II. DIGESTIVE SYSTEM PATHOLOGY

GASTRO-INTESTINAL TRACT PATHOLOGY

GASTRITIS

Chronic gastritis (nonerosive gastritis) refers to chronic inflammatory disease of the stomach that range from mild superficial involvement of the gastric mucosa to severe atrophy. The use of fiberoptic endoscopy has now clearly established that nonerosive gastritis actually comprises a heterogenous group of disorders that have distinct anatomic distributions within the stomach, varying etiologies, and characteristic complications. There are at least four entities, defined by their etiology:

- *autoimmune gastritis* (type A) refers to a chronic, diffuse inflammatory disease of the stomach that is restricted to the body and fundus and is associated with autoimmune phenomena. Autoimune gastritis is so named because of the presence of autoantibodies and the association with other diseases believed to have a similar pathogenesis (pernicious anemia, chronic thyroiditis, Addison disease, vitiligo, and type I diabetes).

- *idiophatic gastritis* is by definition a chronic inflammatory disease of the stomach of unknown etiology (it is considered to be an environmental disease). It typically involves the antrum and adjacent areas of the body.

The pathologic features of autoimmune and chronic idiopathic gastritis are virtually identical, except for the localization: of the autoimmune type confined to the fundus and body; the idiopathic variety mainly to the antrum. On gross examination both forms of nonerosive gastritis display few if any characteristic alterations; identification of the disorder is made on histologic grounds.

Superficial gastritis is the mildest form of nonerosive gastritis. Although superficial gastritis may occasionally revert to normal, it is estimated that it proceeds to atrophic gastritis in nearly half of the cases. Superficial gastritis typically shows lymphocytes and plasma cells, and occasionally neutrophils, in the lamina propria of the mucosa of the antrum and body of the stomach. The inflammation is most intense around the gastric pits (foveolae), where small foci of neutrophils may also be seen, but the glands are spared. The normal columnar epithelium becomes more cuboidal and contains less mucin than normal.

Atrophic gastritis may evolve from superficial gastritis, but there is no sharp distinction between them. Like superficial gastritis, active atrophic gastritis is characterized by prominent chronic inflammation in the lamina propria. However, lymphocytes and plasma cells extend into the deepest zones and reach the mucularis mucosae. Involvement of the gastric glands leads to degenerative changes in their epithelial cells and ultimately a conspicuous reduction in the number of glands, hence the name atrophic gastritis. Atrophic gastritis usually persists indefinitely, but in a few cases it terminates in gastric atrophy, a condition in which the inflammatory features of gastritis are inconspicuous and mucosa is extremely thin / atrophic.

Intestinal metaplasia is a common and important histologic feature of both the autoimmune and idiopathic types of nonerosive gastritis. In this response of the injured gastric mucosa, the normal epithelium is replaced by one composed of cells of intestinal type: mucin - containing goblet cells, enterocytes line crypt - like glands, and many Paneth cells, which are not normal inhabitants of the gastric mucosa.

Persons with atrophic gastritis of the autoimmune or idiopathic type have a high incidence of carcinoma of the stomach.

Infectious gastritis (type B) is a chronic inflammatory disease of the antrum and body of the stomach caused by Helicobacter pylori. It is the most common type of chronic nonerosive gastritis, and the organism causes one of the most common chronic infections in humans. H. pylori infection is also strongly associated with peptic ulcer disease of the stomach and of the duodenum, and with the development of gastric adenocarcinoma and MALT type primary gastric lymphoma.

H. pylori has been found only in association with gastric type epithelium and does not occur in other tissues. Although the bacterium is clearly associated with chronic gastritis it is found only on the epithelial surface and does not invade the gastric mucosa. The organism produces extracellular toxins and a protease. It has been suggested that the latter digests gastric mucin, thereby permitting an attack on

the mucosa by acid - pepsin or possibly by a bacterial toxin. H. pylori also split urea to ammonia, which in turn may injure the epithelium.

Microscopically, H. pylori are found in the surface mucus of the epithelial cells and in the gastric foveolae. Active gastritis features polymorphonuclear leukocytes in the gland necks and increased numbers of plasma cells and lymphocytes in the lamina propria. Chronic infectious gastritis caused by H. pylori can lead to gastric atrophy and intestinal metaplasia, therefore, infection with H. pylori has been linked to the development of gastric adenocarcinoma.

Reflux gastritis refers to chronic gastric injury resulting from the reflux of alkaline duodenal contents and bile into the stomach, usually following partial gastrectomy. A milder form is often identified in intact stomachs from patients with gastric ulcer, gallstone dyspepsia, postcholecystectomy syndrome, and various motor disturbances of the distal stomach.

PEPTIC ULCER DISEASE

"Peptic ulcer disease" refers to breaks in the mucosa of the stomach and small intestine, principally the proximal duodenum, which are produced by the action of gastric secretions**.** Peptic ulcers of the stomach and duodenum are estimated to afflict 10% of the population of western industrialized countries at some time during their lives.

Although peptic ulceration can occur as high as Barrett esophagus and as low as Meckel diverticulum, for practical purposes, peptic ulcer disease affects the distal stomach (the lesser curvature of the stomach, in the antral and prepyloric regions) and proximal duodenum.

A peptic ulcer should be considered chronic when it does not heal readily and when scarring at the base of the ulcer precludes complete restoration of the normal submucosa and muscularis.

Pathogenesis. Many clinical and epidemiological features distinguish gastric from duodenal ulcers; the common factor that unites them is the gastric secretion of hydrochloric acid. With rare exceptions, a person who does not secrete acid will not develop a peptic ulcer anywhere. Current evidence indicates that the production of a duodenal ulcer is the consequence of *excess exposure* of the duodenal mucosa to the aggressive actions of gastric-acid-pepsin that overwhelm the normal defenses. patients with *gastric ulcers* have low-to-normal levels of gastric acid, but never true achlorhydria. Most of the accumulated data favor the existence of some primary *defect in gastric mucosal resistance*.

It is estimated that about 75% of patients with gastric ulcers harbor H. pylori. The remaining 25% of the cases may represent an association with other types of chronic gastritis.

Genetic influences are important in the predisposition to duodenal ulcer, but appear to play no role with gastric ulcer.

Gastric ulcer is usually single and less than 2 cm in diameter, although occasionally they reach a diameter of 10 cm or more, particularly if they are on the lesser curvature. The classic peptic ulcer is a round-to-oval, sharply punched-out defect, with relatively straight walls. The mucosal margin may overhang the base slightly, particularly on the upstream portion of the circumference. The margins are usually at the same level with the surrounding mucosa or only slightly elevated (heaping - up of these margins is extremely rare in the benign ulcer but is characteristic of the malignant lesion). The depth of these ulcers varies from superficial lesions, involving only the mucosa, down to deeply excavated, penetrating ulcers having their base in the muscularis. The base of all peptic ulcers is smooth and clean, owing to peptic digestion of any exudates, but it can be gray and indurated and may exhibit clotted blood or an eroded vessel (sometimes the source of a fatal hemorrhage). Deeply penetrating ulcers produce a serosal exudate, which may cause adherence of the stomach to the surrounding structures. Penetration of the entire wall may occur, and the base of the ulcer may be formed occasionally by the adjacent pancreas, omental fat, or adherent liver. In most peptic ulcers, underlying scars cause puckering of the surrounding mucosa, so that the mucosal folds radiate from the crater in spoke-like fashion. The gastric mucosa surrounding an ulcer is somewhat edematous and reddened, owing to the almost invariable gastritis.

On gross examination it may be exceedingly difficult to distinguish chronic peptic ulcer from an ulcerating gastric carcinoma. Thus, when examining the stomach, the endoscopist must take multiple biopsy specimens from the edges of any gastric ulcer.

Duodenal ulcers are ordinarily located on the anterior or posterior wall of the first part of the duodenum, within a short distance from the pylorus. The lesion is usually solitary, but is not uncommon to find paired ulcers on both walls, so-called “kissing” ulcers.

Microscopically, gastric and duodenal ulcers have a similar appearance. From the lumen outward, the following are noted: (1) a superficial zone of fibrino - purulent exudates and necrotic debris; (2) fibrinoid necrosis and inflammatory cells; (3) granulation tissue; (4) fibrotic tissue at the base of the ulcer, which exhibits variable degree of chronic inflammation.

