional tumor control. Adjuvant chemotherapy is used either as a radiosensitizer or as definitive treatment for presumed systemic metastases.
- Adjuvant radiotherapy
    - Moertel and colleagues randomized postoperative patients with advanced gastric cancer to 40 Gy radiotherapy or 40 Gy radiotherapy with 5-FU as a radiosensitizer, and demonstrated improved survival associated with the combined modality therapy.
    - A series from the Mayo Clinic randomized patients to postoperative radiotherapy with 5-FU versus surgery alone and demonstrated improved survival in the patients receiving adjuvant therapy (23% vs 4%).
- Intraoperative radiotherapy
    - Some centers suggest that intraoperative radiotherapy (IORT) shows promising results.
    - The National Cancer Institute randomized patients with grossly resected stage III/IV gastric cancer to either 20 Gy IORT or 50 Gy postoperative external beam.
- Chemotherapy
    - Numerous randomized clinical trials comparing combination chemotherapy in the adjuvant setting to surgery alone did not demonstrate a consistent survival benefit.
    - The most widely studied regimen is 5-fluorouracil, doxorubicin, and mitomycin C. The addition of methyl-CCNUR, leucovorin, or triazinade did not increase response rates.

Survival

- Prognosis if generally very poor
- Overall 5 year survival is approximately 5%
- Survival is 70%, 32%, 10% and 3% for Stages 1,2,3 and 4 respectively

Other gastric tumours

Leiomyoma: Leiomyomas are the ***commonest benign tumours of the stomach***. They arise from the gastric smooth muscle, and, because they are submucosal and rarely impinge on the lumen, are frequently asymptomatic though may present with haemorrhage; endoscopic ultrasound is ideal investigation when asymptomatic.

Other Gastric Neoplasms

The stomach is an occasional site for metastatic spread, usually from an adenocarcinoma of origin in the pancreas, ovary or breast. Other, non-epithelial, tumours, such as lipomas, neural sheath tumours, and gastric carcinoids, are also seen. Gastric involvement with Kaposi's sarcoma is not infrequently seen in AIDS patients (particularly in the homosexual community). The histological appearance of deep endoscopic biopsies is similar to that of Kaposi's at other gastrointestinal sites.

Ectopic islands of pancreatic tissue may be recognized endoscopically- confusion with neoplasia is readily overcome by biopsy, which reveals normal pancreatic histology. Gastric xanthoma is unlikely to be confused with more sinister pathology.

Leiomyosarcoma

- Accounts for 2-3% of all gastric tumours
- Arises from the smooth muscle of the stomach wall
- ***Lymphatic spread is rare***
- ***75% present with an upper gastrointestinal bleed***
- 60% have palpable abdominal mass
- Diagnosis can be confirmed by endoscopy and CT scanning
- Partial gastrectomy may allow adequate resection
- 5-year survival is approximately 50%

Gastric lymphoma

- ***Stomach is the commonest extranodal primary site for non-Hodgkin's lymphoma***
- Accounts for approximately 1% of gastric malignancies
- Clinically presents similar to gastric carcinoma
- 70% of tumours are resectable
- 5-year survival is approximately 25%
- Both adjuvant radiotherapy and chemotherapy may be useful
- Gastric lymphoma may be an isolated lesion or part of a disseminated process; it is being seen with increased frequency in AIDS.
- Malignant lymphomas of mucosa-associated lymphoid tissue (MALTomas), comprising diffuse sheets of maturing lymphocytes are the most common, but the full range of cytological patterns may occur, including Hodgkin's disease.
- A rare form of 'so-called' benign, follicular, lymphoid hyperplasia (pseudolymphoma) has now been shown by immunocytochemistry to be monoclonal and hence a true lymphoma

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

This condition is second only to inguinal hernia as a reason for surgical intervention during the first year of life.
Results in hypertrophy and hyperplasia of pyloric sphincter in neonatal period
Mainly affects circular muscle fibres of pylorus
Pylorus becomes elongated and thickened (? Due to failure of nitric oxide synthesis)
Results in gastric outflow obstruction, vomiting and dehydration
Affects 3 per 1000 live births
Male : female 4:1. Most common in first born males
Usually presents between 3 and 6 weeks of age
Child hungry and often feeds immediately after vomiting
Biochemically a hypochloraemic alkalosis exists
Non-bilious vomiting, associated with weight loss and dehydration, are typical.
The upper abdomen may be distended with visible gastric peristalsis and a palpable lump representing the hypertrophied pylorus.
confirmation of the diagnosis is by ultrasound scanning.
At laparotomy, pyloromyotomy (Ramstedt's operation) is the usual procedure.

Gastric Outlet Obstruction

Clinical entities that can result in GOO generally are categorized into 2 groups of causes—benign and malignant.
Etiology: The major benign causes of GOO are PUD, gastric polyps pyloric stenosis, congenital duodenal webs, ***gallstone obstruction (Bouveret syndrome)***, pancreatic pseudocysts, and bezoars.
Within the pediatric population, pyloric stenosis constitutes the most important cause of GOO.
Pancreatic cancer is the most common malignancy causing GOO (may occur in 10-20% of pancreatic carcinoma). Other tumors that may obstruct the gastric outlet include ampullary cancer, duodenal cancer, cholangiocarcinomas, and gastric cancer.

Clinical: Nausea and vomiting, usually nonbilious, and it characteristically contains undigested food particles. Early satiety and epigastric fullness are common. Weight loss is frequent. Abdominal pain is not frequent and usually relates to the underlying cause, eg, PUD, pancreatic cancer.
Physical examination demonstrates the presence of chronic dehydration and malnutrition. A dilated stomach may be appreciated as a tympanitic mass in the epigastric area.
Patients with GOO due to benign ulcer disease may be treated medically if results of imaging studies or endoscopy determine that acute inflammation and edema are the principle causes of the outlet obstruction (as opposed to scarring and fibrosis, which may be fixed). If medical therapy conducted for a reasonable period fails to alleviate the obstruction, then surgical intervention becomes appropriate. ***The choice of surgical procedure is vagotomy and antrectomy, against which the efficacy of other procedures should be measured.***

Diagnostic Procedures:

- Upper endoscopy can help visualize the gastric outlet and may provide a tissue diagnosis when the obstruction is intraluminal.
- Nuclear gastric emptying studies measure the passage of orally administered radionuclide over time. Unfortunately, both the nuclear test and saline load test may produce abnormal results in functional states.
- Barium upper GI studies are very helpful because they can delineate the gastric silhouette and demonstrate the site of obstruction.

TREATMENT: **Medical therapy:** Initial management of GOO should be the same regardless of the primary cause i.e. hydration and correction of electrolyte abnormalities. Sodium chloride solution should be the initial IV fluid of choice. Potassium deficits are corrected after repletion of volume status, and after the chloride has been replaced.

Surgical therapy:

Management of benign disease: The most common surgical procedures performed for GOO related to PUD are vagotomy and antrectomy, vagotomy and pyloroplasty, truncal vagotomy and gastrojejunostomy, pyloroplasty, and laparoscopic variants of the aforementioned procedures. Of these, ***vagotomy and antrectomy with Billroth II reconstruction (gastrojejunostomy) seems to offer the best results***. A combination of balloon dilatation and highly selective vagotomy has been described, but it is associated with gastroparesis and a high recurrence rate.

Management of malignant disease

Of patients with periampullary cancer, 30-50% present with nausea and vomiting at the time of diagnosis. Most of these tumors are unresectable (approximately 40% of the gastric cancers and 80-90% of the periampullary cancers). Gastrojejunostomy remains the surgical treatment of choice for GOO secondary to malignancy. Traditionally an antecolic anastomosis has been performed to prevent further obstruction by advancing tumor growth, recent studies favours retrocolic anastomosis.

Gastric Volvulus

Gastric volvulus is defined as an abnormal rotation of the stomach of more than 180°, creating a closed loop obstruction that can result in incarceration and strangulation.
According to the axis of rotation, gastric volvulus is classified into the following:
***Organo-axial*:** The stomach rotates around an axis that connects the gastroesophageal junction and the pylorus. This is the most common type in both children and adults. It is usually associated with diaphragmatic defects. Strangulation and necrosis occurs commonly with this type and has been reported in 5-28% of cases.
***Mesenterico-axial*:** Here the axis bisects both the lesser and greater curvatures. The antrum rotates anteriorly and superiorly so that the posterior surface of the stomach lies anteriorly. The rotation is usually incomplete and occurs intermittently. Vascular compromise is uncommon. This type usually presents without diaphragmatic defects and usually manifests with chronic symptoms.
Combined: This is a rare form in which the stomach twists both mesentero- and organo-axially and usually is seen in patients with chronic volvulus.
Etiology: According to etiology, gastric volvulus can be classified as either type 1 or 2.

Type 1, or idiopathic: This type comprises two-thirds of cases and is presumed to be due to abnormal laxity of the gastro-splenic, gastro-duodenal, gastro-phrenic, and gastro-hepatic ligaments. This allows approximation of the cardia and pylorus when the stomach is full, predisposing to volvulus. This type is more common in adults.

The most common cause of gastric volvulus in adults is diaphragmatic defects. In cases of paraesophageal hernias, the gastroesophageal junction remains in the abdomen while the stomach ascends adjacent to the esophagus, resulting in an upside-down stomach. Gastric volvulus is the most common complication of paraesophageal hernias.

Clinical:

Acute gastric volvulus

- Intra-abdominal gastric volvulus presents most commonly with the sudden onset of severe epigastric or left upper quadrant pain.
- Intra-thoracic gastric volvulus presents with sharp chest pain radiating to the left side of the neck, shoulder, arms, and back.
- Occasionally, some patients present with hematemesis secondary to mucosal ischemia and sloughing.
- ***Borchardt's triad (pain, retching, and inability to pass a nasogastric tube) is diagnostic of acute volvulus*** and has been reported to occur in 70% of cases.

Chronic gastric volvulus

- Intermittent epigastric pain and abdominal fullness following meals.
- Early satiety, dyspnea, and chest discomfort.
- Dysphagia may occur if the gastroesophageal junction is distorted.

Imaging Studies:

Chest x-ray: A retrocardiac gas-filled viscus in cases of intrathoracic stomach confirms the diagnosis.

Plain abdominal radiograph reveals a massively distended viscus in the upper abdomen.

Barium study may be valuable in chronic volvulus with the stomach lying horizontal or upside down.

<table>
<tr>
<td>  </td>
<td>Stomachlocated in the lower chest in a large hiatal hernia. The greater curvature of the stomach lies superior to the lesser curvature in an organoaxial twist.</td>
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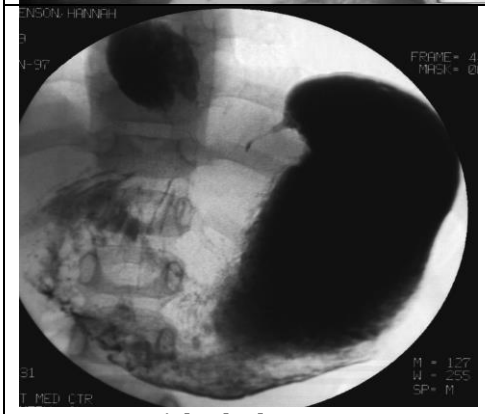
<td> 
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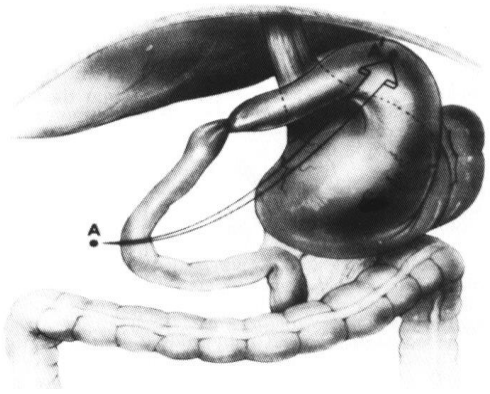
<td> 
Mesenteroaxial volvulus</td>
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TREATMENT

Medical therapy: endoscopic reduction can be attempted in selected cases.

Surgical therapy:

Emergent surgical intervention is indicated for acute gastric volvulus. With chronic gastric volvulus, surgery is performed to prevent complications.

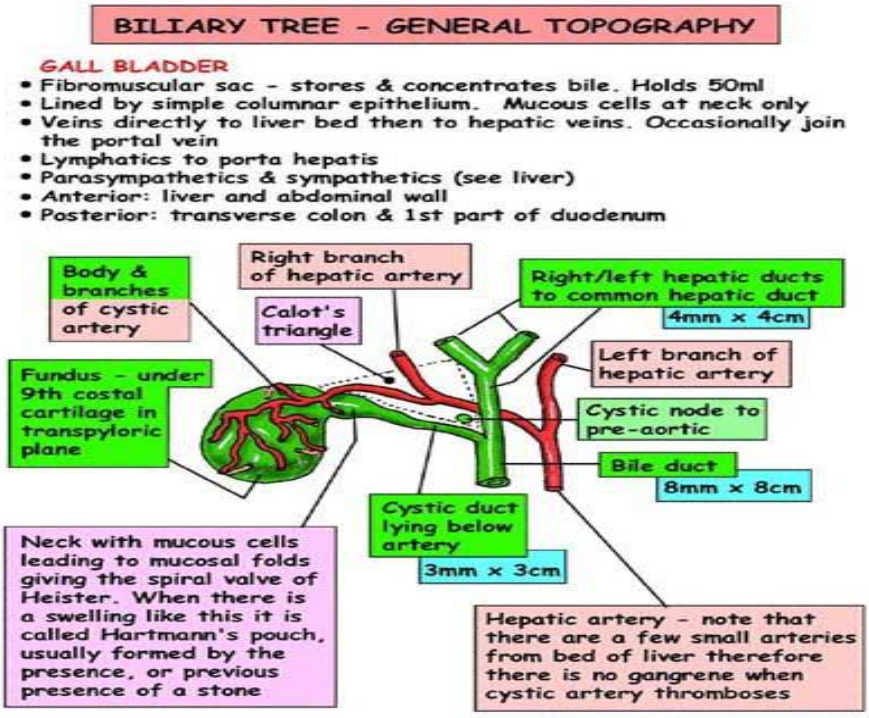
The strategy of surgery is as follows:

- Reduction of the volvulus
- Assessment of gastric viability with resection of the gangrenous portions by segmental, subtotal, or total gastrectomy
- Prevention of recurrence by anterior gastropexy, which is most often accomplished with a gastrostomy tube

COMPLICATIONS: Strangulation and necrosis occur most commonly with organo-axial gastric volvulus and occur in 5-28% of cases. Gastric perforation occurs secondary to ischemia and necrosis. It can also complicate endoscopic reduction.

GALL BLADDER AND BILE DUCTS

The common hepatic duct is formed by right and left hepatic ducts at porta hepatis. The cystic duct joins the common hepatic duct to form the CBD, which enters the 2nd part of duodenum together with the pancreatic duct in the ampulla of Vater. The gall bladder is usually a pear-shaped sac,8-10cm long with a capacity of about 50ml. It is divided into a neck, body and fundus.



The mucosa comprises tall columnar epithelium which is thrown into simple folds.

In the neck of the gall bladder is a small pouch (Hartmann's pouch) which is particularly marked in pathological states, and it is here that stones commonly impact.

The normal gall bladder contracts following fat ingestion.

CHOLELITHIASIS

Cholelithiasis is the presence of gallstones in the gallbladder. The spectrum of gallbladder disease ranges from asymptomatic gallstones to gallbladder colic, cholecystitis, choledocholithiasis, and cholangitis. Gallbladder colic is pain caused by a stone temporarily obstructing the cystic duct or common bile duct (CBD). Cholecystitis is inflammation of the gallbladder from obstruction of the cystic duct or CBD (choledocholithiasis). Cholangitis is infection of the biliary tree.

Pathophysiology: Three types of gallstones exist. They are (1) cholesterol (commonest), (2) pigment, and (3) mixed stones.

Cholesterol stones: Normally, bile acids, lecithin, and phospholipids help to maintain cholesterol as a solute. When bile is supersaturated with cholesterol, it crystallizes and forms a nidus for stone formation. Calcium and pigment also may be incorporated in the stone.

Pigment stones: Pigment stones, which comprise 15% of gallstones, are formed by the crystallization of calcium bilirubinate. Diseases that lead to increased destruction of red blood cells (hemolysis), abnormal metabolism of hemoglobin (cirrhosis), or infections (including parasitic) predispose people to pigment stones. Black stones are found in people with hemolytic disorders. Brown stones are found in the intrahepatic or extrahepatic duct and are associated with infection in the gallbladder.

History: The 3 clinical stages of gallstones are asymptomatic, symptomatic, and with complications (eg, cholecystitis, choledocholithiasis, cholangitis). Most gallstones (60-80%) are asymptomatic. A history of epigastric pain with radiation to the shoulder may suggest symptomatic cholelithiasis. Most patients develop symptoms prior to complications. The best definition of biliary colic is pain that is relatively severe right upper quadrant that lasts 1-5 hours, with radiation to shoulder or back. Associated symptoms are nausea, vomiting, or referred pain.

Imaging Studies:

Asymptomatic gallstones usually are observed incidentally on an x-ray, abdominal ultrasound, or CT scan while imaging for other reasons.

Radiography

10-30% of stones are radiopaque and visible on x-rays. Calcium or pigmented stones are more likely to be observed on x-rays. A porcelain gallbladder is seen on plain films

Ultrasound: Ultrasound is 98% sensitive for gallstones. Cholecystitis is diagnosed sonographically by gallbladder wall thickening (> 2-4 mm), gallbladder distention (diameter > 4 cm, length > 10 cm), pericholecystic fluid from perforation or exudate, and sonographic Murphy sign (pain when a probe is pushed directly on the gallbladder).

TREATMENT: In people with symptomatic gallstones, discuss the option of elective surgery with the patient. Diabetic persons and pregnant women should have close follow-up to determine if they become symptomatic or develop complications.

Patients with a calcified or porcelain gallbladder should consider cholecystectomy due to the increased risk of carcinoma (25%).

MEDICATION: Dissolution of small gallstones (<5 mm) is possible with 6-12 months of therapy; however, recurrence is approximately 50%. Bile acid therapy consists of ursodeoxycholic acid sometimes in combination with chenodeoxycholic acid.

GALL STONES

Translucent Stones: Over 80% of gall stones are radiolucent as they contain too little calcium to render them visible on a plain X-ray. Oral cholecystogram is only successful if the gall bladder function is good enough to concentrate contrast media. Ultrasound is technique of choice as it is quick, accurate, safe and noninvasive. Stones are diagnosed by the ***accoustic shadow***. ERCP may also be used to demonstrate gallstones, but it is not usually employed unless bile duct calculi are suspected.

Bile Duct Stones: Although valuable as a means of detecting bile duct dilatation, ultrasound is a very much **less reliable** technique for identifying calculi within the common bile duct. PTC or ERCP/ MRCP is the preferred techniques. Intravenous cholangiography is no longer recommended for investigating bile duct stones.

Treatment of Gall Stones

Laparoscopic cholecystectomy is currently favoured; the operation is associated with low morbidity and a short postoperative hospital stay, and the smaller surgical incisions.

When undertaken with ERCP, endoscopic sphincterotomy permits the removal of common bile duct stones using either an extraction basket or balloon or mechanical lithotripsy.

Cholecystitis

Stones in the gall bladder can cause either acute or chronic cholecystitis. Occasionally, the cystic duct is blocked by a stone, following which the gall bladder is distended by white mucus and gives rise to a mucocoele.

The histological appearances of the gall bladder in acute cholecystitis may range from acute inflammatory changes to widespread haemorrhagic necrosis. In chronic cholecystitis, the gall bladder is thickenedand degree of inflammation is variable.

Cholesterolosis of the gall bladder is an uncommon condition in which yellow flecks are seen over the mucosal surface, giving an appearance known as the strawberry gall bladder. This is due to large numbers of foamy macrophages in the mucosa andd is a benign asymptomatic abnormality.

In contrast, chronic or recurrent inflammation of the gall bladder may be caused by xanthogranulomatous cholecystitis, a condition in which ulceration of the gall bladder wall may occur with or without associated gall stones.

Limey Bile and porcelain' Gall Bladder

An opaque gall bladder is a rare finding on plain abdominal radiograph. But this can occur when the cystic duct is blocked and concentrated residual bile containing calcium is formed within the gall bladder. Unusually, the wall calcifies, forming the porcelain' gall bladder that appears on the radiograph as an outline of radio-opaque calcium.

Diverticula of the Gall Bladder

Outpouchings of mucosa between the muscle bundles (***Aschoff-Rokitansky sinuses***) are common. They increase with age and have many features in common with colonic diverticula. They are most frequent in the fundus and often become filled with inspissated bile, biliary gravel or cholesterol crystals.

Empyema Gallbladder

Acute cholecystitis in the face of bacteria-containing bile may progress to suppurative infection in which the gallbladder fills with purulent material, a condition referred to as empyema of the gallbladder. (The underlying cause of cholecystitis involves obstruction of the cystic duct; thereby causing the buildup of infected fluid). Systemic antibiotics and urgent drainage or resection are required to reduce the incidence of complications and to avoid or treat associated sepsis.

History: The clinical history is similar to that of a patient with acute cholecystitis. As the disease progresses, severe pain and associated high fever, chills, and even rigors may be reported. Diabetic and immunosuppressed patients may have a paucity of symptoms.

Ultrasound: The finding of an enlarged distended gallbladder and associated pericholecystic fluid points to an acute inflammatory process involving the gallbladder. Though suggestive, this does not adequately differentiate uncomplicated acute cholecystitis from the complication with empyema and/or gangrene.

Medical Care: Intravenous antibiotic therapy is an adjunct to urgent decompression and/or resection of the gallbladder in cases of suspected empyema.

Surgical Care: Surgical decompression and resection of the affected gallbladder is the criterion standard of therapy. Empyema of the gallbladder without significant gangrenous changes or perforation may be treated with a laparoscopic procedure.

Acalculous Cholecystopathy

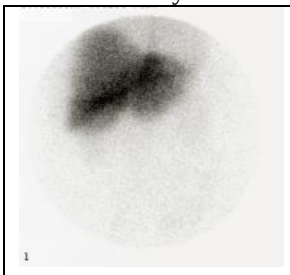
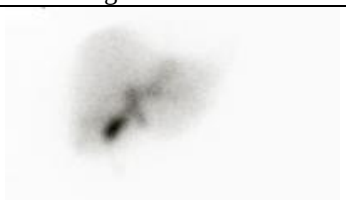
Acalculous cholecystopathy is characterized by biliary colic-type pain in the absence of gallstones. The exact pathophysiology is unknown but likely is due to abnormal gallbladder motility that possibly causes relative obstruction of the cystic duct.

Ultrasound: Ultrasound is most useful to rule out conditions in the D/D. Ultrasound detects abnormalities of the gallbladder, including the presence (or absence) of stones, wall thickening, or pericholecystic fluid.

Hepatobiliary scanning: After the gallbladder fills with the radioisotope, a cholecystokinin analog is administered. This analog stimulates emptying of the gallbladder, allowing an ejection fraction to be calculated. A gallbladder ejection fraction of less than 35% is considered abnormal and suggests that a patient with the appropriate symptom complex may benefit from laparoscopic cholecystectomy.

Medical Care: No effective medical treatment for acalculous cholecystopathy exists.
Surgical Care:

- Laparoscopic cholecystectomy is indicated for the treatment of biliary dyskinesia after all of the other conditions in the differential diagnosis have been ruled out with a reasonable degree of certainty. Laparoscopic cholecystectomy provides symptomatic relief in 90-95% of cases of biliary colic associated with gallstones.

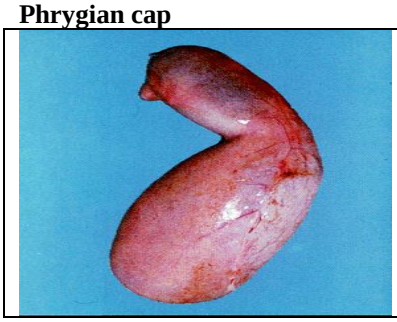
		
Hepatobiliary (HIDA) scan showing liver uptake of the radioisotope	Hepatobiliary (HIDA) scan showing biliary excretion of the radioisotope	Hepatobiliary (HIDA) scan showing persistent gallbladder activity despite washout of radioisotope from liver and remainder of the biliary tree, which is suggestive of acalculous cholecystopathy

Emphysematous Cholecystitis
Emphysematous cholecystitis is an acute infection of the gall bladder wall caused by gas-forming organisms. Four pathogenetic factors are proposed in the development of emphysematous cholecystitis: ***Vascular compromise of the gall bladder, Gallstones,***
Impaired immune protection, Infection with gas-forming organisms *(*clostridial species, *Escherichia coli,* and *Klebsiella* species and less frequently, enterococci and anaerobic streptococci)
History: The typical patient is a male older than 60 years, often with type II diabetes mellitus. Otherwise, the clinical scenario does not differ significantly from that observed in acute cholecystitis.
Abdominal radiographs: Abdominal radiographs show the classic picture of a gallbladder wall containing gas.
Abdominal ultrasound: Obfuscation of the gallbladder by high-level echoes occurs when gas accumulates in the wall and lumen of the gallbladder. Curvilinear gaseous artifacts in the gallbladder, the so-called ***"ring-down effect" or "comet tail" are diagnostic of emphysematous cholecystitis***.
Computerized tomography of the abdomen: CT scan demonstrates emphysematous changes in the gallbladder wall that are diagnostic of this condition. CT scan may also demonstrate possible extension into the pericholecystic tissues and the hepatic ducts.
TREATMENT; Medical Care:

- Intravenous antibiotics of choice are those that have beta-lactamase inhibitor activity or combinations that provide coverage for anaerobic and gram-negative organisms. Fluid replacement and correction of electrolyte deficits should be initiated to prepare the patient for surgery.
- **Surgical Care:** Management of emphysematous cholecystitis is surgical (lap or open cholecystectomy)

CONGENITAL ABNORMALITIES

Phrygian cap



An unusual but harmless finding on cholecystography is a gall bladder bent upon itself, and so resembling the Phrygian cap taken up by the French revolutionaries.

Choledochal Cyst

Choledochal cyst is congenital cystic dilatation of the common bile duct.

Todani classified choledochal cysts into 5 types and several subtypes.

Type I lesions consist of concentric dilatations of the common bile or cystic duct, which may be diffuse or cysti : type IA, in which cystic dilatation involves nearly the entire common bile duct (CBD); type IB, in which there is more segmental dilatation of the CBD; and type IC, in which dilatation is diffuse throughout the CBD and common hepatic duct. ***Type I is the most common variant of bile duct cyst***.

Type II lesions involve a supraduodenal eccentric dilatation.

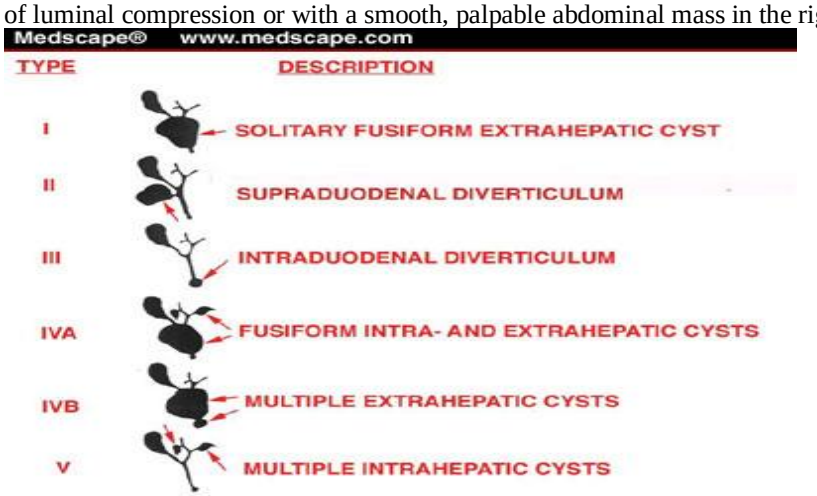
Type III cysts, or choledochoceles, are dilatations of the CBD within the muscular portion of the duodenal wall.

