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with chronic abdominal pain

Guidelines for students and interns

Модуль 3. Внутрішня медицина.
Змістовний модуль № 3.
Тема 4. Ведення хворих з хронічним
абдомінальним болем

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для студентів та лікарів-інтернів

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CHRONIC ABDOMINAL PAIN

General Outcome

The students should be able to list and describe different conditions which can cause chronic abdominal pain, manage the main investigations differentiating it's causes, know modern strategies of diagnostics and treatment of chronic abdominal pain, manage psychosocial presentations of chronic abdominal pain.

Student must know:

- Modern standarts of diagnostics and treatment of patients with chronic abdominal pain.
- Differential diagnosis of different causes of abdominal pain.
- Drawing the plan of appropriate investigations.
- Role of instrumental and laboratory methods of investigations.
- Strategy of management of patients with chronic abdominal pain depending on etiological factors.
- Conservative and surgical treatment.
- Following management of patients.
- Prognosis and working capacity.

The evaluation of any patient with a complaint of abdominal pain is challenging. Abdominal pain can be benign and self-limited or a harbinger of a serious life-threatening disease. Chronic abdominal pain poses a particularly challenging clinical problem. Not only is the management of chronic abdominal pain a frequently daunting task, but also the possibility of overlooking a structural or organic disorder is always a concern. Many disorders discussed elsewhere in this text can produce chronic abdominal pain (*table 1*). Many of these diagnoses require careful consideration and clinical interrogation, in addition to appropriate diagnostic testing, to discern whether the entity is indeed the cause of the patient's pain. Diagnosis of a functional gastrointestinal disorder is generally considered once potential causes of organic chronic abdominal pain have been confidently excluded. Although the causes of chronic abdominal pain are varied, the pathophysiologic pathways that produce chronic pain are common to many of them. Functional abdominal pain syndrome (FAPS) serves as a model to illustrate many of the complex issues involved in caring for patients with chronic abdominal pain.

Table 1.

Differential Diagnosis of Chronic or Recurrent Abdominal Pain

Structural (or Organic) Disorders
Inflammatory: appendicitis, celiac disease, eosinophilic gastroenteritis, fibrosing mesenteritis (mesenteric panniculitis), inflammatory bowel diseases, pelvic inflammatory diseases, primary sclerosing cholangitis
Vascular: celiac artery syndrome, mesenteric ischemia, superior mesenteric artery syndrome
Metabolic: diabetic neuropathy, familial Mediterranean fever, hereditary angioedema, porphyria,
Neuromuscular: anterior cutaneous nerve entrapment syndrome, myofascial pain syndrome, slipping rib syndrome, thoracic nerve radiculopathy
Other: abdominal adhesions, abdominal neoplasms, anaphylaxis, chronic pancreatitis, endometriosis, gallstones, hernias, intestinal malrotation, intestinal obstruction, lactose intolerance, peptic ulcer disease, small intestinal and pelvic lipomatosis
Functional Gastrointestinal Disorders: biliary pain (gallbladder or sphincter of Oddi dysfunction, functional abdominal pain syndrome, functional (nonulcer) dyspepsia, gastroparesis, irritable bowel syndrome, levator ani syndrome

DEFINITION AND CLINICAL APPROACH

Abdominal pain is considered **chronic** when it has been occurring constantly or intermittently over at least six months. Abdominal pain is considered **acute** when it has been occurring for several days and **subacute** when it has been occurring more than several days but less than 6 months. These arbitrary definitions are often helpful when formulating a differential diagnosis. The clinician initially must adopt a broad-based approach, which necessarily becomes more focused as the evaluation ensues. Importantly, although typical patterns of presentation are useful to remember, some patients, especially immunosuppressed and older persons, may present with atypical features.

STEP-BY-STEP DIAGNOSTIC APPROACH

Assessment includes 4 major components:

1. History.
2. Physical examination.
3. Psychosocial assessment.
4. Investigations.

1. The sensitivity of **history** and physical examination are low. Epigastric pain and gastroduodenal pathology, RUQ pain and hepatobiliary pathology, and suprapubic pain and gynaecological pathology are the only findings with specificity >50%. The physical examination should be integrated with findings from the history and other collateral information to focus the diagnostic work-up on possible diagnoses.

Pain may arise from any system, including the genitourinary, gastrointestinal, and gynecologic tracts. The aetiology of chronic abdominal pain is so wide that only the more common causes can be covered here.

Anyhow, the initial step in evaluating a patient with chronic abdominal pain is to elicit a detailed history from the patient. The chronology of the pain, including its abruptness of onset and duration, and its location and possible radiation should be determined. Visceral pain emanating from the digestive tract is perceived in the midline, because of the relatively symmetrical bilateral innervation of the organs, but is diffuse and poorly localized. Referred pain is ordinarily located in the cutaneous dermatomes that share the same spinal cord level as the affected visceral inputs. The patient should be questioned about the intensity and character of the pain, with the understanding that these parameters are subjective. The patient's perception of precipitating, exacerbating, or mitigating factors may be useful when diagnostic possibilities are considered.

Symptoms assessment: The localisation of pain from abdominal viscera, especially the small bowel, is imprecise. Most of the digestive tract is perceived in the midline due to its symmetric innervation. Exceptions include pathologies of the ascending/descending colon and gallbladder, which may present with one-sided pain due to unilateral innervation. The location of pain and the patient's perception of the anatomical distribution can sometimes help to narrow the differential diagnosis and guide diagnostic evaluation:

Epigastric and upper abdominal pain can indicate oesophageal (e.g., gastro-oesophageal reflux), stomach (e.g., gastritis), duodenal (e.g., ulcer), gallbladder (e.g., cholecystitis), or pancreatic (e.g., pancreatitis) origin.

Lower abdominal pain can indicate large bowel involvement, and lateralisation may help to distinguish between descending/sigmoid colon (e.g., left-sided diverticulitis) and ascending/caecum (e.g., Crohn's ileocolitis), or appendix (e.g., appendicitis).

Pelvic pain can suggest gynaecological origin (e.g., ovarian cysts, PID) or chronic pelvic pain syndrome (e.g., interstitial cystitis, endometriosis, urethral syndrome, or changes and dysfunction of the pelvic muscles).

Localised point of maximal pain in the anterior abdomen can indicate chronic abdominal wall pain or abdominal cutaneous nerve entrapment syndrome. Localised pain can also arise at specific sites such as the kidneys, ureters, and ovaries, or from a source of focal peritoneal irritation.

Information about exacerbating and relieving factors may provide further clues: Pain made worse by eating (postprandial pain) may indicate gastric ulcer, chronic pancreatitis, gallstones, abdominal ischaemia (also called abdominal angina), or functional disorders such as irritable bowel syndrome, functional dyspepsia, or postprandial distress syndrome (postprandial fullness). Pain relieved by eating suggests duodenal peptic ulcer disease. Pain relieved by

defecation may indicate irritable bowel syndrome. Pain associated with menstrual cycle suggests gynaecological origin. Additional symptoms of dyspareunia, dysmenorrhoea, pain with defecation, and infertility suggest endometriosis. Pain associated with urinary urgency and frequent urination suggests interstitial cystitis. Pain in the anterior abdomen that is accentuated by physical activity can indicate chronic abdominal wall pain or abdominal cutaneous nerve entrapment syndrome.

Pain due to organic conditions (e. g., ulcers, cholelithiasis, pancreatitis) is generally circumscribed, unlike pain due to functional disorders. Radiation of the pain to the shoulder indicates cholelithiasis, to the inguinal and genital region nephrolithiasis, to the back, pancreatic diseases, aortic aneurysm, or ulcer penetration).

Increased pain while lying down occurs with reflux disease and pancreas diseases. More intense pain while standing occurs with hernias. Increased pain with movement indicates abdominal wall processes (such as trauma), vertebrogenic pain (such as discopathy), or reflux disease.

When initially attempting to determine whether the patient's pain is caused by an organic or functional process, the clinician should search for clues in the patient's history and physical examination that support or refute the diagnosis of a progressive, serious, chronic underlying illness. Such features in the history include fever, night sweats, appetite change, weight loss, and nocturnal awakening.

2. Physical examination. The physical examination should first focus on the vital signs. Fever, tachycardia, tachypnoea, and hypotension suggest an acute illness requiring urgent evaluation. A head and neck examination is useful for non-specific signs of intra-abdominal pathology, including: temporal wasting, sunken eyes, and prominent clavicles, suggesting significant weight loss; dry mucosal membranes, indicating volume depletion; icteric sclera, indicating hepatobiliary disease; pale conjunctiva, suggesting anemia. Peripheral vascular disease is suggested by diminished pulses and may co-exist with intestinal angina or mesenteric ischaemia. Pain on deep inspiration suggests referred pain from the lungs or RUQ/LUQ pain.

The abdominal examination should use a combination of inspection, auscultation, percussion, and palpation. The most critical step for a patient with an acute exacerbation of chronic abdominal pain is to ascertain promptly whether a surgical abdomen is present. Although most causes of chronic abdominal pain do not require immediate surgical treatment, a complication related to a disease process ordinarily associated with chronic abdominal pain may present acutely (e.g., intestinal perforation in a patient with inflammatory bowel disease). Furthermore, a patient who has experienced chronic abdominal pain may present with acute pain related to another disease process (e.g., acute

mesenteric ischemia in a patient with underlying irritable bowel syndrome [IBS]). The abdomen should be auscultated to detect an abdominal bruit, because the presence of a bruit may suggest chronic mesenteric ischemia (intestinal angina). Abdominal palpation for the presence of organomegaly, masses, and ascites and examination for hernias are particularly pertinent.

