First let us review the normal anatomy and histology of the stomach. The stomach consists of the cardia, the fundus, the body, transitional zone, the antrum and pylorus. Histologically the surface epithelium contains many depressions or pits lined by simple columnar epithelium. Below the epithelium of the body and fundus are many straight glands containing chief cells and parietal cells. The glands of the antrum are branching mucous glands. Normal gastric mucosa is pale red in colour on gastroscopic examination. For anatomic study a stomach is opened along its greater curvature. In this specimen the lesser curvature runs down the middle. At the top is the cardia and at the bottom the pylorus.

CHRONIC GASTRITIS.

Chronic superficial gastritis
This is the most common type of chronic gastritis. Gastroscopy reveals a red, congested mucosa. On closer examination a red-white mottling is present. This type of gastritis most frequently affects the antrum. Histologically there are many chronic inflammatory cells in the superficial lamina propria, consisting mainly of lymphocytes and plasma cells.

Chronic atrophic gastritis
The most prominent feature here is atrophy and thinning of the mucosa. In this specimen normal mucosa is present in parts of body. In other parts the rugal folds have become flattened, This gives the surface a granular appearance.

On gastroscopic examination, mucosal atrophy causes the underlying blood vessels to become visible. In severe cases, this change spreads to involve the fundus, the body and the antrum. This shows the irregular mucosal granularity in chronic atrophic gastritis. In this picture compare on the left normal gastric mucosa, and on the right is the mucosa of atrophic gastritis. In this condition there is loss of chief and parietal cells, with replacement by mucous cells. The mucosa of the body resembles that of pylorus, hence this is called pseudopyloric metaplasia.

Another change is called intestinal metaplasia, which is so termed because of the presence of goblet cells, ciliated cells, and paneth cells. These cells belong to intestinal mucosa. Intestinal metaplasia is closely related to the development of the intestinal type of gastric carcinoma. In the lamina propria there is a marked lymphocytic and plasma cell infiltration. Often the lymphocytic and plasma cell infiltration is so marked as to produce lymphoid aggregates, as seen here.

Chronic hypertrophic gastritis
In this condition the rugal folds are thickened and enlarged to resemble cerebral convolutions. The surface of the rugae are dotted with superficial erosions. Gastroscopy reveals the thick mucosa and irregular rugal folds. Here is a close-up of a giant rugal fold.

PEPTIC ULCER
Peptic ulcers are mainly found in the stomach and duodenum. Duodenal ulcers commonly occur in the first part or bulb of the duodenum. Grossly, it is a circular punched-out defect, usually less than 2 cm in diameter. The margins are clean and the base is flat. Note that the small arteries at the base of the ulcer are ruptured and show evidence of bleeding. Gastric ulcers frequently occur in the pylorus and lesser curvature. This ulcer is circular, its margins are clean and the base shows evidence of previous bleeding. The ulcer itself is a depression extending down to the muscle coat. The base and sides of the ulcer are composed of thick fibrous tissue.
On microscopic section, four layers can be clearly identified: the superficial layer is a layer of inflammatory exudate containing polymorphs and fibrin. Lower down is a layer of pink necrotic tissue. Below the necrosis is granulation tissue. This is a newly-formed capillary in the granulation tissue and this is a fibroblast. The deepest layer is fibrous tissue or old scar. Because of the longstanding inflammation, arteries at the ulcer base show changes of obliterator endarteritis. The vessel wall is thickened and its lumen narrowed. Neighboring nerve cells and fibres also proliferate.

With proper conservative treatment, granulation tissue fills in the ulcer defect, the mucosa re-epithelializes, the ulcer shrinks and finally disappears. Active ulcers in the stomach or duodenum may perforate and lead to acute complications such as peritonitis. This specimen shows a perforated gastric ulcer. Another complication is rupture of large arteries at the base of the ulcer which causes serious bleeding, with symptoms of hematemesis, melena and shock. Healing duodenal ulcers can contract, leading to narrowing of the pylorus and causing clinical symptoms of obstruction. A small number of cases of gastric ulcer can undergo malignant change. When this occurs the ulcer enlarges, the margins become irregular, and the edges become elevated.

APPENDICITIS

This is a common condition occurring in surgical wards. Most frequently it is the result of obstruction of the lumen with secondary infection. In this specimen, the distal portion of the appendix is completely obstructed by a large fecolith.

The early stage of acute appendicitis is called acute simple appendicitis. The appendix is slightly distended and congested. Histologically there are polymorphs in the wall with patchy necrosis and sloughing of the mucosa. The lumen contains an inflammatory exudate of fibrin and polymorphs.

With worsening of the inflammation, acute phlegmonous appendicitis results. The serosa becomes heavily congested and covered with suppurative exudate. The lumen is markedly distended and filled with necrotic debris which has partially drained out. The wall shows patches of necrosis and hemorrhage. Histologically, the mucosa shows edema, necrosis and hemorrhage with a heavy polymorphonuclear infiltration. The inflammation extends throughout the entire thickness of the wall to involve the submucosa, muscularis propria and serosa.

At a later stage is gangrenous appendicitis. There is marked distension and congestion. Near the tip is a focus of blackish discoloration or gangrene, which is due to vascular congestion and secondary infection by saprophytic organisms.

Chronic appendicitis is the result of longstanding or repeated attacks of acute appendicitis. Sometimes obstruction of the proximal end by fibrosis leads to accumulation of large amounts of mucus and formation of a mucocele.

Viral Hepatitis

This is a viral infection that affects principally hepatocytes, and causes cellular degeneration and necrosis. This electron micrograph shows the type A virus which cause hepatitis A. These are the type B viral particles which cause hepatitis B.

The histological features of both types of hepatitis are similar. Degeneration of the liver cells produces cell swelling and clearing of the cytoplasm. Later on the cells become rounded and the cytoplasm clear. This is called ballooning degeneration or ballooning change. These ballooned cells may rupture and disappear, a process known as "drop-out" necrosis. Single cells may also undergo shrinkage and condensation of their cytoplasm, with increased eosinophilia. Their nuclei become pyknotic and disappear, to produce round, acidophilic bodies. This portal tract and lobule contain a variable amount of inflammatory cell infiltration consisting mainly of mononuclear cells. Sometimes there may be fibroblastic proliferation and bile ductular proliferation in the portal tracts. Within these ductules bile thrombi may be seen. Another feature is hypertrophy and hyperplasia of kupffer
cells. In the kupffer cells there are phagocytosed granules of bile pigment. Binucleated hepatocytes are evidence of compensatory hyperplasia and liver cell regeneration. Bile thrombi may also be seen within the bile canaliculi.

Acute viral hepatitis
Most cases of viral hepatitis are examples of acute hepatitis. This is a liver biopsy in a case of acute hepatitis. There is diffuse hydropic swelling, lobular disarray, and sinusoidal narrowing. Within the lobule are scattered foci of spotty necrosis. In this area there is loss of one or more liver cells. Regeneration and repair, however, can lead to complete restoration of normal hepatic structure. In the portal tracts is a heavy mononuclear inflammatory infiltrate. Generally speaking, acute viral hepatitis is not life-threatening and most patients recover completely.

Fulminant viral hepatitis
This is an uncommonly serious form of hepatitis B or non-A non-B that produces submassive-to-massive necrosis and is usually fatal. Grossly, the liver is soft and markedly shrunken to 400–600 gms in weight.

The decrease in size produces wrinkling of the capsule, and sharp edges. The cut surface is yellowish-brown and the gross features disappear. This change is called acute yellow atrophy of the liver.

Histologically there is large scale liquefaction necrosis with few hepatocytes remaining. The sinusoids are dilated and congested, and there may even be hemorrhage. Portal tracts contain an inflammatory infiltrate consisting mainly of lymphocytes and macrophages.

Subacute hepatic necrosis
This disease has a longer clinical course than acute fulminant hepatitis. Grossly, the liver is small, firm and its out surface contains brown-yellow areas of necrosis. Necrosis may involve portal tracts or central veins to form bridging necrosis between portal tracts, or between portal tracts and central veins. Bridging necrosis encloses islands of preserved parenchyma. Evidence of nodular regeneration may also be present. When nodular regeneration occurs in an area of fibrosis or collapsed reticulin framework, normal hepatic lobular architecture is lost.

Chronic hepatitis
In China this condition is defined as persistence of clinical or biochemical evidence of acute hepatitis for over one year. The two types are chronic persistent hepatitis shown here on the left and chronic active hepatitis shown on the right.

Chronic persistent hepatitis
In this type of chronic hepatitis, the histological changes are mild, and consist mainly of a chronic inflammatory infiltrate in the portal tracts. There is preservation of the limiting plates, a mild degree of hepatocellular degeneration, and no necrosis. The prognosis is good.

Chronic active hepatitis
This is a more serious disease which produces a greater number of changes in the hepatocytes. The portal tracts contain a heavy infiltrate of inflammatory cells which destroys the limiting plates and spills out into lobule. Cellular degeneration is more severe. There is piecemeal necrosis. In severe cases there may be bridging necrosis. In hepatitis B carriers and in patients with chronic hepatitis, some liver cells have a peculiar appearance, with finely granular eosinophilic cytoplasm. These cells are called "ground glass" cells. In their cytoplasm are large quantities of HBsAg which are immunoperoxidase positive.
CIRRHOSIS OF THE LIVER

This is a common chronic condition of the liver. Cirrhosis may result from any condition in which there is necrosis, fibrosis and regeneration of liver cells. Normal lobular architecture and blood supply are destroyed. Diffuse fibrosis and irregular regeneration transform the entire liver into a firm, distorted, multinodular structure. Histologically, thick bands of fibrous tissue dissect the lobules into irregular islands of cells. These islands are called pseudolobules. The liver cells in these islands are arranged in cords that are two layers thick because of cellular hyperplasia. Hepatocytes that show regeneration are large, deeply-stained and binucleated. The pseudolobules are irregular in shape and size. Some pseudolobules have no central vein; others have one or more than one central vein; or more than one portal tract. Cirrhosis can be subdivided into several types:

**Portal cirrhosis**

The liver is small, firm and nodular and the capsule is thickened. Fibrous septa divide the liver into diffuse islands measuring 0.1~0.5cm in diameter. The septa are thin and the nodules fairly regular in size. This type of cirrhosis is also called micronodular cirrhosis. Note here the destruction of normal liver architecture. Fibrous bands divide the cells into nodules. The fibrous bands are thin and the nodules are fairly uniform in size. Portal cirrhosis generally is the outcome of chronic active hepatitis or chronic alcohol abuse.

**Postnecrotic cirrhosis**

This corresponds to macronodular cirrhosis or mixed micro/macronodular cirrhosis. The liver is shrunken and replaced by nodules of varying sizes. Generally, the septa are thick or the septa vary in thickness. The nodules range in size from 0.5 to 1.5cm in diameter, but may be even larger. On histological section the pseudolobules are of different sizes. Large pseudolobules are several times the size of normal lobules. Fibrous septa are thick and infiltrated by mononuclear cells. Bile ductular proliferation is also seen. This type of cirrhosis is frequently the result of subacute necrosis, recurrent chronic active hepatitis or chronic alcohol abuse.

**Biliary cirrhosis**

Secondary biliary cirrhosis results from biliary tract obstruction and stasis. The liver is stained yellow-green but is not altered in size. Grossly, the lobules are not clearly defined. On closer inspection there are alternating foci of yellow-green staining. Histologically there are fibrosis an inflammation of the portal tracts. Pseudolobules, though are not seen, bile thrombi are present in the canaliculi. Within the hepatocytes bile pigment may also be seen. This can cause swelling and partial clearing of the cytoplasm. In severe cases feathery degeneration may occur.

Fibrosis and regeneration in cirrhosis distort the hepatic vasculature. The portal and systemic circulations are compressed. Portal out-flow in the liver is obstructed. Collateral vessels develop between the hepatic artery and portal vein. This leads to symptoms of portal hypertension.

Shunting of blood from the portal to systemic circulation occurs by several routes: In one route blood flows from the short gastric veins to the esophageal vein, the azygos vein and the superior vena cava. This route leads to dilatation of the veins at the lower segment of the esophagus. Note the tortuous, dilated veins in this specimen of esophagus. Rupture of these varices can cause massive hematemesis. A second route is via the umbilical and paraumbilical veins to the superficial abdominal veins and the superior and inferior vena cavae. This route leads to the formation of umbilical varices as shown in this photograph. The third route is via the superior rectal vein and rectal plexus to the internal iliac vein and the inferior vena cava. This route gives rise to dilatation of the veins of the rectal plexus. These hemorrhoids may rupture and bleed. The portal hypertension and poor liver function lead to ascites. Here is an example of gross ascites.

Disturbance of bile metabolism leads to jaundice. This jaundiced patient has yellow...
discoloration of the sclera and the skin. Impaired the hepatic function causes high circulating estrogen levels which lead to gynecomastia and spider angiomas which are dilated terminal arterioles. Cirrhotic patients have a bleeding tendency, and mucosal and subcutaneous bleeding can occur. This is an example of subcutaneous bleeding in the arm. This picture shows palmar erythema. In the terminal stage hepatic coma occurs and is a frequent cause of death in these patients.

**DISEASES OF THE DIGESTIVE SYSTEM (PART 2)**

In this section we will discuss a few common malignant tumors of the gastrointestinal system.

**ESOPHAGEAL CARCINOMA**

Esophageal cancer is one of the most commonly encountered malignant tumors in China. One high risk area is Lingxian County in Henan Province. The highest incidence occurs in the Taihang Mountain region.

A normal esophagus is lined by stratified squamous epithelium. Beneath the epithelium is lamina propria and muscularis mucosa. The submucosa is loose connective tissue containing mucous glands, blood vessels and lymphatics. The muscularis propria consists of concentric layers of circular and longitudinal muscle which are bound by an outer layer of fibrous adventitia. Most esophageal cancers arise from the squamous epithelium. However there are a small number of adenocarcinomas arising from the submucous glands.

Esophageal cancer is divided into early and advanced stage. This is a case of advanced carcinoma. This is early stage cancer. It has a good prognosis with a 5 year survival rate of over 90%. Early-stage cancer includes carcinoma-in-situ (CIS), intramucosal carcinoma and submucosal carcinoma. In CIS, cancer cells are confined to the epithelium without destruction of the basement membrane. When the tumor infiltrates the basement membrane, it then becomes either intramucosal or submucosa.

Gross examination of early carcinoma may show a papillary, flat or ulcerating lesion. In this specimen there are two separate foci of cancer. This focus is a flat lesion with an uneven surface. This focus is a superficial shaggy erosion. Late-stage carcinoma may disrupt the muscle coat and adventitia to involve neighboring structures or may undergo lymphatic spread.

