7. PATHOPHYSIOLOGY OF THE GASTROINTESTINAL (GI) TRACT AND THE LIVER

The basic role of the gastrointestinal (GI) system is to prepare the food and digest it in order to provide nutrients deemed paramount to the body, and also to specifically perform their intestinal absorption and their transmission via the blood circulated among the various tissue networks of the human body. The liver plays a central role in the transformation of these nutrients to forms that can be directly used by the tissues, however, of similar importance is the detoxication/excretion function of the liver. Although various malabsorptions may result in deficiency of calorically important or accessory substances, eventually causing severe abnormalities of salt- and water-balance, a serious failure of liver functions results in a complex coma state.

7.1. PREPARATION OF FOOD IN THE ORAL CAVITY, SWALLOWING AND THEIR DISORDERS

The preparation and process of food within the oral cavity refers to chewing, grinding and mixing with saliva including digestive enzymes, forming a bolus which can easily be swallowed. Following the appropriate level of saliva production, chewing and grinding the suitably prepared bolus is forwarded to the stomach simply by the reflex of swallowing.

7.1.1. DISORDERS OF SALIVA PRODUCTION

Although 99% of saliva is water, there are also other components which make up its character, including electrolytes (HCO_3^-, Ca^{2+}, fluoride, phosphate), enzymes (amylase, invertase), mucin, immunoglobulins, peroxidase, lysozymes, lactoferrin, etc. Human saliva features a distinct role in the lubrication of food, some role in carbohydrate digestion, in prevention of caries and various oral infections, in taste sensation and in coordinated oral movements during speaking. Xerostomy may develop in autoimmune atrophy of the salivary gland (Sjögren's syndrome), in vitamin-A deficiency as well as in protein-calorie malnutrition, sarcoidosis, sialadenitis, sialolithiasis, and temporary xerostomy often adjoins increased sympathetic tone.

Distinctly, in consideration of the point of view of gastroenterology, deficiencies in saliva production often result in disorder of preparation of food and bolus formation, inevitably, making swallowing much more laborious and difficult. In xerostomy – whether it is caused by lasting oral breathing or some disease (e.g. Sjögren's syndrome) – the oral mucosa is often damaged. Abnormally, a substantial increase in saliva (well over 1.5 liter/day) occurs in parasympathetic overtone (e.g. mushroom poisoning, intoxication by cholinesterase inhibitors, nicotine-action) or local vs. upper gastrointestinal infections, nausea.

Various abnormalities of the oral mucosa may have diagnostic relevance in other associated diseases, including leukoplakia (as seen in a precancerosus state and primarily among heavy smokers), glossitis (vitamin-B_{12} deficiency), cheilitis, stomatitis angularis (Fe-deficiency), bleedings of the gum (vitamin-C deficiency), etc.

7.1.2. DISORDERS OF CHEWING

Disorders in chewing are characteristically associated with the disorders of preparation of food, and generally cause disorders in filling of the stomach. Without chewing and in grinding disorders, a variety of foods cannot be effectively swallowed. Thus, chewing disorders in fact cause defective food intake and induce pathological condition by defective feeding (e.g., in seniors), but they are not considered as major risk factors. Essentially, food reaching the stomach without proper chewing cannot be digested and absorbed. Without such preparation, the bulk food may cause damage to the esophagus.

Acute disorder of chewing in the form of *trism* is characteristic in epilepsy, rabies, tetanus, strychnin-poisoning, most frequently, in the potential injury of the tonsils (mainly inflammatory). Additionally, *trauma* of one or the other mandible/maxilla leads to an acute chewing disorder, consequently, the self-cleaning processes of the oral cavity becomes disorderly, resulting in changes of the oral bacterium flora, therefore various infections of the oral cavity will be far more frequent. *Infections* of the oral cavity, such as *aphthous ulcerations* and also *tumors,* may negatively affect the activity of chewing and grinding. *Missing teeth* and various disorders of the *occlusion line* may cause chronic chewing and consequent digestive disorders. The importance of the dental disorders (and, in some cases, the adequate artificial denture) cannot be overemphasized.

7.1.3. DISORDERS OF SWALLOWING

Swallowing presumes a precisely coordinated reflex activity of the pharynx, larynx and the esophagus. Any abnormality of these (dysphagia, odynophagia = painful swallowing) may lead to disorders of food intake. Apart from these, disorders may present an acutely perilous situation, e.g., due to disordered swallowing reflex and aspiration (obstruction of the airway passage by food), or due to mediastinal damage induced by inflammatory/ulcerous injury. The disorder of the reflex may also develop due to decreased sensitivity of the pharynx (e.g., in the course of dental anesthesia), and also in unconscious patients (e.g., aspiration of vomited substance, during alcohol intoxication). Occasional smaller dysphagias usually have little importance. However, if the swallowing disorder develops into a pattern of regularity, it may be a sign of a disorder in coordination reflex by higher medullary centers or of high intracranial pressure (e.g., brain tumors) – in the event of repeated, chronic dysphagias, these possibilities must also be considered.

Passage of food in the esophagus: The functions within the pharynx include the upper sphincter of the esophagus, characterized by high pressure. Additionally, beneath this sphincter and transcending the esophagus the pressure is low, until the lower sphincter adjacent to the cardia (gastro-esophageal sphincter, generally speaking, beneath the diaphragm), in which the pressure shows a sustained, elevated level. Upon swallowing, a peristaltic pressure-wave runs down along the esophagus, thereby forwarding the food. In order to reach the stomach, the tone of the lower sphincter transiently decreases, allowing the food to enter the stomach (of low pressure), and to do so characteristically with diminished pressure. Following the entrance of food into the chamber of the stomach, the tonal quality of the lower sphincter increases once again and the higher pressure is re-established. This sequence ensures that food substances can be easily forwarded only in a single direction.

An organic disorder of swallowing may be due to an esophageal ulcer, a scar, stricture, scleroderma, tumor, inflammation, and in these cases the peristaltic movement proves to be difficult, resulting in intense difficulty swallowing solid food.

In functional swallowing disorders the act of swallowing fluids is also difficult, and distinctively painful (although gravitation may lessen the problem).

The most important functional disorders:

Achalasia: Primarily, the esophageal peristaltic activity is normal, however, in the lower portion the pressure exceeds what is typically defined as normal. Due to degenerative changes of the myenteric plexus (Auerbach), the cardia does not open (or, in the very least, the cardia is not specifically synchronized to the swallowing reflex), therefore, in the lower esophageal sphincter the peristaltics-induced pressure suddenly and significantly increases, and the act of swallowing becomes painful (severe cramping in and around the cardia). Occasionally, on the basis of reflex abnormalities this may likely worsen, developing a scenario in which ”the biting, chewing and grinding” is momentarily halted, however, at this stage it is of hardly relevant medical importance. Following transient pain, the act of hiccupping may also develop and does so due to transit of the swallowed substance through the cardia causes pressure and excites the diaphragm. In the event of repeated occurrences, however, over time, the congested food causes a lasting dilation of the esophagus with continuously high pressure (at swallowing this will not be decreased below the pressure-level of the stomach, thereby preventing that food could enter the stomach). In the use of an X-ray examination, a ”bird’s peak” serves as a sign and may be observed (thin line of contrast material from the distended esophagus to the stomach). In other cases, through esophagoscopic examination a mucosal thickening (Schatzki ring) and congestion can be seen at the level of the cardia. Whatever is the cause of the congestion, it may cause inflammation and narrowing of the esophagus, the possibilty of an ulcer, and over time, it may lead to metaplasia (Barrett’s esophagus), in worse case to development of a tumor. The inflammation also causes retrosternal

”burning” pain, commonly referred to as ”heartburn”. Esophagitis always presents the risks of dangerous mediastinal spreading of the infection.

Diffuse esophageal spasm: It is based on an innervational disorder (diabetes, emotional stress, old age and reflux esophagitis). Swallowing induces a series of hardly moving simultaneous contractions of immense amplitude all along the esophagus, followed by enormous pain (= nutcracker esophagus). Rigidity all along the esophagus (including minimal contractions) is characterisitic in the case of scleroderma or scarring (e.g., after mucosal damage by corrosive substances).

Gastro-esophageal reflux disease (GERD): GERD is defined as a state when the cardia does not close properly. Characteristically, the pressure found in the lower sphincter of the esophagus is not high enough. This results in frequent opening of the sphincter, backflow of the acidic gastric content and difficulty in normal emptying of the esophagus. Acetylcholine, α-adrenergic effects, a protein-rich diet, high intra-abdominal pressure (not intragastric, but an effect reaching the cardia from outside, since the lower sphincter is positioned primarily below the diaphragm) all serve to enhance the pressure at the lower sphincter of the esophagus and inhibit reflux from the low-pressure stomach. In contrast, VIP, β-adrenergic effects, dopamine, NO, prostaglandins, acidic pH, chocolate, theophylline-like substances, alcohol and hot drinks all serve in helping GERD. In the case of GERD, the acidic stomach content may cause reflux esophagitis, demonstratively and clinically defined as ”gastric burning”, subjectively described as ”heartburn”, since this state resembles angina pectoris. The symptoms are increasingly pronounced, specifically when the patient is in the supine position. The chronic, everlasting presence leads to the tendency and development of metaplasia. The returning acidic gastric content may cause chronic laryngitis, tracheobronchitis, and a host of diagnostic problems. Quite often otorhinolaryngologists or pulmonologists discover and diagnose GERD among patients. Regarding treatment, and in addition to a low-volume, low-fat and no-alcohol containing diet, the suppression of gastric acid production (PPI = proton pump inhibitors) is important, although the lack of acid may alter characteristics of the gut pH and lead to unwanted consequences (gut flora – that would need an alkaline milieu – may change, what promotes enteral infections such as Clostridium difficile).

Diaphragmatic hernia: A near-esophageal part of the diaphragm has a hiatus, and the stomach features a hernial sack at the esophageal-gate. Inflammation may develop in this sack. Recent studies appear to demonstrate similarities of symptoms to those of acid-reflux. The potential for a hernia development includes also other diaphragmatic areas.

Diverticulum: The muscular system of the esophagus gradually loosens. A sac-like distension of mucosa is interwoven among the the muscle fibers. In the sac of the diverticulum acidic endproducts are formed by the remains of nutrients and the process of their breakdown, often resulting in chronic inflammatory state of the mucosa.

Varicosity on the lower portion of the esophagus: varicosity frequently develops in hepatic cirrhosis and other forms of portal hypertension (ch. 7.6.1.7.). The act of swallowing does not increase in difficulty, however, the potentially sensitive thin-walled varices may be injured due to harder food particles or in the act of vomiting, often resulting in immense bleeding.

7.2. MOTILITY DISORDERS OF THE GASTROINTESTINAL SYSTEM

7.2.1. DISORDERS OF MOTILITY AND EMPTYING OF THE STOMACH

7.2.1.1. LESS FREQUENT DISORDERS

Pylorus-stenosis may typically occur among infants. The circular muscles of the pylorus are hypertrophic, and despite the strong contractions of the gastric muscles, these cannot effectively forward the gastric content and cannot normally empty the stomach to the gut. Due to the result of intensely strengthened gastric contractions, *colicky abdominal pain* is a characteristic result, in which the spastic stomach can be seen and palpated through the thin abdominal wall. The gastric contractions inevitably empty the stomach backwards, an aspect commonly aligned with *projectile vomiting*, followed by consequent *exsiccosis*, severe dehydration, and quickly developing severe *fasting* condition. Projectile vomiting is defined in the stretching of the gastric wall and a substantial increase in pressure within the stomach. Food substance is hurled out of the stomach with significant force, in the form of an arch. Projectile vomiting differs when compared with an infant, seated or held in adult arms, and following a routine feeding, results in belching of recently swallowed air, including a small representation of the milk originally consumed,

and is also brought up through the marginalized, weak lower esophageal sphincter – this is not accompanied with the typical gastric contractions. Both exsiccosis and the vomiting-induced rapid starvation behaviors are life-threatening situations in infants. This stenosis can be resolved by a relatively simple surgical procedure (small incision on the circular muscle), thus, the potentially risky consequences can be prevented.

In adults, the stenosis and narrowing of the pylorus may develop due to tumors, to scarring of a peptic ulcer, or in transient functional form as a pyloric cramp.

Gastric atonia (paralysis) is yet another acutely life-threatening abnormality. It is known to be most frequently a consequence of autonomic neuropathies, however, it may develop upon any peritoneal damage, specifically, an abdominal surgical procedure. It is more frequently apparent among seniors. The atonic stomach exhibits neither mixing nor peristaltic activity, therefore, it cannot empty its content either towards the gut or backwards by the act of vomiting. The passive stretch enhances the secretion of gastric juice, consequently, the stomach volume rapidly increases, progressively increasing the stretch and secretion. Since the plasma is the only source of the secreted juices, therefore, rapid exsiccosis and/or hypovolemia (shock) develops. The entire process corresponds to a maximally proximal type of paralytic ileus (ch. 7.2.2.2.).

The accelerated pace in which the stomach empties and rids itself of food substance is defined as, "**dumping syndrome**." It may develop spontaneously, or following various forms of surgical gastro-entero-anastomosis (e.g., Roux-en-Y gastric bypass, Fig. 7.1.).

In the ***early*** form of dumping syndrome, food substance enters the small bowel too quickly thereby induces an unusually large secretion. Due to this secretion and to the osmotic activity of the digested food particles that typically bind more fluid (which ultimately originates from the circulation), often leading to acute hypovolemia and a tendency towards fainting (ch. 2.2.1.). The stretched bowel may induce colicky pain, nausea or trigger vomiting. The fluid eventually may be absorbed from more distal portions of the gut and the symptoms may spontaneously disappear, however, in most cases runny diarrhea ensues

In the other (***late***) form of dumping syndrome a few hours after feeding hypoglycemic type of indisposition develops, due to the too fast glucose absorption and the resultant extreme insulin secretion. Since the glucose absorption does not last for long, the temporary excess

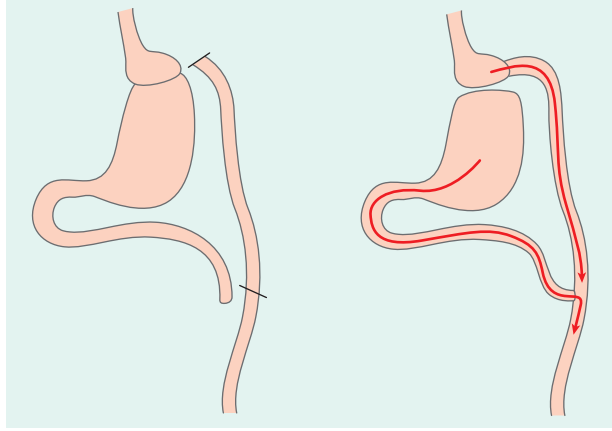

Fig. 7.1.: Roux-en-Y gastric bypass surgery (RYGB).

of insulin induces postalimentary hypoglycemic complaints (ch. 9.2.3.), with particularly strong vegetative symptoms. Following the Roux-en-Y gastric bypass surgery (ch. 8.4.3.4.) of surgical treatment of obesity this late form is more frequent (the simultaneously overproduced GLP-1 peptide also enhances the insulin-secretion and insulin-sensitivity).

Neither forms of the "dumping syndrome" are acutely life-threatening, however, the quality of life is severely diminished by the extremely unpleasant symptoms following each food intake. The lasting presence of either form with repeated indispositions results in early satiety and decreased appetite, often accompanied by diarrrhea, calorie loss, and combined with a disturbed absorption of Ca and Fe, resulting in loss of body weight, osteoporosis and anemia. Consumption of many small portions of food is advised.

In **duodeno-gastric reflux,** the closure of the pylorus proves is insufficient and it is combined with antiperistaltic movement from the duodenum, therefore, bile and pancreatic digestive enzymes may extend themselves back into the stomach. The heterogenous mixture severely irritates the gastric mucosa, often causing mucosal damage. Particularly, it often occurs in smokers and is acutely apparent in cholecystitis, cholelithiasis.