In some cases examination is unremarkable, but rebound tenderness, guarding, or tenderness on palpation require urgent consideration. Precise localisation of the pain in the anterior abdomen with positive Carnett's sign (i.e., increase of pain/tenderness on re-palpation during contraction of abdominal muscles, suggesting abdominal wall origin) can help to differentiate between abdominal wall pain and intra-abdominal pathology. Careful rectal examination and pelvic examination are part of a thorough evaluation. Bleeding, diarrhoea, discharge/mucus, tenderness, rectal masses, or obstruction can provide important additional clues for underlying disease processes. In females with pelvic/lower abdominal pain, gynaecological examination should be considered.

Other physical findings that suggest an underlying organic illness include signs of malnutrition (e.g., muscle wasting or edema), vitamin deficiencies, or extraintestinal processes (e.g., arthropathy or skin changes). Although not entirely specific, the closed eyes sign is often seen in patients with FAPS. Physical examination should include skin and mouth for non-specific findings such as ulcers, vesicles, angiomas, bleeding or bruising, or specific lesions (e.g., erythema nodosum).

The pelvic girdle, lower back, and thorax (ribs and spine) should be examined, since this may yield clues about symptoms wrongly attributed to abdominal organs.

3. Psychosocial assessment. The association between chronic abdominal pain and a history of PTSD, abuse, somatisation, anxiety, and depression is well recognised. Evaluation of psychosocial factors can help to determine an appropriate management plan and minimise unnecessary investigations. Affective disturbance can both result from and contribute to the experience of chronic pain. Clinical presentation, symptom severity, and response to treatment can all vary according to mental state abnormalities. Symptom fluctuations and mental state should be monitored closely.

4. Investigations. Specific algorithms for the diagnostic work-up of chronic abdominal pain do not exist. Appropriate investigations should be tailored to history and examination findings and be made on a case-by-case basis. In the absence of alarm features, laboratory and imaging tests should be ordered in a conservative and cost-effective manner.

1. Laboratory

The laboratory evaluation can be helpful, but the clinician must first distill pertinent facets of the history and physical examination to focus the labora-

tory assessment. Injudicious use of laboratory testing is costly and can confuse the clinical picture and even lead to complications. It is worth emphasizing that an abnormal laboratory test result does not necessarily prove causality in relation to a patient's chronic pain syndrome. The clinician must exercise the utmost discretion when ordering and interpreting the results of laboratory tests. The patient should be asked about previous investigations as, owing to the chronicity of their symptoms, many patients will already have been investigated and existing information may be available for review.

Standard laboratory tests include:

- FBC with differential, to screen for infection or anaemia. The platelet count and ESR may signify an inflammatory process.
- Serum electrolytes, glucose, creatinine, and urea for metabolic causes.
- Liver function tests, lipase, and amylase, particularly in patients with upper abdominal pain.
- Urine analysis and urine culture to help exclude UTI and interstitial cystitis.

Additional laboratory tests based on the individual case include:

- Stool tests for culture, ova and parasites, and Giardia antigen should be done if bacterial, parasitic, or protozoal cause of abdominal pain is suspected.
- Urine or serum pregnancy test: this should also be done prior to radiographic or endoscopic investigations.
- Serology testing for *Helicobacter pylori* in patients with upper GI symptoms, including early satiety and epigastric discomfort (i.e., dyspeptic symptoms).
- Vaginal swabs, pap smears, beta-human chorionic gonadotropin, prostate-specific antigen, and urine cytology can be helpful in certain cases with pelvic and lower abdominal pain.

2. Endoscopy

Endoscopic and imaging studies have important roles in diagnosing and excluding many causes of chronic abdominal pain. Upper endoscopy and colonoscopy, as well as capsule endoscopy, may be indicated in selected cases. Available imaging investigations include barium and radionuclide studies, ultrasonography, computed tomography, magnetic resonance imaging, positron emission tomography (PET), and conventional angiography. The indications for each of these radiologic investigations differ, as do their potential to clarify an individual clinical situation.

All patients >50 years old with abdominal pain should have a GI tract endoscopy.

Colonoscopy is indicated if the pain is in the lower abdomen and/or it is associated with changes in bowel habit.

Upper endoscopy is indicated if the pain is localised in the upper abdomen, particularly if other upper GI symptoms (early satiety, nausea, vomiting) are present. There are no guidelines suggesting when these tests in younger (<50 years old) patients should be ordered.

3. Imaging

Further investigations depend on the clinical findings.

Upper abdominal ultrasound may be indicated to evaluate RUQ or epigastric pain, particularly if elevated liver or pancreatic enzymes are found.

Pelvic abdominal ultrasound and transvaginal and/or transrectal ultrasound is indicated for evaluating lower abdominal pain.

CT scanning can help to evaluate dilated intestinal loops; exclude partial intestinal obstruction; detect abnormalities in other abdominal organs (e.g., pancreas, liver, kidneys); identify inflammatory processes (e.g., inflammatory bowel disease, diverticulitis, abscesses); and investigate retroperitoneal or pelvic masses.

If all investigations are negative, the likely diagnosis is a **functional GI disorder**. The diagnosis of specific functional disorders depends on the presence and characteristics of additional associated symptoms. Irritable bowel syndrome and functional dyspepsia are the most common causes of chronic abdominal pain in adults.

If the pain is located in the abdomen rather than the pelvic region, and is not related to food intake or defecation, a diagnosis of functional abdominal pain syndrome (FAPS) may be appropriate. FAPS, also called chronic idiopathic abdominal pain or chronic functional abdominal pain, describes recurrent, continuous or near-continuous abdominal pain not related to gut function, associated with loss of daily activities, and present for >6 months. Like other functional GI disorders, FAPS cannot be explained by structural or metabolic disorders, and it is believed to be related to altered pain perception and pain modulation circuits.

CAUSES OF CHRONIC ABDOMINAL PAIN ACCORDING TO THEIR ORIGIN

Pain Originating from the Stomach and Small Intestine

Distribution. Pain originating from the stomach and small intestine can be generally classified as follows:

- chronic gastritis
- functional gastric disorders (gastric irritation)
- ulcerous disease (duodenal ulcer, gastric ulcer)
- gastric carcinoma
- rare disorders
- complaints secondary to general diseases.

Diagnosis. The differential diagnosis is based on the *medical history*, clinical findings, *imaging* (endoscopy, radiologic examination), and biopsy with a histologic analysis.

A detailed medical history is particularly important in gastric diseases. Functional stomach disorders (irritable stomach) are characterized by their relatively indefinite character. They generally occur irregularly and have no periodicity. The pain is frequently accentuated immediately after eating.

Endoscopy is most important for diagnosis of obscure epigastric pain, dysphagia, heartburn, and gastrointestinal bleeding. Another indication is an unclear iron deficiency anemia. *Radiologic examinations* are helpful, particularly in cases of paraesophageal hiatus hernia, motility disorders, Zenker diverticulitis, external compression, or stenoses that cannot be detected endoscopically.

Endosonography can be used to detect intramural processes, especially the extent and depth of infiltration of neoplasms, as well as lymph node metastases.

Chronic Gastritis

Type A, B and C gastritis must be distinguished.

Type A Gastritis. Type A gastritis (autoimmune gastritis) primarily affects the gastric body and fundus. It is caused by autoimmune processes. It is typically associated with pernicious anemia. Autoantibodies against parietal cells and intrinsic factor are typical. Gastrin is increased. The risk of development of a gastric carcinoma is significantly increased in chronic-atrophic type A gastritis. Endoscopic surveillance is therefore indicated.

Type B Gastritis. Type B gastritis (bacterial gastritis) is primarily localized in the gastric antrum and is typically caused by *Helicobacter pylori* (Hp). It is more common than type A gastritis and is associated with gastric ulcers, duodenal ulcer, and mucosa-associated lymphoid tissue (MALT) lymphoma.

Type C Gastritis. Type C gastritis (chemical gastritis) is caused by chemical irritation, i. e., reflux of bile (bile gastritis) or duodenal contents (reflux gastritis) and most importantly drugs, in particular use of NSAIDs (NSAID gastropathy).

Rare Cases of Gastritis. Rare, chronic forms of gastritis are lymphocytic, eosinophilic, and granulomatous gastritis.

Diagnosis. Chronic gastritis can only be confirmed by histology. There is no clear relationship to typical clinical symptoms. The majority of patients with histologically demonstrated chronic gastritis are asymptomatic.

Functional Dyspepsia

Continuous epigastric pain, loss of appetite, nausea, and frequent vomiting are the main symptoms. Eating tends to exacerbate the symptoms and there is generally no periodicity or diurnal rhythm. This information from the medical history generally distinguishes this complaint from an ulcer. The lack of the

typical endoscopic changes with irritable stomach is decisive for differential diagnosis.

Ulcers

The central feature of ulcers is infection with **Helicobacter pylori** (Hp). There has been a radical change in the understanding of ulcers. The eradication of the Hp infection in patients with ulcers not only heals the acute lesion but generally prevents recurrence and complications of ulcers. Only about 10% of patients infected with Hp in industrialized countries develop an ulcer, but 95% of patients with a duodenal ulcer are infected with Hp.

This indicates that Hp infection alone is not sufficient to cause an ulcer. Hp generates conditions that, together with additional risk factors, cause an ulcer: stress, smoking, and a genetic predisposition.