Type IVA cysts consist of multiple cystic dilatations that affect both the intra- and extrahepatic ducts; this type accounts for 18% of reported cases. Type IVB cysts affect the extrahepatic ducts and are much less common.

Type V, or classical Caroli's disease describes cysts of only the intrahepatic ducts. Caroli's syndrome applies to Caroli's disease in association with congenital hepatic fibrosis. Caroli's syndrome is transmitted as an autosomal recessive trait and is associated with adult polycystic renal disease.

Choledochal cysts has incidence of 1/1-1.5 lacs live births. Although their etiology is not known, one hypothesis involves anomolous pancreaticobiliary ductal union (APBDU), which impairs sphincter of Oddi function and permits reflux of pancreatic juice into the bile duct, with subsequent weakening of the biliary system. Another hypothesis considers ductal plate anomalies (DPA). This mechanism may involve partial or complete arrest of remodeling of the ductal plate of the larger intrahepatic bile ducts.

Symptoms present mostly in childhood or early adulthood. ***In infancy, painless or intermittent jaundice with acholic stools is common.*** Infants may present with nausea, vomiting, and failure to thrive as a result of luminal compression or with a smooth, palpable abdominal mass in the right hypochondrium.



Complications associated with choledochal cysts are largely due to obstruction and include jaundice, stone formation, recurrent cholangitis, hepatic abcess, portal vein thrombosis, pancreatitis, cyst rupture, secondary biliary cirrhosis, and carcinoma. Malignant change is estimated to occur in 3%-20% of cases.
Abdominal ultrasound and CT scan are valuable. ERCP is a definitive method for diagnosing choledochal cyst. In the absence of any unrelated findings such as mass, lymphadenopathy, or filling defects, no other diagnostic test is needed.
Treatment is usually surgical. ***Complete cyst resection and biliary bypass (***Roux-en-Y choledochojejunostomy***) is the accepted strategy***. Hepatic resection and even liver transplantation has been advocated for intrahepatic cysts.

Caroli's Disease

Caroli's disease comprises multiple intrahepatic and/or extrahepatic dilatations. The condition usually presents with either jaundice or cholangitis, and progression to liver failure frequently occurs.

CHOLANGITIS

Cholangitis is an acute infection of the biliary tree. compounded by presence of bacteria. Common bile duct (CBD) stones are the most common cause of obstruction. Bile stasis may be caused by strictures, stenosis, tumors, or endoscopic manipulation of the CBD.
Partial obstruction is more likely to cause cholangitis than complete obstruction.

History:

In 1877, Charcot described cholangitis as a triad of findings of right upper quadrant pain, fever, and jaundice. Reynold pentad adds mental status changes and sepsis to the triad. Charcot triad of fever, RUQ pain, and jaundice is found in 70% of patients presenting with cholangitis. Most patients complain of ***right upper quadrant pain***;

Imaging Studies:

Sonograms followed by CT scan are used most commonly.
ERCP or percutaneous cholangiogram images and treats the obstruction directly.
Ultrasonography is fairly sensitive for intrahepatic and extrahepatic, including CBD dilation; however, it is not reliable for choledocholithiasis. Ultrasound can differentiate intrahepatic from extrahepatic obstruction and image dilated ducts.
CT scan: Dilated intrahepatic and extrahepatic ducts and inflammation of the biliary tree are imaged. ***Gallstones are visualized poorly with CT scan.***
Biliary scintigraphy (HIDA and DISIDA) are functional studies of the gallbladder.
Obstruction of the common bile duct causes nonvisualization of the small intestine. A HIDA scan with complete biliary obstruction does not visualize the biliary tree.
Advantages include its ability to assess function, and *positive results may appear before the ducts are sonographically enlarged.*

TREATMENT

Standard therapy for cholangitis is broad-spectrum antibiotics with close observation to determine the need for emergency decompression.
From the surgical literature, in patients with mild cholangitis, 70-85% of patients will respond to medical therapy. Approximately 15% will not respond and will require immediate surgical or endoscopic decompression. In severely ill patients, treatment is immediate biliary decompression by percutaneous or endoscopic drainage.
Cholecystectomy or ERCP is best after resolution of the cholangitis.

Recurrent pyogenic hepatitis (Oriental cholangiohepatitis)

It is characterized by formation of intrahepatic pigmented stones with recurrent exacerbation and remission of abdominal pain, frequently associated with jaundice, chills, and fever. The cause is secondary to infections with coliform bacteria or parasites such as *Clonorchis sinensis*, causing pigmented stone formation by inducing the precipitation of bilirubin, acting as nidi for stone formation, or causing biliary strictures that lead to further biliary stasis. The hallmark of the disease is presence of soft pigmented bilirubinate stones within ***dilated intra- and extrahepatic ducts***.
Clinical presentation is characterized by recurrent attacks of right upper quadrant pain, fever, chills, and jaundice. Laboratory findings are polymorphonuclear leukocytes, elevated levels of alkaline phosphatase,

and excretion of urobilinogen in urine. USG is highly sensitivity for the detection of cholelithiasis and hepatic ductal dilatation. Computed tomography can be helpful when sonographic findings are not definitive or are equivocal. Direct cholangiography--such as endoscopic retrograde cholangiography, percutaneous transhepatic cholangiography, operative cholangiography, and T-tube cholangiography--demonstrates the full spectrum of ductal changes and stones.

Treatment of this disease focuses on management of acute cholangitis, followed by either drainage and removal of stones using endoscopic, radiologic, or surgical methods, or hepatic resection for focal disease

HAEMOBILIA

Pain, jaundice and gastrointestinal haemorrhage are the classical presenting symptoms of bleeding into the biliary tree. This may be caused by trauma, an aneurysm, or a hepatic tumour, but it is most commonly associated with liver biopsy. Retrograde cholangiography may reveal clots in the bile duct, but hepatic angiography will define the site of haemorrhage. Selective hepatic angiography with embolization of the bleeding vessel is an effective means of treatment which obviates the necessity for laparotomy.

Bile Duct Strictures

Most benign bile duct strictures are iatrogenic, resulting from operative trauma. Other conditions leading to benign strictures are; pancreatitis bile duct stones, primary sclerosing cholangitis (PSC), HIV cholangiopathy (*Cryptosporidium* and cytomegalovirus may be responsible), **Mirizzi syndrome** (Pressure on the common hepatic duct due to a gallstone impacted in the Hartmann pouch or cystic duct results in jaundice and cholangitis), Choledochal cyst, Recurrent pyogenic cholangitis. Bile duct strictures can cause ascending cholangitis, liver abscess, and secondary biliary cirrhosis. ***Pancreatic cancer is the most common cause of malignant biliary strictures.***

History: Most patients with biliary strictures remain asymptomatic until the lumen of the bile duct is sufficiently narrowed. Occasionally, patients may have intermittent episodes of right upper quadrant pain **(biliary colic)** or features of **obstructive jaundice**; pruritus, yellow discoloration of skin, and steatorrhea. With chronic cholestasis, xanthomas appear around the eyes, chest, back, and on extensor surfaces.

Patients presenting with cholangitis also may have ***fever and right upper quadrant tenderness in addition to jaundice (ie, Charcot triad), hypotension, and altered mental status (ie, Reynold pentad).***

Lab Studies: Elevated serum alkaline phosphatase and gamma-glutamyl transpeptidase. increases in total and conjugated bilirubin. Alkaline phosphatase levels are increased to more than 3-times normal. In malignant strictures causing only partial obstruction (eg, ***Klatskin tumor***), a rise in the alkaline phosphatase level may not be accompanied by a rise in the bilirubin level.

Imaging Studies: ***The initial radiological study should be an ultrasound***. If it shows dilated bile ducts but do not provide clues to the site or cause of the obstruction, magnetic resonance cholangiopancreatography (MRCP) or abdominal CT scans should be performed next. In some patients, endoscopic retrograde cholangiopancreatography (ERCP) may be needed for definitive diagnosis and has the advantage of being therapeutic.

Hepatic iminodiacetic acid scan: HIDA scan is commonly used for the diagnosis of biliary leaks. HIDA scanning can help determine the clearance of bile across strictures and surgical anastomosis. ***HIDA scan findings suggest complete biliary obstruction if the small intestine is not visualized in 60 minutes***. HIDA scanning also is useful for distinguishing cholangitis from cholecystitis.

Staging:

Bismuth proposed an anatomic classification based on location, into 5 types:

- Type 1: Low common hepatic duct stricture. 2 cm of the hepatic duct is intact.
- Type 2: Mid common hepatic duct stricture. The hepatic duct stump is < 2 cm.
- Type 3: This is a hilar stricture. The common hepatic duct is not involved, but the confluence of right and left hepatic ducts is intact.
- Type 4: In this type, the hilar confluence is destroyed. The right and left hepatic ducts are separated.
- Type 5: The aberrant right sectorial duct is involved, alone or with the CBD.

TREATMENT: **Medical Care:** Medical treatment consists of managing complications of bile duct strictures until definitive therapy can be instituted.

Surgical Care: 1) ***endoscopic or percutaneous balloon dilatation and insertion of an endoprosthesis*** (*Sphincterotomy and endoscopic balloon* dilation, *Endoscopic biliary stenting, PTC and biliary stenting*) or

2) surgery: *Operative treatment:* Surgical management consists of restoration of biliary enteric continuity, which usually is achieved with a defunctionalized Roux-en-Y jejunal loop by hepaticojejunostomy, choledochojejunostomy or intrahepatic cholangiojejunostomy.

LIVER

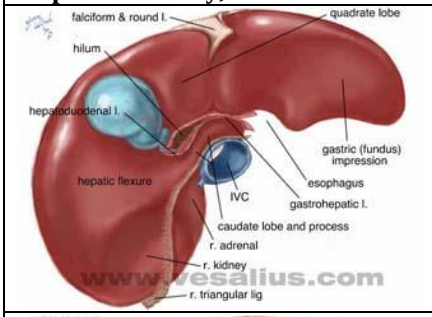
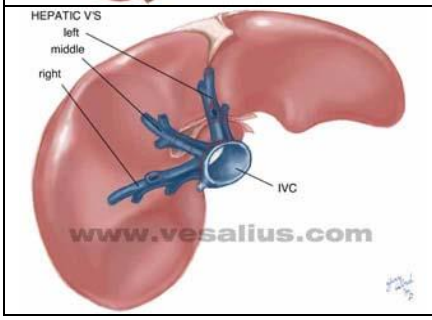
Surgical anatomy of the liver

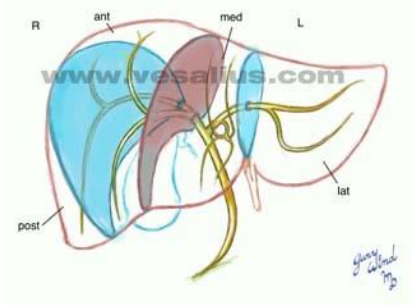
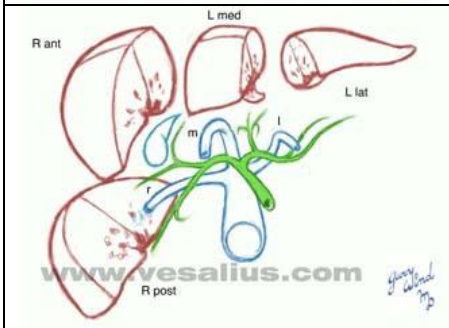
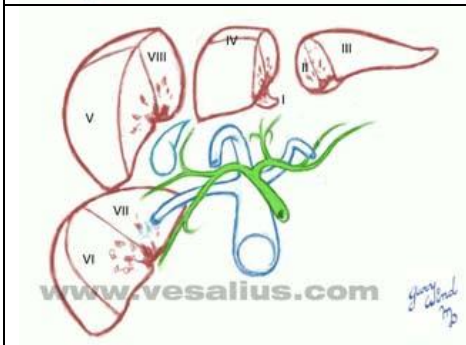
The liver is divided into a large right and a small left lobe by the falciform ligament. The morphology does not correspond to the surgical anatomy of the liver and functionally the liver is divided into a right and left hemi-liver by the principal plane ***(Rex-Cantlie line).*** This is a plane passing through the gallbladder bed towards the vena cava. The middle hepatic vein lies in this plane. Although this was first recognised by Ton That Tung in 1939, it was **Couinaud** in 1957, who provided the definitive description.

The right hemi-liver is divided into anterior and posterior sections by the right hepatic vein The left hemi-liver is divided into lateral and medial sections by the left hepatic vein. Further portal inflow division results in each section in turn being subdivided into two segments. The divisions of the portal vein are mirrored by divisions of the bile duct and hepatic artery forming a 'portal triad', a division of which supplies each segment.

The right portal pedicle is short (less than 1 cm in most) and the vein divides to supply the right anterior section, subdivided into segments V (inferior) and VIII (superior) by portal vein divisions and the right posterior section subdivided into segments VI (inferior) and VII (superior) by portal vein divisions. The left portal pedicle is long. It gives of a caudate branch and thereafter the vein divides to supply a left lateral section and a left medial section. The left medial section is divided into two segments, III and IV, by a further portal vein division. The caudate lobe is a distinct anatomical segment and is labeled segment I. It receives branches of the portal trinity from the right and left liver and drains independently into the vena cava.

As each segment of liver has its own supply from the portal trinity, independent of the other segments, these can therefore be resected independently of other segments.

Hepatic Anatomy, Caudal View	
	This reflected edge with its portal structures is called the hepatoduodenal ligament and forms the anterior boundary of the epiploic foramen. The inferior vena cava below the peritoneal reflection is the posterior margin.
	Three main hepatic veins drain the liver and lie between major hepatic divisions. The middle hepatic vein lies between the right and left lobes. The left hepatic vein lies between the medial and lateral segments of the left lobe. The right hepatic vein lies between the anterior and posterior segment of the right lobe

	The liver is divided into right and left lobes by a plane running through the gallbladder bed and inferior vena cava. Each of the lobes is divided into two major segments. The right lobe is divided into anterior and posterior segments and the left lobe is divided into medial and lateral segments. The three major hepatic veins lie in these planes between lobes and segments. Each of the four major segments is divided into a superior and inferior segment and the caudate lobe lies behind the superior part of the medial segment of the left lobe.
	The right, middle and left hepatic veins lie in the major planes of division. The descriptive nomenclature of Healey and Schroy divides the right lobe into anterior and posterior segments, each with a superior and inferior division. The left lobe segments are called medial and lateral, also each having superior and inferior divisions. The caudate lobe lies behind the superior medial segment.
	Another classification (Couinaud) numbers the segments I-VIII, treating the medial superior and inferior segments as one segment (IV) and the caudate lobe as another (I).

Hydatid disease

Caused by helminth *Ecchinococcus granulosa*

Adult worm is found in the dog & sheep intestine, Man is an accidental intermediate host

Liver is the commonest organ involved

Cysts are unilocular, can be up to 20 cm in diameter and may be multiple

The hydatid cysts form in the liver in 50-79% of patients or in the lung 20% and the remaining 10% may be found in the brain, heart, or the bones

Lung, brain and bone can also be infected

Pathologically hydatid liver cyst has three distinct layers:

- Ectocyst - fibrous advential layer due to host response
- Middle layer - laminated membrane of proteinaceous material
- Endocyst - inner germinal layer from which the scolices may be detached

Clinical features

- Clinical presentation is often non-specific and may be asymptomatic
- 60% have right hypochondrial pain and 15% become jaundiced
- Other features include skin rashes, pruritus and allergic reactions
- Cysts can rupture resulting in broncho-biliary fistula

Investigation

- 30% of patients have an eosinophilia
- Plain abdominal x-ray may show calcification in cyst wall

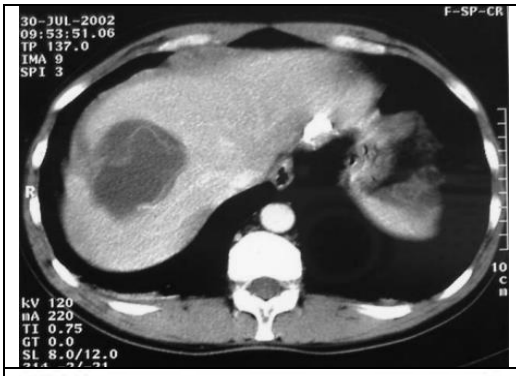
- Cyst can be imaged with ultrasound or CT
- Aspiration should not be performed if hydatid disease is suspected
- Immunoblot (Western blot) and ELISA are 80-100% sensitive for liver cysts but only 50-56% for lungs and other organs.
- When a cyst ruptures there is an abrupt stimulation of antibodies.
- However senescent, calcified, or dead cysts are seronegative.
- If the CT shows a cyst regardless of confirmation by serology the diagnosis should be made.

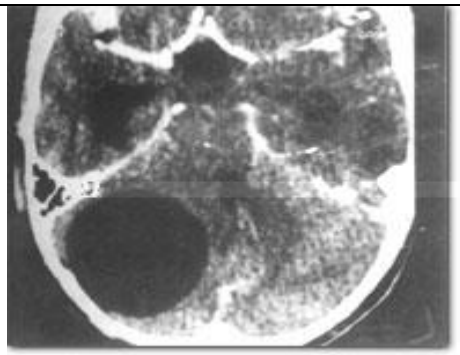
Management

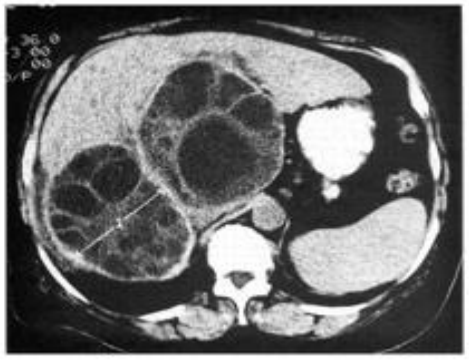
- Pharmacological treatment is not curative
- Used as an adjunct to surgery to kill spilled scolices
- The drugs of choice are albendazole, mebendazole and praziquantel
- Albendazole is the drug of choice in treatment as it is best absorbed.
- Mebendazole is more effective on all other types of worms except tapeworms but can be used as a second drug of choice in higher doses.
- Praziquantel is used as adjunct therapy as it only kills the inside of the hydatid cyst and not the germinal layer. It is currently being used as adjunct therapy with albendazole for pre and post-operative protection against cyst spillage.
- ***Surgical excision of the cyst is the treatment of choice for symptomatic cysts.***
- Hepatic resection may be required for recurrent cysts
- Recurrence rate is approximately 5% at 5 years

Complications

Rupture of cyst or other means of cyst spillage produces infection, occasional obstruction or allergic reaction 90 (very rarely- anaphylactic shock) in affected organ.
Rupture releases smaller cysts that may circulate to other organs.







Hydatid Disease of the Liver: A computed tomographic scan of the liver showing large cystic, lobulated structures with daughter cysts, consistent with hydatid disease.

Amebic Hepatic Abscesses

Amebic liver abscess is the most frequent extraintestinal manifestation of *Entamoeba histolytica* infection, which ascends the portal venous system.

Pathophysiology: *E histolytica* exists in 2 forms. ***The cyst stage is the infective form, and the trophozoite stage causes invasive disease***. The cysts are transmitted primarily by food and water contamination. ***Cysts are resistant to gastric acid, but the wall is broken down by trypsin as it passes through the small intestine.*** Trophozoites are released and colonize the cecum. To initiate symptomatic infection, *E histolytica* trophozoites present in the lumen must penetrate the mucosal layer and adhere to the underlying mucosa.

Liver involvement occurs following invasion of *E histolytica* into mesenteric venules. Amebae then enter the portal circulation and travel to the liver. The abscess contains acellular proteinaceous debris and is surrounded by a rim of amebic trophozoites invading the tissue.

The right lobe of the liver is more commonly affected than the left lobe.

History:

- Patients with amebic liver abscess usually present with fever and abdominal pain.
- The subacute presentation mostly is characterized by weight loss, and, in less than half the cases, abdominal pain and fever are present.

Constitutional symptoms

- Fever (87-100%), Rigors (36-69%), Nausea and vomiting (32-85%) and Weight loss (33-64%).

Diarrhea: Diarrhea is present in < 33% and Bloody diarrhea is present in 7% of cases.

Pulmonary symptoms

- Pulmonary symptoms are (18-26%), cough and chest pain.
- Odorless brown sputum like anchovy paste suggests development of bronchopleural fistula.

Physical:

Fever is the most common sign and is found in as many as 99% of cases.

Hepatomegaly is present in some cases.

Abdominal tenderness

Pulmonary abnormalities

- Dullness and rales at the right lung base and nonproductive cough.
- Breath sounds over the right lung base may be diminished.
- Pleural rub may be audible.

Jaundice (<10% of cases) mostly occurs in complicated cases with multiple abscesses or a large abscess compressing the biliary tract.

Signs of complications

- Signs of peritoneal irritation, such as rebound tenderness, guarding, and absence of bowel sounds, are present when the abscess ruptures in the peritoneal cavity.
- Pericardial friction rub is audible when the abscess extends into the pericardium.
- Signs of pleural effusion when the abscess ruptures in the pleural cavity.

WORKUP

- Leukocytosis- in 75% Eosinophilia is rare.
- Anemia may be present, but the cause usually is multifactorial.

Stool examination

- Less than 30% of patients with amebic liver abscess have concomitant intestinal amebiasis. Hence, the microscopic examination of stool for the identification of trophozoites or cysts is of little value. Fecal findings suggestive of amebic colitis include a positive test for heme, a paucity of neutrophils, and the presence of Charcot-Leyden crystal protein.
- Stool culture for amoeba is sensitive but has limited availability.

Serologic testing

- Serologic testing is a more useful diagnostic tool than stool microscopy. It can be used for (1) diagnosis of symptomatic patients, (2) assessment of the risk of invasive disease in people who are asymptomatic and are passing cysts in nonendemic areas (nonpathogenic strains do not cause seroconversion), and (3) testing patients with inflammatory bowel disease before starting corticosteroid therapy to prevent complications from unsuspected amebiasis.

- ***Indirect hemagglutination (IHA) testing is the most sensitive assay, with positive results occurring in 90-100% of patients with amebic liver abscess.***
- ***Enzyme immunoassay (EIA) has now largely replaced IHA testing.*** EIA is relatively simpler, easy to perform, rapid, stable, and inexpensive.

Imaging Studies:

Ultrasonography is the preferable initial diagnostic test. It is only slightly less sensitive than CT scan (75-80% sensitivity vs 88-95% for CT scan).

- A space-occupying lesion is observed in 75-95% of patients with liver abscesses. The lesions tend to be round or oval with well-defined margins and lack prominent peripheral echoes. The lesions are primarily hypoechoic.

Technetium-99m liver scanning *is useful for differentiating an amebic liver abscess from a pyogenic abscess.*

- Because amebic liver abscesses do not contain leukocytes, they appear as cold lesions on hepatic nuclear scanning, with a typical hot halo or rim of radioactivity surrounding the abscess.
- In contrast, pyogenic liver abscesses contain leukocytes and, therefore, typically appear as hot lesions on nuclear scanning.

Gallium scanning is helpful in differentiating pyogenic abscess (similar to technetium-99m nuclear hepatic scanning) but requires delayed images, which makes the test less helpful.

Plain chest or abdominal films may show elevation and limitation of motion of the right diaphragm, basilar atelectasis, and right pleural effusion or gas within the abscess cavity.

Procedures:

Aspiration of the abscess content is indicated only if rupture of the abscess is thought to be imminent or if differentiation between amebic abscess and pyogenic abscess is critical.

- Aspiration may be done if no response to antibiotic has occurred after 3-5 days.
- ***Amebas rarely are recovered from the aspirate (15%), and often they are present only in the peripheral parts of the abscess, invading adjacent tissue.***

TREATMENT

Medical Care: Most uncomplicated amebic liver abscesses can be treated successfully with amebicidal drug therapy alone.

- Metronidazole remains the drug of choice for amebic liver abscess.
- Chloroquine phosphate may be substituted or added in the event of failure of resolution of clinical symptoms with metronidazole or another nitroimidazole within 5 days or intolerance to metronidazole or a nitroimidazole.
- *Emetine or dehydroemetine has a direct lethal action on the trophozoites of E histolytica.* These agents are very toxic and, therefore, should be used only as a second-line therapy. Their toxicity includes cardiac arrhythmias, precordial pain, muscle weakness, vomiting, and diarrhea. Dehydroemetine is less toxic than emetine.

Surgical Care:

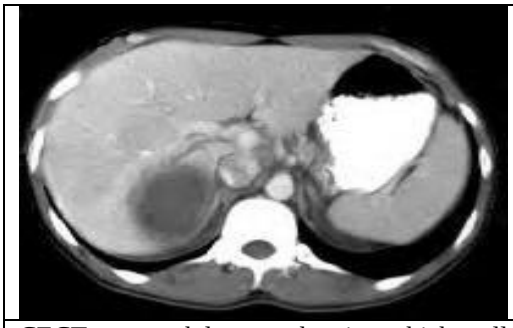
(1) High risk of abscess rupture, as defined by cavity size greater than 5 cm;

(2) Left lobe liver abscess, which is associated with higher frequency of peritoneal leak or rupture into the pericardium; and

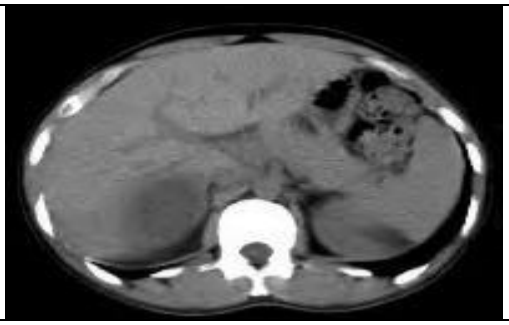
(3) a failure to observe a clinical medical response to therapy within 5-7 days.

Imaging-guided needle aspiration or catheter drainage is the procedure of choice.

Generally, surgical drainage is not necessary and should be avoided; however, consider open surgical drainage when the abscess is inaccessible to needle drainage or a response to therapy has not occurred in 4-5 days.



CECT scan abdomen showing thick-walled cavity with low attenuation center and contrast-enhanced periphery. CT cannot differentiate amebic from pyogenic liver abscess.



CT scan of the abdomen of the same patient in Picture 1 is shown without contrast. A thick-walled cavity with low attenuation center is located in the right lobe of the liver.

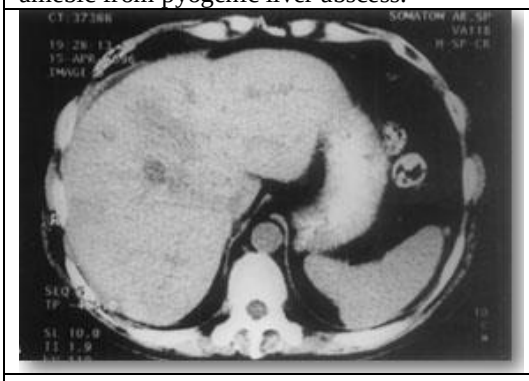


Fig 1: Precontrast.

