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ВЫСШЕГО ПРОФЕССИОНАЛЬНОГО ОБРАЗОВАНИЯ
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ФЕДЕРАЛЬНОГО АГЕНСТВА ПО ЗДРАВООХРАНЕНИЮ
И СОЦИАЛЬНОМУ РАЗВИТИЮ»
КАФЕДРА ПРОПЕДЕВТИКИ ВНУТРЕННИХ БОЛЕЗНЕЙ

Пропедевтика внутренних болезней

Учебно-методическое пособие
Часть VIII

Introduction to Internal Diseases

Manual
Part VIII

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Учебно-методическое пособие составлено в соответствии с Государственным образовательным стандартом высшего профессионального образования (2000), Государственными требованиями к минимуму содержания и уровню подготовки выпускника вуза по специальности 040100 «Лечебное дело», типовой и рабочей программами по дисциплине «Пропедевтика внутренних болезней» (2003). В учебно-методическом пособии подробно освещается содержание занятий, даны теоретические и справочные материалы, описываются практические умения в четкой последовательности действий у постели больного. Пособие предназначено для иностранных студентов медицинских вузов.

CONTENTS
PART VIII

DIAGNOSTICS OF GASTROINTESTINAL DISEASES

Theme 30. SYMPTOMATOLOGY OF GASTRITIS, PEPTIC ULCER DISEASE. GASTRIC CANCER. ENTERITIS, COLITIS (ULCERATIVE COLITIS, CROHN'S DISEASE). LABORATORY, RADIOLOGIC AND ENDOSCOPIC DIAGNOSTICS

Goal: to get a notion about the main gastrointestinal diseases, their symptoms and signs, diagnostic meanings of additional diagnostic methods data; instrumental diagnostics of gastrointestinal diseases; to master skills.

Knowledge objectives:

- to know symptoms and signs of main gastrointestinal diseases, appropriate changes of physical examination data, diagnostic meaning of additional diagnostic methods and their findings in these diseases.

Skill objectives:

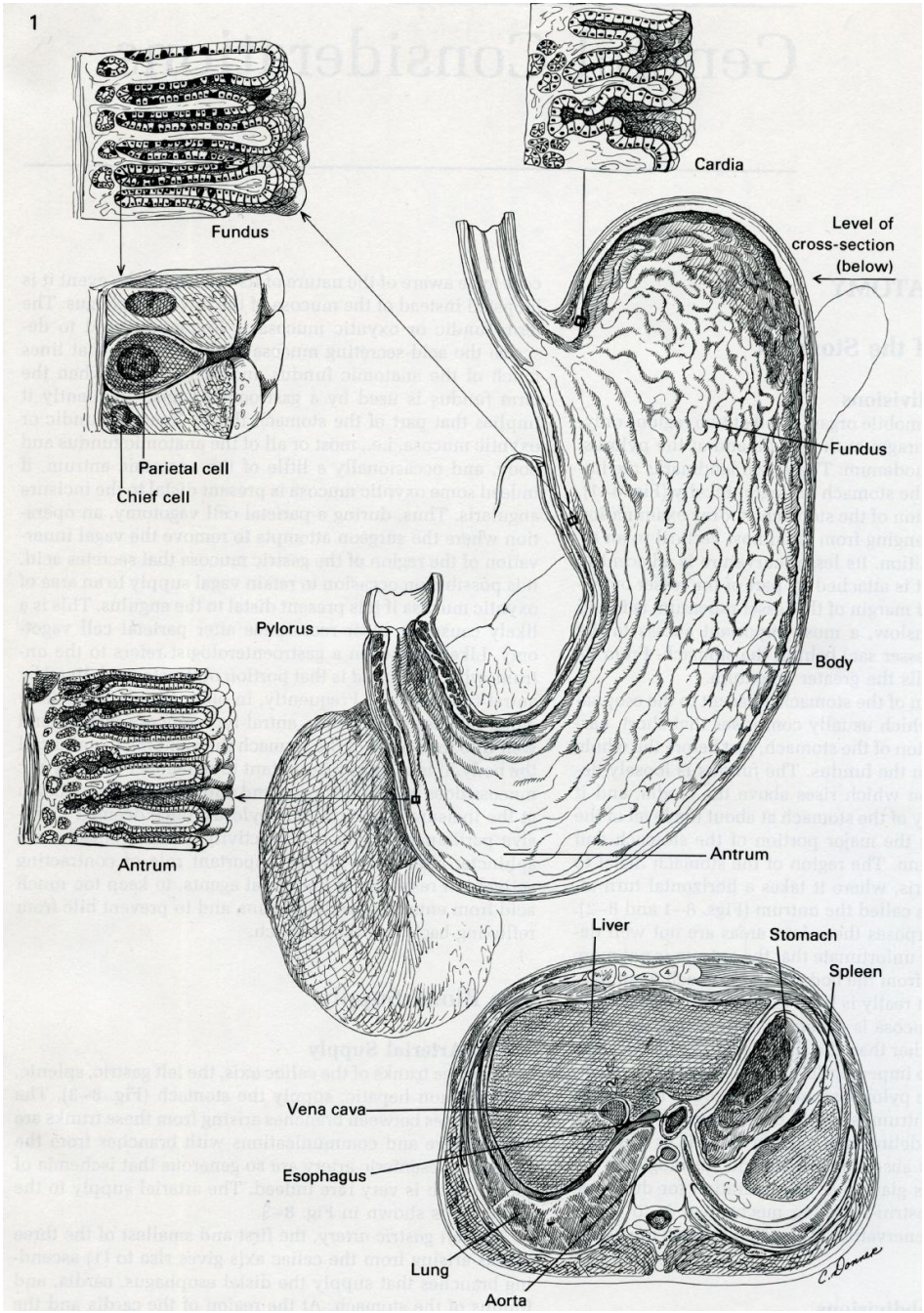
- to collect interviewing data, to perform physical examination of patients with gastrointestinal diseases (inspection, palpation, percussion and auscultation), to interpret data of additional diagnostic methods, to establish diagnosis of main gastrointestinal diseases.

Subject-matter:

1. complaints of patients with acute and chronic gastritis, peptic ulcer disease
2. etiology and pathogenesis of peptic ulcer disease
3. pathogenic role of H. pylori
4. physical examination data in patients with gastritis and peptic ulcer disease
5. complications of peptic ulcer disease
6. instrumental diagnostics of gastritis and peptic ulcer disease
7. laboratory data in diagnostics of gastritis and peptic ulcer disease
8. diagnostics of malabsorbtion syndrome
9. diagnostics of Cohn' disease
10. diagnostics of chronic ulcerative colitis

Equipment required: stethoscope.

EDUCATIONAL MATERIAL



ANATOMIC SUBDIVISIONS

The stomach is a mobile organ, fixed at two regions only, just below the diaphragm at the cardia and at the pylorus, where it joins the duodenum. These two landmarks are important in defining the stomach radiographically (Fig. 1).

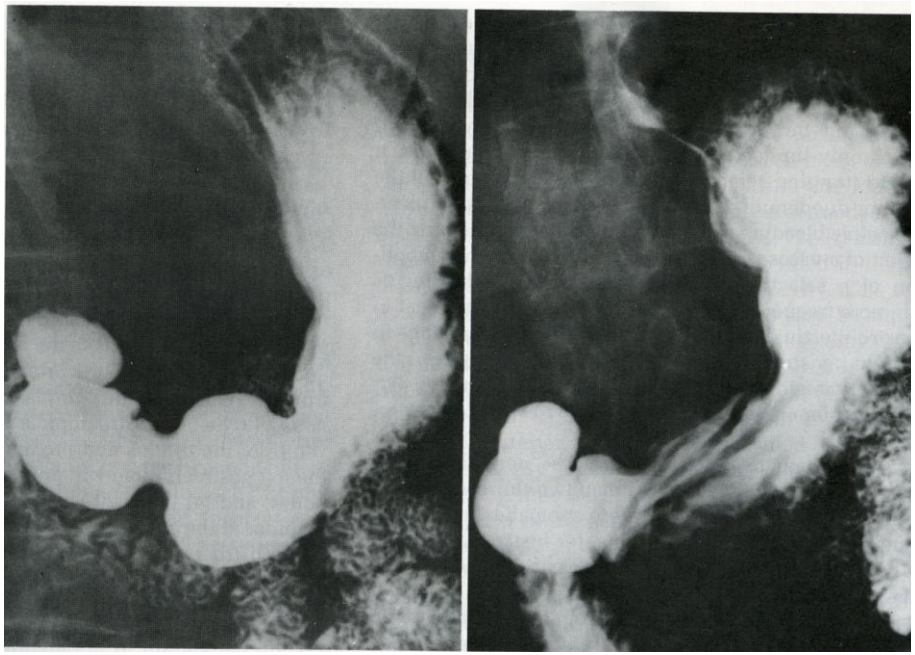


Figure 1 Radiographic appearance of the normal stomach.

The shape and position of the stomach at x-ray examination are quite variable, ranging from an almost vertical to an almost horizontal position. Its lesser curvature is adjacent to the liver, to which it is attached by part of the lesser omentun. From its greater curvature the greater omentum falls.

The upper portion of the stomach adjacent to the esophagus is the cardia, which usually comprises that short, narrowed, vertical portion of the stomach, just before the whole organ bulges to form the fundus. The fundus is loosely defined as that portion which rises above the cardia, and it merges into the body of the stomach at about the level of the

cardia. The body is the major portion of the stomach and extends to the antrum. The region of the stomach distal to the incisura angularis, where it takes a horizontal turn toward the pylorus, is called the antrum (Fig. 1).

PHYSIOLOGIC SUBDIVISIONS

The term fundic or oxyntic mucosa is frequently used to describe the acid-secreting mucosa of the stomach that lines much of the anatomic fundus and body. Likewise, when a gastroenterologist refers to the antrum, what is implied is that portion of the stomach lined by antral-type mucosa. It is therefore important to remember that oxyntic mucosa does not abruptly end and antral-type mucosa begins at the incisura angularis. The pylorus, once deemed a passive participant in the motor activity of the stomach, is a sphincter after all, with the important role of contracting actively in response to hormonal agents, to keep too much acid from entering the duodenum, and to prevent bile from refluxing back into the stomach.

LABORATORY, RADIOLOGIC AND ENDOSCOPIC DIAGNOSTICS

GASTRIC ANALYSIS

Gastric analysis is used to evaluate hyperchlorhydria (eg, Zollinger-Ellison syndrome) or hypochlorhydric states (eg, atrophic gastritis, Ménétrier's syndrome); unexplained hypergastrinemia in patients with planned acid-reducing surgery as part of pre- or postoperative assessment; and the possibility of incomplete vagotomy in patients with recurrent peptic ulcer disease after a surgical vagotomy. Contraindications include recent active bleeding or pain caused by active ulcer disease.

A nasogastric tube is passed. For intubation, the patient sits upright or lies in the left lateral decubitus position. With the patient's head partially flexed, the lubricated tube is inserted through the nares, aimed back and then down to conform with the nasopharynx. As the tip reaches the posterior pharyngeal wall, the patient should sip water through a straw. (Violent coughing with flow of air through the tube during respiration indicates that the tube is misplaced in the trachea.) Aspiration of gastric juice verifies entry into the stomach. The position of larger

tubes may be confirmed by instilling 20 to 30 mL of air and listening with the stethoscope under the left subcostal region for a rush of air.

Gastric contents are aspirated and discarded. Four 15-min samples of gastric juice are collected by continuous manual aspiration (basal acid output [BAO]). Next, pentagastrin (6 μg/kg) is given sc, and again, four 15-min samples are obtained (maximal [or peak] acid output [MAO or PAO]). Samples are titrated with sodium hydroxide to calculate BAO and stimulated MAO secretory rates.

UPPER GASTROINTESTINAL ENDOSCOPY

Upper GI endoscopy is used to establish the site of upper GI bleeding; to visually define and biopsy abnormalities seen on upper GI series (gastric ulcers, filling defects, mass lesions); to follow up treated gastric ulcers; and to evaluate dysphagia, dyspepsia, abdominal pain, and gastric outlet obstruction for infection (Helicobacter pylori, G. lamblia, bacterial overgrowth syndrome). Therapeutic indications include removal of foreign bodies or gastric or esophageal polyps, sclerosis or banding of esophageal varices, and coagulation of hemorrhage. Absolute contraindications include acute shock, acute MI, seizures, acutely perforated ulcer, and atlantoaxial subluxation.

The patient should have taken no food for at least 4 h. A topical anesthetic is gargled or sprayed into the pharynx, and usually a narcotic and sedative medication are given IV for sedation. The patient is appropriately positioned, and the tip of the endoscope is placed in the hypopharynx. As the patient swallows, the endoscope is gently guided through the cricopharyngeal muscle (upper esophageal sphincter) and advanced under direct vision through the stomach into the duodenum. Examination of all structures may be supplemented by photography, cytology, and biopsy sampling. Therapeutic procedures are used as indicated.

COLONOSCOPY

Colonoscopy is used diagnostically to screen for colonic polyps or cancer in high-risk individuals (eg, those with a family history of colon cancer); to evaluate an abnormality seen on barium enema; to determine the source of occult or active GI bleeding or unexplained (microcytic)

anemia; to evaluate patients with colon cancer for other lesions during pre- or postoperative assessment; and to determine the extent of cations include removal of polyps, coagulation of bleeding sites, reduction of volvulus or intussusception, and decompression of acute or subacute colonic dilatation. Absolute contraindications include acute shock, acute MI, peritonitis, intestinal perforation. Relative contraindications include poor bowel preparation or massive intestinal hemorrhage, poor patient cooperation, diverticulitis, recent abdominal surgery, history of multiple pelvic operations, or a large hernia. Patients with cardiac or proximal joint prostheses need antibiotic prophylaxis to prevent endocarditis.

Patient preparation involves taking cathartics and enemas or drinking an intestinal lavage solution (eg, polyethylene glycol electrolyte). The patient is given an IV narcotic and a short-acting benzodiazepine for sedation. After rectal examination in the left lateral position, a colonoscope is gently inserted through the anal sphincter into the rectum. Under direct visualization, air is infused and the instrument is manipulated through the colon to the cecum and terminal ileum. Fluoroscopy is rarely needed. The patient may experience cramplike discomfort that can be relieved by aspiration of air, rotation or retraction of the tube, or additional, usually analgesic, medication. Diagnostic evaluation is performed by visualization of structures, photography, and obtaining brushings or biopsy specimens of abnormal structures.

ABDOMINAL PARACENTESIS

Abdominal paracentesis is used to evaluate the origin of ascitic fluid (eg, caused by portal hypertension, metastasis, TB, pancreatic ascites) and to diagnose a perforated viscus in a patient with a history of blunt abdominal trauma. It can also be used therapeutically to remove ascites caused by portal hypertension and is especially useful in relieving tense ascites causing respiratory difficulties, pain, or acute oliguria. Absolute contraindications include uncorrectable and severe disorders of blood coagulation, intestinal obstruction, and an infected abdominal wall. Poor patient cooperation, surgical scarring over the puncture area, and severe portal hypertension with abdominal collateral circulation are relative contraindications.

CBC, platelet count, and coagulation studies are obtained before the procedure. After emptying the bladder, the patient sits in bed with the

head elevated 45 to 90°. A point is located at the midline between the umbilicus and the pubic bone and is cleaned with an antiseptic solution and alcohol. Under sterile technique, the area is anesthetized to the peritoneum with lidocaine 1%. For diagnostic paracentesis, an 18-gauge needle attached to a 50-mL syringe is inserted through the peritoneum (generally a "pop" is noted). Fluid is gently aspirated and sent for cell count, protein or amylase content, cytology, or culture as needed. For therapeutic (large-volume) paracentesis, a 14-gauge cannula attached to a vacuum aspiration system is used to collect up to 8 L of ascitic fluid. Postprocedure hypotension caused by fluid redistribution is rare as long as interstitial (leg) edema is present.

Hemorrhage is the most common complication. Occasionally, with tense ascites, prolonged leakage of ascitic fluid occurs through the needle site.

GASTRITIS.

Gastritis is inflammation of the gastric mucosa.

Gastritis can be classified as erosive or nonerosive based on the severity of mucosal injury.

It can also be classified according to the site of involvement within the stomach (ie, cardia, corpus, antrum).

Gastritis can be further classified histologically as acute or chronic based on the inflammatory cell type. No classification scheme matches perfectly with the pathophysiology; a large degree of overlap exists.

Acute gastritis is characterized by polymorphonuclear cell infiltration of the mucosa of the antrum and corpus.

Chronic gastritis implies some degree of atrophy (with loss of functional capacity of the mucosa) or metaplasia. It predominantly involves the antrum, with subsequent loss of ***G cells*** and decreased gastrin secretion, or the corpus, with loss of ***oxyntic glands***, leading to reduced acid, pepsin, and intrinsic factor.

ACUTE EROSIVE GASTRITIS

Causes include drugs (especially non-steroid anti-inflammatory drugs [NSAIDs]), alcohol, and acute stress, as occurs in severely ill patients. Less common causes include radiation, vascular injury, and direct trauma (eg, nasogastric tubes).

Endoscopically, superficial erosions are seen as punctate mucosal lesions that do not penetrate into the deeper layers of the stomach. They are frequently accompanied by some degree of hemorrhage (usually submucosal petechiae) (Fig.2).

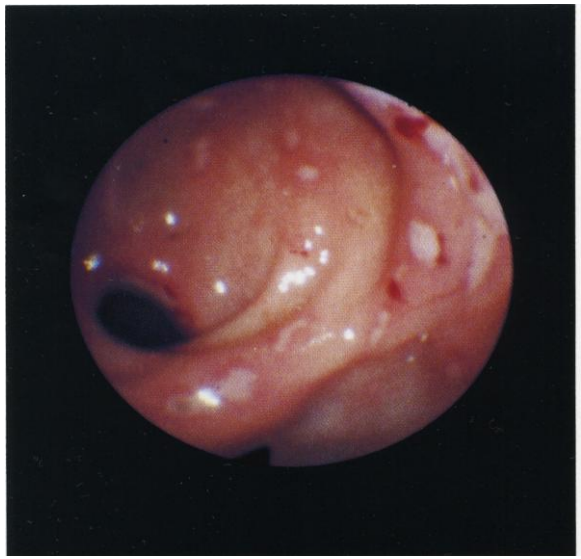


Fig.2. Distal antrum with patent pylorus. Numerous discrete round erosions with white exudate are seen scattered throughout the antrum. This mucosal injury was caused by a nonsteroidal anti-inflammatory agent.

Acute stress gastritis is a form of erosive gastritis in severely ill patients who have an increased rate of clinically significant upper GI hemorrhage from mucosal lesions of the stomach and duodenum. Risk factors include severe burns, CNS trauma, sepsis, shock, respiratory failure with mechanical ventilation, hepatic and renal failure, and multiorgan dysfunction. In general, the more critically ill the patient, the higher the risk of clinically significant bleeding.

The pathogenesis of acute stress gastritis likely involves decreased mucosal defense mechanisms in a severely ill patient.

Symptoms, Signs, and Diagnosis

Acute catharral gastritis is characterized by pains in the epigastric area, dyspeptic syndrome (nausea, vomiting with a touch of mucus and

bile), sometimes — subfebrile fever. Symptoms usually appear 6—8 hours after pathogenic factor impact.

In acute erosive gastritis, typically, the patient is too ill to complain of noticeable gastric symptoms, which (if present) are usually mild and nonspecific. The first obvious sign may be blood in the nasogastric aspirate, usually within 2 to 5 days of the major initial stress.

Acute stress gastritis is diagnosed endoscopically; in certain patients (eg, those with burns, shock, sepsis), acute erosions may be seen as soon as 12 h after the initial insult. The lesions may progress to invade the submucosa and even perforate the serosa or, more commonly, may bleed, usually from multiple sites in the corpus. The antrum may also be involved (Fig.3).

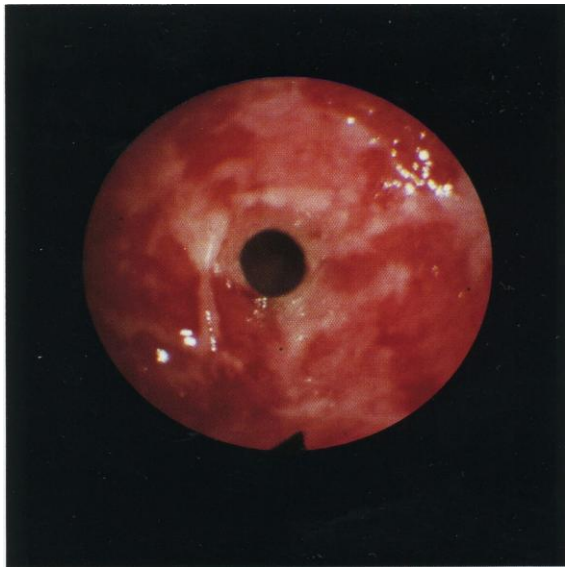


Fig.3. Severe, acute antral gastritis. The pylorus is at the center of the picture. It is surrounded by severely inflamed and partially sloughed off mucosa. This lesion was seen in a patient with upper gastrointestinal bleeding in a setting of sepsis, secondary to ascending cholangitis.

CHRONIC EROSIVE GASTRITIS

This condition is defined by the presence of multiple punctate or aphthous ulcers on endoscopy (Fig.4).

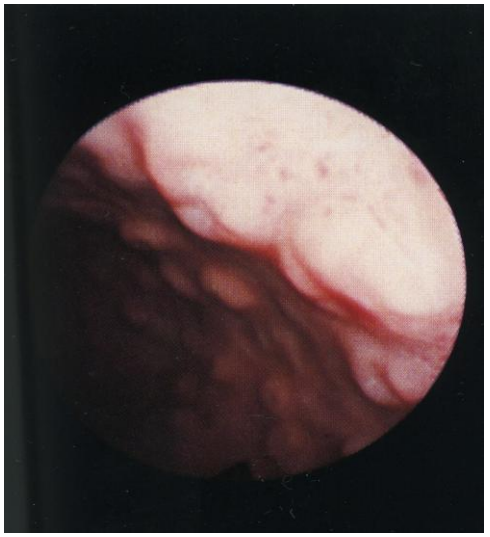


Fig.4, Raised erosions of the gastric antrum. These are circular chronic erosions with heaped-up margins. The mucosa rises discretely to form anthill-like protrusions with a central depression.

Chronic erosive gastritis may be idiopathic or caused by drugs (especially aspirin and other NSAIDs), Crohn's disease or viral infections. *Helicobacter pylori* does not appear to have a major role in the pathogenesis of this condition.

Symptoms are nonspecific and may include ***nausea, vomiting,*** and ***epigastric discomfort***, although patients are often symptom-free. Endoscopically, punctate erosions are revealed most frequently on the ridges of thickened rugal folds, often with a central white plaque or umbilication. Histologically, the degree of inflammation varies. No therapy is universally beneficial or curative.

Treatment is largely symptomatic with use of antacids, H_2 blockers, and proton pump inhibitors as well as avoidance of potentially exacerbating drugs and foods. Remissions and exacerbations are common.

NONEROSIVE GASTRITIS

Etiology

H. pylori is increasingly implicated as the primary cause of nonerosive gastritis. This spiral-shaped, gram-negative organism (Fig.5) causes almost all cases of nonerosive gastritis and its resultant complications.

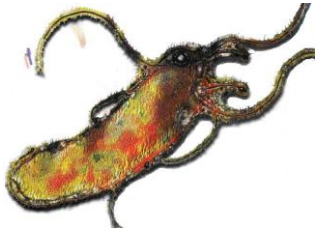


Fig.5. Helicobacter pylori.

Infection invariably leads to gastric mucosal inflammation, which in turn alters gastric secretory physiology, leaving the mucosa more susceptible to damage by acid. Highest concentrations of *H. pylori* are detected in the antrum, where confined infection substantially increases the risk of prepyloric and duodenal ulceration. In some patients, infection involves the entire stomach and appears to be associated with subsequent development of gastric ulcers and gastric adenocarcinoma.

Epidemiology

H. pylori appears to be a very common chronic infection worldwide. In developing countries, infection is most frequently acquired in childhood; suboptimal sanitary conditions, poor hygiene, low socioeconomic status, and crowded living conditions are associated with higher prevalence and earlier infection.

Although the exact mode of transmission is unclear, the organism has been cultured from stool, saliva, and dental plaque, which implicates oral-oral or fecal-oral transmission. Infections tend to cluster in families and in residents of custodial institutions. Nurses and gastroenterologists appear to be at high risk, and bacteria have been transmitted by improperly disinfected endoscopes.

Pathology

***Superficial gastritis*:** The predominant infiltrating inflammatory cells in this condition are lymphocytes and plasma cells mixed with neutrophils; inflammation is superficial and may involve the antrum, corpus, or both. It is usually not accompanied by atrophy or metaplasia. Prevalence increases with age. Given the high prevalence of *H. pylori*-associated superficial gastritis and the relatively low incidence of clinical sequelae (ie, peptic ulcer disease), there is no clear indication to eradicate *H. pylori* with antibiotics in an asymptomatic patient.

***Deep gastritis*:** Deep gastritis is more likely to be symptomatic (vague dyspepsia). Mononuclear cells and neutrophils infiltrate the entire mucosa to the level of the muscularis, but seldom with exudate or crypt abscesses. Distribution may be patchy, and superficial gastritis may coexist. Partial gland atrophy and metaplasia may be present. In symptomatic patients, eradication of *H. pylori* with antibiotics should be attempted.

***Gastric atrophy*:** Atrophy of gastric glands may follow various injuries, especially gastritis, most often secondary to long-standing antral (type B) gastritis. Some patients with gastric atrophy manifest autoantibodies to parietal cells, usually in association with corpus (type A) gastritis and pernicious anemia.

Atrophy may occur without specific symptoms. Endoscopically, the mucosa may appear normal until atrophy is advanced, when the submucosal vascular tree may be visible. As atrophy becomes complete, acid and pepsin secretion diminish and intrinsic factor may be lost, resulting in vitamin B_{12} malabsorption.

***Metaplasia*:** Two types of metaplasia are common in chronic nonerosive gastritis: mucous gland and intestinal. Mucous gland metaplasia (pseudopyloric metaplasia) occurs in the setting of severe atrophy of the gastric glands, which are progressively replaced by mucous glands (antral mucosa), especially along the lesser curve.

Intestinal metaplasia occurs in response to chronic mucosal injury. Gastric mucosa may resemble small intestinal mucosa, with goblet cells, endocrine (enterochromaffin or enterochromaffin-like) cells, and rudimentary villi, and may even assume functional (absorptive) characteristics. Intestinal metaplasia is associated with stomach cancer.

Symptoms and Signs.

Chronic gastritis may be asymptomatic. Clinical picture is characterized by following signs:

- pain in epigastric area, mild expressed and vaguely localized;
- dyspeptic manifestations: fullness sensation in epigastric area, linked with meals; belching, nausea, vomiting, appetite disturbances, bloating, rumbling, flatulence, unstable stool.

Clinical manifestations of gastritis with increased or normal secretory function essentially distinguish from the same of gastritis with secretory insufficiency.