Helicobacter pylori Detection. The presence of Hp can be confirmed

histologically by Giemsa or Warthin–Starry staining of gastric antrum biopsies

by *urease activity* either with a fast urease test in the biopsy specimen or an exhalation test with ¹³C or ¹⁴C labeled urea

by *culture* from gastric antrum biopsies

by *serology*: serology is, however, not generally useful, because Hp colonizes approximately 10% of persons under 30 and approximately 60% of persons of 60 years, while only 10% of infected persons develop an ulcer.

Clinical Features and Differential Diagnosis. Strongly *localized pain* is characteristic for ulcers, as compared to irritable stomach and acute gastritis. In acute gastritis a diffuse pain upon palpation is generally present in the epigastric region. Many patients with ulcers can point to the exact location of the spontaneous pain and the pain upon palpation. The maximum pain is to the left of the abdominal mid-line with gastric ulcers and to the right with duodenal ulcers.

The character of the pain is important in differential diagnosis versus biliary colic (period and diurnal rhythm of the pain). The pain characteristics and the diurnal rhythm typical for ulcers are particularly important. A biliary colic lasts for one to three days, ulcer pain for three to five weeks. Ulcer pain generally disappears after eating within a few minutes while biliary pain does not. Ulcer pain is virtually never accompanied by nausea while nausea is very frequent with biliary diseases. Appetite is not affected, unlike with gastritis and carcinoma. If the character of the pain is not typical in spite of other signs of an ulcer, the possibility of complications must be considered:

with continuous and back pain: penetration

with nausea and vomiting: stenosis.

An ulcer episode, like acute gastritis, can be triggered by stress situations (surgery, serious trauma), alcohol abuse, or drugs (including NSAIDs).

Ulcers occur at all ages, particularly after puberty. Carcinoma incidence increases with age but can also be observed in 20- to 30-year-olds.

Diagnosis. The mainstay of ulcer diagnosis is *endoscopy*. Multiple biopsies from and around the ulcer are key for differentiating benign from malignant stomach ulcers.

Radiologic diagnosis is no longer common, but when performed, an *ulcer niche*, may be visible under tangential setting as a contrast agent bulge in the region of the gastric curvature. The ulcer niche is visible as a persistent contrast spot in the direct frontal view. About 85% of ulcer niches are on the minor curvature of the stomach. The remaining 15% occur at the major curvature, the dorsal wall (back pain), and in the pyloric region. Gastric carcinomas can also form niches. *Indirect ulcer signs* are *spastic retractions* on the wall opposite the ulcer, referred to as ulcer fingers. They are not specific for ulcers, because they are also observed with various tumors. After healing an *hourglass stomach* may develop, which results from shrinkage of the minor curvature by scar tissue and spastic retraction of the major curvature.

Duodenal Ulcer. More than 95% of duodenal ulcers occur in the duodenal bulb. Untreated they are characterized by spontaneous healing and recurrence. 60% of untreated cases recur within one year and 80–90% within two years. 95–100% are associated with Hp infection.

The main symptom is pain, that typically occurs 90 minutes to three hours postprandial and is relieved by eating (food relief). Asymptomatic ulcers are common.

Complications are penetration, particularly into the pancreas (constant pain in the back), stomach outlet obstruction (pain increased postprandially, vomiting), perforation, and hemorrhage.

Postbulbar ulcers are rare. The clinical symptoms correspond to the classical duodenal ulcer, but postbulbar ulcers bleed more frequently.

Gastric Ulcer. The peak incidence of gastric ulcers is in the sixth decade of life and thus about 10 years later than with duodenal ulcers. Men are affected more frequently than women. Benign gastric ulcers are most commonly localized adjacent to the corpus–antrum border. Gastric erosions and ulcers are often caused by NSAIDs. Gastric ulcers not associated with NSAIDs are generally caused by Hp infection. The pain is less typical than in duodenal ulcers and increases after eating. Nausea and vomiting occur even without gastric outlet obstruction, in contrast to the duodenal ulcer. Asymptomatic courses are common.

It is important to note that gastric ulcers, much more commonly than duodenal ulcers, can be caused by carcinoma. Histologic diagnosis is therefore mandatory and the healing must be monitored endoscopically.

Ulcer Associated with Other Diseases. *Duodenal ulcer*, is frequently observed in patients with: cirrhosis of the liver, chronic obstructive jaundice, chronic pancreatitis, chronic lung disease, especially emphysema, chronic renal insufficiency, general arteriosclerosis, polycythemia vera, hyperparathyroidism, systemic mastocytosis.

Gastric ulcers, are frequently observed: with NSAID use, in smokers, after chemotherapy.

Use of aspirin and other NSAIDs causes gastric ulcers much more frequently than duodenal ulcers. Ulcers and strictures of the small and large intestine also occur.

Stress-induced Erosions. Stress-induced erosions and ulcers are often multiple and frequently occur in areas of the stomach with high activity, after shock, massive burns (Curling ulcer), sepsis, and after serious trauma.

Hemorrhage is frequent, particularly in patients on respirators and with coagulation disorders.

Cushing Ulcer. Gastric ulcers frequently occur after brain trauma, brain surgery, or in patients with elevated brain pressure (Cushing ulcer).

Zollinger–Ellison Syndrome. Ulcers are a complication of Zollinger–Ellison syndrome. Gastrinomas (most frequently originating from non- β -pancreatic islet cells or duodenal G cells), through overproduction of gastrin, increase secretion of gastric acid and are thus responsible for the formation of ulcers. Zollinger–Ellison syndrome should be considered in the following situations:

- peptic ulcers with atypical localization (esophagus, postbulbus, jejunal), multiple occurrence (approximately 10%), and resistance to treatment.

- aqueous diarrhea, with or without steatorrhea, with or without hypokalemia and its consequences.

- gastric hypersecretion and increased serum gastrin levels.

- prominent gastric mucosa folds, as with Menetrier disease

- 25% of cases are associated with multiple endocrine adenomatosis type I (Wermer syndrome). Zollinger–Ellison syndrome must be considered in patients with signs of hyperparathyroidism or hypophyseal tumor. The family medical history is particularly important in view of the inheritance.

- Fasting serum gastrin levels are elevated. Massive hyperchlorhydria and hypergastrinemia (> 1000 pg/mL) are diagnostic. Increased serum gastrin levels are also found in achlorhydria (e. g., pernicious anemia, after vagotomy, stomach resection). In Zollinger–Ellison syndrome serum gastrin levels increase significantly in response to calcium infusion or after secretin administration. These provocation tests are useful for identification of Zollinger–Ellison syndrome in patients with borderline serum gastrin levels (200–1000 pg/mL).

Late Complications of Ulcer Disease. *Pyloric Stenosis.* Pyloric stenosis is a late complication of chronic recurring ulcers. The character of ulcer pain is changed and loss of appetite occurs. Feelings of fullness and discomfort after meals, which are not present in uncomplicated ulcers indicate stenosis. A stenosis is very likely with vomiting that relieves or cures late pain and with vomiting of food from the previous day. If endoscopic examination identifies empty stomach secretion and food 12 hours after eating, this supports the diagnosis.

Food and liquid retention can often be detected by sonography. The diagnosis is confirmed radiologically by slow pyloric passage, dilatation of the stomach, and marked dilution of the contrast agent by stomach secretion and food residues. The nature of the pyloric stenosis (benign or malignant) can generally be defined by endoscopy and histology.

Gastric Carcinoma. *Epidemiology and Risk Factors.* 85% of malignant tumors in the stomach are adenocarcinomas. They can grow as space-filling processes or diffusely infiltrate the stomach wall (linitis plastica). Non-Hodgkin lymphoma and leiomyosarcoma are malignant gastric tumors. Nitrates in food, which are converted to carcinogenic nitrites by bacteria, play an important role in the development of the gastric carcinoma. Hp infection also seems to play a significant role. Patients with chronic atrophic type A gastritis are at particular risk for carcinoma. Gastric carcinomas are more frequent in patients with blood group A.

Clinical Features. In contrast to ulcers, the symptoms of gastric carcinoma are less typical. They start slowly, are uncharacteristic, and are not periodic. There is generally no history of stomach complaints. Typical features are the persistence or progression of the complaints and the appearance of general symptoms, particularly weakness (anemia) and weight loss. Iron-deficiency anemia frequently precedes the local symptoms by weeks or months. In contrast to ulcer symptoms, carcinoma pain is not relieved by antacids and is not periodic. In about one-quarter of cases there is no pain, but rather unspecific complaints (feeling of fullness, discomfort, belching, nausea). In other cases the complaints are more diffuse, e. g., loss of appetite and weight loss. Vomiting is typical for tumors in the antrum or cardia. Cardiac carcinoma extending to the esophagus typically causes dysphagia.

Diagnosis. The carcinoma is generally *palpable* only in advanced cases. The early cases are either not sensitive to palpation or present with diffuse pain. A Virchow gland above the left clavicle is typical for advanced gastric carcinoma.

Endoscopy and histology are usually diagnostic. If endoscopy suggests gastric carcinoma, a negative biopsy does not rule out a carcinoma. Close endoscopic-histologic monitoring is necessary for early detection of gastric carcinoma. Failure of an ulcer to heal after four to eight weeks of medical therapy or early recurrence are indications for a malignant or complicated ulcer.

Detection of early cancer by endoscopy improves prognosis. Early cancer, defined as carcinoma restricted to mucosa and submucosa, is generally cured by surgery.

Rare Gastric Diseases. *Malignant Lymphoma.* Malignant lymphoma is similar to gastric carcinoma. Primary gastric lymphoma is rare.