The ulceration typically penetrates the muscle layers, thereby causing them to be interrupted by scar tissue. Blood vessels on the margins of the ulcer may be thrombosed or display obliterating endarteritis. The mucosa at the margins of the ulcer is often hyperplastic, and with healing may grow over the ulcerated area as a single layer of epithelium. However, in a large ulcer, this ingrowth of the epithelium may be insufficient to cover the defect completely.

Gastric ulcers are commonly accompanied by nonerosive gastritis, and the tissue surrounding a gastric or duodenal ulcer is often secondarily inflamed.

Complications. The most common complications of peptic ulcer disease in order of frequency are hemorrhage, penetration with or without perforation, and obstruction. Approximately a third of the patient experience one of these complications at some point during the course of their disease; ulcers most commonly associated with complications are those located in the pyloric channel and in the postbulbar duodenum.

Bleeding occurs when an ulcer erodes into a vessel. The erosion of small vessels is rarely associated with distinctive upper gastrointestinal signs or symptoms; such patients usually present with iron deficiency anemia as a result of the chronic blood loss. Of the major arteries, those most commonly eroded are the gastroduodenal artery in duodenal ulcers, and the left gastric artery in gastric ulcers. Rupture of one of these vessels constitutes a medical emergency, which accounts for approximately 50% of all acute upper gastrointestinal bleeding events. Patients present with hematemesis, melena, and other signs of acute blood loss, such as hypotension, tachycardia, and shock.

Perforation results when the ulcer erodes through the serosa of the viscus. The acute free perforation of an ulcer into the abdominal cavity is accompanied by a dramatic intensification of the patient’s symptoms; it is often accompanied by pneumoperitoneum and peritonitis and is an indication for immediate surgery. The actual perforation may be barely visible and is often obscured by the presence of coagulated blood, fibrin, and other debris. Examination of the serosa in the vicinity of the ulcer will invariably reveal severe acute inflammation.

An ulcer may burrow in an area where the stomach (or the duodenum) is in intimate contact with a solid organ such as the pancreas or liver. In such cases, the ulcer continues its penetration beyond the wall of the viscus and invades the parenchyma of the organ, where it usually elicits a dramatic inflammatory response, followed by fibrous buildup. Rarely, the perforation occurs in the vicinity of another hollow structure, like a small intestinal loop, the transverse colon, or the gallbladder, followed by formation of a fistula.

Gastric outlet obstruction is the clinical syndrome resulting from the distortion and narrowing of the pyloric area caused by fibrosis, edema, or smooth muscle spasm. It occurs almost exclusively in patients with a long-standing peptic ulcer of the pyloric channel or the duodenum.

Malignant transformation of a benign gastric ulcer. It is extremely difficult to distinguish a cancer arising in a preexisting gastric ulcer from an ulcerated carcinoma (malignancy from the beginning). Gross / endoscopic findings (shape, diameter, depth, walls, bottom, surrounding mucosal folds) are of some help, but multiple biopsies from the margins and the base of the defect will show malignant glands only in the walls of the malignant transformed ulcer. The ulcerating gastric carcinoma has the adenocarcinomatous proliferation at the bottom, as well as in the irregular walls). Malignant transformation of a duodenal ulcer is virtually unknown. However, although cancers originating in well-recognized benign peptic ulcers probably account for less than 1% of all malignant tumors in the stomach, such cancers have been documented and present a better prognosis than the gastric ulcerated carcinoma.

GASTRIC MALIGNANT TUMORS

Although the death rate from gastric cancer has been steadily declining in Europe and North America and, to a lesser extent, in many developing countries for the past six decades, it still remains a common cancer. *Atrophic gastritis, pernicious anemia, subtotal gastrectomy,* and *gastric adenomatous polyps* are factors associated with a high risk of stomach cancer.

Adenocarcinoma of the stomach accounts for more than 95% of all malignant gastric tumors and originates primarily from mucous cells of the normal superficial epithelium or from areas of intestinal metaplasia. The tumors are most common in the distal stomach, on the lesser curvature of the antrum and in the prepyloric region. Two general types of gastric adenocarcinoma are recognized, namely *advanced* and *early cancers* with a consistent prognosis impact - the l0-years survival rate for surgically treated advanced gastric cancer is about 20%, compared with 95% for early gastric cancer.

Early gastric cancer was defined by the Japanese gastroenterologists as a tumor that is confined to the mucosa or submucosa. An earlier term, superficial spreading carcinoma, is synonymous with early gastric cancer. In Japan early gastric cancer accounts for fully one third of all stomach cancers, whereas in the United States and Europe it constitutes only about 5% of diagnosed cancers.

Early gastric cancer is strictly a pathologic diagnosis; the term does not refer to the duration of the malignant tumor, its size, the presence of symptoms, the absence of metastases, or the curability. In fact, 5% to 20% of early gastric cancers are already metastatic to lymph nodes at the time of detection.

Most early gastric cancers are found in the distal stomach and have been classified by Japanese investigators according to their *macroscopic / endoscopic* appearance. Three major types are recognized:

1. Type I protrudes into the lumen as a *polypoid* or nodular mass.

2. Type II is a superficial, *flat* lesion that may be *slightly elevated* or *depressed*.

3. Type III is an *excavated* malignant ulcer that does not ordinarily occur alone but rather represents ulceration of type I or II tumors.

The polypoid and the superficial elevated varieties of early gastric cancer are typically well-differentiated adenocarcinomas. In the flattened or depressed superficial early cancers, the pattern ranges from well differentiated to anaplastic. The excavated lesions have the highest proportion of undifferentiated tumors.

One would suppose that early gastric cancer would be the precursor of advanced gastric cancer. However, this is not necessarily the case, and early gastric cancer may actually be a different disease from advanced cancer. It may exhibit a more benign course and greater curability because of an inherently lower biologic potential for invasion.

Advanced gastric cancer is a cancer that has penetrated beyond the submucosa into the muscularis and may extend through the serosa. The macroscopic appearance of these advanced cancers is of great importance not only to the pathologist but also to the radiologist and the endoscopist, who may be called on to distinguish carcinomas from benign lesions and to assess the degree of spread.

Advanced gastric cancers are divided into three major *macroscopic* types:

1. *Polypoid (fungating / exophytic) adenocarcinoma* accounts for about one third of advanced cancers. It is a solid mass, up to l0 cm in diameter, that projects into the lumen of the stomach. The surface may be partly ulcerated, and the deeper tissues usually are infiltrated.

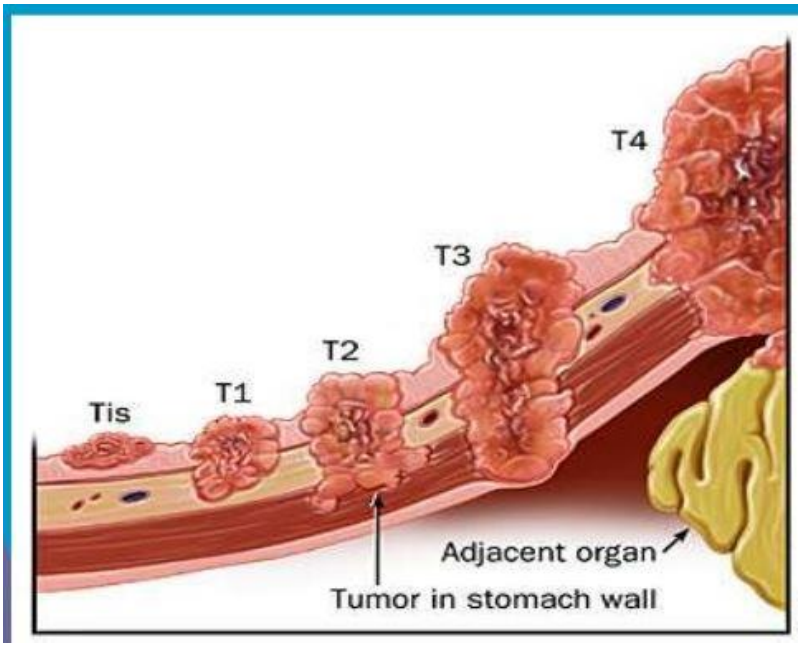
2. *Ulcerated / excavated adenocarcinoma* constitutes another third of all gastric cancers. Visualized as a shallow ulcer, in varies in size from 1 to 10 cm in diameter. The surrounding tissue is firm, raised, and nodular. Characteristically, the lateral margins of the ulcer are irregular and the base is ragged, in contrast to the benign peptic ulcer, which exhibits punched-out margins and a smooth base.