• gastritis with increased or normal secretory function (type B gastritis) is characterized by waterbrash, sour belching, heaviness or dull aching pains in epigastrium after meals (sometimes pains may awaken a patient at night and may be on an empty stomach), tendency to constipations;

• gastritis with secretory insufficiency (type A gastritis) is characterized by fullness sensation and dull pains in epigastric area, nausea, poor appetite, obnoxious taste in a mouth, rotten belching, rumbling, tendency to diarrheas. Besides, there appear signs of hypovitaminosis (dry skin, angular stomatitis, nails changes) and sometimes dumping syndrome appears (weakness, diaphoresis. dizziness and palpitation appearance after meal).

Diagnosis

Nonerosive gastritis is suspected by symptoms but diagnosed with certainty by endoscopy and biopsy. Most patients with *H. pylori*-associated gastritis are asymptomatic; testing for and treatment of infection are not always indicated. For patients in whom diagnosis will alter treatment, diagnostic tests to detect *H. pylor*i consist of noninvasive and invasive techniques.

Noninvasive testing is less expensive and does not require endoscopy. Laboratory and office-based serologic assays most frequently use technology to detect IgA and IgG antibodies to *H. pylori.* Sensitivity and specificity are > 85% for detecting initial *H. pylori* infection.

Urea breath tests use ^{13}C- or ^{14}C-labeled urea po. In an infected patient, the organism metabolizes the urea and liberates labeled CO_2, which is exhaled and can be quantified in breath samples taken 20 to 30 min after ingestion (Fig.6).

Fig.6 Urea breath test equipment (mass-spectrometer).

The sensitivity and specificity are > 90%. Urea breath tests are well suited for confirming eradication of the organism after therapy.

Invasive testing requires gastroscopy and mucosal biopsy and should be reserved for patients with an a priori indication for endoscopy. Histologic staining of gastric mucosal biopsies has a sensitivity and specificity > 90%. Because it is accurate, easy to perform, and relatively inexpensive, RUT should be considered the invasive diagnostic method of choice.

Treatment

Treatment of chronic nonerosive gastritis is directed toward H pylori eradication. In H pylori-negative patients, treatment is directed at symptoms using acid-suppressive medications (eg, H_2 blockers, proton pump inhibitors) or antacids.

Ménétrièr's disease (giant hypertrophic gastritis) is a rare, possibly premalignant condition, in which there is thickening and enlargement of the gastric mucosal folds. It may affect the entire upper gut (Fig.7), and may then be associated with protein loss (protein-losing enteropathy).

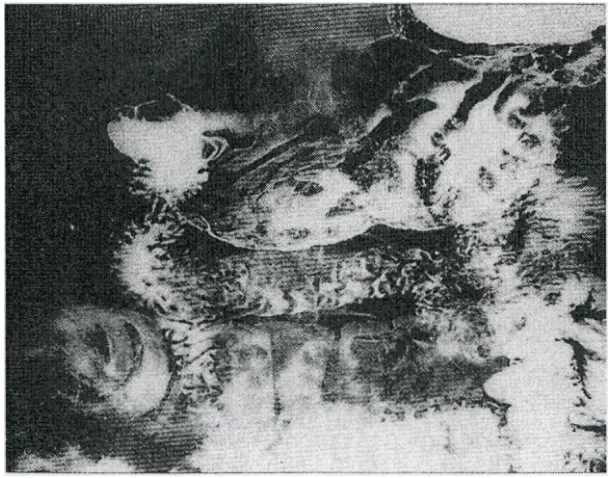


Fig.7. Ménétrièr's disease (giant hypertrophic gastritis). The patient presented with epigastric pain and melaena. Barium meal and follow-through revealed rugal hypertrophy in the stomach and similar changes throughout the small intestine.

PEPTIC ULCER DISEASE

An excoriated segment of the GI mucosa, typically in the stomach (gastric ulcer) or first few centimeters of the duodenum (duodenal ulcer), which penetrates through the muscularis mucosae (Fig.8).

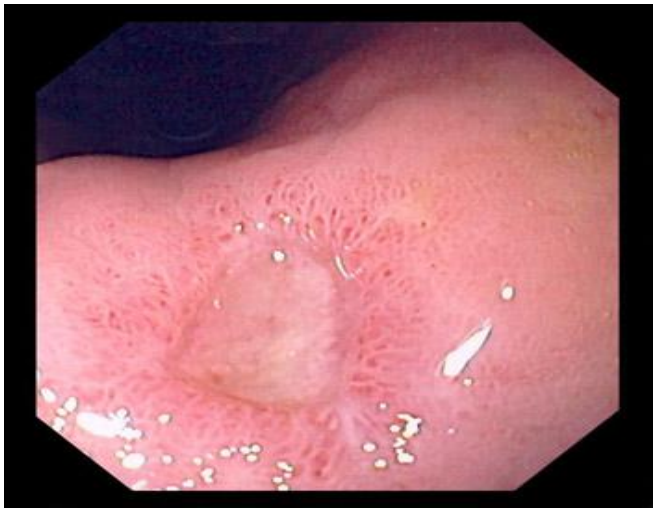


Fig.8. Gastric ulcer.

Ulcers may range in size from several millimeters to several centimeters. Ulcers are delineated from erosions by the depth of penetration; erosions are more superficial and do not involve the muscularis mucosae.

Because understanding of the central role of *H. pylori* in the pathogenesis of acid-peptic disease is growing, diagnosis and treatment of peptic ulcer have changed dramatically.

Etiology and Pathogenesis

Although the traditional theories regarding the pathogenesis of peptic ulcers focus on acid hypersecretion, this finding is not universal, and it is now known that hypersecretion is not the primary mechanism by which most ulceration occurs. It appears that certain factors, namely *H. pylori* and NSAIDs, disrupt the normal mucosal defense and repair, making the mucosa more susceptible to the attack of acid.

Peptic ulcer disease development is caused by imbalance between aggressive factors impact and defense mechanisms, providing integrity of gasric mucous.

• Hydrochloric acid, pepsin, bile acids, *H. pylori* infection, NSAIDs, alcohol are considered to be aggressive factors.

• Defense mechanisms include muco- bicarbonate barrier, prostaglandins, permanent mucous cells repair, availability of divaricated micro vascular net.

• Immune disorders, chronic inflammatory infiltration of gastric mucous, gastrin hyper secretion, accompanying *H.pylori* infection have definite importance.

Hereditary predisposition undoubtedly is of high importance in peptic ulcer disease development.

Unfavorable environmental factors, stress, cigarette smoking, diet derangements have important influence on ulcer formation.

The mechanisms by which *H. pylori* causes mucosal injury are not entirely clear, but several theories have been proposed. Urease produced by the organism catalyzes urea to ammonia. The ammonia, while enabling the organism to survive in the acidic environment of the stomach, may erode the mucous barrier, leading to epithelial damage. Cytotoxins produced by *H. pylori* have also been implicated in host epithelial damage. Mucolytic enzymes (eg, bacterial protease, lipase) appear to be involved in degradation of the mucous layer, making the epithelium more susceptible to acid damage. Lastly, cytokines produced in response to inflammation may play a role in mucosal damage and subsequent ulcerogenesis.

NSAIDs likely promote mucosal inflammation and ulcer formation through both topical and systemic effects. Because NSAIDs are weak acids and non-ionized at gastric pH, they diffuse freely across the mucous barrier into gastric epithelial cells, where H^+ ions are liberated, leading to cellular damage. Systemic effects appear to be mediated through their ability to inhibit cyclooxygenase activity and thereby prostaglandin production. By inhibiting prostaglandin production, NSAIDs induce several changes in the gastric microenvironment (eg, reduced gastric blood flow, reduced mucus and HCO_3 secretion, decreased cell repair and replication), leading to breakdown of mucosal defense mechanisms.

Symptoms and Signs

Symptoms depend on ulcer location and patient age; many patients, particularly the elderly, have few or even no symptoms. Pain is the most common symptom; it is often localized to the epigastrium and relieved by food (milk) or antacids. The pain is described as burning, gnawing, or hunger. Usually they appear 30-40 min after a meal, may radiate to the back, spine (especially ulcers of gastric posterior wall). The course is usually chronic and recurrent. Only about half of patients present with the characteristic pattern of symptoms.

Symptoms of gastric ulcer often do not follow a consistent pattern (eg, eating sometimes exacerbates rather than relieves pain). This is especially true for pyloric channel ulcers, which are often associated with symptoms of obstruction (eg, bloating, nausea, vomiting) caused by edema and scarring.

In duodenal ulcer, pain tends to be consistent. Pain is absent when the patient awakens but appears in midmorning; it is relieved by food but recurs 2 to 3 h after a meal. Pain that awakens a patient at night is common and is highly suggestive of duodenal ulcer.

On the height of pain onset vomiting of sore gastric contents, relieved pain, may occur. Waterbrash and belching may be presented.

On examination coated tongue is usually revealed. On abdominal palpation tenderness in epigastric area or in Choffar's zone may be disclosed.

Diagnosis

Diagnosis of peptic ulcer is suggested largely by history and is confirmed by the studies described below. Stomach cancer may present with similar manifestations and must be excluded, especially in patients who are older, have lost weight, or report particularly severe or refractory symptoms.

Endoscopy, cytology, and multiple biopsies are reliable means of distinguishing malignant from benign gastric ulcers. The incidence of malignant duodenal ulcer is extremely low, so biopsies are generally not warranted. Gastrin-secreting malignancy and Zollinger-Ellison syndrome (gastrinoma) should be considered in a patient who presents with a severe ulcer diathesis, especially when ulcers are multiple and noted in atypical locations (eg, postbulbar).

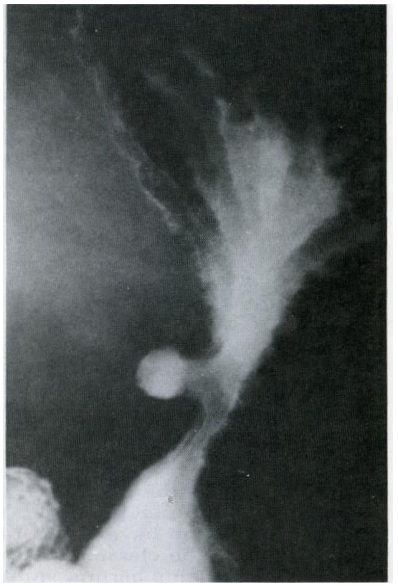


Fig.9. The classical radiologic appearance of a crater filled with barium.

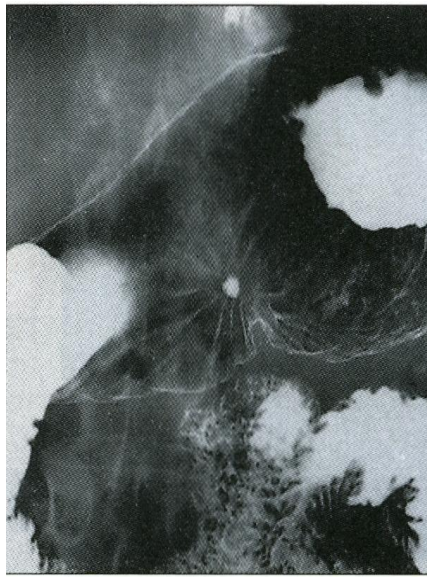


Fig.10. Benign gastric ulcer, as seen in a double-contrast barium meal. The ulcer heals by fibrosis and contraction, and this draws mucosal folds towards the base of the ulcer. These give rise to the streaks of barium that radiate from the ulcer crater in this view. Although these appearances are strongly suggestive of a healing benign gastric ulcer, endoscopy, brush cytology and biopsy are all wise precautions to exclude gastric carcinoma.

Fiberoptic endoscopy is a powerful tool for the diagnosis and management of peptic ulcer disease. An alternative diagnostic study is double-contrast barium x-ray (Fig.9 & 10). Although endoscopy and x-ray have similar sensitivities for detecting ulcer, endoscopy is becoming the diagnostic modality of choice. Endoscopy more reliably detects esophagitis and esophageal ulcers as well as ulcers located on the posterior wall of the stomach and at sites of surgical anastomosis. Conversely, some 10% of duodenal bulb and postbulbar ulcers may be

missed endoscopically, sometimes leading to follow-up with a barium study if the clinical suspicion is high (Fig.11).

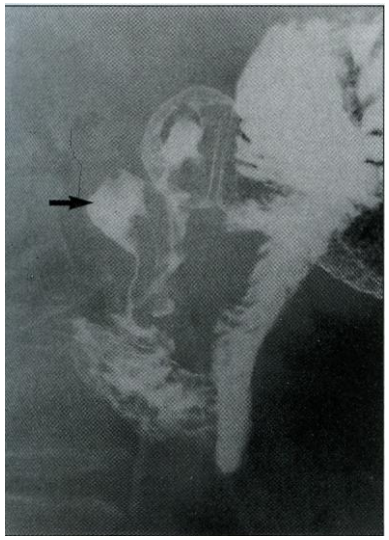


Fig.11. Duodenal ulcer. A deep crater in the second part of the duodenum (a postbulbar ulcer) is demonstrated on this tangential view in a double-contrast barium meal. Note the residual barium in the ulcer crater (arrow). This patient also has osteoarthritis of the spine and was taking a nonsteroidal anti- inflammatory drug, which contributed to his presentation with haematemesis.

Endoscopy also allows for biopsy or cytologic brushing of gastric and esophageal lesions to distinguish between simple ulceration and ulcerating stomach cancer. Endoscopy can also be used to definitively diagnose *H. pylori* infection.

Complications

Hemorrhage: Hemorrhage is the most common complication of peptic ulcer disease. Symptoms include ***hematemesis*** (vomiting of fresh blood or "coffee ground" material); passage of bloody or black tarry stools (***hematochezia*** and ***melena***, respectively); and weakness, orthostasis, syncope, thirst, and sweating caused by blood loss.

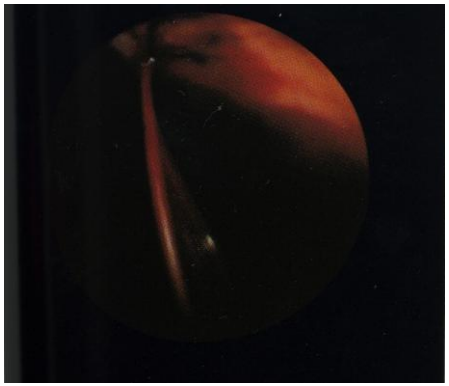


Fig.12 Bleeding gastric ulcer. A spurt of arterial bright-red crosses the lumen of the stomach. The underlying lean is a small ulceration secondary to NSAIDs.

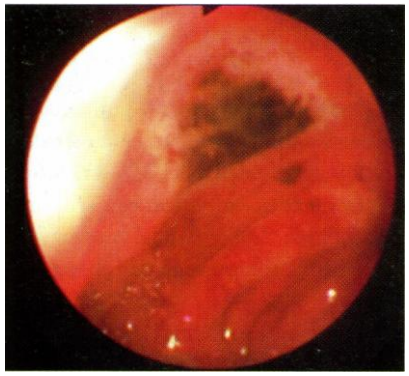


Fig.13. Haemorrhage is one of the most common complications of peptic ulceration. Urgent endoscopy often yields a rather poor view, because of the presence of altered blood and food residues, but this view clearly shows adherent blood clot on a large duodenal ulcer, providing evidence of recent bleeding.

If bleeding from an ulcer persists or recurs, several treatment choices exist. Endoscopy (Fig.12 & 13) may be performed and the bleeding site coagulated by electrocautery, heater probe coagulation, or laser or by injection of alcohol, sclerosant, or epinephrine. Bleeding may recur, even after coagulation

After an ulcer is diagnosed and bleeding is controlled endoscopically, the patient should be given acid suppression with IV H_2 blockers and nothing by mouth. Once the patient's condition has stabilized with no evidence of rebleeding, an oral diet can be resumed, antisecretory therapy (H_2 blockers or proton pump inhibitors) given orally, and anti-*H. pylori* therapy initiated if needed.

Emergency surgery is usually indicated when pulse rate, BP, and Hct indicate continued deterioration in the patient's condition despite treatment and transfusions; more than six transfusions in 24 h have been needed to maintain a stable pulse and BP; or bleeding stops but recurs enough to require multiple transfusions.

Penetration (confined perforation): A peptic ulcer may penetrate the wall of the stomach or duodenum and enter the adjacent confined space (lesser sac) or organ (eg, pancreas, liver) (Fig.14).

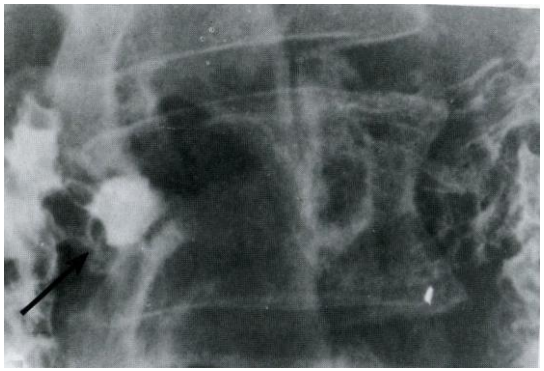


Fig. 14. Posterior penetrating duodenal ulcer. The radiologist was once of great help to the clinician in demonstrating that a patient with a now very rare intractable ulcer did in fact have posterior penetration of the ulcer (arrowed).

Adhesions prevent leakage into the free peritoneal cavity. Pain may be intense, persistent, referred to sites other than the abdomen (usually the back when caused by penetration of a posterior duodenal ulcer into the pancreas), and modified by body position. Radiographic evaluation with contrast study or CT is usually needed to confirm the diagnosis. When medical therapy does not produce healing, surgery is required.

Free perforation: Free perforation usually presents as an acute abdomen. Ulcers that perforate the peritoneal cavity are usually located in the anterior wall of the duodenum or, less commonly, in the stomach. The patient experiences sudden, intense, steady epigastric pain that spreads rapidly throughout the abdomen, often becoming prominent in the right lower quadrant and at times referred to one or both shoulders. The patient usually lies still because even deep breathing can worsen the pain. Palpation of the abdomen is painful, rebound tenderness is prominent (positive Shchetkin-Blumberg's sign), abdominal muscles are rigid (board like), and bowel sounds are diminished or absent. Symptoms may be less striking in the elderly, the moribund, and those receiving corticosteroids or immunosuppressants.

Diagnosis is confirmed if an upright or a lateral decubitus x-ray of the abdomen shows free air under the diaphragm or in the peritoneal cavity (Fig.15), but the diagnosis is not excluded if no air is seen.

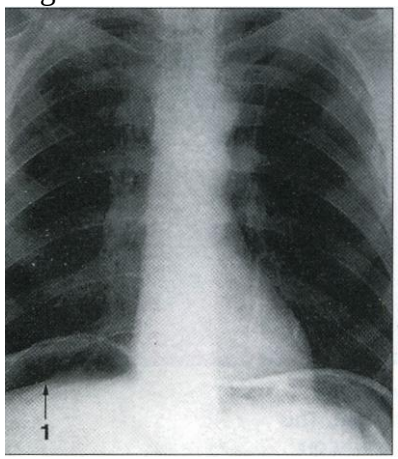


Fig.15 Pneumoperitoneum in a patient with a rigid abdomen caused by a perforated duodenal ulcer. The onset of his pain and rigidity was abrupt. Note the upper edge of the liver (1), and the air under both diaphragms.

Pain and abdominal rigidity may partially subside, and the patient's condition appears to improve several hours after onset. However, peritonitis with a temperature elevation may develop, and the patient's condition seriously deteriorates. Shock may ensue, heralded by increased pulse rate and decreased BP and urine output.

Gastric outlet obstruction: This may be caused by scarring, spasm, or inflammation associated with an ulcer. Symptoms include recurrent large volume vomiting, occurring more frequently at the end of the day and often as late as 6 h after the last meal. Persistent bloating or fullness after eating and loss of appetite also suggest gastric outlet obstruction. Prolonged vomiting may cause weight loss, dehydration, and alkalosis.

If the patient's history suggests obstruction, physical examination, gastric aspiration, or x-rays may provide objective evidence of retention. A succussion splash heard > 6 h after a meal or aspiration of fluid or food residue > 200 mL after an overnight fast suggests gastric retention. If gastric aspiration shows marked retention, the stomach should be

emptied and endoscopy or x-rays performed to determine the site, cause, and degree of obstruction (Fig.16).

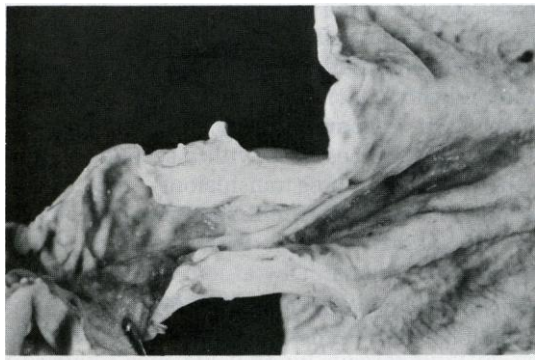


Fig. 16. Pyloric obstruction. Gastric retention may be the result of edema, spasm, or scar tissue, but when it is as pronounced as in this specimen, the physician will advise dilatation by balloon or its operative removal.

Edema or spasm from an active pyloric channel ulcer is treated with gastric decompression and acid suppression (eg, IV H_2 blockers). Dehydration and electrolyte imbalances from protracted vomiting or continued nasogastric suctioning should be vigorously sought and corrected. Prokinetic agents are not indicated. Generally, obstruction resolves within 2 to 5 days of treatment. Prolonged obstruction may be caused by peptic scarring and may respond to endoscopic pyloric balloon dilation. Surgery is necessary to relieve obstruction in selected cases.

Stomach cancer: *H. pylori* is associated with intestinal-type adenocarcinoma of the gastric body and antrum but not cancer of the gastric cardia. Infected persons are three to six times more likely to develop stomach cancer. There are no data to suggest that eradicating *H. pylori* prevents progression of gastritis to more common cancers or lymphomas of the stomach. Therefore, there is no scientific reason to diagnose and treat *H. pylori* to prevent malignant complications, especially because stomach cancer is relatively uncommon.

X-ray (Fig.17), endoscopy (Fig.18), cytology, and multiple biopsies are reliable means of distinguishing malignant from benign gastric ulcers.

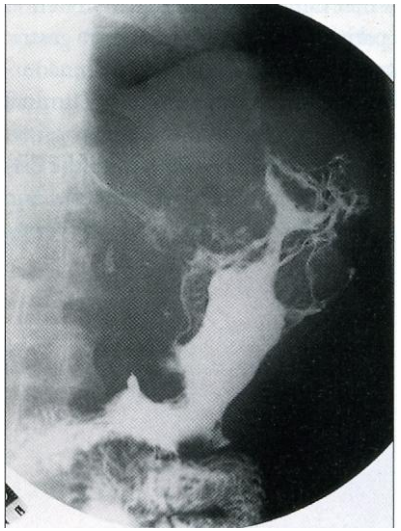


Fig.17. Carcinoma of the stomach. The barium meal demonstrates a large fungating mass in the gastric fundus. The patient presented with severe weight loss and iron-deficiency anaemia.

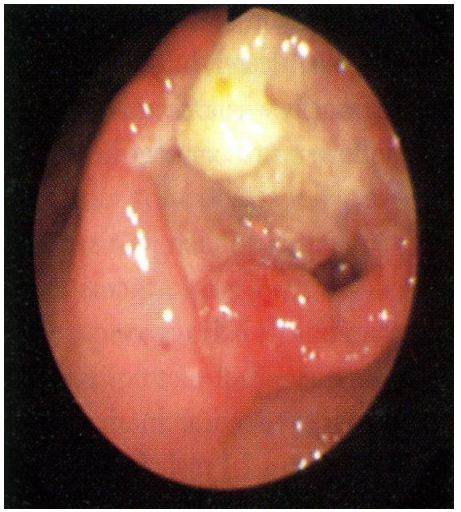


Fig.18. Carcinoma of the stomach. This ulcerated mass is situated between the incisura and the pylorus. The patient was an 80-year-old lady who presented with a 2-month history of dyspepsia and melaena.

Recurrence: The 1-yr relapse rate for gastric and duodenal ulcers is > 60% after cessation of traditional antiulcer therapy. Long-term treatment with H_2 blockers or proton pump inhibitors reduces the risk of recurrence proportionally to the amount of acid suppression achieved. The rate of ulcer recurrence is considerably lower after anti-*H. pylori* therapy (< 10%).

The most common reason for recurrent peptic ulcer is unsuccessful eradication of *H. pylori*. In a patient with recurrent disease, possible persistent infection should be investigated. If infection is documented, a second course of anti-*H. pylori* therapy is warranted.

Other factors that may affect recurrence include NSAID use and smoking. Less commonly, a gastrinoma (Zollinger-Ellison syndrome) may be the cause of refractory or recurrent peptic disease.

ZOLLINGER—ELLISON SYNDROME

Zollinger—Ellison syndrome results from a gastrin-producing tumour, which is often located in the pancreas, but occasionally is elsewhere in the small intestine or in the gastric antrum. The clinical

features are of severe recurrent peptic ulceration (Fig.19), which has a high incidence of bleeding and perforation.

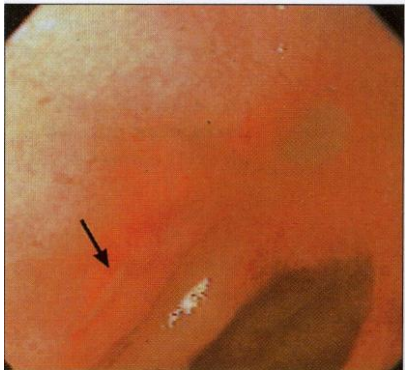


Fig.19. Duodenal ulceration in the second part of the duodenum. This endoscopic view shows a linear ulcer (arrow) and a circular ulcer to the top right of the picture. Patients often prove to have more than one ulcer on endoscopy, but multiple ulcers should raise the suspicion of possible Zollinger—Ellison syndrome.

There may also be diarrhea with malabsorption.

The diagnosis is made by finding a high gastrin level and a high basal secretion. The tumour may be localized by CT or MRI scanning.

Treatment is with a proton-pump inhibitor to block acid secretion and surgery to remove the tumour if it has not already metastasized.

Treatment

Treatment of gastric and duodenal ulcers had previously focused on neutralizing or decreasing gastric acidity. However, attention has shifted toward *eradication of H. pylori.* Antibiotic treatment should therefore be considered in all *H. pylori*-infected patients with acute ulcers and in those who have had a gastric or duodenal ulcer diagnosed in the past by endoscopy or barium x-ray, even if they are asymptomatic or receiving long-term acid suppression therapy. This is particularly important in patients with a past history of complications (eg, bleeding, perforation), because *H. pylori* eradication can prevent future complications.

H_2 blockers have a role in the treatment of peptic ulcer disease but are no longer primary therapy when used alone; they are frequently used as antisecretory drugs in an anti-*H. pylori* regimen.