7.2.1.2. VOMITING (emesis)

Mainly because of its frequent occurrence and possible consequences, vomiting, or clinically referred to as emesis, is the most important disorder among the gastric emptying or purging, due to its freqency and its consequential aftermath. It is regarded as a genuine defence mechanism of the body, and in the case of a defective disgust or nausea it aids the body towards the effective elim-

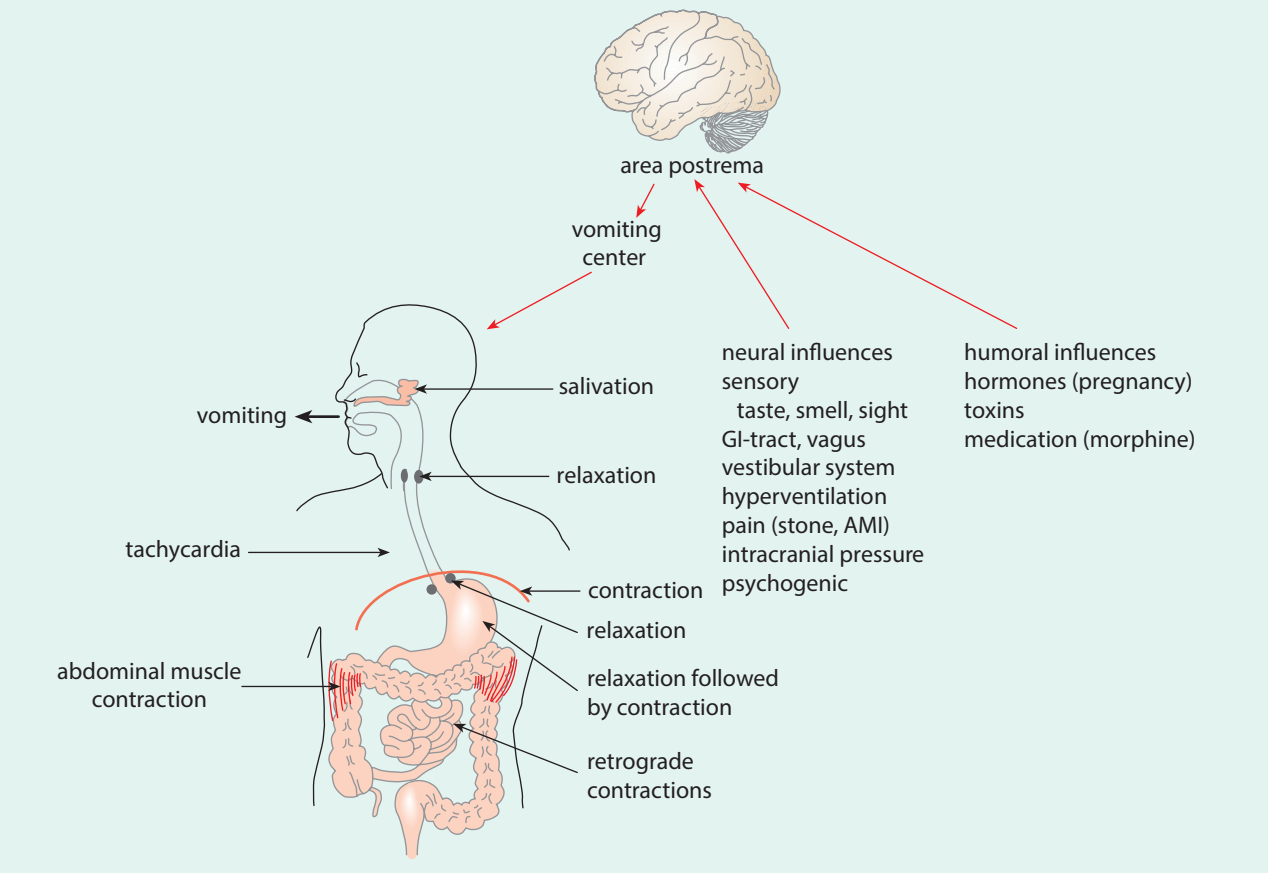

Fig. 7.2.: Reflex of vomiting. By an effect on neural or humoral mechanisms the "vomiting center" (area postrema) is activated, the consequent coordinated effector function is vomiting.

ination of potentially threatening and dangerous substances, if in earlier phases of disgust or nausea proved not enough to prevent the uptake of perilous materials.

In its most characteristic forms, vomiting is first preceeded by a wave of nausea (and sympathetic activation as before fainting), and as a more severe form of disgust in the prevention of additional intake of the specified food or other substance. From a psychophysiological point of view satiety and fullness, both disgust and nausea are the preceding steps prior to vomiting.

Mechanism of vomiting:

The gastic wall inevitably is stretched, the pylorus remains closed while antiperistaltic waves, gastric contraction and abdominal pressure intensify and push through the opening cardia, thereby vacating the gastric content, characteristically demonstrated in a projectile way, accompanied by increased pressure (Fig. 7.2.). In cases when the antiperistaltic movement of the small bowel results in bile reflux, bile becomes apparent in the material vomited. The simultaneous changes of the intrathoracic pressure influence the filling of the heart, the stroke volume and the heart rate. The parasympathetic overweight and accompanying vomiting leads to bradycardia immediately following the emptying of the stomach. Unexpected projectile vomiting with increased pressure (but without nausea), followed by fever may be sign of meningeal excitation/inflammation.

Factors provoking vomiting:

- Effects originating from the GI system (gastritis, enteritis, peritoneal/diaphragmatic excitement, mesenterial disorders, hepatic congestion),
- Various reflexes, in cases such as myocardial infarction (even "silent" postero-inferior AMI), stone-diseases (kidney stone ch. 5.3.3.4., bile stone ch. 7.6.2.), pain characteristically of any other origin, and adjoining pharyngeal reflex,
- Excitement of chemosensitive "vomiting center" in the brainstem, hypersensitivity of the area postrema (e.g. progesterone containing anticoncipients, vomiting in pregnancy or hypocapnia),
- Pressure, damage, hemorrhage of the center, high intracranial pressure (hypotonicity, hemorrhage,

extremely high blood pressure), meningeal excitation,

- Exogenous/endogenous toxic substances (heavy metals, toxic mushroom, medications and/or morphine-derivatives, digitalis, alcohol, or uremic toxins, ketone bodies, cytokines, etc.),
- Psychogenic (fear, excitement, anxiety) or sensory (disgust, taste, smell, scene, pain) effects, vestibular excitation (e.g. "motion sickness") may surreptitiously be lurking in the background.

Consequences of vomiting:

Vomiting on one occasion usually causes only a moderate loss of salt and water, acid loss, and occasionally mucosal damage. Repeated episodes of vomiting appears to be far more important, (Fig. 7.3.) including the consequent significant exsiccosis, metabolic alkalosis, hypokalemia (due to secondary hyperaldosteronism), prerenal azotemia (without acidosis!) and the potential development of calorie/energy deficiency. The ADH level increases already at the stage of nausea, and in chronic vomiting and hypovolemia the increase becomes more pronounced, consequently water retention leads to hypotonicity (hyponatremia) and this promotes the sustained continuation of vomiting (due to swelling of brain cells, high intracranial pressure, ch. 6.1.3.). Additionally, the ADH production is further elevated when the RAAS activation is not sufficient for the normalization of the plasma volume (exsiccosis, which is severe enough for possibly causing shock and subsequent metabolic lactate-acidosis). The hypokalemic (and also hypochloremic) alkalosis, characteristic for vomiting, can be normalized, but only by the simultaneous treatment of the alkalosis, hypovolemia, hypotonicity and hypokalemia. Mechanical injury of the mucosa during the act of vomiting may cause hematemesis by injury of esophageal veins (Mallory-Weiss syndrome). A widely known mechanical disorder may be the result of the aspiration of gastric content, particularly in patients with severely disordered consciousness. Specifically, the recommended position of an unconscious and inebriated patient is laying on his/her side, and stabilized.

Mechanism of vomiting-induced *hypokalemic alkalosis*: loss of gastric acid, hypochloremia, alkalosis, hypovolemia, followed by secondary hyperaldosteronism and increased salt/water reabsorption in the tubules, here the Na^+/K^+ and Na^+/H^+ exchange also increases. The K^+ is replaced from the cells, and, in exchange H^+ repositions into the cells, therefore alkalosis develops in the plasma and excess acid within the cells. Additionally, the same bears true in the case of the distal tubular cells, in which the steadily increasing paradoxical aciduria and kaliuria is the resulting consequence, further increasing the alkalosis in the plasma and also the hypokalemia (with intracellular excess of acid). Without replacing the plasma NaCl, in the distal tubules more water is reabsorbed with relatively less NaCl and more $NaHCO_3$ (instead of NaCl). Due to insufficient attempt at correcting the hypovolemia, the ADH-secretion is also activated, causing pure water reabsorption, there-

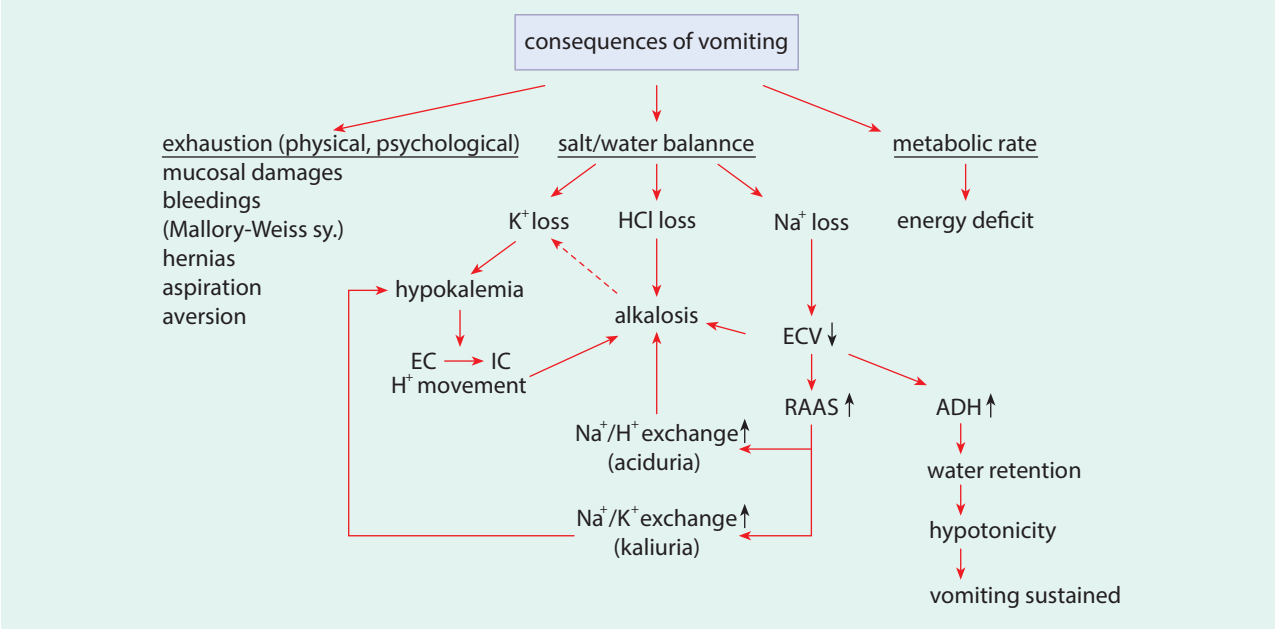

Fig. 7.3.: Basic consequences of vomiting.

by the osmotic pressure of the body decreases and the hypotonicity-induced brain edema contributes to continuation of vomiting. In the final development, hypovolemic shock, lactate-acidosis + hypotonicity are characteristic consequences of vomiting.

Primarily, formerly published literature described *acetonemic vomiting,* which was more commonly seen among children. In these cases, the vomiting induced by specific cause (e.g. psychological excitement) leads to the rapid development of ketonemia (within hours), which cannot be simply explained by the vomiting-induced fasting state. Typically, only far longer fasting would lead to ketosis. In the background, a disorder of the metabolic regulation is assumed: it is likely that the gluconeogenesis is defective (ineffective glucagon?), therefore, the appearance of accelerated starvation is clearly evident (ch. 8.4.2.2.). The ketone bodies excite the vomiting center, therefore, vomiting is continually repeated. Lastly, in addition to ketosis, life-threatening hypovolemia (shock) and hypoglycemia may rapidly develop.

7.2.2. DISORDERS OF INTESTINAL MOTILITY

In the digestion of nutrients and forwarding gut content various mixing and peristaltic bowel movements all imply essential and basic relevance. The motility may be abnormally fast or slow. All forms of diarrhea are coupled with an enhanced motility of the GI system (in the very least, temporarily), while the motility is decreased or missing in obstipation, subileus and ileus.

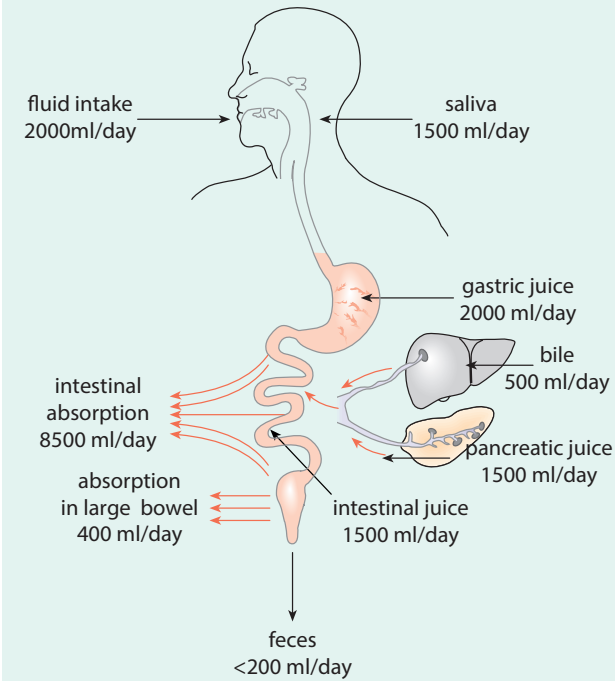

Fig. 7.4.: Salt- and water-exchange in the GI tract.

7.2.2.1. DIARRHEA

Definition and forms

The daily average water content in adult feces is 100-200 ml (Fig. 7.4.). The amount of water is higher in patients experiencing various forms of diarrhea. Consequently, the amount and consistency of feces undergoes significant alteration, including an increase in peristaltic movement, and the purging, or emptying of the bowel becomes increasingly frequent. It is less important to consider the number of purgings, but the water content of the feces proves decisive.

Osmotic diarrhea: In the case of osmotic diarrhea, either the digestion or the absorption is primarily altered, or suffers catastrophic disorder. An immense quantity of unabsorbed nutrients may remain in the gut. The bacterial breakdown of these leads to the production of a host of osmotically active particles, which do not readily permit the reabsorption of water normally secreted to the gut (Figs. 7.5.-7.6.). The extent of diarrhea may be different, the amount of fluid secreted at different points of the GI tract may be 8-10 liters (Fig. 7.4.), therefore, the fluid loss due to diarrhea may prove absolutely significant. In this form of diarrhea it is characteristic that upon withdrawal of food, the severity of diarrhea may decrease due to the absence of food and its bacterial metabolites and the apparent lack of osmotically active substances routinely produced in the bowels. Disorders characteristically leading to osmotic diarrhea include the followings:

- disorders of chewing.
- following consumption of foods rich in fibers.
- insufficiency and ineffectiveness of digestive enzymes.
- stagnation of bowel content and slow passage.
- increase in bacterial growth.
- damage of absorptive surfaces and primary disorders of absorption.
- postoperative states such as, gastrectomy and vagotomy.
- use of over-the-counter and prescription laxatives, high in salt laxatives and osmotic laxatives such as lactulose.