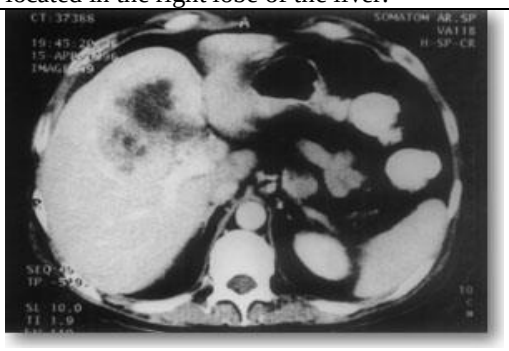


Fig 2 : Post - Contrast.

PORTAL HYPERTENSION

- Normal portal pressure = 5 - 10 mmHg
- Portal hypertension is defined as a pressure > 12 mmHg

Aetiology

Prehepatic	**Intrahepatic**	**Posthepatic**
Portal vein thrombosis Splenic vein thrombosis Tropical splenomegaly Arterio-venous fistula	***Presinusoidal*** Schistosomiasis Primary biliary cirrhosis Chronic active hepatitis Sarcoidosis ***Sinusoidal*** Cirrhosis - post hepatitic, alcohol, cryptogenic, metabolic (e.g. Wilson's, haemochromotosis) Non-cirrhotic - cytotoxic drugs, Vitamin A intoxication ***Postsinusoidal*** Budd-Chiari syndrome Veno-occlusive disease	Caval abnormality Constrictive pericarditis

Pathophysiology

- Increased portal pressure reduces portal venous flow
- Encourages development of porto-systemic anastomoses
- Develop at site of connections between portal and systemic circulation
    - Gastro-oesophageal junction
    - Lower rectum
    - Peri-umbilical veins
    - Retroperitoneal veins of Retzius
    - Peri-hepatic veins of Sappey

Severity of Cirrhosis

Child-Pugh classification	**Variable**	**Score**		
○ Score 5-6 = Class A ○ Score 7-9 = Class B ○ Score > 10 = Class C		1 point	2 points	3 points
	Encephalopathy	Absent	Mild / moderate	Severe or coma
	Bilirubin (μ mol/l)	<34	34-51	>51
	Albumin (g/l)	>3.5	2.8-3.5	<2.8
	Prothrombin time (secs above normal)	1-4	4-6	>6

TREATMENT: **Medical Care:** Gastroesophageal variceal hemorrhage is the most dramatic and lethal complication of portal hypertension. ***Medical care includes emergent treatment, primary prophylaxis, and elective treatment.***

Emergent treatment

Bleeding from esophageal varices

- Initial resuscitation with replacement of blood volume loss
- Diagnosis of source of bleeding
- Specific treatment of bleeding lesion
- Pharmacological therapy
    - **Somatostatin:** is an endogenous hormone that decreases portal blood flow by splanchnic vasoconstriction.
    - **Octreotide** is a synthetic analogue of somatostatin.
    - **Vasopressin** is the most potent splanchnic vasoconstrictor. It reduces blood flow to all splanchnic organs, decreasing portal venous inflow and decreasing portal pressure. Use of vasopressin is limited by adverse effects related to splanchnic vasoconstriction (eg, bowel ischemia) and systemic vasoconstriction (eg, hypertension, myocardial ischemia). Vasopressin always should be accompanied by intravenous nitroglycerin to maintain systolic blood pressure greater than 90 mm Hg.
    - Adding **nitrates** to vasopressin therapy significantly improves efficacy, although adverse effects of combination therapy are higher than those associated with terlipressin or somatostatin.
    - **Terlipressin** is a synthetic analogue of vasopressin with longer biological activity and significantly fewer adverse effects than vasopressin.
- Endoscopic therapy
    - Efficacy in achieving hemostasis is higher than 80%.
    - Several different sclerosants are available: 5% sodium morrhuate, 1% to 3% sodium tetradecyl sulfate, and 5% ethanolamine oleate. The volume used per injection is 1-2 mL, with total volume ranging from 10-15 mL.
    - Complications are related to the toxicity of the sclerosant and include transient fever, stricture, dysphagia, perforation (rarely), chest pain, mediastinitis, ulceration, and pleural effusion.

- Sclerotherapy is very effective emergency treatment for acute variceal bleeding ***(not optimal for patients bleeding from gastric fundal varices).***
- EVL is achieved by a banding device attached to the tip of the endoscope. The varix is aspirated into the banding chamber, and a trip wire dislodges a rubber band carried on the banding chamber, ligating the varix.

- Other interventions
  - Balloon-tube tamponade should be used only in massive bleeding as a temporizing measure until definitive treatment can be instituted.
  - The Minnesota tube has 4 lumens, 1 for gastric aspiration, 2 to inflate the gastric and esophageal balloons, and 1 above the esophageal balloon to suction secretions to prevent aspiration.
  - The Minnesota tube is an adaptation of the Sengstaken-Blakemore (S-B) tube, the difference is that the S-B tube does not have the esophageal suction port to prevent aspiration.
  - Endoscopic administration of cyanoacrylate monomer (superglue) in gastric varices is another intervention.

Prognosis

- Predictors of mortality with variceal bleeding
  - Active bleeding during endoscopy
  - Encephalopathy
  - Ascites
  - Serum Bilirubin increased
  - Aspartate Aminotransferase increased
  - Prothrombin Time increased

Primary prophylaxis: Primary prophylaxis is administered to patients at high risk of bleeding.

- Indications (Endoscopic criteria)
  - Large esophageal varices
  - Small esophageal varices
    - High Child-Pugh Score
    - Varices with red wale markings
  - severe liver failure

- Beta-blockers
  - Beta-blockers include propranolol and nadolol. Beta-blockers are noncardioselective and reduce portal and collateral blood flow. Reduction in cardiac output (blockade of beta1-adrenoreceptors) occurs. Splanchnic vasoconstriction (blockade of vasodilatory adrenoreceptors of the splanchnic circulation) also occurs.
  - Propranolol is contraindicated in patients with asthma, chronic obstructive pulmonary disease (COPD), atrioventricular (AV) block, intermittent claudication, and psychosis.
- Vasodilators
  - Isosorbide mononitrate (ISMN) is a vasodilator and has been demonstrated to reduce HVPG.
  - Vasodilators also reduce esophageal variceal pressure.
- Combination therapy
  - Combination therapy appears to be associated with increased adverse effects and a higher rate of ascites.
  - Combination therapy cannot be recommended presently until further studies prove efficacy.
- Prophylactic sclerotherapy
  - It has no role in primary prophylaxis.
- Prophylactic endoscopic variceal ligation
  - EVL has been demonstrated to be more effective than no treatment in preventing the first variceal bleed.

- Prophylactic EVL has been demonstrated to have an efficacy similar to beta-blockers in prevention of first variceal bleed, but with increased adverse effects.
- Prophylactic EVL currently cannot be recommended as a routine measure for primary prevention but may be an option for patients with grade 3 varices who have contraindications to or cannot tolerate beta-blockers.

Elective treatment: This is for the prevention of rebleeding. Variceal hemorrhage has a 2-year recurrence rate of approximately 80%.

- Nonselective beta-blockers
  - Propranolol and nadolol significantly reduce the risk of rebleeding and are associated with prolongation of survival.
- Endoscopic sclerotherapy
  - Approximately 4-5 sessions are required for eradication of varices, which is achieved in nearly 70% of patients.
- Endoscopic variceal ligation
  - EVL is associated with lower rebleeding rates and a lower frequency of esophageal strictures..
  - *EVL is considered the endoscopic treatment of choice in the prevention of rebleeding.*
- Combination of EVL and pharmacologic therapy
  - A recent randomized trial demonstrates that EVL plus nadolol plus sucralfate is more effective in preventing variceal rebleeding than EVL alone.

Surgical Care: Surgical care includes decompressive shunts, devascularization procedures, and liver transplantation.

Decompressive shunts: These include total portal systemic shunts, partial portal systemic shunts, and other selective shunts.

Role of shunts is to:

- Emergency control of variceal bleeding when no access to TIPS
- Reduce portal hypertension in patients awaiting transplantation
- Relieve intractable ascites
- Reduce bleeding from rectal, colonic or stomal varices

- Total portal systemic shunts
  - These include any ***shunt larger than 10 mm*** in diameter between the portal vein (or one of its main tributaries) and the IVC (or one of its tributaries).
  - ***Eck fistula (classic end-to-side portacaval*** shunt described for historical interest only). The portal vein is divided close to the liver, and the splanchnic end is anastomosed to the IVC. This controls variceal bleeding and decompresses splanchnic hypertension but leaves high pressure in the hepatic sinusoids, thus ascites is not relieved.
  - For the side-to-side portacaval shunt, the portal vein and the infrahepatic IVC are mobilized after dissection and anastomosed. All portal flow is directed through the shunt, and the portal vein itself acts as an outflow from the obstructed hepatic sinusoids. Excellent control of bleeding and ascites is achieved in more than 90% of patients. Encephalopathy (rate of 40-50%) and progressive liver failure are possible. Indications are massive variceal bleeding with ascites or acute Budd-Chiari syndrome without evidence of liver failure.
- Partial portal systemic shunts
  - These reduce the size of the anastomosis of a side-to-side shunt to ***8 mm in diameter.*** Portal pressure is reduced to 12 mm Hg, and portal flow is maintained in 80% of patients.
    - The operative approach is similar to side-to-side portacaval shunts, except the interposition graft (Small bore portocaval H-graft) must be placed between the portal vein and the IVC.
  - Have narrow diameter and partially decompress portal circulation
  - Some portal vein flow is maintained
  - 10% of patients will develop encephalopathy
- Selective shunts

- These provide selective decompression of gastroesophageal varices to control bleeding while at the same time maintaining portal hypertension to maintain portal flow to the liver.
- One example is the ***distal splenorenal shunt***, which is the most commonly used decompressive operation for refractory variceal bleeding.. This shunt provides the best long-term maintenance of some portal flow and liver function with a lower incidence of encephalopathy (10-15%) compared to total shunts. The operation produces ascites because the retroperitoneal lymphatics are diverted.

Devascularization procedures: These include splenectomy, gastroesophageal devascularization, and esophageal transection (at times). Incidence of liver failure and encephalopathy is low following devascularization procedures, presumably because of better maintenance of portal flow. Devascularization could be used in patients who have portal or splenic vein thrombosis in addition to cirrhosis.

- Splenectomy
- Gastroesophageal devascularization (Sugiura procedure)
  - This should devascularize the whole greater curve of the stomach from the pylorus to the esophagus and the upper two thirds of the lesser curve of the stomach; the esophagus should be devascularized for a minimum of 7 cm.

Liver transplantation

Surgery:

Primary prophylaxis: Surgery has no role for primary prophylaxis.

Acute variceal bleeding

- The role of surgery in acute variceal bleeding is exceedingly limited because therapy with endoscopic treatment controls bleeding in 90% of patients.
- TIPS is a viable option.

Prevention of rebleeding

- For prevention of rebleeding, when pharmacological and/or endoscopic therapy has failed, consider surgery.
- TIPS is a useful procedure for continued bleeding despite medical and endoscopic treatment in patients with Child class C disease and selected patients with Child class B disease. ***It is effective only in portal hypertension of hepatic origin.***
  - Indications: Accepted (established in controlled trials) indications include (1) active variceal bleeding despite emergency endoscopic and/or pharmacological treatment and (2) recurrent variceal bleeding despite adequate endoscopic treatment. Potential indications include (1) isolated bleeding from gastric fundic varices and (2) refractory ascites. Experimental indications include (1) bleeding portal gastropathy, (2) Budd-Chiari syndrome, (3) venoocclusive disease, (4) hepatorenal syndrome, (5) hepatic hydrothorax, (6) bleeding ectopic varices, (7) and protein-losing enteropathy due to portal hypertension.
  -

Hepatocellular carcinoma

Hepatocellular cancer is one of the most common cancers in the world, with a 5-year survival rate of less than 5% without treatment.

- **A**ny chronic inflammatory liver disease has the potential to induce hepatocellular carcinoma, but most commonly associated with the disease is cirrhosis, found in up to 80% of cases while 20% of cases are due to noncirrhotic, nonviral causes.
- Chronic viral hepatitis as a cause of cirrhosis and hepatocellular carcinoma is well known. Hepatitis B virus infection is the leading cause of chronic liver disease and hepatocellular carcinoma around the world. Hepatitis C virus RNA is found in about 65% of patients who test negative for hepatitis B surface antigen at diagnosis of their hepatocellular carcinoma.
- Alcohol use is also a common cause of cirrhosis, which can indirectly lead to carcinoma. However, a direct carcinogenic effect of alcohol on the liver has not been proved.

- Certain substances derived from plants, industrial pollutants, and synthetic pharmaceutical agents have been found to cause hepatocellular carcinoma. For example, aflatoxin B (a mycotoxin in inappropriately stored grain), Vinyl chloride an industrial carcinogens. Estrogens and androgens, as found in oral contraceptives and anabolic steroids, have been found to be carcinogenic in rodents.
- Hemochromatosis carries a relative risk of more than 200 for hepatocellular carcinoma, which can occur without cirrhosis.
- $Alpha_1$-antitrypsin deficiency and primary biliary cirrhosis are also associated with the disease.

The incidence of hepatocellular carcinoma varies greatly with geographic location, ethnic background, and sex. Incidence rates among men in sub-Saharan Africa and Asia may be 20 times higher than those among men in the United States.
The male-female ratio is about 4:1

Patient presentation

Hepatocellular carcinoma should be considered in any patient with chronic liver disease whose clinical status indicates sudden decompensation.
Unfortunately, the disease is often clinically silent until it is well advanced or tumor diameter exceeds 10 cm. A few patients present with paraneoplastic syndrome, and the most common and most significant manifestations are erythrocytosis, hypercalcemia, hypoglycemia, carcinoid syndrome, dysfibrinogenemia, cryoglobulinemia, and hypercholesterolemia.

Common presenting symptoms and physical examination findings in hepatocellular carcinoma	
Finding	**Average incidence (%)**
Symptom	
Abdominal pain	91
Abdominal swelling	43
Weight loss	35
Weakness	31
Feeling of fullness and anorexia	27
Vomiting	8
Jaundice	7
Physical examination	
Hepatomegaly	89
Splenomegaly	65
Ascites	52
Jaundice	41
Fever	38
Hepatic bruit	28

Diagnostic approach

Most hepatocellular carcinomas are first suspected based on the results of CAT scans or ultrasound scans. Blood alpha-fetoprotein is a useful marker for the diagnosis of hepatocellular carcinoma. About 70% of patients with hepatocellular carcinoma have elevated blood alpha-fetoprotein concentrations; however, it is not specific for this condition. It is often measured as a part of screening in patients with chronic hepatitis B or chronic hepatitis C and cirrhosis. A rising blood alpha-fetoprotein concentration in someone with chronic liver disease suggests the development of hepatocellular carcinoma. Appropriate adiological scans should be done in such instances.
The definitive diagnosis of hepatocellular carcinoma is made by biopsy. Usually, the liver mass is biopsied by a radiologist under with the help of a radiological scan. Sometimes, the mass is biopsied using a laprascope, a fiber optic instrument that is inserted into the abdomen. Occasionally, open surgical biopsy is necessary.
To help detect hepatocellular carcinoma, alpha-fetoprotein (AFP) should be measured; a level exceeding 500 micrograms/L is considered a positive finding. In the US population, the sensitivity of an elevated AFP

level is only 60%. More sensitive tests, such as soluble interleukin-2 receptor levels, are currently being developed and results are encouraging.
Fine-needle biopsy of the mass should always be considered when the diagnosis is unclear, but theoretically, it carries risks for percutaneous needle tract seeding of tumor and bleeding.

Staging

TNM staging criteria for HCC

- T1 - Solitary tumor without vascular invasion
- T2 - Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
- T3 - Multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic vein(s)
- T4 - Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
- N0 - Indicates no nodal involvement
- N1 - Indicates regional nodal involvement
- M0 - Indicates no distant metastasis
- M1 - Indicates metastasis presence beyond the liver

Stage grouping

- Stage I = T1 + N0 + M0
- Stage II = T2 + N0 + M0
- Stage IIIA = T3 + N0 + M0
- Stage IIIB = T4 + N0 + M0
- Stage IIIC = TX + N1 + M0

Stage IVB = TX + NX + M1

Treatment methods

In those with small tumors (<2 cm in diameter), limited stage I or II disease, and good hepatic function, surgical resection is the treatment of choice. It can achieve 5-year survival rates as high as 60% to 70% and, rarely, cure the disease.
In the United States, liver transplantation for hepatocellular carcinoma is indicated only in patients who have unresectable tumors less than 5 cm in diameter, focal tumor recurrence after resection, or hepatic failure.
Specialized procedures, including transcatheter arterial embolization, chemoembolization, lipoidal-targeted chemotherapy, and transcatheter oily chemoembolization, can improve survival rates in patients with unresectable cancer. However, these techniques are used mainly in Asia as adjunctive methods in patients who are eligible for resection or transplantation.
For patients who are poor surgical candidates but have small numbers of tumors, all less than 3 cm in diameter, percutaneous ethanol injection achieves a 3-year survival rate that is similar to that of resection, plus it is relatively inexpensive and widely available.
Because of their excessive toxicity and lack of survival benefit, systemic chemotherapy and radiation therapy are not considered efficacious approaches to hepatocellular carcinoma.

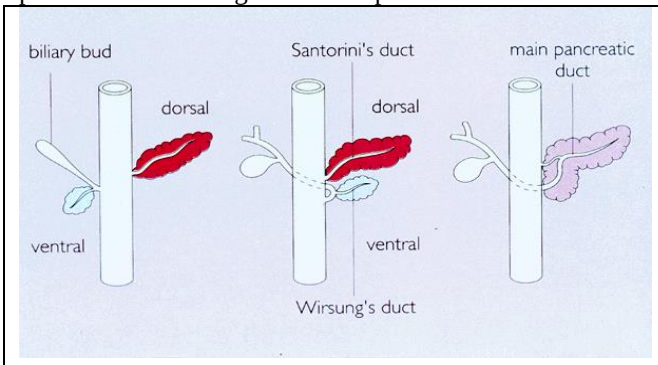
PANCREAS

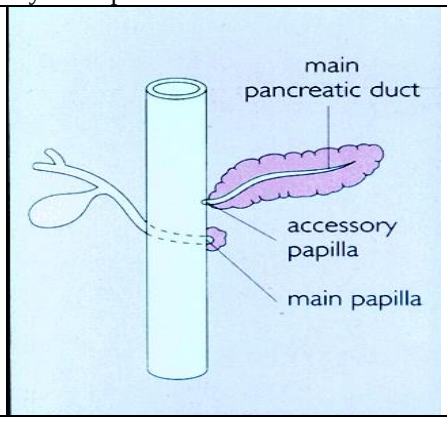
The pancreas is a lobulated gland lying retroperitoneally, measuring 12-15cm in length, with a head and an uncinate process, which lie within the curve of the duodenu.

Embryological development

The pancreas develops from separate ventral and dorsal buds that arise from the junction of the primitive foregut and midgut. The dorsal bud enlarges towards the left, and forms the main bulk of the adult gland. The ventral bud, which is closely associated with the developing common bile duct is brought into apposition with the dorsal system only in the seventh week of intrauterine growth, following its rotation.
Both parts of the primitive pancreas contain axial ducts, the dorsal duct arising from the duodenal wall, and the ventral duct from the common bile duct. When they fuse, the ventral duct (of Wirsung) becomes continuous with the dorsal duct (of Santorini) to form the main pancreatic duct.

The common bile duct and pancreatic ducts therefore enter the duodenum at the main papilla, while the portion of the dorsal duct within the head of the pancreas enters the duodenum proximally to the main papilla, through a small accessory, or minor papilla.
Complete failure of the two duct systems to fuse results in a pancreas divisum (Fig 2- 5%) and may predispose to pancreatitis. Failure of the body of the ventral bud to rotate may give rise to an annular pancreas surrounding the second part of the duodenum. This may be responsible for duodenal obstruction.





PANCREATITIS
Acute pancreatitis is an inflammatory process in which pancreatic enzymes autodigest the gland.
The gland can heal without any impairment of function or any morphologic changes.
It can recur intermittently, contributing to the functional and morphologic loss of the gland. Recurrent attacks are referred to as chronic pancreatitis.
Pathophysiology: Since the pancreas is located in the retroperitoneal space with no capsule, inflammation can easily spread. In acute pancreatitis, parenchymal edema and peripancreatic fat necrosis occur first, called acute edematous pancreatitis.
When necrosis involves the parenchyma, accompanied by hemorrhage and dysfunction of the gland, the inflammation evolves into hemorrhagic or necrotizing pancreatitis.
Pseudocysts and pancreatic abscesses can result from necrotizing pancreatitis, due to enzymes being walled off by granulation tissue (pseudocyst formation) or bacterial seeding of pancreatic or peripancreatic tissue (pancreatic abscess formation).
The inflammatory process can cause systemic effects due to the presence of cytokines such as bradykinins and phospholipase A. These cytokines may cause vasodilation, increase in vascular permeability, pain, and leukocyte accumulation in the vessel walls. Fat necrosis causes hypocalcemia. Pancreatic B cell injury may lead to hyperglycemia.
Trypsin and chymotrypsin are the initiating enzymes; their release can in turn result in the release and activation of other proenzymes (including proelastase, procollagenase and phospholipases). Trypsin damages endothelial cells and mast cells, resulting in the release of histamine. This major inflammatory mediator enhances vascular permeability, leading to edema, hemorrhage and the activation of the kallikrein system, which in turn results in the production of vasoactive peptides or kinins. The latter are thought to cause pain and further aggravate the inflammatory response. The other released enzymes destroy the supporting matrix of the gland and the plasma membrane of the acinar cell, precipitating further release of digestive enzymes, which in turn leads to further damage. Lysolecithin, which is released by the action of phospholipase on lecithin (a phospholipid found in bile), has also been implicated in pancreatic damage, because of its cytotoxic and hemolytic properties. When the pancreas is inflamed but remains viable, the condition is termed *interstitial pancreatitis*; this may occur in up to 80% of cases. In the remaining cases, there is significant pancreatic necrosis resulting from disruption of the microcirculation, destruction of the pancreatic parenchyma and peripancreatic

History:

- Epigastric pain or right upper quadrant pain radiating to the back
- Nausea/vomiting
- Fever
- The patient should be asked about recent surgeries and invasive procedures (i.e., ERCP) or family history of hypertriglyceridemia.
- There is frequently a history of previous biliary colic, and binge alcohol consumption, the major causes of acute pancreatitis.

Physical:

- Tachycardia/ Tachypnea/ Hypotension/ Fever
- Abdominal tenderness, distension, guarding and rigidity. In severe cases, there may be a Grey Turner sign (i.e., bluish discoloration of the flanks) and Cullen's sign (i.e., bluish discoloration of the periumbilical area) due to the retroperitoneal leak of blood from the pancreas in hemorrhagic pancreatitis.
- Mild jaundice
- Diminished or absent bowel sounds
- Basal rales in lungs, (especially in the left due to contiguous spread of inflammation).
- In the extremities, muscular spasm may, be noted secondary to hypocalcemia.
- Multisystem organ failure (ARDS, renal failure from ATN), shock, DIC and hemorrhage.
- Pleural effusions, pneumonia, and atelectasis.
- Formation of pancreatic fluid collections (pseudocysts and abscesses) account for 70% to 80% of mortality.
- Ileus, colonic obstruction, CNS hypoperfusion with confusion, etc.

Causes:

- ***The major causes are long-standing alcohol intake or biliary stone disease.***
- Medications: azathioprine, corticosteroids, sulfonamides, thiazides, furosemides, NSAIDs, mercaptopurine, methyldopa, tetracyclines DDI (dideoxycytosine), DDC (dideoxyinosine), azathioprine, valproic acid, acetaminophen, and others.
- Endoscopic retrograde cholangiopancreatography (ERCP)
- Hypertriglyceridemia: When the triglyceride level exceeds 1000mg/U.
- Peptic ulcer disease
- Abdominal or cardiopulmonary bypass surgery: insulting the gland by ischemia
- Trauma to the abdomen or to the back.
- Carcinoma of the pancreas, which may lead to pancreatic outflow obstruction
- Viral infections: cytomegalovirus, hepatitis virus, EBV, CMV and paramyxovirus [mumps], togavirus [rubella], cytomegalovirus, adenovirus, HIV, coxsackie B,
- Bacterial infections, such as mycoplasma, *Campylobacter, Legionella, Mycobacterium tuberculosis, M. avium* complex
- Intestinal parasites: ascaris, *Opisthorchis* [clonorchiasis], which blocks outflow
- Pancreas divisum
- Scorpion and snake bites
- Vascular factors, such as ischemia or vesculitis, Connective-tissue disorders (SLE, polyarteritis nodosa, sarcoidosis)

Objective measurements such as Ranson's criteria, show a good correlation with the risk of major complications and death.

TABLE *Ranson's criteria*
Ranson developed a series of different criteria for the severity of acute pancreatitis.

On admission	*Within 48 hours*
1. Age > 55 yrs 2. WCC > 16,000 3. LDH > 600 U/l (350 IU/L) 4. AST >120 U/l (250 IU/L) 5. Glucose > 10 mmol/l (200 mg/dL)	1. Haematocrit fall >10% 2. Urea rise >0.9 mmol/l (5 mg/dL) 3. Calcium < 2 mmol (8 mg/dL) 4. pO_2 < 60 mmHg 5. Base deficit > 4 mEq/L 6. Fluid sequestration > 6L
• Can not be applied fully for 48 hours • Also poor predictor later in the disease	

Poor prognostic indicators (Ranson's criteria 1978**, <u>modified by Hollander 1983)</u>**

First 24 hours	***After 24 hours***
Age > 55	Decrease in hematocrit by > 10%
Leucocytosis > 16,000	Hypocalcemia (< 2.0 mmol/L)
Hyperglycemia, serum glucose > 200 mg/dL	Hypoxemia pO_2 < 60 mm Hg
LDH > 350 units/L	Hypovolemia
	Base deficit > 4.0 mmol/L
	Amylase > 1,000

<u>WORKUP</u>
Lab Studies:
A complete blood count will show leukocytosis (WBC > 12000) with the differential being shifted towards the segmented polymorphs.
BUN, Cr and electrolytes (Na, K, Cl, Carbon dioxide, P, Mg) should be ordered. Patient may have hypocalcemia caused by "soap" formation (saponification of triglycerides and calcium). Frequently have hypomagnesemia.
<u>Amylase</u> (preferably the Amylase P): Levels more than 3 times the norm strongly suggest the diagnosis of acute pancreatitis. Amylase is elevated in 80% of those with pancreatitis and is more sensitive early on.
<u>Lipase</u> is more sensitive if symptoms have been present for more than 24 hours. Both amylase and lipase levels may be normal in a patient with CT-proved pancreatitis.
Lipase remains high for 12 days
In patients with chronic pancreatitis (usually due to alcohol abuse), lipase may be elevated in the presence of a normal serum amylase level
Liver function tests (alkaline phosphatase, SGPT, SGOT, G-GT) and bilirubin should be ordered, particularly with biliary origin Pancreatitis.