Proton pump inhibitors are potent inhibitors of the proton (acid) pump (ie, the enzyme H+,K+-ATPase), located in the apical secretory membrane of the parietal cell. Proton pump inhibitors can completely inhibit acid secretion and have a long duration of action.

Certain *prostaglandins* (especially misoprostol) can inhibit acid secretion and enhance mucosal defense.

Sucralfate is a sucrose-aluminum complex that promotes ulcer healing. It has no effect on acid output or gastrin secretion. Its suspected mechanisms of action include inhibition of pepsin-substrate interaction, stimulation of mucosal prostaglandin production, and binding of bile salts.

Antacids give symptomatic relief, promote ulcer healing, and reduce recurrence. They are relatively inexpensive but must be taken five to seven times per day.

Adjunctive treatment: There is no evidence that changing a diet speeds ulcer healing or prevents recurrence. Thus, many physicians recommend eliminating only foods that cause distress (eg, fruit juice, spicy and fatty foods). Milk, which had been a mainstay of therapy, does not aid ulcer healing and actually promotes gastric acid secretion. Although there are no definitive data linking moderate amounts of alcohol to delayed ulcer healing, alcohol is a strong promoter of acid secretion, so ulcer patients are commonly advised to restrict alcohol consumption to dilute and small amounts. Smoking is a risk factor for the development of ulcers and their complications and appears to impair ulcer healing and increase the incidence of recurrence. The risk of recurrence and degree of healing inhibition correlate with the number of cigarettes smoked per day.

Surgery: With current drug therapy, the number of patients requiring surgery has declined significantly. Indications include perforation, obstruction that does not respond to medical therapy, uncontrolled or recurrent bleeding, suspected malignant gastric ulcer, and symptoms refractory to medical management.

MALABSORPTION SYNDROMES:

Syndromes resulting from impaired absorption of nutrients from the small bowel.

Many diseases or their consequences can cause malabsorption (see Table1).

Table 1

CAUSES OF MALABSORPTION.

Level	Condition
Stomach	Post-gastrectomy dumping Zollinger-Ellison syndrome Pernicious anaemia
Hepatic/biliary tree	Biliary obstruction/cholestasis
Pancreas	Cystic fibrosis Pancreatitis Pancreatic carcinoma
Small bowel	Coeliac disease Crohn's disease Surgery and removal of small bowel Fistulae/blind loops Infection - bacterial, parasitic Radiation Lymphoma Drugs e.g. neomycin, cholestyramine Specific enzyme defects of brush border Whipple's disease

The mechanism may be direct impairment of absorption or abnormalities of digestion that lead to impaired absorption. Malabsorption may occur for many nutrients or for specific carbohydrates, fats, or micronutrients.

Symptoms and Signs

Symptoms of malabsorption are caused by the effects of osmotically active substances in the GI tract or by nutritional deficiencies that develop. Some causes of malabsorption have distinct clinical presentations. Dermatitis herpetiformis is often associated with a mild

degree of celiac-like enteropathy; biliary cirrhosis and pancreatic cancer cause jaundice; mesenteric ischemia causes abdominal angina; chronic pancreatitis causes boring central abdominal pain; and Zollinger-Ellison syndrome causes severe, persistent ulcerative dyspepsia.

Malabsorption causes weight loss (Fig.20 &21), glossitis, carpopedal spasms, absent tendon reflexes, cutaneous bruising, flatulence, and abdominal distention, bloating, or discomfort resulting from increased intestinal bulk and gas production. Symptoms of lactase deficiency include explosive diarrhea with abdominal bloating and gas after milk ingestion. Pancreatic lipase deficiency manifests as greasy stools with undigested dietary fat (triglycerides).

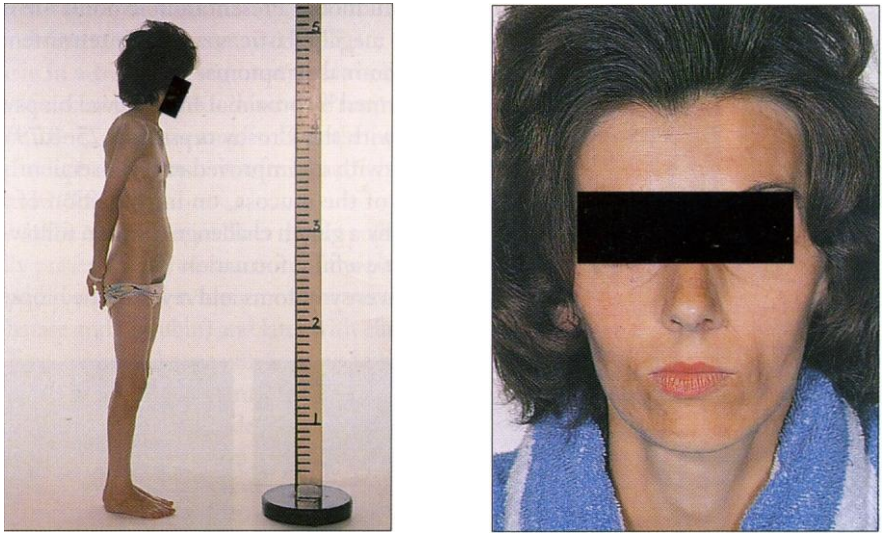


Fig.20 & 21 Malabsorption in coeliac disease may remain undiagnosed for many years. This woman was diagnosed at the age of 32 years, but her height — 1.52 m — was less than all other members of her family, suggesting that her malabsorption dated from childhood. On presentation she weighed 40 kg, she had marked steatorrhea and she was pale and anaemic. Small bowel biopsy showed villous atrophy. A gluten-free diet relieved her steatorrhoea and reversed the changes in her jejunal mucosa. She rapidly gained weight, but should probably remain on a gluten-free diet for life.

Steatorrhea may occur--pale, soft, bulky, malodorous stools that stick to the side of the toilet bowl or float and are difficult to flush away.

Secondary nutritional deficiencies develop in proportion to the severity of the primary disease and the area of the GI tract involved.

Many patients with malabsorption are anemic, usually because of deficiencies of iron (microcytic anemia) and folic acid (megaloblastic anemia). B_{12} deficiency may occur in many years after extensive resection of the distal ileum or stomach. However, the usual 50-cm resection of the terminal ileum for ileocecal Crohn's disease seldom leads to significant B_{12} deficiency. Ca deficiency is common, caused partly by vitamin D deficiency with impaired absorption and partly by Ca binding with unabsorbed fatty acids. Ca deficiency may cause bone pain and tetany. Infantile rickets is rare, but osteomalacia may occur. Thiamine (vitamin B_1) deficiency (as well as B_{12} deficiency) may cause paresthesia, and malabsorption of vitamin K (mainly fat-soluble) can lead to hypoprothrombinemia with bruising and a bleeding tendency. Severe riboflavin (vitamin B_2) deficiency may cause a sore tongue and angular stomatitis, but vitamin A, vitamin C, and niacin deficiencies seldom cause clinical problems.

Protein malabsorption may lead to hypoproteinemic edema, usually of the lower limbs. Dehydration, K loss, and muscle weakness can follow profuse diarrhea.

Diagnosis

Symptoms and signs lead to the diagnostic impression of malabsorption. Any combination of weight loss, diarrhea, and anemia should raise the suspicion of malabsorption. Laboratory studies confirm the diagnosis.

INFLAMMATORY BOWEL DISEASE.

Crohn's disease and ulcerative colitis are characterized by chronic inflammation at various sites in the GI tract. Both cause diarrhea, which may be profuse and bloody. Certain differences in disease patterns justify a distinction between Crohn's disease and ulcerative colitis, although groupings and subgroupings are somewhat artificial. Some cases are difficult, if not impossible, to classify.

The term colitis applies only to inflammatory disease of the colon (eg, ulcerative, granulomatous, ischemic, radiation, or infectious colitis). Spastic or mucous colitis is a misnomer often applied to a functional disorder that is more properly described as irritable bowel syndrome.

CROHN'S DISEASE

(Regional Enteritis; Granulomatous Ileitis Or Ileocolitis)

A nonspecific chronic transmural inflammatory disease that most commonly affects the distal ileum and colon but may occur in any part of the GI tract.

Etiology and Epidemiology

The fundamental cause of Crohn's disease is unknown. Evidence suggests that a genetic predisposition leads to an unregulated intestinal immune response to an environmental, dietary, or infectious agent. However, no inciting antigen has been identified. Cigarette smoking seems to contribute to the development or exacerbation of Crohn's disease.

Pathology

The earliest mucosal lesion of Crohn's disease is crypt injury in the form of inflammation (cryptitis) and crypt abscesses, which progress to tiny focal aphthoid ulcers, usually located over nodules of lymphoid tissue. In some cases, these lesions regress; in others, the inflammatory process evolves with influx and proliferation of macrophages and other inflammatory cells, occasionally forming noncaseating granulomas with multinucleated giant cells (Fig.22)

Fig.22. Crohn’s disease histopathology. Noncaseating granulomas, as seen here in close-up, are found in most patients. The granulomas are composed mainly of lymphocytes, macrophages and plasma cells, and they characteristically contain multinucleated giant cells, as shown here. In contrast to ulcerative colitis, Crohn’s disease is characterized by inflammation of all layers of the gut wall, with submucosal edema, deep ulcers and fibrous scarring.

Transmural spread of inflammation leads to lymphedema and bowel wall thickening, which may eventually result in extensive fibrosis. Development of patchy mucosal ulcers and longitudinal and transverse ulcers with intervening mucosal edema frequently creates a characteristic cobblestone appearance (Fig.23).

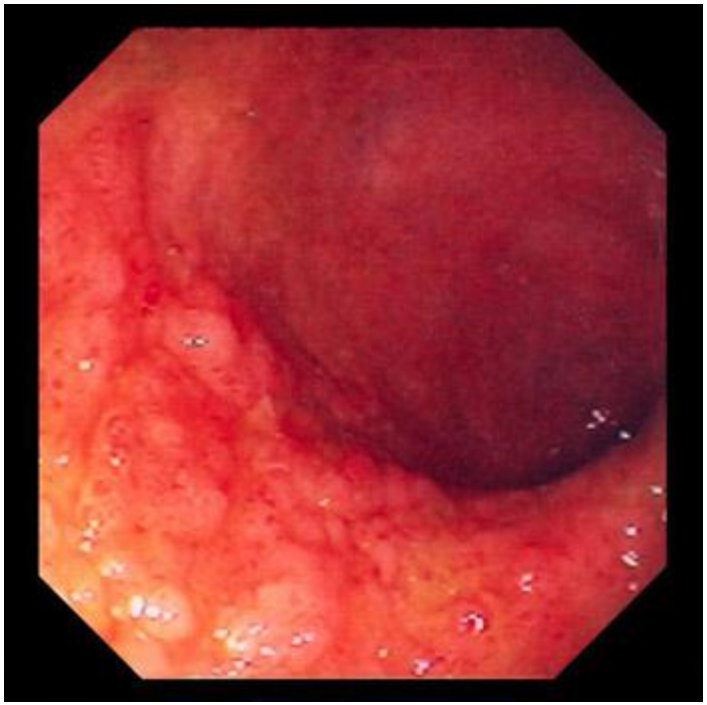


Fig.23. Cobblestone appearance caused by inflammation deep into bowel wall with muscosal edema.

The attached mesentery is thickened and lymphedematous; mesenteric fat typically extends onto the serosal surface of the bowel. Mesenteric lymph nodes often enlarge. Transmural inflammation, deep ulceration, edema, muscular proliferation, and fibrosis cause deep sinus tracts and fistulas, mesenteric abscesses, and obstruction, which are the major local complications.

Segments of diseased bowel are characteristically sharply demarcated from adjacent normal bowel ("skip areas")--thus the name regional enteritis. Of all cases of Crohn's disease, about 35% involve the ileum (ileitis); about 45% involve the ileum and colon (ileocolitis), with a predilection for the right side of the colon; and about 20% involve the colon alone (granulomatous colitis). Occasionally, the entire small bowel is involved (jejunoileitis), and rarely, the stomach, duodenum, or esophagus. The perianal region is also affected in 1/4 to 1/3 of cases.

Symptoms, Signs, and Complications

Chronic diarrhea with abdominal pain, fever, anorexia, weight loss, and a right lower quadrant mass or fullness are the most common presenting features. However, many patients are first seen with an acute abdomen that simulates acute appendicitis or intestinal obstruction.

About 1/3 of patients have a history of perianal disease, especially fissures and fistulas (Fig.24), which are sometimes the most prominent or even initial complaint.

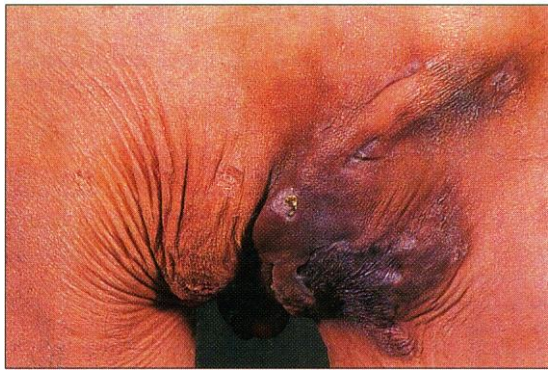


Fig.24. Multiple perianal fistulae resulted in the chronic, painful inflammatory reaction seen here in a patient with long-standing Crohn’s disease.

The most common patterns of Crohn's disease pathology are

(1) inflammation characterized by right lower quadrant abdominal pain and tenderness;

(2) recurrent partial obstruction caused by intestinal stenosis and leading to severe colic, abdominal distention, constipation, and vomiting;

(3) diffuse jejunoileitis, with inflammation and obstruction resulting in malnutrition and chronic debility; and

(4) abdominal fistulas and abscesses, usually late developments, often causing fever, painful abdominal masses, and generalized wasting.

Obstruction; development of enterocutaneous fistulas; and abscess formation are common complications of inflammation.

Diagnosis

Crohn's disease should be suspected in a patient with the inflammatory or obstructive symptoms described above and in a patient without prominent GI symptoms but with perianal fistulas or abscesses.

Laboratory findings are nonspecific and may include anemia, leukocytosis, hypoalbuminemia, and increased levels of acute-phase reactants reflected in elevated ESR, C-reactive protein.

Diagnosis is usually made by x-ray (Fig.25).

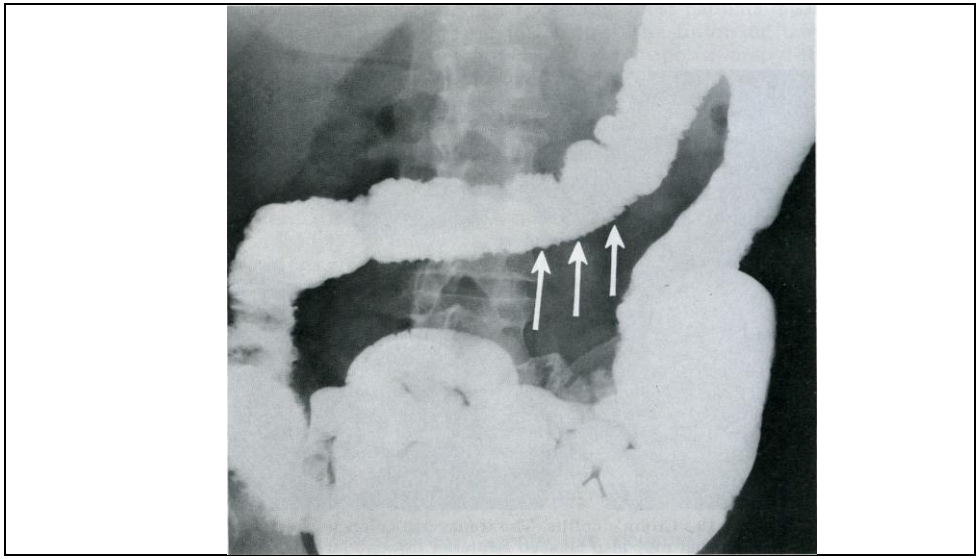


Fig. 25. Crohn’s colitis. Typical changes of Crohn’s colitis are evident in the asymmetric involvement of the transverse colon where the arrows show irregularities on the tower border, with some normal haustra on the upper border.

Barium enema x-ray may show reflux of barium into the terminal ileum with irregularity, nodularity, stiffness, wall thickening, and a narrowed lumen. A small-bowel series with spot x-rays of the terminal ileum usually most clearly shows the nature and extent of the lesion. An upper GI series without small-bowel follow-through usually misses the diagnosis.

In advanced cases, the string sign may be seen with marked ileal strictures and separation of bowel loops. In earlier cases, x-ray diagnosis

may sometimes be difficult, but air double-contrast barium enema and enteroclysis may show superficial aphthous and linear ulcers. In questionable cases, colonoscopy (Fig. 26) and biopsy may help confirm the diagnosis of Crohn's colitis and allow direct visualization and biopsy of the terminal ileum.

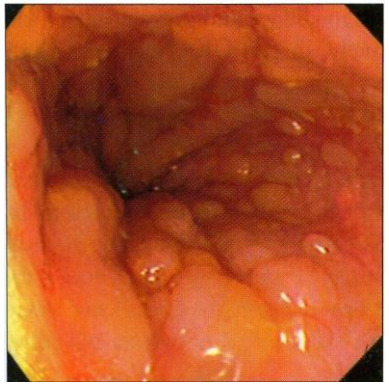


Fig.26. Crohn’s disease in the colon. Multiple edematous inflammatory polyps give a ‘cobblestone’ appearance to the mucosa. Similar changes may be seen in ulcerative colitis.

Although CT can detect extramural complications (eg, fistulas, abscesses, masses), it is not routinely needed for initial diagnosis.

Differential Diagnosis

Crohn's disease of the small bowel (ileitis) requires differentiation from other inflammatory, infectious, and neoplastic disorders in the right lower quadrant. If in the acute presentation a prior history of chronic bowel symptoms has not been elicited, ileitis may be first diagnosed during surgical exploration for suspected acute appendicitis. Periappendiceal abscess may produce more chronic symptoms and thus be more difficult to diagnose clinically.

Prognosis

Although spontaneous remission or medical therapy may result in a prolonged asymptomatic interval, established Crohn's disease is rarely cured but instead is characterized by intermittent exacerbations. In the absence of surgical intervention, the disease never extends into new areas of small bowel beyond its initial distribution at first diagnosis. With

judicious medical and, where appropriate, surgical therapy, most patients with Crohn's disease function well and adapt successfully. Disease-related mortality is very low and continues to decrease.

Treatment

No cure is known. Cramps and diarrhea may be relieved by oral administration up to qid (ideally before meals) of anticholinergics, diphenoxylate 2.5 to 5 mg, loperamide 2 to 4 mg, codeine 15 to 30 mg. Such symptomatic treatments are safe, except in cases of severe, acute Crohn's colitis, which may progress to toxic megacolon as in ulcerative colitis. Hydrophilic mucilloids (eg, methylcellulose or psyllium preparations) sometimes help prevent anal irritation by increasing stool firmness.

Sulfasalazine primarily benefits patients with mild to moderate colitis and ileocolitis but has some efficacy in ileitis as well. It may also maintain remission, although it has not been proven to prevent recurrence after surgery.

Mesalamine (5-aminosalicylic acid), the active moiety of sulfasalazine, is available in several oral formulations designed to release in various segments of the small bowel and colon. It is especially useful in patients who are intolerant of sulfasalazine. In doses of up to 4 g/day, mesalamine is effective for inducing and maintaining remission and is showing considerable promise for inhibiting postoperative recurrence.

Corticosteroid therapy treats the acute stages of Crohn's disease by dramatically reducing fever and diarrhea, relieving abdominal pain and tenderness, and improving the appetite and sense of well-being.

The new topically active corticosteroid budesonide can be given orally or as an enema and has low systemic bioavailability and thus reduced adrenal suppression.

Broad-spectrum antibiotics that are active against enteric gram-negative and anaerobic flora may help reduce disease activity in many patients but are most consistently effective for suppurative complications (eg, infected fistula, abscess).

Immunomodulating drugs, particularly the antimetabolites azathioprine and 6-mercaptopurine, are effective as long-term therapy for Crohn's disease. Methotrexate 25 mg IM or sc once/wk benefits some patients with severe corticosteroid-refractory disease, even those who have failed to respond to azathioprine or 6-mercaptopurine.

Surgery is usually necessary for recurrent intestinal obstruction or intractable fistulas or abscesses. Resection of the grossly involved bowel may ameliorate symptoms indefinitely but does not cure the disease. Moreover, when surgery has been performed for specific complications or failure of medical therapy, most patients experience an improved quality of life.

CHRONIC ULCERATIVE COLITIS

A chronic, inflammatory, and ulcerative disease arising in the colonic mucosa, characterized most often by bloody diarrhea.

Etiology and Epidemiology

The cause of ulcerative colitis is unknown. Evidence suggests that a genetic predisposition leads to an unregulated intestinal immune response to an environmental, dietary, or infectious agent. However, no inciting antigen has been identified. The evidence for a specific microbial etiology for ulcerative colitis is even less convincing than for Crohn's disease, and the familial tendency is less pronounced. Unlike in Crohn's disease, current cigarette smoking appears to decrease risk. Like Crohn's disease, ulcerative colitis may afflict people at any age, but the age-onset curve shows a bimodal distribution, with a major peak at ages 15 to 30 and a second smaller peak at ages 50 to 70; however, this later peak may include some cases of ischemic colitis.

Pathology

Pathologic changes begin with degeneration of the reticulin fibers beneath the mucosal epithelium, occlusion of the subepithelial capillaries, and progressive infiltration of the lamina propria with plasma cells, eosinophils, lymphocytes, mast cells. Crypt abscesses, epithelial necrosis, and mucosal ulceration ultimately develop (Fig.27)

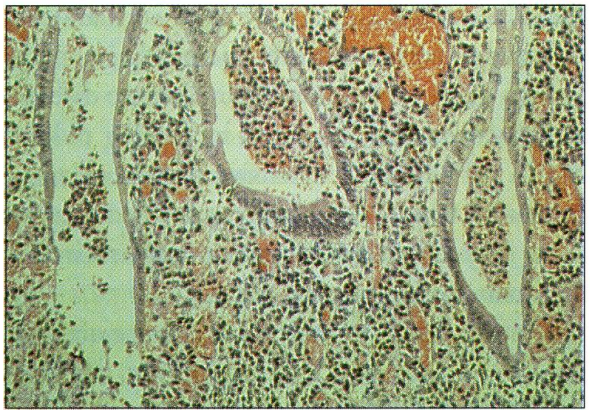


Fig.27 Ulcerative colitis histopathology. In contrast to Crohn's disease, the inflammatory process in ulcerative colitis is usually confined to the mucosal layer of the bowel wall and granulomas are not seen. In active disease, as here, there is an increase in the number of lymphocytes, plasma cells and neutrophils in the lamina propria (beneath the epithelium). The epithelium shows patchy or continuous ulceration, and large numbers of neutrophils migrate through the walls of the glands to form 'crypt abscesses'. Three crypt abscesses are seen in this view.

The disease usually begins in the rectosigmoid and may extend proximally, eventually involving the entire colon, or it may involve most of the large bowel at once.

Ulcerative proctitis, which is localized to the rectum, is a very common and more benign form of ulcerative colitis. It is often refractory to treatment and undergoes late proximal spread in about 20 to 30% of cases.

Symptoms and Signs

Bloody diarrhea of varied intensity and duration is interspersed with asymptomatic intervals. Usually an attack begins insidiously, with increased urgency to defecate, mild lower abdominal cramps, and blood and mucus in the stools. However, an attack may be acute and fulminant, with sudden violent diarrhea, high fever, signs of peritonitis, and profound toxemia. Some cases develop following a documented infection (eg, amebiasis, bacillary dysentery).

When ulceration is confined to the rectosigmoid, the stool may be normal or hard and dry, but rectal discharges of mucus loaded with RBCs and WBCs accompany or occur between bowel movements. Systemic symptoms are mild or absent. If ulceration extends proximally, stools become looser and the patient may have > 10 bowel movements/day, often with severe cramps and distressing rectal

tenesmus, without respite at night. The stools may be watery, may contain mucus, and frequently consist almost entirely of blood and pus. Malaise, fever, anemia, anorexia, weight loss, leukocytosis, hypoalbuminemia, and elevated ESR may be present with extensive active ulcerative colitis.

Complications

Bleeding is the most common local complication. Another particularly severe complication, toxic colitis, occurs when transmural extension of ulceration results in localized ileus and peritonitis. As toxic colitis progresses, the colon loses muscular tone and begins to dilate within hours or days. Plain x-rays of the abdomen show intraluminal gas accumulated over a long, continuous, paralyzed segment of colon--a result of lost muscle tone.

Toxic megacolon (or toxic dilation) exists when the diameter of the transverse colon exceeds 6 cm. The severely ill patient has a fever to 40° C, leukocytosis, abdominal pain, and rebound tenderness (positive Shchetkin-Blumberg's sign). This condition usually occurs spontaneously in the course of especially severe colitis, but some cases may be precipitated by overzealous use of narcotic or anticholinergic antidiarrheal drugs. Treatment must be given in the early stages, preferably before full-blown megacolon occurs, to avert dangerous complications (eg, perforation, generalized peritonitis, septicemia). With prompt, effective treatment, the mortality rate can be held at < 4% but may be > 40% if perforation occurs.

Major perirectal complications, such as those in granulomatous colitis (eg, fistulas, abscesses), do not occur.

The incidence of colon cancer is increased when the entire colon is involved and the disease lasts for > 10 yr, independent of disease activity.

Pseudopolyps (Fig.28) have no prognostic significance but may be difficult to distinguish from neoplastic polyps; thus, any suspicious polyp should undergo excision biopsy.

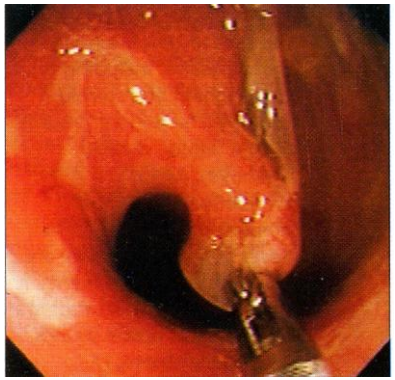


Fig.28. Biopsy of large inflammatory polyps in ulcerative colitis is sometimes advisable to exclude the possiblity of carcinoma, which is a major risk of chronic ulcerative colitis.

Diagnosis

The history and stool examination permit a presumptive diagnosis of ulcerative colitis that should always be confirmed by sigmoidoscopy, which provides a direct, immediate indication of disease activity. The mucosa soon breaks down into a red, spongy surface dotted with many tiny blood- and pus-oozing ulcers. As the mucosa becomes progressively involved, the inflammation and hemorrhage extend into the bowel muscle. Large mucosal ulcers with copious purulent exudate characterize severe disease. Islands of relatively normal or hyperplastic inflammatory mucosa (pseudopolyps) project above areas of ulcerated mucosa. Even during asymptomatic intervals, the sigmoidoscopic appearance is rarely normal; some degree of friability or granularity almost always persists. There is loss of the normal vascular pattern, and biopsy shows evidence of chronic inflammation.