However, the stomach is the most common extranodal localization of a non-Hodgkin lymphoma. The prognosis of malignant lymphoma is significantly better than that of gastric carcinoma. Infection with Hp is associated with the development of gastric lymphoma, particularly the MALT lymphoma. The eradication of the Hp infection causes a regression of the MALT lymphoma in about 50% of patients.

Lymphoma of the small intestine can also be a complication of sprue.

Leiomyoma. This tumor is rare (approximately 1% of all tumors). The most important clinical symptom is hemorrhage. Endoscopy and radiography show a semispherical, well-circumscribed tumor with central ulceration.

Gastrointestinal Stroma Tumors (GIST). GIST are mesenchymal tumors of the gastrointestinal tract, 60–70% of which are localized in the stomach. They were until recently frequently classified as leiomyomas or leiomyosarcomas, but have a specific cellular origin and a specific pathogenesis. GIST are identified by mutations of the *cKIT* protooncogene and activation of the KIT receptor tyrosine kinase, and like chronic lymphatic leukemia, respond to treatment with the specific tyrosine kinase inhibitor imatinib mesylate.

Intestinal Polyposis. In contrast to Menetrier disease, gastric mucosa with intestinal polyposis shows a predominantly normal, smooth aspect with diffusely distributed individual polyps at endoscopy. Gastric polyps are more frequent in patients with chronic atrophic gastritis, particularly in pernicious anemia. The complaints are uncharacteristic. Depending on the extent and location of the tumors, the polyps may be asymptomatic, may present as gastritis, or result in sudden stenosis. The tumors often bleed, resulting in anemia that may dominate the clinical picture. The diagnosis must be histologically confirmed.

Hamartomatous polyps occur in the colon and the small intestine in *Peutz–Jeghers syndrome* and *juvenile polyposis*. Malignancy is rare compared to familial adenomatous polyposis, Gardner and Turcot syndromes, and hereditary nonpolyposis colorectal carcinoma.

Very Rare Gastric Diseases. Syphilis, tuberculosis, sarcoidosis, Crohn disease, eosinophilic gastritis, or phlegmonous gastritis are extremely rare causes of gastric complaints. Endoscopy and biopsy are generally diagnostic. With many diseases the diagnosis can only be confirmed if organs other than the stomach are affected (e. g., sarcoidosis, Crohn disease, tuberculosis).

Duodenal Diverticulitis. Duodenal diverticulitis is generally harmless. Sometimes, however, it may cause complaints similar to duodenal ulcers. An-

nular pancreas must be considered in the differential diagnosis. Periapillary or intraduodenal diverticula originating from the common bile duct may be a rare cause of pancreatitis or cholangitis.

Complaints after Gastric Surgery. The following diseases may be encountered in patients after stomach resection:

Preexisting Disease. The preexisting disease was not detected and continues to cause problems after surgery (e. g., IBS, porphyria).

Jejunal Peptic Ulcer. After stomach resection ulcers recur mostly at the anastomosis or immediately distal in the small intestine. The complaints depend on food intake (mostly late pain) and show a periodic course.

The pain is primarily localized to the left and is only poorly relieved by antacids. Continuous pain as a result of penetration or hemorrhage is a frequent complication.

Carcinoma of the Gastric Stump. Increased occurrence of cancers can be expected 15–20 years after gastric resection.

Dumping Syndrome. Fast evacuation of the stomach and hypertonic nutrition cause *early dumping syndrome*. The accumulation of hypertonic solutions (particularly sugar) in the jejunum leads to inflow of fluids from the extracellular space into the jejunum and to reduced plasma volume. The distension of the jejunum triggers autonomic reflexes and causes dumping syndrome. The signs start during or immediately after a meal with discomfort and signs of hypovolemia, i. e., sudden onset of weakness, dizziness, sweating, tachycardia, shaking, and paleness. Distribution of food intake over several small meals, reduction of fluid intake while eating, avoiding hypertonic food, and, in some cases, lying down immediately after meals, can generally prevent symptoms. Dumping syndrome is diagnosed primarily from the medical history. It is only observed after surgery for duodenal ulcers with pyloric resection (i. e., not after proximal selective vagotomy without pylorus surgery).

Late dumping syndrome presents similarly, but occurs 1.5–3.0 hours after meals and is caused by reactive hypoglycemia.

Sudden evacuation causes postprandial hyperglycemia followed by reactive hypoglycemia. In contrast to early dumping syndrome the symptoms are relieved by eating, particularly sugar.

Leading Loop Syndrome. Recurring pain in the epigastric region combined with vomiting (bile with or without food) is observed with this rare postoperative complication, particularly after Billroth II operation. A feeling of fullness occurs 20–60 minutes postprandial and is often followed by nausea and vomiting. *Blind loop syndrome*, which includes stasis and bacterial colonization in the region of the blind loop of the small intestine, also belongs to this group of disorders.

Bile Acid Reflux Gastropathy (Alkaline Reflux Gastropathy).

This is associated with an early feeling of fullness, abdominal pain, and vomiting.

Postvagotomy Diarrhea. This occurs particularly after truncal vagotomy.

Deficiency Symptoms (Including Agastric Syndrome). The symptoms are: protein deficiency, iron deficiency (common), pernicious anemia (rare), and general symptoms of vitamin deficiency (osteomalacia, particularly after gastrojejunostomy or Billroth II operation).

Pain Originating from the Colon

Irritable Bowel Syndrome (IBS). *Definition.* More than 50% of patients with chronic recurring abdominal pain suffer from an irritable colon.

This disorder is not restricted to the colon and is better named irritable bowel syndrome (IBS). IBS is a syndrome of unexplained etiology, characterized by disordered motility and secretion, primarily in the colon, and by the lack of a detectable organic cause. There are a number of older and newer terms for the varied symptoms of chronic abdominal pain with no organic cause (e. g., dyspepsia, nonulcerous dyspepsia, gastritis, functional dyspepsia, hyperacidity complaints), which, depending on the main symptoms, can be termed irritable stomach or IBS.

Clinical Features. Intermittent abdominal pain of variable intensity and changing location, combined with stool problems (diarrhea, constipation, or both alternating), are clinically detectable. Chronic constipation or diarrhea without organic cause may be variations of IBS. They differ from IBS by the absence of pain. Patients with IBS often consult the physician because of an acute exacerbation of the complaints. A detailed medical history of similar earlier episodes is important for the correct interpretation of the acute event. Important information from the medical history could be an appendectomy due to "chronic appendicitis" (i. e., surgery after 1 or 2 weeks of pain).

The pain with IBS varies from an unpleasant feeling of pressure and bloating to severe abdominal colic. The localization of the pain is highly variable, ranging from the hypogastric and midabdominal regions to the left and right, or diffusely throughout the entire abdomen, and thus imitates diseases of the abdomen and the chest. A long history with similar episodes of pain and no periodic pain is an important characteristic. The pain can sometimes mimic an acute abdomen.

Dyspeptic complaints (e. g., nausea, feeling of fullness, primarily postprandial, bloating, flatulence) are frequent accompanying symptoms. The majority of patients suffer simultaneously from multiple other functional disorders. Laxative use is common.

Subgroups of These Symptoms. Abnormal mucous content in the stool or isolated evacuation of sausage-skinlike membranes combined with abdominal colic are typical for *mucous colitis*, which is a subcategory of IBS. *Proctalgia fugax* is also a subcategory of IBS. It is a syndrome characterized by episodes of very severe cramplike pain in the rectum and perineal region, that last from a few minutes to an hour and usually occur during the day (DD: coccygodynia). The cause here is also unclear and no organic cause can be found (tentative therapy: nitrates or calcium antagonists).

Diagnosis. Clinical examinations are typically normal in IBS. The physical condition is good with stable weight. Laboratory tests are normal. No occult blood and no parasites can be found in the stool (repeated checks).

The colon can often be palpated in the left hypogastric region as a contracted structure (cordon iliaque). Sometimes endoscopic examination shows a slightly reddened mucosa covered with mucous. Endoscopy often triggers spasms. Endoscopy and radiography are typically normal.

Differential Diagnosis. IBS is a *diagnosis by exclusion* (e. g., carcinoma, ulcer, diverticulitis, cholelithiasis, nephrolithiasis, gynecologic conditions, Crohn disease, sprue, lactose intolerance, collagen colitis, parasites [giardiasis], depression, etc.). The individual diagnostic steps are primarily based on clinical experience. The shorter the history and the older the patient the less likely is IBS. On the other hand a young patient, long history, good physical condition, and constant body weight are suggestive of IBS. IBS and duodenal ulcer or cholelithiasis may possibly coexist. Diverticulitis must always be considered in older patients. *Pneumatosis cystoides intestinalis* is characterized by subserous or submucosal gas-filled cysts in the gastrointestinal tract, that can be visualized by plain radiography. All sections of the intestine can be affected. In 85% of cases the pneumatosis is associated with other gastrointestinal diseases (pyloric stenosis, appendicitis, regional enteritis, colitis, anal fistula). The clinical symptoms are uncharacteristic. Hemorrhage is rare.

Pain Originating from Bile Ducts and Liver

In differential diagnosis of pain in the epigastrium complaints originating from the bile ducts must always be considered.

The most important symptoms that indicate a biliary disease are: episodic pain in the epigastric region with or without radiation to the right shoulder, acute exacerbation of the pain over 1–3 days, nausea, vomiting, and occasional jaundice, with pain-free intervals often lasting weeks to months.