3. *Diffuse / infiltrating adenocarcinoma* constitutes one tenth of all stomach cancers. No true tumor is seen macroscopically; instead, the wall of the stomach is conspicuously thickened and firm. When the entire stomach is involved, the term *linitis plastica* (leather-bottle stomach) is applied. In the diffuse type of gastric carcinoma, the invading tumor cells induce extensive fibrosis in the submucosa and muscularis. As a result, the wall is stiff and may be more than 2 cm thick. Whereas the normal stomach has a volume greater than 1 liter, the leather-bottle stomach contains as little as 150 ml.

Microscopically, the histologic pattern of advanced gastric cancer varies from a well-differentiated adenocarcinoma to a totally anaplastic tumor, being recognized 2 major forms: *intestinal* (originated from intestinal metaplasia of gastric mucosa) and *diffuse* (developing from superficial gastric

epithelium) types, with some correlations between gross and histological appearances. The polypoid variant typically contains well - differentiated glands, whereas linitis plastica is characteristically poorly differentiated. Particularly in the ulcerated type of cancer, the tumor cells may be arranged in cords or small foci. Tumor cells may contain clear mucin that displaces the nucleus to the periphery of the cell, resulting in the so-called *signet ring cell carcinoma.* Extracellular mucinous material may be so prominent that the malignant cells seem to float in a gelatinous matrix, in which case it is called a *colloid* or *mucinous carcinoma*. Cancers with papillary infoldings are termed *papillary adenocarcinomas*, and those that form solid tumor masses with no or little intervening stroma are referred to as *medullary carcinomas*.

Being a solid malignancy, the gastric cancer is staged by the international TNM cancer staging system, in which T refers to the level of tumor penetration towards serosa (see the image below). As expacted, the deeper tumor is associated with a poorer prognosis than that of a more superficial one.



Gastric cancer metastasizes principally by the lymphatic route to regional lymph nodes of the lesser and greater curvature, the porta hepatis, and the subpyloric region. Distant lymphatic metastases also occur, the most common being the enlarged supraclavicular nodes, classically called *Virchow's node* – skip metastases (see Tumors chapter from General Pathology). The left supraclavicular nodes receive lymphatic drainage from abdominal cavity organs (from the thoracic duct that enters into the venous circulation via the left subclavian vein). The metastasis may block the thoracic duct leading to regurgitation into the surrounding Virchow's nodes. Such spread typically results in **Troisier's sign**, which is the finding of an enlarged, hard Virchow's node.

Of note:

*Virchow's nodes are named after Rudolf Virchow (1821–1902), the German pathologist who first described the nodes and their association with **gastric cancer** in 1848. The French pathologist Charles Emile Troisier noted in 1889 that other abdominal cancers, too, could spread to the nodes (particularly ovarian, testicular and kidney cancers).*

Hematogenous spread may seed any organ, including the liver, lung, or brain. Direct extension to nearby organs is often encountered. Carcinoma of the stomach can also spread (in women patients) to the ovary, in which case it is termed a *Krukenberg tumor.*

Gastric lymphomas constitute less than 5% of all malignant stomach tumors, but are the most common of all extranodal non-Hodgkin's lymphomas (20% of such neoplasms). Clinically and radiologically, gastric lymphoma mimics gastric adenocarcinoma. The presenting symptoms of gastric lymphoma - weight loss, dyspepsia, and abdominal pain - are similar to those of gastric adenocarcinoma.

The prognosis for gastric lymphoma is considerably better than that for adenocarcinoma - the overall 5-years survival is about 50%, depending on the extent of disease at the time of diagnosis.

A majority of gastric lymphomas present as *high-grade, large-cell immunoblastic lymphomas*. These lesions tend to be visible lesions with thickening of the rugal folds and frequent ulceration. Under the microscope, these high-grade lymphomas may be relatively monomorphic, composed of large cells with abundant cytoplasm and vesicular nuclei endowed with prominent nucleoli. Variants of this type include mixtures of large cells, immunoblasts, and small lymphocytes, or a peculiar sclerosing type with interstitial collagen deposition.

Other lymphomas of the stomach are *low-grade, small lymphocytic well-differentiated B-cell lymphomas*, categorized as MALTomas by Isaacson and coworkers (MALT = mucosa associated lymphoid tissue). These lymphomas are characterized by proliferation of monocytoid cells and by the presence of lymphoepithelial lesions. Most of MALTomas tend to be of low grade and indolent in nature, but some would appear to evolve in later stages into a high-grade type. It has been proposed that such MALTomas arise from the lymphoid follicles that appear in chronic nonerosive gastritis, often associated with peptic ulcer disease and with H. pylori infection.

CELIAC DISEASE (celiac sprue, gluten-sensitive enteropathy) is characterized by generalized malabsorption, small intestinal mucosal lesions and prompt clinical and histopathologic response to withdrawal of gluten-containing foods from the diet.

The microscopic hallmark finding of fully developed celiac disease in small bowel biopsies is a flat mucosa, with (1) blunting or total disappearance of villi, (2) damaged mucosal surface epithelial cells with numerous intraepithelial lymphocytes (T cells), and (3) increased plasma cells in the lamina propria but not in deeper layers

WHIPPLE DISEASE a rare infection of the small bowel, caused by Tropheryma whippelii (an actinomycetes) determines malabsorption as the most prominent clinical feature. White men in their 30s and 40s are most affected. The disease is systemic, and other clinical findings include fever, increased skin pigmentation, anemia, lymphadenopathy, arthritis, pericarditis, pleurisy, endocarditis, and central nervous system involvement.

The bowel wall is thickened and edematous, and mesenteric lymph nodes are usually enlarged. Villi are flat and thickened villi, and the lamina propria is extensively infiltrated with large foamy macrophages whose cytoplasm is filled with large glycoprotein granules that stain strongly with periodic acid Schiff (PAS). The other normal cellular components of the lamina propria (i.e., plasma cells and lymphocytes) are depleted. The lymphatic vessels in the mucosa and submucosa are dilated and large lipid droplets abound within lymphatics and in extracellular spaces, a finding that suggests lymphatic obstruction. In contrast to the striking distortion of the villous architecture, epithelial cells show only patchy abnormalities, including attenuation of microvilli and accumulation of lipid droplets within the cytoplasm. Electron-microscopic examination reveals numerous small bacilli within macrophages and free in the lamina propria.

CROHN'S DISEASE is an idiopathic, chronic, relapsing ulcero-inflammatory disease of gastrointestinal tract that most often affects the terminal ileum. The colon may be affected, either in association with small bowel disease or as an isolated finding (Crohn's colitis).

Chron's disease shows discontinuous segments of disease with large and small ulcers separated by normal (noncongested) mucosa. The earliest gross manifestations of Crohn's disease are aphtoid ulcers. These consist of small mucosal erosions 1 to 2 mm in diameter with a hemorrhagic edge and gray-white base. Commonly they are located on top of lymphoid follicles. As the disease progresses, the aphtoid ulcers enlarge to form discrete, or confluent, serpiginous, or linear fissuring ulcers. Linear longitudinal ulcers often overlie teniae coli and with transverse ulcers may dissect the mucosa into a cobblestone pattern. Segmental thickening of the wall and luminal narrowing - strictures (secondary to ulcers), and fistulas are present. Fistulas may develop between the colon and the duodenum, small bowel, bladder and vagina.

Microscopically, transmural inflammation consisting of lymphoid follicles and non-necrotizing granulomas is seen beneath and around chronic fissuring ulcers. Non-necrotizing granulomas, formed by

epithelioid cells, giant multinucleated cells and many lymphocytes may be found in any layer of the bowel wall, but are not mandatory for a positive diagnosis.

Complications of Crohn's disease are intestinal obstruction, fistulas, perforation and adenocarcinoma.

ULCERATIVE COLITIS is a chronic idiopathic inflammation of the rectal and colonic mucosa that affects a variable length of the large bowel in continuity from the anus (Fig. III.8.). It may be present at any time between infancy and old age, but the primary mode for clinical onset is between l5 and 25 years of age for both sexes.

The pathogenesis of ulcerative colitis is unknown. It seems likely that for the development of the disease, there must be a provoking agent in the bowel lumen (infective or chemical), with an inappropriate host immune response that perpetuates the inflammatory reaction.