Plain x-rays of the abdomen sometimes help to judge the severity and proximal extent of the colitis by showing loss of haustration, mucosal edema, and absence of formed stool in the diseased bowel. Barium enema, like colonoscopy, is not usually necessary before treatment and may be hazardous in active stages because of risk of perforation. Later in the course of disease, however, the entire colon should be evaluated to determine the extent of involvement. Barium studies show loss of haustration, mucosal edema, minute serrations, or

gross ulcerations in severe cases. A shortened, rigid colon with an atrophic or pseudopolypoid mucosa is often seen after several years' duration (Fig.29).

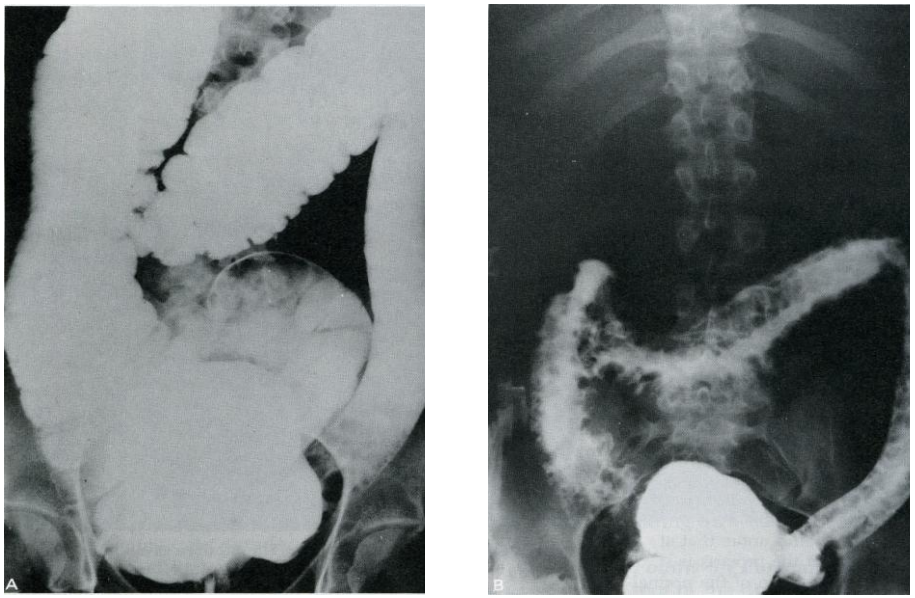


Fig. 29 Rapid progression of ulcerative colitis. The x-rays in A were taken 3 weeks before those in B. During that time this young girl lived at home under some stress. One of the mysteries of ulcerative colitis is how it can so completely destroy a bowel as this so rapidly.

Colonoscopy with biopsy is mandatory to evaluate the nature of a stricture. Biopsy may also help to distinguish ulcerative colitis from Crohn's disease if the inflammation is highly focal or if a granuloma is seen.

Prognosis

Usually, ulcerative colitis is chronic with repeated exacerbations and remissions. Complete recovery after a single attack may occur in another 10%; however, there always remains the possibility of an undetected specific pathogen.

Nearly 1/3 of patients with extensive ulcerative colitis require surgery. Total proctocolectomy is curative: Life expectancy and quality of life are restored to normal, and the risk of colon cancer is eliminated.

Patients with localized ulcerative proctitis have the best prognosis. Severe systemic manifestations, toxic complications, and malignant degeneration are unlikely, and late extension of the disease occurs in only about 20 to 30%. Surgery is rarely required, and life expectancy is normal

Treatment

Avoiding raw fruits and vegetables limits mechanical trauma to the inflamed colonic mucosa and may lessen symptoms. A milk-free diet may help but need not be continued if no benefit is noted. An anticholinergic drug or loperamide 2.0 mg or diphenoxylate 2.5 mg po bid to qid is indicated for relatively mild diarrhea; higher oral doses of loperamide (4 mg in the morning and 2 mg after each bowel movement) or diphenoxylate (5 mg tid or qid), deodorized opium tincture 0.5 to 0.75 mL (10 to 15 drops) q 4 to 6 h, or codeine 15 to 30 mg q 4 to 6 h may be required for more intense diarrhea. These antidiarrheal drugs must be used with extreme caution in more severe cases because they may precipitate toxic dilation.

In mild or moderate disease that does not extend proximally beyond the splenic flexure, remission may sometimes be achieved with a hydrocortisone enema instead of with oral corticosteroid therapy.

Mesalamine may also be given by enema and is beneficial in many cases of refractory proctosigmoiditis and left-sided colitis.

More extensive mild or moderate disease as well as localized disease may respond to oral sulfasalazine.

Once remission is achieved, long-term maintenance therapy with sulfasalazine 1 to 3 g/day is indicated to prevent relapse.

Severe disease, manifested by > 10 bloody bowel movements per day, tachycardia, high fever, or severe abdominal pain, requires hospitalization.

Immunomodulatory drugs are acceptable for some patients with refractory or corticosteroid-dependent ulcerative colitis.

The patient must be watched closely for signs of progressive peritonitis or perforation. Percussion over the liver is important because loss of hepatic dullness may be the first clinical sign of free perforation, especially when peritoneal signs are suppressed by massive corticosteroid dosage. Abdominal x-rays should be obtained every 1 or 2 days to follow the course of colonic distention and to detect free or

intramural air. If intensive medical measures do not produce definite improvement within 24 to 48 h, immediate surgery is required or the patient may die of perforation and attendant sepsis.

Emergency colectomy is indicated for massive hemorrhage, fulminating toxic colitis, or perforation.

CONTROL QUESTIONS

1. Etiology, pathogenesis, and classification of gastrites.
2. Clinical manifestations of acute and chronic gastritis.
3. Etiology and pathogenesis of peptic ulcer disease.
4. Symptomatology and complications of peptic ulcer disease.

Theme 31. MAJOR CLINICAL SYNDROMES IN HEPATIC AND BILIARY DISORDERS (JAUNDICE, PORTAL HYPERTENSION, HEPATO-LIENAL SYNDROME, HEPATIC INSUFFICIENCY). CHOLECYSTITIS. CHOLELYTHIASIS (GALLSTONE DISEASE). HEPATITIS AND CIRRHOSIS.

Goal: to get a notion about the major clinical syndromes in hepatic and biliary disorders, their symptoms and signs, diagnostic meanings of additional diagnostic methods data; instrumental diagnostics of hepatic and gallbladder diseases; to master skills.

Knowledge objectives:

- to know symptoms and signs of main hepatic and gallbladder diseases, appropriate changes of physical examination data, diagnostic meaning of additional diagnostic methods and their findings in these diseases.

Skill objectives:

- to collect interviewing data, to perform physical examination of patients with gastrointestinal diseases (inspection, palpation, percussion and auscultation), to interpret data of additional diagnostic methods, to establish diagnosis of main gastrointestinal diseases.

Subject-matter:

1. complaints of patients with chronic hepatitis, cirrhosis
2. etiology and pathogenesis of chronic hepatitis,
3. pathogenic role of hepatic viruses B and C
4. physical examination data in patients with chronic hepatitis
5. etiology and pathogenesis of cirrhosis
6. physical examination data in patients with cirrhosis
7. instrumental diagnostics of chronic hepatitis and cirrhosis
8. laboratory data in diagnostics of chronic hepatitis and cirrhosis
9. diagnostics of acute cholecystitis
10. diagnostics of cholelythiasis (gallstone disease)

Equipment required: stethoscope.

EDUCATIONAL MATERIAL

MAJOR HEPATIC SYNDROMES

JAUNDICE

Clinical and laboratory assessment should address specific questions:

Is the jaundice caused by hemolysis or an isolated disorder of bilirubin metabolism (uncommon), hepatocellular dysfunction (common), or biliary obstruction (intermediate)?

If hepatobiliary disease is present, is the condition acute or chronic?

Is it caused by primary liver disease or by a systemic disorder involving the liver?

Is a viral infection, alcohol, or another drug responsible?

Is cholestasis of intrahepatic or extrahepatic origin?

Is surgical therapy needed?

Are complications present?

A detailed history and physical examination are crucial, because diagnostic errors usually result from inadequate clinical judgment and overreliance on laboratory data.

Symptoms and Signs

Mild jaundice without dark urine suggests unconjugated hyperbilirubinemia caused by hemolysis rather than hepatobiliary disease. More severe jaundice or dark urine clearly indicates a liver or biliary disorder. Signs of portal hypertension, ascites, or skin and endocrine changes usually imply a chronic rather than an acute process. Patients often notice dark urine before skin discoloration; thus, the onset of dark urine better indicates the duration of jaundice. Nausea and vomiting preceding jaundice most often indicate acute hepatitis or common duct obstruction by a stone; abdominal pain or rigors favor the latter. More insidious anorexia and malaise occur in many conditions but particularly suggest alcoholic liver disease or chronic hepatitis.

A systemic disorder should also be considered; eg, distended jugular veins suggest heart failure or constrictive pericarditis in a patient with hepatomegaly and ascites. Cachexia and an unusually hard or lumpy liver are more often caused by metastases than by cirrhosis. Hepatosplenomegaly without other signs of chronic liver disease may be caused by an infiltrative disorder (eg, lymphoma, amyloidosis), although jaundice is usually minimal or absent in such disorders; schistosomiasis and malaria commonly give this picture in endemic areas.

Laboratory Findings

Mild hyperbilirubinemia with normal aminotransferase and alkaline phosphatase levels usually reflects hemolysis rather than liver disease; this is usually confirmed by bilirubin fractionation. In contrast, the severity of jaundice and bilirubin fractionation do not help differentiate hepatocellular from cholestatic jaundice. Aminotransferase elevations > 500 U suggest hepatitis or an acute hypoxic episode; disproportionate increases of alkaline phosphatase suggest a cholestatic or infiltrative disorder. In the latter, bilirubin is typically normal or only slightly increased. Bilirubin levels > 428 to 513 μmol/L are usually caused by hemolysis or renal dysfunction superimposed on severe hepatobiliary disease; the latter alone rarely causes such severe jaundice. Low albumin and high globulin levels indicate chronic rather than acute liver disease. An elevated prothrombin time that improves after giving vitamin K favors a cholestatic over a hepatocellular process, but this has limited diagnostic value because patients with hepatocellular disease may also improve when given vitamin K.

Imaging is most valuable for diagnosing infiltrative and cholestatic disorders. Abdominal ultrasound, CT, and MRI often detect metastatic and other focal liver lesions. However, these procedures are less helpful

in diagnosing diffuse hepatocellular disorders (eg, cirrhosis) because findings are usually nonspecific.

Percutaneous liver biopsy has great diagnostic value but is seldom required in jaundice. Peritoneoscopy (laparoscopy) permits direct inspection of the liver and gallbladder without the trauma of a full laparotomy and is useful in selected patients. Rarely, diagnostic laparotomy is needed in some patients with cholestatic jaundice or unexplained hepatosplenomegaly.

Unconjugated Hyperbilirubinemia

Hemolysis: Although the normal liver can metabolize excess amounts of bilirubin, increased bilirubin formation in hemolysis may exceed this capacity. Even in brisk hemolysis, serum bilirubin rarely is > 3 to 5 mg/dL (> 51 to 86 μmol/L), unless liver damage is also present. However, the combination of moderate hemolysis and mild liver disease may result in more severe jaundice.

Conjugated Hyperbilirubinemia

Obstructive Jaundice - a clinical and biochemical syndrome that results when bile flow is impaired.

The term "cholestasis" is preferred to "obstructive jaundice" because a mechanical obstruction need not be present.

Bile flow may be impaired at any point from the liver cell canaliculus to the ampulla of Vater. For clinical purposes, a distinction between intrahepatic and extrahepatic causes is crucial.

The most common ***intrahepatic causes*** (***parenchymatous jaundice***) are hepatitis, drug toxicity, and alcoholic liver disease. Less common causes include primary biliary cirrhosis, cholestasis of pregnancy, metastatic carcinoma, and numerous uncommon disorders.

The most common ***extrahepatic causes*** (***mechanical jaundice***) are a common duct stone and pancreatic cancer. Less common causes include benign stricture of the common duct (usually related to prior surgery), ductal carcinoma, pancreatitis or pancreatic pseudocyst, and sclerosing cholangitis.

The pathophysiologic effects reflect backup of bile constituents (most importantly, bilirubin, bile salts, and lipids) into the systemic circulation plus their failure to enter the intestine for excretion. Bilirubin retention produces mixed hyperbilirubinemia with spillover of conjugated pigment into the urine; stools are often pale because less

bilirubin reaches the intestine. High levels of circulating bile salts are traditionally thought to cause pruritus (itching), but correlation is poor and the pathogenesis of itching remains unclear. Because bile salts are needed for absorption of fat and vitamin K, impaired biliary excretion of bile salts can produce steatorrhea and hypoprothrombinemia. In long-standing cholestasis (eg, primary biliary cirrhosis), concomitant Ca and vitamin D malabsorption may result in osteoporosis or osteomalacia. Cholesterol and phospholipid retention produces hyperlipidemia, although increased liver synthesis and decreased plasma esterification of cholesterol also contribute; triglyceride levels are largely unaffected.

Jaundice, dark urine, pale stools, and generalized pruritus are the clinical hallmarks of cholestasis. Chronic cholestasis may produce muddy skin pigmentation, excoriations from pruritus, a bleeding diathesis, bone pain, and cutaneous lipid deposits (xanthelasmas or xanthomas). These features are independent of the cause. Abdominal pain, systemic symptoms (eg, anorexia, vomiting, fever), or additional physical signs reflect the underlying cause rather than cholestasis itself and therefore provide valuable etiologic clues.

Intrahepatic and extrahepatic cholestasis must be differentiated. A detailed history and physical examination are important because most diagnostic errors result from inadequate clinical judgment and overreliance on laboratory data. Intrahepatic cholestasis is suggested by symptoms of hepatitis, heavy alcohol ingestion, recent use of potentially cholestatic drugs, or signs of chronic hepatocellular disease (eg, spider nevi, splenomegaly, ascites). Extrahepatic cholestasis is suggested by biliary or pancreatic pain, rigors, or a palpable gallbladder.

Laboratory tests have limited diagnostic value.

Cholestasis is not an emergency. Diagnosis should be based on clinical judgment plus special techniques, if available. If the diagnosis is uncertain, ultrasound (or CT) should be obtained. Mechanical obstruction can be reliably diagnosed if a scan shows dilated bile ducts, especially in a patient with progressing cholestasis. If biliary dilation is not apparent on ultrasound, an intrahepatic problem is more likely, and liver biopsy should be considered.

HEPATOMEGALY

Enlargement of the liver, indicating primary or secondary liver disease, although its absence does not exclude a serious disorder.

The lower border of a normal liver is often palpable at or slightly below the right costal margin. The upper border of a palpable liver should be percussed to ensure that the organ is not merely low-lying. Serial determinations of liver size may be of prognostic value; eg, a rapidly shrinking liver in fulminant hepatitis or an enlarging organ in metastatic carcinoma implies a poor outcome. Acute, tender enlargement may accompany hemorrhage into a cyst or the liver parenchyma.

The quality of the liver on palpation is as important as its size. Normally, its edge is rubbery-soft, sharp, and smooth. This consistency is often maintained when the liver is enlarged because of acute hepatitis, fatty infiltration, passive congestion, or early biliary obstruction. The cirrhotic liver edge is usually firm, blunt, and irregular; individual cirrhotic nodules are rarely palpable, and discernible lumps suggest malignant infiltration. Audible friction rubs or bruits over the liver, although rare, are other valuable clues to tumor.

Liver tenderness is overdiagnosed, usually because of the patient's anxiety during palpation. True tenderness (a deep-seated ache) is best elicited by punch percussion or compression of the rib cage. It is most often felt in acute hepatitis, passive congestion, and malignancy. Spontaneous right upper quadrant discomfort is usually minimal in these disorders, but occasionally severe pain and tenderness may mimic an acute surgical condition.

PORTAL HYPERTENSION

Increased pressure in the portal venous system.

The portal vein is formed by the superior mesenteric and splenic veins. It drains blood from the abdominal GI tract, spleen, and pancreas into the liver. At the porta hepatis, it divides into segmental branches; within the sinusoids, blood from the terminal portal venule merges with hepatic arterial blood. Blood flows out of the sinusoids via the hepatic veins, which drain into the inferior vena cava.

The portal vein provides about 75% of the liver's blood flow and about 60% of its O_2 supply. Normal portal pressure is 5 to 10 mm Hg (7 to 14 cm H_2O), which exceeds inferior vena caval pressure by 4 to 5 mm

Hg (the portal venous gradient). Higher values are defined as portal hypertension.

Portal hypertension results from, in most cases, increased resistance to flow. Increased resistance to flow can arise from blockage of the splenic or portal vein (uncommon), disease within the liver itself (common), or impaired hepatic venous outflow (uncommon). Table 2 shows the classification and most common causes of portal hypertension.

TABLE 2. CLASSIFICATION AND MAJOR CAUSES OF PORTAL HYPERTENSION

Classification	Cause
Prehepatic	Portal or splenic vein thrombosis
	Increased portal flow: arteriovenous fistula, massive splenomegaly from primary hematologic disease
Hepatic	Presinusoidal: schistosomiasis, other periportal disorders (eg, primary biliary cirrhosis, sarcoidosis, congenital hepatic fibrosis), idiopathic portal hypertension
	Sinusoidal: cirrhosis (all etiologies)
	Postsinusoidal: veno-occlusive disease
Posthepatic	Hepatic vein thrombosis (Budd-Chiari syndrome)
	Membranous obstruction of inferior vena cava
	Cardiac causes (eg, constrictive pericarditis, restrictive cardiomyopathy)

In industrialized nations, cirrhosis is by far the most common cause of portal hypertension, although schistosomiasis predominates in some tropical and subtropical climates. In cirrhosis, vascular compression and

distortion by the fibrosis and regenerating nodules enhance resistance in the sinusoids and terminal portal venules. This is traditionally ascribed to fixed anatomic abnormalities. Swelling of hepatocytes may also contribute to portal hypertension in alcoholic liver disease. Because of these hemodynamic and functional alterations, portal hypertension is partially treatable by drugs.

Characteristic manifestation of portal hypertension is clinical triad: venous collaterals development (dilatation of portocaval shunts), ascites and splenomegaly.

Portal-systemic venous collaterals. These may partially decompress portal hypertension but can produce important complications. The most critical collaterals occur in the distal esophagus and gastric fundus, producing engorged serpentine submucosal vessels known as varices. These can rupture, causing sudden GI hemorrhage. Visible abdominal wall collaterals are common; veins radiating from the umbilicus (***caput medusae***) are much rarer and indicate extensive flow in the umbilical and periumbilical veins. Collaterals around the rectum can produce rectal varices, often confused with hemorrhoids; bleeding occasionally results.

Portal-systemic collaterals shunt blood away from the liver, thereby diminishing hepatocellular reserve. In addition, toxic substances from the intestine gain direct access to the systemic circulation, a critical factor in the pathogenesis of portal-systemic encephalopathy. Splanchnic congestion from portal hypertension is central to the formation of ascites, via altered Starling's forces. Gastric mucosal congestion, known as portal hypertensive gastropathy, can also occur, with acute or chronic blood loss independent of varices.

Clinical findings result from its complications. The most important is acute variceal bleeding--usually from the distal esophagus, less often from the gastric fundus, and only rarely from other sites. The trigger for variceal rupture is unknown, but bleeding almost never occurs unless the portal pressure gradient is > 12 mm Hg. Patients typically present with sudden painless upper GI hemorrhage, often massive. Bleeding from portal hypertensive gastropathy may also be acute but is more often subacute or chronic.

Esophagogastric varices are best diagnosed by endoscopy (Fig.30), which may also identify a high bleeding risk (eg, red markings on

a varix). Portal hypertensive gastropathy requires endoscopy for diagnosis.

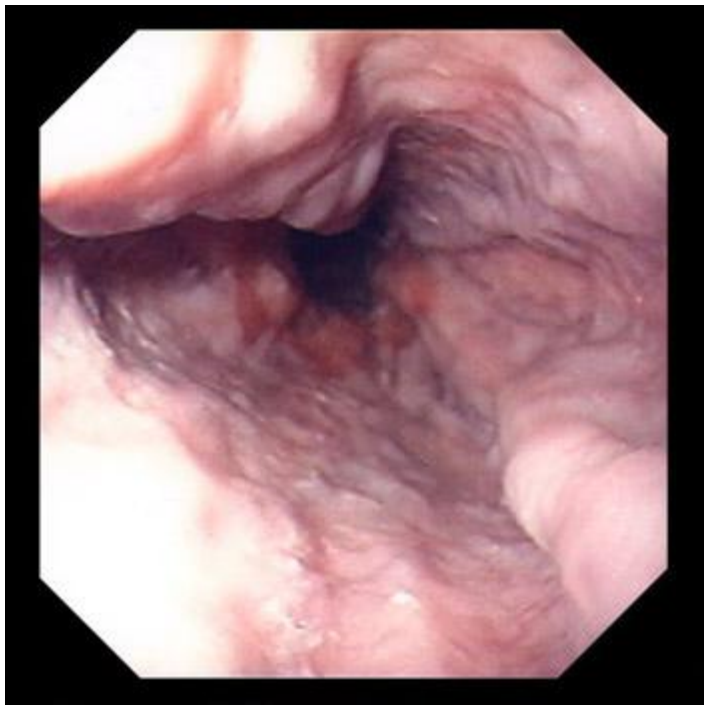


Fig.30. Esophageal varices.

Ascites - free fluid in the peritoneal cavity (Fig.31 & 32).

In liver disease, ascites indicates a chronic or subacute disorder and does not occur in acute conditions. The most common cause is cirrhosis, especially from alcoholism. Other hepatic causes include chronic hepatitis, severe alcoholic hepatitis without cirrhosis, and hepatic vein obstruction (Budd-Chiari syndrome).

Nonhepatic causes of ascites include generalized fluid retention associated with systemic disease (eg, heart failure, nephrotic syndrome, severe hypoalbuminemia, constrictive pericarditis) and intra-abdominal disorders (eg, carcinomatosis, tuberculous peritonitis). Hypothyroidism occasionally causes marked ascites, and pancreatitis rarely causes large amounts of fluid (pancreatic ascites). Patients with renal failure,

especially those on hemodialysis, occasionally develop unexplained intra-abdominal fluid (nephrogenic ascites).

Mechanisms that produce ascites are complex and incompletely understood. Two important factors in liver disease are

(1) low serum osmotic pressure caused by hypoalbuminemia and

(2) high portal venous pressure; these appear to act synergistically by altering the Starling's forces that govern fluid exchange across the peritoneal membrane.

Fig.31. General appearance of a patient with decompensated cirrhosis: pronounced weight-loss, ascites, gynecomastia, skin hemorrhages, extended subcutaneous veins, umbilical hernia are presented.

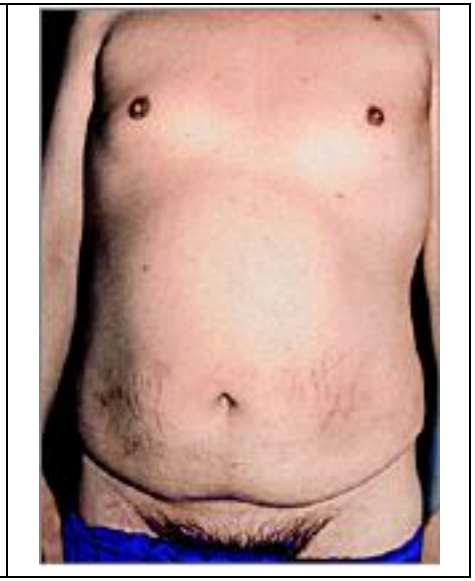


Fig.32. Striae from strain in a patient with cirrhosis. Gynecomastia, feminine type of hair distribution, redistribution of fat (apron type) are presented.

Massive ascites may cause nonspecific abdominal discomfort and dyspnea, but lesser amounts are usually asymptomatic. Ascites is diagnosed by detecting shifting dullness on abdominal percussion (Fig.33), although ultrasound or CT can detect much smaller amounts of fluid. In advanced cases, the belly is taut, the umbilicus is flat or everted, and a fluid wave can be elicited. Clinical examination usually differentiates ascites from obesity, gaseous distention, pregnancy, or

ovarian tumors and other intra-abdominal masses, but imaging or diagnostic paracentesis may occasionally be required.

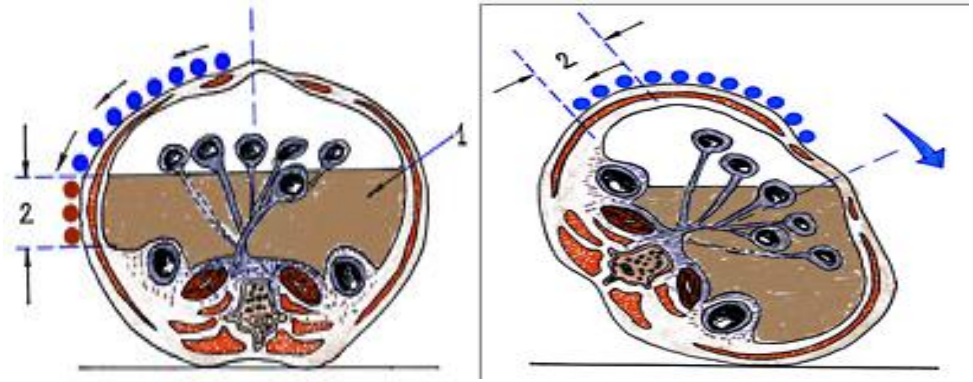


Fig.33. Detecting of shifting dullness on abdominal percussion: 1 – free fluid in abdominal cavity, 2 – zone of dull percussion notel.

Therapeutic paracentesis is a common approach. Removal of 4 to 6 L/day is safe, provided that salt-poor albumin (about 40 g/paracentesis) is concomitantly infused IV to prevent intravascular volume depletion. Even single total paracentesis appears safe. Therapeutic paracentesis shortens the hospital stay with relatively little risk of electrolyte imbalance or renal failure; nevertheless, patients require ongoing diuretics and tend to reaccumulate fluid more rapidly than those given traditional therapy.

Splenomegaly and hypersplenism commonly occur as a result of increased splenic vein pressure; thrombocytopenia, leukopenia, and less often hemolytic anemia may result, although correlation with the severity of portal hypertension is relatively poor.

Usually, however, portal hypertension is inferred by the presence of collateral circulation, splenomegaly, ascites, or portal-systemic encephalopathy in a patient with chronic liver disease. Imaging may be helpful.

HEPATOCELLULAR INSUFFICIENCY

Hepatocellular insufficiency syndrome develops in acute and chronic hepatic disorders as a result of sharp decrease of functioning

hepatocytes amount. Clinical picture includes portal systemic encepha;opathy, progressing ascites and hemorrhagic syndrome, progressing jaundice.

PORTAL SYSTEMIC ENCEPHALOPATHY (HEPATIC ENCEPHALOPATHY, HEPATIC COMA)

A neuropsychiatric syndrome caused by liver disease and usually associated with portal-systemic shunting of venous blood.