Four gross patterns of advanced carcinoma are recognized:

1. Medullary type. These tumors spread along the wall of the esophagus, leading to circumferential thickening and narrowing of the esophageal lumen. Cut surface is grey and the tumor has a soft consistency.

2. Fungating type. Fungating tumors form large intraluminal masses that protrude above the surrounding mucosa.

3. Ulcerative type. These tumors form large ulcers that have irregular elevated borders and rough uneven bases. Generally these cancers involve large portions of the esophagus.

4. Stenosing type. Direct infiltration of the entire lower end of the esophagus has led to narrowing of the lumen. Because of the large proportion of fibrous tissue within the tumor the esophagus is thickened and firm, giving rise to clinical symptoms of dysphagia, or obstruction.

Twenty percent of all esophageal cancers arise in the upper third. From this location they metastasize to LN of the neck and upper mediastinum. Another 50% arise in the middle third. These tumors can spread by direct infiltration, and lead to the formation of tracheo-esophageal fistulae. Lymphatic spread to the tracheo-bronchial LN may also occur. Another 30% arise in the lower third, and metastasize to the LN of the cardia and abdomen.
CARCINOMA OF THE STOMACH

Gastric cancer is a common gastrointestinal malignancy in China. Cancer mortality statistics rank gastric cancer as the number 1 or 2 killer in many parts of the country. The most frequently involved site is the antrum.

The distinction between early and late stages depends on involvement of the muscle coat. This tumor has infiltrated the muscle. Early cancer includes both intramucosal and submucosal cancer. This is an example of intramucosal cancer. The 5-yr survival rate of early gastric cancer following surgical resection is around 90% and is much higher than that for late stage tumors. The following gross types of early cancer are recognized:

1. Protruding type, or type 1: This tumor is polypoid, and has a short wide stalk and uneven surface.
2. Superficial type or type 2: The surface of this lesion is flat. According to gross morphology three subtypes are distinguished:
   ① This is superficial elevated or type 2A, which is also known as sessile malignant polyp. This tumor is only slightly elevated above its surroundings.
   ② This is the superficial flat type or type 2B. In this specimen the tumor is represented by a linear ulcer surrounded by flat rough mucosa that has rugal folds.
   ③ This is superficial depressed type, or type 2C. This tumor consists of a central erosion with an uneven base. Typically the rugal folds radiate from the margins of the erosion.
3. The third pattern of early carcinoma is the excavated type. Here tumor presents as a deep ulcer extending down to the muscle coat. The ulcer has dirty white base and uneven margins which contain early cancer. The rugal folds converge on the margins of the ulcer.

Late gastric carcinoma has four gross patterns:
1. Polypoid type: These are large fungating tumors protruding into the gastric lumen.
2. Ulcerative type: This tumor resembles a crater. The margins of the ulcer are irregular and elevated, the ulcer base is uneven, and shows evidence of hemorrhage and necrosis.
3. Infiltrating tumors: The stomach wall is diffusely infiltrated. There are no distinct tumor margins. Rugal folds are effaced. Many shallow erosions may be present. Grey tumor streaks can be seen extending through the muscle to the serosa. The stomach becomes thickened, rigid and contracted, hence the name "leather bottle stomach" or linitis plastica.

Mucoid carcinoma is a histological variant of the types mentioned above, and is also readily recognized on gross examination. This ulcerating mucoid cancer is soft and has a gelatinous appearance because of the mucus produced by the tumor. These tumors are also known as colloid carcinoma.

Histologically there are four types.
1. Adenoacarcinoma is the most frequent variety. The tumor cells are arranged in glandular formation. The three subtypes are tubular adenocarcinoma, with tall columnar cells, papillary adenocarcinoma, with papillary ingrowths within the glands, and acinar adenocarcinoma in which low cuboidal cells form acini that enclose small glandular spaces.
2. This is medullary carcinoma. This highly malignant tumor grows in sheets composed of large anaplastic pleomorphic tumor cells.
3. This is scirrhouls carcinoma. In this variety, cords of round or spindled malignant cells are embedded in dense fibrous stroma. This tumor is highly malignant.
4. This is mucoid carcinoma. This tumor is made up of signet-ring cells. The cytoplasm of these cells contain mucus. The nuclei are pushed to one side producing the characteristic signet-ring cells. This is also a highly malignant type of gastric cancer.

Metastasis occurs mainly by the lymphatic route. From the lesser curvature and subpyloric
lymph nodes tumor spreads to the lymph nodes of the porta hepatis and then to the liver. Tumors along the greater curvature spread to the greater curvature nodes and the omental nodes. Late stage peritoneal seeding and spread may also occur.

**CARCINOMA OF THE LARGE INTESTINE**

In China cancer of the colon has a lower incidence than cancer of either the stomach or esophagus, but nevertheless it is frequently seen. Fifty percent of large intestinal cancers arise in the rectum; 20% arise in the sigmoid colon; another 16% arise in the cecum and ascending colon; and the remainder arise in the transverse and descending colon. The majority of colonic cancers are adenocarcinoma. There are a small number of squamous carcinomas that arise from the anal canal.

Adenocarcinomas have the following histological patterns:

1. papillary adenocarcinomas with papillary structures lined by columnar cells;
2. tubular adenocarcinomas which contain malignant cells arranged in tubular formation;
3. mucoid adenocarcinoma in which large amounts of secreted mucus form mucus lakes with fragments of tumor cells floating in the mucus;
4. another pattern of adenocarcinoma is the signet-ring carcinoma composed of signet-ring cells.

According to gross morphology there are four patterns of colon cancer.

1. Polypoid type, which is a large bulky cauliflower growth with papillary surface projections.
2. Ulcerating tumors are crater-like ulcers with hemorrhage and necrosis in the base and heaped-up margins. These tumors have a firm consistency.
3. Infiltrating tumors contain plenty of fibrous tissue. These tumors in filtrate diffusely to lead to stenosis, thickening and obstruction of the bowel. Note here the proximal dilatation caused by obstruction.
4. The fourth type is mucoid carcinoma. On cut section mucoid carcinoma is gelatinous because of the large amount of secreted mucus. It has an appearance like colloid.

The prognosis of large intestinal cancer is based on depth of invasion and presence of LN metastasis. According to Dukes classification there are three stages:

1. Stage A: Tumors invade the muscle, but do not extend to the serosa and do not have LN metastasis. Five-year-survival-rate is close to 100%.
2. Stage B: Tumors penetrate to serosa, but there is no LN metastasis. Survival is 70%.
3. Stage C: Tumors are transmural with regional and LN metastasis. Survival is 30%. Early diagnosis and treatment, therefore, are essential.

**PRIMARY CARCINOMA OF THE LIVER**

This is a common malignancy that arises from liver cells or bile duct epithelium. Prognosis is poor, with an overall mortality of 95% 6 months after diagnosis. The tumor is considered early stage when there are not more than two nodules less than 3 cm in diameter. Grossly, the tumors are either infiltrating or encapsulated. This is an encapsulated tumor. It has a grey cut surface and is well demarcated from the surroundings.

**Two main histological types are differentiated:**

1. Hepatocellular carcinoma
   - Here the tumor cells resemble normal hepatocytes. The cells are polygonal and have plenty of pink granular cytoplasm. The nuclei are large and hyperchromatic. Tumor cells are arranged in nests and trabeculae, separated by sinusoids. This is a sinusoidal lining cell.

2. Colangiocarcinoma
   - Most of these are well-differentiated tubular adenocarcinomas consisting of columnar or cuboidal cells arranged in a glandular pattern.
Grossly, three patterns of liver cancer are recognized:

1. Massive tumors. These are big solid tumors that often occur in the right lobe and may occupy the entire lobe. The tumors have a yellow-green color and usually there is central necrosis and hemorrhage. The main tumor is surrounded by small discrete satellite nodules.

2. Nodular tumors. There are multiple round and oval tumor nodules of varying sizes. These tumors frequently invade branches of the portal vein.

3. Diffuse tumors. Here the liver is diffusely involved by multiple small nodules. Grossly this pattern closely resembles cirrhosis.

Liver cancer has a propensity to invade branches of the portal vein to form large tumor thrombi that may obstruct the portal vein and lead to portal hypertension. Secondary tumor nodules may develop within the liver or in the lymph nodes of the porta hepatis.

This concludes our discussion of the digestive system.

Chapter 8

DISEASES OF THE URINARY SYSTEM

An adult human kidney measures approximately 12×6×4 cm, and weighs 120~140gms. It has a smooth shiny surface. The cortex and medulla are clearly demarcated. The cortex is roughly one-third the thickness of the medulla. Around the pelvis is a small amount of fatty tissue. The pelvic mucosa is smooth, white, and glistening. From the bases of the renal pyramids, parallel streaks radiate outwards to form the medullary rays. The interlobar vessels run between the pyramids. At the corticomedullary junction they give rise to the arcuate arteries.

The functional and structural unit of the kidney is the nephron, which consists of renal glomerulus and tubule. The renal glomerulus consists of a tuft of capillaries each of which is surrounded by a double-walled epithelial capsule called Bowman's capsule. The parietal layer of Bowman's capsule is a single layer of epithelium. The visceral layer consists of cells called podocytes, and is separated from the parietal layer by the capsular space. The glomerulus is formed of 7~8 capillary tufts which are not clearly discernible. The capillaries are lined by endothelial cells. This is the glomerular stalk or vascular pole. Between the capillaries is the mesangium, which contains mesangial cells. Silver stains reveal the thin continuous layer of capillary basement membrane (BM). This is the BM of Bowman's capsule. With SEM the glomerular tuft is revealed as a tortuous network of capillaries. The podocytes can be seen on the capillary surface. From the podocytes arise primary processes which give rise to secondary processes that interdigitate and are separated by filtration slits. The secondary processes are separated from the capillary lumina by BM and endothelium.

Let us examine this filtration barrier. This is the capillary lumen and endothelial cell nucleus. The endothelial cell cytoplasm is fenestrated. Here is endothelial cytoplasm, BM and filtration slits. The filtration slits and BM are negatively charged, a fact which is of vital importance to the filtration process. Capillary blood is filtered through the endothelial cell fenestrations, BM and filtration slits, and enters the urinary space. These three layers constitute the filtration barrier.

**GLOMERULONEPHRITIS**

Glomerulonephritis (GN) is nonsuppurative inflammation of the renal glomeruli, which is hypersensitive in etiology.

It is divided into two groups according to pathogenesis. One group of GN results from formation of in-situ immune complex. This group has two subtypes: one subtype is anti-BM
nephritis. Here antibodies combine with intrinsic cross-reacting antigens in the BM. This results in complement activation and release of chemotactic factors. Neutrophil diapedesis, platelet aggregation, and fibrin exudation occurs, with resulting glomerular injury. This type of injury is uncommon, but is a serious form of glomerular injury that leads to renal failure. Examples include Goodpasture's disease and other forms of rapidly progressive GN. In the second subgroup, antigens lodge in the BM where the resulting antigen-antibody reactions damage the glomeruli. Examples include membranous and membrano-proliferative GN.

The second large group of GN is due to circulating immune complexes. Antibodies against nonglomerular antigens form antigen-antibody complexes in the circulation. These small and medium-sized complexes enter the kidneys and are trapped within the BM to cause injury. This is the commonest mechanism of injury in GN. Acute diffuse proliferative GN belongs to this group. Immune complexes are deposited as subepithelial humps, as shown here. In this disease there is also endothelial and mechanical proliferation, protein leakage and red cell diapedesis.

**Acute diffuse proliferate GN.**

This disease occurs most frequently in school-aged children. The majority of patients have a recent history of streptococcal B throat infections, hence this is also called acute post-streptococcal GN. This is an immune complex GN. Large numbers of medium-sized soluble immune complexes in the circulation are deposited between the epithelium and BM. Under BM these complexes form electron-dense deposits or humps as shown here. This is the BM. Immunofluorescence (IF) reveals granular deposits of IgG and C3 in a punctuate pattern. These complexes are the direct cause of the GN.

Under light microscopy (LM), the glomeruli appear swelling. There is increase in the number of cells. These cells consist of mesangial cells, endothelial cells and neutrophils. Swelling and proliferation of endothelial cells lead to capillary narrowing. As a result of capillary narrowing, glomerular ischemia, and clinical oliguria result. The glomeruli contain large numbers of neutrophils. Within the Bowman’s space are small numbers of neutrophils and RBCs. These changes are diffuse and bilateral. The majority of glomeruli show these changes.

Sometimes red cell extravasation is marked and this is called acute hemorrhagic GN. When fibrinoid necrosis is present, it is called acute necrotic GN. The renal tubules may contain protein-derived hyaline casts, or cellular casts derived from red and white blood cells. With disintegration of the red cells these casts become granular casts. These casts constitute part of the urinary abnormalities in these patients. This is a granular cast. Gross examination reveals bilateral symmetrical enlargement of the kidneys. The outer surface is tense, shiny and red due to congestion. Sometimes multiple petechia are present. Such kidneys are called flea-bitten kidneys.

This disease occurs more commonly in children. Important clinical findings are hematuria and proteinuria. This is a normal urine specimen. This urine specimen is red from massive hematuria, and this urine specimen is orange due to mild hematuria. Patients develop mild to moderate edema that is most evident in the periorbital loose connective tissue. Edema is the result of salt and water retention and increased capillary permeability. This disease presents clinically as acute nephritic syndrome. Acute diffuse proliferative GN carries a good prognosis. With treatment the majority of patients recover within a month. In rare cases the disease develops into crescentic GN or chronic sclerosing GN.

**Crescentic glomerulonephritis**

This is also called rapidly progressive GN. It has sudden onset and a rapid clinical course. Patients tend to become very ill. There is marked bilateral renal enlargement and petechial hemorrhages. Crescentic GN may evolve from any of the nephritides in which there is damage to the BM. BM perforations or defects lead to proliferation of cells of Bowman’s capsule which then form
EM reveals an unevenly thickened BM with many dense deposits at different levels. This is an intramembranous deposit. The BM defects are then filled by podocyte cytoplasm. This damage to the BM leads to leakage of blood cells, mononuclear cell infiltration and proliferation of cells of the Bowman's capsule. Light microscopy reveals proliferation of parietal cells and increase in mononuclear cells which lead to crescent formation. This is the pathognomonic feature of crescentic GN. Crescents may occupy a large portion of the urinary space, compressing the glomrulus. Crescents can also surround the entire glomerulus and obstruct the urinary tubule. PAS + ve material in the crescent represents fibrin, which is responsible for stimulating the growth of the epithelial cells. These changes are bilateral, diffuse and may affect over 50% of all glomeruli, causing severe decrease in renal function, anuria, oliguria, azotemia and uremia. With healing and organization of the crescents an irreversible change occurs. The glomeruli become sclerotic and hyalinized, and the surrounding tubules atrophy and disappear. Some of the crescents are of the immune complex type. Circulating immune complexes (IC) can be detected in the blood. Immunofluorescence shows finely granular staining that is + ve for Ig and complement.