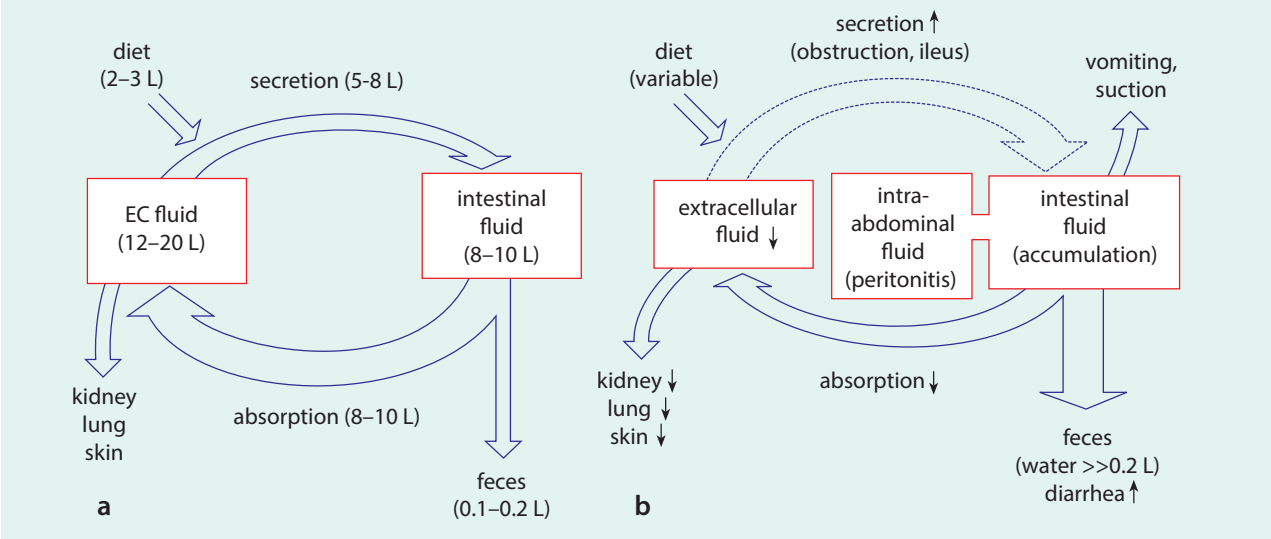

Fig. 7.5.: Salt- and water-exchange in GI tract normally (A) and its possible disorders (B). Both defective absorption and enhanced secretion may increase the water content of the feces, causing osmotic or secretory type of diarrhea. Other Salt- and water-balance disorders are also presented and it is shown that the GI disorders may decrease the whole extracellular volume.

Secretory type diarrhea: If the daily secretion of digestive enzymes significantly exceeds 8-10 liters, the excess amount cannot be absorbed, even if the absorption is normal. Characteristically, "runny diarrhea" or "watery diarrhea" (apparent in cholera, referred to as "rice water stool"), diarrhea persists and may exhibit an extreme volume, without any food intake (Figs. 7.5.-7.6.). Notably, in cholera (with continuous venous volume replacement), within a window of 4 to 5 days, the loss of fluid may considerably exceed the original total body weight. The diarrhea-induced exsiccosis may still prove to be more moderate if the absorption capacity of the small bowel is somehow increased (Na-glucose symport mechanism). Specifically, this "oral rehydration" treatment is preferred when the infusion treatment is not possible (e.g. in the jungle): it is performed by drinking a solution of 3-5 g NaCl, 1-5 g KCl, 2-5 g $NaHCO_3$ and 20 g glucose per liter water.

The most important causes of secretory diarrhea include the following:

- inflammation of the intestinal wall (allergy, some bacteria, gluten enteropathy and ischemic-inflammatory bowel diseases).
- oversecretion of GI hormones which enhance secretion of bowel juices (e.g. VIP causes WDHA, gastrin causes ZES /ch. 7.3.1.1./ - however, GIP and CCK secretion may also be overproduced).
- poor circulation within the bowel wall and non-occlusive mesenterial ischemia.
- carcinoid (massive production of serotonin, histamine and prostaglandins).
- potential infections such as cholera and enterotoxic E. coli.
- stimulation of the mucosal cAMP-system (enterotoxin, coffein, PG, VIP and bile acid).
- premature deconjugation of bile acids, or a rapid increase and immense production of bile acids entering the colon (ch. 7.6.1.4.).

Inflammation of the intestinal wall and the consequent occurrence of diarrhea prevalent among developing countries is far more responsible in the resulting fatalities than widely known starvation and malnutrition. The microorganisms are attached to the epithelial cells (the receptor-ligand binding is species-specific, and is influenced by phenotype, biological age, and the affected area of the bowel). Characteritics of diarrhea vary, and are largely dependent upon the area affected. Additionally, the behavior of diarrhea and the activity among microbes varies, as seen below:

1. *Enterotoxic* types, e.g. enterotoxic E. coli (= ETEC): Rather, it should be aptly referred to as enterotonic, since it enhances active secretion and decreases reabsorption. Cholera-toxin and substances of similar action (coffein, PG, VIP, hydroxy-bile acids) exert this effect by the activation of the cAMP system of basolateral membranes. Similar effect, yet independent of cAMP, is also possible (secretin, CCK, GIP, bacterial infection: e.g. Shigella). Historically, such forms of enteritis had been responsible for the large number of fatalities among small children (e.g. in a single family numbering 8 full term pregnancies,

and as a result due to illnesses with diarrhea, only 3 to 4 children, on average, reached adulthood).

2. *Enteropathogenic* types, e.g. enteropathogenic E. coli (=EPEC): E-coli cause mucosa injury without invasion. Microvillus extensions surround the bacterium, thereby the microvillus and cytoskeleton is lost, the absorption decreases, and inevitably, inflammation develops. Due to the severity of the inflammation, the secretion level is increased. Distinctly, the pathomechanism of Giardia works in a similar fashion.
3. *Enteroinvasive* types, e.g. enteroinvasive E. coli (=EIEC), Shigella, Salmonella: This type of E-coli may injure the surface of epithel cells, may fusionate with the cell (paramyxovirus), and/or endocytosis inevitably develops. In all cases, toxins extend themselves into the cell's interior, thereby inhibiting protein synthesis, lead to demise of the cell, followed by ulceration and inflammation.
4. *Translocation-inducing* types, e.g. Salmonella, Yersinia: Originating from the epithel cell, the bacterium extends itself into the lamina propria, induces acute inflammation, invades the lymphatic system and circulation, resulting in bacteriemia.

Motoric type diarrhea: The primary increase of motility may also result in diarrhea, e.g., on an emotional basis, such as in the case of acute fright or fear, or severe *parasympathetic* tension, as seen in mushroom poisoning or intoxication, and it is associated with cholinesterase inhibitor organophosphates, irritable bowel syndrome (abdominal pain, irregular defecation, dyspepsia – referring to a digestion problem resulting in a poorly defined, however, not entirely severe, yet, disturbing abdominal complaints). Characteristic compliants include mild, colicky pain, meteorism, irregular/diarrhea-type feces. However, as a secondary result, an increase in motility joins nearly all other types of diarrhea. Interestingly, some data suggests that Crohn's disease possibly occurs also in the small intestine.

Within the sphere of clinical practice, these pathological forms often appear in a mixed way, e.g. as seen in several viral enteral infections, the first problem includes the loss of enzymes regarding digestion on the intestinal surface, suggesting an osmotic type of abnormality, however, the increase and stretching of the gut also increases the amount of secretion and motility. Among the VIP-type peptides, bile acids enhance not only the secretion but also the motility. Diabetic neuropathy may cause diarrhea, however, in other cases, obstipation results.

Diarrhea of a clearly colonic origin can be seen among inflammatory diseases of the colon including colitis ulcerosa, Crohn's disease and ileitis terminalis, however, the secretion and motility may experience an increase in their levels if and when the amount of bile acids, metabolites and phytotoxins extending into the colon is too high.

Consequences of diarrhea (Fig. 7.7.)
Severe diarrhea may be potentially dangerous and acute, primarily due to the loss of salt and water, consequently resulting in exsiccosis, extrarenal uremia and shock. *K^+-loss* develops partly due to the enteral loss (K-content of

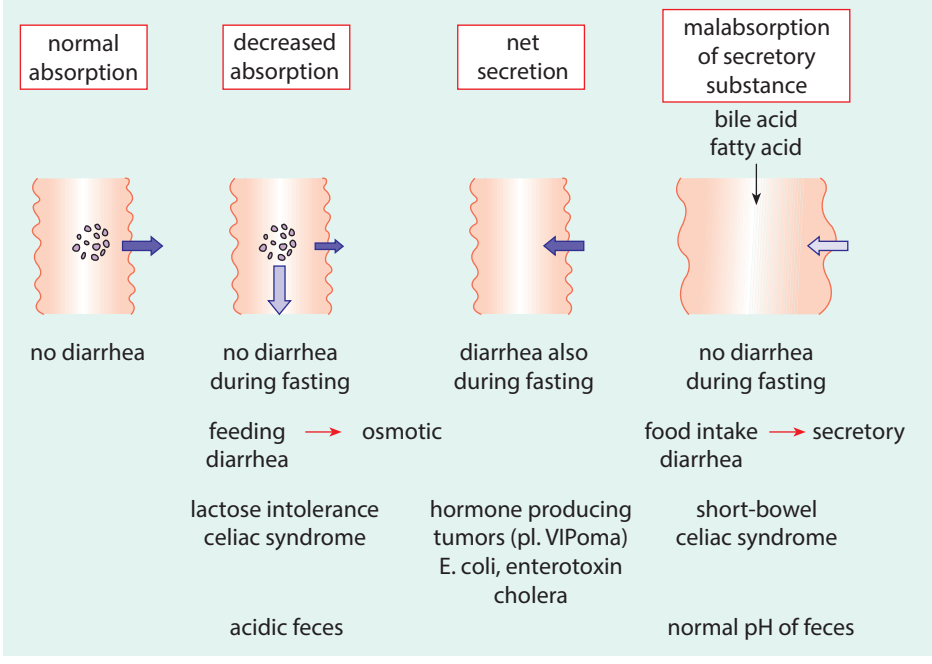

Fig. 7.6.: Osmotic (decreased absorption) and secretory (net secretion increased) types of diarrhea. Due to small bowel malabsorption bile acids and fatty acids may pathologically reach the large bowel and enhance the secretion. In the clinical practice the pathomechanisms are often combined.

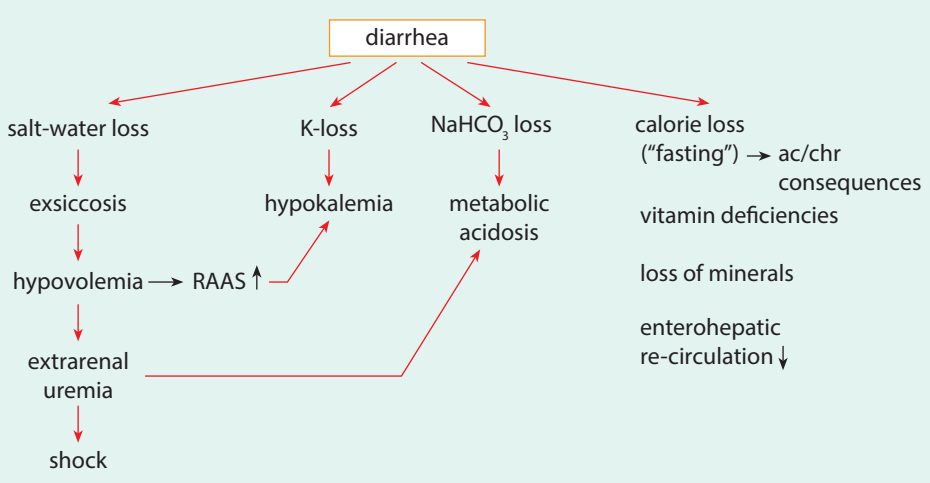

Fig. 7.7.: General consequences of diarrhea.

the bowel juice and the loss of the destroyed mucosal cells from which the K^+ normally is reabsorbed). Additionally, the RAAS activation also leads to K^+ loss. Similarly, as seen in nearly all cases, once and if the *RAAS activation* is not sufficient to normalize the volume, the *ADH secretion* also witnesses an increase, resulting in hyponatremia-hypotonicity. The *metabolic acidosis* can be explained by the lost bicarbonate among the bowel juices. *Caloric loss* is acute, however, its relevance lies only in specific cases, such as newborns, infants and originally anorectic indivuals. In chronic cases, in addition to the abnormalities of salt and water balance, acid/base balance, the defect of calorie-containing and additional non-calorie-containing nutrients (*vitamins, Ca, Fe, Mg and other mineral substances*) is important. In chronic diarrhea, the enterohepatic circulation is interrupted, and consequently, bile acid deficiency may develop, resulting in a potential tendency for bile stone formation (cholesterol, bilirubin stones, ch. 7.6.2.).

7.2.2.2. ILEUS

Definition and forms

The passsage of bowel content stops, what may be due to a mechanical obstruction (obstructive type of ileus) or atonia of the bowels (paralytic ileus). In rare cases, by diffuse spasm (spastic ileus). Paralytic and spastic types are collectively defined as dynamic forms of ileus.

Symptoms of ileus

Neither stool nor gases are purged, vomiting or miserere (vomiting bowel content) is frequent. An X-ray depicting an empty abdominal cavity (without contrast materials!) reveals niveau-production (severely distended intestinal loops filled with fluid and gas, in which the fluid is highlighted in the shape of a half moon, separated by a straight line /=niveau/ differentiating it from gas). A characteristic symptom is the splashing sound upon sudden release of the slowly displaced abdomen ("splash of Hippocrates"). Other symptoms include colicky, intestinal pain and rumbling in mechanical forms, what may be followed later by „silence of the grave" above the abdomen (this is characteristic for the paralytic ileus from its beginning). The appropriate treatment includes the following: volume-replacement, pH-normalization, K-replacement, the removal of lumen content (suction by cannula), surgical treatment of the injured bowel, etc. It is important that without immediate treatment and responsive therapy, the patient generally succumbs within 1 to 3 days (sometimes more), and does so while in a state of progressive shock.

Pathomechanism of ileus (Fig. 7.8.)

It is not the lacking passage of bowel content in itself means the decisive factor in the pathomechanism of ileus, as, notably, much longer lasting obstipation may persist without severe consequences. Following the resection of the bowel, connection between the proximal and distal endings generally secures continuous passage. In animal experiments, however, despite such eventual passage following resection, the symptoms and consequences of ileus develop if the resected section (with normal blood supply and neural connections, and closed by sutures at the ends) is left within the abdominal cavity.

A decisive role is assumed for the fact in which the secretion of salt, water, bicarbonate and K^+ increases, originating from the plasma to the stretched bow-

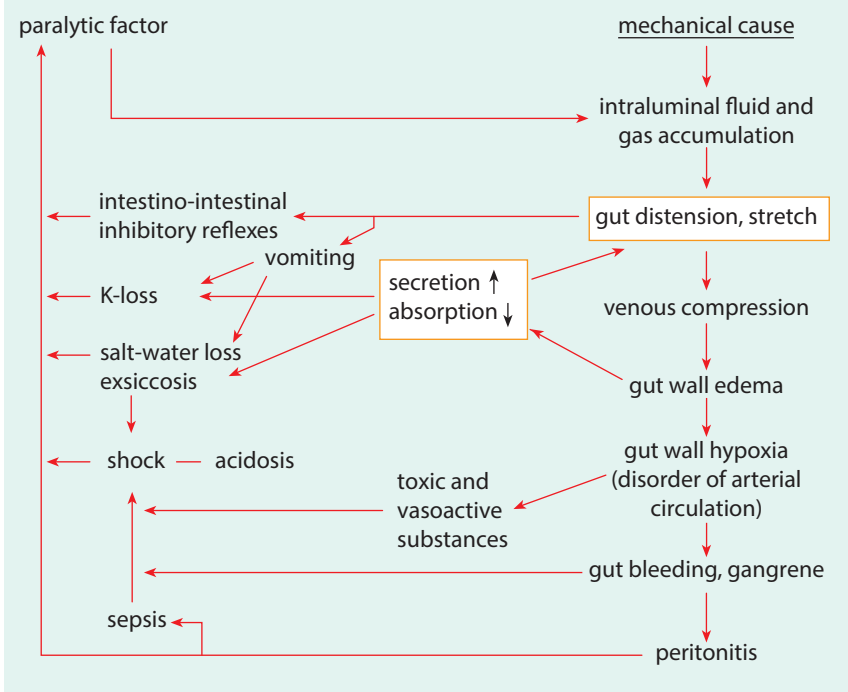

Fig. 7.8.: Pathomechanism of obstructive (mechanical) and paralytic ileus.

el loops and consequently ***exsiccosis*** (hypovolemic shock), ***acidosis*** and ***hypokalemia*** inevitably develops. The bacterial destruction of bowel content leads to an enhanced gas production, further increasing the ***stretch of the gut wall*** (instead of the normal 2-4 H_2Ocm, it may increase to 8-10, in colicky pain extending up to 30-60 H_2Ocm) and this further enhances the secretory rate. In regards to the gut content, ***toxic*** substances may be absorbed (passively), further worsening the circulatory shock. The blood perfusion of the stretched wall decreases, ***hypoxia*** develops and the ***permeability*** increases, bacterial translocation, necrosis, peritoneal damage and peritonitis may develop (septic shock). The stretch activates various pathological inhibitory reflexes, which together, including the peritoneal excitement and hypokalemia, produce a paralytic factor.