<u>Extrapancreatic conditions may cause hyperamylasemia</u>
Abdominal conditions that may cause elevations in the serum amylase includes:

Perforated peptic ulcer/ Cholecystitis/ Generalised peritonitis/ Intestinal obstruction
Mesenteric infarction/ Ruptured AAA/ Ruptured ectopic pregnancy

Two-thirds of diabetic ketoacidosis is associated with hyperamylasemia and may present a confusing clinical picture, particularly when it is associated with shock
It has been estimated that as many as 2-5% of cases of hyperamylasemia are due to macroamylasemia, a benign condition resulting from the binding of amylase to macro-molecules too large to be filtered through the kidneys
<u>Serum lipase also rises rapidly, within hours after an attack</u>
Reference range for serum lipase is ,130 U/l
Lipase is measured via turbidimetric method:
Sensitivity of lipase for acute pancreatitis approaches 100%

Lipase lacks specificity and may be elevated in

- Acute cholecystitis
- Choledocholithiasis
- Mesenteric infarction
- Intestinal obstruction

Urine amylase

Urine amylase rises a few hours after the rise sin serum amylase and lipase

Urine amylase remains elevated for approximately seven to ten days

The rise in urine amylase is secondary to an increase in the renal clearance of amylase

Amylase clearance is used to differentiate between a patient with macroamylasemia secondary to hyperamylasemia from a patient with pancreatitis

Normal ratio for amylase clearance is between 2-5%

In macroamylasemia, the ratio is decreased

In pancreatitis, the ratio is increased

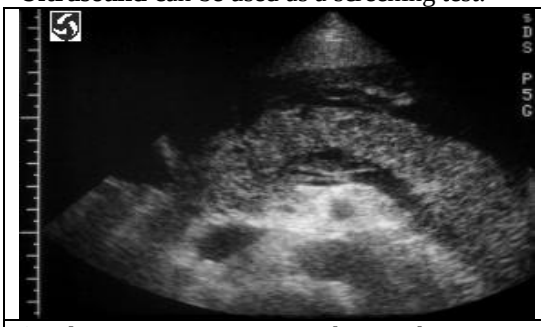
Amylase clearance= Urine amylase concentration x Serum creatinine concentration / Serum amylase concentration x Urine creatinine concentration

Imaging Studies:

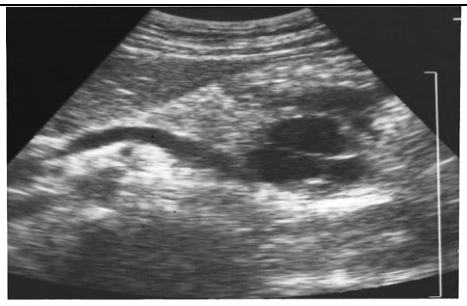
Plain KUB (Kidney/Ureter/Bladder):

Perform in the upright position to exclude viscus perforation (air under the diaphragm). In case of a recurrent episode of chronic pancreatitis, peripancreatic calcifications may be noted. Radiography may reveal a "sentinel loop," a localized ileus in the midepigastric region. Pleural effusions may also be present.

Ultrasound can be used as a screening test.



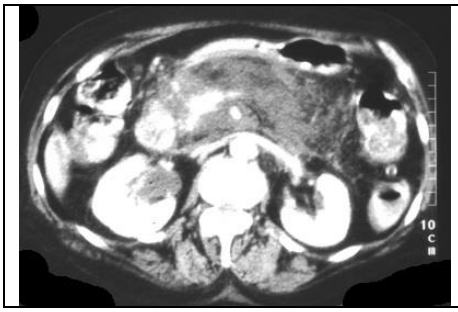
Single transverse image shows that pancreatic echogenicity is within normal limits, but the gland is mildly enlarged. In addition, a complex fluid collection lies anterior to the pancreas, and abnormal sonolucency surrounds the splenic vein.

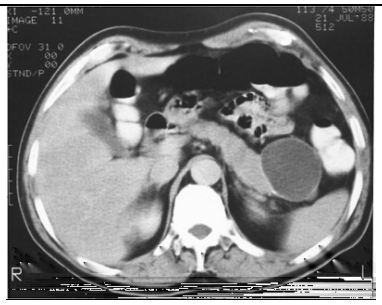


Ultrasonography demonstrating pancreatic enlargement, ductal dilation or pseudocysts

CT scan is the most reliable imaging modality in the diagnosis of acute pancreatitis. The criteria for the *diagnosis are divided by Balthazar and colleagues into 5 grades*

- Grade A: Normal pancreas
- Grade B: Focal or diffuse gland enlargement
- Grade C: Intrinsic gland abnormality seen by haziness on the scan
- Grade D: Single ill-defined collection or phlegmon
- Grade E: Two or more ill-defined collections or the presence of gas in or nearby, the pancreas





TREATMENT

Emergency Department Care: 80% patients respond to conservative treatment.

Fluid Resuscitation:

Accurate intake/output and electrolyte balance of the patient should be monitored

Crystalloids are used but other infusions, such as packed red blood cells (PRBCs), are occasionally administered, particularly in the case of hemorrhagic pancreatitis

Patients should be kept as NPO and a nasogastric tube should be inserted to assure an empty stomach and to keep the GI at rest

Parenteral nutrition should be started if the prognosis is poor and the patient is going to be kept in the hospital for more than 4 days.

Analgesics: Meperidine is preferred on morphine due to the greater spastic effect of the latter on the sphincter of Oddi

Antibiotics are used in severe cases associated with septic shock or when a phlegmon of the pancreas has evolved as seen by CT scan. Other conditions, such as biliary pancreatitis associated with cholangitis, also need antibiotic coverage.

The preferred antibiotics are the ones secreted by the biliary system, such as *ampicillin and third generation cephalosporins*

Continuous oxygen saturation should be monitored by pulse oxymetry and acidosis should be corrected. When tachypnea and pending respiratory failure develops, intubation should be performed

General Surgery should be consulted in the following cases:

- *Phlegmon of the Pancreas:*
- *Hemorrhagic Pancreatitis:*
- *Patients who fail to improve despite optimal medical treatment*, or patients who push the Ranson score even further.
- *Biliary Pancreatitis:* Sphincterotomy would relieve the obstruction. A cholecystectomy may be performed to clear the system from biliary stones

Complications:

- Infected pancreatic necrosis ia due to seeding of bacteria into the inflammation.
- An acute pseudocyst is an effusion of pancreatic juice that is walled off by granulation tissue after an episode of acute pancreatitis.
- Hemorrhage into the GI tract retroperitoneum or the peritoneal cavity is possible.
- Intestinal obstruction or necrosis
- ComCBD obstruction by a pancreatic abscess, pseudocyst or biliary stone.
- Internal pancreatic fistula from pancreatic duct disruption or a leaking pseudocyst

Metabolic	Hypocalcemia, hyperglycemia, hypertriglyceridemia, acidosis
Respiratory	Hypoxemia, atelectasis, effusion, pneumonitis Acute respiratory distress syndrome (ARDS)
Renal	Renal artery or vein thrombosis Renal failure
Circulatory	Arrhythmias Hypovolemia and shock; myocardial infarct Pericardial effusion, vascular thrombosis
Gastrointestinal	Ileus Gastrointestinal hemorrhage from stress ulceration; gastric varices (secondary to splenic vein thrombosis) Gastrointestinal obstruction
Hepatobiliary	Jaundice Portal vein thrombosis
Neurologic	Psychosis or encephalopathy (confusion, delusion and coma) Cerebral emboli, Blindness (angiopathic retinopathy with hemorrhage)
Hematologic	Anemia, DIC (disseminated intravascular coagulopathy) Leucocytosis
Dermatologic	Painful subcutaneous fat necrosis

CHRONIC PANCREATITIS

Chronic pancreatitis is defined as a continued inflammation characterized by ***irreversible morphologic changes***.

These changes include fibrosis, ductal abnormality, calcification and cellular atrophy. Alcohol is the major etiologic factor, accounting for about 75% of the cases.

Repeated attacks of gallstone-related pancreatitis can rarely cause chronic pancreatitis. Other causes include diabetes, protein-calorie malnutrition, hereditary pancreatitis, cystic fibrosis and idiopathic causes.

Alcohol presumably causes pancreatic injury by the intraductal formation of protein plugs secondary to increased protein concentration and precipitation, with or without calcification. These plugs lead to obstruction and secondary pancreatic damage.

Classification

- Chronic pancreatitis is divided into two clinical types: Chronic pancreatitis and chronic relapsing pancreatitis In both, regardless of the cause, the gland is permanently damaged, morpho-logically and functionally causing recurrent painful attacks resembling acute pancreatitis.
- In contrast, the type referred to simply as **chronic pancreatitis** is often illustrated by idiopathic disease, in which the gradual destruction of the gland, with resulting pancreatic insufficiency, often proceeds without discrete painful exacerbation

Pathology

- A cardinal feature of chronic pancreatitis is the presence of protein plugs and calcifications
- Proteinaceous material precipitates in the ducts and ductules, initially consisting mainly of pancreatic enzyme protein and a glycoprotein
- In late stages, calcium carbonate is added to the precipitates, giving rise to stones (pancreatic calculi)
- Protein plugs and calculi are rare in chronic obstructive pancreatitis
- Chronic obstructive pancreatitis is the result of occlusion of main pancreatic duct
- Any obstructing lesion--a tumor, a scar resulting from trauma, papillary inflammation, a congenital structure--is a potential cause
- Fibrosis is accompanied by uniform acinar atrophy
- Exocrine insufficiency ensues, but it's partially reversible if the obstruction is removed

CLINICAL MANIFESTATIONS

The clinical picture of chronic pancreatitis is dominated by three features; ***abdominal pain, maldigestion, and diabetes (loss of exocrine and endocrine pancreatic function)***. The pain is localized to the upper abdomen, with radiation to subcostal regions and to the back. The pain is aggravated by meals and improves with fasting.

When more than 90% of exocrine pancreatic function is lost, maldigestion and malabsorption ensue. This is manifested by steatorrhea (fat malabsorption) associated with diarrhea and bloating, azotorrhea (protein malabsorption) and progressive weight loss. These patients frequently present with loss of adipose tissue, judged by hanging skin folds, and more objectively by demonstrating that the skin fold at the mid-triceps is less than 8 mm in males and less than 12 mm in females. Latent fat-soluble vitamin deficiency (vitamins A, D, E and K) in addition to deficiencies of magnesium, calcium and essential fatty acids may occur and are closely related to dysfunction of fat digestion. Endocrine insufficiency presenting as diabetes mellitus may present at the same time as exocrine insufficiency or a few years later.

COMPLICATIONS

- Pseudocyst
- Common Bile Duct Obstruction
- Pancreatic Ascites
- Pancreatic Pleural Effusion
- Splanchnic Venous Obstruction

Pancreatic pseudocyst

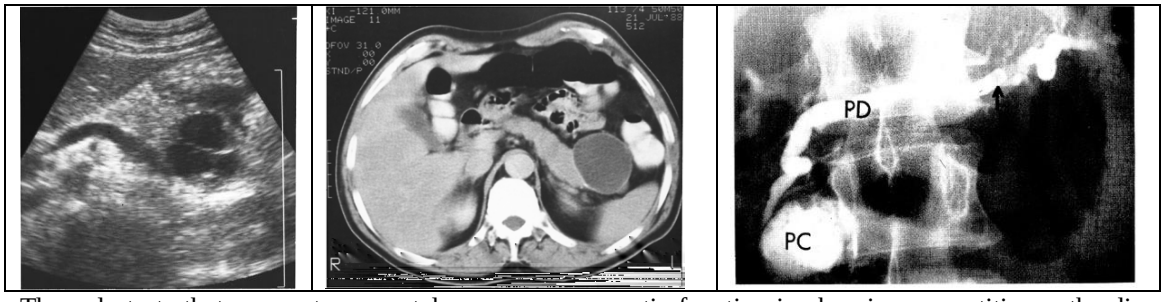
Pancreatic pseudocyst is localized fluid collection occurring within a pancreatic mass or in the peripancreatic spaces following acute or chronic pancreatitis.

Pancreatic ascites: Pancreatic ascites results from the leakage of pancreatic juices into the peritoneal cavity through a fistula or ruptured pseudocyst. It presents with gradually increasing massive ascites, high levels of amylase, abdominal pain and weight loss. Painful areas of subcutaneous fat necrosis result from the high levels pancreatic lipase.

Common bile duct stricture: Common bile duct compression is another manifestation of chronic pancreatitis. As the distal common bile duct traverses the head of the pancreas, it may be narrowed secondary to inflammation, with edema or fibrosis of the gland.

DIAGNOSTIC AND RADIOGRAPHIC EVALUATION

Radiological evidence such as calcification (in up to 30%) seen exclusively in the ductal system on plain radiographic abdominal films, by ultrasonography or on computerized tomography suggests chronic pancreatitis. Abnormalities of the ducts associated with chronic pancreatitis can also be demonstrated by ERCP. In severe disease there is narrowing and dilation of ducts, stenosis and filling of side ductules. Examination may reveal a tortuous main duct containing stones or protein plugs, or obstruction of the CBD.



The only tests that appear to accurately measure pancreatic function in chronic pancreatitis are the direct tube tests that measure the response of the pancreas to various stimuli. The commonest manifestation is a decreased bicarbonate concentration (<50 mEq/L) and decreased volume of secretion.

Tests of pancreatic function

- Measurement of pancreatic exocrine function: The severity of maldigestion, its contribution to weight loss, & efficacy of pancreatic enzymes can be assessed
- Pancreatic function may be inferred by direct measurement of the components of pancreatic secretion
- Enzyme activity may be estimated by the ability of the pancreas to cleave a given substance
- Pancreatic integrity may be reflected by the level of pancreatic enzymes or hormones secreted in the bloodstream or by recovering enzymes from the stool
- Pancreatic dysfunction can be appreciated by the amount of undigested nutrients recovered in the stool

1. Invasive Tests
   - The Secretin Test
   - The Lundh Test
2. Noninvasive Tests
   - The NBT-PABA Test (Bentiromide Test)
   - Fecal Fat

TREATMENT

The ultimate goals of treatment in chronic pancreatitis are to alleviate pain, maintain adequate nutritional status, and reduce symptoms associated with steatorrhea such as abdominal pain, bloating and diarrhea.

Pain management: Abstinence from alcohol may decrease the frequency and severity of painful attacks. Large meals with foods rich in fat should be avoided. Analgesics should be given prior to meals. Large doses of pancreatic extracts may reduce the frequency and severity of the pain. Patients with more severe disease, whose peak bicarbonate output is > 50 mEq/L, tend not to respond to this regimen. Patients with intractable pain who fail to respond to medical therapy may benefit from surgical intervention.

- When there is a dilated pancreatic duct with obstructive areas, ***longitudinal pancreatojejunostomy (modified Pustow operation)*** may relieve pain.
- An alternative to surgical drainage may be achieved by endoscopic insertion of an an endoprosthesis (stent) into the pancreatic duct.
- Octreotide, a long-acting somatostatin analogue, appears to decrease the pain of chronic pancreatitis.

Denervation: Denervation procedures aim at interrupting the transmission of pain from the pancreas through the sympathetic nerve fibers

- Since the majority of sensory nerves to the pancreas transverse the celiac ganglia and splanchnic nerves, both transthoracic splanchnicectomy and ganglionectomy have been used. They offer variable degrees of pain relief

Endoscopic Therapy

Considerable progress has been achieved in applying endoscopic techniques to the management of chronic pancreatitis

- It is possible to remove stones in the pancreatic duct, directly by use of a basket
- Stents may be placed in strictured areas of the pancreatic duct.
- In cases of chronic pancreatitis associated with pancreas divisum, endoscopic sphincterotomy of the minor papilla and stent placement across the papilla are successful in decreasing the frequency and severity of the attacks

Malabsorption: Administration of high-potency, enteric-coated pancreatic enzymes remains the main therapy for the treatment of steatorrhea in the majority of patients with idiopathic and alcoholic pancreatitis. This will improve fat digestion, increase absorption and allow weight gain, although it will not correct the steatorrhea completely. Azotorrhea is more easily reversed than steatorrhea, as trypsin is more resistant to acid inactivation than lipases.

Treatment with these enzymes is life long. Pancreatic enzymes are inactivated by pH 4 or below; hence, enteric-coated preparations may be appropriate. In patients who do not respond well, the use of histamine

H_2-receptor antagonists (cimetidine, ranitidine or famotidine) or antacids with meals may overcome the detrimental effect of acid.

Hypersensitivity to pancreatic enzymes has been reported in patients who have hypersensitivity to pork proteins. Hyperuricosuria may occur in patients receiving high doses of pancreatic extracts. It appears that oral pancreatic enzymes may bind to folic acid, thereby impairing its absorption. Fat-soluble vitamins (e.g., vitamins A and E) are poorly absorbed when steatorrhea exceeds 20 g of fat loss per day. Vitamin D and calcium malabsorption leads to osteopenia and tetany. Vitamin K is also malabsorbed, but bleeding is rare. This malabsorption is thought to be due to the failure of R factor to cleave from the vitamin B_{12}-intrinsic factor complex, resulting in failure to absorb vitamin B_{12}.

Diabetes

- Exogenous insulin, unopposed by glucagon (low or absent in pancreatic disease), may cause hypoglycemia, so tight glycemic control is potentially dangerous
- Since the development of diabetic vasculopathy is infrequent, it is unnecessary to maintain blood sugar within the normal range
- Plasma glucose value of 200 to 250 mg/dl throughout the day is a desirable target
- Therapy should control symptoms, principally polydypsia and polyuria and prevent the excessive loss of calories in the urine

Hereditary Pancreatitis and Shwachman's Syndrome

Hereditary Pancreatitis is probably inherited as an autosomal dominant condition with a bimodal incidence with peaks at about 10 and 17 years of age. Pancreatic calcification develops early, in the first decade, but in most respects, clinical course is similar to that of chronic pancreatitis of other causes. Children are from an affected family or have a structural abnormality in the pancreas or biliary tree (particularly pancreas divisum or choledochal cyst).

The association of pancreatic malabsorption, steatorrhoea, and failure to thrive, with metaphyseal dysplasia, neutropenia and other haematological abnormalities, is known as Shwachman's syndrome and accounts for a high proportion of children presenting with ***painless*** pancreatic insufficiency. It is probably inherited as an autosomal recessive condition. With appropriate dietary modification and enzyme supplements, the prognosis is good.

Complications of Pancreatitis

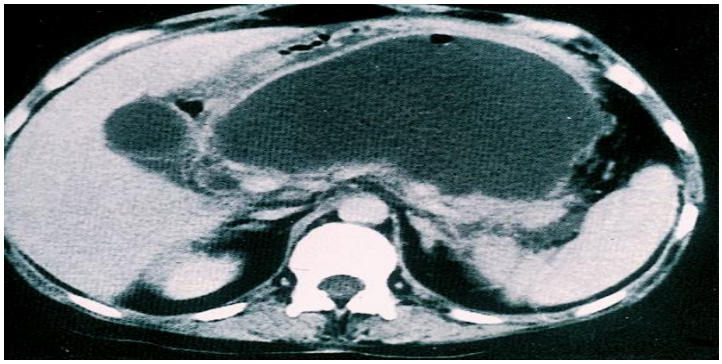
Edema of pancreatic head may be responsible for bile duct obstruction and cholestasis.

Pancreatic Pseudocyst

Pancreatic pseudocysts are a relatively common complication of pancreatitis, especially alcoholic pancreatitis. Pseudocysts are localized collections of fluid and contain concentrations of pancreatic enzymes; they are usually confined to the retroperitoneal areas by a fibrous membrane that is devoid of endothelial lining. They develop after 15% to 50% of all attacks of acute pancreatitis, many resolving spontaneously, and are seen in 20% to 40% of patients with chronic pancreatitis. They typically result from disruption of the pancreatic duct with extravasation of pancreatic enzymes. Pseudocysts are prone to cause complications, including hemorrhage, infection, pancreatic ascites, obstruction, and, infrequently, fistula formation to other viscera in the gastrointestinal (GI) tract.

Although outside the peritoneal cavity, pseudocysts may migrate to the mediastinum or pelvis, and associated pleural effusions also occur. Ultrasound has demonstrated that such cysts represent a very common complication although rarely it warrants intervention.

Most lesions of 5cm or less resolve spontaneously. When larger, pseudocysts may cause pain, gastrointestinal obstruction or a palpable mass.



CARCINOMA OF THE PANCREAS

Among cancers of the gastrointestinal tract, it is the third most common malignancy and the fifth leading cause of cancer-related mortality. Of pancreatic tumors, ***95% develop from the exocrine portion of the pancreas***, including the ductal epithelium, acinar cells, connective tissue, and lymphatic tissue. Approximately 75% of all pancreatic carcinomas occur within the head or neck of the pancreas. Approximately 15-20% occur in the body of the pancreas, and 5-10% occur in the tail. *Pancreatic cancer typically first metastasizes to regional lymph nodes, then to the liver and, less commonly, to the lungs*.

The male-to-female ratio for pancreatic cancer is 1.2-1.5:1.

History: Patients typically report the gradual onset of anorexia, malaise, nausea, and midepigastric abdominal pain. Significant weight loss is a characteristic feature of pancreatic cancer. ***Pain is the most common presenting symptom in patients with pancreatic cance***r. Back radiation of the pain indicating retroperitoneal invasion of the splanchnic nerve plexus by the tumor.

The most characteristic sign of head pancreatic carcinoma, is obstructive jaundice.

Patients with jaundice may have a palpable gallbladder (ie, Courvoisier sign) and may have evidence of excoriations from pruritus.

Causes: Overall, 40% of pancreatic cancer cases are sporadic in nature. Another 30% are related to smoking, and 20% are associated with dietary factors. Only 5-10% are hereditary. Fewer than 5% of all pancreatic cancers are related to chronic pancreatitis.

Lab Studies:

General laboratory studies

Tumor markers

- Carcinoembryonic antigen (CEA) is a high molecular weight glycoprotein found normally in fetal tissues. The reference range is $\leq$ 2.5 mg/mL. Only 40-45% of patients with pancreatic carcinoma have elevations in CEA levels.
- CA 19-9 is a murine monoclonal antibody originally made against colorectal cancer cells. The reference range of CA 19-9 is < 37 U/mL. In pancreatic carcinoma, 75-85% have elevated CA 19-9 levels. In the absence of biliary obstruction or benign pancreatic disease, a CA 19-9 value greater than 100 U/mL is highly specific for malignancy, usually pancreatic.

Imaging Studies:

Computed tomography scan: Standard abdominal CT scan can detect 70-80% of pancreatic carcinomas. CT scans can be used to direct fine-needle aspiration of masses.

Percutaneous ultrasound: Percutaneous abdominal ultrasonography is useful for patients with pancreatic cancer who present with jaundice, by detecting intrahepatic bile duct dilation/extrahepatic biliary obstruction.

Cholangiopancreatography (MRCP) should usually be performed to definitively diagnose the source of extrahepatic obstruction.

Endoscopic ultrasound: EUS has detection rates of 99-100% for pancreatic carcinomas.

Endoscopic retrograde cholangiopancreatography: Brush cytology and forceps biopsy at the time of ERCP have been used to histologically diagnose pancreatic carcinoma.

Magnetic resonance imaging

Histologic Findings: 80% are adenocarcinomas of the ductal epithelium. Only 2% of tumors of the exocrine pancreas are benign.

TREATMENT: ***The only therapy that has definitively been shown to increase the survival of patients with pancreatic cancer is surgical resection.*** The mean survival for patients with unresectable disease remains 4-6 months.

Chemotherapy

- Pancreatic carcinoma has been markedly resistant to chemotherapeutic regimens, either alone or in combination therapy. The most active agents have been 5-fluorouracil (5-FU) and the more recently ***gemcitabine***.

Surgical Care: Only 20% of patients present with resectable disease.

Pancreaticoduodenectomy (Whipple operation)

- The standard operation for carcinoma of the head of the pancreas is a pancreaticoduodenectomy (ie, Whipple procedure). This operation involves en bloc resection of the pancreatic head; the first, second, and third portions of the duodenum; the distal antrum; and the distal common bile duct.
- The patient's gastrointestinal tract is reconstructed with a gastrojejunostomy.
- The common bile duct and residual pancreas are anastomosed into a segment of small bowel.
- A more recent variation of the operation spares the pylorus, allowing for a more natural physiologic emptying of the stomach. Some surgeons prefer total pancreatectomy to avoid the risks of anastomotic leaks and pancreatic fistulas. This has the disadvantage of leaving the patient with brittle diabetes postoperatively.

ENDOCRINE PANCREATIC TUMOURS

Subsequent to initial description of insulinoma syndrome, 4 other classic pancreatic endocrine tumor syndromes have been described. The first is Zollinger-Ellison syndrome (also termed gastrinoma syndrome); second types comprise a group of 3 tumor syndromes, termed Verner-Morrison syndrome, WDHA (watery diarrhea, hypokalemia, and achlorhydria) syndrome, and pancreatic cholera (also termed [VIP]–releasing tumor or VIPoma); The third is glucagonoma syndrome. The fourth is somatostatinoma syndrome.

The cells in pancreatic endocrine neoplasms are termed amine precursor uptake and decarboxylation (APUD) cells because they have a high amine content, are capable of amine precursor uptake, and contain an amino acid decarboxylase. The tumors arise from APUD stem cells, which are pluripotential neuroendocrine cells located within the ductular epithelium of the exocrine pancreas and elsewhere in the distal foregut

Insulinoma*:* Insulinomas are insulin-secreting tumors associated with the Whipple triad. The triad includes (1) symptoms of fasting hypoglycemia, (2) documented fasting hypoglycemia with a serum glucose < 50 mg/dL, and (3) relief of hypoglycemic symptoms after glucose administration (Hypoglycemic symptoms typically occur when glucose levels are < 50 mg/dL; concurrent serum insulin levels often exceed 25 mU/mL).

Gastrinoma: The classic triad of Zollinger-Ellison syndrome includes (1) severe gastrointestinal ulcerative disease, (2) gastric acid hypersecretion, and (3) nonbeta islet cell tumors of the pancreas (Zollinger, 1955). Abdominal pain and peptic ulceration of the upper gastrointestinal tract are the most common symptoms and are observed in 90-95% of patients with Zollinger-Ellison syndrome. (Fasting serum gastrin test: Levels greater than 200 pg/mL are suggestive of gastrinoma, and levels greater than 1000 pg/mL are virtually diagnostic of gastrinoma)

VIPoma: Symptoms of ***Verner-Morrison or WDHA syndrome*** (ie, watery diarrhea, hypokalemia, achlorhydria, acidosis) are the result of the physiologic effects of overproduction of VIP by pancreatic endocrine neoplasms. <u>The primary symptom of patients with a VIPoma is watery diarrhea.</u> Abdominal cramps are common, and flushing episodes may occur. (The level of serum VIP ranges from 225-1850 pg/mL. The normal serum VIP level is <170 pg/mL)

Glucagonoma: Glucagonomas secrete excessive amounts of glucagon and cause a syndrome characterized by <u>dermatitis, stomatitis, weight loss, and anemia</u> The dermatitis associated with glucagonoma syndrome is termed ***necrolytic migratory erythema***. This dermatitis is characterized by the cyclic migration of

erythematous patches that spread serpiginously and then reveal central points of healing. Patients with glucagonoma syndrome have secondary thromboembolic phenomena; therefore, they may have a history consistent with deep venous thrombosis and/or pulmonary embolism. (Serum glucagon levels >1000 pg/mL are diagnostic, levels less than 150 pg/mL are normal)

Somatostatinoma: Patients often have ***diabetes mellitus***, which is probably secondary to the inhibitory action of somatostatin on insulin and glucagon release. Inhibition of the action of cholecystokinin by somatostatin causes relative biliary stasis and the formation of **gallbladder calculi**. Patients may also have diarrhea and/or steatorrhea.