Other forms of crescentic GN are due to anti BM antibodies. For example, in Goodpasture's disease there is linear staining due to BM antibody. Apart from the renal changes, these patients also suffer from pulmonary hemorrhages. This is a lung from a patient with Goodpasture's disease. Immunofluorescence (IF) shows + ve linear staining for Ig in the alveolar BM. Some cases of crescentic GN, however, are negative on IF examination, indicating that the pathogenesis of crescentic GN is complex and multifactorial.

Membranous glomrulonephritis (MGN)

MGN is a chronic immune complex disease. There is prolonged deposition of medium-sized circulating immune complexes on the epithelial side of the glomerular BM. It shows granular staining + ve for IgG and C3. The antibodies in this condition may be produced against endogenous antigens, such as antinuclear antibodies in SLE. Examples of exogenous antigens are HBV, penicillamine etc. In a light microscope slide there is uniform thickening of the capillary walls, but there is no mesangial proliferation and no inflammatory infiltrate. In the late stages the BM is markedly thickened, and the capillaries narrowed and obstructed. The glomerulus becomes hyalinized.

With silver stains the thickened BM and characteristic deposits in the form of spikes and domes are clearly seen. There are many electron dense deposits located between the BM and epithelial cell. The BM is thickened with irregular spikes protruding from the capillary lumen. There are fused foot processes and this is an electron dense deposit. The gross appearance is that of swollen and large pale kidneys.

The main clinical feature is heavy proteinuria. The test tube on the left contains a specimen of freshly voided urine that is frothy because of the large amount of protein. In the tube on the right, boiling has led to precipitation of the contained protein. This protein loss is secondary to leakage due to BM damage. Protein loss leads to hypoproteinemia and generalized edema, or anasarca. This is peripheral edema in the lower extremities. This group of symptoms is called the nephrotic syndrome.

Mesangiocapillary GN

This condition is also called membranoproliferative GN. The majority are due to large circulating immune complexes which are trapped between the endothelium and BM. In this position they activate complement and lead to inflammation. Both granular and linear deposits of IgG and C3 can be detected on IF. The presence of these deposits stimulate the proliferation of mesangial cells and matrix. The cells and mesangial matrix extend into the BM, causing it to thicken and to split into an outer and inner layer. The increase in mesangial cells and mesangial matrix, BM thickening and
splitting are characteristic features of mesangiocapillary GN.

Under LM increased mesangial cells and matrix are seen. As a result of this mesangial proliferation the glomeruli show clear lobulations. The capillary lumina are narrowed and almost obliterated by the irregularly thickened capillary walls. This thickening is revealed in a PAS stain. The splitting of the BM gives the capillary walls a "train-track" appearance. Recurrent episodes of disease lead to a hyaline change in the mesangial matrix. Frequently the disease is chronic and progressive. Patients develop chronic renal failure. In a small number of patients the prognosis is poor. The disease runs an acute course, with florid crescent formation.

**Minimal change GN**

This condition is also called lipoid nephrosis. Both kidneys are swollen and pale yellow in colour. Under LM the glomeruli appear normal. There is no increase in cellularity, no inflammatory infiltrate and no BM abnormalities. However, in the cells of the proximal convoluted tubules, there are fatty vacuoles, or hyaline droplets. EM shows fusion and obliteration of the podocyte foot processes. Hence this is sometimes called foot process disease. These are fused foot processes, BM and this is the endothelial cell cytoplasm, this disease also has an immune basis, but is not due to immune complex deposition. Possibly, it is due to the presence of a lymphokine-like substance. Minimal change GN has a good prognosis.

**Chronic Sclerosing GN**

This is also known as chronic GN. It is the end stage of many other forms of GN. Crescentic GN progresses rapidly to chronic sclerosing GN, most mesangiocapillary and most membranous GN evolve more slowly. There are a few cases of acute diffuse progressive GN and rare cases of minimal change GN that may also develop into CSGN. Grossly the kidneys are small, pale and firm, with a granular surface. The cortex is thin and shows loss of normal linear streaks. Peripelvic fat is increased. Most of the cortical glomeruli are fibrosed or hyalinized. The surrounding tubules either atrophy or disappear. The normal glomeruli remaining hypertrophy and their tubules dilate. The lining cells of the proximal convoluted tubules become high columnar and contain hyaline droplets. There is interstitial fibrosis and lymphocytic infiltration. Patients with chronic renal failure (CRF) develop hypertension, anemia, azotemia, polyuria, nocturia, hypotonic urine and uremia. These symptoms and signs are known as chronic nephritic syndrome, and are secondary to renal parenchymal damage. This is a patient with CRF.

**Pyelonephritis (PN)**

PN is suppurative inflammation of the pelvis and interstitium. Urinary and tissue cultures are +ve for pathogenic organisms. The infection may originate from distant sites and reach the kidneys via the blood stream. Staphylococcal infections commonly use this route. The other route is ascending infection from the bladder and urethra. The principle organism here is E. Coli. Urethral obstruction from any cause predisposes to infection. Commonly these are stones, uretero-pelvic fibrosis, gravid uterus and tumors. In acute PN, multiple small and large abscesses may be seen on the surface of the kidney. The abscesses are surrounded by rims of congestion. In hematogenous infections abscesses occur in the cortex, as shown in this slide.

In ascending infections suppuration begins in the pelvis, then spreads through the tubules. In this slide large numbers of polymorphs are seen in the tubules. Destruction of the tubules with spread of infection into the interstitium to produce the characteristic abscesses.

The majority of acute PN heal with treatment, but a small number of cases become chronic. This is a specimen of CP. The kidney is atrophic. The surface is uneven, the capsule is thick, and subcapsular abscesses are visible. Because of ureteric obstruction, calyces are dilated and the pelvic papillae are blunt. The pelvic mucosa shows focal ulceration. Cortico-medullary junction is not
clearly defined and there are small abscesses in the parenchyma. The interstitium contains large numbers of inflammatory cells and fibrous tissue. As with all chronic inflammations, infiltrate consists of mononuclear cells such as lymphocytes and plasma cells. In some areas of acute inflammation neutrophils predominate. Atrophic tubules are replaced by fibrous tissue. Beneath the mucosa of the pelvis and calyces are large numbers of chronic inflammatory cells. Some of tubules contain large numbers of neutrophils. Other tubules are dilated and filled with pink proteinaceous casts. The tubular epithelial cells are flattened and the tubules resemble thyroid follicles. Glomeruli are unaffected until the late stages, when fibrosis may occur. Chronic PN frequently occurs, and if these recurrences are bilateral and untreated will lead to persistent hypertension, uremia and death.

**RENEWAL CELL CARCINOMA**

This tumor originates from tubular epithelium. It arises most often in older individuals. It usually arises from one of the kidney poles, commonly the upper pole, as shown here. The tumor may be very large and grey-yellow on cut section, with central necrosis. The tumor is clearly demarcated and separated from the surrounding tissue by a pseudo-capsule.

There are two histological types according to the appearance of the cells. One type is clear cell carcinoma in which the cells are large and polygonal, with clear cytoplasm and well-defined cell borders. The nuclei are central, small and dark-staining. Clear cell renal cell carcinoma may grow in solid nests. Sometimes they may have a glandular or papillary histological appearance. Another cell type of renal cell carcinoma is the granular cell type. Granular cells are round or oval and resemble the cells of the PCT. These tumors are more pleomorphic than the clear cell variants. In mixed tumors both types of cells may be present. Renal cell carcinomas infiltrate surrounding tissue. Here we observe the tumor infiltrating the renal parenchyma. Very often the tumor invades blood vessels and lead to hematogenous metastases. The most common sites for secondary tumor are the lungs, bone and liver. This is a granular renal cell carcinoma metastasing to the lung.

**Nephroblastoma**

Also known as wilm's tumor. This tumor is one of the commonest childhood malignancies. They are large and bulky tumors which are very destructive. Tumor demarcation is clear because of the presence of a pseudocapsule. The tumor is grey-white, soft. It resembles fish flesh. There are large areas of hemorrhage and necrosis. Under light microscopy two components are distinguished: one is the stroma which consists of spindle cells with round or elongated nuclei. The other component consists of primitive glomeruli and tubules. This combination of epithelial and mesenchymal elements make this an adenosarcoma or carcinosarcoma. These patients present chiefly with abdominal masses or pressure symptom such as abdominal pain and vomiting. In the late stages patients may present with lymphatic and hematogenous metastases.

**TUMORS OF BLADDER**

Most of these tumors arise from the bladder epithelium. The majority are therefore transitional cell carcinoma. Sometimes squamous cell carcinomas may also occur. Adenocarcinomas, however, are uncommon. Benign bladder tumors called papillomas are uncommon tumors that frequently arise from the ureteric orifices or the bladder trigone. These tumors may be solitary or multiple. Their surface consist of friable fibropapillary structures which may break off and give rise to painless hematuria. This is a cross-section of a benign papilloma. The central fibrovascular stalk is covered with transitional epithelium. High power reveals an orderly arrangement of the epithelial cells in five layers resembling normal bladder epithelium. There is no anaplasia, but the tumor recurs easily and may undergo malignant change.

Transitional cell carcinoma is the commonest malignant tumor of the bladder. There are three types based on gross appearance. Papillary tumors are exophytic and covered with papillary
structures. The bladder wall shows trabecular hypertrophy because of distal urinary obstruction. A second type of bladder tumor is the cauliflower tumor which is large and bulky. A third type is the flat tumor which spreads intramucosally. Grossly, there are many elevated plaques with ulceration and hemorrhage.

These tumors are divided into three histological grades. This is grade 1 transitional cell carcinoma (TCC). The epithelium is approximately seven layers thick. The cells are arranged in an orderly fashion with slight anaplasia. This is grade 2 TCC; the epithelium is 10~12 layers thick and the cells are more anaplastic. In grade 3 TCC there is marked anaplasia. In this slide there are nests of TCC invading the bladder wall. The prognosis of bladder carcinoma depends on the depth of invasion. When it is confined to the mucosa and superficial muscle the prognosis is good. However when TCC becomes transmural or invades deep muscle the prognosis is very poor.

We have come to the end of our chapter on disease of the urinary system.

**Chapter 9**

**DISEASES OF THE BREAST AND GENITAL SYSTEM**

**CHRONIC CERVICITIS**

Chronic cervicitis is a common gynecological problem encountered in clinical practice. The gross lesion resembles an erosion. The cervical os is surrounded by a well-demarcated area of bright red mucosa. The original squamous epithelium has become necrotic and replaced by regenerated columnar epithelium. In the underlying connective tissue is an infiltrate of lymphocytes and plasma cells.

When the lesion heals squamous epithelium will once again replace columnar epithelium. Regenerating squamous epithelium may extend into glands, and lead to squamous metaplasia of the glands. It is important to distinguish this process from squamous cell carcinoma which it resembles histologically. Sometimes squamous metaplasia in the necks of the glands causes obstruction and cystic dilatation of the underlying glands. In chronic cervicitis the mucosa may proliferate and form polyps. This is a polyp in the cervical canal that has prolapsed through the os.

**ENDOMETRIAL HYPERPLASIA**

Endometrial hyperplasia is a common gynecological disorder which presents as heavy and irregular menstruation. It is due to the effects of continuous and unopposed estrogen on the endometrium.

In this specimen this is the uterine fundus and uterine body. The endometrium shows chronic hyperplasia. It is thickened with many small cysts and pinpoint hemorrhages. A section shows that the thickened endometrium consists of hyperplastic glands and stroma. The cystically dilated glands give it a Swiss cheese appearance. The glandular epithelium is thrown into papillary folds which protrude into the glandular lumina. The cells are pseudostratified, crowded, with many mitotic figures. Some of the hyperplastic epithelial cells are atypical, having large dark nuclei and irregular arrangement. These atypical cells can be considered premalignant and closely related to the development of uterine adenocarcinoma.

**HYPERPLASIA OF PROSTATE**

Also known as benign prostatic hypertrophy, it is common in older men and is related to levels of sex hormones. The prostate becomes large, firm and nodular. On cut surface there are many grey-white nodules and tiny cysts filled with a milky secretion. The enlarged prostatic lobes often
compress urethra causing difficulty in micturition. This predisposes to secondary bladder infection.

This specimen of hemorrhagic cystitis shows severe mucosal congestion and hemorrhages. Under light microscopy the prostate is enlarged and shows cystic hyperplasia. Hyperplastic epithelium projects into the glandular lumina. The cystic spaces contain pink bodies known as corpora amylacea. The lining cells are tall columnar cells, with basal nuclei. In the interstitium there is marked hyperplasia of smooth muscle and fibrous tissue. In this field smooth muscle hyperplasia is marked. A chronic inflammatory infiltrate is present in the interstitium. Studies indicate that prostatic hyperplasia is related to low testosterone levels and high estrogen levels in older men.

**ENDOMETRIOSIS**

In this condition endometrial tissue is found outside the uterine cavity. According to location it is divided into two types uterine and extruterine.

This is uterine endometriosis. The uterus is diffusely involved. The uterine wall is greatly thickened. In the myometrium are many small, discrete hemorrhagic cysts. Diffuse uterine endometriosis is also called adenomyosis. Localized endometriosis is also known as adenomyoma. Histologically, there are nests of endometrial glands and stroma within the myometrium. A comparrison of normal and ectopic endometrium reveals identical histologic features.

The commonest site of endometriosis are the ovaries which become large and cystic. Because of cyclic menstrual changes the cysts are filled with altered blood, the so-called chocolate cysts. This slide shows endometrial glands and stroma within an ovary. Endometriosis may also occur in surgical scars especially pelvic scars. During menstruation these small nodules along the scar become enlarged and tender.

**HYDATIDIFORM MOLE**

Molar pregnancies occurs most frequently in multiparous Women 20–30 years old. Gross examination reveals dilated chorionic villi filled with clear amniotic fluid. The villi resemble clusters of grapes connected by thin stalks.

Histologically the villi are markedly edematous and avascular. It is believed that hydatidiform moles occur after embryo death early in pregnancy. The vessels disappear but villus epithelium continues to absorb mniotic fluid leading to hydropic swelling. The chorionic epithelium is hyperplastic. It contains two kinds of cells. These are cytotrophoblast cells. They have well-defined borders, pale cytoplasm and prominent nucleoli. This is syncytiotrophoblast cells which have indistinct borders, pink cytoplasm and dark nuclei. Since these cells secrete gonadotrophins, markedly elevated levels of HCG are detected in the urine.