Cholelithiasis. *Clinical Features.* So-called gallstone colic is generally triggered by food intake. After a few minutes the pain reaches its peak and can be extremely intense. It is generally clearly different from the pain associated with duodenal ulcers, which increases slowly and is rarely as severe. The term “colic” is not always accurate, because it is generally a severe continuous pain,

lasting for several hours. The *pain* is not always circumscribed, is most intense below the right ribs but can also be localized along the mid-line. Radiation to right back and the right shoulder is typical. Nausea is an almost obligatory accompanying symptom. Fat intolerance is very common. Fat intolerance alone, however, without painful colic, is very common and unspecific. Examination during the pain episode usually reveals an intensive, sometimes only low-grade, sensitivity to palpation in the gall bladder region and a low-grade defense in the right epigastric region.

Epidemiology. Cholelithiasis affects women about twice as often as men. Predisposing factors are pregnancy, obesity, diabetes, and increasing age. The majority of patients with gallstones show no or atypical symptoms, particularly symptoms of IBS. In Europe and America gallstones are mostly *cholesterol stones* (two-thirds not radio-opaque, about one-third with calcification).

Pigmented gallstones are more frequent in Japan, whereas in the West they are found mostly in patients with hemolytic anemia, particularly with congenital spherocytosis and sickle cell anemia. Patients with cirrhosis of the liver also have an increased incidence of pigmented stones for unknown reasons.

Differential Diagnosis. In general, gallstone colic is so typical that it is easily diagnosed. The following must be excluded in differential diagnosis: right-sided kidney colic, thromboses of mesenteric veins or arteries, acute inflammation of a dorsally and cranially placed appendix, duodenal ulcer, hepatitis, and pancreatitis, which is often caused by biliary obstruction. Epigastric and umbilical hernias are also rare causes of pain. Myocardial infarction and right-sided heart failure with acute congestion of the liver are two diseases of organs outside of the abdomen that may mimic gallstone colic. An acute perihepatitis, which is mostly observed in young women, can easily be misinterpreted as cholelithiasis.

Diagnosis. Sonography is the method of choice to confirm cholecystolithiasis. Stones are a frequent finding at sonography of patients with atypical or no biliary symptoms. Calcium-containing stones are detected by plain radiography. Choledochus stones can be detected by ERCP. It is assumed that 10% of patients with gallbladder stones also have choledochus stones. The symptoms vary. Typical is either an intermittent obstructive jaundice, mostly in connection with a pain attack, pancreatitis, or cholangitis. However, many patients have no or only minor symptoms. In contrast to cholecystolithiasis, biliary colic with choledocholithiasis is often associated with vomiting. About three-quarters of all patients with choledocholithiasis have pain, which is virtually indistinguishable from that of cholecystolithiasis with respect to localization, severity, and radiation.

Complaints after Cholecystectomy. If symptoms continue or recur after cholecystectomy, which occurs in 10–15% cases, the following three possibilities must be considered:

□ *extrabiliary causes of the complaints*, which were present beforehand and were not corrected by the cholecystectomy

□ symptoms originating from the *bile ducts*, which were overlooked during the surgery (e. g., choledocholithiasis)

□ *surgical complications in extrahepatic bile ducts* (e. g., postoperative strictures, fistulas, ligation or transection of the bile duct).

Symptoms persisting after cholecystectomy, particularly after removal of a stone-free gall bladder, frequently indicate an underlying extrabiliary problem (e. g., pancreatitis, ulcer, carcinoma, IBS, etc).

Choledochus Stones and Papillary Stenoses. Choledochus stones or papillary stenoses are the two most common causes of persistent symptoms after cholecystectomy.

Diagnosis is based on the biochemical confirmation of intermittent obstruction (increase of alkaline phosphatase with normal bilirubin), best done immediately after a pain attack. Often a transient hyperamylasemia can be detected. The diagnostic method of choice is ERCP. In choledocholithiasis an endoscopic papillotomy is frequently required to remove the stones.

If obstruction of the common bile duct by a process in the head of the pancreas exists (pancreatitis, carcinoma) additional studies are required: sonography, endosonography, CT and cholangio-MRI.

A long cystic stump after cholecystectomy rarely causes clinical symptoms, unless new gallstones are formed.

Differential Diagnosis of Pain in the Right Hypogastric and Midabdominal Region

Biliary and Extrabiliary Causes. Differential diagnosis must include, in addition to biliary causes, duodenal ulcers, pancreatitis, hepatopathies (alcohol-induced hepatitis, congestion of the liver, space occupying processes), parasites (e. g., *Fasciola hepatica*), acute perihepatitis, renal affections, neoplasm of liver, bile ducts, pancreas, duodenum, kidneys, colon, and a radicular pain syndrome from the back. Metabolic diseases, collagenosis, and pain from vascular causes must also be considered. Indistinct pressure sensations occasionally occur with the rare Chilaiditi syndrome, which is characterized by the interposition of the colon in the right hypochondriac region between the liver and the diaphragm. This syndrome must not be misinterpreted as free intraabdominal air.

Functional Complaints. Differentiation between bile duct dyskinesia (functional motility disorders) and physical obstruction (primarily adenomyomatosis in the cervical region of the gall bladder) is not possible by

clinical examination. Dyskinesia is probable when other functional complaints are present.

Diseases of the Pancreas

Clinical Features. The main clinical symptoms that indicate disease of the pancreas are:

- pain
- cholestasis
- weight loss
- diabetes mellitus
- diarrhea/steatorrhea.

Chronic Pancreatitis

Causes. Chronic pancreatitis is characterized initially by recurring episodes of pancreatitis and later by exocrine and endocrine pancreatic insufficiency. The primary cause of chronic pancreatitis in more than 60% of cases is alcohol use. Other cases have no clear cause or the causes are rare (e. g., pancreatic duct obstruction, hyperparathyroidism, hyperlipidemia, trauma, analgesic use, or hereditary). Mutations of the gene for cationic trypsinogen can cause the rare *hereditary pancreatitis*. Mutation of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR), also without any clinical signs of a cystic fibrosis, or of the serine protease inhibitors Kazal type 1 (SPINK1) are associated with some cases of chronic pancreatitis that were formerly classified as idiopathic. Cholelithiasis rarely causes chronic pancreatitis.

Epidemiology. Men are affected approximately seven times more often than women.

Clinical Features. Approximately 10–20% of patients with chronic pancreatitis have no pain, particularly in nonalcoholic chronic pancreatitis (idiopathic-senile form, hyperparathyroidism, analgesic use). Diabetes mellitus or steatorrhea is generally the first clinical manifestation. Local complications (e. g., obstructive jaundice) are rarely caused by chronic pancreatitis.

Chronic pancreatitis in the *early stage* presents typically with episodic attacks of epigastric pain followed by weeks or months without pain. Continuous pain over weeks, particularly postprandial or recurring at short intervals, indicates local complications, particularly pseudocysts. Elevated pressure in dilated pancreatic ducts often causes continuous pain. Local complications can be diagnosed by sonography, endosonography, CT, MRT, or ERCP. A pancreatic carcinoma must always be considered. In older patients with continuous pain for less than 18 months, weight loss, and no history of pancreatitis, a pancreatic carcinoma is more probable than chronic pancreatitis.

The *pain episode* in chronic pancreatitis is clinically and biochemically virtually identical to acute pancreatitis. Spontaneously occurring, continuous pain in the epigastrium, persisting for hours to a few days and often associated

with vomiting and subileus, is characteristic. The intensity of the pain is very variable and ranges from mild stomach discomfort to very severe pain with the feeling of dying.

Weight loss of 5–10 kg or more is almost always associated with chronic pancreatitis and generally occurs in the early stages of the disease, before diabetes mellitus or steatorrhea develop.

Chronic pancreatitis always leads to *diabetes mellitus*, generally within three to five years, and can be diagnosed by an oral glucose tolerance test. Pancreatogenic diabetes must be suspected especially in younger, non-obese patients without family history and with a history of recurring abdominal pain or alcohol use.

Persistent meteorism may indicate chronic pancreatitis. Diarrhea and steatorrhea generally develop later. Fatty stools, not occurring otherwise, are pathognomonic for pancreatogenic steatorrhea. Steatorrhea is a later complication. With the development of pancreatic calcifications, diabetes, and severe exocrine pancreatic insufficiency the pain generally disappears spontaneously unless there are local complications (burntout pancreatitis).

Diagnosis. Early exocrine pancreas insufficiency can only be detected by relatively complex function tests. Pancreatic calcifications can be detected in > 60% of patients by plain radiography. Stones are formed primarily in the pancreatic duct system and are detected by sonography, endoscopy, CT or ERCP.

Various imaging procedures are used for the assessment of pancreatic diseases. Sonography, as well as endosonography and CT, are very useful for diagnosis and monitoring of acute pancreatitis, for detection of pseudocysts, cholelithiasis, pancreatic carcinoma, and in cholestasis/jaundice. ERCP and magnetic resonance cholangiopancreatography (MRCP) are primarily used in etiologically unclear, recurring pancreatitis and local complications of pancreatitis. In early chronic pancreatitis imaging procedures are of limited value, in particular in differentiating acute pancreatitis.

Complications. Local complications of chronic pancreatitis are common: pseudocysts, pancreatogenic ascites, cholestasis with or without jaundice, thrombosis of the splenic veins, duodenal stenosis, gastrointestinal hemorrhage, and stenoses or fistula formation in the colon. Many of these local complications also occur with acute pancreatitis.