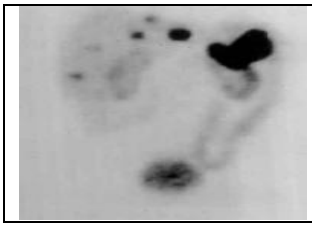
MEN 1 syndrome, or **Wermer syndrome**, is an autosomal dominant disorder. The syndrome is characterized by **hyperparathyroidism, adenomas of pituitary, and neoplasms of endocrine pancreas**. In pituitary; prolactin-secreting tumors are most common type.The pancreatic tumors in these patients tend to be multiple and usually secrete multiple hormonally active products.

Imaging Studies:

High-resolution contrast-enhanced spiral CT scanning with thin sections is the initial imaging technique used to localize most neoplasms of the endocrine pancreas.

Magnetic resonance imaging

Somatostatin receptor scintigraphy: Radiolabeled octreotide is a somatostatin analogue that preferentially binds to somatostatin receptors; the intravenous administration of octreotide can be used to identify such tumors.



Neoplasms of the endocrine pancreas. Octreotide scan (anterior view) in a patient with a pancreatic endocrine tumor. The large pancreatic-tail neoplasm is seen retaining tracer in the patient's left upper quadrant. Several tracer-enhancing hepatic metastases are seen in the patient's right upper quadrant and epigastrium. Tracer is also seen in the bladder following renal excretion (round density in the hypogastrium)

Medical Care:

- Upon initial presentation, patients with insulinoma may require immediate potassium replacement and dextrose administration.
- The primary initial concern in the treatment of a patient who presents first with VIPoma-associated diarrhea is the replacement of volume losses and the correction of acid-base and electrolyte abnormalities.
- Patients with glucagonomas requires preoperative control of hyperglycemia.

Surgical Care:

Surgical management of the primary tumor is similar for the different types of pancreatic endocrine neoplasms:

- Small benign lesions remote from the main pancreatic duct can be enucleated.
- Tumors deep in the substance of the pancreatic gland, and therefore close to the main duct, have ill-defined capsules, and tumors larger than 2 cm in diameter should be treated with regional pancreatectomy.
- Tumors in the tail of the pancreas can be managed with distal pancreatectomy
- Lesions in the head or uncinate process of the pancreas can be resected with pancreaticoduodenectomy.

PERIAMPULLARY CARCINOMA

Obstructive jaundice is the usual presenting feature, and ultrasound (especially endoscopic) or a CT scan may demonstrate the lesion. At ERCP, the endoscopic appearance is immediately suggestive of a malignant tumour at the ampulla, and the absence of extension along the pancreatic duct or bile duct helps in the distinction from an infiltrating pancreatic carcinoma or extension of a cholangiocarcinoma.

Biopsies, taken at endoscopy or ERCP, should confirm the diagnosis.

Ampullary neoplasms are usually papillary or solid tumours which invade locally. The usual histological pattern is of moderately well-differentiated adenocarcinoma.

Ampullary Carcinoma

The periampullary region is anatomically complex, representing the junction of 3 different epithelia, pancreatic ducts, bile ducts, and duodenal mucosa. Carcinomas originating in the ampulla of Vater by gross inspection can arise from 1 of 4 epithelial types, (1) terminal common bile duct, (2) duodenal mucosa, (3) pancreatic duct, or (4) ampulla of Vater. In general, ampullary cancers produce sialomucins, whereas periampullary tumors secrete sulfated mucins.

History: Patients with carcinoma of the ampulla of Vater often complain of anorexia, nausea, vomiting, ***jaundice***, pruritus, or weight loss, abdominal pain. Diarrhea may be associated with an absence of lipase in gut because of pancreatic duct obstruction.

Physical: Some patients might demonstrate a distended, palpable Courvoisier gallbladder (ie, palpable gall bladder in a patient with jaundice). *A rising bilirubin level due to obstructive jaundice often is the sole presenting symptom.*

Ultrasound of the abdomen is the initial study (dilation of these ducts essentially is diagnostic for extrahepatic obstruction).

CT scan often demonstrates a mass but is not helpful in differentiating ampullary carcinoma from tumors of the head of the pancreas or periampullary region. Both CT scan and ultrasound findings can help reveal metastatic disease in the liver or regional lymph nodes

ERCP can show irregular pancreatic duct narrowing, displacement of the main pancreatic duct, destruction or displacement of the side branches of the duct, and pooling of contrast material in necrotic areas of tumor.

Lab Studies: Routine laboratory studies include a complete blood cell count, electrolyte panel, liver function studies (prothrombin time, bilirubin [direct and indirect], transaminases, alkaline phosphatase), CEA, and CA 19-9 (CA 19-9 and CEA is often is elevated in pancreatic malignancies and might have a role in assessing response to therapy or predicting tumor recurrence).

Staging: Martin proposed a 4-stage system, as follows:

- Stage I - Vegetating tumor limited to the epithelium with no involvement of the sphincter of Oddi
- Stage II - Tumor localized in the duodenal submucosa without involvement of the duodenal muscularis propria but possible involvement of the sphincter of Oddi
- Stage III - Tumor of the duodenal muscularis propria
- Stage IV - Tumor of the periduodenal area or pancreas, with proximal or distal lymph node involvement

Surgical Care: The standard surgical approach is pancreaticoduodenal resection (Whipple procedure). ***The procedure involves en bloc resection of the gastric antrum and duodenum; a segment of the first portion of the jejunum, gallbladder, and distal common bile duct; the head and often the neck of the pancreas; and adjacent regional lymph nodes.*** .

For patients with unresectable disease, endoscopic stenting to achieve biliary decompression is an appropriate palliative procedure.

NORMAL DUODENUM

The duodenum is approximately 25cm long and its configuration divides it into four parts: the duodenal bulb, and the descending, horizontal and ascending portions.

In the submucosa, and peculiar to the duodenum, are Brunner's glands. These mucus-secreting glands are most numerous in the first part of the duodenum. Paneth cells and cells of the APUD system are also found within the crypts.

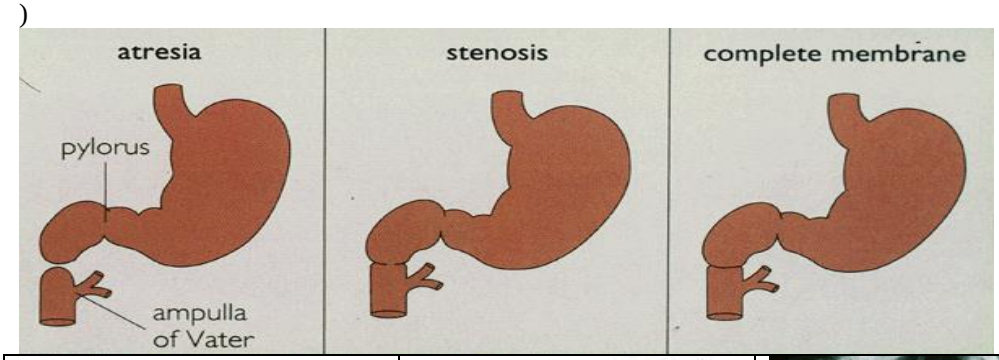
DUODENAL DIVERTICULA

Duodenal diverticula may be acquired or congenital. Acquired or Pseudodiverticula are the product of the scarring of chronic peptic ulceration in the proximal duodenum. Congenital examples typically arise from the second part of the duodenum; the ampulla of Vater is usually closely adjacent, and may lie within the diverticulum. There is a definite but unexplained asssociation between common bile duct stones and

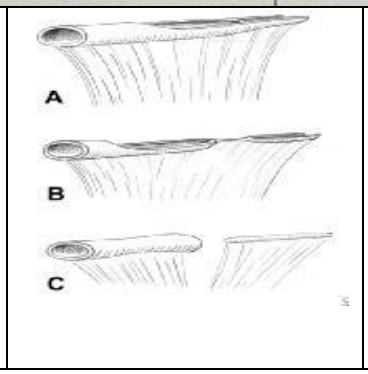
duodenal diverticula. Stasis within large and/or multiple diverticula of the duodenum. *Treatment is by choleduodenostomy*

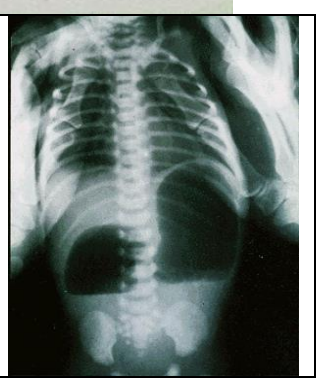
CONGENITAL DUODENAL OBSTRUCTION

Congenital obstruction of the duodenum varies from a simple stenosis or diaphragm partially obstructing the lumen, to a complete block with a gap between the two ends of bowel (duodenal atresia). The site of obstruction is distal to the ampulla of Vater in about 80% of cases. Vomiting, which occurs within a few hours of birth, is of bile-stained fluid. Its common with ***Down's syndrome***(25-33%). (Anomaly associated with down synd. are: 11 or 13 ribs, duodenal atresia / stenosis, tracheo-esophageal fistula, Hirschsprung dis)



Duodenal atresia. Types of duodenal recanalization anomalies. A. Diaphragm, B. Solid cord and atresia, C. Segmental absence. Dilatation of proximal normal segment in all.





The typical **double bubble' sign** with absence of distal abdominal gas may be seen on abdominal radiograph (*Other less common causes of the "double bubble" include annular pancreas, and peritoneal bands*). Obstetric ultrasound shows ***polyhydramnios (in 50%)***.

Management varies accordingly to the type of stenosis: Ladd's bands are lysed. Pure stenosis is opened longitudinally and closed transversely (Heineke-Mickulicz). Membranous stenosis is resected. ***Duodeno-duodenostomy is the procedure of choice*** for annular pancreas. Duodenojejunostomy has higher risk of long-term complications.

Annular pancreas: A congenital anomaly characterized by a ring of normal pancreatic tissue encircling and sometimes obstructing the descending part of the duodenum. The annulus represents the ventral part of the pancreas that remains fixed to the duodenum. In the extramural type, the annulus is drained by ducts running around the duodenum to join the main pancreatic duct. **Associated features with Annular pancreas are:** *Absent spleen, Duodenal stenosis, Ectopic spleen, Polysplenia, Situs inversus-abdominal, Small bowel atresia/ obstruction*.

INTESTINAL OBSTRUCTION

Mechanical obstruction may be within the lumen, within the bowel wall, or extrinsic (as in the case of adhesions and herniae), and it has to be differentiated from functional causes or pseudo-obstruction, and from the paralytic ileus.

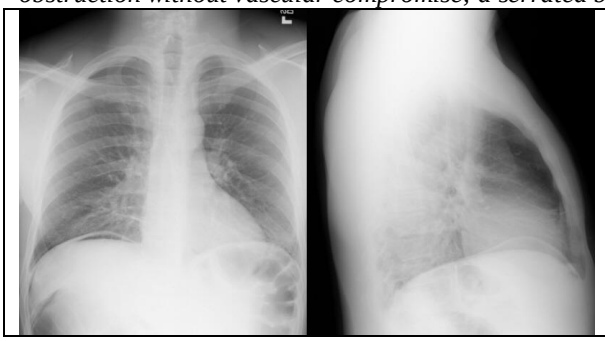
Causes: ***Postoperative adhesions*** can cause acute obstruction within 4 weeks; chronic obstruction may occur decades later. Other etiologies include malignant tumors (20%), hernias (10%), inflammatory bowel

disease (5%), volvulus (3%), and miscellaneous causes (2%). The causes of small bowel obstruction in pediatric patients include congenital atresia, pyloric stenosis, and intussusception.

Presentation: The associated clinical features vary according to the site of obstruction: if the obstruction is high, then pain and bilious vomiting with little distension will predominate; lower small bowel obstruction is more often associated with distension and faeculent vomiting. Peristalsis may be visible in thin patients until motility becomes impaired, and examination may demonstrate the cause of the obstruction.

The plain radiograph is usually confirmatory. ***Dilated small bowel loops with air fluid levels indicate SBO.*** Small bowel distension is differentiated radiologically from colonic distension by the *outlining of the valvulae conniventes by intestinal gas, and by the distribution of distended loops, which mainly occupy the centre of the abdomen*; in small bowel obstruction of mechanical cause there is usually little or no colonic gas. Absent or minimal colonic gas indicates SBO.

CT scanning is sometimes indicated and may reveals both the anatomical site of obstruction and its etiology. *Obstruction is present if the small bowel loop is greater than 2.5 cm in diameter dilated proximal to a distinct transition zone of collapsed bowel less than 1 cm in diameter. A smooth beak indicates simple obstruction without vascular compromise; a serrated beak may indicate strangulation.*



Free intraperitoneal air under the right hemidiaphragm suggesting perforation

SMALL BOWEL CARCINOMA

Adenocarcinomas of the small bowel constitute less than 2% of all gastrointestinal malignancies. The duodenum is most often affected, and 90% of carcinomas occur within 20cm of the ligament of Treitz.

A number of conditions predispose to intestinal carcinoma, the most important of which are *coeliac disease and familial adenomatous polyposis, Peutz-Jeghers syndrome and Crohn's disease*.

Presentation is usually in the 6th and 7th decades. Bleeding is common. The diagnosis may be apparent from barium studies or CT scan.

Macroscopically, a ***polypoid pattern*** is commonest, and this often leads to bleeding or intussusception, but sessile, stenosing, and ulcerating tumours are also seen. The histological appearances are those of gastrointestinal adenocarcinoma.

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome is inherited as an ***autosomal dominant condition***. ***Multiple hamartomatous polyps*** occur throughout the gastrointestinal tract and are accompanied by pigmentation of the lips and buccal mucosa. Symptoms are relatively unusual, but are most likely from small bowel polyps which may ***bleed or cause obstruction or intussusception***. Histologically, the lesions have a lobulated surface with a core of muscle fibres (derived from the muscularis mucosae) which arborizes around the crypts and mucosal glands, thinning out towards the surface. ***There is an associated increased risk of malignancy in the small intestine and other sites***.

MECKEL'S DIVERTICULUM

The Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract, and affects approximately 2% of normal caucasians.

Meckel's diverticulum is a true intestinal diverticulum that results from the failure of the vitelline duct to obliterate during the fifth week of fetal development. It arises from the antemesenteric border of the ileum, 50-100cm proximal to the ileocaecal valve. It is usually about 2-5 cm in length and wide-mouthed. In approximately 50% of cases, the mucosa is ileal, but duodenal, colonic, pancreatic, and particularly gastric

mucosa may be present. Ectopic tissue, found in approximately 50 percent of cases of Meckel's diverticulum, is most commonly gastric in origin.
Most remain asymptomatic but bleeding and intestinal obstruction, do occur. Bleeding is usually the result of ulceration in gastric mucosa and this allows the possibility of diagnosis by scintigraphy which will usually identify tissue containing parietal cells.
Diagnosis: The diagnosis cannot be made with plain radiographs, and arteriography is not always diagnostic because arterial supply is not always abnormal. Contrast studies such as upper gastrointestinal series with small bowel follow-through are of limited value because the layers of barium-filled intestine will obstruct the view of the diverticulum. Computed tomographic scans are often nonspecific but occasionally helpful. ***The most useful method of detection of a Meckel's diverticulum is technetium-99m pertechnetate scanning. However, the technetium scan depends on uptake by heterotopic gastric mucosa.*** Not all diverticula contain ectopic tissue; because complications such as bleeding are often caused by ectopic gastric tissue, diagnosis may be assisted in symptomatic cases. The accuracy of the scan can be improved with the use of pentagastrin. Cimetidine improves diagnostic accuracy by inhibiting the intraluminal release of technetium, and glucagon does so as an antiperistaltic.
Complications and Treatment: ***Bleeding is the most common complication but*** obstruction, intussusception, diverticulitis and perforation may also occur, especially in adults. Intestinal obstruction is a dangerous complication, since torsion and gangrene can be fatal if early operation is not done. A bleeding diverticulum with an indurated area in the adjacent ileum requires resection of this section of the bowel and the diverticulum. A bleeding diverticulum without ileal induration requires only resection of the diverticulum. Small, asymptomatic diverticula encountered incidentally at laparotomy need not be removed. Whenever a normal appendix is found during an exploration for appendicitis, Meckel's diverticulum should be suspected.

Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu Syndrome)

It is an **autosomal dominant** condition with high penetrance. Lesions usually appear in childhood. *Telangiectases are commonly found on the lips, tongue, and oral mucosa and less often on conjunctivae, ears, and digits.*
Lesions in the gastrointestinal mucosa often lead to a low-grade iron deficiency, and may be responsible for troublesome haemorrhage, because their number and extensive distribution throughout the intestine makes a surgical approach impractical.

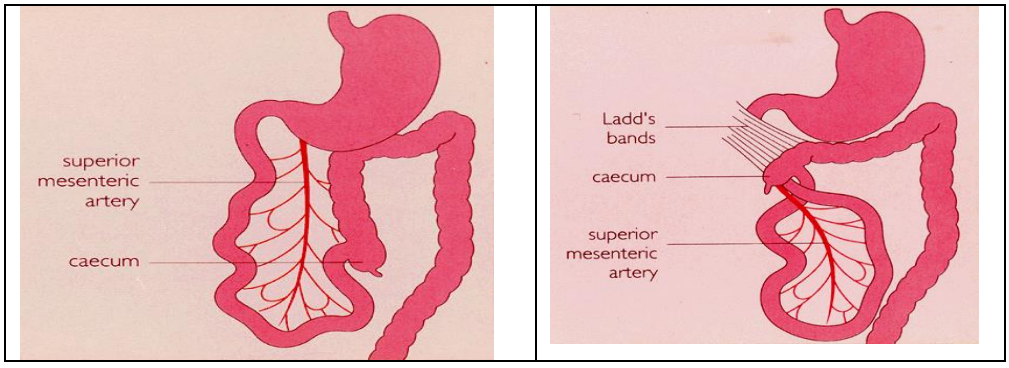
CARCINOID TUMOURS

Carcinoid tumours occur most often in the ileum and appendix, and are usually chance findings at appendicectomy. The tumour arise from the argentaffin of Kulchitzky cells which lie deep in the crypts of Lieberkühn and are derived from neural crest tissue. Like other APUD tumours, carcinoids contain numerous neurosecretory granules.
Large tumours may cause obstruction or intussusception, but symptoms are otherwise rare unless ***metastases to the liver are responsible for the carcinoid syndrome (seen only in 1% of cases)***. This syndrome is due to the excessive production of a variety of gut hormones - particularly *5-hydroxytryptamine, but also histamine, kinins, catecholamines, and prostaglandins*.
Typically, patients present with episodic ***facial flushing, watery diarrhoea, and abdominal cramps, and may have pellagra-like skin lesions as a result of niacin deficiency***. Involvement of the right side of the heart is also well recognized, and there may be bronchial lesions. Auscultation may indicate pulmonary and/or tricuspid valve lesions.
Macroscopically, the primary tumours are generally small and extra-appendiceal; and the liver may be almost completely replaced by metastases. Intestinal biopsy shows solid groups of regular polyhedral cells spreading through the submucosa and muscle; the specific neuroendocrine characteristics may be determined from immunocytochemical stains.
Surgical resection is the standard curative modality. If the primary tumor is localized and resectable, 5-year survival rates are excellent (70%-90%). Radiation therapy has a minor role in patients with regionally unresectable disease and may palliate the pain of bone metastasis. ***Patients with carcinoid syndrome can usually be effectively palliated by injections of somatostatin analogue***.

MALROTATION OF THE GUT

During embryological development, the gastrointestinal tract undertakes a series of movements, mainly during the 6th week of intrauterine life. Rotation of the midgut occurs in an anticlockwise direction through 270°, about an axis formed by the superior mesenteric artery, which thus divides the gut into pre- and post-arterial segments.

If this process is incomplete or abnormal, or if it fails completely, intestinal symptoms may result. Complete **failure of rotation** is uncommon and causes the post-arterial segment (the caecum and terminal ileum) to lie on the left side of the body. The duodenum then runs vertically on the right of the superior mesenteric artery, with the small intestine lying to the right of the abdominal cavity; the ileum enters the right of the caecum. **Incomplete or malrotation** is commoner: the caecum is left at the splenic, or more often, at the hepatic level.



Malrotation frequently causes abnormalities of fixation, which can result in neonatal volvulus, but more often it causes recurrent abdominal pain in childhood, culminating in obstruction from intestinal volvulus or fibrous bands.

Up to 70% of children with intestinal malrotation also have another congenital (present at birth) malformation. These include the following:

- Abdominal wall defects and digestive system abnormalities, including gastroschisis, omphalocele, congenital diaphragmatic hernia, intestinal atresia, Hirschsprung's disease, gastroesophageal reflux, intussusception, and anorectal malformations.
- Cardiac (heart) abnormalities
- Abnormalities of the liver or spleen

Surgical repair is performed as soon as possible. The bowel is untwisted and checked carefully for damage. If the intestine is healthy, an operation called the **Ladd's procedure is performed to repair the malrotation.** Since the appendix is not in its normal anatomic location, and it would be difficult to diagnose a future appendicitis, it is usually removed at this time.

INTUSSUSCEPTION

It occurs when one part of bowel invaginates (intussusceptum) into an adjacent section (intussuscipiens) and results in intestinal obstruction and venous compression which if uncorrected it can result in arterial insufficiency and necrosis. Peak incidence is between 6 and 9 months. Frequently occurs after a recent upper respiratory infection, by Adenovirus type 3 that causes a reactive lymphoid hyperplasia that act as lead point (of Peyer's patch). 5% are due to Meckel's diverticulum, polyps, Henoch's Schonlein purpura, hematoma, lymphoma, foreign bodies, and duplications. **Commonest site involved is the ileocaecal junction**

Three types of intussusception can occur:

- Ileocolic – the small intestine invaginates into the right colon; this is the most common intussusception
- Ileoileal – the small intestine invaginates into itself
- Colocolic – the large intestine invaginates into itself

Clinical features

- Intermittent colicky abdominal pain and vomiting
- Passage of blood - 'red currant jelly' per rectum
- Sausage shaped abdominal mass
- Diagnosis confirmed with water soluble contrast enema or ultrasound

Treatment

- Resuscitation with intravenous fluids and nasogastric tube
- Attempt reduction with air or contrast enema under radiological guidance
- Failure of hydrostatic reduction requires urgent operation through a **right lower quadrant horizontal incision**. The intussusception is reduced by pushing on the distal bowel like a tube of toothpaste rather than pulling the proximal bowel
- If peritonitis, shock or failed reduction requires surgery
- If bowel necrosis requires resection with primary anastomosis

Meconium Ileus

Meconium Ileus (MI) is the earliest clinical manifestation of CF and occurs in approximately 10-15% of neonates with CF2. It occurs due to the increased viscidity of the meconium associated with its high protein and low carbohydrate content. The most common presentation is abdominal distension with or without bilious vomiting and a failure or delay in passing meconium after birth. Occasionally it is diagnosed prenatally on ultrasound scans.

MI can be categorised as either simple or complicated. Complicated MI includes those with volvulus, atresia, perforation or giant cystic peritonitis. Abdominal x-ray is likely to show *several loops of dilated small bowel without air-fluid levels; and possibly a soap bubble appearance in the right lower quadrant, the so-called* ***Neuhauser sign***. Complicated cases may present with greater bowel dilatation and air-fluid levels. Perforation or giant cystic meconium peritonitis calcifications are often noted. Most babies then undergo barium enema to confirm the diagnosis. Since the publication of Noblett's report on the use of gastrograffin enemas (GGE) in the treatment of simple MI, non-operative management has become increasingly important. All neonates with complicated and those with 2 unsuccessful GGE require operative intervention.

The surgical management options of MI are varied and include:

1) Enterotomy/appendicectomy with irrigation
2) Enterostomy with/out resection
3) Resection with primary anastomosis

Treatment is Enterotomy and irrigation for simple MI as they had a 20% leak rate with Bishop-Koop (End-to-distal side ileal anastomosis with a distal end ileostomy which allows post-operative irrigation of the meconium pellets) or Santulli (Side-to-end anastomosis with a proximal enterostomy after resection of the dilated segment of bowel) ileostomies.

Acute Mesenteric Ischemia

AMI is a syndrome in which inadequate blood flow through the mesenteric circulation causes ischemia and eventual gangrene of the bowel wall. The syndrome can be classified generally as arterial or venous disease. Arterial disease can be subdivided into nonocclusive mesenteric ischemia (NOMI) and occlusive mesenteric arterial ischemia (OMAI).

Practically, AMI is divided into 4 different primary clinical entities: acute mesenteric arterial embolus (AMAE), acute mesenteric arterial thrombosis (AMAT), NOMI, and mesenteric venous thrombosis (MVT). OMAI includes both AMAE and AMAT.

Anatomy

Typically the celiac artery (CA) supplies the foregut, hepatobiliary system, and spleen; the superior mesenteric artery (SMA) supplies the midgut (ie, small intestine and proximal mid colon); and the inferior mesenteric artery (IMA) supplies the hindgut (ie, distal colon and rectum. Venous drainage is through the superior mesenteric vein (SMV), which joins the portal vein.

AMI arises primarily from problems in the SMA circulation or its venous outflow. Collateral circulation from the CA and IMA may allow sufficient perfusion if flow in the SMA is reduced because of occlusion,

low-flow state (NOMI), or venous occlusion. The inferior mesenteric artery seldom is the site of lodgment of an embolus. Only small emboli can enter this vessel because of its smaller lumen. When lodgment occurs, the embolus lodges at the site of division of the inferior mesenteric artery into the left colic, sigmoidal, and superior hemorrhoidal arteries. In such instances, collateral flow from the middle colic and middle hemorrhoidal arteries (through the vascular arcades of the inferior mesenteric artery distal to the embolus) may sustain the perfusion of the left colon.

Pathophysiology: Embolic phenomena account for approximately 50% of all cases, arterial thrombosis for about 25%, NOMI for roughly 20%, and MVT for less than 10%. Hemorrhagic infarction is the common pathologic pathway whether the occlusion is arterial or venous.

The mucosal barrier becomes disrupted as the ischemia persists, and bacteria, toxins, and vasoactive substances are released into the systemic circulation. This can cause death from septic shock, cardiac failure, or multisystem organ failure before bowel necrosis actually occurs. As hypoxic damage worsens, the bowel wall becomes edematous and cyanotic. Fluid is released into the peritoneal cavity, explaining the serosanguinous fluid sometimes recovered by diagnostic peritoneal lavage. Bowel necrosis can occur in 8-12 hours from the onset of symptoms. Transmural necrosis leads to peritoneal signs and heralds a much worse prognosis.

NOMI is precipitated by a severe reduction in mesenteric perfusion, with secondary arterial spasm from such causes as cardiac failure, septic shock, hypovolemia, or the use of potent vasopressors in patients in critical condition.

History: The most important finding is pain disproportionate to physical examination findings. Typically, pain is moderate to severe, diffuse, nonlocalized, constant, and sometimes colicky.

Onset varies from type to type. Nausea and vomiting are found in 75% of affected patients. Anorexia and diarrhea progressing to obstipation are also common. Abdominal distension and GI bleeding are the primary symptoms in up to 25% of patients. Pain may be unresponsive to narcotics. As the bowel becomes gangrenous, rectal bleeding and signs of sepsis (eg, tachycardia, tachypnea, hypotension, fever, altered mental status) develop. This syndrome has a catastrophic outcome if not properly and rapidly treated.