This is a normal chorionic villus from an early pregnancy. The internal layer is cytotrophoblast. Surrounding it is syncytiotrophoblast. Developing vessels are also present. In molar pregnancy the hyperplastic trophoblast also possess greater invasive properties than normal, hence moles can be regarded as true neoplasms.

Clinically, the uterus is disproportionately large for the stage of pregnancy. Since there is no fetus, fetal heart beat and fetal parts are not detected and patients feel no fetal movements. The ability of trophoblastic cells to invade blood vessels causes repeated episodes of vaginal bleeding. The high levels of HCG secreted by trophoblastic cells lead to formation of corpus lutein cysts in the ovaries.

The majority of hydatidiform moles can be treated by simple D&C(dilatation and curettage), but 16% of cases become invasive. Trophoblasts of invasive moles infiltrate and invade the myometrium, causing hemorrhage or life-threatening bleeding. This section shows a hydropic villus surrounded by trophoblastic cells which have infiltrated the deep myometrium. This ability to invade is diagnostic of invasive moles. The trophoblast of invasive moles may be very atypical, but
generally speaking, invasive moles do not metastasize to distant sites, and their prognosis is good.

**CHORIOCARCINOMA**

The development of choriocarcinoma is related to pregnancy. Choriocarcinoma may follow normal pregnancy, molar pregnancy or abortions. Grossly the tumor is dark red, nodular, friable and resembles a hematoma. Necrosis is a common finding.

Choriocarcinomas are highly invasive tumors that often penetrate the uterine wall to invade the pelvic cavity. Two histologic components are present: one is cytotrophoblast with clear cell borders, round nuclei, prominent nucleoli and clear nuclear membranes. The other component is syncytiotrophoblast consisting of eosinophilic, pleomorphic cells with indistinct cell borders and dark nuclei. These two types of cells are arranged in sheets. No chorionic villi are found. Necrosis and hemorrhage are prominent and are important diagnostic features of choriocarcinoma.

The principle route of metastasis is the bloodstream. This specimen of lung shows many metastatic nodules which are typically hemorrhagic. The liver is also a frequent metastatic site.

**CARCINOMA OF THE CERVIX UTERI**

Carcinoma of the cervix is one of the commonest malignant tumors in women. Women who develop these tumors tend to be multiparous, marry early, and have a history of cervical trauma or cervical erosions. The majority of cervical carcinomas arise from the squamo-columnar junction of the endocervix. Epithelial dysplasia is the precursor to cervical squamous carcinoma.

Normal cervical squamous epithelium consists of basal cells, prickle cells and granular cells arranged in layers. In dysplasia the basal cells are replaced by cells which have large, irregular and hyperchromatic nuclei. When such atypical cells occupy half the thickness of the epithelium it is known as moderate dysplasia. In severe dysplasia the atypical cells occupy two-thirds or more of the entire thickness of the epithelium. When atypical cells replace the entire thickness of the epithelium the diagnosis is carcinoma-in-situ. Dysplasia is generally considered premalignant, but can be cured with appropriate treatment.

There are three gross patterns for cervical cancers:

1. In the erosive type tumor resembles cervical erosions. The mucosa is red, granular, friable and bleeds easily. Patients develop leukorrhea and contact bleeding. In tumor cells cytoplasmic glycogen is markedly diminished. This negative Schiller test is of diagnostic importance.

   This is a slide of carcinoma-in-situ. The entire epithelium is replaced by tumor. The cells are dark, irregular, and the cell layers are disorganized. The basement membrane, however, is intact. In carcinoma in-situ tumor can extend into glands to replace a part or the entire gland without breaking through the basement membrane, this is called carcinoma-in-situ with glandular involvement. Infiltration of the basement membrane occurs with invasion. Stromal invasion to a depth of 3 to 5 mm is called microinvasive carcinoma.

2. The second gross pattern is the exophytic or cauliflower type. Here a dark red bulky tumor mass protrudes into the uterine cavity. The surface is necrotic. An early symptom is contact bleeding. In the late stages patients complain of copious bloody or foul-smelling discharge because of infection. Sometimes frank bleeding occurs.

3. The third type is the excavating/endophytic type, where the tumor infiltrates deeply into the cervical stroma. The cervix becomes firm and bulky. Necrosis and sloughing may occur to leave a large ulcer or crater. Both the cauliflower and excavating tumors can infiltrate deeply into the stroma.

According to cell type and differentiation cervical cancers can be well-differentiated squamous carcinomas. Here cells have little pleomorphism or anaplasia and there are many keratin pearls. In poorly differentiated squamous carcinoma the cells are spindled, markedly atypical and there are few
or no keratin pearls. A small percentage of cervical carcinomas, are adenocarcinomas arising from endocervical glands.

Extension to adjacent structures may occur. For example, lateral extension to the fornices, upward to the endocervix. Anteriorly involvement of the bladder may cause thickening of the bladder wall and formation of cysto-vaginal fistula. Posterior involvement of the rectum with formation of recto-vaginal fistulae also occur. The principle route, of metastasis in cervical cancers is lymphatic. Tumor spreads from the paracervical nodes to the obturator nodes, the external iliac nodes and then to the common iliac nodes. Hematogenous spread to the lungs and liver may occur in the late stages.

**CARCINOMA OF THE CORPUS UTERI**

This is a common endometrial malignancy of post-menopausal women. The development of uterine adenocarcinoma is related to estrogen levels.

Grossly three microscopic patterns are seen.

In the diffuse type the tumor involves most or all of the endometrium. The endometrium increases, thickens, and becomes shaggy and rough. The tumor is grey white, friable and sloughs easily.

This specimen shows localized tumor involving part of the fundus and posterior wall.

The third type, or polypoid tumors protrude into the uterine cavity as a polypoid masses. When the tumor is very localized, it can be entirely removed by D&C. Later examination of the gross specimen may reveal absence of any residual tumor.

Histologically the majority of uterine cancers are adenocarcinomas which arise from endometrial glands. The glands are crowded, back-to-back, and may share epithelial walls. The glands vary in size and shape and intraglandular tufting may be present. Tumor cells may be atypical, with dark nuclei and frequent mitoses. A few adenocarcinomas have focal squamous metaplasia. These tumors are called adenoacanthomas or adenosquamous carcinomas.

**FIBROCYSTIC DISEASE OF THE BREAST**

This condition is also known as cystic hyperplasia and is common in middle-aged women. It is endocrine related, possibly secondary to high estrogen levels. Fibrocystic disease is commonest in the upper outer quadrant, tends to be bilateral and recurrent, and is related to breast cancer.

Grossly the lesions are non-encapsulated, grey-white and fibrotic. Their cut surfaces contain many small cysts and nodules. Clinically the breast nodules are firm but mobile, a helpful differentiating feature from cancer nodules.

Histology reveals fibrous hyperplasia, ductular hyperplasia and cystically dilated ducts. The epithelia lining the cystic glands are hyperplastic. Lymphocytes are present around the acini. The hyperplastic epithelium is thrown into papillary folds. More marked hyperplasia gives a cribriform pattern to the glands. Sometimes the glands show apocrine metaplasia and apical type of secretion.

**CARCINOMA OF BREAST**

Breast cancer is one of the commonest malignant tumors in women especially women over 40 years of age. The tumor arises from the epithelium of the terminal ductules. Most frequent site of carcinoma is the upper outer quadrant, followed by the upper inner quadrant, the nipple and areola, the lower outer quadrant and lower inner quadrant.

In the early stage the tumor is small and firm and not easily palpated. Often it is discovered only during regular physical check-up. This specimen shows early breast carcinoma. The tumor is grey-white, fibrotic and infiltrates crab-like into the surrounding tissue. Superficial tumors may involve the skin, leading to skin retraction and puckering. Infiltration of dermal lymphatics may be
so extensive as to cause obstruction and lymphedema. The skin becomes thick and pitted because of sweat glands and hair follicles. This change is known as orange peeling. Sometimes an affected breast is shorter than the normal breast because of the proliferation of fibrous tissue which shortens the ducts and causes nipple retraction. In the late stages the tumor enlarges and becomes fixed because of involvement of deep fascia and pectoral muscles. When tumor invades the subcutaneous tissue and skin necrosis and ulceration may occur.

Since the breast is so richly supplied with lymphatics, the main pathway of metastasis is lymphatic. Lateral tumors metastasize first to the axillary nodes, then to subclavicular nodes, and supraclavicular nodes. Medial tumors metastasize to the internal mammary nodes, the parasternal nodes and the mediastinal nodes. There is a small number of breast tumors that appear suddenly and have a rapid clinical course. They infiltrate dermal lymphatics and capillaries, causing symptoms of heat, redness, pain and swelling. The clinical picture resembles an inflammatory process, hence this is called inflammatory carcinoma.

The common histology of infiltrating duct carcinoma shows compressed, distorted ducts or solid cords or nests of tumor in a dense fibrous stroma. This is also called scirrhous carcinoma. Another type of infiltrating duct carcinoma is medullary carcinoma. These are cellular tumors composed of large polygonal cells with plenty of pink cytoplasm and vesicular nuclei.

Intraductal carcinomas have nests of tumor cells in ducts. Frequently their centers are necrotic. Another infiltrating duct carcinoma is Paget's disease of breast. Paget cells infiltrate along the epidermis of the nipple and areola. These cells are large, anaplastic with pale cytoplasm and dark nuclei.

TUMORS OF OVARY

According to histogenesis ovarian tumors can be divided into three groups. In the first group are surface epithelial tumors which include the common serous and mucous tumors.

Serous cystadenoma and cystadenocarcinoma
Serous cystadenomas are smooth-walled, usually unilocular cysts that contain a pale transparent serous fluid. Frequently they are bilateral. Along the inner lining of the cyst are many papillary structures. The tumor is lined by a single layer of low columnar epithelium that resembles fallopian epithelium. The cells are uniform. These are the papillary structures along the inner wall of the tumor. Characteristic calcium deposits called psammoma bodies are present. Malignant serous cystadenocarcinomas are more cellular tumors. Glands are closely packed and lined by markedly atypical cells. The majority of such tumors develop from borderline tumors, but some are malignant from the outset.

Mucinous cystadenoma and cystadenocarcinoma
Muinous cystadenomas vary greatly in size. Most often they are unilateral, unilocular cysts filled with thick secretions. The lining is a single layer of high columnar cells. The cells have basal nuclei and clear cytoplasm containing mucous droplets. The incidence of malignant change is very low. This slide of mucinous cystadenocarcinoma shows that the cyst wall is more complex. The outer wall is formed of columnar cells. The inner wall is stratified with many blunt projections. In the cavity is necrotic debris. High power reveals many abnormal mitotic figures and marked cellular atypia.

Gonadal stromal tumors
The second group of ovarian tumors are the gonadal stromal tumors. Gonadal stromal tumors include granulosa cell and theca cell tumors. Granulosa cell tumors are composed of uniform cells
Germ cell tumors

The third category of ovarian tumors are the germ cell tumors. Since primordial germ cells are pluripotent, many different germ cell tumors are seen. According to this histogenetic scheme, one type of tumor is dysgerminoma, which differentiates along the line of germ cells. When primitive germ cells differentiate towards embryonic tissue, benign teratomas or frank embryonal carcinoma may result. Extra-embryonic differentiation leads to choriocarcinoma or yolk sac tumor.

The majority of teratomas are benign cystic tumors with a smooth surface and thick cyst wall. Within the cyst hair, bone, teeth and organoid structures may be found. In this slide all three mature germ layers are present- this squamous epithelium with hair follicles; these are serous and mucous glands. Cartilage, bone and smooth muscle can also be seen. Dysgerminomas are the female counterpart of the testicular seminoma. The tumor is arranged in sheets and nests. The cells are uniform, round or oval, with clear cytoplasm and round vesicular nuclei. Embryonal carcinomas are highly malignant tumors. The architecture is disorganized but glandular structures may be present. There is little intervening stroma between the markedly atypical cells. Endodermal sinus tumors follow yolk sac differentiation, and so contain characteristic glomerular structures. These structures have a vascular connective tissue core surrounded by low columnar cells and an empty space.

Ovarian germ cell tumors are highly malignant and tend to occur in young patients.

Chapter 10

DISEASES OF THE HEMOTOPOIETIC SYSTEM

MALIGNANT LYMPHOMA (ML)

Malignant lymphoma is a malignancy of lymph nodes and extra-nodal lymphoid tissue, and is one of the commonest malignancies seen in China.

The chief component of the lymphoid system are the lymph nodes. In order to understand the histological classification and pathological changes of ML, let us first review the normal morphology of lymph nodes.

A lymph node (LN) has an outer cortex and inner medulla. The cortex contains lymphoid follicles paracortex and sinuses. The lymphoid follicle is composed of a dense peripheral zone of small, mature lymphocytes. Within this mantle of lymphocytes is a pale staining germinal centre which is the site of B cell activation. Within the germinal center are many activated lymphocytes and plasma cells.

B cell activation occurs in the follicles in four distinct stages. These include small cleaved cells, large cleaved cells, small noncleaved cells and large noncleaved cells. The large noncleaved cell ultimately enlarges to form immunoblasts. Immunoblasts give rise to antibody-producing plasma cells, or they may revert to small memory B lymphocytes.

Subjacent to the cortex is the paracortex. The paracortex contains predominantly T cells and is the site of T cell transformation. The characteristic feature of the paracortex are the numerous post-capillary venules.

Deep to the paracortex is the medulla, with its medullary cords and sinuses. The cords contain small lymphocytes, while the sinuses contain histiocytes.
Malignant lymphomas are subdivided into two large categories.

**Hodgkin's disease**

This is a common lymphoma involving the superficial LN. This gross specimen of cervical nodes shows a group of nodes which are enlarged and matted together. The cut surface has a fish-flesh appearance and focal hemorrhage. Involvement of deep nodes can also occur in HD. These are the para-aortic nodes in the abdomen. Note the enlarged and densely adherent lymph nodes.

Extranodal involvement of the liver, spleen and bone marrow (BM) can also occur in Hodgkin's disease.