Obstruction may be caused by tumors growing within the lumen of the bowel or compressing the bowel from the outside. Additionally, bowel obstructions may be the result of strangulations, strangulated hernia, volvulus, invagination, bile-stone ileus, etc. The enhanced dynamics still cannot press the bowel content through the obstruction. The greater part of the obstruction happens within the small bowel: the more proximal it is, the more perilous is the consequence (occlusion at the duodenum may cause death within 1-2 days, in the case of sigma, death may occur after one week).

The causes of **paralytic ileus** (atonia, dynamic ileus) are manifold. Antagonists of the parasympathetic system (e.g. *severe* organophosphate intoxication, what can be treated by atropin), opiates and phenothiazine-derivatives, hypothyroidism, autonomic neuropathies (dia-

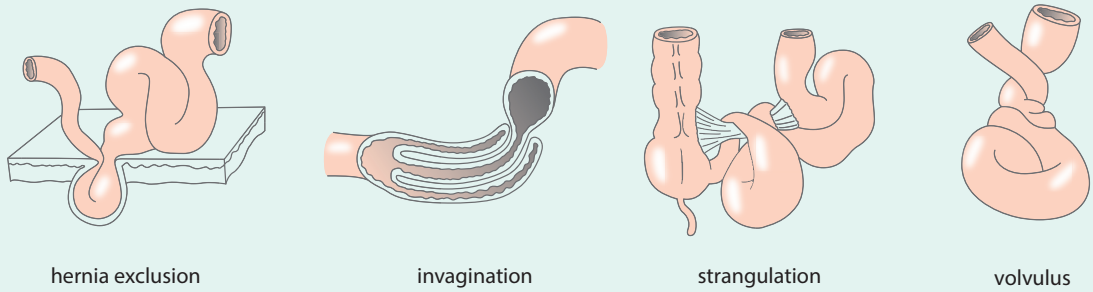

Fig. 7.9.: Forms of obstructive ileus.

betes mellitus, aging neuropathies), sclerosis multiplex, Parkinson-disease and amyloidosis, all are relatively frequent. Other causes of paralytic ileus include the followings: excitation of the peritoneum (e.g. abdominal operation, intraabdominal bleeding, pancreatitis, perforations), occlusive, or non-occlusive ischemia of the gut wall (Fig. 7.10.), retroperitoneal bleeding (disc-compression, renal trauma and renal bleeding, acute pancreatitis), pyelonephritis, ureter-stone, intrathoracic disorders (lower lobar pneumonia, AMI, broken rib), and hypokalemia are the most important. The solution and therapy of these is usually more difficult, in comparison with the obstructive forms which can be surgically resolved. Additionally, in the late, severe phase, the obstructive ileus turns into paralytic form (Fig. 7.8.).

Particular emphasis should be placed on the ***non-occlusive mesenterial ischemia***, since it often remains unchecked, and rarely do doctors consider the remote possibility. According to data from dissecting wards, the cause of death can be related to *non-occlusive mesenterial ischemia*, and it can be demonstrated in 3% of fatality cases of any cause (in the cases of neonates, stemming from intensive care units, it may be 5%). In its severe forms paralytic ileus develops, and in less severe forms bloody diarrhea and malabsorption are characteristic, particularly among seniors. However, in contrast, bloody or Weber positive diarrhea was also found in 20% among younger marathon runners, but they recovered quickly and spontaneously. In general, states with decreased cardiac output such as heart failure, arrhythmia, hypovolemia or digitalis, papaverin, vasopressors are lurking in the background. The result of these triggering factors often leads to a redistribution of cardiac output, and to decreased local (intestinal) blood flow, therefore, hypoxia develops, free radicals accumulate, endotoxins and other toxins and digestive enzymes are translocated.

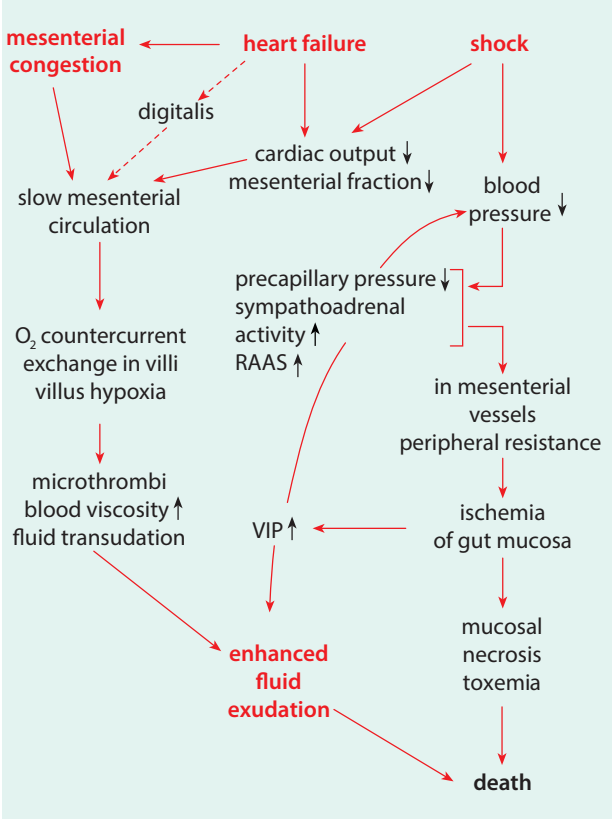

Fig. 7.10.: Consequences of non-occlusive mesenterial ischemia. The functional consequence is paralytic ileus.

A far less acute state is referred to as **subileus**. The gradual slow down or complete stop of peristaltics is only transient and will remain paused but for several days. The newly initiated motility first serves in helping to purge a thickened plug of feces, followed by the proximally accumulated and rather watery (wall stretch-induced hypersecretion) gut content. This may be followed by malabsorption, due to injured mucosa and osmotic/secretory diarrhea, or incontinence. Once again, obstipation may reoccur and does so in various, alternating forms of obstipation and diarrhea. Its reappearance is characteristic regarding tumors of the colon, yet may also be observed in more severe cases of common diverticulosis (ch. 7.2.2.4.).

Spastic ileus (also dynamic form of ileus, however, the dynamics are halted due to the presence of spasms): the most frequent occurrence is due to heavy metal poisoning, nicotine poisoning, uremia, porphyrias and multiple intestinal ulcer.

7.2.2.3. DISORDERS OF THE MOTILITY OF THE LARGE BOWEL

Inflammations of the large bowel mucosa are accompanied by diarrhea. Similarly to the hypersecretory states of the small bowel, this is also a secretory form of diarrhea. This may be consequence of an abnormally large amount of bile acid reaching the colon. Disorders of vegetative innervation may also increase the motility of large bowel. Activation of an assumed gastro-colonic reflex implies how food reaching the stomach leads to higher colonic motility and diarrheic feces. Abnormal innervation is presumed to be directly associated with an irritable colon exhibiting a high rate of motility. The

smaller increase in colonic tone may result in motoric type of diarrhea, while a stronger enhancement of tone such as a spastic colon, inhibits peristaltics. The vegetative disorders are often coupled with an overproduction of mucus. The colonic motility may also decrease in autonomic neuropathies (diabetes, uremia, old age, etc.), although, in these forms, temporary hypermotility and often subileus, may also occur.

In *megacolon congenitum, or* Hirschsprung's disease, a colonic section congenitally is missing the neural elements of the myenteric plexus (aganglionic section). This section is unable to support the forward movement of the gut content, therefore the congested bowel content of the increased proximal dilated colonic sections secures passive forwarding of the bowel content by enhanced pressure.

Motility disorders of the last section include various disorders in purging the feces. The basic abnormality may be an injury of the medullary reflex (with consequent passive incontinence = emptying continuously), or a disorder of the connection between lumbosacral and higher centers (active incontinence = based on stretch reflexes, unregulated but occasional purging, as in babies).

7.2.2.4. OBSTIPATION (CONSTIPATION)

Obstipation (or constipation) is defined as the slowed movement that proves detrimental in effectively forwarding the gut contents. Consequently, the content increases in thickness, becomes harder than normal and it is typically, rarely and irregularly emptied. Commonly seen among seniors, and in elderly patients suffering from minimal mobility: in these patients the content is not only hardened, but appears in the form of a stone, clinically referred to as coprolith, and remains in the bowel further inhibiting the passage. The slow motility and congestion of content is accompanied by an accumulation of gases and may cause stretch (meteorism), subsequently, many of the complaints highlight general discomfort. Formerly, it was believed that toxic substances were absorbed from the congested gut content, resulting in complaints of discomfort. However, immediately following defecation, the complaints cease, implying that intestinal stretching induced neurogenic/reflex mechanism was their causative factor, explaining the obstipation-induced complaints, similarly to those seen in subileus.

Obstipation may occur in an isolated form, as an idiopathic abnormality, however, it may also be a part of systemic disorder. More frequently, it can still be seen in anomalies of the autonomic nervous system, particularly in autonomic neuropathies, including diabetes mellitus and old age, in general. Hypokalemia leads to decreased motility of the GI system. Hypomotility may also be evoked by the hypoxia of the intestinal wall. Following abdominal surgical procedures or other injuries of the peritoneum, the intestinal motility temporarily ceases, or slows down. In this event, it is paramount to examine the effective reinitiation of motility following such surgeries. In cases of physical inactivity and/or immobilization, there is a lasting decrease in motility. In consideration of lifestyle factors, the diet may also be a triggering factor, such as in the case of a diet comprised of low fiber content, in which the bowel content decreases and the resulting motility is slowed. Diminished fluid intake also supposed to result in the thickening of the bowel content often leading to obstipation. Mechanical factors may also cause obstipation, e.g. diverticulosis, polyposis, undue compression from the exterior, such as adhesions.

Diverticle is generally observed in the large bowel and rarely encountered in the ileum, due to mucosal herniation through the muscular layer of the gut, the mucosal sac does not participate in the passage, often is easily inflamed, ceases the passage and/or results in peritonitis. Notably, it is often difficult to differentiate between obstipation and tumor-induced subileus.

Therapeutic considerations: Eventually, motility enhancing laxatives can be considered to effectively increase motility and ease the pain and general discomfort. However, this approach should not be used regularly, as it often results in hypokalemia, and further worsens the condition. The problematic discomfort should be lessened partly by the appropriate diet, increased physical activity, and osmotic laxatives (lactulose, mannitol and a diet rich in fibers).

7.3. DISORDERS OF SECRETION AND DIGESTION

7.3.1. SECRETION OF DIGESTIVE ENZYMES

Although salivary amylase contributes to the digestion of carbohydrates, the predominant digestive enzymes are produced in the more distal sections of the

GI tract. Enzymes produced throughout the stomach and the pancreas are important, mainly in the luminal digestion and the effective breakdown and mincing of larger food particles. The resultant particles are not yet suitable for absorption, therefore, additional digestion regarding the mucosal cell surface is also necessary. The latter is performed by the cell surface-bound enzymes (oligosaccharidases, oligopeptidases, etc.). Effective digestion of lipids needs lipases and also necessitates the emulsive role of the bile, however, bile is also required in the absorption of lipids and lipid-soluble vitamins.

In the regulation of digestive juices, ***gastrointestinal hormones*** perform a fundamental role. Apart from the *cholinergic* role of the vagus, the hydrochloric acid secretion of the stomach is also enhanced partly by *gastrin* produced in the antral G-cells, and partly by activating enterochromaffin-like (ECL) cells and via their *histamine,* since these enhance the hydrochloric acid secretion of parietal cells of the stomach (Figs. 7.11., 7.12.). The G- and ECL-cell activities are inhibited by *somatostatin (SST)* of the D-cells which are activated by CCK, VIP, GIP, CGRP, noradrenaline and a high H^+-concentration.

The SST also inhibits the pepsinogen production of the chief cells. *Secretin* produced in the intestinal mucosa enhances the amount of pancreas juice and its bicarbonate content, the cholecystokinin (*CCK*) increases the enzyme production and bile secretion, the vasoactive intestinal peptide (*VIP*) stimulates the intestinal and pancreatic secretion, and all of these aspects serve to inhibit the secretion of hydrochloric acid. Somatostatin (SST) decreases the secretion of both secretin and hydrochloric acid, while the gastric inhibitory peptide (*GIP*) inhibits mainly the acid production. Dozens of other gastrointestinal peptides may perform additional roles common to the various secretory processes. These hormones do not exclusively influence the secretion. For example, *gastrin* also enhances gastric motility, as well as differentiation and proliferation of epithelial cells, and the lasting suppression and lack of acid production causes G-cell hyperplasia, stronger non-excretory actions, hypermotility, epithel proliferation and carcinoid production. The *enteroglucagon* exhibits trophic effects. *Motilin* enhances bowel motility. The glucagon-like insulinotropic peptide (*GLIP*) is important primarily for its metabolic and endocrine, including enhancement of insulin-secretion. The L-cells of the intestinal epithelium produce glucagon-like peptide-1 (*GLP-1*), which is an incretin hormone and also increases insulin secretion, and, while acting in the brain, serves in decreasing the appetite and increasing the metabolic rate. Additionally, nearly all GI hormones perform some role in the central nervous system (ch. 7.3.1.1.), and this system is referred to as the *brain-gut axis*.

7.3.1.1. GASTROINTESTINAL HORMONES

Common features:

- Peptides (chains of various length are possible)
- They are produced in diffuse cell groups within the walls of hollow organs (not in circumscribed endocrine organs)
- They can also be found in the brain (”brain-gut-axis”). The peripheral and central actions are often different: e.g. peripheral CCK acts mainly on CCK1 (CCK-A) type receptors, induces satiety and hypothermia, while centrally, it binds to CCK2 (CCK-B) receptors and also causes satiety but induces hyperthermia.

Several hormones may derive from one gene:

- Gene splitting (calcitonin, calcitonin gene-related peptide /CGRP/)
- Peptide shortening (gastrins, CCK-variants)
- More precursors in one prohormone (pro-opiomelanocortin /POMC/: ACTH, MSH, opioids)
- Produced in hollow organs (possibility of local regulation)
- Many of them act upon motility, secretion, blood flow, or trophically, in the thickness of mucosa of the bowel wall and mucosa
- They are aligned to the APUD (amine precursor uptake and decarboxylation) system

Possible ways of action:

- Endocrine: they reach the target organ by blood flow (i.e. GI system or central nervous system)
- Paracrine, autocrine: act locally and directly upon neighboring cells, or act upon the secreting cells themselves
- Neurocrine, transmitter: in the often referred to, enteral, or ”third” autonomic nervous system

Classification:

1. Gastrin family (gastrin, CCK)
2. Secretin family (secretin, GIP, VIP, PHI, glucagon, enteroglucagon, /GLP-1/, PACAP)
3. Insulin family (insulin, IGF-I, IGF-II, relaxin, amylin)

4. Tachykinins (substance P /SP/, neurokinin A and B)
5. Pancreatic polypeptid family (PP, PYY, NPY)
6. Somatostatin family (SST)
7. EGF family (EGF, TGF)
8. Else (neurotensin, galanin, CGRP, etc.)

Pathophysiology:

Hyperfunction, hypersecretion, hyperplasia and tumor:

GASTRIN

- gastrinoma (Zollinger-Ellison syndrome, ZES)[1]
- G-cell hyperplasia
- gastric ulcer, pernicious anemia [2]
- VIP-oma (+secretinoma, new data: peptide together with histidine-methionine excess)
- WDHA syndrome[3] (Verner-Morrison syndrome)
- INSULIN-oma, GLUCAGON-oma, SOMATOSTATIN-oma
- MEN (multiple endocrine neoplasia)
- CARCINOID syndrome (serotonin hypersecretion and hypermotility)

Hypofunction: (Very rare. Other hormone(s) usually replace the function.)

- Coeliakia (= celiac syndrome): due to gut mucosal atrophy less CCK production, this leads to a disorder of gallbladder motility. This contributes to the complex malabsorption picture, by the decrease of absorption surface of the intestine.
- Cholelithiasis with low CCK (in a hypokinetic gallbladder, the bile becomes thicker)
- Atrophic gastritis (achylia gastrica): autoimmune origin, gastric mucosa atrophizes, no HCl, no pepsin or intrinsic factor. B_{12} vitamin deficiency – pernicious anemia. (Due to high gastric pH the gastrin secretion increases and the non-secretory gastrin-functions are enhanced).