Ulcerative colitis varies in extent from a distal proctitis affecting a few centimeters of bowel to total colonic involvement with extension into the terminal ileum. The gross, microscopic, and clinical features vary considerably with the degree and duration of disease activity. Endoscopic and gross features of active disease are mucosal hyperemia, friability, granularity, ulcers, and erosions with blood in the lumen.

Inflammatory polyps are found endoscopically in about 20% of cases. They occur after episodes of severe disease, in which ulcers undermine the mucosa. These ulcers coalesce to form irregular shallow ulcerated areas that surround islands of intact mucosa. When epithelium regenerates over the floors of the ulcers the islands remain elevated and become inflammatory polyps ("pseudopolyps").

Histologic examination in an active phase revels a diffuse increase in inflammatory cells within the lamina propria, including plasma cells, eosinophils, lymphocytes, macrophages, and neutrophils. The capillaries are congested and dilated. The crypts show evidence of regeneration: branching, shortening, irregularity, dilatation, and villiform change. Neutrophils infiltrate the surface and crypt epithelium and accumulate in crypt lumens to form abscesses. Traditionally, neutrophils infiltration is regarded as the prime indicator of disease activity. Crypts that contain abscesses invariably show small foci of ulceration if serially sectioned. Macroscopic ulcers originate when crypt abscesses expand into the lamina propria and destroy the mucosa. Such ulcers are extensive only in fulminant cases. As the disease undergoes resolution, neutrophils disappear from the epithelium and lamina propria. Later, chronic inflammatory cells diminish.

The mucosa in inactive colitis may show minimal or no inflammation and may have a villiform appearance because of crypt dilatation. It may be thinned and atrophic with short crypts that fail to reach the muscularis mucosae, branching crypts, and crypt dropout.

During evolution of ulcerative colitis some complications can be encounter: hemorrhage, toxic megacolon, perforation and adenocarcinoma.

BENIGN TUMORS OF SMALL INTESTINE are: *adenomas*, *leiomyomas* and *lipomas* (the most common). As in other portions of gastrointestinal tract, *neurogenic* tumors, *fibromas*, *angiomas* and *hamartomas* may be encountered.

Adenomas, known also as adenomatous polyps, can be tubular or villous or a mixture of these types (as in the colon). The villous adenoma is rare, usually occurring in the ileum. Although most adenomas remain benign, some, especially the villous type, undergo malignant transformation. Benign adenomas are ordinarily asymptomatic, but bleeding and intussusception are occasional complications.

Peutz-Jeghers syndrome is an autosomal dominant hereditary disorder characterized by intestinal polyps and mucocutaneous melanin pigmentation, which is particularly evident on the face, buccal mucosa, hands, feet, perianal and genital areas. The polyps occur most commonly in the proximal regions of the small intestine, but are sometimes seen in the stomach and in the colon, too. The polyps are not true neoplasms, but rather *hamartomas*. Histologically, a branching network of smooth muscle fibers continuous with the muscularis mucosa supports the glandular epithelium of the polyp. Peutz-Jeghers polyps are generally considered benign; however, 2% to 3% of patients develop adenocarcinoma.

Leiomyomas are smooth muscle tumors that occur at all levels, but are most common in the jejunum. This lesion ordinarily presents as an intramural mass covered by intact mucosa. However, it

may protrude into the lumen, where necrosis of tumor tissue and ulceration of the overlying mucosa give rise to bleeding. Intestinal obstruction is uncommon, but volvulus may be a complication.

Lipomas are fatty tumors that occur throughout the length of the small intestine, but are most common in the distal ileum. These submucosal tumors may become large and produce intestinal obstruction. The overlying mucosa may become ulcerated and may bleed.

MALIGNANT TUMORS OF SMALL INTESTINE

Adenocarcinomas constitute half of all malignant small bowel tumors. The large majority of adenocarcinomas are located in the duodenum and jejunum. Most occur in middle-aged persons, and there is a moderate male predominance. A risk factor for adenocarcinoma is the inflammatory disease of the small intestine. Patients with Crohn disease are known to be at significantly increased risk, perhaps as high as 100 folds compared with a patient without such illness.

It may be polypoid or ulcerative or annular and stenosing. In addition to cause intestinal obstruction directly, a polypoid tumor may be the lead point of an intussusception. Microscopically, adenocarcinomas, which originate from the epithelium of the crypts rather than the villi, resemble colon cancer.

Adenocarcinoma being usually annular, the symptoms are commonly those of progressive intestinal obstruction. Occult bleeding is also common and often leads to iron-deficiency anemia. Adenocarcinoma of the duodenum may involve the papilla of Vater, in which case it is termed ampullary carcinoma. This tumor causes obstructive jaundice or pancreatitis. Most symptomatic adenocarcinomas have already metastasized to local lymph nodes and the overall 5 years survival is less than 20%.

Primary lymphoma originates in nodules of lymphoid tissue within the bowel wall and represents the second most common malignant tumor of the small intestine. It accounts for about 15% of small bowel cancers. There are two types of lymphoma which have distinct epidemiological, clinical and pathologic features:

- *Mediterranean type lymphoma.* It typically occurs in poor countries in young men of low socioeconomic status. This neoplasm has been associated with α-chain disease, a proliferative disorder of intestinal B lymphocytes that secrete IgA. It involves predominantly the duodenum and proximal jejunum. The lymphoma typically presents as a diffuse infiltration of the mucosa and submucosa by plasmocytoid lymphocytes. Lymphomatous infiltration of the mucosa leads to mucosal atrophy and severe malabsorbtion.
- *Western type lymphoma.* It affects adults older than 40 years of age of and children younger than 10 years old. It is most common in the ileum where it presents as: fungating mass, an elevated ulcerated lesion, a diffuse segmental thickening of the bowel wall or as plaque-like mucosal nodules. As a result, intestinal obstruction, perforation, occult bleeding are important complications.

Microscopically, all varieties of malignant lymphoma are encountered. Patients with *Mediterranean type lymphoma* tend to survive longer than those with the *Western type*.

Carcinoid tumor of the gastrointestinal tract arises from cells of the neuroendocrine system of the gut, at the base of the mucosal crypts. These cells are included in the amine precursor uptake and decarboxylation (APUD) system. The most commonly secreted hormone is serotonin. It represents less than 1% of all gastrointestinal tumors and 20% of all malignant tumors. The carcinoid tumor is often multicentric with multiple primary sites, either simultaneously or at different times. Macroscopically, the small tumors present as submucosal nodules covered by intact mucosa. Large tumors may grow in a polypoid, intramural or annular pattern and often undergo secondary ulceration. The cut surface is firm and white to yellow. Microscopically, the neoplasms appear as nests, cords and rosettes of uniform, round cells.

BENIGN TUMORS OF LARGE INTESTINE

Polyps of the colon. A gastrointestinal polyp is defined as a mass that protrudes into the lumen of the gut. Polyps are subdivided according to their attachment to the bowel wall (sessile or pedunculated), their histologic appearance (non-neoplastic or adenomatous) and to their malignant transformation potential. Colonic polyps are classified broadly as neoplastic (or adenomatous) and non-neoplastic.

Adenomatous / neoplastic polyps arise from the colon mucosal epithelium. They are composed of crypt cells that have migrated to the surface and have accumulated beyond the needs for replacement of the cells sloughed into the lumen. Almost half of all adenomatous polyps of the colon are located in the rectosigmoidian region and can therefore be detected by digital examination or by sigmoidoscopy. The macroscopic appearance of an adenoma varies from a barely visible nodule or small pedunculated mass to a large, sessile, villous adenoma.

- *Tubular adenomas* constitute two thirds of benign large bowel adenomas. There are typically smooth-surfaced spheres, usually less than 2 cm in diameter, which are attached to the mucosa by a stalk. Microscopically, they exhibit closely packed epithelial tubules, which are embedded in a fibrovascular stroma.
- *Villous adenomas* are found predominantly in the rectosigmoidian region. They are typically large, broad-based, elevated lesions that grossly display a shaggy, cauliflower-like surface. More than half of them are larger than 2 cm in diameter and on occasion they reach a size of 10 to 15 cm across. Microscopically, they are composed of thin, finger-like processes that superficially resemble the villi of the small intestine. They are lined externally by epithelial cells and are supported by a core of fibrovascular connective tissue corresponding to the normal lamina propria.
- *Tubulovillous adenomas* tend to be intermediate in distribution and size between the tubular and villous forms, one fourth to one third being larger than 2 cm across.