In this specimen of liver, many diffuse, yellow-grey nodules are visible. In the spleen small grey nodules are also grossly visible. Tumor necrosis and fibrosis lead to scarring. This characteristic gross appearance is called porphry spleen. Histologically, HD is characterized by a polymorphic infiltrate composed of malignant and reactive cells. Of diagnostic importance are the malignant Reed-Sternberg cells or RS cells. These are large mononucleated, binucleated or multinucleated cells with abundant amphophilic cytoplasm. The nuclei are large with coarse chromatin and thick nuclear membranes. Each nucleus has a large acidophilic nucleolus surrounded by a clear halo. The chromatin may be arranged in a radial pattern. In binucleated a RS cells the nuclei are often arranged as mirror images of each other. This EM of a RS cell shows the abundant cytoplasm, the mirror-image nuclei and deeply staining nucleoli.

A variant of the RS cell is the mononuclear Hodgkin cell. Except for the presence of a single nucleus, this cell has all the cytoplasmic and nuclear features of the classic RS cell, and may represent an earlier stage in its evolution. Another variant is the lacunar cell. Lacunar cells have well-defined cell borders, single large multilobated nuclei, and abundant pale-staining cytoplasm, which cause them to stand out prominently against a background of densely-packed lymphocytes. Another type of cell found in HD is the pleomorphic sarcoma-like cell. Reactive cells for the background in HD, and comprise eosinophils, neutrophils and lymphocytes.

According to the cell population present, HD is classified into four subgroups.

1. **Lymphocyte predominant Hodgkin's disease**
   In this subtype lymphocytes or histiocytes predominate. There are few malignant cells and classic RS cells are uncommon. Lymphocyte predominant HD is usually diffuse, although a nodular variant is also described. It has the best prognosis of the four groups.

2. **Nodular sclerosing Hodgkin's disease**
   The two characteristic features are one, broad bands of collagen enclosing nodules of lymphoid tissue, and two, lacunar cells. Also present are rare RS cells and a background of histiocytes, lymphocytes and eosinophils.

3. **Mixed cell Hodgkin's disease**
   This type is characterized by many reactive cells, and numerous RS and mononuclear Hodgkin cells. The reactive cells are lymphocytes, histiocytes, eosinophils and plasma cells.

4. **Lymphocyte depleted Hodgkin's disease**
   In this group of HD there are few lymphocytes and a relative abundance of malignant cells. Lymphocyte depleted Hodgkins is subdivided into diffuse fibrosis and reticular variants. This is a slide of the diffuse fibrosis subtype. There is proliferation of fibrous tissue which is not arranged in bands but in a disorderly fashion. Occasional fibroblasts can be seen. There are scanty reactive cells. The reticular variant shown here, is much more cellular, with many pleomorphic malignant cells which resemble sarcoma cells. There are few reactive cells, which reflect the diminished immunological competence of the host. Lymphocyte depleted HD carries the worst prognosis.
Except for nodular sclerosis, one type of HD can evolve into another. For example, lymphocyte predominant type may progress to mixed cellularity type. With further progression, mixed cellularity type may evolve into the lymphocyte depleted type. Nodular sclerosing Hodgkin's is distinct in that it does not transform.

**Non-Hodgkin's lymphoma (NHL)**

The second group of ML is non-Hodgkin's lymphoma.

Non-Hodgkin's Lymphoma (NHL) includes all ML that are not HD. This is one of the NHL involving a group of lymph nodes. The nodes are enlarged, of different sizes, and matted together. Enlarged nodes may become confluent to form one large nodular tumour. The tumor is soft in consistency. Its cut surface has a fish-flesh appearance with focal necrosis and hemorrhage. These mesenteric lymph nodes involved by lymphoma have become transformed into one large tumor mass.

NHL can also involve extranodal lymphoid tissue such as the spleen. The spleen is markedly enlarged. The spleen this gross specimen contains diffuse tumor nodules. In small intestinal lymphoma, tumor nodules in the wall of the gut protrude into the gut lumen. Necrosis and hemorrhage may be present.

The histological features of NHL are as follows:

1. Normal nodal architecture is destroyed and replaced by tumor cells.
2. The cells are clearly malignant.
3. The cell population is monomorphic, unlike the polymorphic cells of HD. All the cells present have uniform features.
4. The cell proliferation is monoclonal. This can be demonstrated by immunoperoxidase staining which reveals the presence of either kappa or lambda immunoglobulin light chains.

NHL may arise from one of three different cell types normally present in lymph nodes - B cells, T cells and histiocytes. According to the cell of origin, NHL is classified into the following categories:

1. B cell lymphoma
2. T cell lymphoma
3. Histiocytic lymphoma

Of these three groups, B cell lymphomas are the most commonly encountered.

**B cell lymphoma**

According to the classification of Lukes and Collins, B cell lymphomas can be subdivided into the following:

1. small lymphocyte type
2. small cleaved type
3. large cleaved type
4. small noncleaved type
5. large noncleaved type
6. B-cell immunoblastic lymphoma
7. Burkitt's lymphoma

In the **small lymphocyte** type the cells are mainly mature lymphocytes. The cells are small, with round, dark nuclei and scanty cytoplasm.

In the **small cleaved** type the cells measure 3-8 microns in diameter. The nuclei are irregular and clefted or indented. Nuclear membranes are wrinkled. Cytoplasm is scanty. On electron microscopy, the nuclear indentations are clearly visible.

In the **large cleaved** type the cells measure 8-15 microns in diameter. There is abundant cytoplasm. Nuclear folds and indentations are clearly visible. These large cells comprise 2/3 of the
In the small noncleaved cell type, the nuclei are round and uniform. Chromatin is vesicular and one or nuclei are present.

The large noncleaved type contains large cells with round nuclei As a rule, the noncleaved tumors are more rapidly proliferating and more malignant than the cleaved cell lymphomas.

B cell immunoblastic lymphomas are tumors of immunoblasts which are large cells with large nuclei, basophilic cytoplasm, and prominent centrally located nucleoli. These tumors are diffuse and highly aggressive.

Burkitt's lymphoma is a special form of B cell lymphoma composed of small noncleaved cells. Characteristically the tumor has many scattered reactive histiocytes. On low magnification these pale histiocytes give the tumor a starry-sky appearance. Burkitt's tumor is also a highly aggressive tumor.

**T cell lymphoma**

This group is divided into four types according to Lukes:

1. small lymphocyte type
2. immunoblastic lymphoma (IBL)
3. convoluted lymphocyte type
4. mycosis fungoides

T small and T cell IBLs are difficult to differentiate from their B cell counterparts on the basis of H&E sections. With the help of immunohistochemistry, however, it is possible to diagnose the cell of origin as a B cell or T cell. In convoluted lymphoma the cells have highly convoluted nuclei, with many folds and indentations. EM reveals the complex invaginations and indentations in the nuclei. the appearance of these cells has been likened by many pathologists to chicken footprints.

Mycosis fungoides is a cutaneous T cell lymphoma characterized by a subepidermal infiltrate of small and large lymphocytes of T cell origin. These cells also have convoluted nuclei and nuclear folding.

**Histiocytic lymphoma**

These are tumors of histiocytes. The cells are large with abundant pale-staining cytoplasm and indistinct cell borders. The nuclei are kidney-shaped, oval or round. Often, nucleoli are present. Chromatin is coarse. Well-differentiated histiocytic lymphomas closely resemble normal monocytes and histiocytes. In this slide there are some abnormal mitotic figures.

The cells in histiocytic lymphoma often retain their phagocytic properties. This cell contains a phagocytized RBC.

**LEUKEMIA**

Leukemia is a malignancy of the white cell precursors of the blood. The main pathological feature is abnormal proliferation of white cell precursors in the bone marrow and extra-medullary hematopoietic organs. Both increased numbers of white cells and increased immature white cells are present.

Leukemia are classified according to the particular type of white cell involved, into lymphocytic, granulocytic and monocytic types. In China the most frequent type is granulocytic leukemia followed by lymphocytic and monocytic leukemias.

**Acute granulocytic leukemia.**

In the peripheral blood (PB) there are large numbers of circulating myeloblasts. Myeloblasts have large round vesicular nuclei and scanty basophilic cytoplasm. The nuclear/cytoplasmic (NC) ratio is 4:5. Often pale blue nucleoli are present. The bone marrow (BM) is diffusely packed with...
these immature cells. The erythroid and megakaryocytic series are markedly decreased. The myeloid : erythroid (M:E) ratio may be as high as 10:1. Clinically, patients suffer from anemia and bleeding tendency because of the low red cell count and platelet count.

Chloromas are special tumors that may develop in acute granulocytic leukemia. Chloromas are tumor-like infiltrates of immature white cells that occur frequently in flat bones. In this specimen there is a chloroma developed within a rib. Because of the presence of the enzyme myeloperoxidase, chloromas have a characteristic green color on gross examination. In acute granulocytic leukemia leukemic infiltrates in the liver are diffusely scattered throughout the lobule. They are present in between the liver cords compressing the liver cells. The liver is mildly to moderately enlarged. In the spleen infiltrates obliterate the architecture of the white and red pulps. In LNs infiltrates can be found in the lymph node sinuses. Without treatment acute granulocytic leukemias have a clinical course of 6 months.

**chronic granulocytic leukemia (CGL)**

The white cell count in the peripheral blood is markedly elevated, greatly exceeding that in acute granulocytic leukemia. 90% of the white cells are granulocytes. In this BM smear all stages of white cell maturation are present. These range from myelocytes to metamyelocytes. The nuclei change from round to slightly indented, while pink granules appear in the cytoplasm. In addition we can also see more mature bands, and early segmented form of eosinophils, basophils and neutrophils. In fact, granulocytes at all stages of maturation are present, with a predominance of metamyelocytes, bands and segmented forms.

In chronic leukemia sudden increase in myeloblasts and promyelocytes can occur. This is known clinically as blast crisis. In the bone marrow red or yellow fatty marrow is replaced by white tumor masses. This is leukemic involvement in a long bone marrow. The spleen shows striking enlargement and may weigh anywhere from 1500 to 5000 gms. Some of the largest spleens in pathology occur in chronic granulocytic leukemias. Compare such a spleen on the left with a normal one on the right of the screen. Histologically no normal architecture is completely effaced by the leukemic infiltrates. The liver is also enlarged. The edges become rounded and the cut surface bulges. In the sinusoids and portal tracts, are large numbers of malignant cells compressing the liver cords. LNs are either normal in size or slightly enlarged. Malignant cells can be found in the medulla and in the sinuses. Gradual destruction of the LN occurs. CGL is usually fatal within a year.

**Acute lymphocytic leukemia (ALL)**

There is an increase in immature lymphocytes in the PB, BM and other organs. These lymphoblasts are difficult to differentiate from myeloblasts. The cells are large, and have basophilic cytoplasm, round nuclei with high N:C ratio of 4:5. In the PB and BM, lymphoblasts and prolymphocytes predominate. Cells of the granulocytic, erythroid and megakaryocytic series are markedly reduced. BM is replaced by grey-white tumor. LN architecture is completely destroyed and LNs are replaced by immature cells. The nodes are enlarged, but remain discrete and not matted together. In the liver the infiltrates of ALL are located predominately in the portal tracts. Within the sinusoids are smaller numbers of malignant cells. ALL is common in children, it has a sudden onset and runs a short clinical course of around 6 months.

**Chronic lymphocytic leukemia (CLL)**

Unlike the case in ALL, the PB and BM contain few lymphoblasts. The majority of cells are mature lymphocytes. An important clinical feature is generalized lymphadenopathy. These mesenteric LNs are enlarged, firm and adherent, with a grey-white cut surface. Histologically, normal structures are effaced and replaced by a diffuse infiltrate of mature lymphocytes. Among these cells mitotic figures are present. The infiltrates in the liver are generally confined to the portal areas. Sinusoidal
infiltration is inconspicuous.

The pattern of leukemic infiltrations is different in granulocytic and lymphocytic leukemias. On the right hand side of the screen is granulocytic leukemia where the infiltrate is mainly in the sinusoids. In lymphocytic leukemia, on the left, there is a heavy infiltrate in the portal zones. Although white cell proliferation occurs mainly in the BM, LN, spleen and liver, infiltrates can be found in almost any organ. In this slide of kidney there is a heavy interstitial infiltrate that compresses the renal parenchyma. Many of the glomeruli and tubules have been replaced by infiltrates. This is a section of heart muscle showing a collection of leukemic cells in the interstitial connective tissue.

This concludes our chapter on hematopoietic diseases.

Chapter 11

DISEASES OF THE ENDOCRINE SYSTEM

PITUITARY ADENOMA

Pituitary adenomas can be divided into three histological types:

- Chromophobe adenoma
- Acidophilic adenoma
- Basophilic adenoma

Pituitary adenomas are one of the commonest intracranial tumors. Grossly they are round encapsulated, dull red tumors that are usually slow-growing. This is a large chromophobe adenoma that is compressing the optic nerve. Its cut surface is pale yellow with foci of hemorrhage.

Chromophobe adenomas comprise two-thirds of all pituitary adenomas. Generally they are nonfunctioning tumors which enlarge and produce compression symptoms. The cells are uniform with round or oval nuclei and pink cytoplasm. Many capillaries may be present.

Acidophilic adenomas comprise 15-30% of all pituitary adenomas. The tumor cells are round or polygonal with pink cytoplasm that contains many acidophilic granules. Hemorrhage may be present. Acidophilic adenomas may be functionally active and secrete hormones such as growth hormone. Excessive growth hormone secretion before puberty leads to gigantism, shown in this picture of a 2.10m giant standing beside a normal man 1.70m tall. Excessive growth hormone secretion following puberty leads to acromegaly. The jaw, maxilla and facial features enlarge and coarsen. Fingers and hands show similar changes, hence the name acromegaly.

Basophilic adenomas are very rare. The tumor cells are identical except that they contain basophilic granules.

Craniopharyngioma

This tumor arises from remnants of Rathke's pouch. Generally it is located in the infundibulum or anterior lobe of the pituitary. It size is variable. The tumor shown here is very large. It has destroyed the pituitary gland and is growing upward into the third ventricle, causing obstruction and dilatation of the ventricle. The tumor is usually cystic, and contains dark brown fluid. The histologic pattern shows nests or cords of tumor cells. The tumor nests are lined by columnar epithelium. Squamous cells are present beneath the columnar cells. The central portion contains loose spindle or stellate cells. Many craniopharyngiomas are cystic tumors.
DISEASES OF THE THYROID GLAND

Goiter

Goiters are usually the result of iodine deficiency. According to their functional status goiters are classified into toxic i.e. functioning, and nonfunctioning.

Toxic goiter

This is an autoimmune disease with a marked female predilection. It is accompanied by the classic clinical features of hyperthyroidism that include tachycardia, sweating, increased appetite, weight loss. In exophthalmic goiters patients also have proptosis.