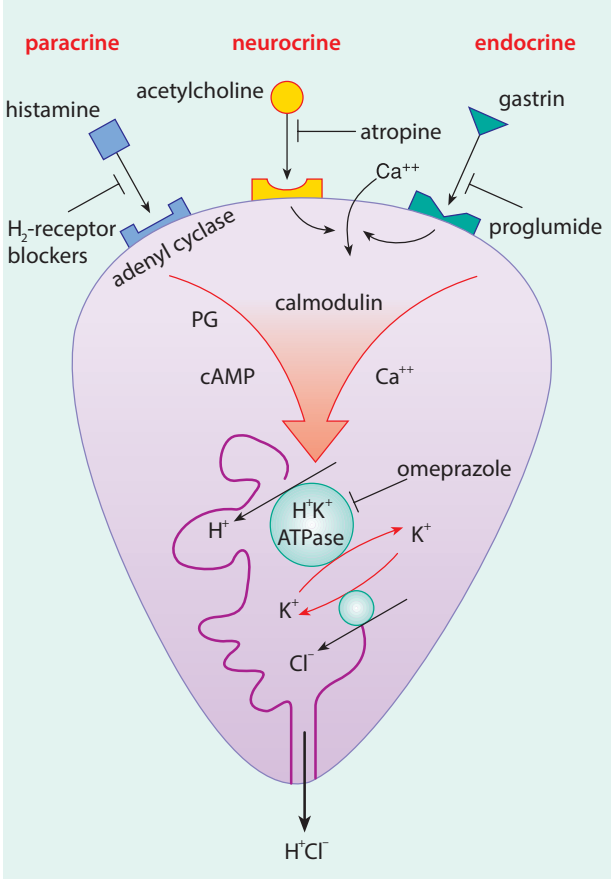

Fig. 7.11.: Classical view on the way of action of factors stimulating hydrochloric acid production in the stomach (paracrine histamine, transmitter acetylcholine, endocrine gastrin) and ways of inhibiting these. Physiologically the most important is gastrin, its production is stimulated by high pH and food in the stomach, some gastrointestinal hormone decrease the production.

[1] Zollinger-Ellison syndrome (ZES): Ectopic (e.g. in pancreas, in duodenum) gastrinoma. The consequent hyperacidity does not give negative feed-back signal (gastrin in the G-cells of the stomach is continuously produced, the somatostatin feed-back is not enough). Severe hyperacidity develops and repeatedly many small, deep, painful ulcers are formed in the stomach, duodenum, sometimes in the jejunum. The duodenal pH becomes acidic, therefore the effects of pancreatic enzymes are insufficient and this causes malabsorption. Possibly part of MEN-1 (ch. 10.).

[2] B_{12} vitamin deficiency: apart from the bone marrow the cellular division decreases also in the gastric mucosa. Consequently the gastric mucosa atrophizes, acid - pepsin - intrinsic factor production strongly decreases. The G-cells are released from the negative feed-back and the gastrin production increases (this gastrin increases the motility, and with its proliferative effect promotes tumor formation).

[3] WDHA (watery diarrhea, hypokalaemia, achlorhydria), or WDHHA (watery diarrhea, hypokalaemia, hypochlorhydria, acidosis) syndrome (= Verner-Morrison syndrome): overproduction of VIP, secretin, or other peptid of similar action. These normally (well after feeding) enhance production of bowel juice and the motility, but in a feedback-like way they inhibit the gastrin and HCl production in the already emptied stomach. Pathologically, these cause secretory diarrhea, hypokalemia with acidosis (enteral K^+ and bicarbonate loss), in addition to achlorhydria, or hypochlorhydria. Secondary hyperaldosteronism contributes to K^+-loss.

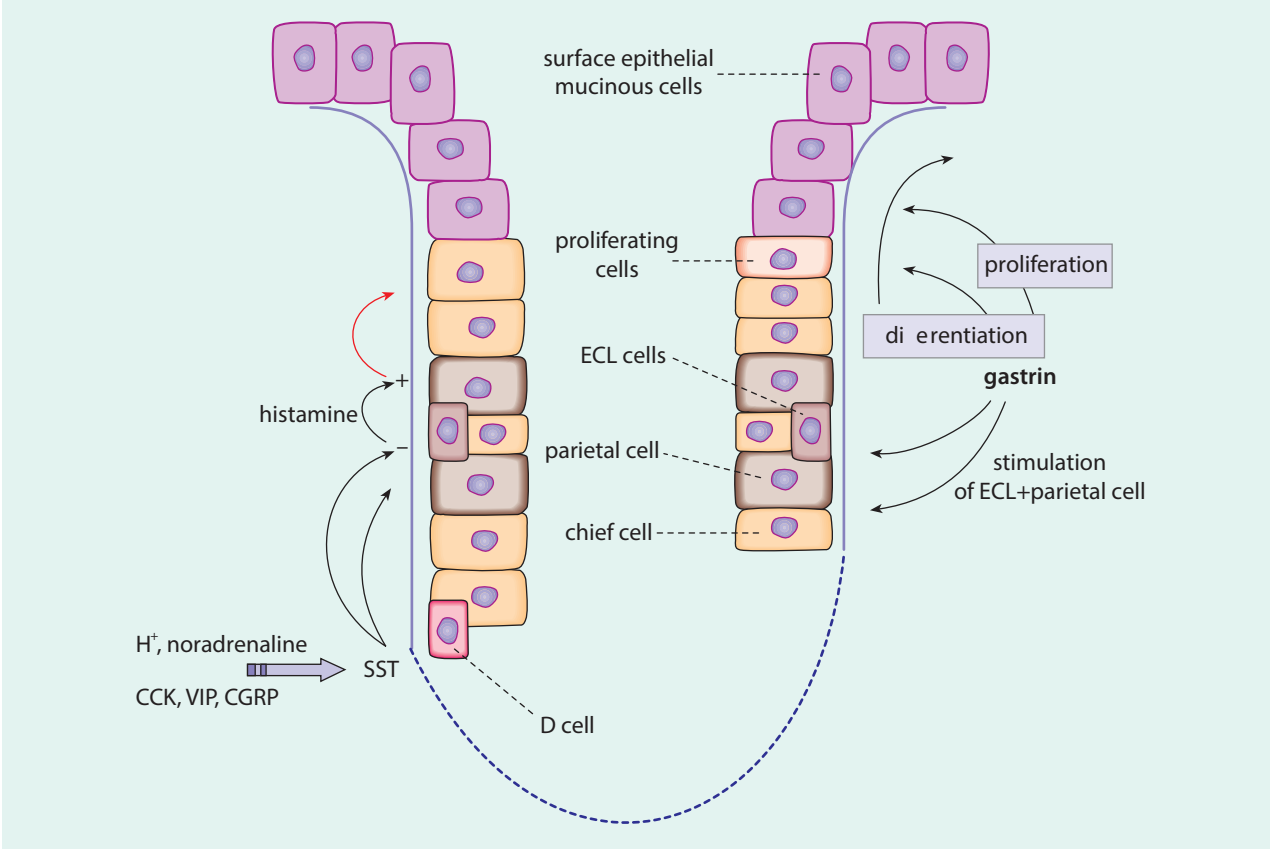

Fig. 7.12.: Gastrin, besides its stimulating effect on parietal cells also act on ECL-cells (ECL = enterochromaffin-like) to increase acid secretion, but it also increases differentiation and proliferation of mucosa cells. SST produced in D-cells inhibits the action of gastrin. D-cells are activated by norepinephrine, CCK. VIP, CGRP, and high acid concentration. Without D-cell activity more gastrin is produced, the non-secretory effects become enhanced, causing hyperplasia or eventually carcinoid.

7.3.1.2. POTENTIAL APPLICATION OF GI-PEPTIDES

- Glucagon: at endoscopy, to decrease motility
- Secretin: to increase blood perfusion of pancreas at angiography
- CCK: to increase bile flow, to decrease appetite (in animal experiments, it decreases food intake, but due to side effects and difficult administration and/or destruction during oral administration, cannot be effectively used in humans)
- SST analogues, such as, octreotide: general hormone-release inhibitor, trials of treating endocrine tumors, prolactinoma and acromegalia

7.3.2. SECRETION OF GASTRIC JUICE AND ITS DISORDERS

In response to food and its amino acids, the daily gastric juice production in the cells of the antral mucosa averages 1.5-2.0 liters. In the composition of gastric juice, apart from HCl (produced by the parietal cells of the oxynthic glands), the K^+, salt, pepsinogen (from chief cells), mucoproteins (from mucus-producing cells) and the intrinsic factor (together with R-protein responsible for transient binding of B_{12} vitamin) all prove to be highly relevant. Another group of glands in the vicinity of the pylorus produces a lot of mucus and some gastrin (gastrin is produced by the G-cells).

The fasting secretory rate of gastric juice is 30-40 ml/h, and contains 1-4 mEq acid (basal acid output, BAO). The secretion of the parietal cells contains 150-160 mEq/l HCl and 5-15 mEq/l KCl, and will be diluted within the lumen of the stomach. For maximal stimulus (earlier performed by histamine, then later, with pentagastrin) the secretion may be increased 5-10-times (maximal acid output, MAO). Due to the secreted acids, normally the gastric juice features a pH of 1.5-4.0 even following the combination of the gastric content, and this is essential in the transformation of pepsinogen to pepsin, corresponding to the optimal pH in support of pepsin. Further production of gastrin in the mucosal G-cells is limited by the acidity of the gastric content.

The quantity of gastric juice may prove higher than normal (***hypersecretion***) or significantly less than normal (***hyposecretion***). Its acid content may be higher (***hyperchlorhydria***), smaller (***hypochlorhydria***), or may be entirely absent (***achlorhydria***). Fasting hyperchlorhydria is often seen in a duodenal ulcer, while an atrophizing stomach which is insensitive even to the earlier used histamine ("histamine-refractory achlorhydria") (nowadays pentagastrin-stimulation is used) may be characteristic in cases of severe chronic gastritis, gastric-tumor and/or pernicious anemia. On the basis of autoimmune processes or at a later stage of chronic gastritis, atrophy of the gastric mucosa may develop, the production of hydrochloric acids decreases, later decreased pepsinogen production develops, and ultimately, the intrinsic factor production ceases or becomes insufficient (***achylia gastrica***). However, gastrin production may be maintained (since the acid-feedback is missing), and in such cases the non-secretory actions of gastrin are more pronounced.

The role of gastric juice throughout digestion is rather minor and insignificant, since the pancreatic trypsin can replace the pepsin and the acids are not indispensable for digestion. In the case of gastric hyposecretion, *dyspepsia* may still be observed. The explanation lays in the acceleration of purging the stomach. Without acid, increased levels of gastrin are produced and this can enhance the motility, and the trypsin production cannot be effectively adapt. Due to the lack of acids, an antibacterial effect is missing. In addition to the problems of digestion, the lack of gastric juice leads to the deficiency of intrinsic factors and diminished levels of vitamin B_{12}, and the absorption of iron also proves to be deficient. In contrast, hypersecretion also leads to digestive problems, since an abundance of acid extends into the duodenum and the intestine, in which the pH-optimum of the digestive enzymes is normally alkaline.

Disorders of gastric juice secretion may often be seen throughout inflammatory anomalies of the stomach (gastritis), and in ulcer disease (ventricular or duodenal ulcer). Ventricular ulcers often, yet not always, are accompanied by higher levels of acid secretion (induced by histaminergic, cholinergic or gastrin effect), while in the case of the duodenal ulcer, the acid production is abundantly high in nearly every case. Ulcers may also be produced within the esophagus and the bowels. ***Ulcer***, by definition, refers to those tissue defects which are deep to the point of reaching at least the submucosa or even penetrating deeper into the circular and longitudinal muscles. The intensely superficial injuries are referred to as *erosion* (these usually develop acutely, and may be characterized by an increase in size, resulting in potentially larger quantities of blood loss. In regards to chronic ulcers of the stomach (*peptic ulcer*), chiefly proteolytic enzymes promote their development, and their scarry crater is filled with detriment of mucosa cells (the "peptic" title is due to the pepsin-like effects). The relevance of various ulcers lays partially in their frequency, partially in the complaints and severe complications (perforation, bleeding, pyloric stenosis, later tumor development). Obviously, the most frequent complaint is pain, however, this may be explained not so much by the injury itself, but rather by the surrounding periulceral inflammatory circle. In case the inflammation is missing, such as during steroid treatment, there is practically little pain and the ulcer remains unrecognized, yet, alarmingly, causes perforation and bleeding. Lastly, steroids also inhibit mucin production, bicarbonate production and mucosa cell proliferation.

7.3.2.1. FORMS OF GASTRITIS

Various forms of gastritis are rather frequent throughout the clinical practice. Although in most cases, they only generate burning, epigastric pain and dyspepsia, dependent upon development and on their duration, various consequences may subsequently follow.

Frequently, **acute gastritis** occurs. It results in an acute inflammatory scenario including neutrophilic dominance upon the gastric mucosa. Apart from the epigastrial burning sensation, or pain, it occasionally causes nausea and/or vomiting, and it is usually accompanied by hypochlorhydria. Causative factors include, extreme feeding abuses, reactions to certain medications, such as aspirin, or other NSAID drugs, alcohol, erosive substances, severe stress (e.g. due to a surgical procedure), a mechanical injury, undue stretching, yet infections are the most important. It may also adjoin insufficiency of the kidney, liver or respiration.

Nearly 10% of **chronic gastritis** cases are of autoimmune origin. They affect the corpus or the fundus (with parietal cells and the intrinsic factor) and, due to their damage, low acid secretion yet higher levels of gastrin typically ensue. The consequent *atrophic gastritis* may cause carcinoid or adenocarcinoma, and additionally, the preponderance of pernicious anemia (apart from the low acid, the production of pepsin and intrinsic factor is also insufficient, however, the gastrin level is abundantly elevated). The remaining 90% affects primarily the antrum and corpus (pangastritis). It develops on the basis of environmental factors including alcohol consumption,

stress, various medications, steroid use, NSAID, bile-reflux, etc., or Helicobacter pylori infection. Regarding the presence of inflammation, characteristically mononuclear cells, lymphocytes and macrophages are all evident. In these cases, neither the alteration of gastrin levels nor that of acid is considerably typical, but due to the insufficiency of defensive factors, a peptic ulcer, or over an extended period of time, adenocarcinoma may develop within the stomach. If and when the Helicobacter pylori infection affects the antrum pylori, it induces hypergastrinemia and higher levels of acid secretion (often with metaplasia), in which an immense quantity of acids is extending into the duodenum, directly responsible for the development of duodenal ulcer.

7.3.2.2. GASTRIC ULCER DISEASE (erosion vs. peptic ulcer)

Distinctively, the classic questions persists: If, in the presence of acid and pepsin, the gastric juice effectively digests a number of nutrients, why does it not digest itself? How can it remain intact? Why do ulcers develop as seen in a variety of other cases? What may be the forms and causes of a gastric ulcer disease?

Intensified superficial damage of the gastric mucosa is best defined as **erosion**, and it affects the epithelial cells, the muscularis mucosae and often the submucosa including the vessels embedded within them. This may lead to bleeding, particularly during *acute* stress, burning trauma, steroidal reactions, etc. It is particularly frequent among senior patients, in whom the gastric blood flow is relatively low and who are often treated with NSAID-s: upon a relatively minor non-specific stress the gastric blood flow exhibits a further severe decrease due to redistribution of cardiac output. A smaller erosion may spontaneously normalize, hence, the mucosa cells become flattened in order to cover more of the damaged part, they also migrate and proliferate. The real **peptic ulcer** develops in a more *chronic* form, it is deeper, extends to the "outer" circular and longitudinal muscles beneath the submucosa. Deep in the crater there is sediment originating from peptic decomposition of the necrotizing tissues, and it is surrounded by an inflammatory ring (in fact, the pain is due to this inflammation). Spontaneous normalization is very unlikely to occur, therefore acid-production decreasing pharmaceuticals and dietary treatment are necessary.

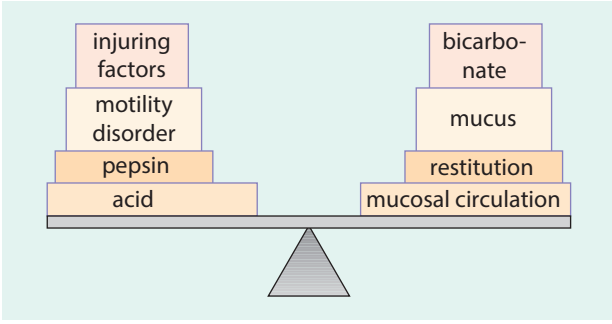

Fig. 7.13.: In the stomach protection against the aggressive factors are secured by defensive factors. In the background of ulcer disease there is an imbalance of these factors.