Of greater importance is the fact that adenomas, and most of all the villous adenomas, which measure more than 2 cm in greatest dimension, may shift to an invasive carcinoma.

Familial adenomatous polyposis (FAP) is inherited as an autosomal dominant trait and is characterized by the progressive development of innumerable adenomatous polyps of the colon, particularly in the rectosigmoidian region. Although a few polyps are usually present by 10 years of age, the mean age for the occurrence of symptoms is 36 years, by which time cancer is already present in more than a half of the patients.

Whereas all adenomatous polyps may be considered to occupy places on the same developmental spectrum, the **non-neoplastic** polyps are entirely different entities from one another and are grouped together only for their gross appearance as raised lesions of the colonic mucosa:

- *Hyperplastic polyps (metaplastic polyps)* are small, sessile mucosal excrescences that display exaggerated crypt architecture. They are the most common polypoid lesions of the colon and are particularly frequent in the rectum. They are small, sessile raised mucosal nodules which are up to 0,5 cm in diameter. Histologically, the crypts are elongated and may exhibits cystic dilatation. The epithelium is composed of well-differentiated goblet cells and absorptive cells.
- *Juvenile polyps (retention polyps)* may be single or multiple and occur most commonly in the rectum. Most polyps are pedunculated lesions, with a smooth, rounded surface. Histologically, dilated and cystic epithelial tubules are embedded in a fibrovascular lamina propria.
- *Inflammatory polyps / pseudopolyps* are rather elevated masses of chronically inflamed and regenerating epithelium over ulcerations caused by an inflammatory disease of the colon. Such polyps are commonly found in association with ulcerative colitis and Crohn disease. Microscopically, are composed of distorted and inflamed mucosal glands. When the surface of the polyp is ulcerated, granulation tissue may be prominent.
- *Lymphoid polyps* represent submucosal accumulations of lymphoid tissue. Almost invariably appears in the rectum, as a single, sessile nodule measuring from a pinpoint size to 5 cm in diameter. Microscopically, they are covered by intact mucosa and are composed of prominent lymphoid follicles with germinal centers.

MALIGNANT TUMORS OF LARGE INTESTINE

The **colorectal cancer** is second in incidence only to carcinoma of the lung in men and is third after breast and lung cancer in women. The importance of environmental factors in the pathogenesis of colon cancer is emphasized by the high incidence of the disease in industrialized countries.

The **gross appearance** of colorectal cancer is similar of adenocarcinomas elsewhere in the gastrointestinal tract. They may be polypoid, ulcerating or infiltrative, in the last case customarily annular and constrictive. Polypoid cancers are most common on the right side of the colon, particularly

in the cecum. Annular constricting tumors occur most often in the distal portions of the colon. Ulceration of the tumors, irrespective of the growth pattern, is usual.

The vast majority of colorectal cancers are **adenocarcinomas**, which are microscopically similar to their counterparts in other portions of the gastrointestinal tract. Most are well differentiated and secrete small amounts of mucin. 10 – 15% secrete considerable quantities of mucin in which case they are classed as mucinous adenocarcinomas. The degree of differentiation influences the prognosis, the better differentiated tumors being associated with a more favorable outlook. Occasionally, the predominant mucus-producing cell is of the "*signet ring*" variety in which case the cancer is associated with a particularly poor prognosis.

The prognosis of colon cancer is more closely related to the extension of the tumor through the wall of the colon than to its histologic characteristics. In its penetration of the muscular layers, colon cancer tends to exploit the same gaps that house the penetrating arteries. The connective tissue of the serosa offer little resistance to the spread of the tumor and cancer cells are often found in the fat and serosa at some distance of the primary tumor.

Colorectal cancer invades lymphatic channels and initially involves the lymph nodes immediately underlying the tumor. Venous invasion leads to blood-borne metastases, which involve the liver in 75% of patients with metastatic disease. The lungs, bones and brain are not uncommon sites of metastases.

In its initial stages colorectal cancer is clinically silent. As the tumor grows, the most common sign is *occult intestinal bleeding* when the tumor is in the proximal portions of the colon, or *bright red blood* when the lesion is in the rectum. Cancers of the left side of the colon often *constrict* the lumen producing obstructive symptoms. Occasionally, colon cancer *perforates* early. It may produce enterocutaneous and rectovaginal *fistulas*. Intraabdominal spread may cause small intestinal obstruction and ascites.

As mentioned in the Tumors chapter of General Pathology, for colonic carcinoma the Dukes' staging system is complementary to TNM system with better correlation with prognosis according to organ anatomical and functional specificity. In this perspective, Duke's staging of colorectal carcinoma presents:

Stage A tumors are confined to the bowel muscle wall.

Stage B cancers show invasion completely through the muscle wall.

Stage C is defined by the presence of lymph node metastases, irrespective of the depth of invasion of the primary tumour.

Local extension estimates prognosis as in TNM system: penetration of the tumor in serosa of the bowel is associated with a poorer prognosis than that of a more superficial tumor, but the regional lymph node involvement overcome the significance of tumor size.

Other malignant tumors of the colon are: **carcinoid tumor, lymphoma.**

LIVER PATHOLOGY

ALCOHOLIC LIVER DISEASE

The spectrum of *alcoholic liver disease* spans 3 major morphologic and clinical entities: **fatty liver** (described in "General Pathology" – Ist semester), **alcoholic hepatitis** and **cirrhosis.** Although these lesions usually occur sequentially, they may coexist in any combination or may be independent entities.

Alcoholic hepatitis is an acute necrotizing lesion along with collagen deposition, superimposed, usually, on an existing fatty liver, characterized by: 1) necrosis of hepatocytes, predominantly in the central zones, 2) cytoplasmic hyaline inclusions within hepatocytes - Mallory bodies, 3) a neutrophilic inflammatory response, and 4) perivenular fibrosis. Associated lesions consist of: variable hydropic swelling of hepatocytes, steatosis (microvacuolar and/or macrovacuolar steatosis) and cholestasis. Collagen deposition is a constant feature of alcoholic hepatitis, especially around the central vein (terminal hepatic venule). In severe cases the venule and perivenular sinusoids are obliterated and surrounded by dense fibrous tissue, in which case the lesion has been termed *central hyaline sclerosis.*

Alcoholic cirrhosis. In about 15% of alcoholics, hepatocellular necrosis, fibrosis, and regeneration of liver cells lead to the formation of fibrous septa surrounding hepatocellular nodules (see further details).

CHRONIC VIRAL HEPATITIS. There are two basic morphologic types of chronic hepatitis with prognostic significance:

Chronic persistent hepatitis is a mild form of chronic hepatitis characterized by lymphocytic infiltration limited to portal tracts. About half of those clearly identified as having HBV infection manifest chronic persistent hepatitis and do not progress to more severe disease. The others, with little portal change are referred to as "asymptomatic" HBV carriers show only minimal or sporadic increases in serum aminotransferase.

Thus, the so-called asymptomatic carrier simply represents the most inactive extreme of the spectrum of persistent viral hepatitis. Characteristically, the limiting plate is intact. Liver cell necrosis and lobular inflammation are minimal, and the Kupffer cells appear normal, scattered cells display a large granular eosinophilic cytoplasm, which contains abundant HB_sAg ("ground glass hepatocytes"). "Ground glass" hepatocytes are not present in chronic hepatitis C, instead fatty change / steatosis of the liver cells is a constant finding.

Chronic active hepatitis is a necrotizing inflammatory disease that may progress to cirrhosis. Chronic inflammation and focal necrosis early in the course of the disease are distributed irregularly among the lobules, without the predominantly centrilobular localization as in acute viral hepatitis. Later the portal tracts become densely infiltrated by lymphocytes, macrophages and, occasional, plasma cells. Lymphoid aggregates in the portal tracts, even with germinal centers, are often seen in HCV infection. The expanded portal tracts show a mild to severe proliferation of bile ductules, particularly in cases of HCV hepatitis, which probably represents a nonspecific response to lobular changes.