Grossly the gland is diffusely enlarged and firm. It is dull red on cut surface, with diminished colloid and no nodule formation. Sections show diminished colloid in the follicles. The colloid in some follicles has typical scalloped margins. The hyperplastic follicular epithelial cells are tall columnar, and may project as folds into the lumen. Interstitial lymphocytic infiltrate and lymphoid follicles may also be present.

Non-toxic goiter

NG can be divided into two forms: endemic and sporadic. Endemic goiters tend to occur in inland mountainous and semimountainous regions, and are due to iodine deficiency in the soil and water.

Iodine deficiency leads to oversecretion of thyrotropic hormone by the pituitary, causing diffuse enlargement of the thyroid. This enlarged gland has a smooth, non-lobulated surface. Its large size has caused tracheal compression and dyspnea. The cut surface is dull brown, with a semi-transparent appearance. The follicles are distended with colloid and the follicular lining cells are flattened.

In time the thyroid enlarges further and becomes nodular. This condition is called nodular colloid goiter. The nodularity results from uneven hyperplasia and regression in the gland. The nodules are well-defined but are not completely encapsulated. The cut surface shows nodules of varying sizes, with foci of hemorrhage and scarring.

The nodules are composed of large and small follicles. Some follicles are highly distended and filled with homogeneous colloid. Others have papillary projections in their lumen. Fibrous hyperplasia with scarring and calcification are also present.

Patients with NTG are only rarely hypothyroid. Hypothyroidism in adults is called myxoedema, or waxy edema because these patients have swollen, waxy skin. Myxoedema is associated with tumors of the hypothalamic-pituitary axis, and may occur following thyroid surgery and thyroid irradiation. Hypothyroidism in newborn infants is associated with abnormal growth and maturation of bone. Patients have short extremities and are mentally retarded. The clinical syndrome is known as cretinism or hypothyroid dwarfism, and is not uncommon in regions with endemic iodine deficiency.

Thyroiditis

Thyroiditis is classified into three types:

Acute thyroiditis
Subacute thyroiditis
Chronic thyroiditis

Acute thyroiditis is a very rare condition.

Subacute thyroiditis is a disease of unknown etiology. In the early stage thyroid follicles become transformed into microabscesses. The lining cells degenerate and slough, causing rupture of follicles and extrusion of colloid into the interstitium. This leads to a cellular response around the
ruptured follicles, made up of lymphocytes, macrophages and multinucleate giant cells. These foci become transformed into granulomas like tuberculous granulomas, but lacking caseous necrosis. This is why the disease is also called giant cell thyroiditis. In the late stages fibroblastic hyperplasia occurs.

Chronic thyroiditis includes chronic lymphocytic thyroiditis and chronic fibrous thyroiditis. Another name for chronic lymphocytic thyroiditis is Hashimoto's disease. Hashimoto's disease is an autoimmune disease in which the thyroid gland is diffusely enlarged and firm, with a grey-yellow cut surface. The normal glandular architecture is destroyed. Follicles are small. Colloid is diminished. There is a heavy lymphocytic and plasma cell infiltrate in the interstitium. Lymphoid follicles may be present.

Fibrous thyroiditis, or Riedel's struma, is a rare condition. The gland is large, grey-white, with a woody hardness. In this specimen the left lobe and isthmus are completely involved while the right lobe is partially involved. The follicles are markedly atrophic. There is florid fibrous hyperplasia and a mild lymphocytic infiltration.

**Adenoma of thyroid**

Adenomas are common benign tumors of the thyroid. They are usually completely encapsulated. The cut surface is solid, homogeneous, with foci of scarring and hemorrhage. Cystic change, illustrated in this large tumor, is a common finding.

Histologically adenomas are divided into papillary and follicular varieties. The hallmark of all adenomas is the presence of follicles.

Follicular adenomas are divided into different patterns or subtypes:

Those that resemble normal thyroid are called simple adenomas.

Fetal adenomas contain small, widely-separated follicles lined by low cuboidal cells. There is edema and mucoid degeneration of the interstitial connective tissue.

Embryonal adenomas resemble the thyroid gland in the developing embryo. Only rarely are follicles present, the tumor being arranged in cords and sheets.

Colloid adenomas have large follicles distended with colloid.

Papillary adenomas are often cystic tumors lined by single or branched papillary structures. The lining cells resemble normal cells having little or no atypia. These tumors have a relatively high frequency of malignant change.

**Carcinoma of the thyroid**

Carcinoma of the thyroid is a common malignant tumor with a female predilection. The tumor is firm, grey-white and has a tendency to infiltrate surrounding structures such as the trachea, causing compression or destruction. Metastasis is to regional lymph nodes, lung bone etc.

The commonest histological variant is papillary carcinoma, in which the papillary structures are thin, long and complex. The epithelium may be single or stratified, and the cells are big, atypical, and have large nuclei. Characteristic calcium deposits known as psammoma bodies are present.

Follicular carcinoma contains follicular structures at varying degrees of differentiation. Poorly differentiated tumors have atypia and frequent mitotic figures. Well-differentiated follicular carcinomas are difficult to distinguish from follicular adenomas.

When the carcinoma contains a large proportion of eosinophilic cells the tumor is a Hurthle cell carcinoma.

Medullary carcinoma is a tumor of parafollicular or C cells. The tumor resembles a carcinoid, with small uniform cells arranged in cords or small follicles. Interstitial amyloid depositions are usually present. Patients may have elevated serum calcitonin or multiple endocrine malignancies.

Undifferentiated carcinoma is highly malignant and has a poor prognosis. This cellular tumor is a small cell undifferentiated carcinoma composed of diffuse small cells that resemble lymphocytes.
but have no follicle formation.

**DISEASES OF ADRENAL GLAND**

**Adrenocortical hyperplasia**

Diffuse adrenocortical hyperplasia is usually bilateral and results in increased size and weight of the adrenal glands. The large glands shown on the right are hyperplastic while those on the left are of normal size. On cut surface the cortex is convoluted and measures over 2 mm thick.

This is an example of nodular adrenocortical hyperplasia. Note the overall hyperplasia as well as the small hyperplastic nodules within the gland. Nodular and diffuse hyperplasia can both cause adrenocortical hyperfunction with clinical manifestations of Cushing's syndrome.

**Adrenocortical adenoma**

Adrenal cortical adenomas are unilateral tumors. The tumors are generally solitary, fully encapsulated and yellow on cut surface because of high lipid content. Focal hemorrhage is not uncommon. A fibrous capsule surrounds the tumor which is arranged in sheets. The cells are large and the cytoplasm is clear because of their high lipid content. The tumor is vascular with many large sinusoidal blood vessels.

**Adrenocortical carcinoma**

The cells of adrenocortical carcinomas are pleomorphic. Many multinucleated cells and giant cells may be seen.

Some cases of adrenocortical hyperplasia, adenoma or carcinoma are accompanied by hyperfunction in the form of Cushing's syndrome, hyperaldosteronism, and pseudohermaphroditism. Patients with Cushing's have the concentric or truncal obesity with small and short extremities. Moon-face and facial plethora are present. Purplish red striae are commonly seen on the abdomen.

**Chronic adrenocortical insufficiency (CAI)**

CAI is also known as Addison's disease. Patients are hypoglycemic, have muscular weakness, weight loss and skin pigmentation. The pigmentation results from low adrenal cortical hormone acting on the pituitary gland and causing increased secretion of ACTH and melanocyte-stimulating hormone.

One frequent cause of chronic adrenocortical insufficiency is bilateral adrenal tuberculosis. Caseous tuberculosis can destroy the glands and diminish their function. Among the many other causes are adrenal hemorrhage, necrosis, and tumor metastasis. This specimen shows nodules of metastatic pulmonary carcinoma in the adrenal gland causing destruction of a large portion of the gland.

**Chapter 12**

**DISEASES OF THE NERVOUS SYSTEM**

First let us review the basic anatomy and histology of the nervous system. The central nervous system consists of the cerebral hemisphere, the cerebellum, the brain stem and spinal cord. The cortical surface contains sulci and gyri. Blood vessels are found in the sulci. The brain is covered by the pia and arachnoid. Between these two membranes is a potential space containing loose connective tissue and blood vessels.

Brain tissue is composed of nerve cells and neuroglial cells. Nerve cells are also called neurons.
Neurons are highly differentiated cells. These neurons are large and small pyramidal cells. These are Purkinje cells and granular cells. Although their size, shape and function are different, all neurons share common characteristics. They have abundant cytoplasm containing purplish-blue Nissl bodies. Under EM Nissl bodies are highly developed rough endoplasmic reticulum with large numbers of ribosomes, an indication of the high level of metabolic activity in nerve cells. The nerve cell cytoplasm extends as one long myelin covered axon and many peripheral processes supplying the effector organs.

Neuroglial cells comprise the following types:
1. Astrocytes
2. Oligodendrocytes
3. Ependymal cells
4. Microglia

Let us now study the basic pathologic changes that occur in the nervous system.

**NEURONAL LESIONS**

1. Chromatolysis. This occurs in infectious and toxic conditions and in transected axons. The cell swells and Nissl bodies disappear. ER reveals dilatation, rupture and degranulation of the rough endoplasmic reticulum.

2. Ischemic change. Brain ischemia and anoxia cause nerve cells to shrink and become triangular in shape. The nucleus becomes pyknotic and the cytoplasm deeply eosinophilic. This is an acute change.

3. Neuronal shrinkage. This is a chronic change. The nerve cell and nucleus shrink. The cell becomes triangular, and the cytoplasm basophilic. This change is commonly seen in dementia, cerebral atherosclerosis and other chronic diseases.

4. Nerve cell loss. Extensive loss of neurons may be the result of cerebral atrophy, degeneration and necrosis. Nerve cell loss is the final common pathway of many disease conditions. This slide shows loss of Purkinje cells of the cerebellum. Such nerve cell loss is always accompanied by neuroglial proliferation. Large-scale neuronal loss can result in global atrophy of the brain with narrowing of the gyri and widening of the sulci.

5. Changes of Aging. One such change is the presence of neurofibrillary tangles, in which neuroglial fibres become twisted, thickened and irregularly condensed. It is apparent only with silver stains. Another change consists of amyloid-containing foci known as senile plaques.

**Changes of axon and myelin**

When nerve cells are damaged or injured, corresponding changes occur in the axon. These include fragmentation and demyelination. This is a normal nerve fibre in which the myelin is stained blue. In this slide this is normal myelin, and this pale clear area represents demyelination. Demyelination can occur throughout the length of a nerve fibre. These serial cross-sections reveal demyelinated fibres as localized clear pale areas at different levels of the brain-stem.

When an axon is transected, degeneration and fragmentation of the axon and myelin sheath occur, which is known as Wallerian degeneration. Distal to the transection the axon swells, thickens and fragments. Nerve repair eventually occurs with the help of Schwann cells which proliferate from the proximal end of the severed nerve.

**Neuroglial lesions**

This is a normal astrocyte showing its abundant cytoplasm and vesicular nucleus. Following injury astrocytes proliferate. Astrocytic proliferation or gliosis, results in the formation of a glial scar. This is gliosis surrounding an area of necrosis.

This cell is an oligodendrocyte. It has a characteristic pale halo around the nucleus.
Oligodendrocytes can also proliferate during injury. When a group of oligodendrocytes surround a neuron, this is known as satellitosis.

Microglia are a part of the mononuclear-phagocytic system, and are seen in great numbers in inflammatory conditions. When they contain phagocytosed degenerated and necrotic neurons they are called neuronophages. This microglial cell appears to be inside a neuron. Sometimes several microglial cells are seen surrounding a single neuron. During inflammatory processes, foci of microglial proliferation occur which are called glial nodules.

**Common complications of intracranial disease are brain herniation, cerebral edema, and hydrocephalus.**

**Brain herniation.**

This refers to displacement of a portion of brain tissue as a result of increased intracranial pressure. In cingulate herniations, expansion of one hemisphere causes displacement of the cingulate gyrus under the free margin of the falx cerebri. This is called hippocampal herniation. This is cerebellar herniation. These are the commonly encountered brain herniations.

In a cerebellar herniation increased intracranial pressure displaces the cerebellar tonsils downwards into the foramen magnum, causing tonsillar herniation. The inferior surface of the cerebellum shows notching from compression of the tonsils against the foramen magnum. The tonsils in turn compress the midbrain. This is a life-threatening situation, and a direct cause of death in intracranial diseases.

**Cerebral edema**

This refers to brain swelling or increase in fluid content of the brain. Fluid accumulates around blood vessels and cells. This results in dilatation of the perivascular Virchow-Robin spaces. Fluid can accumulate between cells. When fluid accumulates inside a cell it is called cytotoxic edema.

**Hydrocephalus**

This refers to dilatation of the ventricles secondary to increase in CSF. CSF from the choroid plexus travels from the lateral ventricles to the third ventricle, aqueduct, and fourth ventricle and into the subarachnoid space. In the subarachnoid space it is absorbed by the arachnoid villi.

Infectious adhesions, tonsillar compression and congenital malformations may obstruct CSF flow and cause hydrocephalus. When this occurs the ventricles become dilated and filled with fluid. With severe hydrocephalus there is brain compression and atrophy.

**Epidemic Meningitis**

Epidemic meningitis is infection by Neisseria meningitides. The organism is inhaled through the respiratory tract. Infection usually begins in the nasopharynx, followed by entry of organisms into the bloodstream and meninges. The disease is more frequent in winter and spring and among children under ten years of age. The organism causes a diffuse purulent inflammation in the subarachnoid space.

This is a section of normal brain showing cortex, pia and arachnoid. In menigitis the brain is edematous with widening of the perivascular spaces. Many inflammatory cells are present in the subarachnoid space. The organism may extend into the superficial cortex around the perivascular spaces. The inflammatory cells are predominantly neutrophils and dead white cells. Grossly there is an exudate over the cerebral convexities. The subarachnoid space is filled with greyish-yellow pus which may obscure the superficial blood vessels.
In severe cases there may be involvement of the ventricles. This picture shows ventricular dilatation following purulent infection of the ventricles. Meningitis gives rise to symptoms of meningismus. Adult patients have stiff neck or nuchal rigidity. Newborns and infants show head retraction or opisthotonus due to irritation to nerve roots causing spasm of the neck muscles. Suppurative exudation and edema cause increased intracranial pressure. Adhesions are a common sequela of meningitis and may lead to obstruction in CSF circulation, hydrocephalus and ventricular dilatation.

**Waterhouse-friderichsen syndrome**

This is a special form of epidemic meningitis which results from organisms multiplying in the bloodstream, producing endotoxin and serious symptoms. Meningeal inflammation may be mild but is accompanied by septicemia, shock and DIC. There is diffuse skin and mucosal bleeding. These are petechial hemorrhages in the skin. There is diffuse bilateral adrenal hemorrhage and necrosis. Acute adrenal failure results. This disease is also called fulminant meningococcal meningitis, because of its acute onset, rapid clinical course and high mortality rate.