Differential Diagnosis of Pancreatic Carcinoma. Differential diagnosis of chronic pancreatitis versus carcinoma of the head of the pancreas can be very difficult. Positron emission tomography (PET) may be helpful. Nevertheless, it is often not possible, even during surgery, to decide whether a small pancreatic carcinoma with accompanying pancreatitis or chronic pancreatitis only is present. With the exception of papillary carcinoma, which causes obstructive jaundice very early and has a good prognosis with radical surgery, the prognosis for pancreatic carcinoma is very poor.

Pancreatic Carcinoma. *Epidemiology and Localization.* The symptoms of pancreatic carcinoma are unspecific. This diagnosis must always be considered in older patients with abdominal pain without evidence of gastric or hepatic disease (average age 55 years, men affected twice as often as women). Risk factors for pancreatic carcinoma are poorly defined. Heavy smokers seem to be affected more often than nonsmokers. More than 90% of pancreatic carcinomas are ductal adenocarcinomas. Islet cell carcinomas represent only a small proportion. Pancreatic carcinoma occurs in the head of the pancreas in about 70% of cases, in the body in 20%, and rarely in the tail. The clinical symptoms vary depending on the size and localization of the tumor.

Clinical Features and Diagnosis. Carcinoma of the pancreas head is primarily characterized by *periampullar localization* with the triad of *pain, weight loss, and progressive obstructive jaundice* with dark urine, acholic stool, and pruritis. An enlarged, palpable gall bladder (*Courvoisier sign*, > 50% of cases) indicates distal choledochus obstruction. Painless obstructive jaundice is found in about 25% of patients. Dilated bile ducts can usually be visualized by sonography. Diagnosis generally requires ERCP and/or biopsy guided by sonography, endosonography or CT. Percutaneous biopsy should be avoided in resectable tumors because of the risk of needle tract metastases. Positron emission tomography (PET) can be useful here to differentiate between inflammatory and neoplastic processes.

Pain and weight loss without jaundice are initial symptoms for *nonpapillary carcinomas*. The pain, initially intermittent, later continuous, is localized in the epigastric region, primarily to the left and typically radiates to the back.

Increased pain when lying down, and improvement when standing and bending forward, is typical, similar to chronic pancreatitis. Pancreatitis episodes resulting from duct obstruction may be the first manifestation of a pancreatic carcinoma. Signs of poor assimilation, particularly diarrhea, steatorrhea, and weight loss, may precede other manifestations of the tumor by months.

Thrombophlebitis migrans is present in < 10% of cases. A pancreatic carcinoma or an acute pancreatitis is rarely the cause of *panniculitis nodularis (Pfeifer–Weber–Christian syndrome)*.

Amylase and lipase are almost always in the normal range. The oral glucose tolerance is pathologic in 30–50% of cases. Exocrine pancreatic insufficiency can generally be detected with carcinoma of the pancreatic head. CEA and CA19–9 are frequently elevated, with the latter being relatively specific for pancreatic carcinoma.

Functional abdominal pain syndrome (FAPS)

A special attention should be paid at functional abdominal pain syndrome (FAPS). FAPS is a distinct medical disorder. Evidence suggests that the syndrome relates to central nervous system (CNS) amplification of normal

regulatory visceral signals, rather than functional abnormalities in the gastrointestinal tract. The disorder is characterized by continuous, almost continuous, or at least frequently recurrent abdominal pain that is poorly related to bowel habits and often not well localized. FAPS is properly understood as abnormal perception of normal (regulatory) bowel function rather than a motility disorder. The syndrome appears to be closely related to alterations in endogenous pain modulation systems, including dysfunction of descending and cortical pain modulation circuits. The Rome III diagnostic criteria for FAPS are shown in Table 2. Studies that included patients who meet diagnostic criteria for FAPS have revealed that only rarely is an organic cause of chronic abdominal pain found during long-term follow-up.

FAPS is commonly associated with other unpleasant somatic symptoms, and, when it persists or dominates the patient's life, it usually is associated with chronic pain behaviors and comorbid psychological disturbances. Patients with FAPS typically define their illness as medical, and their symptoms tend to be more severe and associated with greater functional impairment than those of patients with IBS. Psychological disturbances, if present, must be considered as comorbid features of FAPS rather than as part of a primarily psychiatric problem. When compared with patients who have chronic back pain, those with chronic abdominal pain report significantly better physical functioning

Table 2

Rome III Criteria for Functional Abdominal Pain Syndrome

Must include <i>all</i> the following:		
1.	Continuous or almost continuous abdominal pain	
2.	No or only occasional relationship of pain with physiologic events (e.g., eating, defecation, menses)	
3.	Some loss of daily functioning	
4.	Pain is not feigned (e.g., no malingering)	
5.	Insufficient symptoms to meet criteria for another functional gastrointestinal disorder that would explain the pain	

** Criteria fulfilled for the past three months with symptom onset at least six months prior to diagnosis.*

Epidemiology. In the U.S. Householder Survey of Functional Gastrointestinal Disorders, FAPS was estimated to be present in 2% of the sample and was less frequent than IBS (9%). A female predominance was noted (F:M = 1.5). Patients with FAPS missed more work days because of illness and had more physician visits than those without abdominal symptoms. A substantial proportion of patients are referred to gastroenterology practices and medical centers;

they have a disproportionate number of health care visits and often undergo numerous diagnostic procedures and treatments.

Pathophysiology. Chronic pain is a multidimensional (sensory, emotional, cognitive) experience explained by abnormalities in neurophysiologic functioning at the afferent, spinal, and CNS levels. Unlike acute pain arising from peripheral or visceral injury or disease, chronic functional pain is not associated with increased afferent visceral stimuli from structural abnormalities and tissue damage. FAPS is considered what is termed a *biopsychosocial disorder* related to dysfunction of the brain-gut axis. Clinical expression of FAPS is derived from psychological and intestinal physiologic input that interacts via the CNS-gut neuraxis. This model integrates the clinical, physiologic, and psychosocial features of FAPS into a comprehensible form, providing the basis for understanding psychological influences and application of psychopharmacologic treatments.

Research relating to the pathophysiology of painful functional gastrointestinal disorders has focused on the concepts of visceral hypersensitivity and alterations of brain-gut interactions. Visceral hypersensitivity is facilitated by up-regulation of mucosal nociceptors and sensitization of visceral afferent nerves. Dysregulation of the brain-gut axis can be manifested as central enhancement of afferent visceral signals. The brain-gut dysregulation can, in turn, be initiated or modified by a variety of events. I

n a large-scale, prospective, controlled investigation of the development of chronic abdominal pain in women undergoing gynecologic surgery for non-painful indications, pain developed significantly more frequently in the surgical group (15%) than in a nonsurgical control group (4%). The development of chronic abdominal pain in the postoperative setting was predicted only by psychosocial, and not surgical, variables, implying that the development of pain is associated closely with central registration and amplification of the afferent signal. This study lends strong support to the biopsychosocial model, documenting the importance of cognitive and emotional input during the development of postoperative FAPS.

Ascending Visceral Pain Transmission. The afferent transmission of visceral abdominal pain involves first-order neurons that innervate the viscera, carry information to the thoracolumbar sympathetic nervous system, and subsequently synapse in the dorsal horn of the spinal cord.

Second-order neurons cross and ascend from the dorsal horn via the spinothalamic and spinoreticular tracts. These second-order neurons synapse in the thalamus with third-order neurons that synapse with the somatosensory cortex (sensory-discriminative component), which is involved in the somatotypic or point-specific localization and intensity of afferent signals, and with the limbic system (motivational-affective component), which contains the anterior cingu-

late cortex. The insular cortex receives input from the sensory thalamus and the nucleus tractus solitarius and integrates visceral sensory and emotional information. The limbic system serves as a modulator of the pain experience, based on the individual's emotional state, prior experiences, and cognitive interpretation of the signal. This multicomponent integration of nociceptive information in the CNS explains the variability in the experience and reporting of pain. Motivational-affective regions of the CNS are important contributors to the chronic pain experience by modulating afferent sensory information from the intestine.

This conceptual scheme of pain modulation has been demonstrated through PET imaging with the use of radiolabeled oxygen. In a group of healthy subjects who immersed their hands in hot water, half were hypnotized to experience the immersion as painful and the other half as not painful or even pleasant. The changes in cortical activation were compared between the two groups, and no difference was found in activity in the somatosensory cortex; however, those who experienced pain had significantly greater activation of the ACC of the limbic system, which is involved in the affective component of the pain experience.

Functional brain imaging studies comparing patients with functional gastrointestinal disease and normal controls have shown abnormal brain activation mainly in the motivational-affective pain regions, including the prefrontal cortex, ACC, amygdala, and insula. These regions generally show increased activation in patients with chronic pain, thereby suggesting abnormal afferent input as well as central modulation, which could be caused in part by increased attention to visceral stimuli, abnormal cognitive or affective processing of afferent input, or comorbid psychiatric disorders.

Descending Modulation of Pain. Afferent transmission of visceral pain can be modulated by descending impulses from the cortex down to the visceral nerves. In this model, the central descending control of the gating system occurs primarily through the descending inhibitory system. This system is an endorphin- or enkephalin-based neural network that originates from the cortex and limbic system and descends to the spinal cord, with major links in the mid-brain (periaqueductal gray) and medulla (caudal raphe nucleus).

This system inhibits nociceptive projection directly on the second-order neurons or indirectly via inhibitory interneurons in the spinal cord. Then, the dorsal horn of the spinal cord acts as a gate to modulate (i.e., increase or decrease) transmission of afferent impulses from peripheral nociceptive sites to the CNS. In effect, this descending pain modulation system determines the amount of peripheral afferent input from the gut that is allowed to ascend to the brain. Descending inhibitory systems can be diffuse and, when activated, inhibit pain sensitivity throughout the body—so-called diffuse noxious inhibitory

control (DNIC). Patients with chronic pain syndromes, including FAPS, appear to have an impaired ability to activate DNIC.