The inflammatory cells penetrate the limiting plate and surrounds individual hepatocytes and groups of hepatocytes on the borders of the portal tract. The resulting irregular appearance of the periportal zone ("moth-eaten") has been termed *piecemeal necrosis* / *periportal necrosis* and historically has been considered a hallmark of progressive disease. Nowdays, the inflammatory infiltrate that spill over the limiting plate into the parenchyma to cause necrosis of periportal hepatocytes is designed as *interface hepatitis*.

It is not uncommon to observe intralobular changes similar to those of acute hepatitis, including single cell necrosis, acidophilic bodies, ballooned hepatocytes and central phlebitis. In patients with chronic active hepatitis B, "ground glass" cells are scarce in areas of necrosis and inflammation, presumably because they are destroyed by immune response. Fatty change is mild and is unusual except with HCV infection.

When seen in the context of chronic active hepatitis, confluent hepatic necrosis, in the form of *bridging necrosis*, is an ominous predictor of rapid progression to cirrhosis. Strands of connective tissue extend from the portal tracts into the lobules, giving the former a stellate appearance. Threads of

connective tissue also envelop single hepatocytes and groups of cells, particularly adjacent to the portal tracts.

The end-stage is characterized by the presence of dense collagenous septa, which destroy the lobular architecture and divide the liver into hepatocellular regenerative nodules - an appearance termed post-necrotic or post-hepatitis cirrhosis.

CIRRHOSIS is defined as the destruction of the normal hepatic architecture by fibrous septa that encompass regenerative nodules of hepatocytes and represents an end-stage (irreversible and progressive) of chronic liver disease. There is a large number of diseases associated with cirrhosis, that have little in common, except for the fact that they are all accompanied by persistent liver cell necrosis.

The *causes* of cirrhosis are:

- alcoholic liver disease;
- chronic active hepatitis;
- primary biliary cirrhosis;
- extrahepatic biliary obstruction;
- hemochromatosis (hereditary and secondary); heritable disorders (Wilson disease, cystic fibrosis, α_1-antitrypsin deficiency); inborn errors of carbohydrate metabolism (glycogen storage diseases, galactosemia, hereditary fructose intolerance); tyrosinemia hereditary storage diseases (Gaucher, Niemann-Pick, Wolman, mucopolysaccharidoses); Zellweger syndrome; Indian childhood cirrhosis; congestive heart failure (cardiac cirrhosis); Budd – Chiari syndrome.

Whatever the cause, four *mechanisms* are involved in the production of hepatic cirrhosis: (1) hepatocellular necrosis, (2) replacement of the dead liver cells with fibrosis and inflammation, (3) vascular derangement with impediment of flow and (4) hyperplasia of surviving liver tissue – liver cells, forming irregular nodules and bile ducts hyperplasia.

On *gross examination* the liver is shrunken, firm, with rough surface due to the nodules formation:

- micronodular type, with small, less than 3 mm in diameter nodules, separated by thin fibrous septa (it was termed, in the past, Laennec's or nutritional cirrhosis).
- macronodular type, exhibits nodules of varying size (some several cm in diameter) and broad bands or areas of depressed scarring (formerly labeled post-necrotic, posthepatitis cirrhosis).
- mixed type, micro-macronodular cirrhosis.

Alcoholic cirrhosis is the final form of alcoholic liver disease. At first, the cirrhotic liver is yellow tan, fatty and enlarged, weighing more than 2 kg. Over the span of years, it is transformed into a brown, shrunken (less than 1 kg in weigh), non-fatty organ, with a micronodular surface (nodules less than 3 mm in diameter) – Laennec's cirrhosis. With time, nodularity becomes more prominent (some nodules have more than 2 cm in diameter). Parenchymal islands are engulfed by ever wider bands of fibrous tissue, so the liver becomes more fibrotic and it is converted into a mixed micronodular and macronodular pattern.

By microscopy, the parenchymal nodules show no landmarks of lobular architecture in the form of portal tracts or central venules. Hepatocytes may present eosinophilic Mallory bodies and steatosis (microvacuolar and macrovacuolar fatty change). At the beginning the connective tissue septa are thin and extend themselves from portal region to central veins, as well as from portal tract to portal tract, but irregular progressive collapse of parenchyma may lead to wider septa. In active stages of the cirrhotic process, numerous mononuclear inflammatory cells (lymphocytes mainly), capillaries, venules, fibroblasts and reactive bile duct proliferation inhabit the collagenous septa.

Postnecrotic cirrhosis. After several years of persistent intrahepatocyte viral infection (HBV and HCV), chronic active hepatitis causes cirrhosis. The nodules are irregularly sized, large (more than 2 cm in diameter), encompassed by broad bands of fibrosis. Severe collapse may leave a shrunken liver less than 1 kg in weigh. The large nodules (more than 2 cm in diameter) often contain portal tracts and efferent venous channels, evidence that the original process was characterized by multilobular necrosis (postnecrotic cirrhosis), that healed with the formation of large scars surrounding more than a single

lobule. The connective tissue septa in macronodular cirrhosis are characteristically broad and contain elements of preexistent portal tracts, mononuclear inflammatory cells, and proliferated bile ductules.

Primary biliary cirrhosis is a chronic, progressive and often fatal cholestatic liver disease, characterized by the non-suppurative destruction of intrahepatic bile ducts, portal inflammation and scarring, with a final micronodular pattern of liver cirrhosis.

The etiology is unknown, but a striking feature of the disease is autoantibodies, especially antimitochondrial antibodies (IgM) in more than 90% of patients, suggesting an immunological process.

Macroscopically, the liver has a green appearance due to bile stasis, with a fine granularity towards a uniform micronodularity.

The essential lesion is a chronic inflammation restricted, at first, to portal tracts, which destroys the small intrahepatic bile ducts, followed by progressive damage to parenchyma. The destruction of interlobular and septal bile ducts by granulomatous inflammation (lymphocytes + lymphoid follicle formation; histiocytes, plasma cells, eosinophils) is named "florid duct lesion". Both inflammation and cholestasis at periphery of lobules lead to loss of adjacent hepatocytes (piecemeal necrosis), with extension of inflammation within lobular parenchyma and replacement fibrosis. With time, inflammation subsides, and granulomas and florid duct lesion become infrequent. Hepatocyte loss, fibrosis, and nodular regeneration lead to the gradual development of true cirrhosis.

Secondary (obstructive) biliary cirrhosis is the end result of prolonged obstruction of the extrahepatic biliary tree. The conditions that may produce the obstruction are: an impacted gallstone in the common bile duct, malignancy of the bile duct or surrounding tissues (pancreas, ampulla of Vater, enlarged neoplastic lymph nodes in the porta hepatis), postoperative benign strictures, congenital biliary atresia.

The liver exhibits a striking yellow-green pigmentation and is accompanied by marked icteric discoloration of body tissues and fluids. On cut surface, the liver is hard, with a finely granular appearance.

Microscopically, cholestasis first appears around hepatic venules and spreads towards portal tracts. Damaged hepatocytes contain large amounts of bile causing a reticulated aspect of the cytoplasm, termed "feathery degeneration" or may become necrotic – foci of "bile infarcts". As obstruction proceeds, inflammatory cells (lymphocytes, plasma cells and polymorphs) infiltrate the portal tracts, which are edematous. In the portal tracts, hyperplastic, tortuous and dilated bile ducts may rupture, leading to the formation of "bile lakes", a diagnostic feature of extrahepatic biliary obstruction. Leakage of bile into the portal tracts causes the appearance of foamy, lipid-laden macrophages, which often aggregate as granulomas. Other diagnostic features of extrahepatic biliary obstruction are biliary concretions within bile ducts and proliferated ductules. With time the portal tract become fibrotic and the extension of inflamed septa into lobules, associated with regenerative nodules result in a micronodular cirrhosis. The condition may be complicated by acute ascending infection of the obstructed biliary passages with suppurative cholangitis, intraluminal pus, and even intrahepatic abscesses.

LIVER PRIMARY TUMORS:

1. Benign

- *cavernous hemangioma* (see tumors chapter);
- *liver cell adenoma* tend to occur in young women who used oral contraceptives
- *bile duct adenoma.*

2. Malignant

- *hepatocellular carcinoma (HCC)* appear grossly as (1) solitary large tumor; (2) multifocal nodular form or (3) diffusely infiltrative cancer. On microcope examinantion, HCC range from well-differentiated (malignant cells disposed, most common, in a trabecular pattern) to undifferentiated lesions (resemble spindle cell sarcoma).
- *cholangiocarcinoma* may present the same 3 patterns of gross appearance as HCC, and microscopically resembles adenocarcinoma, often with a dense collagenous stroma = desmoplastic tumor. It's impossible to distinguish, only on slide, intrahepatic cholangiocarcinoma from metastatic adenocarcinoma.