Physical: Early in the course of the disease, in the absence of peritonitis, physical signs are few and nonspecific. Tenderness is minimal to nonexistent. Stool may be guaiac positive. Peritoneal signs develop late, when infarction with necrosis or perforation occurs. Signs reflecting risk factors for AMI may be noted. Patients with embolic AMI may have atrial fibrillation or heart murmurs. Those with thrombotic AMI or NOMI may have an abdominal murmur or a scar from a recent abdominal aortic repair with or without reimplantation of the SMA. Those with MVT may have evidence of tumor, cirrhosis, DVT, or recent abdominal surgery.

Lab Studies:

- Currently, no serum marker is sensitive or specific enough to establish or exclude the diagnosis of AMI.
- CBC count may be within the reference range initially, but the WBC count eventually rises as the disease progresses. Leukocytosis and/or leftward shift are observed in over 50% of cases. The hematocrit is elevated initially from hemoconcentration due to third spacing, but it decreases with GI bleeding.
- Amylase levels are moderately elevated in over 50% of patients.
- Phosphate levels were initially thought to be sensitive, but later studies showed a sensitivity of only 25-33%.
- Lactate is elevated late in the clinical course. Levels that are persistently within the reference range strongly indicate a diagnosis other than AMI (sensitivity 96%, specificity 60%).

Imaging Studies:

Plain abdominal films

- Plain films are warranted to exclude identifiable causes of abdominal pain such as perforated viscus with free intraperitoneal air.
- Positive findings are usually late and nonspecific and include ileus, small bowel obstruction, edematous/thickened bowel walls, and paucity of gas in the intestines. More specific signs, such as

pneumatosis intestinalis, ie, submucosal gas; thumbprinting of bowel wall; and portal vein gas, are late findings.

Computed tomography scan

- This technique has a sensitivity of 71% and specificity of 92%. It is not as useful as angiography, but it is noninvasive and preferred for MVT (90% sensitivity).
- CT scan may show pneumatosis intestinalis, portal vein gas, bowel wall and/or mesenteric edema, abnormal gas patterns, thumbprinting, and streaking of mesentery. Bowel wall edema is the most common finding on CT scan.

Angiography

- Sensitivity is reported to be 88% for AMI.
- An embolus appears as a sharp cutoff of flow near the origin of the middle colic artery. Thrombus appears as a more tapered occlusion near the origin of the SMA. NOMI is characterized by narrowing of the origins of multiple SMA branches, alternating dilation and narrowing of the intestinal branches (ie, "string of sausages" sign), spasm of the mesenteric arcades, and impaired filling of the intramural vessels.
- Angiography is actually a second-line study in patients with a strong suspicion of MVT because false-negative findings are common. Findings with MVT include thrombus in the SMV, reflux of contrast into the aorta, prolonged arterial phase with accumulation of contrast and thickened bowel walls, extravasation of contrast into bowel lumen, and filling defect in the portal vein or complete lack of venous phase.

Ultrasonography

- Duplex sonography studies are highly specific (92-100%) but not as sensitive (70-89%) compared to angiography. The examination cannot detect clots beyond the proximal main vessels nor can it be used to diagnose NOMI. Ultrasound is considered a second-line study for AMI.

Magnetic resonance imaging and/or magnetic resonance angiography

- MRI and MRA provide findings similar to CT scan in AMI. Sensitivity of MRA is 100% and specificity is 91%. MRA is particularly effective for evaluating MVT.

Other Tests:

- Intraoperative fluorescein administration: During laparotomy, 1 g of fluorescein is infused. Viable bowel fluoresces brightly under a Wood lamp.
- ECG may show myocardial infarction or atrial fibrillation.

TREATMENT

Medical Care: Make all efforts to improve patients' cardiovascular status. Provide oxygen at 100% or by intubation if needed. Fluid resuscitation is accomplished with isotonic sodium chloride solution, and blood products are provided as needed. Adequacy of resuscitation can be monitored by urinary output, central venous pressure, or Swan-Ganz pressure monitoring. Insert a nasogastric tube, and optimize cardiac status by treating arrhythmia, CHF, or myocardial infarction. Start broad-spectrum antibiotics early. Provide pain control while maintaining stable blood pressure.

Angiographically infused papaverine

- Papaverine infused in the affected vessel is useful for all arterial forms of AMI. It relieves reactive vasospasm in occluded arterial vessels and is the only treatment for NOMI other than resection of gangrenous bowel.

Angiographically infused thrombolytics

- Thrombolytics infused through the angiogram catheter can be a life-saving therapy for selected patients with embolic AMI.
- Bleeding is the main complication. Thrombolytic administration is risky and should only be undertaken if peritonitis or other signs of bowel necrosis are absent. It must be started within 8 hours of symptom onset.
- If symptoms do not improve within 4 hours or if peritonitis develops, stop the infusion and perform surgery.

Angioplasty after thrombolysis

- A very select group of patients who have atherosclerotic plaques at the origin of the SMA after thrombolysis are eligible for angioplasty.

Heparin for MVT

- Heparin anticoagulation is the main treatment for MVT.
- Administer heparin as a bolus of 80 U/kg, not to exceed 5000 U, and then as an infusion at 18 U/kg/h until full conversion to oral warfarin. Appropriate monitoring of anticoagulation using activated partial thromboplastin time (aPTT) is mandatory.

Surgical Care: Prompt laparotomy is indicated in patients with suspected AMI when expeditious angiography is not available. A second-look procedure is indicated whenever bowel of questionable viability is not resected.

Preoperative care: Stabilize patients using IV fluids, antibiotics covering the colonic flora, nasogastric tube decompression, and bladder catheterization, with heparin or papaverine administered as indicated. Blood should be available.

Operative care: All types of AMI may require resection of necrotic bowel if signs of peritonitis develop. Differentiation of nonviable versus viable bowel can be enhanced by intraoperative fluorescein use. Because of fat absorption, fluorescein can be used only once. Most patients can benefit from a 24- to 48-hour second-look operation to assess for viability of remaining bowel.

Gastrointestinal stromal tumors

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. Overall, GISTs are third in prevalence after adenocarcinomas and lymphomas among the histologic types of gastrointestinal tract tumors.

Historically, these lesions were classified as leiomyomas or leiomyosarcomas because they possessed smooth muscle features when examined under light microscopy but it lacks ultrastructural and immunohistochemical features characteristic of smooth muscle differentiation, as are seen in leiomyomas and leiomyosarcomas. Therefore, the determination was made that GISTs do not arise from smooth muscle cells, but from another mesenchymal derivative such as the progenitors of spindle and epithelioid cells and the actual cell of origin of GISTs is a pluripotential mesenchymal stem cell programmed to differentiate into the interstitial cell of Cajal.

Pathophysiology: They are submucosal lesions, which most frequently grow endophytically in parallel with the lumen of the affected structure. Approximately 50-70% of GISTs originate in the stomach. The small intestine is the second most common location, with 20-30% of GISTs arising from the jejunoileum. Less frequent sites of occurrence include the colon and rectum (5-15%) and esophagus (<5%).

Outcomes in patients with GISTs are highly dependent on the clinical presentation and the histopathological features of the tumor. The overall 5-year survival rate ranges from 28-60%. This can be stratified for patients presenting with localized primary disease and those presenting with metastatic or recurrent disease. The median survival rate in the former group is 5 years, while the median survival rate in the latter group is approximately 10-20 months.

Tumors can be classified into high- and low-risk categories based on size and mitotic activity.

GISTs are most commonly diagnosed in 55-65 yrs.

Causes:

- Gain-of-function mutations in exon 11 of the c-*kit* proto-oncogene are associated with most GISTs. These mutations lead to constitutive overexpression and autophosphorylation of c-Kit, provoking a cascade of intracellular signaling that propels cells toward proliferation or away from apoptotic pathways.
- The c-*kit* proto-oncogene is located on chromosome arm 4q11-12. It encodes KIT, which is a transmembrane tyrosine kinase.
- A small minority of GISTs are associated with hereditary syndromes.
    - GISTs occur with a higher than expected frequency in patients with type 1 neurofibromatosis.

- GISTs are also a feature of the rare Carney triad, which is observed predominantly in young women. This triad consists of epithelioid gastric stromal tumors, pulmonary chondromas, and extra-adrenal paragangliomas.

Histologic Findings: The morphologic features that appear to be most predictive of outcome and biological behavior are tumor size and the mitotic rate. Unfortunately, no absolute determinations can be made because even small lesions with low mitotic rates can metastasize or behave in a locally aggressive fashion. GISTs typically stain intensely for the CD117 molecule, which is an epitope of KIT. In contrast, desmoids, schwannomas (S-100–positive, KIT-negative), leiomyomas, and leiomyosarcomas (desmin-positive, KIT-negative) do not. In GISTS, according to Fletcher et al, CD117 appears diffusely in the cytoplasm in a punctate or Golgilike pattern. CD34 staining results are also positive in approximately 60% of GISTs.

TREATMENT

The only effective, specific, nonsurgical therapy for GISTs is imatinib mesylate.

Surgery is the definitive therapy for patients with GISTs. Radical and complete surgical extirpation offers the only chance for cure.

THE COLON

The colon is commonly considered to consist of five segments: the caecum, with the vermiform appendix at its base and the orifice of the ileocaecal valve above; then the ascending, transverse, descending, and sigmoid portions.

The proximal colon, extending to the distal transverse colon, is derived from the embryonal midgut and shares its blood supply (from the superior mesenteric artery) with the small intestine. This part of the colon is mainly concerned with absorption of water and electrolytes and to a lesser extent with reabsorption of bile acids.

The more distal colon arises from the embryonal hindgut and is supplied by the inferior mesenteric artery; it has less absorptive capacity and - with the rectum - functions mainly as a storage site for faeces prior to evacuation.

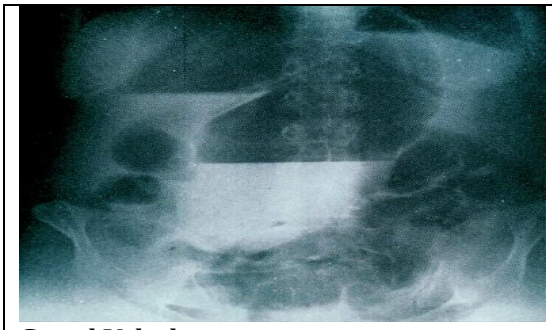
The colon and rectum are, together, a little over 1m in length, and the diameter diminishes from caecum to sigmoid, increasing again in the rectum. Most of the outer longitudinal muscle coat is gathered into 3 distinct bands - the taeniae coli - 6 to 10mm in width. These run from the tip of the caecum to the rectum, where they merge to form a more continuous covering. The taeniae are shorter then the colon and therefore gather' it into sacculations, or haustra. The mucosa of the colon is thrown into folds, the plicae semilunares, which take on a triangular appearance in the transverse colon.

Unlike the small intestine, the colon is relatively fixed, particularly the ascending and descending segments. The more mobile transverse colon has a short mesentery, whilst the sigmoid, with a broader, longer mesentery is generally the most mobile. Covering the serosal surface of the colon are fatty structures arising within the mesentery known as the appendices epiploicae.

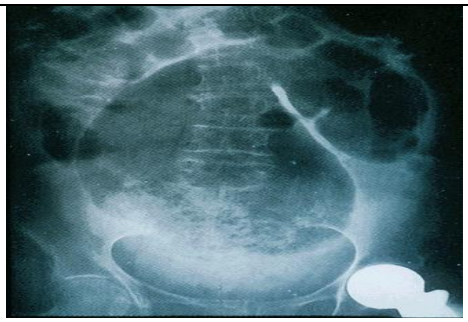
VOLVULUS

A volvulus occurs when a portion of the alimentary tract rotates or twists about itself, and in the colon this usually involves the caecum or the sigmoid.

In caecal volvulus, rotation is usually between a particularly mobile caecum and the ascending colon, which may in turn be associated with malrotation. Sigmoid volvulus is more likely when its mesentery is long with a narrow attachment, or when the sigmoid colon is itself abnormally long. Sigmoid volvulus is substantially commoner in populations with a high fibre intake, and tends to affect elderly people.



Caecal Volvulus



Sigmoid Volvulus

Volvulus of the large bowel presents with intestinal obstruction, which may be acute, recurrent, or chronic. The plain abdominal radiograph is usually highly suggestive.
Sigmoid volvulus can often be reduced by the passing of a flatus tube or colonoscope, but the results of endoscopic intervention are less good with caecal volvulus. When conservative measures fail, and when the arterial supply to the gut has been compromised, open reduction with fixation or resection will be necessary.

Colonic Obstruction

Large bowel obstruction may be caused by neoplasms or anatomic abnormalities such as volvulus, incarcerated hernia, stricture, or obstipation.
Large bowel obstruction from an anatomic abnormality leads to colonic distention, pain, anorexia, and, late in the course, feculent vomiting. Distinguishing colonic ileus from organic obstruction is important.

Imaging Studies:

- Flat and upright abdominal roentgenography demonstrates dilation of the small and/or large bowel and air fluid levels.
- Tracing colonic air around the colon, into the left gutter, and down into the rectum or demonstrating an abrupt cut-off in colonic air suggests the anatomic location of the obstruction.
- **A dilated colon without air in the rectum is more consistent with obstruction.** The presence of air in the rectum is consistent with obstipation, ileus, or partial obstruction.
- The characteristic **bird's beak of volvulus** may be seen.

Flexible endoscopy preceded by rectal enema may be useful in evaluating left-sided colonic obstruction.

Procedures:

- *Endoscopic reduction of volvulus*
- *Barium enema for reduction of intussusception*
- *Cleansing enemas*

Surgical Care:

- Surgical care is directed at relieving the obstruction.
- In most patients, the obstructing lesion is resected.
    - Because the colon has not been cleansed, anastomosis often is risky.
    - After resection, most surgeons perform a proximal colostomy if the obstruction is on the left side or ileostomy if it is on the right side.
- In patients with substantial comorbidity and surgical risk or in the presence of an unresectable tumor, a diverting proximal colostomy or ileostomy may be performed without resection.

ISCHAEMIC COLITIS

Ischaemic colitis arises from a failure of the blood supply to the colon and occurs most commonly in conjunction with advanced atherosclerotic disease affecting at least two of the major branches of the aorta. Acute occlusion of a major artery leads to a surgical emergency with colonic gangrene or to a less acute syndrome typified by abdominal pain and bloody diarrhoea.
Arterial emboli, dissecting aortic aneurysm, and vasculitic cases may also be responsible.

The most vulnerable areas of the colon are around the ***splenic flexure***, and, to a lesser extent, the rectosigmoid region, both of which lie in relatively poorly vascularized

The plain abdominal radiograph may show ***thumbprinting***', representing oedema of the mucosal folds. Contrast radiology shows swollen mucosal folds, ***sawtooth irregularities*** and narrowing.

In acute ischaemia, the involved section of bowel undergoes infarction; it is dilated and darkly congested with a friable wall, and is usually filled with blood. Mucosal ulceration and intense submucosal oedema with haemorrhage and necrosis are seen. Granulation tissue is later replaced by fibrosis which may lead to post-ischaemic stricturing.

In chronic ischaemia, it is common to find a stricture together with ulceration and granulation tissue. Fibrosis of the submucosa and circular muscle coat is also characteristic. Where mucosa survives, iron-laden macrophages are often prominent in the lamina propria.

DIVERTICULAR DISEASE

Diverticula are acquired pouches of mucosa and submucosa herniating through the muscular layers of the bowel. They are commoner with ageing and in populations where typical diets are low in fibre content.The sigmoid is affected in 95% but diverticula may occur throughout the colon. They usually arise in rows between the lateral and mesenteric taenii at the site of (potential) weakness in the bowel wall, where large blood vessels penetrate the interfascicular connective tissue of the circular muscle layer.

Haemorrhage from a diverticulum in the absence of inflammation may be responsible for brisk and usually self-limiting rectal bleeding. As diverticulosis is usually accompanied by marked thickening of the circular muscle layer of the colon, barium studies show shortening and narrowing of the sigmoid segment as well as of the diverticula. Flexible sigmoidoscopy and/or colonoscopy is indicated to help with the diagnosis.

A small minority of patients with diverticulosis develop diverticulitis. This results when an inflamed diverticulum becomes, effectively, an abscess, generally with subsequent perforation and localized peritonitis. Lower abdominal pain and tenderness with fever and leucocytosis are usual.

Diverticulitis may be complicated by free perforation and generalized faecal peritonitis, fistula formation (typically to the gynaecological organs or the bladder, but occasionally to the pelvic floor), intra-abdominal abscess, or haemorrhage.

Symptoms vary according to the nature of the fistula, but pneumaturia, recurrent urinary tract infection, or passage of faeces from the vagina will often be more indicative than routine investigations.

The typical pathology of diverticular disease includes a narrowed length of sigmoid colon with thickened bands of circular muscle, giving the bowel a concertina-like appearance.

COLO-RECTAL CANCER

Risk Factors

Age: The incidence of colorectal cancer is relatively low in individuals up to age 50. **Diet:** Frequency of colorectal cancer may be associated with high intakes of meat and fat.

Medical Factors: Colorectal cancer is more common among individuals with histories of: intestinal polyps (noncancerous mushroom-shaped growths), chronic inflammatory bowel disease (ulcerative colitis or Crohn's colitis), and previous colorectal cancer.

Women who have had cancers of the breast, uterus or ovary also have a higher risk.

Ethnic Group: Another genetic defect, or mutation, called I1307K, has been found in Ashkenazi Jews (those of Eastern European descent). This defect causes another mutation that can cause uncontrolled cell growth. This may lead to the development of cancer.

Genetic or Family Predisposition: There are a number of genetic disorders which can predispose a person to develop colorectal cancer. There are two classifications of these genetic disorder:

- Familial Polyposis Syndromes
- Hereditary Non-Polyposis Colon Cancer(or HNPCC) Syndromes

Familial Polyposis Syndromes

*Familial Adenomatous Polyposis***:** This is a relatively rare condition affecting approximately 1 in 8000 individuals. Without intervention virtually all people with this condition will develop colon cancer. The condition is characterized by multiple polyps throughout the entire colon. The polyps are not present at birth but develop over time.

Gardner's Syndrome: In this syndrome the entire large and small bowel may be affected by adenoma. Other abnormalities may coexist such as desmoid tumors, lipomas and sebaceous cysts.
Oldfield Syndrome: This syndrome is composed of sebaceous cysts in association with polyposis and cancer (specifically adenocarcinoma).
Turcot Syndrome: Here CNS tumors are associated with bowel polyposis.

Hereditary Non-polyposis Colon Cancer (HNPCC) Syndromes

A category of genetic defects where the DNA is unable to make self-repairs when copying itself. Patients are classified as HNPCC when there is a strong family history of developing colorectal cancer at an early age — that is, under 50. They are sometimes further divided into Lynch I and Lynch II groups depending on age and other cancers to which they are predisposed.

- Lynch I: In this condition successive generations develop colon cancer at an extremely early age (some studies showed the average age to be 46).
- Lynch II: In this syndrome there is a hereditary predisposition to the development of cancer (specifically of the breast, colon, ovary, pancreas, uterine and gastric systems).

Criteria for HNPCC syndrome (Amsterdam criteria)

- At least one family member who has developed colorectal cancer by age 50.
- Colorectal cancer involving at least two successive generations.
- Histologically verified colorectal cancer in three or more relatives, one of whom is a first degree relative of the other two.

There are other medical conditions, which may predispose one to the development of colon cancer; these are ulcerative colitis and Crohn's disease.

Symptoms

Approximately 50% of patients present with abdominal pain, 35% with altered bowel habits, 30% with occult bleeding, and 15% with intestinal obstruction. Right-sided colon cancers tend to be larger and more likely to bleed, whereas left-sided tumors tend to be smaller and more likely to be obstructing.
Feeling tired and weak; jaundice; pain in the abdomen; differences in the patient's usual bowel habits: constipation, diarrhea, narrowing of stool; feeling of fullness in bowel that is not relieved by a bowel movement; blood in stool; and reduced appetite.

Diagnosis

Carcinoembryonic antigen
(1) CEA may be elevated for reasons other than colon cancer, such as pancreatic or hepatobiliary disease, and elevation does not always reflect cancer or disease recurrence; (2) recurrence remains a possibility when CEA is not elevated, even if CEA was elevated preoperatively. Findings of other tests, such as CT scans and colonoscopy, must be incorporated in detection of recurrence.

Imaging Studies:

Chest x-ray: It may reveal metastatic spread to the lungs.
Computed tomographic scanning

- Abdominal/pelvic CT scans can be useful in diagnosis of colon cancer that has metastasized to lymph nodes and liver.
- CT scans also are very helpful in the follow-up of patients with resected, as well as metastatic, disease. Imaging can diagnose recurrent disease and can document response to chemotherapy.

Procedures: *Flexible sigmoidoscopy* is a screening tool that can detect polyps or cancers as far as 60 cm from the anus.
colonoscopy allows examination of the entire colon, and can be used to obtain a biopsy of suggestive lesions or to remove polyps.
Double-contrast barium enemas are an option for screening for colorectal cancer and can aid in establishing the diagnosis of colon cancer.

Staging

- Modified Duke Staging System
- TNM Staging
- Stage Grouping

Modified Duke Staging System

Modified Duke A	The tumor penetrates into the mucosa of the bowel wall but no further.
Modified Duke B	**B1**: tumor penetrates into, but not through the muscularis propria (the muscular layer) of the bowel wall. **B2**: tumor penetrates into and through the muscularis propria of the bowel wall.
Modified Duke C	**C1**: tumor penetrates into, but not through the muscularis propria of the bowel wall; there is pathologic evidence of colon cancer in the lymph nodes. **C2**: tumor penetrates into and through the muscularis propria of the bowel wall; there is pathologic evidence of colon cancer in the lymph nodes.
Modified Duke D	The tumor, which has spread beyond the confines of the lymph nodes (to organs such as the liver, lung or bone).

Treatment

Surgery

This is the most common and usually the first treatment for patients who have colorectal cancer.

There are several forms of surgical treatment used for rectal cancer that don't involve cutting into the abdomen:

- Electrofulgeration: use of electricity to destroy tumors.
- Local excision: cutting off a layer of the rectum that contains cancer.
- Local full-thickness resection: cutting out cancer from all layers of the rectum.

Chemotherapy, radiation therapy and biological therapy, either individually or in various combinations, may be used after surgery.

Chemotherapy

Eloxatin

Eloxatin is a platinum-based anticancer drug used to treat colorectal cancer that has recurred or advanced colorectal cancer. It is administered intravenously in combination with 5-fluorouracil plus leucovorin (5FU/LV).

Temporary side effects include numbness or tingling in the fingers, toes, throat, and around the mouth.

Radiation Therapy

Biological or Immunotherapy

Appendicitis

Obstruction of the appendiceal lumen is the primary cause of appendicitis. Obstruction of the lumen leads to distension of the appendix due to accumulated intraluminal fluid. Ineffective lymphatic and venous drainage allows bacterial invasion of the appendiceal wall and, in advanced cases, perforation and spillage of pus into the peritoneal cavity.

History: The classic history of anorexia and periumbilical pain followed by nausea, right lower quadrant (RLQ) pain, and vomiting occurs in only 50% of cases.

Migration of pain from the periumbilical area to the RLQ is the most discriminating historical feature. When vomiting occurs, it nearly always follows the onset of pain.

Physical: RLQ tenderness is present in 96% of patients but is a very nonspecific finding.

The most specific physical findings are rebound tenderness, pain on percussion, rigidity, and guarding.

Rovsing sign (ie, RLQ pain with palpation of the LLQ), obturator sign (ie, RLQ pain with internal rotation of the flexed right hip), and psoas sign (ie, RLQ pain with hyperextension of the right hip) are present in a minority of patients with acute appendicitis.

Lab Studies:

Complete blood count: *80-85% of adults with appendicitis have a WBC count greater than 10,000 and Neutrophilia greater than 75%.*

C-reactive protein: *C-reactive protein (CRP) is an acute-phase reactant synthesized by the liver in response to bacterial infection. Serum levels begin to rise within 6-12 hours of acute tissue inflammation.* a normal CRP has a negative predictive value of approximately 100% for the presence of appendicitis.

Imaging Studies:

Computed tomography scan

Ultrasound: ***An outer diameter of greater than 6 mm, noncompressibility, lack of peristalsis, or presence of a periappendiceal fluid collection characterizes an inflamed appendix.*** The normal appendix is not visualized in most cases.

Abdominal x-rays: Visualization of an appendicolith in a patient with symptoms consistent with appendicitis is highly suggestive, but this occurs in < 10% of cases.

Radionuclide scanning: Whole blood is withdrawn. Neutrophils and macrophages are labeled with technetium 99m albumin and administered intravenously. Images of the abdomen and pelvis are obtained serially over 4 hours. Localized uptake of tracer in the RLQ suggests appendiceal inflammation.

TREATMENT

Open or laparoscopic appendectomy when no lump formation is there.

Conservative management (Ochsner Sherren Regime) after lump formation and appendicectomy is done after 6 weeks (interval appendicectomy).

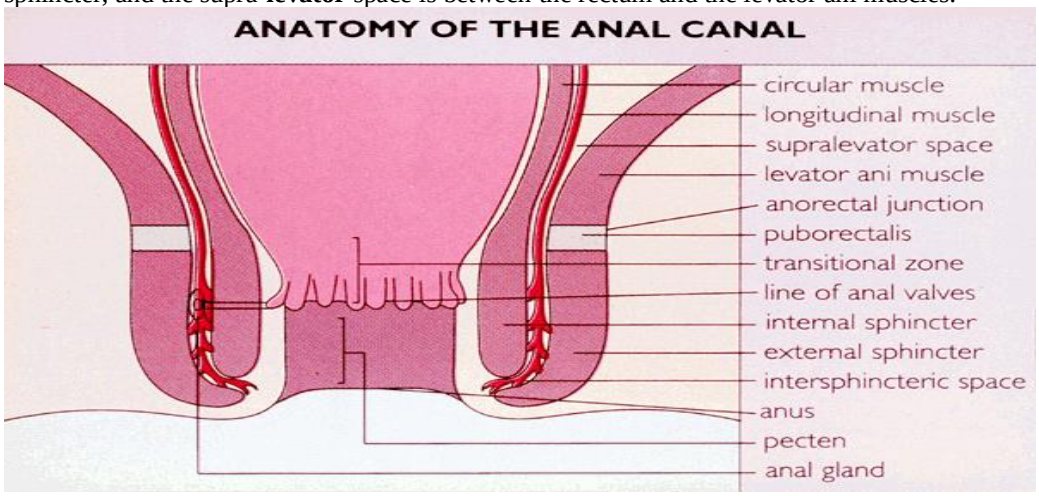
ANATOMY OF THE ANAL CANAL

The anal canal is 3-4cm in length and runs from the anorectal junction to the anus verge. The line of the anal valves, often called the dentate line, is approximately half way along the anal canal. Anal columns extend upwards from this line.

The columnar epithelium of the rectum is replaced by mixed columnar and squamous epithelium in the upper anal canal, corresponding to the zone of fusion between the embryological hindgut and the proctodeum. Between the line of the anal valves and the lower border of the internal sphincter, the epithelium is stratified squamous and often referred to as the pecten. At the anal margin, the epithelium becomes hair-bearing skin.