Visceral Sensitization. Recurrent peripheral stimulation is thought to up-regulate afferent signals or inhibit descending pain control mechanisms, thereby sensitizing the bowel and producing a state of visceral hyperalgesia (increased pain response to a noxious signal) and chronic pain. Several clinical studies have supported this concept, and the increase in pain appears to occur to a greater degree in patients with functional gastrointestinal disorders than in healthy subjects. Furthermore, preoperative treatment with local or regional anesthesia or NSAIDs reduces the severity of postoperative pain, suggesting that the CNS response to peripheral injury can be modified by prior reduction of afferent input to the spinal cord and CNS.

Conversely, recurrent peripheral injury, such as repeated abdominal operations, may sensitize intestinal receptors, thereby making perception of even baseline afferent activity more painful (allodynia). Visceral sensitization may develop through different mechanisms at one or more levels of the neuraxis, including the mucosal level (via afferent silent nociceptors) and spinal level (spinal hyperexcitability). Patients with IBS may also experience hyperalgesia. Studies of rectal balloon distention in patients with IBS have demonstrated that a greater proportion of patients report discomfort to balloon distention than normal volunteers at a given volume of inflation; in addition, the intensity of the discomfort in patients is higher than in the normal volunteers. Rectal hypersensitivity induced by repetitive painful rectal distention is seen in patients with IBS, but not FAPS. This observation supports the contention that IBS and FAPS are distinct functional gastrointestinal disorders.

Biochemical Mechanisms of Sensitization. The biochemical basis of visceral sensitization is under active study, and this research may identify future targets for therapy. Serotonin (5-hydroxytryptamine [5-HT]) has received considerable attention because the gastrointestinal tract is its main source within the body. 5-HT is found primarily in mucosal enterochromaffin cells, where it appears to serve as a neurotransmitter of the enteric nervous system (ENS) and as a paracrine molecule that signals other (e.g., vagal) neural activity. 5-HT mediates numerous gastrointestinal functions, and modulation of various receptor subtypes, such as 5-HT₁, 5-HT₃, and 5-HT₄, and of 5-HT reuptake affects gastrointestinal sensorimotor function.

Role of the Central Nervous System. Although peripheral sensitization may influence the onset of pain, the CNS is critically involved in the predisposition to and perpetuation of chronic pain. In FAPS, the preeminent role of the CNS is evident by the lack of peripheral motor or sensory abnormalities and the strong association with psychosocial disturbances. In addition, comorbid psy-

chiatric diagnoses, major life stressors, a history of sexual or physical abuse, poor social support, and maladaptive coping all are associated with more severe chronic abdominal pain and poorer health outcomes. These factors in patients with FAPS and other functional gastrointestinal pain conditions may impair or diminish descending inhibitory pain pathways that act on dorsal horn neurons or may amplify visceral afferent signals.

Functional brain imaging has been useful in clarifying brain-gut interaction and has demonstrated that links between emotional distress and chronic pain may be mediated through impairment in the ability of the limbic system to modulate visceral signals. The motivational-affective component of the central pain system, specifically the ACC, is dysfunctional in patients with IBS and other chronic painful conditions. Functional magnetic resonance imaging (MRI) and PET brain imaging in response to rectal distention in patients with IBS have shown differential activation of the ACC in patients compared with normal subjects and increased activation of the thalamus.

Similar results have been found in patients with a history of abuse, somatization, and post-traumatic stress disorder. Furthermore, the return of ACC activity to baseline in depressed patients is associated with clinical improvement and predicts response to antidepressant treatment. As the pain and emotional distress of a patient with IBS improve, the activity within the ACC changes correspondingly. The observed synergistic effect of IBS and abuse history on differential ACC activation suggests a mechanism to explain how afferent processing in the CNS can be associated with reporting of greater pain severity and poorer outcomes in this patient population. This and other research has suggested that dysregulation of central pain modulation is critical and may occur in various medical and psychological conditions. The challenge remains to alter this dysregulated afferent processing network reproducibly and to reverse the findings on functional brain imaging studies (by pharmacologic, psychological, or other therapeutic means), with a concomitant improvement in patient outcomes.

Clinical Implications. The concept of FAPS as a dysregulation of CNS–enteric nervous system function at varying levels of the neuraxis, rather than a purely psychiatric or structural gastrointestinal disorder, suggests that chronic pain results from enhanced pain perception as a result of combinations of the following: (1) activation of silent nociceptors; (2) dorsal horn transmission of impulses stimulated by release of cytokines or other substances; and (3) chronic or frequently recurring psychosocial stresses that influence central pain modulation. By linking psychosocial factors to the pathophysiology of chronic abdominal pain, this conceptual scheme alters the therapeutic approach from one that is purely psychiatric

in nature to one that encompasses a broader array of potential therapies. Early pharmacologic and psychological treatment ultimately may be proven to prevent the development of a subsequent chronic pain syndrome.

Clinical features

History. Typically, patients with FAPS are middle-aged and female. The history is one of chronic abdominal pain, often for more than 10 years, and the patient is often in distress at the time of initial consultation. The pain is frequently described as severe, constant, and diffuse. Pain is often a focal point in the patient's life, may be described in emotional or bizarre terms (e.g., as nauseating or like a knife stabbing), and is not influenced by eating or defecation. The abdominal pain may be one of several painful symptoms or part of a continuum of painful experiences often beginning in childhood and recurring over time. FAPS sometimes coexists with other disorders, and the clinician must determine the degree to which one of these other conditions contributes to the FAPS. Frequently, FAPS will evolve in a patient who has had another well-defined gastrointestinal disorder, but who has been operated on one or more times and, following these operations, has developed chronic abdominal pain.

Repetitive surgery in such patients is often performed for alleged intestinal obstruction caused by adhesions.

Patients with FAPS often have a psychiatric diagnosis of anxiety, depression, or somatization. They may minimize the role of psychological factors, possibly having learned in childhood that attention is more likely received when reporting illness but not emotional distress. A history of unresolved losses is a common feature. Symptoms frequently worsen soon after these events and recur on their anniversaries or during holiday seasons. A history of sexual and physical abuse is frequent and is predictive of poor health, refractoriness to medical care, and a high number of diagnostic and therapeutic procedures and health care visits. Because patients do not usually volunteer an abuse history, physicians should inquire about this possibility, particularly in those with refractory symptoms.

Finally, patients with FAPS may report poor social networks and exhibit ineffective coping strategies. They feel unable to decrease their symptoms and may “catastrophize” — that is, view their condition in pessimistic and morbid ways without any sense of control over the consequences. These cognitions are associated with greater pain scores that lead to a cycle of more illness reporting, more psychological distress, and poorer clinical outcomes. For many, the illness provides social support via increased attention from friends, family, and physicians.

Patient Behavior. Certain behavioral traits are common in patients with FAPS. Often, these patients demand that the physician not only diagnose the problem promptly, but also relieve their chronic symptoms rapidly.

They similarly deny a relationship between their problem and psychologically disturbing issues and often attribute depression to pain rather than recognizing it as a primary factor. Frequently, an accompanying spouse or parent takes responsibility for reporting the patient's history, an observation that suggests the possibility of family dysfunction. A history of narcotic use is not uncommon, as is a request by the patient for such medication during the initial visit. This type of behavior reflects the patient's consideration of his or her situation as an acute condition requiring immediate symptom relief, rather than as a chronic condition in which treatment must be directed toward enhancing coping and adaptive strategies.

Physical Examination. Certain physical findings help support a diagnosis of FAPS, yet none is perfectly sensitive or specific. Abdominal palpation should begin at an area remote from the perceived site of maximal intensity. The patient's behavior during abdominal palpation should be noted, with an emphasis on whether a change is noted during distracting maneuvers. Patients with FAPS usually lack signs of autonomic arousal.

The presence of multiple abdominal surgical scars without clearly understood indications may suggest chronic pain behaviors that have led to unnecessary procedures. The closed eyes sign may be noted; when the abdomen is palpated, the patient with FAPS may wince, with her or his eyes closed, whereas those with acute pain caused by organic pathology tend to keep their eyes open in fearful anticipation of the examination. Often, the stethoscope sign (i.e., gentle, distracting compression on a painful site of the abdomen with the diaphragm of the stethoscope), elicits a diminished behavioral response in a patient with FAPS, thereby affording a more accurate appraisal of the complaint of pain.

Diagnosis and differential diagnosis. After obtaining a complete history, performing a thorough physical examination, and paying appropriate attention to psychosocial factors in the patient's life, the scenario will often point the physician toward a diagnosis of FAPS. A physical examination that does not suggest evidence of organic intra-abdominal pathology, as well as normal results of a battery of routine laboratory tests, lends support to the contention that the patient's pain is not the result of an identifiable structural disease.

Recognition of the diagnostic criteria for FAPS, and failure to find evidence of another cause of chronic abdominal pain, should lead the physician to a diagnosis of FAPS. If the features of FAPS are absent or atypical, or if concerning abnormalities are found on physical examination (e.g., abdominal mass, enlarged liver) or on screening laboratory studies (e.g., anemia, hypoalbuminemia), another diagnosis should be considered and pursued accordingly.

Not uncommonly, nonspecific abnormalities are found (e.g., a liver cyst) and require determination of their relevance to the patient's symptoms.