- *hemangiosarcoma* (see tumors chapter).

LIVER SECONDARY / METASTATIC TUMORS are far more common than primary neoplasia, any cancer in any site of the body (especially those situated in gastrointestinal tract) may spread to the liver. Typically multiple nodular implants, gray-white, at the periphery of the circulation underneath the liver capsule, are found that, often, cause striking hepatomegaly.

GALLBLADDER DISEASES

CHOLELITHIASIS is defined as the presence of stones within the lumen of the gallbladder or in the extrahepatic biliary tree. ¾ of gallstones in the industrialized countries consist primarily of cholesterol and the remainder are composed of calcium bilirubinate and other calcium salts (pigment gallstones). The latter stone specimens predominate in the tropics and the Orient.

Cholesterol stones arise exclusively in the gallbladder and consist of 100% down to around 50% cholesterol. Pure cholesterol stones are pale yellow, round or ovoid and have a finely granular, hard external surface, which on transection reveals a glistering radiating crystalline palisades. With increasing proportions of calcium carbonate, phosphates, and bilirubin, the stones exhibit discoloration and may be laminated and gray-white to black on transection. Most often they are multiple stones with faceted external surface, due to tight apposition. Stones composed largely of cholesterol are radiolucent; sufficient calcium carbonate is found in 10 – 20% of cholesterol stones to render them radiopacity.

Pigment stones are *"black"* and *"brown".*

"Black" pigment stones are found in sterile gallbladder bile and are composed of oxidized polymers of the calcium salts of unconjugated bilirubin, lesser amounts of calcium carbonate, calcium phosphate, mucin, glycoprotein and few cholesterol crystals. They are small (less than 1 cm in diameter), spiculated, present in great number, and may crumble to the touch. Because of calcium carbonates and phosphates, about 50 – 75% of black stones are radiopaque.

"Brown" pigment stones are found in infected intrahepatic or extrahepatic ducts and contain pure calcium salts of unconjugated bilirubin, mucin glycoprotein, a substantial cholesterol fraction, and calcium salts of palmitate and stearate. They tend to be laminated and soft and may have a soap-like or greasy consistency. Because they contain only calcium soaps, they are radiolucent.

Although most gallstones are not radiopaque, they are readily visualized by ultrasound examination.

	Cholesterol stones	**Pigment (black or brown) stones**
Risk factors	- advancing age; - obesity + cholesterol rich diet; - female sex hormones; - gallbladder stasis; - hyperlipidemia; - disorders of bile metabolism.	- chronic hemolytic syndromes; - biliary infection; - gastrointestinal disorders (Crohn's disease, ileal resection, cystic fibrosis).
Pathogenesis	3 conditions must be met: (1) bile supersaturated with cholesterol, so it can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals; (2) bile' kinetic favorable for nucleation; (3) the persistence of cholester crystals within gallbladder long enough to aggregate into stones	Precipitation of abnormal insoluble calcium salts of unconjugated bilirubin. The presence of unconjugated bilirubin in the biliary tree is possible in some circumstances: (1) increased hemolysis; (2) infections of the biliary tract.

CHOLECYSTITIS is defined as an acute or chronic inflammation of the gallbladder.

Acute cholecystitis most commonly (90 – 95%) follows an occlusion of the cystic duct by gallstones, thus the term **acute calculous cholecystitis**.

The gallbladder is enlarged, tense, with a bright red or violaceous to green-black discoloration, imparted by subserosal hemorrhages. There is a fibrinous / suppurative exudate on the serosa. In most cases, an obstructive stone is present in the neck of the gallbladder or the cystic duct. In addition to other possible stones, the gallbladder lumen is filled with a cloudy mixture of bile, blood, fibrin and pus. The gallbladder wall is thickened, edematous and hyperemic. In more severe cases, the gallbladder may contain pure pus, condition called *empyema* or the gallbladder is transformed into a green-black necrotic organ, termed *gangrenous cholecystitis*, with small – to – large perforations.

Histologically, the covering epithelium is desquamated or severe ulcerated and throughout entire wall thickness there are present various kind of acute inflammatory reactions: vascular congestion, edema, erythrocyte effusions, neutrophilic infiltrate, frank abscess formation or gangrenous necrosis.

The following complications may occur: gallbladder rupture / perforation with diffuse biliary peritonitis or pericholecystic abscess formation; biliary enteric (cholecystenteric) fistula; cholangitis; chronic cholecystitis.

Chronic cholecystitis is the most common disease of the gallbladder and it is almost invariable (more than 90% of cases) associated with gallstones. It may result from repeated attacks of acute cholecystitis, or, more often, from longstanding gallstones. In latter case, the pathogenesis is related to chronic irritation and chemical injury to the gallbladder epithelium. Two main variations may appear:

- *Hypertrophic chronic cholecystitis:* the wall of the gallbladder is thickened and firm, and the serosal surface may show fibrous adhesions to surrounding structures as a result of previous episodes of acute cholecystitis. The mucosa may be intact or with ulcerated foci and presents thickened folds. Gallstones are found within the lumen, and the bile often contains "gravel". Microscopically, the epithelium is intact and pouches deeply the wall to form prominent *Rokitansky – Aschoff sinuses* ("buried" epithelial crypts within the gallbladder wall). The submucosa can lodge focal accumulations of cholesterol-laden macrophages, termed cholesterolosis foci, or, if they are large, cholegranulomas. The muscle bundles are hypertrophied and fibrosis is present around muscle and in subserous layer. Throughout the wall thickness there is an inflammatory infiltration by lymphocytes, plasma cells and eosinophils.
- *Atrophic chronic cholecystitis* appears when there has been a longstanding and complete blockage of the cystic duct by an impacted stone. The wall is very thin, mucosa is flattened and the content is clear, watery and abundant enough to put the atrophic wall under pressure and distend it like a sac (*mucocele*). Microscopically, the mucosal villi are tiny, the muscle is almost absent and replace by some fibrosis and inflammatory cells (a thin, fibrous wall).

Besides these two chronic inflammatory forms, sometimes the dystrophic changes of the gallbladder wall predominate:

- extensive cholesterol-laden macrophage accumulations, so the whole mucosa surface presents scattered, yellow flecks, aspect termed as *strawberry gallbladder.*

- extensive dystrophic calcification within the gallbladder wall may yield a *porcelain gallbladder*, notable for a markedly increase incidence of associated cancer.

GALLBLADDER TUMORS

The most common tumor of the gallbladder is adenocarcinoma. It is incidentally found in 2% of patients who undergo gallbladder surgery (cholecystectomy). Because this cancer is usually associated with cholelithiasis (gallstones) and chronic cholecystitis, it is considerably more common in women than in men. 80% of cases of carcinoma are associated with gallstones, but only 2% or less of patients with gallstones develop carcinoma. The calcified gallbladder (porcelain gallbladder), which represents an extreme variant of chronic cholecystitis, is particularly prone to the development of gallbladder cancer.

Gallbladder carcinoma may occur anywhere in the gallbladder, but most frequently appears in the fundus. The tumor is characteristically an infiltrative, well-differentiated adenocarcinoma. Frequently give lymphatic metastases, although vascular dissemination and direct spread into the liver and contiguous structures can occur.

Clinical symptoms produced by carcinoma of the gallbladder are similar to those encountered with gallstone disease. As the gallbladder is not a vital organ, the tumour is often advanced at the time of clinical presentation, and invasion of the liver and other adjacent structures defeats attempts for surgical removal. Therefore it is almost invariably incurable, with poor prognosis.

PANCREAS DISEASES

PANCREATITIS is defined as an inflammatory condition of the exocrine pancreas that results from injury of acinar cells. Depending on its duration and severity, pancreatitis can be:

(1) **acute pancreatitis**, a mild, self-limited disease, consisting of acute inflammation and edema of the stroma, with little or no acinar cell necrosis;
(2) **acute hemorrhagic pancreatitis**, with massive pancreatic necrosis;
(3) **chronic pancreatitis**, with progressive pancreatic fibrosis, after repeated episodes of acute pancreatitis, leading to pancreatic insufficiency.