"Portal-systemic encephalopathy" is a more descriptive term of the pathophysiology than "hepatic encephalopathy" or "hepatic coma," but clinically all three are used interchangeably.

Portal-systemic encephalopathy may occur in fulminant hepatitis caused by viruses, drugs, or toxins, but it more commonly occurs in cirrhosis or other chronic disorders when extensive portal-systemic collaterals have developed as a result of portal hypertension. The syndrome also follows portacaval shunt or similar portal-systemic anastomoses. In patients with chronic liver disease, encephalopathy is usually precipitated by specific, potentially reversible causes (eg, GI bleeding; infection; electrolyte imbalance, especially hypokalemia; alcoholic debauches) or iatrogenic causes (tranquilizers, sedatives, analgesics, diuretics).

The liver metabolizes and detoxifies digestive products brought from the intestine by the portal vein. In liver disease, these products escape into the systemic circulation if portal blood bypasses parenchymal cells or if the function of these cells is severely impaired. The resulting toxic effect on the brain produces the clinical syndrome. Ammonia, a product of protein digestion, probably plays an important role, but biogenic amines, short chain fatty acids, and other enteric products may also be responsible or may act with ammonia. Aromatic amino acid levels in serum are usually high.

The pathogenesis of the cerebral toxicity is also uncertain. Pathologic changes are usually confined to hyperplasia of astrocytes with little or no neuronal damage, but cerebral edema is common in fulminant hepatitis.

Clinical manifestations develop 4 stages of hepatic encephalopathy:

• 1st stage (prodromal period) — Personality changes (eg, inappropriate behavior, altered mood, impaired judgment) are common

early manifestations that may antedate apparent change in consciousness. Sophisticated psychomotor tests can often detect such abnormalities not suspected clinically. Initially, subtle sleep pattern changes or sluggish movement and speech may be present. Inversion of sleep is also typical.

• 2nd stage — stage of profound neuropsychic derangements (inadequate behaviour, twenty-four-hour lethargy). Usually, impaired consciousness occurs.

Constructional apraxia, in which the patient cannot reproduce simple designs (eg, a star), is a characteristic early sign. A peculiar, characteristic ***flapping tremor***, asterixis, is elicited when the patient holds his arms outstretched with wrists dorsiflexed; as coma progresses, this sign disappears.

• 3d stage — precoma stage - somnolence, confusion, stupor indicate increasingly advanced encephalopathy. Dysarthria, appearance of pathologic reflexes and Cheyne-Stokes or Kussmaul breathings, growth of flapping tremor are observed. A typical musty sweet odor of the breath, called ***fetor hepaticus,*** often occurs. Sharp decrease of the liver dimensions; jaundice without pruritus and hemorrhagic syndrome progressing, hypoalbuminemia, fever are characteristic.

• 4th stage — frank coma stage is characterized by areflexia, hypoalbuminemai, hyperbilirubinemia, and low blood cholesterol and prothrombin value.

The diagnosis is clinical. There is no correlation with liver function tests. Blood ammonia levels are usually elevated, but values correlate poorly with clinical status; bedside judgment is a better guide. Encephalopathy in chronic liver disease usually responds to treatment, especially if the precipitating cause is reversible.

Coma associated with fulminant hepatitis is fatal in up to 80% of patients, despite intensive therapy; patients with advanced chronic liver failure often die with portal-systemic encephalopathy.

Treatment. Precipitating causes should be sought; treating the cause is usually sufficient in mild cases. Eliminating toxic enteric products is the other main therapy:

(1) The bowels should be cleared with enemas.

(2) Dietary protein should be eliminated (20 to 40 g/day may be allowed in mild cases), and oral or IV carbohydrate should be given to supply lost calories.

(3) Oral lactulose should be given (it can be tube-fed to comatose patients). This synthetic disaccharide syrup alters colonic pH and flora and also acts as an osmotic cathartic.

(4) Oral neomycin, 4 to 6 g/day in four divided doses, helps minimize bacteria-formed toxins and can be used instead of lactulose.

Sedation deepens encephalopathy and should be avoided, even if the patient is agitated.

Treating coma caused by fulminant hepatitis with high-dose corticosteroids or with exchange transfusion and other complex procedures designed to remove circulating toxins has not proved effective. Instead, meticulous nursing care and attention to associated complications give the best chance of survival

Deteriorating patients with fulminant liver failure should be promptly referred to a transplant center because emergency liver transplantation can be lifesaving.

RENAL AND ELECTROLYTE ABNORMALITIES

Renal and electrolyte abnormalities are common, especially in chronic disease with ascites. Hypokalemia is caused by excess urinary K loss from increased circulating aldosterone, renal retention of ammonium ion in exchange for K, secondary renal tubular acidosis, and diuretic therapy. The kidney may avidly retain Na. Blood urea concentrations are often low because of impaired liver synthesis; superimposed GI bleeding causes elevations because of an increased enteric load rather than true renal impairment, since creatinine values usually remain normal.

Renal failure in liver disease may reflect

(1) disease directly affecting both organs (eg, carbon tetrachloride toxicity--rare);

(2) circulatory failure with decreased renal perfusion, with or without frank acute tubular necrosis; or

(3) functional renal failure, often called ***hepatorenal syndrome.*** This is a progressive disorder with no apparent morphologic abnormality in the kidney; it usually occurs in fulminant hepatitis or advanced cirrhosis with ascites. Its unknown pathogenesis probably involves neural or humoral alterations of renocortical blood flow. Insidiously progressive oliguria and azotemia herald its onset. Low urinary Na concentration and benign sediment usually distinguish it from tubular necrosis, but prerenal

azotemia may be more difficult to differentiate; in doubtful cases, response to a volume load should be assessed. Once established, renal failure is almost invariably progressive and fatal; there is no effective therapy. Terminal hypotension with tubular necrosis may complicate the clinical picture, but the kidneys are characteristically unremarkable at autopsy.

SYSTEMIC ABNORMALITIES

Anorexia, fatigue, and weakness are common features of liver disease caused by ***hepatocellular dysfunction***. Fever may occur, especially in viral or alcoholic hepatitis, but rigors are rare and, in a jaundiced patient, suggest biliary obstruction with cholangitis. Profound anorexia and nausea are especially common in viral and alcoholic hepatitis. Marked deterioration of general health and development of a cirrhotic habitus (ie, wasted extremities, protuberant belly) often signal advanced cirrhosis.

SKIN AND ENDOCRINE CHANGES

Patients with chronic liver disease can develop several cutaneous abnormalities. ***Spider nevi*** (vascular spiders) (Fig.34 & 35), ***palmar erythema*** (Fig.36), and ***Dupuytren's contractures*** (Fig.47) are common, especially in alcoholic cirrhosis. Chronic cholestasis often causes muddy skin pigmentation, excoriations from constant pruritus (itching), and cutaneous lipid deposits (xanthelasmas or xanthomas).

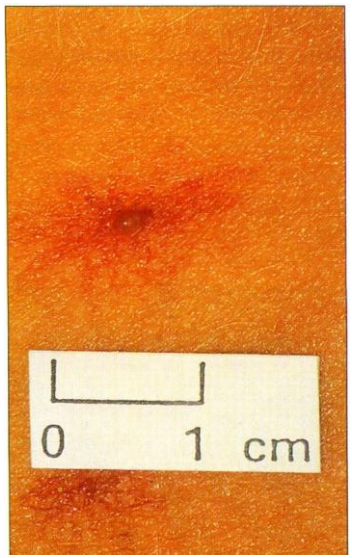


Fig.34. A typical spider naevus consists of a central spiral arteriole, which supplies a radiating group of small vessels. This spider naevus is of typical size, though larger and smaller examples may occur.

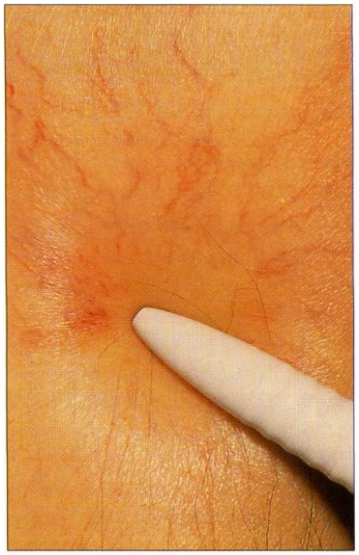


Fig.35. The spider naevus blanches if the central spiral arteriole is occluded by pressure, demonstrating that this is the single source of its blood supply.

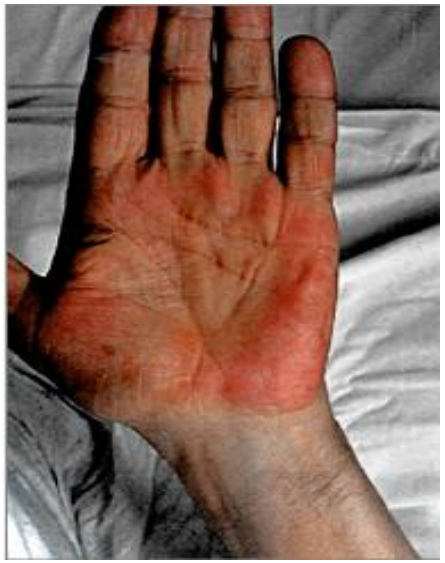


Fig.36. Palmar erythema in patient with cirrhosis.

Endocrine derangements are common. Glucose intolerance, hyperinsulinism, insulin resistance are often present in cirrhosis; the elevated insulin levels reflect decreased hepatic degradation rather than increased secretion.

Complex derangements occur in the metabolism of sex hormones. Amenorrhea and decreased fertility are common in women with chronic liver disease. Males with cirrhosis, especially alcoholics, often have both hypogonadism (testicular atrophy, impotence, decreased spermatogenesis) and feminization (gynecomastia, female habitus) (Fig.37 & 32).

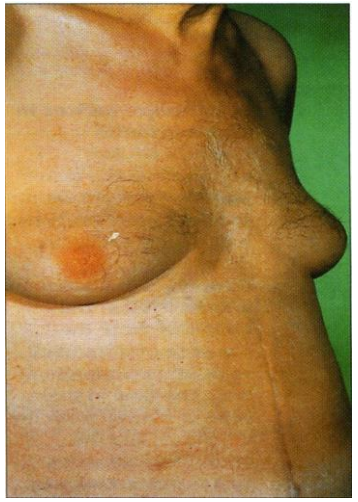


Fig.37. Gynaecomastia in a male patient. This patient had cirrhosis, and a hepatocellular carcinoma.

The biochemical basis is incompletely understood. Circulating testosterone levels are low, resulting mainly from decreased synthesis but also from increased peripheral conversion to estrogens. The levels of minor estrogens are usually increased. These changes are more prevalent in alcoholic liver disease than in cirrhosis of other etiologies; evidence indicates a direct toxic effect of ethanol on the testis.

HEMATOLOGIC DISTURBANCES

Many hematologic abnormalities are associated with liver disease. Anemia is frequent. Its pathogenesis may involve blood loss, nutritional

folate deficiency, hemolysis, marrow suppression by alcohol, and chronic liver disease per se. Leukopenia and thrombocytopenia often accompany splenomegaly in portal hypertension, whereas leukocytosis occurs in cholangitis, tumor, alcoholic hepatitis, and fulminant liver necrosis.

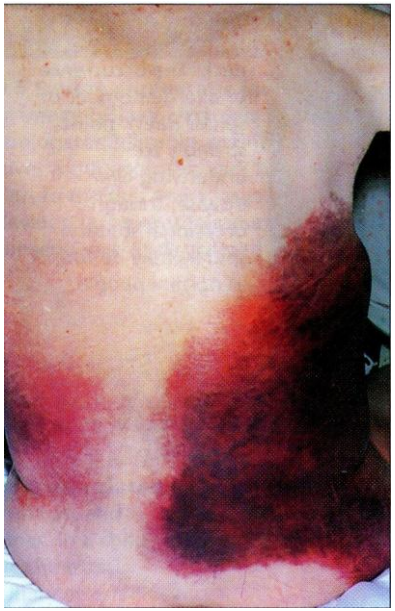


Fig.38. Spontaneous bruising in a patient with cirrhosis. Disturbance of coagulation mechanisms is a common problem in chronic liver disease, and the risk of excessive bleeding should always be assessed by coagulation studies before liver biopsy or other operative procedures.

Coagulation disturbances are common (Fig.38) and complex. Liver synthesis of clotting factors is frequently impaired and results from hepatocellular dysfunction or inadequate absorption of vitamin K, which is required for the synthesis of factors II, VII, IX, and X. An abnormal prothrombin time results. Thrombocytopenia, disseminated intravascular coagulation, and dysfibrinogenemia also contribute to clotting disturbances in many patients.

BANTI'S [HEPATOLIENAL] SYNDROME

This syndrome is characterized by associated enlargement of the liver (hepatomegaly) and spleen (splenomegaly) in primary disorder of

either organ (Fig.39). Hepatolienal syndrome frequently is associated with hypersplenism – spleen more actively participates in blood corpuscles destruction process.

Fig.39. Hepatomegaly and splenomegaly commonly coexist in chronic liver disease in the presence of portal hypertension; hepatomegaly may also occur alone in many liver disorders. This patient shows signs of weight loss, and has dilated abdominal veins. Her hepatomegaly has just been further investigated by CT-guided biopsy.

The most frequent causes of Banti's syndrome (up to 90%) are acute and chronic diffuse hepatic diseases, rarely – chronic infectious and parasitogenic diseases, metabolic disorders, hematologic diseases.

Splenomegaly in cirrhosis usually follows hepatomegaly and depends on disease stage and intensity of portal hypertension. Tenderness on spleen palpation may be noticed in perisplenitis development.

Clinical symptomatology may be different according to cause of syndrome:

- in hepatic disoreders both organs consistency is firm, especially in cirrhosis and cancer; in portal hypertension spleen may be significantly enlarged, accompanied by pancytopenia.

- in passive congestion spleen is slightly enlarged and hypersplenism is absent.
- In infectious disorders (eg, sepsis, bacterial endocarditis) organs enlargement may be equal.

CYTOLYTIC SYNDROME

Cytolytic syndrome is characterized by increase of serum transaminase, which reflects level of hepatocytes necrosis in acute and chronic hepatic diseases of different etiology. The peak increase is detected in acute viral hepatitis.

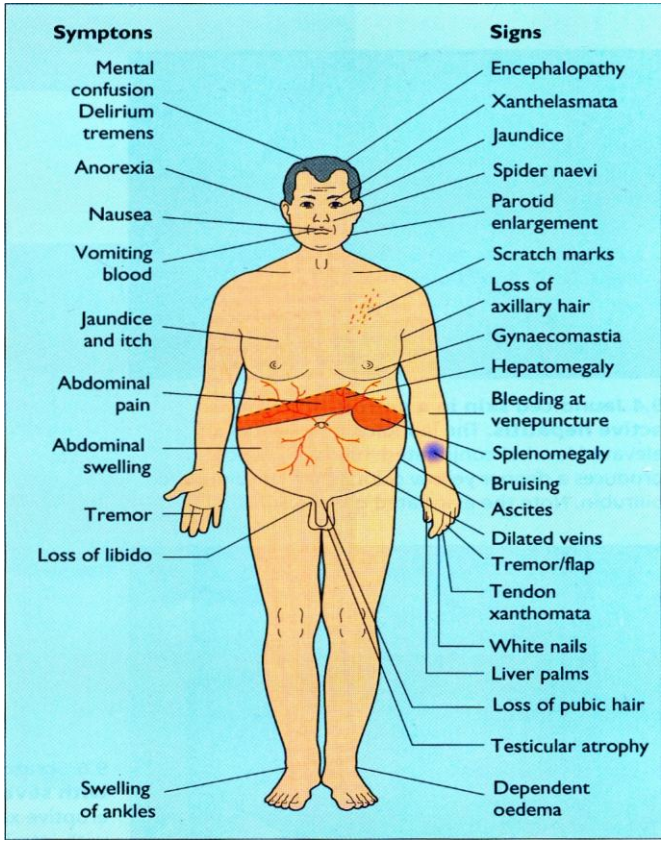


Fig.40. Common symptoms and signs in liver disease.

Fig.40 shows common symptoms and signs in liver disease.

HEPATITIS:

An inflammation of the liver characterized by diffuse or patchy necrosis affecting all acini.

The major causes of hepatitis are specific hepatitis viruses, alcohol, and drugs. Less common causes include other viruses (eg, infectious mononucleosis, yellow fever, cytomegalovirus) and leptospirosis. Parasitic infections (eg, schistosomiasis, malaria, amebiasis) affect the liver but do not cause true hepatitis.

CHRONIC HEPATITIS

A spectrum of disorders between acute hepatitis and cirrhosis.

Hepatitis lasting for 6 mo is generally defined as chronic, although this is arbitrary. Complex terminology has created confusion. Until recently, cases were classified histologically as chronic persistent, chronic lobular, or chronic active hepatitis, with generally differing clinical courses and sequelae. With greater knowledge of the multiple causes of chronic hepatitis, however, the recent trend is to instead specify the etiology, modified by the histologic status if known (eg, chronic hepatitis C with mild periportal inflammation, autoimmune hepatitis with early cirrhosis).

Etiology and Pathogenesis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are major causes of chronic hepatitis; 5 to 10% of cases of hepatitis B (with or without hepatitis D virus co-infection) and about 75% of cases of hepatitis C become chronic. Infection with hepatitis A virus or hepatitis E virus is not a cause. The mechanism of chronicity is uncertain, but a direct cytopathic effect of the virus appears to be only minor, especially with HBV infection; instead, liver injury is largely caused by an immune-mediated host reaction to the infection. The role of hepatitis G virus in chronic hepatitis is not clear.

Various drugs can cause chronic hepatitis, including isoniazid, methyldopa, nitrofurantoin, and possibly acetaminophen. The pathogenesis varies with the drug and may reflect an altered immune response, cytotoxic intermediate metabolites, or genetically determined metabolic defects.

The rare Wilson's disease may present as chronic hepatitis and should be considered in children and young adults with the disorder. Occasionally, α_1-antitrypsin deficiency produces chronic hepatitis, although inactive cirrhosis is more common.

Many cases are idiopathic. A high proportion of these cases have prominent immune features; this is considered a specific variant of the disorder *(autoimmune hepatitis*). Overwhelming evidence points to immunologic mechanisms of hepatocellular injury in these patients, including coexisting clinical and serologic immune markers; an association with HLA-B8 haplotype; extensive periportal infiltration with T lymphocytes and plasma cells; complex *in vitro* defects in cellular immunity and immunoregulatory functions; and response to therapy with corticosteroids or immunosuppressive drugs. Despite this, proof of true autoimmune causation is lacking because auto-antibodies directed uniquely against liver cell antigens have not been proven.

Symptoms and Signs

Clinical features vary. About 1/3 of cases follow acute hepatitis, but most develop insidiously de novo. Many patients are asymptomatic, especially in chronic hepatitis C. Nonspecific *malaise*, *anorexia*, and *fatigue* are common, sometimes with low-grade *fever* and nondescript *upper abdominal discomfort*. *Jaundice* is variable and is often absent. Signs of chronic liver disease (eg, splenomegaly, spider nevi, fluid retention) may eventually develop, but in many patients the disorder remains subclinical for many years or even decades. In the autoimmune variant, multisystemic or "immune" manifestations often occur, especially in young women. These can affect virtually any body system and include acne, amenorrhea, arthralgia, ulcerative colitis, pulmonary fibrosis, thyroiditis, nephritis, and hemolytic anemia. A minority of patients develop predominant cholestatic features suggesting primary biliary cirrhosis.

Laboratory Findings

These include evidence of active hepatocellular inflammation, with predominant aminotransferase elevations and variable bilirubin and alkaline phosphatase values. ALT and AST are typically 100 to 500 IU/L, although values occasionally exceed 1000 IU/L and can create confusion with acute hepatitis; in such cases, other laboratory clues to chronicity may aid the diagnosis (eg, low serum albumin). Cholestatic

laboratory features occasionally dominate. Serologic "immune" markers are common in the autoimmune variant.

Clinical and laboratory features are helpful, but liver biopsy is essential for definitive diagnosis. Mild cases may have only minor hepatocellular necrosis and inflammatory cell infiltration (Fig.41), usually in portal regions, with normal acinar architecture and little or no fibrosis. Such cases only uncommonly develop clinically important liver disease or cirrhosis.

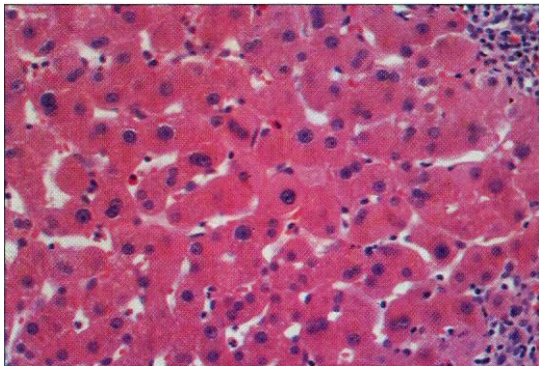


Fig.41 Mild case of chronic hepatitis. The liver parenchyma is normal, but there is persistent infiltration with small mononuclear inflammatory cells in the portal tracts (seen at two edges in this view). The hepatocytes are normal, even in the ‘limiting plate’ (the zone adjacent to the portal tract).

In more severe cases, biopsy typically shows periportal necrosis with mononuclear cell infiltrates (so-called piecemeal necrosis) accompanied by variable periportal fibrosis and bile duct proliferation (Fig.42). The acinar architecture may be distorted by zones of collapse and fibrosis, and frank cirrhosis sometimes coexists with signs of ongoing hepatitis. In most instances, the specific cause cannot be discerned, although cases caused by HBV can be distinguished by the presence of ground-glass hepatocytes and special stains for HBV components. Autoimmune cases usually have a more pronounced infiltration by lymphocytes and plasma cells.

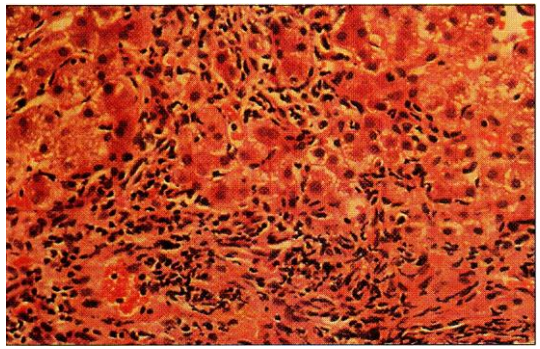


Fig.42 Chronic active hepatitis. Here the inflammatory infiltrate is not confined to the portal tracts. Small inflammatory cells can be seen in bands through the liver parenchyma, and some of the parenchymal cells are swollen and vacuolated. This form of hepatitis commonly leads to cirrhosis and liver failure.

With drug etiology, disease may regress completely when offending agent is withdrawn. Cases associated with HBV or HCV tend to progress slowly and are usually relatively resistant to therapy. Autoimmune cases generally improve substantially with treatment. With adequate therapy, patients usually live several years or decades, but hepatocellular failure, cirrhosis, or both eventually develop in many cases.

Treatment

Treatment includes cessation of causative drugs and management of complications (eg, ascites, encephalopathy). Autoimmune hepatitis is best treated by corticosteroids with or without azathioprine. These drugs suppress the inflammatory reaction, perhaps partly by beneficially altering the immune response, and have increased long-term survival.

Therapy for chronic hepatitis B and C is evolving. Corticosteroids are contraindicated, because viral replication is enhanced. Interferon- is now widely used to suppress viral replication, but overall results are relatively disappointing.

Liver transplantation has not generally been suitable for end-stage liver disease caused by HBV, because of aggressive disease reference in the graft. Transplantation for advanced hepatitis C is much more successful; although HCV infection universally recurs, the clinical course is generally indolent, and long-term survival rates are relatively high. In many transplant centers, hepatitis C is now the most common indication for adult liver transplantation.

CIRRHOSIS

Diffuse disorganization of normal hepatic structure by regenerative nodules that are surrounded by fibrotic tissue.

The nodules typically contain liver cell plates two to four cells thick and sparsely placed venules. The pathologic changes in cirrhosis generally involve the entire liver. Extensive fibrosis, even with regenerating nodules (ie, cirrhosis), is usually irreversible, although fibrosis in animals can resolve, depending on experimental design. In humans, cirrhotic damage is permanent; nodule regeneration is a vain attempt at repair.

Fibrosis is not synonymous with cirrhosis, which also includes nodule formation and scarring sufficient to cause deteriorated liver function. Partial nodule transformation or nodular regenerative hyperplasia (ie, nodules without fibrosis) and congenital hepatic fibrosis (ie, widespread fibrosis without regenerating nodules) are not true cirrhosis.

Etiology

In the Western world, cirrhosis is the third leading cause of death in patients aged 45 to 65 (after cardiovascular disease and cancer); most cases are secondary to chronic alcohol abuse. In many parts of Asia and Africa, cirrhosis resulting from chronic hepatitis B is a major cause of death.

The etiology of cirrhosis is similar to that of fibrosis: infection, toxins, altered immune response, biliary obstruction, and vascular disturbance. Hepatitis C and other forms of chronic hepatitis (from autoimmune chronic active hepatitis and certain drugs) result in cirrhosis. Metabolic causes include hemochromatosis, Wilson's disease, α_1-antitrypsin deficiency, galactosemia, and congenital tyrosinosis. Even diabetes mellitus has been associated with the development of cirrhosis. Prolonged biliary obstruction (secondary biliary cirrhosis), chronic venous outflow obstruction (eg, Budd-Chiari syndrome), and malnutrition can lead to cirrhosis. Cirrhosis of unknown etiology, termed cryptogenic, is diagnosed less frequently as more specific diagnoses (eg, chronic hepatitis C virus infection) become available.

Pathogenesis

Cirrhosis is the end stage of many forms of liver injury characterized initially by fibrosis. The progression of fibrosis to cirrhosis

and the morphology of the cirrhosis depend on the extent of injury, the presence of continuing damage, and the response of the liver to damage. Cirrhosis is related not so much to the injurious agents as to the kind of injury and the liver's response to it. The liver may be injured acutely and severely (as in submassive necrosis with hepatitis), moderately over months or years (as in biliary tract obstruction and chronic hepatitis), or modestly but continuously (as in alcohol abuse). Cytokines and hepatic growth factors are presumably responsible for the response to injury: fibrosis plus regenerating nodules (Fig.43).

During the repair process, new vessels form within the fibrous sheath that surrounds the surviving nodules of liver cells; these "bridges" connect the hepatic artery and portal vein to the hepatic venules, restoring the intrahepatic circulatory pathway.