Characteristically**, contributing factors in the development of an ulcer disease** include both the overweight of well known agressive factors and the insufficiency of defensive mechanisms (Fig. 7.13.).

Hydrochloric acid is the most predominant ***aggressive factor*** regarding ulcer disorders. It has been accepted among medical circles for nearly a century that in an acid-free stomach ulcer never develops. In contrast, in Zollinger-Ellison syndrome, (ch. 7.3.1.1.) acid overproduction is the direct cause of ulcer. Aggressive role is also linked to *pepsin,* to *physical* (mechanical, heat and/or osmotic) and *chemical* factors extending into the gastric mucosa, and additionally, to disorders of *motility*. The bacterium, *Helicobacter pylori,* is capable of survival among the acidic milieu of the stomach (by producing an ammonia coat), then over an enduring process, it binds to mucosal cells and, primarily due to its urease and catalase enzyme activity, produces toxic ammonia and other toxins, thereby damages the mucosa. This infection is more frequent among individuals living in poor hygienic conditions and predominantly seen in seniors. Additionally, the Helicobacter pylori produces histamine products, and elevates the gastrin level by disinhibition of the gastrin-producing G-cells (partly inhibiting the SST release, perhaps leading to D-cell damage and thereby the inefficacy of the local decrease in pH level), thereby, promotes the development of hyperacidity and gastritis/ulcer. Additionally, the bacterium promotes proliferation and has a tendency for production of gastric tumors.

The ***defensive factors:*** Quite likely, the most important factor is the *circulation of the mucosa*, which corresponds to 70% of the total gastric circulation and implies the potential "washout" for the acid diffused into the interstitium and provides bicarbonate towards the mucosa barrier. The partially improved circulation probably explains the favorable effect of capsaicin upon the gastric mucosa. From another perspective,

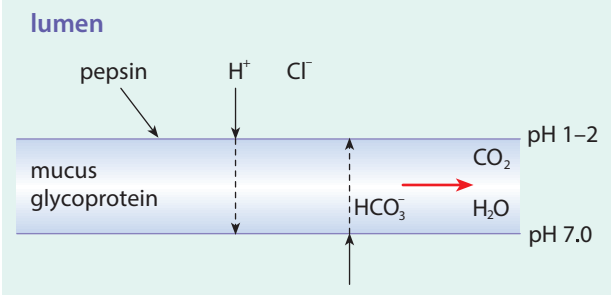

Fig. 7.14.: Function of the mucosa-barrier. H^+ ions diffuse through the mucin from the lumen towards the epithelial cells, the HCO_3^- ions diffuse in the opposite direction. The two ions produce carbonic acid, what dissociates to CO_2 and water to be transported by the circulation. In the luminal part of the mucin the pH is low (1-2), at the epithelium it is pH 7.0, with a gradient in the mucin layer. In the lumen Cl^- binds to Na^+ of the bicarbonate. Circulation carries away the remaining H^+ that still cross the mucin.

decreased circulation may be responsible for the acute stress ulcer (such as, large bleeding erosions that are particularly frequent among seniors). Defensive factors include the mucosa-barrier, the mucin and bicarbonate-production (Fig. 7.14.). The *mucin* is a 5-400 µm thick glycoprotein layer, responsible for providing mechanical defence and also inhibits the direct contact of gastric content with epithelial cells, while the *bicarbonate* diffusing within the mucus layer in the opposite direction binds a large portion of H^+ (if the luminal pH is 2-3, the gradient is stable). Additionally, the mucus can bind free radicals and toxins. A further characteristic defensive mechanism is the *restitutive and regenerative* capacity of the epithel (Fig. 7.15.). Restitution is the movement of living cells in order to cover the damaged area (this is possible if pH >2, if the basement membrane is intact and if the circulation is good /salicylate inhibits!/). Regeneration is a mitotic process, and requires 1-2 days to recover (steroids inhibit). In the mucosa, the *prostaglandin*-synthesis performs a cytoprotective role, and takes place via the circulation, the increased bicarbonate- and mucin-secretion and the decreased acid secretion. A potential disorder of all these may be due to stress, medicines (COX-antagonists, glucocorticoids) and detergent substances (bile-regurgitation) (Fig. 7.16.).

SPACE/TIME-RELATED ORGANIZATION OF DEFENCE OF GASTRIC MUCOSA

1. Substances of mucosa: mucin, bicarbonate, immunglobulins, lactoferrin, HCl (very little, as an irritant)
2. Mucosa barrier: cell restitution, surface-active phospholipid layer
3. Mucosa microcirculation: suitable for the rinsing of the rediffused HCl and for regeneration
4. Mucosal immuncells: mastocyte, macrophage (but increased levels lead to inflammation)
5. Regeneration of mucosa-damage: vessels, vasodilatative CGRP, PGE, PGI (COX-1, COX-2), eNOS/nNOS (with the aid of endothelial/neuronal NO-synthase).

In the case of a **duodenal ulcer,** genetic factors may also play a role, such as an increased occurrence among individuals associated in the O-blood group. In the case of a duodenal ulcer, mucin is omitted from the defensive factors (in the duodenum there is no need for it since the pH is alkaline), however, the arrival of either acid or H. pylori has greater significance. Otherwise, in this case the development of ulcer can also be explained by the disturbed balance between agressive/defensive factors.

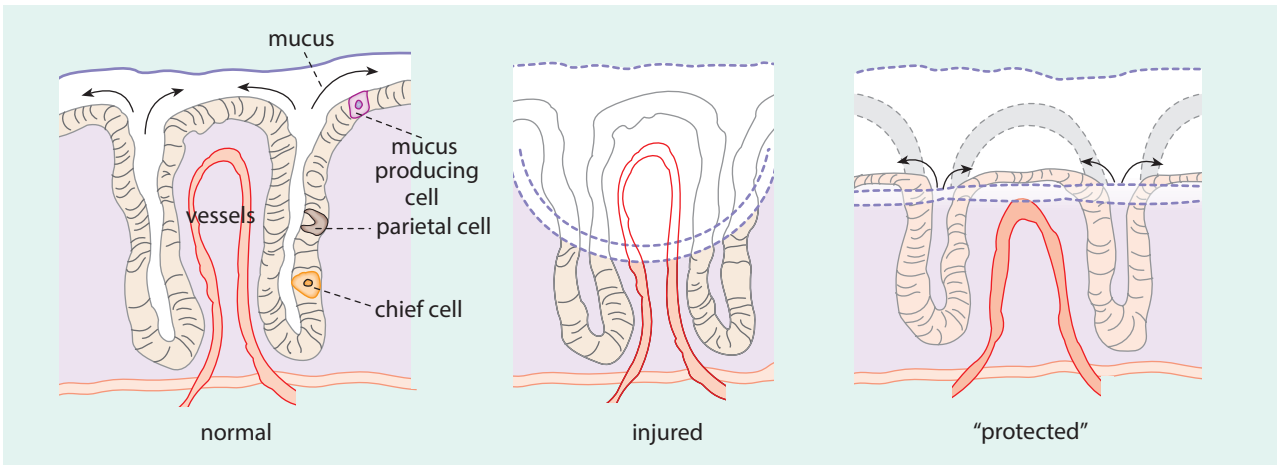

Fig. 7.15.: Fast restitution/regeneration of the mucosa cells provides protection. In superficial erosions viable cells from the vicinity "migrate" (the migration is shown by arrows). Deeper injuries also affect the vessels (middle panel), the regeneration is not sufficient, and "migration" cannot any more secure continuity of the tissue.

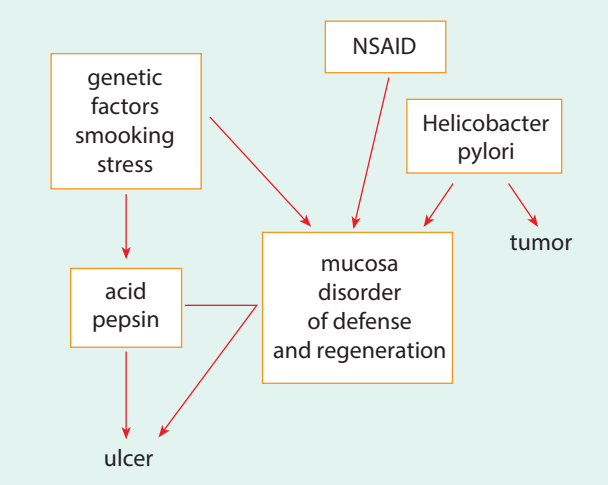

Fig. 7.16.: Important risk factors of peptic ulcer.

In the development of the ulcer-disease lifestyle, smoking (this causes decreased epithelial bicarbonate secretion, decreased mucosal perfusion, decreased PG-synthesis, slow motility, and increase in duodenogastric reflexes with GERD), eating habits and alcoholism may also promote the development of an ulcer.

BASIC CONSIDERATIONS IN THE EFFECTIVE TREATMENT OF AN ULCER-DISEASE:
It is difficult to enhance the defensive factors, apart from the extinction of H. pylori, therefore the most important factor in consideration is the decrease of acid production (Fig. 7.11.). This happens by either (H2)-receptor antagonists, such as famotidin, which can be administered over a lengthy period of time, or proton-pump inhibitors (PPI), and/or omeprazol, while the specific acetylcholin antagonists and gastrin antagonists possess an abudance of potential side-effects. Great importance should be assigned to acquiring appropriate lifestyle factors, and the avoidance of various risk-factors.

N.B.: the sustained usage of any HCl-decreasing substance leads to high gastrin levels what may have a tendency for tumor production due to the proliferation and differentiation increasing effect of this peptide. From another perspective, the sustained lack of gastric acid may lead to an alteration of bowel pH and bacterial flora, thereby leading to digestion and absorption abnormalities potentially resulting in chronic diarrhea.

7.3.3. SECRETORY DISORDERS OF THE PANCREAS

The most important enzymes of luminal digestion are produced by the pancreatic acini. Apart from these enzymes, the daily 1.5-2 liters of secreted fluid contain an immense quantity of bicarbonate and various electrolytes which are produced in the ducts. The enzyme production may be acutely low in acute pancreatitis and febrile infectious diseases. Chronically diminished levels of production is more frequently associated with sclerosis of the pancreatic vessels, protein deficiency, cachexia, toxic injury of the pancreas, chronic pancreatitis, cystic fibrosis, post-vagotomy state, decreased secretin- and CCK-effect (somatostatinoma, low duodenal pH in ZES and celiac syndrome). The generalized deficiency of various digestive enzymes of the pancreas leads to defective digestion of all types of food and to combined, generalized malabsorption. It is not the lack

Table 7.1.

Risk factors of the ulcer disease

– NSAID (COX-antagonists)	PG-synthesis blockers, direct cytotoxic effects blood flow + regeneration ↓, mucosa penetration ↑
– ethanol	vascular damage, stasis, cytotoxics (spirits!), enhanced acid-secretion (4-15% alcohol)
– smoking	PG-synthesis inhibition (?), enhanced acid-secretion
– corticosteroids	inhibition of regeneration, modifying inflammation
– methylxanthines (coffee, tea, Coke)	enhanced acid-secretion
– shock, trauma, burns, stress	mucosa perfusion decreases
– Helicobacter pylori	injuring effects of ammonia and toxins

The bacterial urease of H. pylori produces alkaline NH3 fom urea, histamine-derivative is produced, the SST release is inhibited (via H3-receptors), the G-cell inhibition is insufficient, hyperacidity, gastritis, ulcer.

of enzymes but their inactivation what leads to malabsorption, if and when an increase in the level of acid proves extensive. A sustained increase of pancreatic secretion such as, in chronic renal failure, due to elevated levels of CCK-gastrin-GIP-glucagon, in VIP-oma, in cirrhosis (decreased secretin-elimination, in a high gastrin-level, high Ca^{++}) and in hypercalcemia, all which may induce precipitation of proteins or stone formation throughout the various pancreatic ducts, causing their obstruction and leading to chronic pancreatitis. Disorders of gastrointestinal hormones may increase the secretion of pancreatic juice. In liver cirrhosis, the secretin level increases and enhances the secretion, while the VIP-producing tumors induce an acutely enormous secretion of pancreatic juice and induce a secretory type of diarrhea.

7.3.4. DISORDERS OF INTESTINAL SECRETION AND DIGESTION

In the intestinal system, a daily level of 1.5-3 liters of juice is produced. Its production and composition is influenced by paracrine (or endocrine) effects of gastrointestinal hormones (secretin, CCK and VIP). The local stretch via the neural elements of the gut wall also enhances the secretion. The intestinal juice features a high K^+ and bicarbonate content, and also contains several of the surface enzymes of digestion (oligosaccharidase, oligopeptidase, etc., and these enzymes are located primarily on the "surface" in the brush border). Excessive secretion is observed in ileus and in a secretory type of diarrhea. A lack of certain enzymes results in difficulty regarding the final steps of digestion and leads to absorption disorders. A typical example regarding the lack of surface enzymes is seen in lactase deficiency[4], which appears more frequently with increasing age. The combined lack and deficiency of surface enzymes of digestion is characteristic for the relatively simple transient infections of intestinal mucosa, such as viral enteritis, and also following gastrectomy. In case of gastrectomy the likelihood is the resulting pathological bacterial flora increases due to the lack of gastric acid. In other cases, the "dumping syndrome" very likely lurks in the background. In such cases, a common consequence is an osmotic type of diarrhea, and its actual form is largely dependent upon the characteristics of maldigestion.

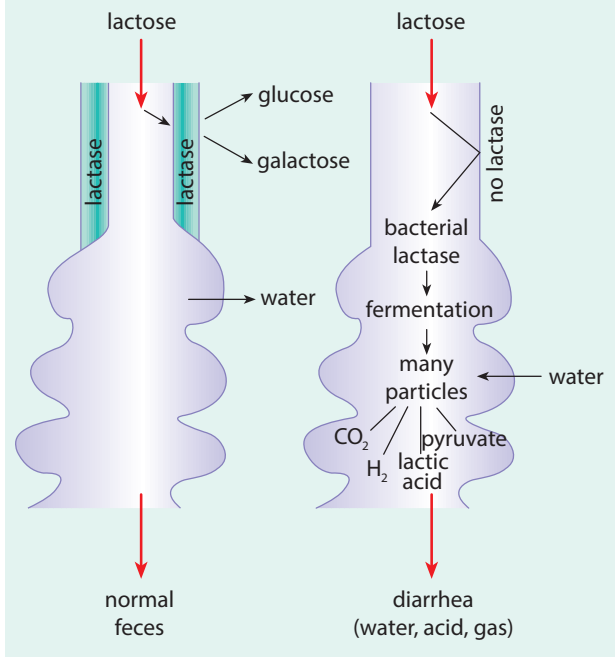

Fig. 7.17.: Development of diarrhea in lactase deficiency.

Normally, there is rarely any secretion in the colon, however, there is water absorption, and only a small amount of mucus is produced. Pathologically, the mucus production may significantly increase. The secretion may also be increased, as seen when potentially increased amounts of bile acids extend into the colon, causing diarrhea even without food intake, and notably, this is one possible cause of irritable bowel syndrome.

7.4. INTESTINAL ABSORPTION AND ITS DISORDERS

Regarding luminal and surface digestion, intestinal enzymes reduce nutrients to fine particles which can be effectively absorbed. In the course of absorption, these particles first enter the cells, in their luminal side, through

[4] Lactase enzyme is required for digestion of lactose in milk. Lactose is a disaccharide (glucose + galactose). In lactase deficiency (Fig, 7.17.), the undigested lactose cannot be absorbed, and it extends into more distal parts of the GI tract where bacterial anaerobic glycolysis produces immense quantities of lactic acid, pyruvic acid, carbonic acid and other molecules derived from lactose. These small acidic molecules are all osmotically active, retain water in the colon, and the increased volume combined with gas compounds stretches the gut wall, the stretch and acids stimulate the wall, leading to the inevitable result in the form of the rapid development of watery/gaseous (acidic) diarrhea accompanied by colicky abdominal pain.

the brush-border of villi of epithelium cells, and next, they pass the basolateral membrane. Eventually, they extend into the villous interstitium and inevitably, into the blood and/or lymphatic capillaries. Absorption through the cell may be through diffusion, facilitated diffusion, active transport, endocytosis, however, several substances are transported through the intercellular tight junctions. Absorption takes place primarily at the tip of the villus, while at its base (crypts of Lieberkühn) secretion happens and the formation of new epithelium cells. Cells from the base migrate towards the tip with various, and generally rapid, transit time, in which they mature in support of transport processes by obtaining enzymes and transport proteins. Once they reach the peak, the cells are already in apoptotic form to be lost to the lumen. Due to the characteristic counter-current blood perfusion of the villi (Fig. 2.20), the tips are very sensitive to hypoxia and circulatory disorders, any events leading to a decrease in the speed of blood flow, affect absorption prior to secretion, all of which is a predispotition to diarrhea.