Acute hemorrhagic pancreatitis *("necrotizing pancreatitis")* is caused by the action of liberated pancreatic enzymes, with extensive fat necrosis in and about the pancreas and other intra-abdominal fatty deposits, and hemorrhage into the parenchyma of the pancreas. It occurs most often in middle life and about 80% of cases are associated with two conditions: alcoholism (more commonly in men) and cholelithiasis (more commonly in women). Some of the *mechanisms* that initiate the inappropriate activation of pancreatic digestive enzymes and the consequent autodigestion of pancreatic tissue may be the following:

- *main pancreatic duct obstruction* by gallstones impacted in the ampulla of Vater. Continued pancreatic secretion produces increased ductal pressure, leading to rupture of small pancreatic ductules, extravazation of pancreatic secretions into the interstitium, digestive enzyme activation, and subsequent pancreatitis.
- *acinar cell injury*, due to alcohol abuse, a directly toxic to acinar cells, leading to severe intercellular leak of digestive enzymes.
- *deranged intracellular transport of pancreatic enzymes.* Alcohol inhibits apical secretion of enzymes, so these are missorted to a vacuole containing lysosomal enzymes, leading to enzymes activation and rupture of these organelles.

The ultimate pathogenetic processes in acute hemorrhagic pancreatitis are the proteolysis, lipolysis, and hemorrhage resulting from the destructive effect of pancreatic enzymes released from acinar cells. Thus proteases (trypsin, chymotrypsin), lipases and phospholipases (which degrade lipids and membrane phospholipids), and elastase (which breaks down the elastic tissue of vessels) are the keys to pancreatic destruction.

The patient with acute hemorrhagic pancreatitis presents severe epigastric pain that is referred to the upper back and is accompanied by nausea and vomiting. Within a matter of hours, catastrophic peripheral vascular collapse and shock ensue. Elevation of serum amylase and lipase levels as early as 24 to 72 hours after onset is diagnostic.

Grossly, the pancreas is initially edematous and hyperemic. Within a day, pale, gray foci appear, rapidly becoming friable and hemorrhagic. As the disease progress, these foci enlarge and become so numerous that most of the pancreas is converted into a large retroperitoneal hematoma, in which pancreatic tissue is barely recognizable. Yellow-white areas of fat necrosis appear at the interface between necrotic foci and fat tissue in and around the pancreas, including mesentery, omentum, peritoneum. These nodules of necrotic fat have a pasty consistency, which becomes firmer and chalk-like as more calcium and magnesium soaps are produced. Saponification reflects the interaction of cations with free acids released by the action of activated lipase on triglycerides in fat cells. With severe pancreatic necrosis, a variegated pattern of blue-black hemorrhages and gray-white necrotic softening alternates with sprinkled foci of yellow-white, chalky fat necrosis. Occasionally, liquefied areas are walled off by fibrous tissue to form small or large cystic spaces, known as "pancreatic abscesses" / pseudocyst.

The basic morphological alterations are: proteolytic destruction of pancreatic substance; necrosis of blood vessels with hemorrhage; necrosis of fat, and an accompanying inflammatory reaction. Soon

after an interstitial edema, focal and confluent areas of frank necrosis of exocrine and endocrine tissue develop. Neutrophilic infiltration and interstitial hemorrhage ensue. The most characteristic histologic lesions are the focal areas of *fat necrosis* that occur in the pancreatic and peripancreatic fat. Adipocytes are transformed into shadowy outlines of cell membranes filled with pink, granular material. Amorphous basophilic calcium precipitates may be visible within the necrotic foci.

Chronic pancreatitis is characterized by the progressive destruction of the pancreas with accompanying irregular fibrosis and chronic inflammation. The disease occurs most commonly in the middle-aged, male alcoholic, patients.

The pathogenesis of chronic pancreatitis considers two hypotheses: *ductal obstruction by concretions*, resulting from alcohol-induced alterations in acinar and ductal secretions, and in the biosynthesis of lithosthatine and *interstitial fat necrosis* and *hemorrhage*, which initiate a sequence of perilobular fibrosis, duct distortion, and altered pancreatic secretion and ductal flow.

Chronic pancreatitis can present as repeated attacks of mild to moderate abdominal pain, or persistent abdominal and back pain. Alternatively, the local disease may be entirely silent until exocrine pancreatic insufficiency (steatorrhea) and endocrine pancreatic insufficiency (diabetes) develop.

Grossly, the gland is hard and exhibits foci of calcification and fully developed pancreatic calculi "chronic calcifying pancreatitis". Cut surface lacks the usual lobular appearance. True cysts and poorly defined pseudocysts formed distal to ductal obstruction are common. Microscopically, large regions of the pancreas display large areas of fibrosis, and the exocrine and endocrine elements are reduced in number and size. Fibrotic areas present activated fibroblasts, lymphocytes and plasma cells, particularly around surviving pancreatic lobules. Pancreatic ducts of all sizes contain variably calcified proteinaceous material. The ductal epithelium may be atrophied or hyperplastic or may show squamous metaplasia. Remaining islets become embedded in sclerosed tissue before their disappearance.

Carcinoma of the pancreas. The term is applied to malignancy arising in the exocrine portion of the gland, from the ductal epithelium, less common the acinar type and in almost all cases it is an adenocarcinoma. Adenocarcinoma arises anywhere in the pancreas, with the most frequent focus in the head (60%), followed by the body (10%) and the tail (5%). In the remaining 25%, the pancreas is diffusely involved, a finding that suggests either a late diagnosis or a multicentric origin. Carcinomas of the head of the pancreas tend to be smaller than those of the body and tail and show a more limited spread to regional lymph nodes or to more distant sites. In large part, these differences reflect earlier diagnosis of cancer of the head of the pancreas, which causes early biliary obstruction and jaundice by compressing the ampulla of Vater and the common bile duct.

On gross examination, pancreatic carcinoma is firm, gray, poorly demarcated multinodular mass, often embedded in a dense connective tissue stroma (desmoplastic / scirrhous tumor). Larger tumors extend beyond the pancreas to invade the duodenum and common bile duct (carcinoma of the head) or the vertebral column, the retroperitoneal space, the spleen, the adrenal gland, the transvers colon (carcinoma of the body and tail). There can be lymph node involvement: peripancreatic, portohepatic, mesenteric, omental and liver metastases via the splenic vein. Microscopically, the appearance of pancreatic carcinoma ranges from well-differentiated mucinous adenocarcinoma to poorly differentiated form with abortive tubular structures and cell clusters, exhibiting an aggressive infiltrative growth pattern. Dense stromal fibrosis (desmoplastic reaction) and perineural invasion accompany tumor invasion.

Islet cells tumors are endocrine pancreatic tumors derived from the islet cells. They are quite rare and comprise about 10% of pancreatic neoplasms. Most are nonfunctional and are discovered as incidental findings at autopsy. Functional islet cell tumors may occur alone or as part of the multiple endocrine neoplasia syndrome type I (MEN I). The clinical symptoms of the endocrine pancreatic tumors are usually do to hypersecretion of a specific hormonal type:

- *Insulinomas* (beta cell tumors) they may release enough insulin to induce severe hypoglycemia;
- *Glucagonomas* (alpha cell tumors) producing secondary diabetes and a distinctive skin rash;
-*Pancreatic Gastrinomas* (G cell tumors) with Zollinger-Ellison syndrome, a disorder characterized by (1) intractable gastric hypersecretion, (2) severe peptic ulceration of the duodenum and jejunum, and (3) high blood gastrin levels;

- *Somatostinomas* (delta cell tumors) manifested by a syndrome consisting of mild diabetes, gallstones, steatorrhea, and hypochlorhydria;

- *VIPomas* (D_1 cell tumors) elevation of the vasoactive intestinal peptide (VIP) levels produces the Verner-Morrison syndrome characterized by explosive and profuse watery diarrhea (pancreatic cholera), accompanied by hypokalemia and hypochlorhydria;

- *Enterochromaffin cell tumors* resemble intestinal carcinoids and produce high levels of serotonin manifested with severe facial flush, hypotension, periorbital edema, and lacrimation.

Histologically, the tumors are usually composed of cellular nodules within the pancreatic tissue containing monotonous sheets of small round cells with uniform nuclei resembling normal islet cells. Immunohistochemistry may be used to identify the hormonal content of the cells. These tumors often invade and metastasize, but it is difficult to distinguish between benign and malignant on the basis of histology alone.