Treatment

Establishing a Successful Patient-Physician Relationship. Once other diagnoses have been excluded, formation of a successful relationship between the physician and patient with FAPS is necessary for effective management. Several factors must be taken into account to help establish this relationship and move toward successful treatment. An understanding of the psychosocial background is helpful, because a detailed knowledge of this aspect of the patient's life aids in selecting the most useful treatment strategies. Having an appreciation of the degree of the patient's understanding of the illness is also important, particularly for enhancing the success of a treatment plan.

Early in the development of the patient-physician relationship, it is important to determine whether there are abnormal illness behaviors and associated psychiatric diagnoses, which are often present in patients with FAPS. The role of the family in relation to the patient's illness should also be understood. Normally, family experiences with illness lead to emotional support and a focus on recovery. With dysfunctional family interactions, stresses are not managed in an optimal fashion, and diverting attention toward illness serves to reduce family distress. Dysfunction is seen when family members indulge the patient, assume undue responsibility in the patient's management, or become the spokesperson for the patient. If such family dysfunction is observed, counseling may help the family develop more useful coping strategies. Cultural belief systems must also be understood, because patients may not comply with treatments that are inconsistent with their cultural values. It is important to gain knowledge of the patient's psychosocial resources (i.e., the availability of social networks) that may assist in buffering the adverse effects of stress and improve the outcome.

It is essential for the physician to convey validation of illness to the patient by acknowledging the patient's illness and the effect it has had on his or her life in a nonjudgmental fashion. This step is important in ensuring that the patient understands that the physician considers FAPS to be a medical illness. Empathy is primary, because it acknowledges the reality and distress associated with the patient's pain. Providing an empathetic approach can provide benefit by improving adherence to a treatment plan, patient satisfaction, and clinical outcomes. It does not, however, equate with overreacting to the patient's wish for a rapid diagnosis and overmedication or performing unnecessary diagnostic studies. Education is provided by eliciting the patient's knowledge of the syndrome, addressing any concerns, explaining the nature of the symptoms, and ensuring understanding in all matters that have been discussed. It is helpful to

reiterate that FAPS is a medical disorder and that symptoms can be attenuated by pharmacologic or psychological treatments that modify the regulation of pain control. Reassurance should be provided, because patients may fear serious disease. After the evaluation is complete, the physician should respond to the patient's concerns in a clear, objective, and nondismissive manner. Both patient and physician must then negotiate the treatment.

This approach will enable the patient to contribute to and take some responsibility for the treatment plan. Within the context of the patient's prior experience, interests, and understanding, the physician should provide choices rather than directives. Adherence to a treatment plan is more likely when the patient has confidence that it will benefit him or her and its rationale is understood. Finally, the physician must set reasonable limits in relation to time and effort expended. The key to success is to maintain a trusting relationship, while setting proper boundaries.

Instituting a Treatment Plan. Successful treatment rests on formulating a plan that encompasses ongoing interviews to ensure that the patient does not expect a cure. The physician should explain that a realistic treatment goal is to attenuate the symptoms and improve daily function. The patient should increase his or her responsibility for the illness by identifying the circumstances surrounding episodes of pain, including emotional and cognitive responses. This technique helps the patient achieve insight into aggravating factors and also characterizes the patient's coping style. Such information helps identify a strategy for behavioral treatment. The treatment chosen should be based on the severity of symptoms and degree of associated disability. Symptoms that are intermittent and less severe and those that are clearly linked to psychological distress are frequently amenable to psychological treatment. If the pain is continuous and severe, pharmacotherapy targeted to achieve central analgesia may be helpful.

Pharmacotherapy. There is a paucity of evidence from prospective, randomized, controlled trials to support the use of drug therapy in FAPS. Drug development in the area of functional gastrointestinal disorders, particularly FAPS, has been slow. A major reason for this slow progress is the rather empirical process for experimental testing that necessarily occurs in a symptom-based syndrome. Pharmacologic brain imaging approaches hold promise as a means to accelerate drug discovery and subsequent development. Despite these limitations, some specific medications have been used in the treatment of FAPS (see later). Peripherally acting analgesics (e.g., acetaminophen, aspirin, other NSAIDs) offer little benefit to patients with FAPS, given the pathophysiology of the disorder (i.e., a biopsychosocial disorder related to dysfunction of the brain-gut neuraxis). Moreover, narcotics and benzodiazepines should not be prescribed for treatment of FAPS, because of the potential for increased pain

sensitivity and a lowering of the pain threshold, respectively. Furthermore, the omnipresent potential for drug dependency with these types of medications must be borne in mind. Importantly, prescribing such medications subordinates the development of more comprehensive treatment strategies to that of providing medication, can be counterproductive by leading to narcotic-induced potentiation of visceral pain, and can thus result in the narcotic bowel syndrome. Narcotic bowel syndrome may occur in patients with other gastrointestinal disorders or in patients with no other structural intestinal disease who have been exposed to high doses of narcotic medication. The clinical scenario is dominated by chronic abdominal pain that continues to worsen, despite the use of escalating doses of narcotics. The keys to successful management of this disorder include the timely recognition of the syndrome followed by the establishment of an effective physician-patient relationship and graded tapering of the narcotic, with simultaneous institution of medical therapy to mitigate the effects of opiate withdrawal.

As in the treatment of other chronic pain disorders, tricyclic antidepressants (TCAs) can be helpful in FAPS. The benefit of these medications is derived from their ability to improve pain directly and treat associated depression. In general, TCAs have been shown to be effective but can cause anticholinergic effects, hypotension, sedation, and cardiac arrhythmias. They can be given in dosages lower than those used to treat major depression (e.g., desipramine, 25 to 100 mg/day at bedtime) to reduce side effects. However, dosage increases may be needed, particularly if the patient has psychiatric comorbidity. There is less evidence for the use of selective serotonin reuptake inhibitors (SSRIs) in FAPS. These medications may cause agitation, sleep disturbance, vivid dreams, and diarrhea but are much safer than TCAs if taken in an overdose. In most cases, administration of a single daily dose (e.g., 20 mg of fluoxetine, paroxetine, or citalopram) will suffice. Although the efficacy of SSRIs for pain control is not well established, this class of drugs has additional benefits because they are anxiolytic and helpful for patients with social phobia, post-traumatic stress disorder, panic disorder, and obsessional thoughts related to their condition. Drug combinations (e.g., TCAs with SSRIs) have little support for their use in patients with functional gastrointestinal disorders.

Anticonvulsants such as carbamazepine and gabapentin have been evaluated in other chronic pain syndromes but have no proven efficacy in FAPS. These drugs may find a role as adjunctive agents in the future. As is the case for other peripherally acting analgesics, topical capsaicin would not be expected to be helpful in the management of FAPS. Leuprolide acetate may be of benefit for premenstrual females with FAPS, but the consequent reproductive hormonal effects of this therapy have dampened enthusiasm for this approach.

To enhance compliance, especially in the case of TCA use, the physician should explain that these medications work as central analgesics and are not simply being used to treat a psychiatric condition. Investing the time to explain that these drugs induce neurotransmitter changes in the brain and thereby alter pain perception, and that the dosage is usually lower than that typically chosen for treatment of psychiatric disorders, is often helpful. Further, it may be beneficial to emphasize that the lag time for clinical effect may be several weeks; most side effects diminish after a few days and can be reduced by temporarily lowering the dose of the drug.

Mental Health Referral and Psychological Treatments. Patients may be reluctant to see a psychologist or psychiatrist because they lack knowledge of the benefits of referral, feel stigmatized for being thought to have a psychiatric problem, or see referral as a rejection by the medical physician. Psychological interventions are best presented as vehicles that are orchestrated in parallel with medical visits and are used to help manage pain and reduce the psychological distress caused by the symptoms.

The mental health consultant may recommend any of several types of psychological treatments for pain management. Cognitive-behavioral treatment, which identifies maladaptive thoughts, perceptions, and behaviors, may be beneficial. Evidence from functional brain imaging suggests that this psychological intervention decreases activation from rectal stimulation in the central emotional regions that are typically hyperactive in chronic pain, such as the amygdala, ACC, and frontal cortex. Hypnotherapy has been investigated primarily in IBS, where the focus is on relaxation of the gut. Hypnotherapy is superior to standard medical therapy in reducing pain at one year of follow-up. Dynamic or interpersonal psychotherapy and relaxation training have less evidence to support their use in FAPS.

List of suggested reading

1. Feldman M. , Friedman L. S. , Brandt L. J. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management, Ninth Edition. – Elsevier. – 2010. – Vol. 1 (Chapter 11 – Chronic Abdominal Pain. J. C. Yarze, L. S. Friedman).

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3. Differential diagnosis in internal medicine: From Symptom to Diagnosis / [edited by] Walter Siegenthaler; with contributions by A. Aeschlimann ... [et al.] ; specialist consultants, A. Aeschlimann ... [et al.]. – 2 nd English ed. – Thieme, 2007. – 1104 p.

4. Chronic Abdominal and Visceral Pain: Theory and Practice / Edited by P.J. Pasricha, W. D. Willis, G. F. Gebhart © 2007 by Informa Healthcare USA, Inc. – 532 p.

Навчальне видання

**Модуль 3: Внутрішня медицина.
Змістовний модуль № 3.
Тема 4. Ведення хворих з хронічним
абдомінальним болем**

*Методичні вказівки
для студентів та лікарів-інтернів*

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Theme 4. Management of patients
with chronic abdominal pain

Guidelines for students and interns



Модуль. Внутрішня медицина.
Змістовний модуль № 3.
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*Методичні вказівки
для студентів та лікарів-інтернів*