7.4.1. MALABSORPTIONS

Disorder of absorption may be secondary in the consideration of maldigestion, when components of poorly digested food naturally cannot be effectively absorbed. In primary disorders of absorption, a decrease or injury of the absorption surface, such as seen in mucosa cell damage, a deficit in the conditions (ATP, O_2, Na^+) of active transport, or a postabsorptive anomaly (such as in a lymphatic obstruction), therefore, does not allow absorption of well-digested substances. Irrespective of the cause of defective absorption, it is defined as *malabsorption*.

FORMS OF MALABSORPTIONS

According to the level of functional disorder, malabsorption may be gastric, pancreatic, hepatobiliary, or intestinal. According to the nutrients affected, it may be substrate-specific (carbohydrate malabsorption, lactose malabsorption, protein malabsorption, etc.) or may be generalized when many or all substrates are affected (e.g. celiac syndrome, mucoviscidosis, enteritis). Intestinal carbohydrate malabsorption is e.g., the lactase deficiency (substrate-specific). Those clinical states are defined as *malabsorption syndromes*, in which chronic generalized malabsorption is the leading symptom or exclusive manifestation.

CAUSES OF MALABSORPTIONS

1. Maldigestion (gastrectomy, deficiency of luminal/surface enzymes)
2. Decreased concentration of bile acids (liver diseases, bacterial overgrowth, disorder of enterohepatic circulation of bile acids, antibiotics). Normally, nearly all of the conjugated bile acids are reabsorbed from the small bowel, in the case of early deconjugation (e.g., in bacterial overgrowth) this cannot happen, as the free bile acids excite the bowel mucosa and therefore, cause malabsorption.
3. Decreased absorptive surface (gut resection, bypass, gastro-ileostomy, RYGB)
4. Lymphatic obstruction
5. Cardiovascular disorders (mesenterial congestion and/or ischemia)
6. Primary mucosa damage (inflammation, celiac syndrome, Salmonella and/or mucoviscidosis)
7. Endocrine/metabolic disorders (diabetes, hypothyroidism and/or Addison's disease)

SUBSTRATE-SPECIFIC MALABSORPTIONS

Carbohydrate malabsorption: Glucose and galactose are absorbed by active transport, which needs ATP and Na^+, while fructose is accomplished by simple diffusion. It occurs frequently in oligosaccharidase deficiency (in genetically determined deficits, such as, lactase deficiency, and in viral infections, etc.), or in carrier-deficiency such as in galactose absorption disorder. Bacteria digest the non-absorbed carbohydrates by anaerobic glycolysis, producing gas (H_2 is in the exhaled air) and watery-acidic diarrhea (with K^+ and bicarbonate loss).

Protein malabsorption: L-aminoacids and di/tripeptides are absorbed by active transport (it needs ATP and Na^+ and it is inhibited by the deficiency of pyridoxine or energy) and certain immunoglobulins all can be absorbed by pinocytosis. Cystinuria and methionine-absorption deficiencies are based on transport disorders. In protein absorption disorders, proteins of the digestive enzymes are not absorbed, thus the protein loss may be fast and very pronounced (ch. 9.1.1.). In protein malabsorption, bacterial decomposition leads to less watery, however, due to the rotting of sulphur-containing amino acids, very putrid diarrhea, and, consequently, hypoproteinemia may occur. In exhaled air CH_4 can be demonstrated.

Fat malabsorption: Fatty acids are taken up by active transport, and glycerol by diffusion into the epithelial cell, where re-esterification takes place, then the com-

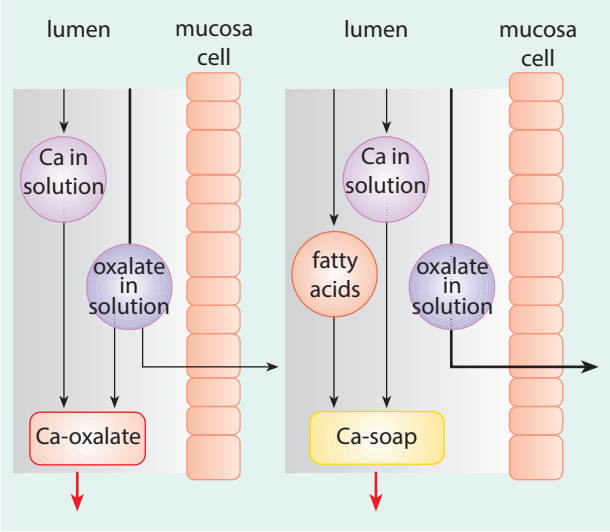

Fig. 7.18.: Fat malabsorption causes enhanced absorption of soluble oxalate.

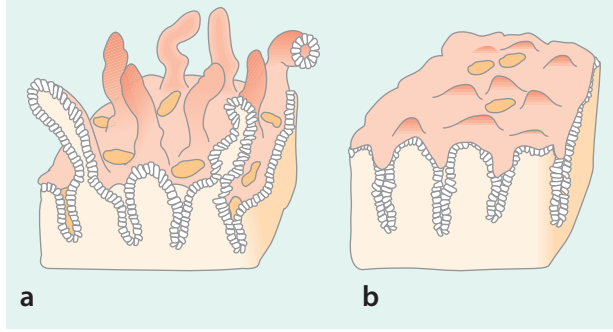

Fig. 7.19.: Normal intestinal villi (a) and their flattening in celiac syndrome (b).

plex extends into the chylomicron fraction in the form of a β-lipoprotein. Medium-chain fatty acids can be absorbed directly in ester form, thus they do not appear in the chylomicrons, rather the portal vein carries them to the liver. In absence of the β-apoprotein, the epithelium cells are filled with fats, however, these cannot be absorbed. In lipase deficiency (≤10% function remaining), the malabsorption of long-chain fatty acids leads to steatorrhea and calorie loss, however, absorption of bile acids, cholesterol and fat-soluble vitamins is maintained. In contrast, in deficiencies of the bile, neither fats (daily fat loss ≥30 g) nor fat-soluble substances can be absorbed. Fats remaining in the gut form soaps with Ca, therefore the Ca-loss is marked and the absorption of oxalate increases (Fig. 7.18.) leading to oxalate stones in the kidney. The majority of bile acids is absorbed from the ileum, and, if and once it is disordered, the enterohepatic turnover (recycling) is poor, and an increase in bile acids inevitably extend into the colon, causing secretory-motor diarrhea of colonic origin.

COMPLEX MALABSORPTION SYNDROMES

Several ways exist in support of the development of complex malabsorption syndromes. The various syndromes may be acquired or involve hereditary factors.

Pancreatic malabsorption: Pancreatic malabsorption is most often seen in chronic pancreatitis (ch. 7.5.2.), however, prolonged hyposecretion of pancreatic juice also occurs in sustained bouts of starvation, in cachexia, protein deficiency, sclerosis of the pancreatic artery, low levels/action of secretin or active somatostatinoma and/or low duodenal pH, etc., and the juice may be completely missing, as seen in mucoviscidosis. In the severe absence of pancreatic juice, one third of the ingested proteins are lost, and 40-70% of fats are not absorbed. The least affected is the carbohydrate absorption.

Celiac syndrome (coeliakia, gluten enteropathy, "flour sensitivity"): Among the protein fractions of certain cereals (wheat, oat, barley and rye), however, excluding rice, maize, beans, potatoes, participates the gluten protein, the gliadin component of which induces an immune reaction and inflammation in the mucosa of the small intestine. As a result, flattened villi are characteristic (Fig. 7.19.), and the remaining villus-cells are immature and therefore, incapable for any absorption. The absorption surface markedly decreases, and the secretin and CCK secretions are diminished, although intestinal juice is still produced at the bases of the villi. Altogether, absorption of nutrients, vitamins, Ca, iron, other minerals and bile acids is considerably, very low. In its development, primarily hereditary factors are assumed, however, since it is also seen if babies are fed too early with gluten-containing foods, the early sensitization may also have a pivotal role. The persistent osmotic diarrhea leads to retardation of growth and development among children, yet diarrhea and severe deficiency symptoms are also present in adults. Dietary treatment of the disease including the complete elimination of these cereals often proves successful, however, the dietary restriction must be intensely adhered to, throughout life, including both children and adults, specifically, without interruption. Following one single interruption, several months are required for regaining the normal state. Partial forms of celiac syndrome are also known to exist, in which cases, diarrhea is less pronounced, yet the deficiency symptoms continue to develop.

Cystic fibrosis (mucoviscidosis): This hereditary disease primarily affects the ion channel, and is referred to as a congenital disorder of chloride-transport. Sever-

al disorders may occur in practically all organs/tissues (lungs, sweat glands, parotid gland, liver, reproductive organs, etc.), since chloride transport is ubiquitous. In the GI system, primarily the glands of the pancreas and the small intestine are affected. Cysts develop in the fibrotically transformed tissues, and these cysts are filled with a viscous mass rich in NaCl and proteins, often leading to the obstruction of ducts. The amount of digestive enzymes is diminished and the absorptive surface is small, both are contributing factors that lead to the combined and generalized defect of digestion and absorption. Regarding its diagnostics, the first step is the measurement of NaCl content of sweat. Distinctly, premature demise in most cases is due to pneumonia and respiratory failure.

Short bowel syndrome: If a longer section of the small bowel has to be surgically removed, for any reason, the removal is followed by a complex intestinal dysfunction. Apart from the digestive and absorptive functions, the motility and the immunological defense roles are also gravely compromised and suffer deterioration. Bacterial overgrowth may contribute. The defective absorption of bile acids allows the forwarding an immense abundance, and these acids cause functional injury to the distal small bowel and the colon. Secretory diarrhea generally ensues. From another perspective, the lack of bile acids tends to promote biliary stone formation (ch. 7.6.2.).

Bacterial overgrowth: The small bowel normally contains $<10^5$/ml aerobic and no anaerobic bacteria, while within the colon, the figures are 10^8/ml aerobic and $10^{10\text{-}11}$/ml anaerobic bacteria. Overgrowth of bacteria in the small bowel is prevented by the motility, ileocecal valve, gastric acid, bile and mucin, including the normal gut flora and secretory IgA. Diverticula, blind loop, slow passage (in diabetes, scleroderma, old age, hypokalemia, mesenterial ischemia, etc.), adhesions, tumors, etc., all inhibit motility and allow multiplication of aerobic flora and even the appearance of anaerobic bacteria more proximally in the stagnating content of the small bowel. Insufficiency of the ileo-coecal valve may produce similar results. Overgrowth may also originate from a lack of gastric acid, an absence of the antimicrobial effect of normal flora (e.g., upon administration of wide-spectrum antibiotics), defective functionality of bile and mucin, or from an insufficiency of specific IgA immunity. Bacteria produce more ammonia (to be detoxified by the liver), and they also deconjugate bile salts prematurely resulting in a substantial increase in bile acids. The result is that the released bile acids excite the intestine and enhance secretion. The enterohepatic circulation of bile acids proves defective. Additionally, bacterial digestion (glycolysis and rotting) produces an increase in gases, leading to meteorism, flatulence, osmotic-motor diarrhea and complex malabsorption. In regards to the bacterial activity, H_2 extends into the circulation through the gut wall, and it appears in the lung and can be demonstrated in the exhaled air (breath H_2-test). Enhanced bacterial activity also produces CH_4, CO_2, acetate, butyrate, propionate.

Extensive enteritis and enterocolitis: Chronic inflammatory changes may cause complex disorders of absorption. The inflammation is not necessarily bound to infection by a specific pathogenic agent.

GENERAL CONSEQUENCES OF MALABSORPTIONS

These can be deduced partly from the deficiency of various nutrients, and partly from bacterial decomposition of non-absorbed substances at distal segments of the intestine. Although the bacterial products are dependent upon the type of malabsorption, it is a common feature of all in which an abundance of small, osmotically active particles are produced, which retain water from the normally secreted juices throughout the intestinal lumen, thereby causing an osmotic type of diarrhea. Another commonality is the meteorism and flatulence due to gases originating from glycolysis and bacterial rotting.

Characteristic symptoms of chronic malabsorptions (cf. Fig. 7.20.):

- Osmotic type diarrhea, enhanced gas production and meteorism
- Enteral protein loss (by bowel juice), protein deficiency, poor resistance to infections, water loss, salt loss, hypokalemia and hypocalcemia
- Decreasing body weight, low physical performance and retardation of growth and development
- Hypovitaminoses, deficiency of trace elements and osteoporosis
- Anemia and bleeding tendencies
- Neuropathies

MALABSORPTION TESTS:

Fat content of the stool: Normally max. 6 g/day fat is in the feces (5% of the intake). Sudan III staining of the stool shows presence of fat in the feces.

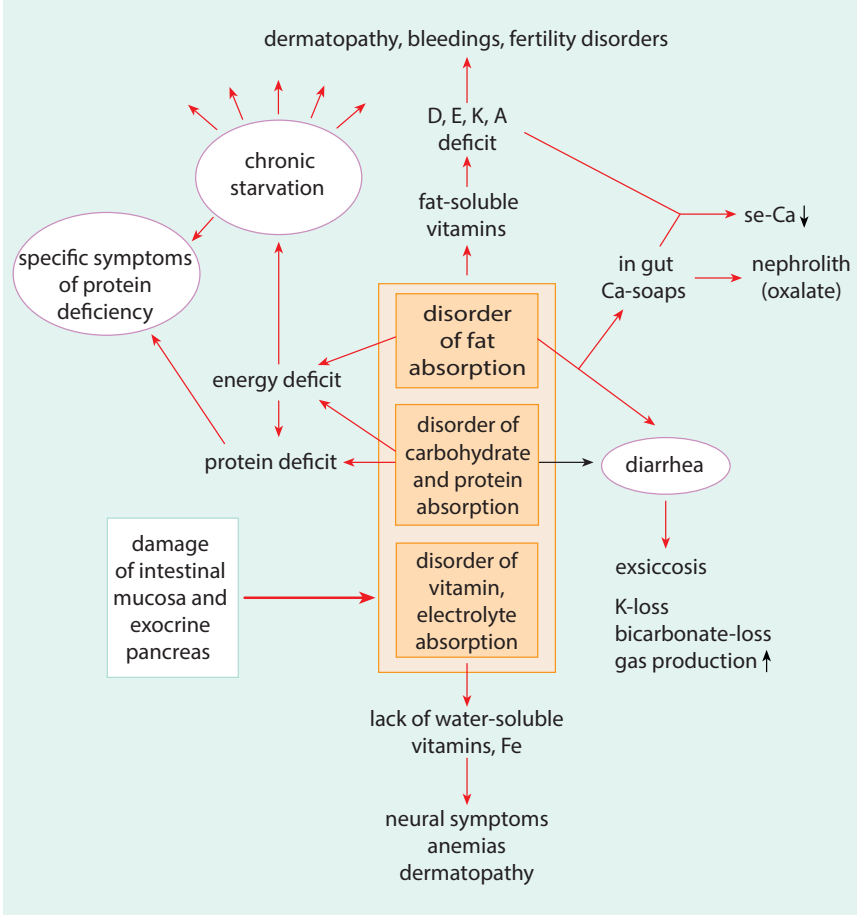

Fig. 7.20.: General consequences of complex malabsorption syndrome. Injury of intestinal mucosa, the pancreas, or other damages may cause disordered absorption of calorie-containing nutrients, vitamins and minerals. The energy deficit corresponds to starvation, with all of its consequences. In addition, the protein deficiency is more severe, due to protein-catabolism of starvation and to non-reabsorption of enzyme-proteins. Osmotic diarrhea is characteristic, but its actual appearance depends on the type of malabsorption.

^{14}C-triolein-test: Orally administered ^{14}C-triolein is metabolized according to its absorption, and the produced $^{14}CO_2$ can be detected in the exhaled air.

^{14}C-bile acid breath-test: Cholyl-^{14}C-glycin is administered orally, which is absorbed by the enterohepatic circulation at the terminal ileum. All non-absorbed residuum is deconjugated in the colon (cholic acid + ^{14}C-glycin) and ^{14}C-glycin metabolism results in $^{14}CO_2$ in exhaled air.