Sphincters: Two sphincters surround the anal canal: the internal sphincter, which is the expanded distal portion of the circular smooth muscle; and the external sphincter, which is derived from the striated muscle of the pelvic floor and becomes continuous with the puborectalis and the levator ani muscles.

Spaces: There are three important spaces in the area. The **intersphincteric space** contains the terminal fibres of the longitudinal muscle of the gut and the anal intermuscular glands. These anal glands are important in the pathogenesis of abscesses and fistulae. **The ischiorectal fossa** lies outside the external sphincter, and the supra-**levator** space is between the rectum and the levator ani muscles.



CONGENITAL ANORECTAL ANOMALIES

It occurs in 1:5000 births with a slight male predominence. Anorectal anomalies, varies from anal stenosis and imperforate anus to complete ano-rectal agenesis. Agenesis accounts for over 75% of anorectal atresias and is often complicated by vaginal, vesical or urethral fistula. Anal stenosis is usually manifest at birth with the presence of a small anal aperture containing a dot of meconium. The abdomen may be distended, and defaecation - if possible - results in a ribbon-like stool.

Anorectal anomalies are one component of the VACTERL association (Vertebral, Anal, Cardiac, Tracheal, Esophageal, Renal, and Limb abnormalities). The diagnosis of anorectal anomalies is clinical by inspection of the perineum. Rectal atresia presents clinically with abdominal distension and failure to pass meconium.

Anal atresia, also called imperforate anus, may be membranous in which the bowel is patent to the anal membrane and usually meconium staining or greenish bulging membrane may be visible. The management of anal stenosis and imperforate anal membrane is generally with dilatation or simple surgical incision **(Cut back).**

In infants with anorectal agenesis, the most important prognostic and management factor is the site of the abnormality; high supralevator or low translevator. The outlook following surgery is good if the bowel has passed through the puborectalis sling. However, higher abnormalities are usually associated with a rectourethral fistula in the male or rectovaginal fistula in the female. An imperforate anus is also associated with anorectal atresia, in which both the anus and the distal rectum are atretic. The terminal bowel may be blind but commonly is associated with a fistula to the bladder, prostate, perineum or vagina. Meconium may be passed per vaginam or urethram. Initial surgery is a colostomy with definitive surgery being delayed. During this the fistula is closed and a pull through operation is performed.

Imaging

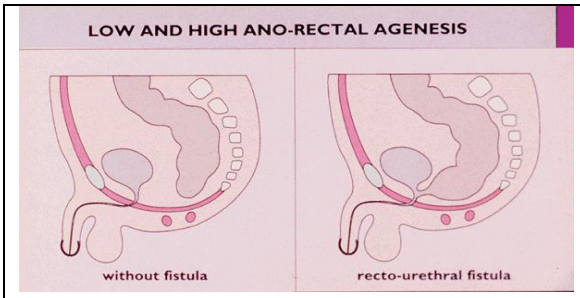
A lateral decubitus radiograph is taken, the anal dimple being marked with barium. The film should not be taken before 12 hours to allow sufficient passage of air distally. In a low lesion air reaches the perineum. In a high lesion the bowel ends above the pelvic sling and lies above the M line, a line running horizontally through the junction of the lower 1/3 and upper 2/3 of the ischia and the sacrococcygeal junction.

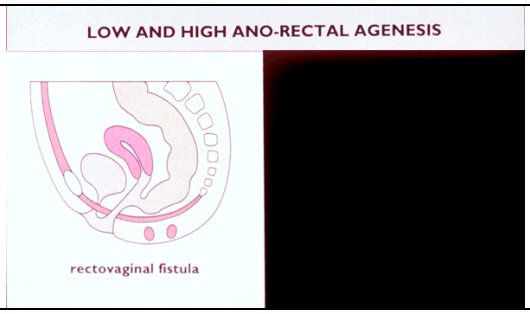
Ultrasound of the renal tract should be performed to rule out renal anomalies.

The exact site of the blockage is better determined by running contrast medium into the distal loop of the colon after a colostomy has been performed (distal colonogram). It is also required to assess the length of distal colon and to identify a fistula.

Main Repair: (Posterior Sagittal Anorectoplasty)

Long term colonic complications of anorectal anomalies relate to deficiency of puborectalis and levator ani muscles which leads to faecal incontinence. Constipation may occur from stenosis of the pull through or deficiency of the nerve supply to the pelvic floor secondary to sacral nerve deficiency.



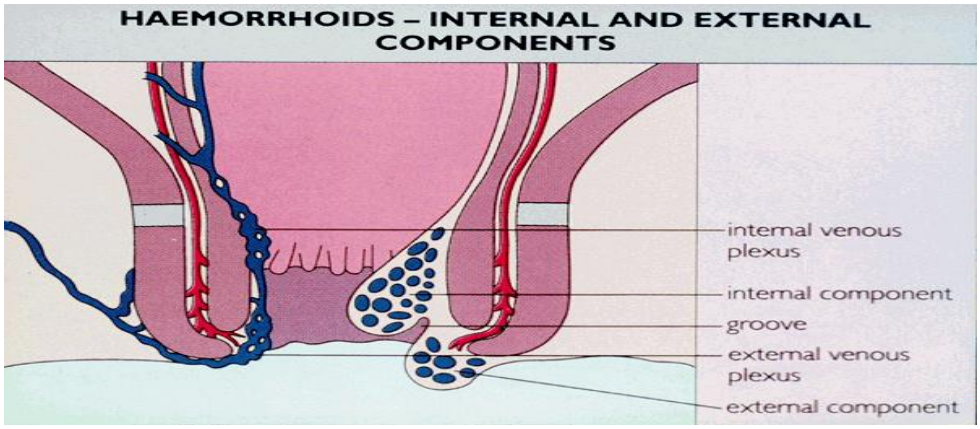


HEMORRHOIDS

Hemorrhoids are masses of normal vascular tissue in the anal canal. The prevalence of hemorrhoids is equal in both sexes. They arise from a plexus of dilated veins originating from the superior and inferior hemorrhoidal veins, are located in the submucosal layer.

Hemorrhoids are classified as internal or external, based on whether they arise above or below the dentate line, and often coexist. Internal hemorrhoids arise from the superior (internal) hemorrhoidal vascular plexus, and their primary locations are the 3, 7, and 11 o'clock positions corresponding to the end branches of the middle and superior hemorrhoidal veins. External hemorrhoids are dilations of the inferior (external)

hemorrhoidal plexus and lie below the dentate line, covered with squamous epithelium that contains numerous somatic pain receptors. External skin tags represent residual excess skin associated with prior thrombosis of external hemorrhoids,
Internal and external hemorrhoids communicate with each other and drain into the internal pudendal veins. Hemorrhoids may reside in proximity to rectal varices in patients with cirrhosis but are not more common in patients with portal hypertension.
Hemorrhoids has been associated with increasing age, chronic diarrhea, pregnancy, pelvic tumors, prolonged sitting and straining, and possibly chronic constipation.
Haemorrhoids usually present with the passage of bright red blood. Bleeding is usually self-limited but may be associated perianal pain, prolapse, mucous discharge and pruritus.
Internal haemorrhoids that do not prolapse are known as 1st degree, those that prolapse but reduce spontaneously, 2nd degree, and those that require digital reduction, 3rd degree.
Thrombosis may affect external or internal components.
A small area of involvement of the external plexus is often referred to as a perianal haematoma. These are painful and may progress to ulceration and/or haemorrhage.



Management of Hemorrhoids
Conservative treatment includes proper diet, use of bulk-forming agents, warm sitz baths and avoidance of prolonged sitting.
Minimally invasive interventions are rubber band ligation, sclerotherapy, infrared or laser photocoagulation, bipolar diathermy, cryosurgery, and dilation of the internal anal sphincter, wich are usually, reserved for grades I and II hemorrhoids.
Surgical management is generally reserved for: continued symptoms despite conservative procedures, or as the initial treatment in cases of symptomatic grade IV hemorrhoids or in patients with strangulated internal hemorrhoids. The most common technique is a **closed hemorrhoidectomy** in which an elliptical incision is made on the external hemorrhoidal tissue and alll 3 hemorrhoidal columns are treated at a time, and the defect is closed with a continuous absorbable suture. This procedure has a 95% success rate and a low rate of wound infection. **Open hemorrhoidectomy** involves excision and ligation of internal hemorrhoids without mucosal closure.

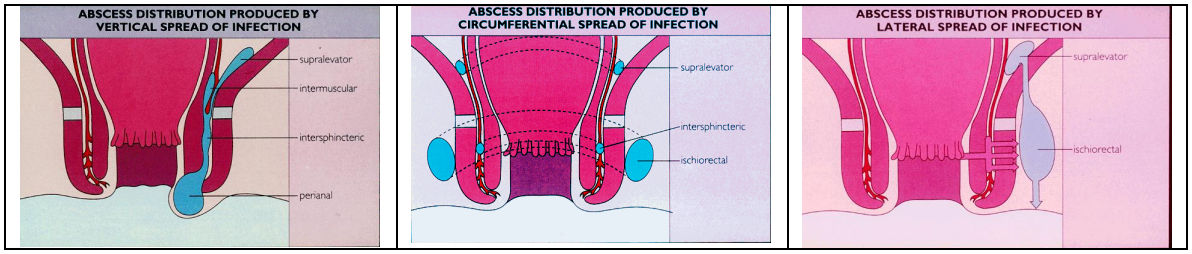
ANAL FISSURES
An anal fissure is a laceration in the lining of the anal canal distal to the dentate line, which most commonly occurs in the posterior midline and is often caused by local trauma such as the passage of hard stool. Anal fissures can occasionally be seen in patients with leukemia, tuberculosis, and Crohn's disease. The internal anal sphincter muscle, which is exposed beneath the tear, goes into spasm, pulling the edges of the fissure apart, impairing wound healing and leading to further tearing of the anal mucosa with subsequent passage of bowel movements. In addition, ischemia can contribute to the development of a chronic anal fissure. The patient describes a tearing pain with the passage of hard stool, accompanied by bright red blood, which is usually limited to the surface of the stool or as a stain on the toilet paper. A fresh

laceration usually signifies an acute fissure, whereas a chronic fissure has raised edges exposing the white horizontally oriented fibers of the internal sphincter at its base and is often accompanied by external skin tags distally and hypertrophied anal papillae proximally.
Large or multiple fissures, and particularly those away from the midline, should always raise the suspicion of Crohn's disease.

Therapy for anal fissures is aimed at breaking the cycle of sphincter spasm and tearing of anal mucosa and promoting subsequent healing of the fissure. Medical therapy is often successful which includes fiber supplementation, stool softeners, and warm sitz baths. Topical anesthetic creams such as topical nitroglycerin can often soothe the inflamed anoderm in the setting of an acute fissure. Stretching of anal sphincter causes anal dilatation and cures anal fissures by reducing the anal canal pressure. *Botulinum toxin*, which is a potent inhibitor of acetylcholine release from nerve endings, can be injected into the anal sphincter. Botulin toxin is known to cause paresis of the sphincter and thus 2.5 to 5 units, is injected bilaterally to the fissure. This causes sphincter paresis for about 3 months.
Surgical management can be performed by excising the anal fissure (fissurectomy) or by doing a lateral internal sphincterotomy to relax and reduce internal sphincter pressure. This technique divides the internal anal sphincter from its distal end for a distance equal to that of the fissure or up to the dentate line. The sphincterotomy heals best if it is performed in the lateral position.

ABSCESS AND FISTULA
Abscesses and fistulae begin as a nonspecific infection of the anal glands which may produce an abscess between the two sphincters - the so-called intersphincteric abscess, but infection may then spread, to the anal margin gives rise to a perianal abscess, upward spread produces either an intermuscular abscess or a supralevator abscess, horizontal spread carries infection back into the anal canal across the internal sphincter, or across the striated muscle into the ischiorectal fossa forming an ischiorectal abscess.If the primary track passes through the external sphincter, it is termed trans-sphincteric, but if above the puborectalis, suprasphincteric. Circumferential spread carries infection in the intersphincteric space, supralevator space or the ischiorectal fossa to the opposite side
Fistulae are classified according to the position of the primary track - intersphincteric if it lies between the sphincters, trans-sphincteric when it crosses the external sphincter and suprasphincteric when it crosses above the puborectalis muscle.
Perianal fistulae are a major feature of Crohn's disease and are usually associated with rectal involvement; rarely do they represent spread from more proximal bowel disease.
Anorectal fistulas can develop in other medical disorders such as anorectal malignancy, lymphogranuloma venereum, radiation proctitis, actinomycosis, tuberculosis, and leukemia.
Classification of anorectal fistulas

Fistula Type	**Description**
Intersphincteric	Travels along intersphincteric plane to the perianal skin
Transsphincteric	Encompasses a portion of the internal and external anal sphincters and terminates on the skin overlying the buttock
Suprasphincteric	Encompasses the entire anal sphincter
Extrasphincteric	Extends from an internal opening in the bowel proximal to the anus, encompasses the entire anal sphincter, and opens onto the skin overlying the buttocks



The goal of surgical management is to eradicate the fistula while preserving fecal continence. Intersphincteric fistulas are managed by a primary fistulotomy; the base of the wound is then curetted and left open to heal by secondary intention. Transsphincteric fistulas are divided into low and high fistulas. Low fistulas are managed by a primary fistulotomy. High transsphincteric and anterior fistulas are managed with a conservative approach whereby a cutting section is often performed. This procedure involves placing a reactive suture or elastic through the fistulous tract and tightening it sequentially until it cuts through the tract. A relatively new therapy involves the injection of fibrin glue.

SOLITARY RECTAL ULCER SYNDROME (Mucosal prolapse syndrome)

SRUS is a benign condition and usually presents in women during the third and fourth decades of life. SRUS pursues a chronic course of constipation, mucorrhea-associated rectal prolapse, rectal bleeding, and tenesmus. It is characterized by an indolent, shallow, whiteish ulcer surrounded by hyperaemic mucosa on the anterior wall of the rectum, typically 7-10 cm from the margin. There is usually some degree of intussusception of the anterior rectal wall into the anal canal, and the ulceration is probably caused by trauma to the mucosa during excessive straining against an actively contracting puborectalis. Once clinical symptoms are elucidated flexible sigmoidoscopy is performed to confirm the diagnosis.

Management of SRUS is based on the presence of symptoms. Usually conservative therapy with bulk laxatives, application of local steroids or 5-acetylsalicylic acid (ASA) and bowel retraining is attempted before considering surgical options.

RECTAL PROLAPSE

Rectal prolapse represents an intussusception of the rectum from a point typically some 8cm above the anus. Prolapse is usually associated with generalized laxity of the pelvic floor and defective sphincter function, but it also occurs with conditions in which intra-abdominal pressure is raised, such as cystic fibrosis, and should be distinguished from prolapse of an adenoma or other neoplasm.

Types -

Partial - only the mucosa protrudes out. This is the more common type. It is seen at the extremes of age. Treatment in children is digital reposition, or rarely sub-mucosal injections of a mixture of phenol & almond oil causing aseptic inflammation and later on fibrosis & adherence of mucosa to muscle. Operative treatment is required only in the severe & recurrent cases where Thiersch's operation can be performed.

Total (procidentia)- entire wall of rectum protrudes out. This is less common. It is actually a hernia - en - glissade of the rectum, where it slides down, & may bring along the surrounding structures or a peritoneal pouch along with it. Commonly starts in anterior wall, where the support is weakest, especially in women. Anal sphincter is patulous & gapes widely on straining. It is usually >4 cm in length. Concentric folds can be seen on mucosa (radial in partial).

Definitive treatment is for complete prolapse is surgery.

Perineal approach -

- Delorme's operation - Stripping of redundant mucosa + plication of muscle wall to create a ring + re-suturing of anal mucosa to rectal mucosa

Abdominal approach - mostly "sling" procedures to hold rectum to a fixed structure.

- Well's operation - rectum held to sacrum by polyvinyl alcohol sponge - evokes a fibrotic reaction.
- Ripstein's - held to sacral promontory by Teflon sling.
- Lahaut's - rectum passed through a rectus sheath.

- Anterior resection
- Gracilis sling procedure - corrects the incontinence.

PILONIDAL SINUS

Pilonidal sinus is common in young adults (particularly males). It comprises one or more openings in the natal cleft. The subcutaneous component has a base of granulation tissue and often contains hairs which may project from the mouth of the sinus. It is thought that pilonidal sinuses follow folliculitis and localized abscess formation within the subcutaneous fat. The relevance of hair is probably secondary, being responsible, once trapped within the sinus, for continued infection and a foreign body reaction. Treatment is mainly surgical, where whole of the excised along with its shin margin is excised and tract is layed open to heal with secondary intention.

RECTAL CANCER

Adenocarcinomas (98%)

The incidence peaks in the seventh decade and is slightly higher in males than in females. **CLINICAL: Colorectal carcinoma**

Right-sided lesions	*Left-sided lesions*
• Iron deficiency anaemia due occult GI Blood loss • Weight loss • Right iliac fossa mass	• Abdominal pain • Alteration in bowel habit • Rectal bleeding • 40% present as a surgical emergency with either obstruction or perforation
Rectal Cancer: **Bleeding**- (most common symptom- in 60% of patients may be accompanied by the passage of mucus); **Change in bowel habits**- (43% of patients, Often in the form of diarrhea or change in the caliber of the stool. Large tumors can cause obstructive symptoms); Tumors located low in the rectum can cause a feeling of incomplete evacuation and **tenesmus**; **Abdominal pain** or **peritonitis from perforation**	

CAUSES:

- No specific risk factors: 75%.
- With significant risk factors: 25% [(15-20% in a positive family history or a personal history of colorectal cancer or polyps), rest in people with certain genetic predispositions, eg. hereditary nonpolyposis colorectal cancer (HNPCC, 4-7%) and familial adenomatous polyposis (FAP, 1%) or in people with inflammatory bowel disease (IBD, 1%).
- Most related to environmental factors - dietary red fat and animal fat

Adenoma - carcinoma sequence

- Of all adenomas - 70% tubular, 10% villous and 20% tubulovillous
- Most cancers arise within pre-existing adenomas. Risk is greatest in villous type.
- 3% patients present with more than one tumour (synchronous tumours). Series of mutations results in epithelial changes from normal→ dysplasia to invasion
- Important genes - APC, DCC, k-ras, p53.

Genetic disorders

Familial adenomatous polyposis:

- An autosomal dominant syndrome that causes more than 100 adenomatous polyps and a variety of extraintestinal manifestations like ***osteomas, desmoid tumors and brain tumors***.
- Increased number of polyps predisposes patients to a greater risk of cancer. If left untreated, colorectal cancer develops in nearly 100% of these patients by age 40 years.
- 80% has a documented hereditary link, rest are caused by spontaneous mutation.

Hereditary nonpolyposis colorectal cancer

- HNPCC is an autosomal dominant syndrome.
- Patients have the same number of polyps as the general population, but their polyps are more

likely to become malignant. ***These patients also have a higher incidence of endometrial, gastric, thyroid, and brain cancers***.

Inflammatory bowel disease

Ulcerative colitis

- After 10 years, the incidence of colorectal cancer in UC is approximately 1% per year.
- Evaluate patients for dysplastic changes with annual colonoscopies.

Crohn disease

- Colorectal cancer in Crohn disease is 4-20 times greater than in general population. Cancers often develop in areas of strictures and in defunctionalized segments of intestine. Patients with Crohn colitis undergo the same surveillance regimen as those with UC.

WORKUP

Routine laboratory study & CEA.

Metastatic workup.

- Liver function tests. Chest radiograph
- Carcinoembryonic antigen test: A CEA higher then 100 ng/mL usually indicates metastatic disease and warrants a thorough investigation.

Rigid proctosigmoidoscopy / Flexible sigmoidoscopy

- This procedure is used to obtain biopsies of the lesion, assess ulceration, and determine the degree of fixation.

Colonoscopy

Double contrast barium enema

- In patients presenting with large bowel obstruction ***single contrast enema*** (after rigid sigmoidoscopy) is the investigation of choice

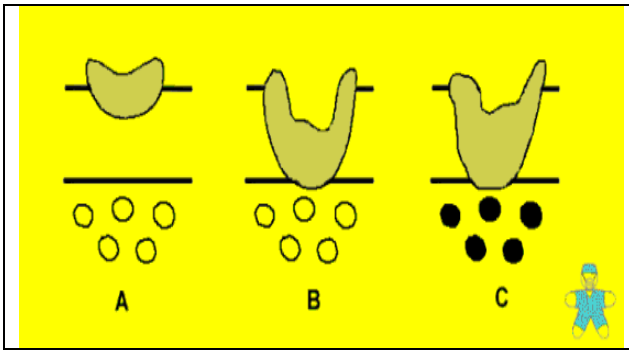
Computed axial tomography scan generally is used to determine the presence or absence of metastases and to assess regarding depth of penetration of the primary rectal tumor.

STAGING: ***Dukes classification:*** Developed by Cuthbert Duke in 1932.

- Those limited to the rectal wall (Dukes A)
- Those that extended through the rectal wall into extrarectal tissue (Dukes B)
- Those with metastases to regional lymph nodes (Dukes C)

This system was modified to include subdivisions of stages B and C, as follows:

- Stage B became B1 (tumor penetration into muscularis propria) and B2 (tumor penetration through muscularis propria).
- Stage C became C1 (tumors limited to the rectal wall with nodal involvement) and C2 (tumors penetrating through the rectal wall with nodal involvement).
- Stage D was added to indicate distant metastases.



Stage A - Tumour confined to the mucosa
Stage B - Tumour infiltrating through muscle
Stage C - Lymph node metastases present

Five year survival - 90%, 70% and 30% for Stages A, B and C respectively

TNM classification for cancer of the colon and rectum (AJCC)

Primary tumor (T)	*Regional lymph nodes (N)*	*Distant metastasis-M*
TX - Primary tumor cannot be assessed T0 - No evidence of primary tumor Tis - Carcinoma in situ (mucosal) T1 - Tumor invades submucosa T2 - Tumor invades muscularis propria. T3 –(Invasion through muscularis propria into the subserosa or into nonperitonealized pericolic or perirectal tissue T4 - Perforates the visceral peritoneum or directly invades other organs or structures.	NX - Regional lymph nodes cannot be assessed N0 - No regional lymph node metastasis N1 - Metastasis in 1-3 pericolic or perirectal lymph nodes N2 - Metastasis in 4 or more pericolic or perirectal lymph nodes N3 - Node along the course of a main vascular trunk	MX – Mets. cannot be assessed M0 - No distant metastasis M1 - Distant metastasis

Stage	**T**	**N**	**M**	**Dukes stage**
0	Tis T1 T2	N0 N0 N0	M0 M0 M0	A
II	T3 T4	N0 N0	M0 M0	B
III	Any T Any T	N1 N2, N3	M0 M0	C
IV	Any T	Any N	M1	

TREATMENT: Medical Care:

Treatment of polyps

- Ten percent of polyps larger than 1 cm contain carcinoma.
- Sessile polyps that contain invasive carcinoma require resection. Pedunculated, cancer-containing polyps may be removed colonoscopically.
- If the following requirements are not met, surgical resection is indicated: (1) the carcinoma must be well or moderately differentiated with no venous or lymphatic invasion. (2) The carcinoma must not invade further than the stalk of the polyp, and the margins of resection must not contain tumor.

Preoperative radiation therapy: Preoperative radiation therapy decreases tumor recurrence in patients with stage II and III disease. In stage I disease, the morbidity and mortality are higher, and there is no proven benefit to giving preoperative RT.

Surgical Care:

Transanal excision:

- Patients with stage 0 or I cancer with a T1 lesion.
- The lesion is excised with full thickness of the rectal wall, leaving a 1-cm margin.
- Lesions that display unfavorable histology but are excised completely may be treated with adjuvant radiation therapy.

Surgical options

- **1 cm distal clearance of rectal lesions adequate if mesorectum resected**
- Radial margin should be histopathologically free of tumour if possible
- Lymph node resection should be performed to the origin of the feeding vessel
- *En Bloc* resection of adherent tumours should be performed
- Depending on site of lesion surgical options are:
- Upper rectum – Anterior resection (Consider defunctioning loop ileostomy is anastomosis <12 cm From anal margin).
- Lower rectum – Abdomino-perineal resection

Sphincter-sparing procedures:

Low anterior resection

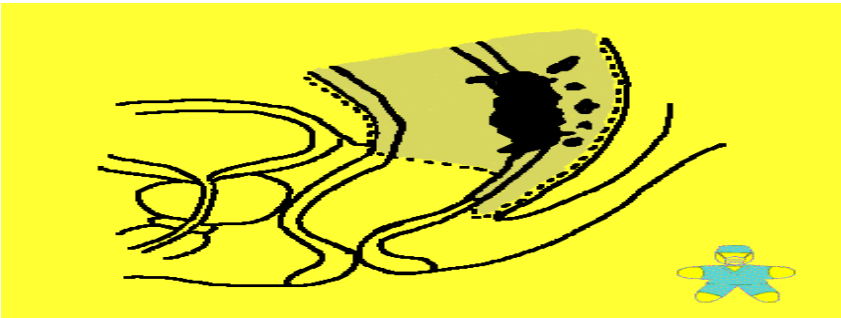
- Low anterior resection (LAR) procedure is performed generally for lesions in the middle and upper third of the rectum,
- A 2-cm margin distal to the lesion must be achieved.

Coloanal anastomosis

- Very distal rectal cancers, located just above the sphincters can be resected without the need for a permanent colostomy. In this pelvic dissection is carried down to below the level of the levator ani muscles from within the abdomen. A straight-tube coloanal anastomosis (CAA) can be performed.
- An alternative to the straight-tube CAA is the creation of a colonic J pouch. The advantages of the J pouch include decreased frequency and urgency of bowel movements because of the increased capacity of the pouch.

Abdominal perineal resection

- Abdominal perineal resection (APR) is performed in patients with lower-third rectal cancers who cannot undergo a sphincter-sparing procedure.



Adjuvant radiotherapy

- Risk factors for local recurrence include:
  - Local extent of tumour
  - Nodal involvement
  - Circumferential margin status
- Risk of local recurrence can be reduced by radiotherapy
- Can be given either preoperatively or postoperatively
- Combination chemotherapy and radiotherapy may produce better outcome

Adjuvant chemotherapy

- Improves survival in Duke's C tumours
- Not required in Duke's A tumours which already have a good prognosis
- Role in Duke's B tumours remains to be defined

Generally, patients with T1 or T2 disease can undergo local surgical excision. Patients with T3 or N1 disease benefit from a course of preoperative neoadjuvant chemotherapy and radiation therapy prior to planned surgical resection, which could include either a low anterior resection or abdominoperineal resection. Patients with T4 disease often require palliative therapies including chemotherapy, radiation therapy, and surgery.

RECTAL ADENOCARCINOMA

T1 N0 T2 N0	T3	T4
Trans-anal local resection (If not too large)	consider pre-op – chemo/RXT; followed by surgery: APR/ Ant resection	pre-op – chemo/RXT pelvic resection Palliative surgery +/- RXT

True anal cancers arise from the transitional mucosa between the rectal mucosa and the squamous epithelium of the anal margin; most are squamous carcinomas or basaloid carcinomas, so termed because of their histological resemblance to basal cell lesions, but a spectrum from squamous through basal and transitional epithelium to a glandular pattern is recognized.

The clinical behaviour of most types is similar to that of a low rectal carcinoma. The malignant melanoma, from its bluish/black polypoid appearance, is easily mistaken for a thrombosed external haemorrhoid. The tumour is highly malignant and metastasizes rapidly.