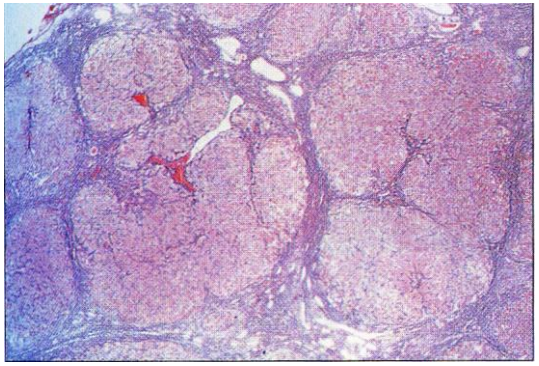


Fig.43. Cirrhosis. In this typical histopathological section, bands of fibrous tissue run between nodules of regenerated hepatocytes. Only some nodules contain a central vein, and the bile ducts and portal vessels run in the fibrous septa. These changes are associated with portal hypertension.

Such interconnecting vessels receive blood from the sinusoids and provide relatively low-volume, high-pressure drainage that is less efficient than normal and results in increased portal vein pressure (portal hypertension). Disordered blood flow to the nodules and compression of hepatic venules by regenerating nodules also contribute to portal hypertension.

Cirrhosis is not static; its features depend on the disease activity and stage. Morphologic classification of cirrhosis does little to reveal its cause.

Histopathologic classification:

Micronodular cirrhosis is characterized by uniformly small nodules (< 3 mm in diameter) and regular bands of connective tissue. Typically, nodules lack portal organization; terminal (central) hepatic venules or portal tracts are difficult to identify.

Macronodular cirrhosis is characterized by nodules that vary in size (3 mm to 5 cm in diameter) and contain some normal lobular structure (portal tracts, terminal hepatic venules). Broad fibrous bands of varying thickness surround the large nodules. Collapse of the normal liver architecture is suggested by the concentration of portal tracts within the fibrous scars.

Mixed cirrhosis (incomplete septal cirrhosis) combines elements of micronodular and macronodular cirrhosis. Regeneration in micronodular cirrhosis can result in macronodular or mixed cirrhosis. Conversion from micronodular to macronodular cirrhosis takes >= 2 yr.

Symptoms and Signs

Cirrhosis results in some features unique to the cause (eg, pruritus in primary biliary cirrhosis) and in major complications: portal hypertension with variceal bleeding, ascites, or liver failure leading to renal failure and coma.

Many patients with cirrhosis are asymptomatic for years. Others show generalized weakness, anorexia, malaise, and weight loss. With obstruction to bile flow, jaundice, pruritus, and xanthelasmas become prominent. Malnutrition is common, secondary to anorexia with poor food intake, fat malabsorption, and fat-soluble vitamin deficiency caused by the effects of reduced bile-salt excretion. In alcohol-related liver disease, pancreatic insufficiency may be a more important factor. A more dramatic presentation is massive upper GI bleeding from esophageal varices secondary to portal hypertension. The initial presentation may occasionally be that of hepatocellular failure with ascites or portal-systemic encephalopathy.

A palpable, firm liver with a blunt edge is typical, but at times the liver is small and difficult to palpate. Regenerating nodules are only occasionally palpable. Ascites may be present with portal hypertension, splenomegaly, and a collateral venous circulation (Fig.44).

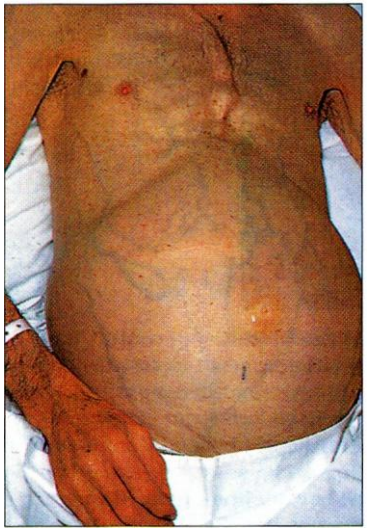


Fig.44. A peritoneovenous shunt in a patient with cirrhosis and severe ascites. The subcutaneous course of the valved shunt is clearly seen. Despite the presence of the shunt, which has helped to maintain his serum albumin level, this patient still has severe ascites.

Other clinical signs may suggest chronic liver disease, particularly in alcoholics, but none is specific: muscle wasting, palmar erythema (Fig.36), Dupuytren's contractures (Fig.47), vascular spiders (< 10 may be normal), gynecomastia (Fig.37), parotid gland enlargement (Fig.48), axillary hair loss, testicular atrophy, and peripheral neuropathy.

Complications

Many severe complications of cirrhosis are secondary to portal hypertension because hypertension leads to the development of collateral flow from the portal venous system to the systemic circulation. Portal hypertension is associated with splenomegaly and hence hypersplenism; the development of collateral vessels lining the esophagus and stomach produces varices. Esophageal varices (Fig.45) and, less often, gastric varices are particularly prone to bleeding, which is often massive.

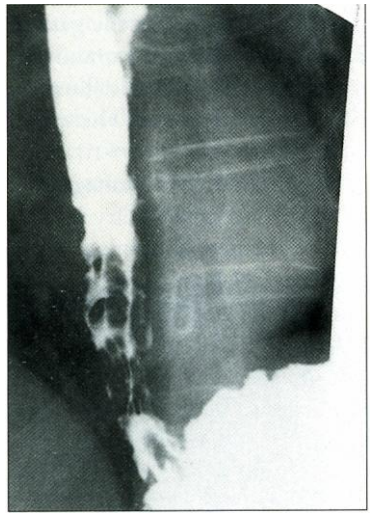


Fig.45. Esophageal varices. A barium swallow, showing the typical appearance of multiple lower oesophageal varices, evident as barium-coated filling defects. In addition, gastric varices can be seen, along the lesser curvature of the stomach. These thin- walled varices are easily damaged, and bleeding is a frequent complication.

In addition, jaundice, ascites, renal failure, and hepatic encephalopathy may develop because of portal hypertension, portal-systemic shunting, other circulatory disturbances, and impaired hepatic metabolic function. Lastly, hepatocellular carcinoma frequently complicates cirrhosis associated with chronic hepatitis B and C viruses, hemochromatosis, and long-standing glycogen storage disease.

Routine laboratory tests of liver function may be normal in cirrhosis. Decreased serum albumin and a prolonged prothrombin time directly reflect impaired hepatic function. Serum globulin increases in many forms of chronic liver disease. Transaminase is often modestly elevated, while alkaline phosphatase may be normal or increased, particularly with biliary obstruction. Bilirubin is usually normal. Anemia is fairly common and usually normocytic, but it may be microcytic, hypochromic from chronic GI bleeding, macrocytic from folate deficiency (in alcoholism), or hemolytic from hypersplenism. Alcohol directly suppresses the bone marrow. Hypersplenism also can lead to leukopenia and thrombocytopenia.

Ultrasound may reveal textural abnormalities suggestive of cirrhosis, confirm hepatosplenomegaly, and detect features of portal hypertension: enlargement or obstruction of the portal or splenic veins and the presence of esophageal varices. Doppler ultrasound can demonstrate portal blood flow. CT better evaluates liver size (Fig.46) and texture and density.

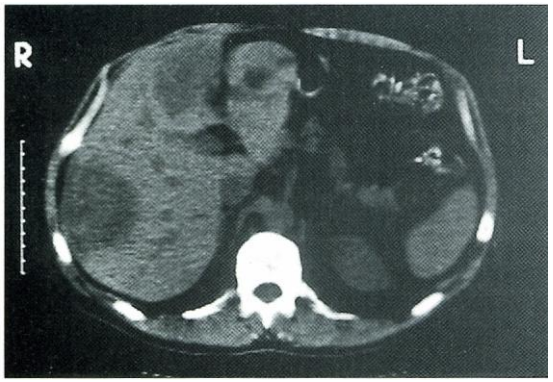


Fig.46. CT is of major value in the assessment of patients with many disorders of the liver and pancreas. This patient has multiple secondary tumour deposits of various sizes throughout the liver, which have contributed to marked hepatomegaly. The primary tumour was in the breast.

Endoscopy is best for diagnosing esophageal varices.

Treatment

In general, treatment of cirrhosis is supportive: withdrawal of toxic agents, attention to nutrition (including supplemental vitamins), and treatment of complications as they arise. Liver transplantation for patients with advanced cirrhosis has changed the long-term outcome for many patients.

ALCOHOLIC LIVER DISEASE:

A spectrum of clinical syndromes and pathologic changes in the liver caused by alcohol (ethanol).

Pathogenesis

The major factors are the quantity of alcohol consumed, the patient's nutritional status, and genetic and metabolic traits. A linear correlation

generally exists between the dose and duration of alcohol abuse and the development of liver disease. As little as 20 g of alcohol in women or 60 g in men can produce liver injury when consumed daily for years. For example, ingestion of 150 to 200 g of alcohol for 10 to 12 days produces fatty liver even in otherwise healthy men. For alcoholic hepatitis, patients consume 80 g of alcohol daily for almost a decade, whereas the average threshold to develop cirrhosis is 160 g daily over 8 to 10 yr. Duration is important.

By providing empty calories, decreasing the appetite, and causing malabsorption through its toxic effects on the gut and pancreas, alcohol promotes malnutrition. Malnutrition alone does not cause cirrhosis, but a lack of one or more nutritional factors may hasten the effects of alcohol.

Alcohol is a hepatotoxin whose metabolism creates profound liver cell derangements. Apparent variations in susceptibility (only 10 to 15% of alcoholics develop cirrhosis) and the greater susceptibility of females (even when adjusting for smaller body size) to alcohol-induced liver disease suggest that other factors are also significant. One may be that females have decreased alcohol dehydrogenase in their gastric mucosa, lessening metabolism.

Metabolism of Alcohol

Alcohol is readily absorbed from the GI tract, and > 90% is metabolized by the liver through oxidative mechanisms involving mainly alcohol dehydrogenase and certain microsomal enzymes (microsomal ethanol oxidizing system). Alcohol cannot be stored and must be metabolized.

Whether alcoholics metabolize alcohol differently from nonalcoholics is unknown. Clearly, chronic ingestion of alcohol leads to hepatic adaptation with hypertrophy of the smooth endoplasmic reticulum and increased activity of the hepatic drug-metabolizing enzymes. Alcohol induces the microsomal ethanol oxidizing system, which is responsible in part for alcohol metabolism. Alcohol also induces microsomal P-450, which is involved in drug metabolism. Thus, the alcohol abuser acquires an increased tolerance to alcohol and drugs (eg, sedatives, tranquilizers, antibiotics), and neurologic adaptation develops. The result is a complex interaction between drugs, other chemicals, and alcohol.

Pathology

The spectrum of hepatic pathology associated with prolonged alcohol consumption ranges from the simple accumulation of neutral fat in hepatocytes to cirrhosis and hepatocellular carcinoma. The widely accepted fatty liver-alcoholic hepatitis-cirrhosis spectrum is a concept of convenience. The findings usually overlap, and many patients present with features of the entire spectrum. The key lesion may be fibrosis around the terminal hepatic venules and perhaps also the perisinusoidal space. From the perspective of pathology, it is better to diagnose alcoholic liver disease and describe the specific findings in each patient.

Fatty liver or steatosis appears to be the initial change and is the most common response to alcohol ingestion. The liver is large; the cut surface, yellow. The increased liver fat is derived from the diet, from free fatty acids mobilized from adipose tissue, and from lipid synthesized in the liver and inadequately degraded or excreted. Fat droplets of varying size are found in most hepatocytes except in regenerating areas. Other features include hydropic change in early stages of alcoholic liver injury and giant spherical mitochondria. The former--swollen, balloonlike hepatocytes--result from impaired release of protein and lipoproteins. These cells degenerate and disintegrate.

Alcoholic hepatitis includes the macrovesicular fatty change plus a diffuse inflammatory response to injury and necrosis (often focal); established cirrhosis may also be present.

Mallory (alcoholic hyaline) ***bodies*** are fibrillar proteins of intracytoplasmic inclusions within swollen hepatocytes; these cells contain little or no fat. With hematoxylin and eosin stain, Mallory bodies appear as irregular aggregates of purplish red material. Although characteristic of alcoholic hepatitis, Mallory bodies are also found in some cases of Wilson's disease, Indian childhood cirrhosis, cirrhosis following small-bowel bypass surgery, primary biliary cirrhosis (or other causes of prolonged cholestasis), diabetes mellitus, morbid obesity, and hepatocellular carcinoma. A polymorphonuclear reaction develops locally in response to the Mallory-containing and necrotic liver cellsıo

Alcoholic hepatitis, with its diffuse inflammatory cell infiltrate and necrosis, is often viewed as the intermediary step between fatty liver and cirrhosis. Cell necrosis and centrizonal hypoxia can stimulate collagen formation. Fibrosis, however, occurs from the transformation of fat-storing into fibroblasts. Thus, fibrosis can proceed to cirrhosis without an intervening stage of alcoholic hepatitis. About 20% of heavy drinkers develop cirrhosis, in which the liver is finely nodular, with its architecture disorganized by fibrous septa and nodules.

Alcoholic cirrhosis represents end-stage disease, developing in 10 to 20% of those who are chronically heavy drinkers. Micronodular cirrhosis is evident, although this may be a lingering feature of fatty liver and alcoholic hepatitis. Some regeneration occurs from the surviving liver cells. The cirrhosis may slowly progress to a nonspecific macronodular pattern. The liver shrinks and becomes small.

Symptoms, Signs, and Diagnosis

Variations in drinking patterns, individual susceptibility to hepatotoxic effects of alcohol, and the many kinds of tissue damage promote a highly variable clinical picture. For a long time, no manifestations may be referable to the liver. Symptoms generally can be related to the quantity of alcohol ingested and the overall duration of alcohol abuse. As a guideline, symptoms usually become apparent in patients during their 30s, and severe problems tend to appear in patients in their 40s.

Some characteristic features of alcohol abusers are shown on Fig.47 and Fig.48.

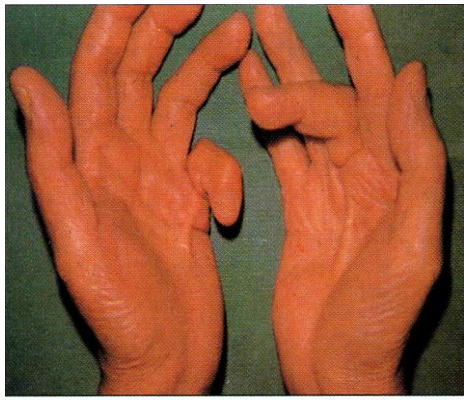


Fig.47. Dupuytren’s contracture may be seen in association with alcoholic cirrhosis, though it may also occur as a completely independent abnormality. Contracture of the palmar fascial bands produces flexion contracture of the metacarpophalangeal and proximal interphalangeal joints, the flexor tendon apparatus and the skin itself. In this patient, the condition particularly affects the right middle finger and the left little finger Surgical correction is usually possible.

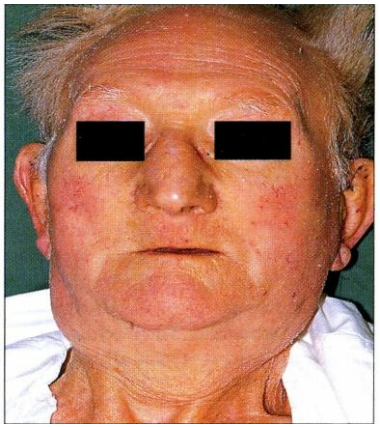


Fig.48. Parotid enlargement in association with cirrhosis is most common when alcohol is the cause of the cirrhosis. In addition to painful parotid enlargement, this patient had multiple vascular spiders and early acne rosacea.

Patients with a fatty liver are usually asymptomatic. In 33%, the liver is enlarged, smooth, and occasionally tender. Routine biochemical

studies are often within normal limits; γ-glutamyl transpeptidase (GGT) is often elevated. Vascular spiders and features of hyperestrogenism and hypoandrogenism from the alcoholism per se may be evident.

Alcoholic hepatitis can be suspected clinically, but the diagnosis depends on examination of a biopsy sample. The histologic lesion can be found throughout the clinical spectrum of alcoholic liver disease. Patients with alcoholic hepatitis may present with fatigue, fever, jaundice, right upper quadrant pain, a hepatic bruit, tender hepatomegaly, and leukocytosis, but so may patients with sepsis, cholecystitis, or mechanical extrahepatic biliary obstruction.

Cirrhosis may also be relatively asymptomatic, have features of alcoholic hepatitis, or be dominated by complications: portal hypertension with splenomegaly, ascites, hepatorenal syndrome, hepatic encephalopathy, or even hepatocellular carcinoma.

Laboratory Findings

Although sometimes suggestive, routine blood and biochemical tests are nonspecific and do not permit a definitive diagnosis. Thrombocytopenia is common, either from the direct toxic effects of alcohol on the bone marrow or secondary to hypersplenism.

In alcoholic hepatitis, transaminase levels are moderately raised (about 250 U/L). Conjugated bilirubinemia actually deepens in the hospital. The activity of serum ALT is depressed (caused by a depletion of pyridoxal 5′-phosphate) relative to that of serum AST (AST:ALT ratio > 2). The activity of the serum GGT may help detect alcohol consumption. The value of GGT lies not in its specificity but in its being markedly elevated in patients with excessive alcohol intake or alcoholic liver disease. Liver biopsy is the only basis for a secure diagnosis, particularly in alcoholic hepatitis.

Treatment

With abstinence, nonfibrotic liver damage may be reversed, and the survival of patients with alcoholic hepatitis, fibrosis, and cirrhosis improves.

In theory, treatment of alcoholic liver disease is simple and straightforward; in practice, it is difficult: the patient must stop drinking alcohol. It helps to point out to the patient that much of the damage caused by alcoholic liver disease is reversible. Otherwise, management focuses on nonspecific supportive care.

GALL BLADDER DISORDERS

PHYSIOLOGY OF BILE ACID METABOLISM

Bile is formed in the liver as an isosmotic solution of bile acids, electrolytes, bilirubin, cholesterol, and phospholipids. Bile flow is generated by the active transport of bile salts and electrolytes and the accompanying obligate passive movement of water.

The liver synthesizes water-soluble bile acids from water-insoluble cholesterol, but precise mechanisms are not completely understood. Cholic and chenodeoxycholic acids form in the liver in a ratio of about 2:1 and constitute 80% of bile acids. Bile acids are excreted in bile, which flows from the intrahepatic collecting system into the proximal or common hepatic duct. About 50% of bile secreted in the fasting state passes into the gallbladder via the cystic duct; the rest flows directly into the distal or common bile duct. Up to 90% of water in gallbladder bile is absorbed as an electrolyte solution, principally via gallbladder mucosal intracellular pathways. Bile remaining in the gallbladder is thus a concentrated solution consisting primarily of bile acids and sodium.

During fasting, bile acids are concentrated in the gallbladder, and little bile acid-dependent bile flows from the liver. Food entering the duodenum initiates an exquisite hormonal and neural sequence. Cholecystokinin is released from duodenal mucosa and stimulates the gallbladder to contract and the biliary sphincter to relax. Bile flows into the duodenum to mix with food contents and to perform its several functions:

(1) Bile salts solubilize dietary cholesterol, fats, and fat-soluble vitamins to facilitate their absorption in the form of mixed micelles.

(2) Bile acids induce water secretion by the colon as they enter that organ, thus promoting catharsis.

(3) Bilirubin is excreted in bile as degradation products of heme compounds from worn-out RBCs.

(4) Drugs, ions, and endogenously produced compounds are excreted in bile and subsequently eliminated from the body.

(5) Various proteins important in GI function are secreted in bile.

Food entering the duodenum stimulates gallbladder contraction, releasing much of the body pool (total, 3 to 4 g) of bile acids into the small intestine. Bile acids are poorly absorbed by passive diffusion in the

proximal small intestine; most of the pool reaches the terminal ileum, where 90% is absorbed into the portal venous circulation by active transport. Bile salts are efficiently extracted by the liver, promptly modified, and secreted back into bile.

Bile acids undergo enterohepatic circulation 10 to 12 times per day. During each pass, a small amount of primary bile acids reaches the colon, where anaerobic bacteria containing 7-hydroxylase form secondary bile acids. Cholic acid is thus converted to deoxycholic acid, which is largely reabsorbed and conjugated. Chenodeoxycholic acid conjugates are converted in the colon to their secondary bile acid form, lithocholic acid. This insoluble secondary bile acid is partially reabsorbed; the rest is lost in the feces.

Anatomy of the Biliary Tract

Other than absorptive functions of the normal gallbladder and bile storage mediation by the sphincters, the extrahepatic ductal system is a passive conduit. There are no functional smooth muscle fibers in the biliary duct walls. Ductal secretions stimulated by secretin contain a high concentration of bicarbonate and contribute variably to total bile volume.

The ampulla of Vater (Fig.49) consists of the terminal intramural segments of the biliary and pancreatic ducts and of the two or three sphincter segments and surrounding soft tissue.

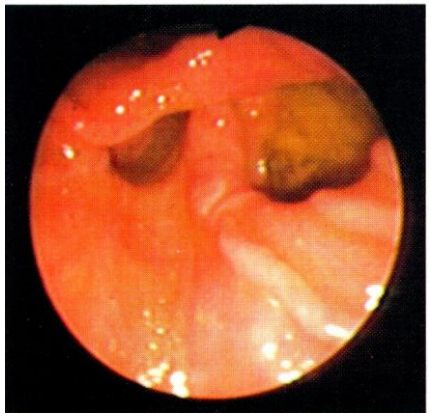


Fig.49. Duodenoscopy with a side-viewing endoscope is an essential preliminary to common bile duct cannulation and endoscopic retrograde cholangiopancreatography (ERCP). It may also reveal abnormalities in the duodenum or the ampulla of Vater. Here, a normal ampulla (centre of picture) is flanked by two duodenal diverticula. These abnormalities are found in 10—15% of patients endoscoped, and are usually of no clinical significance.

The sphincter of Oddi surrounds both ducts or their common channel, and each duct has its separate (inconstant) sphincter. Normal sphincter function results in timely release of bile and pancreatic enzymes during food passage; during fasting, however, gallbladder filling is facilitated. The two systems normally remain independent (ie, bile does not flow retrograde into the pancreatic duct).

ACUTE CHOLECYSTITIS

Acute inflammation of the gallbladder wall, usually as a response to cystic duct obstruction by a gallstone.

Although acute cholecystitis is the most common consequence of cholelithiasis, the pathophysiology is incompletely understood. Concentrations of bile, including bile salts, phospholipids, and even cholesterol, may be altered, thus inducing mucosal inflammation. Acute cholecystitis is accompanied by cholelithiasis in >= 95% of patients.

Symptoms and Signs

Acute cholecystitis begins with recurrent colicky pain in 75% of patients. Pain becomes severe, localizing to the right upper quadrant, often radiating to the right lower scapula. Nausea and vomiting are usual. Within a few hours, the primary physical finding is involuntary guarding of right-sided abdominal muscles, without rebound tenderness at first. The gallbladder becomes palpable in < 50% of cases. Painful splinting of respiration during deep inspiration and right upper quadrant palpation (Murphy's sign) is frequent. Fever is low grade at first, and neutrophilia is modest.

A typical episode of acute cholecystitis improves in 2 to 3 days and resolves within 1 wk. Failure to do so suggests serious complications. When acute cholecystitis is accompanied by jaundice or cholestasis, partial common duct obstruction may result from calculi or contiguous inflammation. Amylase elevation suggests (but does not confirm) gallstone pancreatitis. Finally, in rare cases, large stones erode through the gallbladder wall and may obstruct the small intestine (gallstone ileus).

Clinically suspected acute cholecystitis is most accurately confirmed by ultrasound. Although ultrasound is the preferred test for diagnosing cholelithiasis, it is less accurate for diagnosing acute

cholecystitis. Demonstration of a sonographic Murphy's sign, gallbladder wall thickening, or pericholecystic fluid is helpful.

Clinical diagnosis of acute cholecystitis may be difficult when findings are atypical.

Treatment

Management includes rehydration with IV fluids and electrolytes. No oral feedings are given, and nasogastric suction is instituted. Parenteral antibiotics are usually initiated when the diagnosis is suspected.

Cholecystectomy cures acute cholecystitis and biliary colic in nearly all patients.

Acute acalculous cholecystitis (ie, cholecystitis without stones) is a serious disease that tends to occur in adults and children already ill from trauma, operations, burns, sepsis, or critical illness. Ultrasound, cholescintigraphy, and CT may aid in diagnosis. When the disease is present, prompt intervention with either percutaneous cholecystostomy or surgical management is indicated.

CHRONIC CHOLECYSTITIS

Pathologically, a thick-walled, fibrotic, contracted gallbladder; clinically, chronic gallbladder disease characterized by symptoms that include recurrent colic.

The mucosa may be ulcerated and scarred, and the lumen may contain sludge or stones that often obstruct the cystic duct. It is tempting to ascribe these findings to the ravages and repair of previous episodes of acute cholecystitis, but the clinical history may not include any record of such events. Clinical and pathologic manifestations are poorly correlated. Both are nearly always associated with calculi in the gallbladder.

CHOLELITHIASIS

Formation or presence of calculi (gallstones) in the gallbladder.

Most clinical disorders of the extrahepatic biliary tract are related to gallstones. Factors that increase the probability of gallstones include female sex, obesity, increased age, a Western diet, and a positive family history.

Pathophysiology

Cholesterol, the major component of most gallstones, is highly insoluble in water, and biliary cholesterol is solubilized in bile salt-phospholipid micelles and phospholipid vesicles, which greatly increase the cholesterol-carrying capacity of bile. Bile salt micelles are aggregates of bile salts in which water-soluble (ionic) regions of the molecule face outward into aqueous solution, while the water-insoluble (nonpolar) steroid nuclei face inward. Cholesterol is soluble inside these spheroid micelles, and their cholesterol-carrying ability is further enhanced by lecithin, a polar phospholipid. The amount of cholesterol carried in micelles and vesicles varies with the bile salt secretion rate.

Supersaturation of cholesterol in bile is a necessary condition, but not a sole cause, of cholesterol gallstone formation because supersaturation is frequent in the bile of fasting persons without gallstones. The other critical factor in determining whether gallstones form is regulation of the initiating process, cholesterol monohydrate crystal formation. In gallbladder bile that is lithogenic (ie, prone to stone formation), there is supersaturation of cholesterol and relatively rapid nucleation of cholesterol crystals. The dynamic interplay of forces for and against cholesterol crystal nucleation and growth in the gallbladder includes the actions of specific proteins or apoproteins, gallbladder mucin, and gallbladder stasis.

Virtually all gallstones form within the gallbladder, but stones may form in the bile duct after cholecystectomy or behind strictures as a result of stasis.

Symptoms and Signs

The clinical consequences of stone formation in the gallbladder are exceedingly variable. Most patients remain asymptomatic for long periods, frequently for life (Fig.50). Stones may traverse the cystic duct with or without symptoms of obstruction. Transient cystic duct obstruction results in colicky pain, whereas persistent obstruction usually produces inflammation and acute cholecystitis.

In contrast to other types of colic, ***biliary colic*** typically is constant, with pain progressively rising to a plateau and falling gradually, lasting up to several hours. Nausea and vomiting are often associated. Fever and chills are absent in uncomplicated gallbladder colic. Pain most often

occurs in the epigastrium or right upper quadrant, radiating to the right lower scapula.