**TYPE B EPIDEMIC ENCEPHALITIS**

This viral disease is transmitted from infected to healthy people through mosquito bite. Since it is mosquito-borne the peak incidence occurs in summer. Children are more commonly affected because of their relatively immature blood-brain barriers. The virus infects and replicates in nerve cells to produce parenchymal damage. The cortex and basal ganglia are the most commonly affected regions, whereas cerebellum and brain stem infections tend to be mild.

Severe disturbance of intracranial circulation, with congestion, edema and even thrombus formation may be seen in tissue sections. Neurons are markedly degenerated and necrotic due to ischemia, with swelling, lysis, shrinkage and disappearance. Proliferated oligodendrocytes form satellite cells around degenerating neurons. Phagocytosis of these neurons is also evident. This degenerated neuron is being phagocytosed by a number of microglial cells. Collections of astrocytes and neutrophils form filial nodules. The perivascular space is filled with an inflammatory infiltrate, a feature known as perivascular cuffing.

In severe cases the brain may completely dissolve to form small areas of softening. This clear area represents a focus of softening. These areas of softening are loose collections of neurofibrils and cellular debris. At the periphery of these necrotic areas microglia proliferates and phagocytoses the dead tissue. The cytoplasm of microglia contains large amounts of ingested lipid which are clear with H&E stains. These cells are called gitter cells. These pinpoint foci visible grossly are the result of cerebral necrosis.

Type B encephalitis is a serious disease. Cerebral edema and herniation are the major causes of death. Dementia may result from extensive neuron loss.

**POLIOMYELITIS**

This is an acute infection caused by the polio virus. The virus gains entry through the digestive tract, hence peak incidence occurs in summer and autumn. Children are more frequently affected.

Poliomyelitis and encephalitis are both examples of alteration inflammation but with differing sites of involvement. Polio affects predominantly the spinal cord; involvement of the brain is infrequent and mild. In the spinal cord, involvement of the latter enlargement is most frequent. The virus replicates in the motoneurons of the anterior horn. These are normal anterior horn cells. These are degenerated and necrotic anterior horn cells in poliomyelitis. The remaining neurons may become lysed, shrunken or phagocytosed.
This is an affected neuron. Marked neuroglial proliferation is seen as glial nodules or a diffuse infiltrate. Perivascular cuffing and areas of softening can also occur. In severe cases the spinal cord may atrophy. These changes resemble those of epidemic encephalitis, but involve different parts of the CNS. Degeneration of motorneurons leads to weakness and paralysis of affected muscles, hence this disease is also called infantile paralysis. Infection of different levels of the spinal cord causes involvement of different muscle groups and other long-term sequelae.

TUMORS OF THE CENTRAL NERVOUS SYSTEM

Glioma
These are tumors of neuroglial cells. Most of these tumors are benign, and include the following types:

Astrocytomas
This is the commonest benign neuroglial tumor. Grossly the tumor is nodular and ill-defined. In adults it occurs most frequently in the frontal, temporal and parietal lobes. Sometimes it is diffusely infiltrating. This is a pontine astrocytoma in a child. The tumor is well-differentiated. It may be composed of uniform cells resembling fibrous astrocytes, with bipolar processes. Other times the tumor cells resemble protoplasmic astrocytes with abundant pink cytoplasm. Between the tumor cells is a network of pale pink neuroglial fibres. Poorly-differentiated astrocytomas are also called anaplastic astrocytomas. The cells are pleomorphic and atypical. The tumors may be very vascular, and contain proliferated endothelial cells.

Oligodendroglioma
This is a tumor of oligodendrocytes. It frequently occurs in the white matter of the cerebral hemispheres, where it is a slow-growing, often cystic tumor. The tumor cells are uniform with round nuclei, and dark cell borders. The cytoplasm is clear, giving the typical fried-egg appearance. Oligodendroglioma frequently contain blue calcium deposits called psammoma bodies.

Ependymoma
This is a tumor of ependymal cells. It arises most frequently in the ventricles and spinal canal. This specimen shows a lateral ventricular ependymoma. Ependymomas are slow-growing tumors that are more common in children and young adults.

Glioblastoma multiforme
This is a highly malignant tumor, with densely packed cells that are markedly pleomorphic and anaplastic. Often multinucleated giant cells and abnormal mitotic figures are present. Here is an abnormal mitotic figure. Malignant tumors of the CNS are often highly vascular, with proliferation and hypertrophy of endothelial cells and pericytes. Vascular obstruction predisposes to tumor necrosis. Areas of necrosis and hemorrhage are accompanied by their characteristic colour changes.

Medulloblastoma
This highly malignant tumor occurs more often in children and young adults. The most frequently affected site is the cerebellum. The tutors often compress the fourth ventricle, obstruct
CSF flow, and cause the ventricles to dilate. The tumor is composed of small, uniform, densely-packed cells with scanty cytoplasm, and round or carrot-shaped nuclei. Often the cells are arranged in circles with acellular centres. These rosettes are diagnostic of medulloblastomas. Medulloblastoma is a rapidly growing tumor that infiltrates and may give rise to intracranial metastases. It has a poor prognosis. In this specimen we see a cerebellar medulloblastoma with multiple cerebral metastases.

**Meningioma**

This tumor arises from arachnoid villi cells, and hence are superficial tumors. This meningioma is situated over the frontal lobe. Meningiomas exhibit many histological patterns. In fibroblastic meningiomas the cells look like fibroblasts. Such tumors have characteristic cellular whorls. At the tumor center degeneration and psammoma bodies may be present.

Some tumors are composed of round or polygonal cells resembling arachnoid cells and with indistinct cell borders and are called meningotheliomatous meningiomas. Angioblastic meningiomas have many blood vessels. Meningiomas are usually benign, well-circumscribed tumors, but they may be deep-seated and a small proportion may undergo malignant change.

**TUMORS OF PERIPHERAL NERVOUS SYSTEM**

**Neuroblastoma**

This is a highly malignant tumor of primitive cells that is more common in infants and young children. It arises frequently in adrenal medulla and in the sympathetic ganglia. This is a neuroblastoma in a thoracic sympathetic ganglion. Neuroblastoma is composed of primitive undifferentiated cells resembling those of medulloblastomas. This is a typical rosette found in these tumors. Early metastasis, often to liver and bone, is a characteristic feature.

**Neurilemmoma (Schwannoma)**

Schwann cell tumors may arise in either peripheral or cranial nerves and are usually benign. This is an acoustic nerve schwannoma.

Schwannomas are lobulated and fully encapsulated tumors. They are composed of elongated, slightly curved spindle cells. In some areas the cells are close together and parallel, known as palisading. Other areas are reticulated, with a loose and acellular structure. These tumors are well-differentiated and are generally cured by surgical excision.

**Neurofibroma**

Neurofibromas are found along nerve fibres and in subcutaneous tissue. This is a subcutaneous neurofibroma. Here is the epidermis and this is the tumor. The tumor cells are fusiform and arranged in parallel or interlacing bundles. There is a fine neurofibrillar network between the cells which may appear homogeneous. These tumors are usually solitary. The occurrence of multiple tumors is called neurofibromatosis, a condition with widespread subcutaneous nodules.

We have discussed a few of the tumors of the nervous system. Although the majority is histologically benign, their location within the brain may produce serious consequences such as increased intracranial pressure, cerebral herniation and impairment of central nervous system function.
Chapter 13

INFECTIOUS DISEASES (PART I)

TUBERCULOSIS

Tuberculosis is a chronic infectious disease caused by Mycobacterium tuberculosis. The bacteria have many biochemical components. Of these the lipid fraction is of greatest importance with regard to virulence, host hypersensitivity response, and disease pattern. The protein fraction is antigenic, and elicits an immune reaction from the host. Bacterial protein combined with polysaccharide hapten is also able to produce an immune reaction in the host.

The outcome of exposure to tubercle bacilli depends on the number of organisms and their virulence, but is also closely linked with the host's immune status. Koch's phenomenon illustrates this point. In this experiment tubercle bacilli are injected into a healthy guinea pig. Two weeks later there is localized swelling, necrosis and ulceration, followed by generalized infection. This is because the animal has not been previously sensitized to the organism. However, if a small inoculum of attenuated TB bacilli is given, and is followed 8 to 10 weeks later by the regular inoculum, a completely different response is obtained. The reaction develops rapidly. Localized swelling and ulceration occur, but the infection does not become generalized, because of the presence of immunity.

The tuberculin test is used clinically to determine the presence and type of tuberculous infection. In a person who has not been previously infected with tubercle bacilli, intradermal injection of bacterial protein will only produce a mild local reaction, individuals with a history of TB develop redness and swelling 24 hours after injection, because of the presence of immunity.

Basic pathology

TB is a special type of inflammation. It demonstrates the three basic pathological changes of alteration, exudation and proliferation.

Let us first discuss exudation. Exudation occurs when hypersensitivity is very pronounced, such as with early infections, to host immunity, and high bacterial virulence. In this specimen of tuberculous serositis, note the large amounts of exudate and fibrin. The majority of cells in the exudate are mononuclear phagocytes and lymphocytes.

Proliferative changes dominate when there are few organisms of low virulence, or when host immunity is high or resistance to infection is high. The chief feature is the presence of granulomas, which represent a localization of the infection. Granulomas are of great significance in the diagnosis of TB.

In TB both exudation and proliferation can evolve into alteration inflammation and caseous necrosis. These three basic pathological changes can interchange, hence the disease may manifest differently according to host conditions and stage of disease.

Let us review simply, the development of tuberculosis. The organisms enter the body through the respiratory tracts, stimulating neutrophils and macrophages. The macrophages phagocytise the organisms and become transformed into epithelioid cells and Langhans giant cells. Collections of epithelioid cells form tubercles, or tuberculous granulomas. The granulomas have a central core of caseation necrosis. This is a pulmonary tubercle. The amorphous pink material in the center is caseous necrosis. Surrounding it are epithelioid cells. These are large cells with abundant cytoplasm, closely aggregated together. This is a Langhans giant cell. It is a very large cell, which may contain ten or more nuclei in a horseshoe pattern around the periphery of the cell. At the margins of the tubercle is an infiltrate of fibroblasts and lymphocytes. Granulomas are seen in every type of
tuberculous infection.

Gaseous necrosis is of equal diagnostic importance in tuberculosis. Caseous necrosis is pale yellow, dry and cheesy in consistency. Large areas of necrosis are a sign of disease progression. With inactive infections there is fibrous encapsulation and calcification of lesions. This grey-white brittle material is calcium.

Pulmonary tuberculosis is the most frequently encountered form of the disease. Pulmonary TB is divided into primary and secondary types.

I. Primary Pulmonary Tuberculosis

The gross morphology of primary pulmonary TB consists of three components. The first component is the primary lung focus. The second is tuberculous lymphangitis in the draining lymphatics, and the third is tuberculous involvement of the hilar LN. These three components constitute the primary complex. Primary pulmonary TB is more frequent in children and is also called childhood TB.

In this specimen this is the primary focus with extension into surrounding tissue. These are the hilar nodes infected by TB, with caseous necrosis. Infection can spread along lymphatics to involve the paratracheal, clavicular, and cervical nodes:

Primary pulmonary TB is usually mild and heals spontaneously. In some patients with low resistance, the disease progresses and can spread by three routes:

1. Bronchial Dissemination. Bronchial extension can damage bronchial walls and give rise to multiple foci of pulmonary infection, and even involve the opposite lung.
2. Lymphatic Dissemination. Extension along the lymphatics can lead to involvement of hilar, peribronchial, cervical and even distant lymph nodes.
3. Hematogenous Dissemination leads to miliary disease in the lungs as well as generalized miliary tuberculosis. In this specimen of a child's lungs we can see the primary focus, with predominantly exudation and necrosis. Infection has spread throughout the entire lung, the lymph nodes, producing miliary infection. There are multiple, scattered uniform nodules in the lung parenchyma. These nodules are round, well demarcated, grey, and of uniform size, distribution and consistency. Many of these foci are also visible beneath the pleural surface.

On this chest X-ray of miliary TB there are many scattered, bilateral, uniform foci of similar appearance. With progression of the disease generalized miliary infection may occur. This is a miliary lesion in the liver.

II. Secondary Pulmonary Tuberculosis

This form predominates in adults. The lung infection is chiefly the result of bronchial dissemination. Infection spreads from the apex downwards. The course of the disease is usually protracted. The pathology is a combination of old and fresh lesions. The following six types are recognized.

1. Focal pulmonary tuberculosis

In this type there are one or more small apical foci. The foci may not be the same age. They have small amounts of caseous material in their centers and are surrounded by fibrous proliferation and organization. These foci may calcify. This is a chronic or quiescent form of infection.

2. Infiltrative pulmonary tuberculosis

This disease usually occurs in the upper part of the lungs and is acute and exudative. On chest X-ray many soft woolly infiltrates are seen. The infection is easily cured and usually has a short clinical course.

3. Tuberculosis with cavitation.

Acute cavitary TB usually starts in the upper lungs. Necrotic lung drains along the bronchi to leave irregular cavities. In these cavities blood vessels may be exposed. Tubercle bacilli carried in
the bronchi may cause exudation and necrosis in the lower lung. These patients expectorate large amounts of bacteria and necrotic material. The disease progresses rapidly. Frequently patients have fatal hemoptysis from ruptured blood vessels in the cavities.

As the infection progresses the disease evolves into chronic fibrocavitary tuberculosis. The lung contains multiple cavities of varying sizes. The fresh cavities are lined by a scanty amount of necrotic material. Older cavities which surrounded by fibrous tissue formed the thick-walled cavities. There may be coexisting bronchial disseminated lesions and diffuse fibrosis. Generally, the upper lung has more lesions and older lesions than the lower lung. Chronic cavitary TB evolves into fibrosclerotic TB. Marked fibrosis leads to small, indurated lungs, pleural adhesions and thickening, and severely compromised lung function.

4. Gaseous Pneumonia
This is the result of rapid disease progression. Exudation and necrosis transform normal lung tissue into large areas of grey-white consolidation. Drainage of the necrotic material leaves large and small cystic spaces in the consolidated area. These lesions are bronchial disseminated lesions.

Gaseous pneumonia is a serious condition that may involve one lobe or an entire lung. Young patients are more frequently affected. Tissue sections show severe exudation and necrosis. Serous exudate in the alveoli contains monocytes and lymphocytes. Increased hypersensitivity is responsible for the extensive necrosis in these patients. This section shows tissue necrosis.