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 4th to 14th somites and consists of 6-10 pairs of tubules.
- It disappears completely by 4th 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 (*Intravenous 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

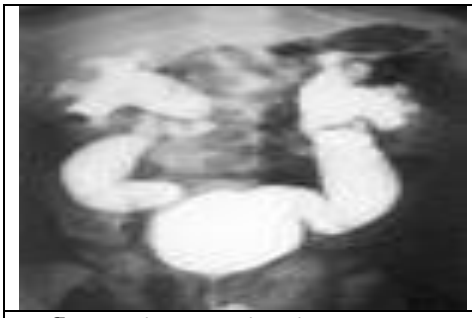
Clinical features are those of urinary tract infection. Suspicion should be raised after a single infection in boys or two in girls.

Other features include:

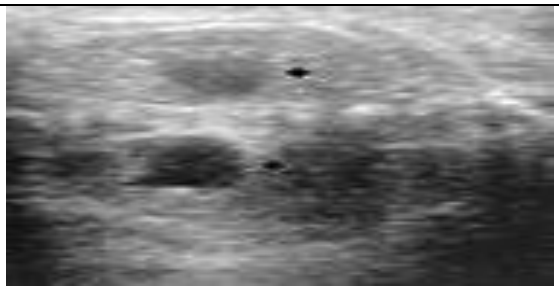
- Incontinence/ frequency/ dysuria/ abdominal pain

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.

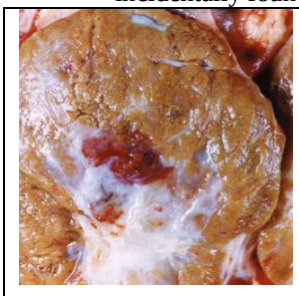
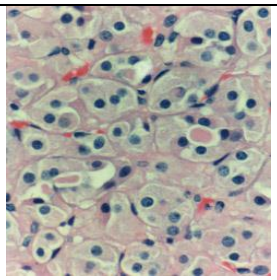
Histologic Findings (The Mainz Classification of Renal Cell Tumors): Renal cell carcinoma has 5 histological subtypes, as follows: clear cell (75%), chromophilic (15%), chromophobe (5%), oncocytoma (3%), and collecting duct (2%).

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 rectal infection	**Ceftrioxone 125 mg IMI + Doxycycline 100 mg BD for 7 days**	1. Cefixime 400 mg stat 2. 2. Ciproflloxacin 500 mg 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

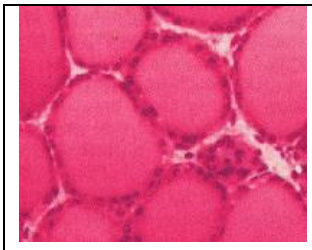
The gland receives fibers from both sympathetic and parasympathetic divisions of the autonomic nervous system. The sympathetic fibers are derived from the cervical ganglia and enter the gland along the blood vessels. The parasympathetic fibers are derived from the vagus and reach the gland by branches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

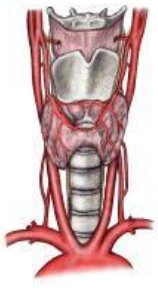
The Secretory Unit - The Follicle

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.

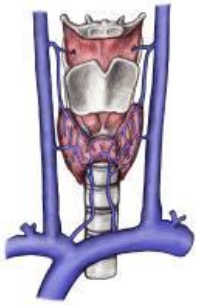
In addition to the acinar cells, there are individual cells or small groups of cells that are seen not to extend to the follicular lumen and which may appear as clusters between follicles. These light cells, or C-cells, are a distinct category probably derived from the neural crest via the ultimobranchial 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.



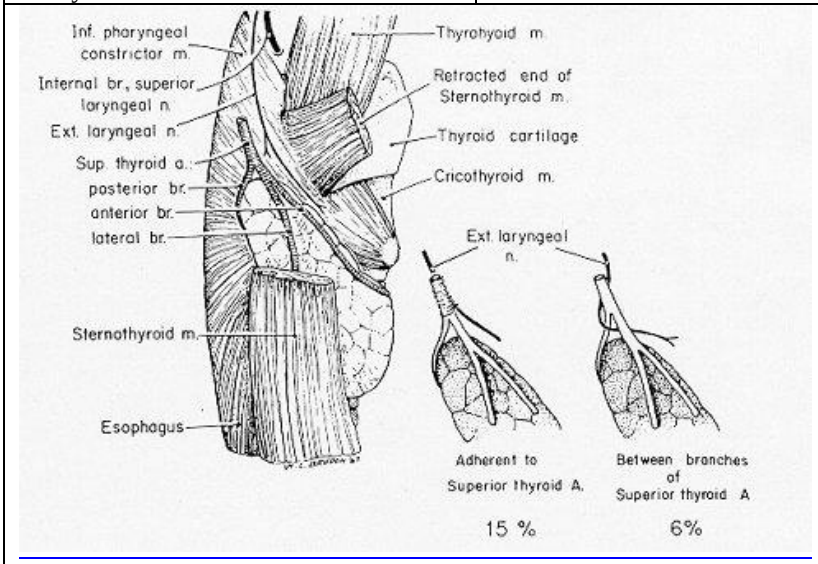
Histology of the thyroid gland shows the structural units of the gland and follicles, consisting of a layer of simple epithelium enclosing a colloid-filled cavity.



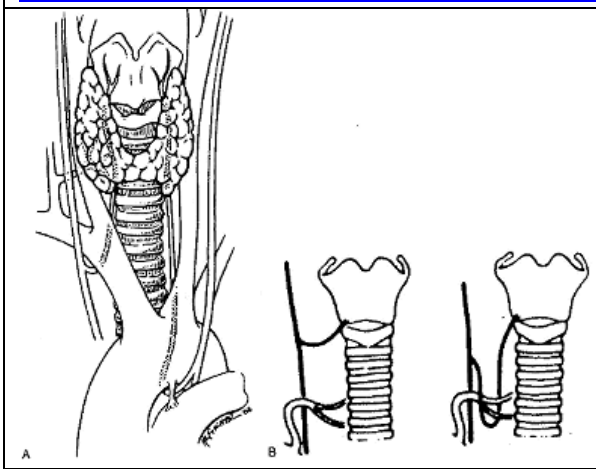
Distribution of thyroid arteries with associated laryngeal nerve, anterior view.



Distribution of thyroid veins



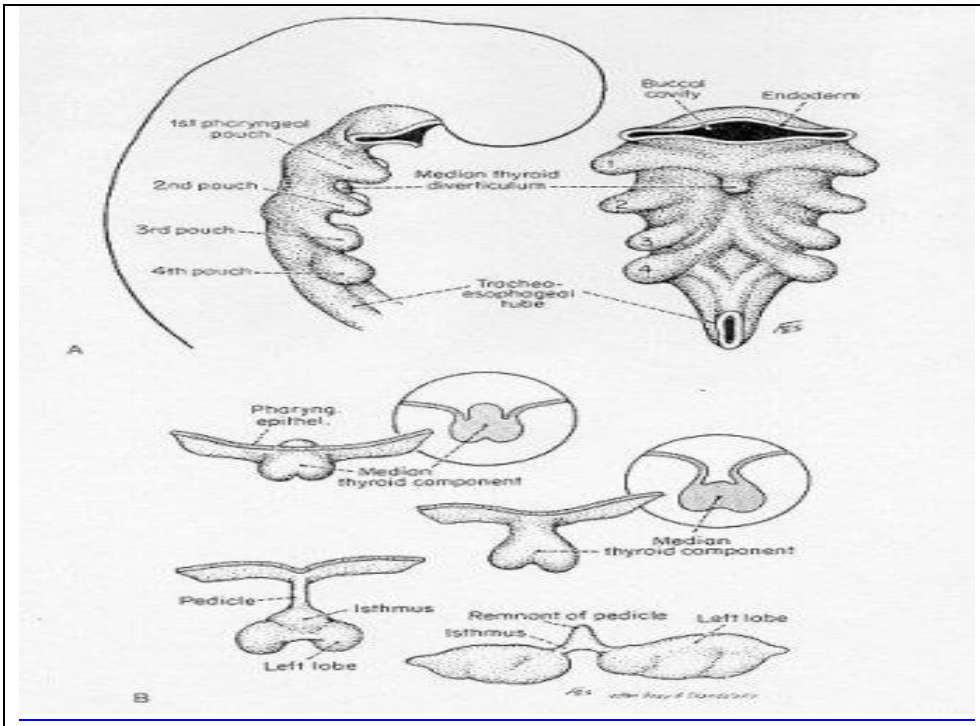
Proximity of the external branch of the superior laryngeal nerve to the superior thyroid vessels is clearly shown.



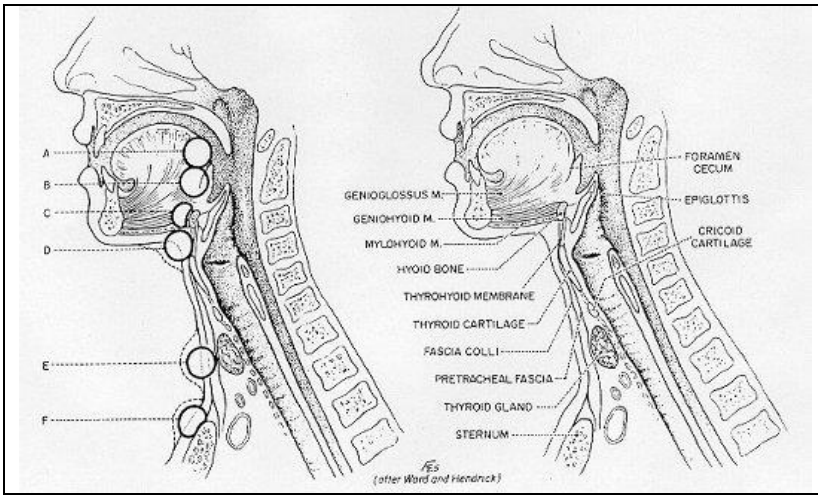
A) Normal anatomy of the recurrent laryngeal nerve. Note that on the right side the recurrent laryngeal nerve hooks around behind the subclavian artery, while on the left side this nerve passes around behind the aortic arch before ascending in the neck. B) When there is a vascular anomaly of the right 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:

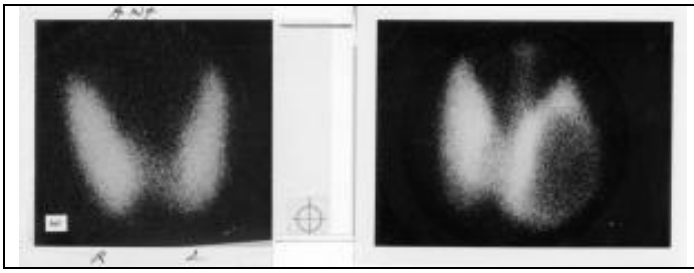
- Most patients of malignant thyroid nodule are euthyroid.
- If the patient has elevated T3 and T4 with low TSH then thyroid scan is indicated to determine hot, warm or cold nodule.
- Serum level of thyroglobulin may be used as tumour markers for well defferentiated carcinoma (its level is normal or 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:

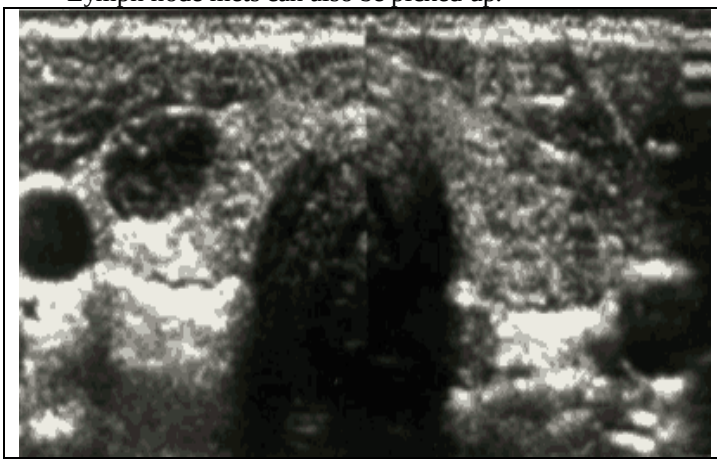
- I 123 does not have the high Beta emission of I 131 Beta emission useful therapeutically, it does not help in diagnostic information and adds to patient's radiation dose.
- I 131 uptake study is indicated for metastatic work up.
- Roughly a thyroid nodule is cold in 85% warm in10% and cold in 5.5%.
- 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.

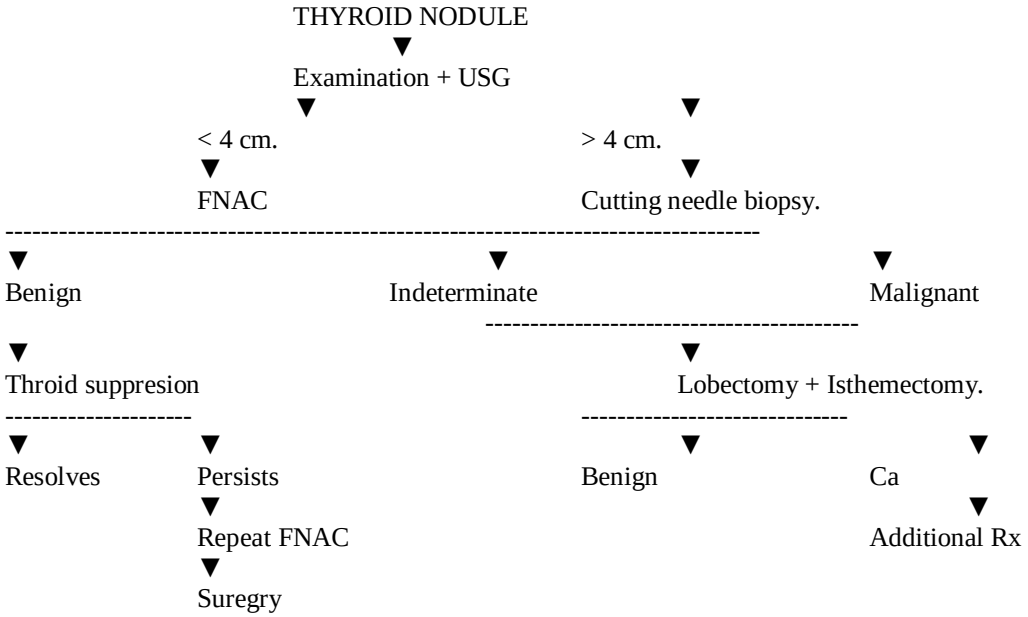


Ultrasooigraphic examination by transverse image of the thyroid containing a solid nodule in the right lobe and a homogeneous appearance of the left lobe. The structure peripheral to the nodule is the internal jugular vein

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

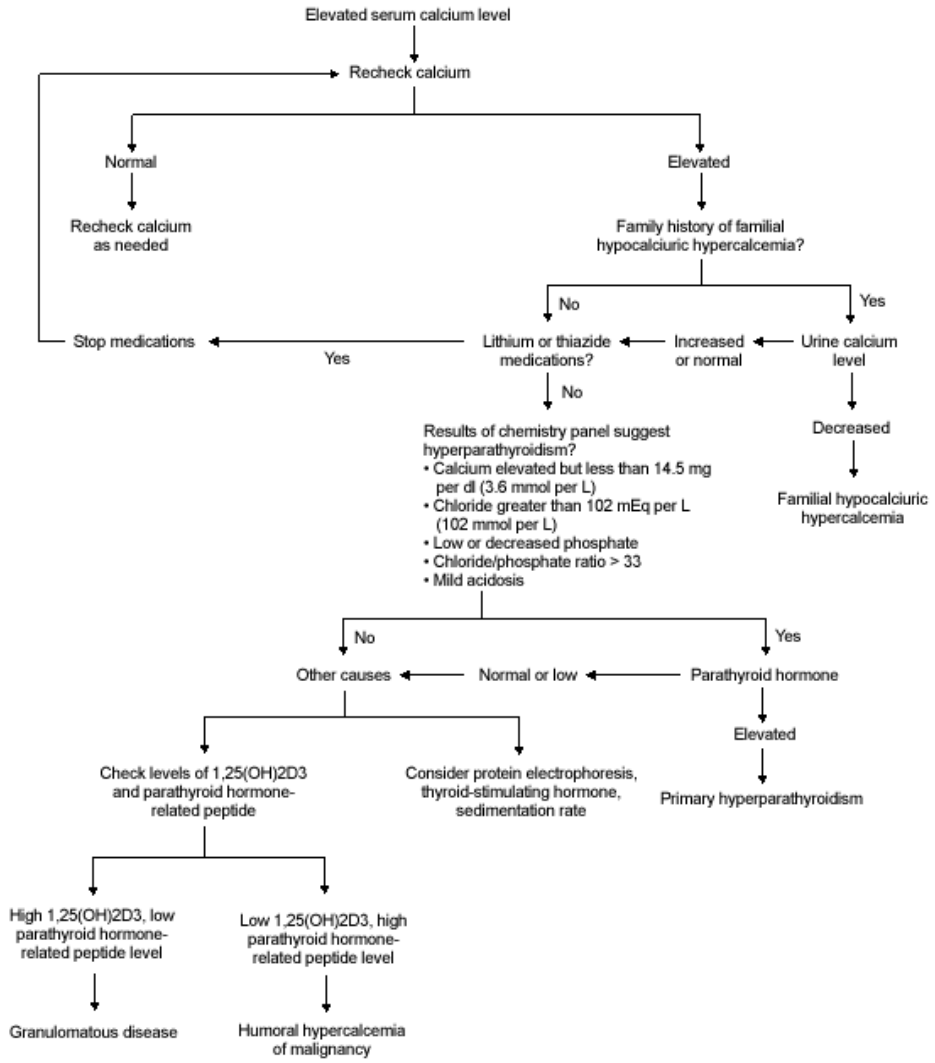
- familial benign (hypocalciuric) hypercalcemia (FHH)
- lithium-induced hypercalcemia, and
- Tertiary hyperparathyroidism.

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.

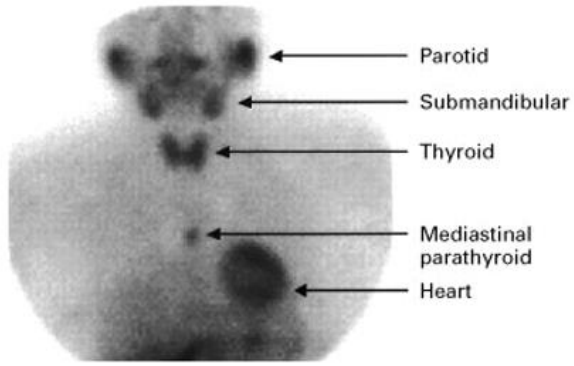
Workup:



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

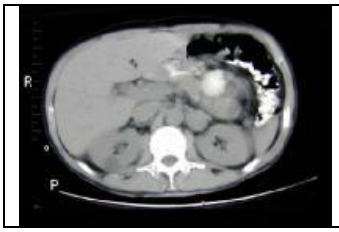
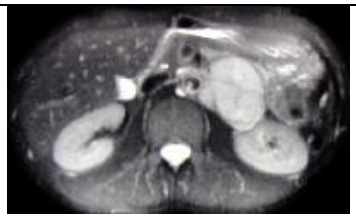
Surgical resection of the tumor is the treatment of choice and usually results in cure of the hypertension.
Careful treatment with alpha- and beta-blockers is required preoperatively to control blood pressure and prevent intraoperative hypertensive crises.

- 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.

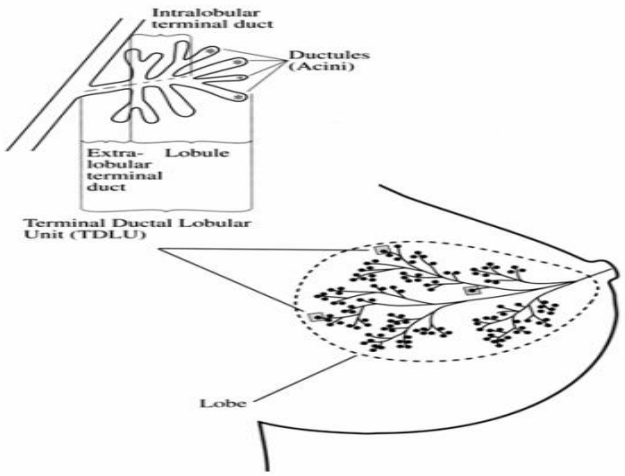
If aldosterone is also deficient, it is replaced with oral doses of fludrocortisone acetate. Patients with secondary adrenal insufficiency do not require aldosterone replacement therapy.

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.

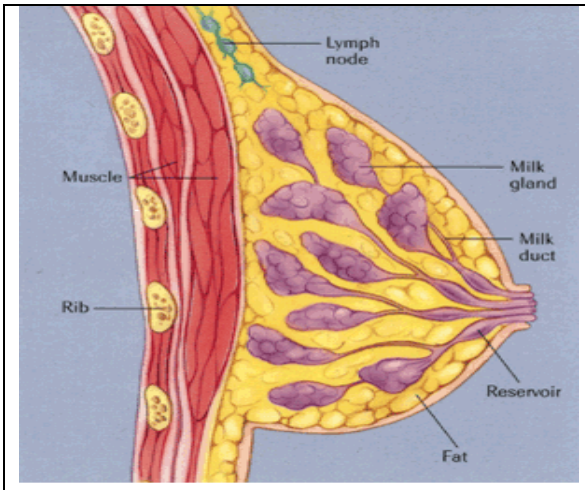
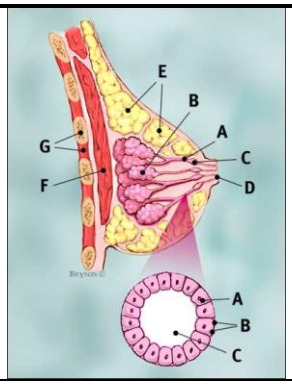
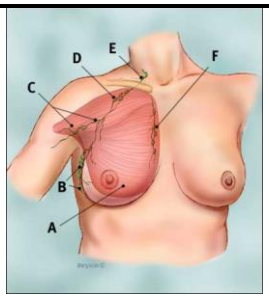


Image made available by a generous grant from Bristol-Myers Squibb

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

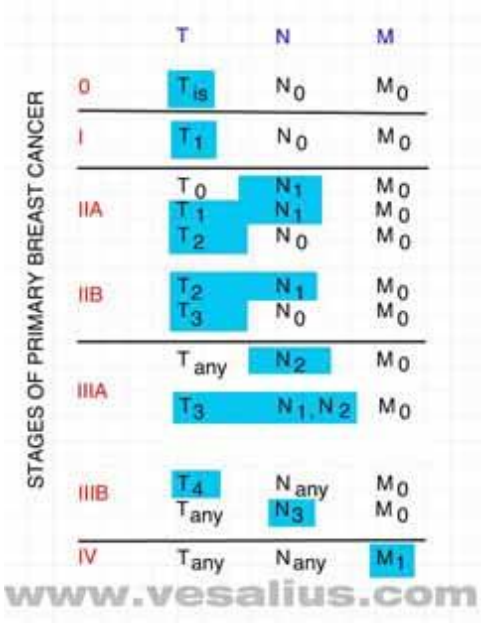
T0: no evidence of primary tumor **Tis**: carcinoma in situ **T1**: < 2cm **T1a**: <0.5cm **T1b**: 0.5-1cm **T1c**: 1-2cm **T2**: 2-5cm **T3**: >5cm **T4**: any size, extension to skin or chest	**N0**: no regional lymph node metastasis **N1**: cancer in movable nodes, same side **N2**: cancer in fixed 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.

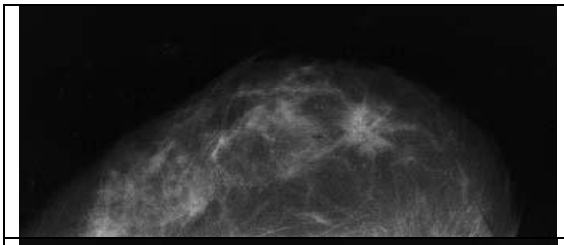
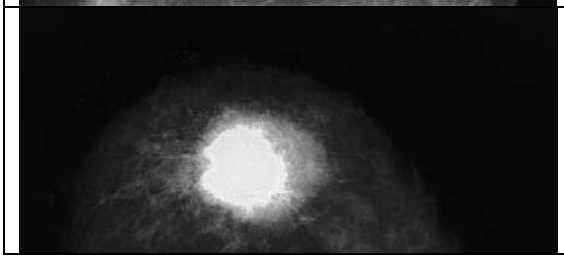
Stage IV is distant **metastasis** (including supraclavicular lymph nodes on the same side as the primary tumor).
Breast cancer most commonly spreads to **bone, lungs, brain** and **liver**. Diagnosis of metastasis may be made by bone scan, brain scan, X-ray, abdominal CT and lab tests. Stage IV disease 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

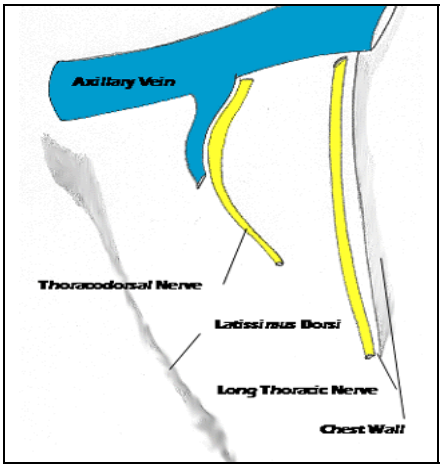
MASTECTOMY: Definitions of Standard Mastectomy Types

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.***

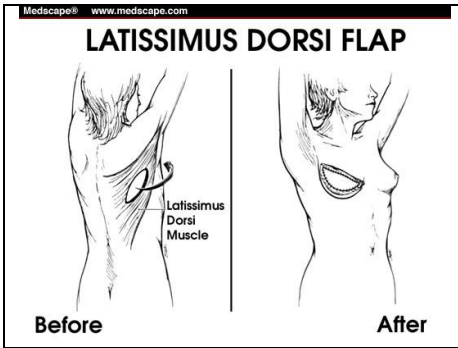
The *latissimus dorsi flap* utilizes the back muscle with its overlying tissue and skin, rotated around to the mastectomy defect. The latissimus dorsi flap is appropriate for replacing small- to moderate-sized breasts; candidates include women who smoke, have extensive abdominal scarring, or are morbidly obese. The

disadvantages: This surgery requires an additional scar on the patient's back and occasionally diminishes overhead strength.

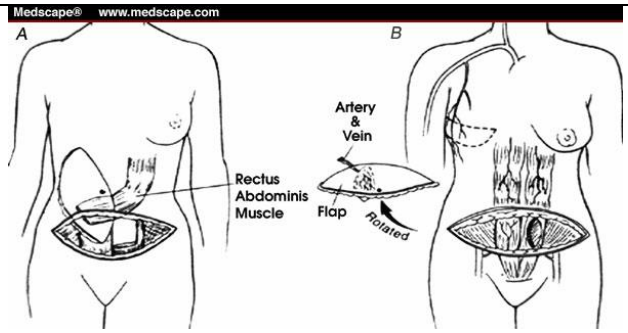
The *transverse rectus abdominis myocutaneous (TRAM) flap* is currently considered the gold standard of breast reconstruction. This autologous tissue transfer is well suited for immediate reconstruction. ***The conventional TRAM flap or pedicle flap is supplied superiorly by the superior epigastric artery 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.