Symptoms of dyspepsia and fatty food intolerance are often inaccurately ascribed to gallbladder disease. Belching, bloating, fullness, and nausea are associated about equally with cholelithiasis, peptic ulcer disease, or functional distress. Such symptoms may disappear after cholecystectomy but should not be the only indication for operation. Postprandial fatty food intolerance is likely to be caused by cholelithiasis if symptoms include right upper quadrant pain; however, the prevalence of postprandial functional distress is so high in the general population that symptoms alone are insufficient for diagnosis of gallbladder disease without supportive clinical signs and diagnostic studies.

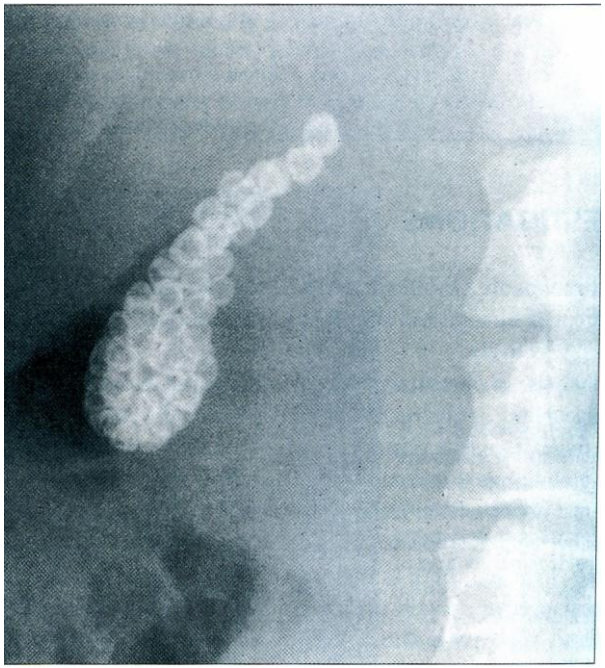


Fig.50. Calcified gallstones seen on plain X-ray. Only about 10% of gallstones contain enough calcium to be visible on the plain film. This patient had had remarkably few symptoms before the incidental discovery of her gallstones.

Real-time ultrasonography is the method of choice for diagnosing possible gallbladder calculi (Fig.51). Sensitivity (probability of a positive test when disease is present) is 98%; specificity (probability of a negative test when the disease is absent) is 95%. Static B mode ultrasonography and oral cholecystography are also sensitive and specific.

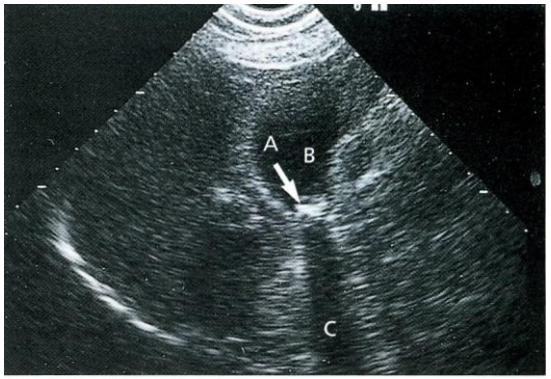


Fig.51. Ultrasound is the optimal initial investigation for gallstones. The scan shows a typical gall stone (A) in the gall bladder (B). The acoustic shadow (C) cast by the stone is typical.

Treatment

Asymptomatic gallstones: Most patients with clinically silent stones decide that the discomfort, expense, and risk of elective surgery are not worth removing an organ that may never cause clinical illness, although the potential complications represent serious disease. If symptoms appear, prompt therapy is advisable.

Symptomatic gallstones: Biliary colic recurs with irregular, pain-free intervals of days or months. Symptoms often do not progress in severity or frequency, but neither do they cease. Symptomatic patients are at increased risk of developing complications, and cholecystectomy is indicated.

Ursodeoxycholic acid reduces biliary secretion of cholesterol and decreases the cholesterol saturation of bile, resulting in gradual dissolution of cholesterol-containing stones in 30 to 40% of patients. Recurrence of stones is common after cessation of the drug.

CONTROL QUESTIONS

1. Jaundice: types, pathogenesis, clinical and laboratory diagnostics.
2. Portal hypertension syndrome: notion, classification, clinical manifestations.
3. Hepatocellular insufficiency: notion, pathogenesis, clinical and laboratory manifestations.
4. Chronic hepatitis: notion, forms, diagnostics.
5. Cirrhosis: notion, etiology, pathogenesis, classification.
6. Symptomatology of cirrhosis.
7. Cholecystitis: notion, etiology, pathogenesis, classification.
8. Symptomatology of acute cholecystitis.

Theme 32. SYMPTOMATOLOGY OF PANCREATIC DISORDERS. EXOCRINOUS INSUFFICIENCY. LABORATORY AND INSTRUMENTAL DIAGNOSTICS

Goal: to get a notion about the main gastrointestinal diseases, their symptoms and signs, diagnostic meanings of additional diagnostic methods data; instrumental diagnostics of gastrointestinal diseases; to master skills.

Knowledge objectives:

- to know symptoms and signs of main gastrointestinal diseases, appropriate changes of physical examination data, diagnostic meaning of additional diagnostic methods and their findings in these diseases.

Skill objectives:

- to collect interviewing data, to perform physical examination of patients with gastrointestinal diseases (inspection, palpation, percussion and auscultation), to interpret data of additional diagnostic methods, to establish diagnosis of main gastrointestinal diseases.

Subject-matter:

1. complaints of patients with acute and chronic pancreatitis
2. etiology and pathogenesis of pancreatitis
3. physical examination data in patients with acute pancreatitis
4. physical examination data in patients with chronic pancreatitis
5. instrumental diagnostics of pancreatitis
6. laboratory data in diagnostics of pancreatitis
7. diagnostics of pancreatic exocrinous insufficiency

Equipment required: stethoscope.

EDUCATIONAL MATERIAL

The anatomy of the pancreas and its ducts is now so wonderfully displayed by endoscopy, ultrasonography, computed tomography, and magnetic resonance imaging studies that physicians must become aware of the many normal variations in pancreatic and ductal anatomy.

CLINICAL ANATOMY (Fig. 52)

The pancreas may be divided into three parts:

1) a head embraced by the duodenal curve,

2) a body that crosses the vertebral column, and

3) a tail that lies in the hilum of the spleen.

The blood supply of the head of the pancreas is so intermingled with that of the duodenum that the pancreas cannot be readily separated from the duodenum without destroying the blood supply of the latter. The transverse colon overlies the head of the pancreas, a relation that leads occasionally to involvement of the transverse colon in pancreatic disorders; the common duct is embedded in the head of the pancreas, which explains how processes in the head of the pancreas are associated with jaundice. The body and the tail of the pancreas pass to the left and somewhat obliquely upward and lie more behind the stomach than the

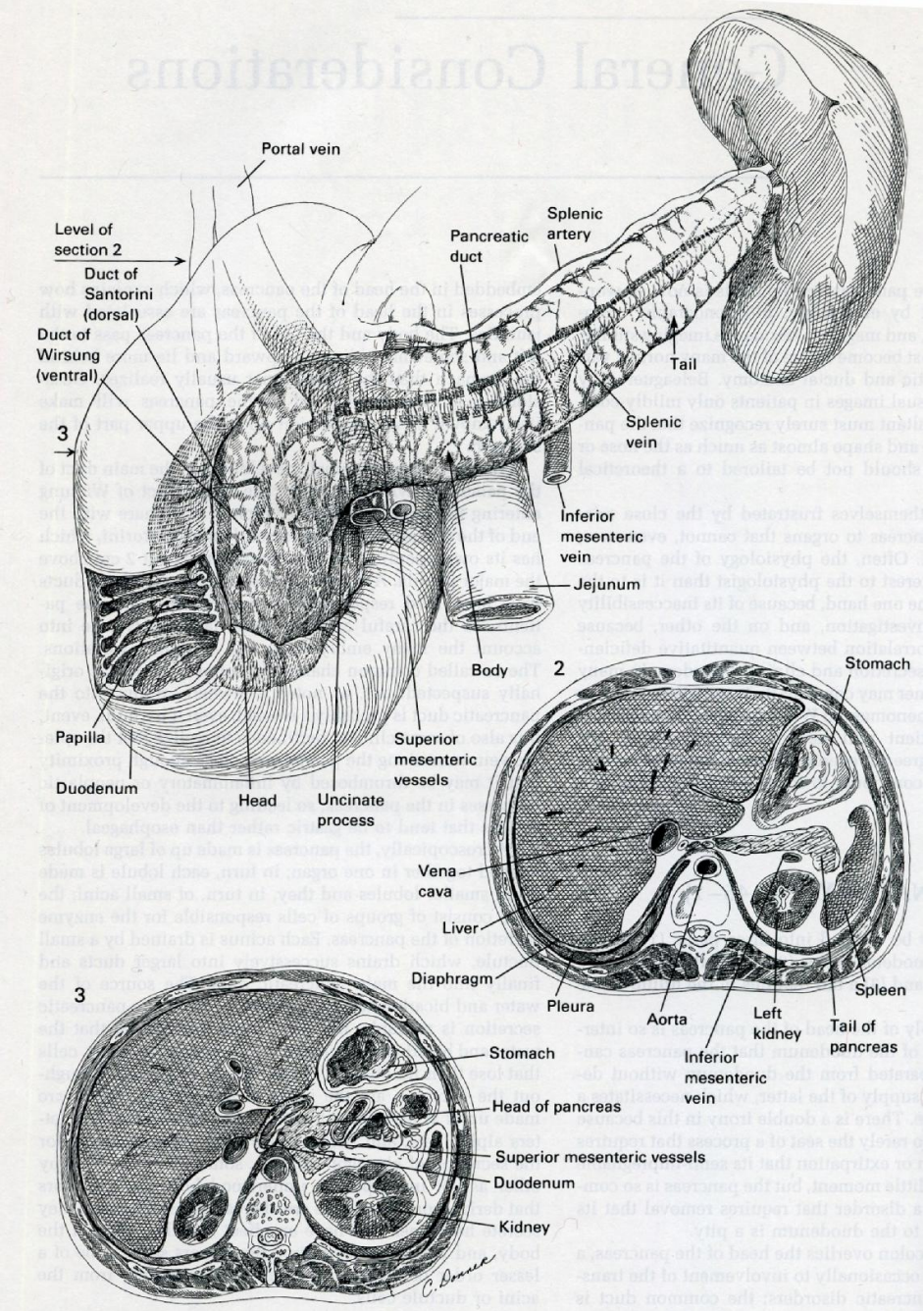


Fig.52. Normal anatomy of the pancreas and environs.

practitioner usually realizes. Occasionally a mass in the tail of the pancreas will make itself known by an impression upon the upper part of the stomach.

Thanks to its embryologic development, the main duct of the pancreas divides into two: the major *duct of Wirsung* entering the papilla of Vater, which it may share with the end of the common duct; the lesser *duct of Santorini*, which has its own opening into the duodenum about 2 cm above the major papilla. The so-called common channel is not as common as originally suspected, but, as noted elsewhere, reflux into the pancreatic duct is probably a normal, even if harmful, event.

Microscopically, the pancreas is made up of large lobules welded together in one organ; in turn, each lobule is made up of smaller lobules and they, in turn, of small acini; the acini consist of groups of cells responsible for the enzyme secretion of the pancreas. Each acinus is drained by a small ductule, which drains successively into larger ducts.

It is fitting to consider that the water and bicarbonate arise from cells lining the ducts, cells that lose their function in cystic fibrosis. Scattered throughout the pancreas are the ***islets of Langerhans***, which are made up of at least three types of cells, given the Greek letters *alpha*, *beta*, and *delta*. These cells are responsible for the secretion of glucagon, insulin, somatostatin, and many other as yet incompletely understood hormones.

PHYSIOLOGIC CONSIDERATIONS

Pancreatic juice, an alkaline fluid ordinarily of pH 8, is composed of two major components; one is fluid and electrolytes and the other enzymes. The most important component of fluid secretion is bicarbonate. As pancreatic flow increases, so does the concentration of bicarbonate. Sodium makes up 95 percent of the cations in pancreatic juice, and its secretion also parallels the volume of secretion. Pancreatic secretion is also rich in calcium. The other portion is made up of enzymes that help to digest fat, protein, and carbohydrate, which are represented in large part by lipase, trypsin, and amylase. Acting in concert with bile acids and colipase, pancreatic lipase is important to the digestion of fat because it hydrolyzes triglycerides to fatty acids and monoglycerides. Fat in the duodenum is a potent stimulant for cholecystokinin release and pancreatic secretion.

The pancreas has a remarkable reserve capacity; fat and protein are not lost in the stool until lipase and trypsin output is reduced to 10 percent of normal.

Stimuli to Secretion. The pancreas is stimulated by nervous as well as hormonal factors with the usual cephalic, gastric, and intestinal phases to its secretion. As might be expected from its duodenal embrace, the major secretion of the pancreas is under duodenal and intestinal control, through the action of secretin and cholecystokinin. Surprisingly, the cholecystokinin released in response to a meal stimulates enzyme secretion by acting on neural pathways and not directly on the acinar cell. Acid is the principal stimulant to pancreatic secretion of water and bicarbonate because it evokes secretin from the duodenal mucosa. Duodenal bile acids may also stimulate bicarbonate secretion by augmenting secretin release.

DIAGNOSTIC TECHNIQUES

The inability of the clinician to recognize most pancreatic disorders is counterbalanced by the exquisite precision of the diagnostic armamentarium. Imaging techniques are so good that the duty of the clinician is to try to put the patient's symptoms into context. For example, the pancreas varies greatly in size and shape so that abnormalities of contour should be germane to the patient's complaints, not simply investigated always and merely because the imager says they are there. At least in the ideal world without lawyers to raise the specter of delayed diagnosis, this would be true.

Ultrasonography

Ultrasonography provides the initial screening test for pancreatic disease. Along with computed tomography, it has changed the pancreas from an organ that could he evaluated only very indirectly, and then by inference, to one that has become the focal point of numerous imaging techniques.

That ultrasonography is relatively cheap, readily available, and capable of scanning the pancreas in several image planes, for a while made it the primary diagnostic study for the pancreas.

Ultrasound can display the size, contour, and texture of the pancreas and will show masses in it, usually with decreased echoes or changes in the gland contour. The normal pancreas is readily identified by ultrasonography in relation to the great vessels and the kidney (Figs. 53, 54).

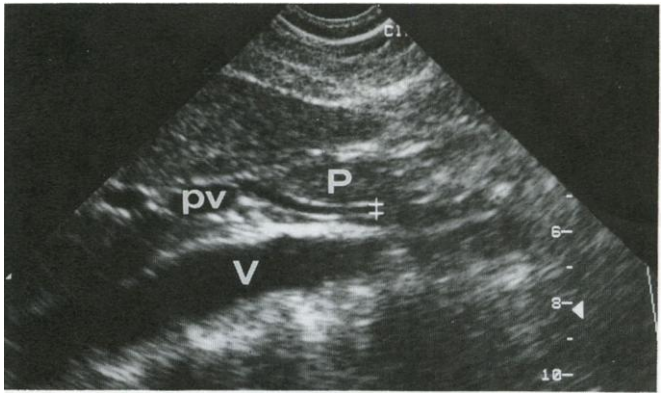


Fig. 53. Longitudinal sonogram of normal pancreas. The pancreatic head (P) is seen just to the right of the midline. The common bile duct (‡) arches over the portal vein (pv) and descends to the posterior pancreatic head just anterior to the inferior vena cava (V).

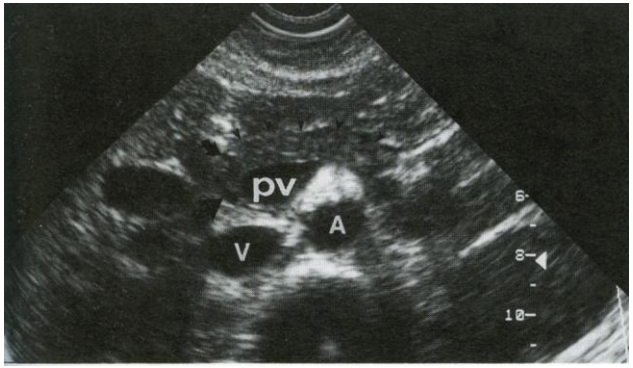


Fig. 54. Transverse sonogram of normal pancreas. The normal pancreatic parenchyma (arrowheads) is well seen surrounding the portal vein (pv). The right lateral margin of the pancreatic head is posteriorly bordered by the common bile duct (arrow) and anteriorly by the gastroduodenal artery (curved arrow). (A = aorta, V = inferior vena cava.)

Over the past few years the size of the pancreas has been a matter of debate, with 3 cm set as the upper limit of normal for the head, and somewhat lower limits for the body and tail.

Texture is important in the assessment of pancreatic disease, the pancreas normally producing higher-level echoes than the liver. Areas of decreased echoes suggest fibrosis or infiltration by tumor, whereas cysts and pseudocysts can be readily identified. The pancreatic duct can be recognized at ultrasonography as a curved tube coursing toward the body and tail, at least when it is dilated.

Computed Tomography

The pancreas is readily displayed by computed tomography (Fig.55).

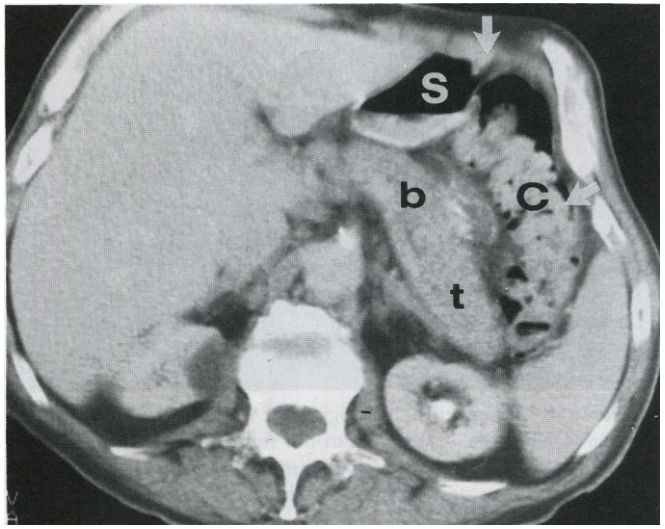


Fig. 55. Normal CT of pancreatic body and tail. This CT slice illustrates why sonography often has a hard time seeing the pancreatic body (b) and tail (t). The colon (c) and stomach (S) lie directly in the typical path (arrows) used for ultrasound imaging.

Of all the noninvasive imaging techniques, computed tomography displays the pancreas with greater detail than any other. That it is expensive, that it exposes the patient to radiation, and that the image planes or “cuts” are fixed for a while made it a procedure that followed ultrasound rather than preceding it (Figs. 56, 57).

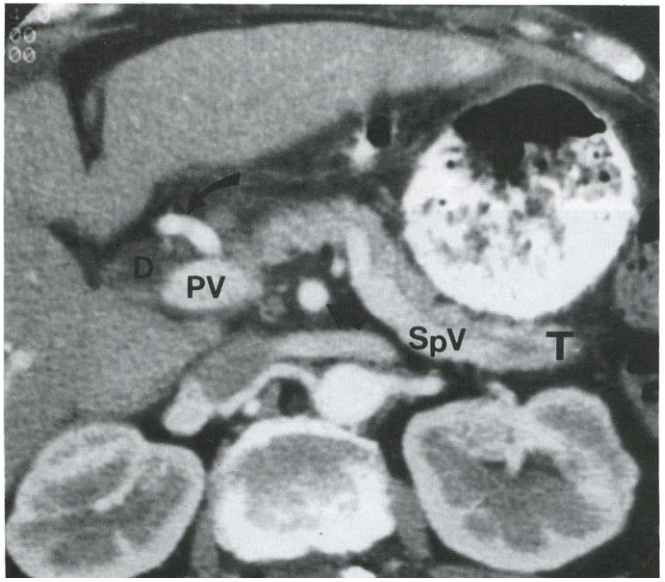


Fig. 56. CT of normal pancreas. The pancreatic body and tail (T) are well seen in their usual retrogastric location. Contrast enhancement is noted in the normal splenic vein (SpV), portal vein (PV), and superior mesenteric artery (arrow). The hepatic artery (curved arrow) is arching anterior over the bile duct (D).

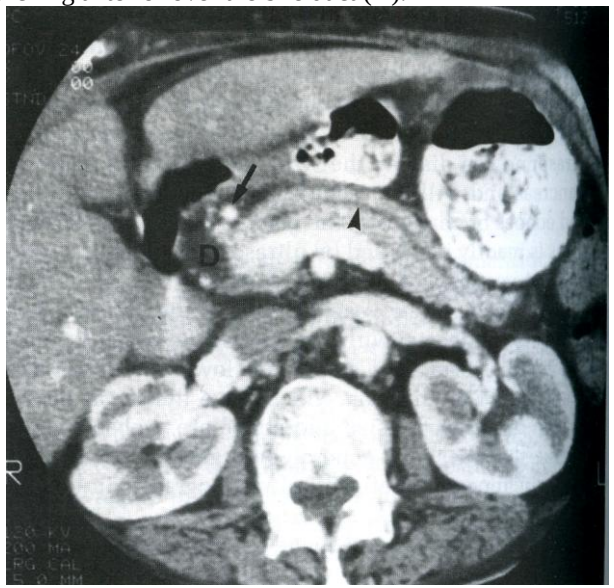


Fig. 57. CT of normal pancreas. The normal pancreatic duct (arrowhead) is seen within the pancreatic body. The gastroduodenal artery (arrow) is seen just above and anterior the pancreatic head. (D = bile duct.)

Measurement of Pancreatic Enzymes in the Blood

A hallmark of pancreatic disease is an increased level of pancreatic enzymes in the blood.

Although a number of extrapancreatic sources may supply pancreatic or salivary-type amylase to the serum, for practical purposes in the patient with abdominal pain, clinicians should consider pancreatic disease first whenever the serum amylase is elevated.

Ordinarily, the serum amylase level rises within a few hours after the onset of acute pancreatitis to levels 10 to 12 times normal or more, rapidly dropping to normal within 2 or 3 days. In acute pancreatitis, the serum amylase level tends to increase in parallel with the lipase, but decrease more rapidly than the lipase.

The ***urinary amylase*** tends to remain elevated for a longer period than serum amylase and may be elevated for 5 to 7 days after the serum amylase level has returned to normal. Their clinical utility is largely supplanted by serum lipase levels and by imaging techniques.

Chronic pancreatic disease is reflected in deterioration of pancreatic endocrine as well as exocrine function, with disordered glucose tolerance and evidence of malabsorption. It is often necessary to carry out a full malabsorption workup to pinpoint the origin of steatorrhea in the pancreas.

Stool Trypsin and Chymotrypsin The quantitative measurement of stool trypsin and chymotrypsin appears to be popular in the diagnosis of chronic pancreatic insufficiency, but studies of stool trypsin and chymotrypsin are of little diagnostic value in the patient with mild pancreatic insufficiency.

Pancreatic Secretion. The direct study of pancreatic secretion can be accomplished in two ways, neither of which is currently very popular.

(1) The *secretin test* is the more standard and more sensitive, though detecting alterations in pancreatic function sometimes so slight as to lack clinical reflection.

(2) The *Lundh test meal* evaluates by direct aspiration of a test meal from the duodenum the status of the digestive process. The test is reliable only when there is a moderate diminution of pancreatic secretion.

Because the secretin test is less physiologic and its stimulus of greater potency, it will usually display lesser degrees of pancreatic dysfunction than the Lundh test meal.

Endoscopic Cholangiopancreatography (ERCP).

This technique appears so valuable in the differential diagnosis of jaundice (Fig.58).

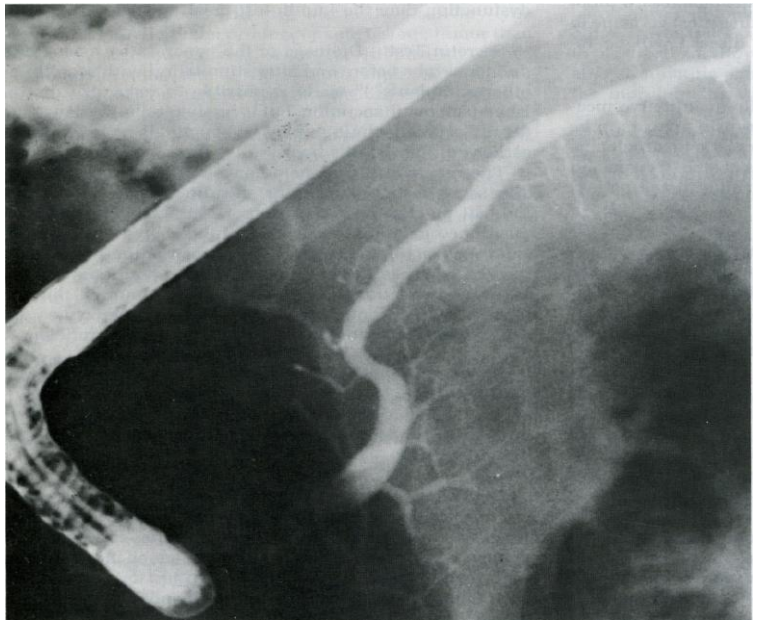


Fig. 58. Normal pancreatic duct. The normal pancreatic duct is smooth and tapers very gradually toward its distal end. Note here the small ducts rising from it which tapered distally without clubbing or dilatations. In the original a pancreatic blush can be seen.

Pressure Recordings from the Sphincter It is possible to measure the pressure in the sphincter of Oddi during endoscopic retrograde cholangiopancreatography, with a considerable amount of specialized equipment, expertise, and patient cooperation.

Pure Pancreatic Juice Obtained at ERCP. It was perhaps inevitable that diagnosis of pancreatic disease by measuring the constituents of pure pancreatic juice obtained at ERCP would be attempted. So far, these measurements are not of sufficient clinical value

to be advised in general medicine. The results, however, suggest that pancreatic juice protein concentrations and viscosity are increased in chronic pancreatitis, suggesting a reflection of the protein plugs now so commonly accepted as the early morphologic marker of chronic pancreatitis.

PANCREATITIS:

Inflammation of the pancreas.

Pancreatitis is classified as either acute or chronic. Acute pancreatitis refers to an acute inflammation that resolves both clinically and histologically. Chronic pancreatitis is characterized by histologic changes that persist even after the cause has been removed. The histologic changes in chronic pancreatitis are irreversible and tend to progress, resulting in serious loss of exocrine and endocrine pancreatic function and deterioration of pancreatic structure. However, possible discordance between clinical and histologic components may complicate classification; eg, alcoholic pancreatitis may initially present as acute clinically but may already be chronic histologically.