5. Tuberculoma
This is a solitary pulmonary lesion. It is well-demarcated, usually 2-5 cm in diameter with, central caseation necrosis surrounded by fibrosis. On chest X-ray it is easily mistaken for tumor. Tuberculomas represent quiescent disease.

6. Tuberculous pleuritis
In the early stage there is serous exudation. Later the exudate becomes fibrinous. Organization of the exudate leads to pleural thickening and adhesions, which compromise pulmonary function.

TUBERCULOSIS OF EXTRA-PULMONARY ORGANS

1. Tuberculous Meningitis
The base of the brain is usually affected. The subarachnoid space is filled with a large amount of yellowish gelatinous exudate. The brain surface is covered with small tubercles. Incomplete resorption and organization of the exudate result in meningeal adhesions.

Adhesions may obstruct CSF flow and lead to hydrocephalus. In this specimen the lateral ventricles are dilated.

2. Tuberculous peritonitis
This is a serofibrinous inflammation. The grey-white shaggy material on the serosal surface of this segment of intestine is fibrin. Organization of the exudate may cause adhesions and intestinal obstruction.

3. Tuberculosis of Bone and Joint
This specimen is spinal column. Several of the vertebral bodies have been damaged and deformed by tuberculosis. This is caseous necrosis. Only a small portion of normal bone is left. Destruction of bone predisposes to compression fractures and deformity of the spinal column.

This is a small joint in the hand with preserved normal metacarpal bone. Infection has destroyed some of the bone and the articular surface. The joint contains necrotic material. Infection can destroy the synovial capsule and surrounding soft tissue. Extension to the subcutaneous tissue can cause fistula formation. The skin shows tuberculous ulceration.

4. Tuberculosis of Kidney
The disease begins at the cortico-medullary junction. Necrotic material is discharged through
the ureter leaving multiple cavities. Involvement of the entire kidney, pelvic mucosa and urinary bladder via the ureters may occur. The renal surface is irregular, rough and adherent to surrounding structures. Renal tuberculosis can spread to involve the ureters, urinary bladder, urethra, prostate, seminal vesicles and reproductive organs.

5. Genital tuberculosis
Females are more frequently affected. Tuberculosis of the uterus, fallopian tubes and ovaries are most common. This is involvement of the fallopian tube. The tube is tortuous and adherent and filled with caseous material. The wall of the tube may be destroyed.

6. Laryngeal tuberculosis
In patients with pulmonary tuberculosis organisms may infect the larynx when they are coughed up in the sputum. If the sputum is swallowed infection of the stomach and intestine may occur. This laryngeal specimen shows mucosal sloughing and TB ulceration.

7. Intestinal Tuberculosis
Most cases of intestinal tuberculosis are due to swallowing of infected sputum in cases of cavitary TB of the lungs. A few cases are due to hematogenous spread.

There are two morphological forms of the disease. In the ulcerative type bacteria multiply in intestinal lymphoid tissue, and then spread through the submucosal lymphatics to form circumferential ulcers. Fibrosis will cause thickening of the intestinal wall and stricture formation. The proximal segment dilates.

The proliferative type most frequently affects the ileo-cecal region. Mucosal proliferation forms multiple polyps, thickening of the wall and a mass on clinical examination. Mesenteric lymph nodes can be involved and become necrotic. These small polyps are evidence of proliferative TB.

8. Tuberculous lymphadenitis
Tuberculous lymphadenitis is the result of lymphatic dissemination. The infection involves groups of nodes which become enlarged and adherent, with central caseation necrosis.

This is preserved lymphoid tissue. In the infected area are many tuberculous granulomas composed of central caseation surrounded by epithelioid macrophages. A Langhans giant cell can be seen. The cervical nodes are most commonly affected. Necrosis and chronic sinus formation may result.

Let us now review simply some of the features of tuberculosis: - Primary pulmonary TB contains three components.

Infection spreads via the bronchi, lymphatics and blood.
- Secondary TB usually occurs in adult patients who have some degree of immunity. Bronchial spread gives rise to multiple lung lesions.

Extrapulmonary TB is the result of hematogenous spread from primary pulmonary TB, and can occur in the brain, liver, gut, spleen, kidney, and genitourinary organs.

The expression of the disease varies according to difference in virulence, number of infecting organisms, host immunity and organ histology.

We hope that our brief introduction to the different types of tuberculosis help students in their understanding of its basic pathologic mechanism.

INFECTIOUS DISEASES(PART 2)

TYPHOID FEVER
Typhoid fever is an acute infection caused by Salmonella typhi. The predominant pathological change is generalized proliferation of mononuclear phagocytes. This is most pronounced in the
ileum.

The disease is acquired from ingestion of food and water contaminated with organisms from the urine and stools of patients and carriers. Flies and patients' hands are important vectors. In the digestive tract, organisms that escape digestion by acid peptic juices enter the lymphoid tissue in the wall of the small intestine. Then they are carried through lymphatics to the mesenteric lymph nodes.

After ingestion by macrophages, the organisms multiply inside the cells. Then they enter the bloodstream through the thoracic duct and are carried to the liver, bone marrow, spleen and kidneys. Ingestion by phagocytic cells causes generalized hyperplasia of the mononuclear phagocytic system. After a ten-day latency period, toxemia and severe bacteremia produce persistent high fever, paradoxical pulse, hepatosplenomegaly, and cutaneous Rose spots. The most prominent change is in Peyer's patches and solitary lymph follicles of the distal ileum.

Four pathologic stages can be differentiated:

The first stage is the stage of lymphoid hyperplasia. In the first week of infection there is swelling of the solitary lymphoid follicles and Peyer's patches. The surface of the lymphoid tissue is convoluted, like the surface of the brain. This section of a Peyer's patch shows congestion and marked proliferation of macrophages. These cells have abundant pale cytoplasm with round or oval eccentric nuclei. Macrophages have increased phagocytic activity, and may contain ingested RBC's, lymphocytes and cellular debris. These so-called "typhoid cells" have diagnostic significance. Collections of these cells form typhoid nodules or granulomas.

The stage of necrosis occurs in the second week. Lymphoid tissue undergoes necrosis, forming greyish-white or greyish-green areas. Necrosis is due to re-entry of large numbers of organisms from the gallbladder to the intestine, evoking a hypersensitivity reaction.

The stage of ulceration occurs in the third week. Necrotic mucosa sloughs off, leaving round or oval ulcers. They have slightly elevated margins, and their long axis is parallel to the long axis of the small intestine. Ulcers may penetrate to the serosa and cause intestinal perforation and peritonitis. Erosion of blood vessels at the ulcer base can cause severe massive hemorrhage. Perforation and hemorrhage are both serious complications of typhoid fever.

Typhoid ulcers can be differentiated from tuberculous ulcers. Tuberculous infection spreads along submucosal lymphatics to form circumferential ulcers. Ulcer healing may result in stricture. Typhoid ulcers, on the other hand, lie parallel to the long axis of the intestine, and hence healing will not cause strictures.

The fourth week is the stage of healing. Ulcers heal by granulation and re-epithelialization. Patients become afebrile.

Sections of enlarged spleen in typhoid fever show congestion and dilatation of splenic sinuses. Diffuse macrophage proliferation and typhoid granulomas are present. The enlarged liver shows sinusoidal dilatation and degeneration and necrosis of liver cells. Typhoid granulates are also seen.

Patients generally recover in four to five weeks. Serious complications such as hemorrhage and perforation are unusual because of the use of antibiotics. In a small number of patients organisms persist in the gall-bladder and are excreted in the stools. These patients are chronic carriers.

BACILLARY DYSENTERY

This is a common infection of the intestine caused by Shigella organisms. Patients present with headache, fever, blood and pus in the stools, and tenesmus. Patients and carriers serve as sources of infection. Organisms are ingested orally through focally-contaminated food, water or utensils. Flies serve as important vectors in transmission.

The disease mainly affects the large intestine, especially the sigmoid colon and rectum. The mucosa of the affected gut is swollen and covered with a dirty exudate. Exudate and underlying
necrotic mucosa form a pseudomembrane. When the pseudomembrane sloughs it leaves shallow ulcers of varying sizes. Patients have severe tenesmus and diarrhea with blood and pus, or blood and mucus.

Infection is present predominantly in the mucosa and submucosa. There is an extensive fibrinopurulent exudate on the mucosal surface. In areas of mild inflammation mucosal glands are preserved. In severely affected areas there are superficial necrosis, absent glands, submucosal edema, hemorrhage, and neutrophilic infiltration.

Most patients recover with treatment. A small minority develop chronic bacillary dysentery, with persistence of infection for months. Multiple small and large ulcers may develop that extend to the muscular coat and are covered by purulent exudate. Between the ulcers are islands of preserved mucosa with congestion and edema. Patients with chronic bacillary dysentery may develop intestinal stricture because of fibrosis, but this is rare.

In some patients the onset of infection is sudden. Intestinal symptoms are mild, but there are severe generalized toxic symptoms which may lead to toxic shock, hence this is also called toxic dysentery. This intestine from a case of toxic dysentery shows marked mucosal edema and swelling of lymphoid follicles. This is also called follicular enteritis. In severely toxic patients peripheral vascular collapse and respiratory failure may ensue.

**AMEBIASIS**

Amebiasis is caused by Entameba histolytica. The primary lesions are in the colon; hence it is also called intestinal amebiasis.

Patients and carriers excrete trophozoites which do not survive outside the body. Infection is transmitted by amebic cysts, which are ingested in contaminated food and water. The cysts are able to withstand the high stomach acidity. In the ileum and proximal colon trophozoites are released. The low oxygen partial pressure in the colon favors their growth. The life cycle is completed with the development of trophozoites into uninucleate, binucleate and quadrinucleate cysts.

Trophozoites have the histolytic and erythrophagocytic properties. In the ileum, mucosal necrosis and ulceration occur. These patients excrete copious amounts of pasty, putrid stools containing blood and mucus.

Amebiasis affects the cecum and ascending colon, followed by the sigmoid colon and rectum. Multiple necrotic mucosal ulcers are found. The ulcers are flask-shaped, with narrow openings and wide bases and are filled with necrotic material. Small ulcers may coalesce to form larger ulcers.

In this section of the ascending colon there are multiple foci of mucosal necrosis. These foci are surrounded by a mild inflammatory reaction consisting of plasma cells and lymphocytes. Many trophozoites can be found at the bases of these lesions. Trophozoites can be recognized by their relatively large size and small, pale, round nuclei. They must be differentiated from monocytes.

Some trophozoites migrate in portal venules to the portal vein and liver, where they form abscesses. This is the most common complication of amebic infections. Amebic abscesses may also occur in the lungs. They may be blood-borne, but are usually the result of diaphragmatic extension of liver abscesses. The most serious complication is amebic brain abscess. It has a poor prognosis and high mortality rate.

In this liver specimen there is a large abscess in the right lobe. The abscess is lined by liquefied, necrotic connective tissue, blood vessels and bile ducts. The abscess wall has a shaggy inner lining. The chocolate colored pus in the abscess cavity has been drained.

**SCHISTOSOMIASIS**

Schistosomiasis is one of the major endemic parasitic diseases in China, with a 2,000 to 3,000-year history. Patients and domestic animals serve as reservoirs of infection. Schistosome ova are excreted by the definitive host. If deposited in water and at suitable
temperatures, the ova hatch into free-swimming miracidia. After infecting the snail intermediate host, miracidia develop into fork-tailed cercariae. Histolytic enzymes permit cercariae to actively penetrate skin or mucosa of people in contact with the contaminated water.

At the site of entry the skin develops an itchy reddish papule or rash known as cercarial dermatitis. This is caused by cercarial movement and reaction to the histolytic enzymes. In the skin or mucosa cercariae develop into young worms. These enter the circulation by way of veins and lymphatics. After passing through the liver they migrate into the mesenteric and portal veins where sexual maturity occurs. Parasites carried to other organs or tissues in the body cannot mature and die.

Three weeks after infection the fully mature parasites copulate. This is the male parasite. This is the female parasite. Ova are released 25 days later, and can reach 1000-3000 per day. Dead flukes in the portal and mesenteric veins can cause embolic phlebitis. Parasite metabolites can give rise to anemia, eosinophilia and splenomegaly. In the liver and spleen there are large quantities of home-derived pigment in the mononuclear phagocytes.

Some ova are carried by the bloodstream to the liver where they can cause series of pathologic changes. Nest of the ova deposited by female parasites reach the intestine by retrograde blood flow. The ova rupture through the mucosa into the intestinal lumen and are excreted in the stools. In severe cases ova may be carried to mesenteric and retroperitoneal lymph nodes and to the lungs and brain. The most important pathologic effects result from the inflammatory response to deposited ova.

The early response consists of microabscess formation. These mature ova at the center are surrounded by large numbers of eosinophils and necrotic material. This is also called an eosinophilic abscess. In time the center also becomes necrotic. Co the surface of the ova there may be same radiallyarranged eosinophilic material. This is immune complex. At the periphery of the granuloma are epithelioid cells in a radial distribution. Eosinophils are fewer. Lymphocytes and histiocytes are increased. This is an early acute lesion.

After 10 days the miracidia in the ova die. The ova rupture and calcify. Surrounding histiocytes transform into epithelioid cells and foreign body giant cells. The granulomas resemble tuberculous granulomas because of the lymphocytic infiltration. Hence they are called pseudotubercles. This is a schistosome granuloma.

The schistosome granulates eventually undergo fibrosis. Progression of the granuloma through the stages of exudation, necrosis, proliferation and fibrosis is due to the release of soluble antigens by the ova. All affected organs show the same histologic changes.

Since the mature worm lives in the portal circulation, ova may enter the portal tracts by way of the portal vein radicles. These are ova in the portal tracts. The ova evoke granuloma formation and fibrosis.

Eventually portal fibrosis and cirrhosis occur.

On the cut surface of this liver specimen there are grey-white slightly depressed areas of fibrosis around the portal venules. The fibrosis is due to recurrent massive deposition of ova in the portal circulation. In severe cases fibrosis along the portal vein has a tree-branching appearance, with coarse nodules. This is known as pipe-stem cirrhosis, and carries complications such as portal hypertension, splenomegaly and esophageal varices.

Mature worms lodge in the mesenteric and hemorrhoidal veins, and hence lesions in the sigmoid colon and rectum are most pronounced. This is a section of a late sigmoid lesion. Note the submucosal ova and surrounding fibrosis. Chronic intestinal schistosomiasis predisposes to colonic cancer.

Our discussion of typhoid fever, bacillary dysentery, amebiasis and schistosomiasis brings this chapter on infectious diseases to an end.