ACUTE PANCREATITIS

Etiology and Pathogenesis

CAUSATIVE FACTORS IN ACUTE PANCREATITIS
Gallstones and common bile duct obstruction
Excessive alcohol intake
Viral infections, e.g. mumps, coxsackie B, Epstein-Barr virus, hepatitis A and B
Trauma – during ERCP and other instrumentation – major abdominal injury, blunt trauma
Metabolic – hyperlipidaemia, hypercalcaemia, renal failure
Drug-associated – corticosteroids, azathioprine, thiazide diuretics, valproate, oestrogens
Anorexia and bulimia nervosa

Biliary tract disease and alcoholism account for >= 80% of hospital admissions for acute pancreatitis. The remaining 20% are attributed to drugs (eg, azathioprine, sulfasalazine, furosemide, valproic acid), estrogen use associated with hyperlipidemia, infection (eg, mumps), hypertriglyceridemia, endoscopic retrograde pancreatography, structural abnormalities of the pancreatic duct (eg, stricture, cancer, pancreas divisum), structural abnormalities of the common bile duct and ampullary region (eg, choledochal cyst, sphincter of Oddi stenosis), surgery (particularly of stomach and biliary tract and after coronary artery bypass grafting), vascular disease (especially severe hypotension), blunt and penetrating trauma, hyperparathyroidism and hypercalcemia, renal transplantation, hereditary pancreatitis, or uncertain causes.

In biliary tract disease, attacks of pancreatitis are caused by temporary impaction of a gallstone in the sphincter of Oddi before it passes into the duodenum. The precise pathogenetic mechanism is unclear; recent data indicate that obstruction of the pancreatic duct in the absence of biliary reflux can produce pancreatitis, suggesting that increased ductal pressure triggers pancreatitis.

Alcohol intake > 100 g/day for several years may cause the protein of pancreatic enzymes to precipitate within small pancreatic ductules. In time, protein plugs accumulate, inducing additional histologic abnormalities. After 3 to 5 yr, the first clinical episode of pancreatitis occurs, presumably because of premature activation of pancreatic enzymes.

Pathologic anatomy. Edema or necrosis and hemorrhage are prominent gross pathologic changes. Tissue necrosis is caused by activation of several pancreatic enzymes, including trypsin and phospholipase A_2. Hemorrhage is caused by extensive activation of pancreatic enzymes, including pancreatic elastase, which dissolves elastic fibers of blood vessels. In edematous pancreatitis, inflammation is usually confined to the pancreas, and the mortality rate is < 5%. In pancreatitis with severe necrosis and hemorrhage, inflammation is not confined to the pancreas, and the mortality rate is >= 10 to 50%.

Pancreatic exudate containing toxins and activated pancreatic enzymes permeates the retroperitoneum and at times the peritoneal cavity, inducing a chemical burn and increasing the permeability of blood vessels. This causes extravasation of large amounts of protein-rich fluid from the systemic circulation into "third spaces," producing hypovolemia and shock. On entering the systemic circulation, these activated enzymes and toxins increase capillary permeability throughout the body and may reduce peripheral vascular tone, thereby intensifying hypotension. Circulating activated

enzymes may damage tissue directly (eg, phospholipase A_2 is thought to injure alveolar membranes of the lungs).

Symptoms and Signs

In pancreatitis, pancreatic enzymes activate complement and the inflammatory cascade, thus producing cytokines. Patients typically present with fever and an elevated WBC count. It may thus be difficult to determine if infection is the cause or has developed during the course of pancreatitis.

Most patients suffer severe abdominal pain, which radiates straight through to the back in about 50%; rarely, pain is first felt in the lower abdomen. Pain usually develops suddenly in gallstone pancreatitis versus over a few weeks in alcoholic pancreatitis. Pain is severe, often requiring large doses of parenteral narcotics. The pain is steady and boring and persists without relief for many hours and usually for several days. Sitting up and leaning forward may reduce pain, but coughing, vigorous movement, and deep breathing may accentuate it. Most patients experience nausea and vomiting, at times to the point of dry heaves.

The patient appears acutely ill and is sweating. Pulse rate is usually 100 to 140 beats/min. Respirations are shallow and rapid. BP may be transiently high or low, with significant postural hypotension. Temperature may be normal or even subnormal at first but may increase to 37.7 to 38.3° C within a few hours. Consciousness may be blunted to the point of semicoma. Scleral icterus is occasionally present. Examination of the lungs may reveal limited diaphragmatic excursion and evidence of atelectasis.

About 20% of patients experience upper abdominal distention caused by gastric distention or a large pancreatic inflammatory mass displacing the stomach anteriorly (Fig.59).

Pancreatic duct disruption may cause ascites (pancreatic ascites). Abdominal tenderness always occurs and is often severe in the upper abdomen and less severe in the lower abdomen. Mild-to-moderate muscular rigidity may exist in the upper abdomen but is rare in the lower abdomen. The entire abdomen rarely exhibits severe peritoneal irritation in the form of a rigid board like abdomen. Bowel sounds may be hypoactive. The stool usually tests negative for occult blood.

Laboratory tests cannot confirm a diagnosis of acute pancreatitis but can support the clinical impression. Serum amylase and lipase

concentrations increase on the first day of acute pancreatitis and return to normal in 3 to 7 days.

The WBC count usually increases to 12,000 to 20,000/μL. Third space fluid losses may increase the Hct to as high as 50 to 55%, indicating severe inflammation. Serum bilirubin increases in 15 to 25% of patients because pancreatic edema compresses the common bile duct.

Supine and upright ***plain x-rays*** of the abdomen may disclose calculi within pancreatic ducts (evidence of prior inflammation and hence chronic pancreatitis), calcified gallstones.

Ultrasound should be performed; it may detect gallstones or dilation of the common bile duct, indicating biliary tract obstruction. Edema of the pancreas may be visualized, but overlying gas frequently obscures the pancreas.

CT usually offers better visualization of the pancreas (unless the patient is very thin). CT is recommended for severe pancreatitis or if a complication ensues (eg, hypotension or progressive leukocytosis and elevation of temperature). Although > 80% of patients with gallstone pancreatitis pass the stone spontaneously, ***ERCP*** with sphincterotomy and stone removal is indicated for patients who do not improve over the initial 24 h of hospitalization.

Prognosis

Pancreatitis associated with necrosis and hemorrhage has a mortality rate >= 10 to 50%. This diagnosis is suggested by a progressive decrease in Hct, presence of hemorrhagic fluid within ascites, reduction in serum Ca, and Grey Turner's sign (indicating extravasation of hemorrhagic exudate to the flanks or umbilical region, respectively) (Fig.59).

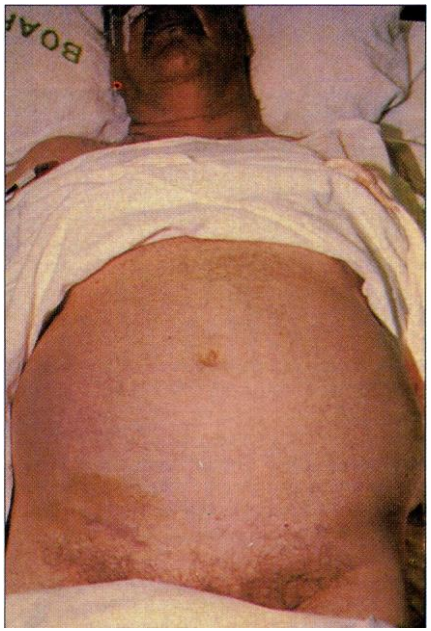


Fig.59. Grey Turner's sign in acute pancreatitis. This patient with severe acute pancreatitis presented with severe abdominal pain, distension and vomiting. Within 2 days of his admission, he developed characteristic discoloration in both flanks, which spread forwards to the iliac fossae. Grey Turner's sign results from the tracking of blood from the pancreatic area of the retroperitoneum.

If CT shows only mild pancreatic edema, the prognosis is excellent; a markedly swollen pancreas denotes a more severe prognosis, especially when extravasation of fluid (eg, within retroperitoneal spaces and lesser sac) or pancreatic necrosis is evident.

Treatment

Treatment of mild edematous pancreatitis aims to maintain the patient in a fasting state until manifestations of acute inflammation subside (ie, cessation of abdominal tenderness and pain, normalization of serum amylase, return of hunger and well-being) and to infuse sufficient IV fluids to prevent hypovolemia and hypotension. Insertion of a nasogastric tube and removal of gastric fluid and air are helpful if nausea and vomiting persist or ileus is present.

The need to treat severe acute pancreatitis in an ICU can frequently be determined on hospital day 1 by any of the following danger signals:

hypotension, oliguria, hypoxemia, or hemoconcentration (ie, Hct > 50%, indicating severe third space losses). Fasting is maintained for 2 wk and possibly 3 to 4 wk. A nasogastric tube usually counteracts vomiting and intestinal ileus. Parenteral H_2 blockers are given. Additional efforts to reduce pancreatic secretion with drugs (eg, anticholinergics, glucagon, somatostatin) have no proven benefit.

Heart failure should be treated by appropriate correction of volume status. Renal failure should be treated by increased fluid replacement if there is prerenal azotemia. Dialysis (usually peritoneal) may also be required.

Antibiotic use had been controversial.

The patient's nutritional needs must be adequately met. A seriously ill patient should not be fed for >= 2 to 3 wk (often 4 to 6 wk).

Surgical intervention during the first several days is justified for severe blunt or penetrating trauma.

CHRONIC PANCREATITIS

Etiology and Pathogenesis

Chronic pancreatitis most commonly results from alcoholism and idiopathic causes. Similar to acute pancreatitis, microlithiasis has been implicated in some cases of chronic pancreatitis. Rare causes are hereditary pancreatitis, hyperparathyroidism, and obstruction of the main pancreatic duct caused by stenosis, stones, or cancer. Rarely, severe acute pancreatitis causes sufficient pancreatic ductal stenosis to impair drainage and result in chronic pancreatitis. In India, Indonesia, and Nigeria, idiopathic calcific pancreatitis occurs among children and young adults.

Symptoms and Signs

Symptoms and signs may be identical to those of acute pancreatitis.

1. Pain syndrome – basic sign of chronic pancreatitis. Although there is occasionally no pain, severe epigastric pain may last many hours or several days. Possible causes include acute inflammation not recognized by conventional tests, distention of pancreatic ducts caused by strictures or calculi, a pseudocyst, perineural inflammation, or obstruction of either the duodenum or the common bile duct caused by fibrosis of the head of the pancreas. Pain appears early enough. In inflammatory process location in pancreatic head area

pains are felt mainly in the right epigastrium, right hypochondrium, radiate to the area of VI-XI thoracic vertebra. In pancreatic body involvement pains are localized in the epigastrium, pancreatic tail – in the left hypochondrium, at that pain radiates to the left and upwards from VI thoracic up to I lumbar vertebra.

In total pancreas involvement pains are localized in the whole of abdominal upper half and have engirdling character.

Mostly pains occur after abundant meals, particularly fatty, fried food, alcohol and chocolate consumption.

Often enough pains appear on fasting or 3-4 h after meal, that demands to differentiate from duodenal ulcer. Pains relieve on starvation, so many patients eat a little and lose weight (Fig.60).

There is definite diurnal rhythm of pancreatic pains: in the morning they bother not much, but in the afternoon they increase (or appear, if they were absent heretofore) and culminate in the evening.

Pains may be constricting, burning, gnawing; significantly more pronounced in supine position and decrease in sitting position leaning forward. In expressed exacerbation of chronic pancreatitis and severe pain syndrome a patient takes forced sitting position with bended in knee joints and adducted to the abdomen legs.

On abdominal palpation the following algesic zones and points are defined:

- ***Choffar's zone*** — between vertical line, passing through umbilicus and bisector of angle, formed by vertical and horizontal lines, passing through umbilicus. Tenderness in this zone is characteristic of pancreatic head inflammation;

- ***Gubergritz -Skoolsky's zone*** — is analogous Choffar's zone, but is situated at the left side. Tenderness in this zone is characteristic of pancreatic body inflammation;

- ***Dejardin's point*** — is situated 6 cm above umbilicus along the line, connecting umbilicus with the right axilla. Tenderness in this point is characteristic of pancreatic head inflammation;

- ***Gubergritz's point*** — is analogous Dejardin's point, but is situated on the left side. Tenderness in this point is characteristic of pancreatic tail inflammation;

- ***Mayo-Robson's point*** — is situated on the border of external and middle third of the line, connecting umbilicus and the middle of the left

costal arch. Tenderness in this point is characteristic of pancreatic tail inflammation;

- area of the ***left costovertebral angle*** — tenderness in this zone is characteristic of pancreatic body and tail inflammation.

Grot's sign is defined in many patients – atrophy of subcutaneous fat in the projection area of the pancreas on the anterior abdominal wall.

"Red drops" sign may be observed — presence of red spots on the abdominal, chest and back skin, and also brownish skin colouring above the pancreas area.

2. Dyspeptic syndrome (pancreatic dyspepsia) — is characteristic enough of chronic pancreatitis, particularly frequent it is expressed in exacerbation or severe course of disease. Dyspeptic syndrome is revealed by increased salivation, air or eaten food eructation, nausea, vomiting, loss of appetite, fatty food intolerance, flatulence.

3. Weight loss develops due to restrictions in diet (on starvation pains are decreased), and also owing to pancreatic exocrinous function disorders and intestinal absorption impairment (Fig.60). Loss of appetite also predisposes to weight loss. It is particularly expressed in severe forms of chronic pancreatitis and is accompanied by general weakness, and dizziness.

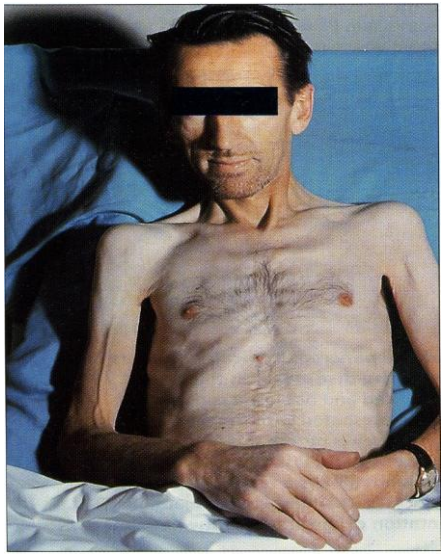


Fig. 60. Chronic pancreatitis. The patient had a history of recurrent episodes of abdominal pain, associated with chronic pancreatitis, and leading to laparotomy on one occasion. Over the previous 2 years he developed steatorrhoea and weight loss, associated with pancreatic exocrine dysfunction.

4. Pancreatic diarrheas and ***malabsorption and maldigestion syndromes*** are characteristic of severe and protracted forms of chronic pancreatitis with pronounced impairment of pancreatic exocrinous function. Diarrheas are caused by alterations of pancreatic enzymes release and intestinal digestion. Abnormal chyme content irritates intestine and causes diarrheas. Alteration of gastrointestinal hormones secretion also plays role. At that passing of big amount of bulky, foul-smelling pappy stools, greasy in appearance (steatorrhea) and particles of indigested food is characteristic.

Fig. 61. Typical steatorrhea. The stool is pale, with the consistency of pale clay. It often floats in the lavatory (because of its high air and fat content) and is difficult to flush away.

Major causes of steatorrhea are:

• pancreatic acinar cells destruction and decrease of pancreatic lipase synthesis and secretion;

• obturation of ductal system and alteration of pancreatic juice entry into duodenum;

• decrease of bicarbonate secretion by pancreatic ductal cells, decrease of duodenal pH and lipase denaturation under these conditions;

• bile acids precipitation due to decrease of duodenal pH.

In grave forms of chronic pancreatitis malabsorption and maldigestion syndromes develop, that leads to weight loss, dryness (xeroderma) and damage of skin, hypovitaminosis (insufficiency of A,B,E,K and other vitamins), dehydration, electolyte disbalance (decrease of blood Na, K, chlorides, Ca), anemia; fat (steatorrhea), starch (amylorrhea), and indigested muscular fibers (creatorrhea) are revealed in feces.

5. Incretory insufficiency is manifested as diabetes mellitus or impaired glucose tolerance.

6. Palpable pancreas. Pathologically changed pancreas is palpated in chronic pancreatitis in about 50% as horizontally located consolidated, sharply painful bundle, situated 4-5 cm above umbilicus or 2-3 cm above gastric greater curvature. On pancreas palpation pain may radiate to the back.

Classification.

I. Clinical forms.

1. *Latent (painless) form* — is observed in approximately 5% of patients and has clinical peculiarities:

• pains are absent or expressed slightly;

• periodically patients are troubled by non-pronounced dyspeptic disorders (nausea, food eructation, decrease of appetite);

• sometimes diarrheas or pappy stools appear;

• laboratory investigations reveal derangements of exocrine or endocrine pancreatic function;

• on systemic coprology (fecal) investigations steatorrhea, creatorrhea and amylorrhea are disclosed.

2. *Chronic recurrent (painful) form* — is observed in 55-60% of patients and is characterized by periodical onsets of intensive engirdling or epigastric pains, sometimes they may locate in the left hypochondrium. During exacerbation there is vomiting, enlargement and swelling of pancreas are observed (according to ultrasound and X-ray data), blood and urine amylase level is increased.

3. *Pseudotumourous (icteric) form* — is met in 10% of patients, more frequently in men. Inflammatory process is located in the pancreatic head, causing its enlargement and compression of common bile duct. The major clinical signs are:

• jaundice;

• pruritus (itching);
• epigastric pains, mostly in the right side;
• dyspeptic disorders (caused by exocrine insufficiency);
• dark urine;
• pale stools;
• significant weight loss;
• enlargement of pancreatic head (revealed by ultrasound).

4. *Chronic pancreatitis with permanent pain syndrome*. This form is characterized by steady pains in the upper abdominal half, radiated to the back; poor appetite, weight loss, unstable stool, flatulence. Enlarged and consolidated pancreas may be palpated.

5. *Sclerosing form of chronic pancreatitis*. This form is characterized by pains in the upper half of the abdomen, increasing after meal; poor appetite, nausea, vomiting, diarrheas, weight loss, pronounced disorders of exocrinous and endocrinous pancreatic functions. On ultrasound examination expressed consolidation and decrease of pancreatic dimensions are detected.

II. Degree of severity.

1. *Mild course* is characterized by following signs:
• rare and brief exacerbations (1-2 times a year), rapidly stopped;
• moderate pain syndrome;
• satisfactory patient's state of health out of exacerbation;
• no weight loss;
• pancreatic functions are normal;
• coprologic analysis is normal.

2. *Moderate course* has the following criteria:
• exacerbations 3-4 times a year with typical prolonged pain syndrome;
• pancreatic hyperfermentemia is detected; moderate decrease of exocrinous pancreatic function and weight loss are revealed; steatorrhea, creatorrhea, and amylorrhea are marked.

3. *Severe course* of chronic pancreatitis is characterized by:
• frequent and prolong exacerbations with persistent pain syndrome and pronounced dyspeptic syndrome;
• pancreatic diarrheas;

• weight loss down to cachexia, rough derangements of exocrinous pancreatic function;
• complications (diabetes mellitus, pseudocysts and pancreatic cysts, obturation of *ductus choledochus*, partial duodenal stenosis by enlarged pancreatic head, peripancreatitis etc.).
• disorder of major pancreatic duct emptying.

Examples of ***diagnosis wording:***

1. Chronic pancreatitis, recurrent form, moderate course, exacerbation period, complicated by pancreatic cysts.

2. Chronic pancreatitis, painful form, moderate course, exacerbation period; insulin-independent diabates mellitus, moderate gravity.

Diagnosis

Laboratory tests, including amylase and lipase, are frequently normal, probably because of significant loss of pancreatic function. Markers of inflammation (eg, WBC count) are generally minimally elevated as well.

Structural abnormalities can be visualized by plain x-ray of the abdomen (showing pancreatic calcification, which indicates intraductal stones) (Fig.62),

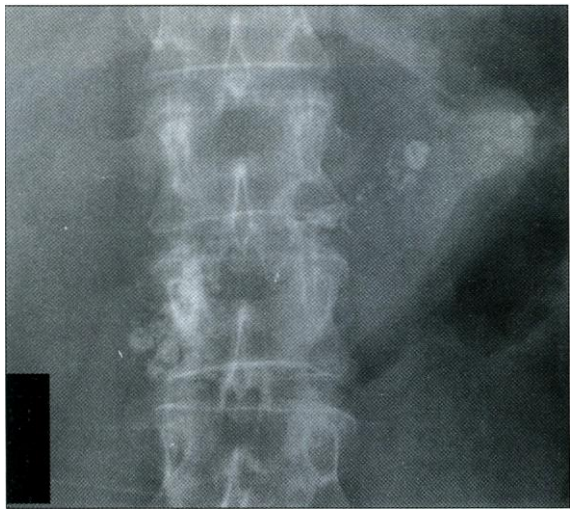


Fig. 62. Chronic pancreatitis. The plain X-ray shows calcification throughout the pancreas, especially evident in the head. This patient was a chronic alcoholic. Pancreatic calcification is most common in malnutrition-associated chronic pancreatitis, as seen in many parts of the developing world — often in association with diabetes.

abdominal ultrasound or CT (showing abnormalities in size and consistency of the pancreas, pancreatic pseudocyst, or dilated pancreatic ducts), and ERCP (showing abnormalities of the main pancreatic duct and secondary branches) (Fig.63).

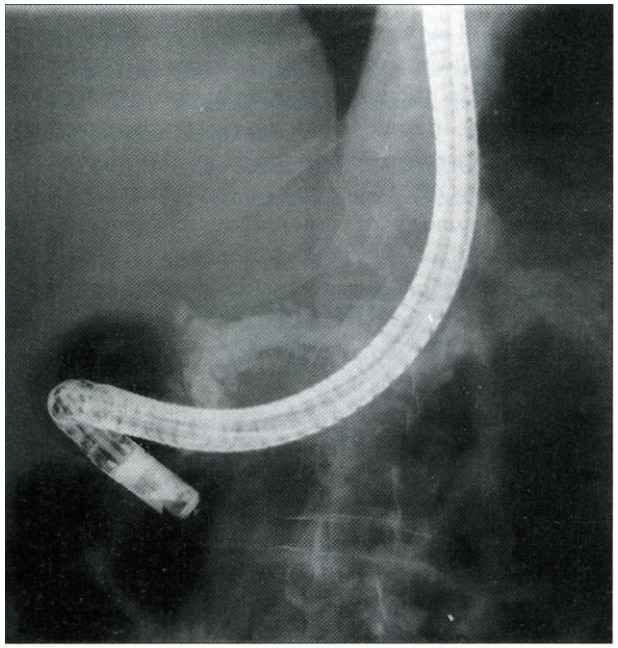


Fig. 63. Endoscopic retrograde cholangiopancreatography (ECRP) in severe chronic pancreatitis. The pancreatic duct is grossly dilated and irregular.

However, these imaging studies may be normal in the first few years of disease.

Tests of pancreatic function assess ***endocrine*** and ***exocrine*** function. Diabetes mellitus is present if a 2-h postprandial serum glucose level is > 11.1 mmol/L or two fasting serum glucose levels are > 6.66 mmol/L.

The most sensitive test of pancreatic exocrine function, the secretin test, is unavailable in most hospitals. It involves positioning a tube in the duodenum and collecting pancreatic secretions stimulated by IV secretin alone or with cholecystokinin. Duodenal contents are collected for volume determination, HCO_3 concentration, and enzyme concentration.

A collection that is of normal volume (> 2 mL/kg) and low in HCO_3 (< 80 mEq/L) suggests chronic pancreatitis; low volume (< 2 mL/kg), normal HCO_3 (> 80 mEq/L), and normal enzyme levels suggest pancreatic duct obstruction, perhaps secondary to tumor, and should prompt ERCP.

A 72-h test for stool fat is insensitive for pancreatic exocrine dysfunction because steatorrhea does not occur until lipase output is < 10% of normal. Other, more sensitive tests include measurement of serum trypsinogen, fecal chymotrypsin, and urinary p-aminobenzoic acid (bentiromide test).

Treatment

A relapse of chronic pancreatitis may require treatment similar to that of acute pancreatitis. The patient must eschew alcohol. At times, IV fluids and fasting prove beneficial. Dietary measures of uncertain benefit include small feedings restricted in fat and protein (to reduce secretion of pancreatic enzymes) and an H_2 blocker or antacids (to reduce acid-stimulated release of secretin, increasing the flow of pancreatic juice). Too often, these measures do not relieve pain, requiring increased amounts of narcotics, with the threat of addiction. Medical treatment of chronic pancreatic pain is often unsatisfactory.

There has been recent interest in the use of potent pancreatic enzymes to treat chronic pain because enzymes given in quantity inhibit the release of cholecystokinin from the duodenal mucosa, thereby reducing the secretion of pancreatic enzymes. The use of pancreatic extracts to ameliorate chronic pancreatic pain appears to be more successful in mild idiopathic pancreatitis than in alcoholic pancreatitis. Because the duodenum requires high-dose enzymes, sustained-release preparations are not effective in relieving pain. Octreotide, a long-acting somatostatin analog, has also been examined to "rest" the pancreas. However, pain relief appears minimal.

Steatorrhea can be improved, but rarely abolished, with four to six tablets of potent pancreatic extracts with meals. Although non-sustained-release pancreatic extracts may be enhanced by H_2 blockers to reduce intragastric acidity and thereby protect enzymes that are denatured in an acid milieu, sustained-release preparations (one to three capsules with meals) are generally effective alone. Favorable clinical responses include weight gain, fewer daily bowel movements, elimination of oil droplet

seepage, and improved general well-being. Clinical response can be measured by comparing tests for stool fat before and after enzyme therapy. Supplementation with fat-soluble vitamins (A, D, K) is sometimes required.

Oral hypoglycemic drugs rarely help treat diabetes mellitus caused by chronic pancreatitis. Insulin should be given cautiously because the coexisting deficiency of glucagon secretion by α-cells means that the hypoglycemic effects of insulin are unopposed and prolonged hypoglycemia may occur. Diabetic ketoacidosis rarely occurs in chronic pancreatitis. For most patients, serum glucose levels of 200 to 250 mg are acceptable and do not require treatment; it is better to maintain the patient in a slightly hyperglycemic range than to risk hypoglycemia caused by overzealous administration of insulin.

Patients with chronic pancreatitis are at increased risk for pancreatic cancer. Worsening of symptoms, especially with development of a pancreatic duct stricture, should prompt an examination for malignancy. This may include brushing of strictures for cytologic analysis or measurement of serum markers.

CONTROL QUESTIONS.

1. Complaints of patients with acute and chronic pancreatitis
2. Eiology and pathogenesis of pancreatitis
3. Physical examination data in patients with acute pancreatitis
4. Physical examination data in patients with chronic pancreatitis
5. Instrumental diagnostics of pancreatitis
6. Laboratory data in diagnostics of pancreatitis
7. Diagnostics of pancreatic exocrinous insufficiency

Theme 33. CONTROL SUMMING-UP

Goal: to check-up knowledge and practical skills of the main pulmonary syndromes and diseases diagnostics.

Knowledge objectives:
- to know educational materials to themes 30-32.

Skill objectives:
- to perform inspection, auscultation, percussion and palpation of patients; to interpret data of additional diagnostic methods.

Equipment required: stethoscope.

Classes include control tests according to themes 30-32 and work-up with patients on bedside. Physical examination skills will be assessed.

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