Pancreas function tests: Trypsin content of the duodenal juice is observed following i.v. administration of secretin/CCK or after feeding.

Schilling-test: Following i.m administration of saturating dose of vitamin $B_{12,}$ a dose of $^{58}CoB_{12}$ is given orally. In case of normal absorption capacity, the isotopic substance is absorbed, but excreted by the urine. In malabsorption, very little is extended into the urine.

Breath-H_2-test: Following ingestion of the presumedly malabsorbed sugar (e.g., lactose) bacterial activity produces H_2, which can be demonstrated in the exhaled air.

D-xylose absorption: Xylose is absorbed similarly as glucose/galactose. Little is metabolized, thus, following oral ingestion of 25 g, normally at least 4 g reaches the urine. Since digestion is not needed, excretion of less than 4 g suggests malabsorption (except in renal failure).

7.5. PANCREATIC DYSFUNCTIONS

7.5.1. ACUTE PANCREATITIS

In the pancreas, normally enzyme activation and self-digestion does not start due to the followings:

- The digestive enzymes are produced in inactive proenzyme form and are stored in the form of membrane-circumvented zymogenic granulas in the acinar cells. Activation requires alkaline pH, provided by the ductal bicarbonate secretion, and they are eventually activated by the bile in the duodenum.
- Within the ducts, the pressure is smaller than in the parenchyma.
- The α_1-antitrypsin of the parenchyma specifically prevents the activation of (pro)enzymes that are produced in the pancreas and eventually enter the pancreatic parenchyma from the ducts.

In the case of acute pancreatitis, the parenchyma of the pancreas is damaged due to acute inflammation.

This simultaneously affects the exocrine and endocrine systems of the pancreas. Consistently lurking in the background is the pathological activation of digestive enzymes (trypsinogen/trypsin, lysosomal hydrolase: e.g., catepsin B). The active enzymes extend into the tissues and inevitably cause injury of the parenchyma (experimental pancreatitis may be prevented by inhibition of lysosomal hydrolase enzymes).

The severity of the acute inflammatory process may be very different: It ranges from pictures of mild pain and malabsorption to a quickly lethal outcome – anything is possible. It may be cured without lasting consequences, and only very few cases become chronic in form.

EVOKING FACTORS

Bile flow into the pancreatic ducts (gallstone, tumor or inflammation in the pancreatic ducts occludes the Vater papilla – in Europe these cases have been demonstrated to exhibit the greatest incidence). Characteristics associated with bile flow include the followings:

- it decreases the bicarbonate secretion of the ducts, therefore the bile cannot be rinsed out from the ducts
- upon entering the ducts and acini, it causes severe mitochondrial damage, Ca^{++} signalization, and consequently, cell death
- it activates trypsinogen, which, in turn, activates lipase, amylase and elastase enzymes
- in highlighting its detergent action, it damages the ductal mucosa and the intercellular connections, allowing the enzymes to leak into the parenchyma
- by activating tissue hydrolase, it enhances the activation of those enzymes that enter into the parenchyma and cause parenchymal injury

Obstruction of the duct and the potential increase of ductal pressure promotes outfiltration of pancreatic juice into the parenchyma, where it is activated. Activation may happen without bile. However, early animal experiments had shown that ligation of the main pancreatic duct did not result in pancreatitis, only in atrophy of the exocrine tissue compartments, provided that the animals had received no oral feeding (i.e. the pancreatic enzyme secretion was not stimulated). In human studies obstruction of the duct of non-functioning (non-activated) pancreas (e.g. compression by tumor) without backflow of bile or stimulation of secretion (e.g. parenteral nutrition instead of feeding) in itself does not typically cause pancreatitis, rather pancreas atrophy (and naturally chronic insufficiency of the exocrine pancreas functions).

The second frequent form: ***Immense (fatty) food intake***, and/or unusually large amount of ***alcohol consumption.*** In these cases, an increase in protein-rich viscous juice is produced, thereby protein plugs may be formed in it, particularly if it cannot be emptied due to alcohol what enhances the tone of the Oddi sphincter. Additionally, alcohol inhibits the az α_1-antitrypsin activity. The juice from overstimulated pancreas is pressed into the pancreatic tissue, where it becomes activated (activation should be prevented by α_1-antitrypsin). It occurs, characteristically not in chronic alcohol abuse, but in eventual alcohol-intoxication of non-drinkers (overeating or binge drinking following a fast, a captivity, a starvation, or attending banquets, etc.). Interestingly, in the clinical practice one sees an increased occurrence of acute pancreatitis cases during and immediately following popular and widely celebrated holidays.

Similarly, ***enhanced secretion*** is seen at elevated levels of se-Ca (e.g. hyperparathyroidism); the ***secretagogue hormones*** (e.g. CCK) exert their action by the oscillating elevation of IC Ca-level, and their overproduction causes the hypersecretion of pancreatic juice. Additionally, viscosity increases during ***steroid*** treatment. Pharmaceuticals (e.g. ***morphine***) are thought to increase the sphincter tone. In sustained episodes of ***fasting***, coupled together with an atrophy of the GI system, the pancreatic juice increases in thickness, and it is less easy to purge or empty it (a sudden increase of juice production by an increased volume of rich foods may provoke acute pancreatitis).

Acute alcohol abuse, per se, may induce acute pancreatitis, however, it does so as a cofactor, and it is present in about half of the clinical cases. The possibility of alcohol abuse among children („secretely tasting daddy's whisky") is particularly important due to the pancreatic injury in addition to the vomiting and consequent accelerated fasting.

Microcirculatory damage *(shock, hypoxia):* Following states of prolonged low blood pressure, including coronary bypass surgery and lengthy surgerical procedures, acute pancreatitis is a possible complication. In experimental hemorrhagic shock of rats, acute pancreatitis was demonstrated, and endothelin-1 was shown to deteriorate the situation.

Less frequent causes:

Surgical/traumatic injury of the pancreas, such as the impact from a steering wheel associated with automo-

bile accidents, and the blunt force injury sustained from bicycle handle-bars, *hypoxia* or a tumor may cause the spasm and/or narrowing of the Oddi sphincter, or its compression due to tissue edema. In *pregnancy,* tissue compression, hyperlipemia, biliary duct angulation and gallstone may all be contributing factors. Recently it was repeatedly described following endoscopic retrograde cholangiopancreatography (ERCP).

In *viral infections* (parotitis, Coxsackie, HIV-infection, cytomegalovirus, etc.), *autoimmune* diseases (SLE), also in parasitic infections inflammatory edema may develop in the pancreas.

In *hyperlipoproteinemias* (particularly in type I and type V with high triglyceride levels) fatty infiltration and fat embolism may occur: the lipase diffusing from the ducts acts at the outer side of the duct, the released fatty acids cause damage and edema, and the cellular damage activates trypsinogen.

Strong cholinergic stimuli, induce an extraordinary rise in the rate of secretion (organophosphates, scorpion-bite), and they promote the development of acute pancreatitis.

Kwashiorkor disease (ch. 9.1.1.1.): the aflatoxin may have a role.

Snake venoms may activate trypsinogen.

Certain *pharmaceuticals* (a few diuretics, oral anticoncipients, tetracyclines, sulfonamides, cytostatic drugs) promote the development of acute pancreatitis.

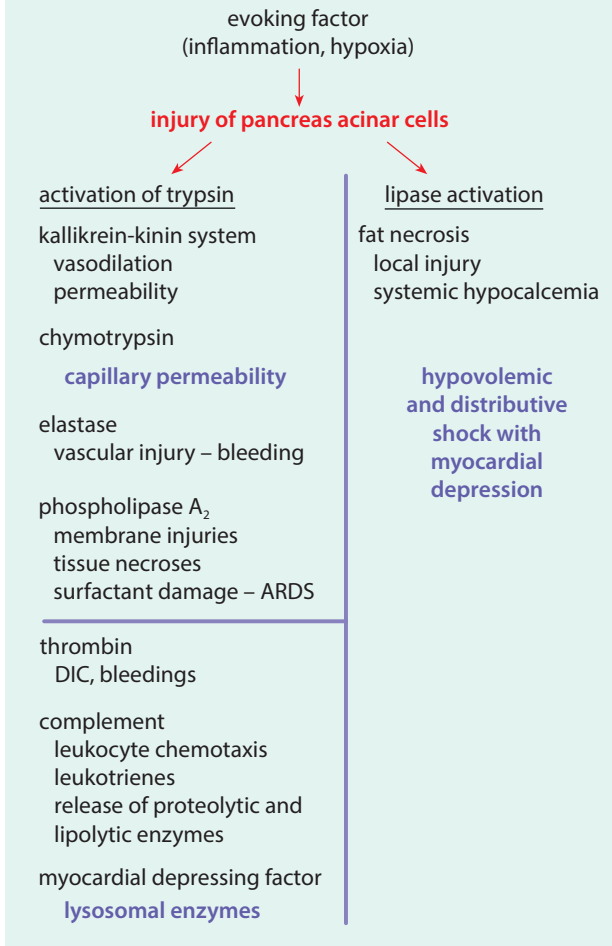

Fig. 7.21.: Factors participating in the pathomechanism of acute pancreatitis.

PATHOMECHANISM (Fig. 7.21.)

In less severe forms, the elevated intraductal pressure, tissue edema and acinar compression may attenuate further enzyme secretion, and as a potential result, the process may be halted. Most often the activated enzymes are squeezed out among the edematous tissues surrounding the ducts and acini (or they are activated in the tissues) and initiate a self-digestive process, while further inflammatory-edematous changes continue enhancing the ductal compression. The method of activation of the digestive enzymes (trypsinogen) is not entirely clear, and assumedly, trypsinogen may be activated not only by the bile, but also by lysosomal hydrolase enzymes of the parenchyma. From another perspective, some trypsin may normally be present, which is inhibited by trypsin-inhibitors (α_1-antitrypsin); in the absence of inhibitors, the trypsin activity is more pronounced. Activation of digestive enzymes initiates an inflammatory process (inflammatory cytokines: IL-1, IL-6, TNF-α, PAF etc., are produced, and their level is proportional to the severity of the process). Fever, hypermetabolism, leukocytosis (12-20 G/L), high sedimentation rate, etc., are the **general signs of acute inflammation**. The complement system is also activated and a local self-digestion gradually begins.

Intrapancreatic activation of trypsin is followed by the activation of lipase, phospholipase-A_2, elastase and the kallikrein-kinin system. Lipase induces **fat-necrosis** in the vicinity of the pancreas and in retroperitoneal fat tissue. The released fatty acids bind Ca and Mg (Ca-soap formation) and a **decreased level in se-Ca** may lead to symptoms of hypocalcemia (tetany), while at low Mg levels, the parathormone is unable to re-elevate the se-Ca. Elastase damages both tissues and vessels. Lysosomal enzymes cause further digestion. Due to the tissue damage, vasoactive substances (histamine and/or bradykinin) may accumulate, as a result vasodilation develops and the permeability increases. In the peritoneum, fluid accumulates (from the vessels), it is rich in proteins and enzymes. In addition to such fluid loss, increasingly severe bleedings (from injured vessels) may contribute to the development of **hypovolemic shock**.

While the digestive enzymes cause vascular and tissue injuries locally, the phospholipase-A_2 enters the circulation and may cause damage at distant organs, e.g. in the lungs (ARDS). The activated complement system and the kallikrein-kinin system induce a generalized inflammatory state (SIRS) and **distributive shock**. The ischemic pancreas produces MDF, which results in a **cardiogenic** factor seen in shock.

In addition to local changes, among systemic vessels, the inflammation causes precapillary vasodilation, while in capillaries platelet adhesion, activation and endothelial damage develop, with unmasking the collagen fibers the factor XII is activated, and the coagulation cascade is initiated intravascularly. Factor XII also activates the permeability increasing mediators of the kallikrein-kinin system, and this contributes to fluid loss from vessels to the interstitium throughout the entire body. Microthrombi and slow perfusion at the capillary level lead to tissue ischemia, necrosis and local bleedings. Activation of factor XII also enhances the fibrinolytic activity, and this promotes continuation of bleedings. The full picture of **DIC** is now fully witnessed. Due to concomitant bleedings, the hematocrit may decrease.

Retroperitoneal-peritoneal bleeding and inflammatory fluid excite the peritoneum and lead to an "**acute abdomen**". The characteristic **pain** is explained primarily by injury and compression of peripancreatic nerve fibers. The abdominal bleeding and peritoneal excitation may cause **ileus**-subileus, and very often **vomiting**. The local edema may obstruct the biliary ducts, as in the case in which **jaundice** may also be observed. In contrast, there is no initial pain, if the obstructed biliary tract and consequent jaundice is caused by carcinoma of the head of the pancreas.

The released enzymes, in joint association with vasoactive (dilatory) and permeability-increasing substances (e.g. bradykinin and/or histamine), with toxic substances from the damaged tissues (**MDF**), including a host of pro-coagulation factors (tissue thromboplastin), extend into the systemic circulation through the lymphatic system (escaping the liver), and this is shown by the elevation of se-amylase, se-lipase and se-transaminase levels. MDF adds a cardiogenic component to **shock**. The elevation of phospholipase-A_2 destroys the surfactant and speeds up the development of **ARDS**, however, the GI (**non-occlusive mesenterial ischemia**), and renal (**ATN**) consequences of shock also appear rather quickly. Metabolic plus respiratory acidosis and hypoxemia are all characteristic.

Additionally, the elevation of **blood glucose** shows how the endocrine pancreas is (transiently) affected.

The ingestion of large amounts of food enhances the production and action of secretin and CCK, including enzyme production of the pancreatic acinus cells, and it dramatically deteriorates the situation – the pancreatic enzyme production should be minimized. Accordingly, the *oral feeding must be transiently suspended!* Instead, it may require the enteral (nasogastric and/or nasojejunal tube) feeding with readily absorbable nutrients, and in a worse scenario, parenteral feeding may provide enough energy for restoration of ductal functions.

Secondary superinfection with Gram-negative bacteria occurs in about 50% of the cases. Later on, fistulas, abscesses, cysts (pseudocysts without epithel lining) may develop from the surrounding necrotic regions. In these cases, chronic pancreatitis is also possible, however, the retained intact areas typically provide a normal pancreatic function, therefore, *restitutio ad integrum* is possible.

7.5.2. CHRONIC PANCREATITIS

Acute pancreatitis very rarely develops into a chronic situation, i.e. the chronic form is primary, it begins latently and progresses with smaller or bigger acute recurrences. However, all causative factors of acute pancreatitis (e.g. alcohol and/or triglyceridemia) may worsen the chronic form. Although the original initiating factor yet remains unknown, the possible factors of exacerbations have to be avoided to slow down the progression.

While the exacerbations may eventually be severe, chronic malabsorption and pain worsens the quality of life, even without such recurrences. Since the entire mass of pancreatic tissue is affected and gradually becomes fibrotic, diabetes mellitus (secondary, insulin-deficient) often develops. By the end of disease progression, both the exocrine and the endocrine pancreatic functions are lost (Fig. 7.22.).

MOST COMMON CAUSES AND FACTORS OF PROGRESSION

Chronic alcoholism: Due to a high level of alcohol-dehydrogenase content in the pancreas tissue, a large portion of the ingested alcohol is transformed into toxic acetaldehyde within the gland. In the subsequent reaction, NADH is produced, which injures cellular metab-

olism (the decrease of NAD/NADH is pseudohypoxia, a redox state equivalent to hypoxia, and it leads to anaerobic glycolysis and lactic acidosis). At the beginning more viscous juice is produced, the α_1-antitrypsin effect decreases, and the tone of Oddi sphincter is elevated. Later, the secretion rate decreases.

Idiopathic: Relatively frequent and seen primarily in seniors, in whom it possibly develops due to an autoimmune mechanism.

Cystic fibrosis: It is a genetically determined disease, which may cause chronic pancreatitis already during childhood (Fig. 7.22.).

Chronic protein-deficient nutrition (dating from childhood): It is likely explained by the slow emptying of the juice. Due to concomitant thickening of this juice, protein-plugs are formed in the ducts, and these cause obstruction. A lack of essential fatty acids and minerals (Zn, Se, Cu) may promote the process. In kwashiorkor disease, aflatoxin plays a role in addition to protein-calorie malnutrition.

Chronic hypercalcemia: The crystals precipitating within the ducts and combined with proteins of the juice, may also form plugs and pancreatic stones, which obstruct the ducts. In protein deficiency this may happen more easily, since the lack of a Ca-stabilizing special protein allows Ca-precipitation.

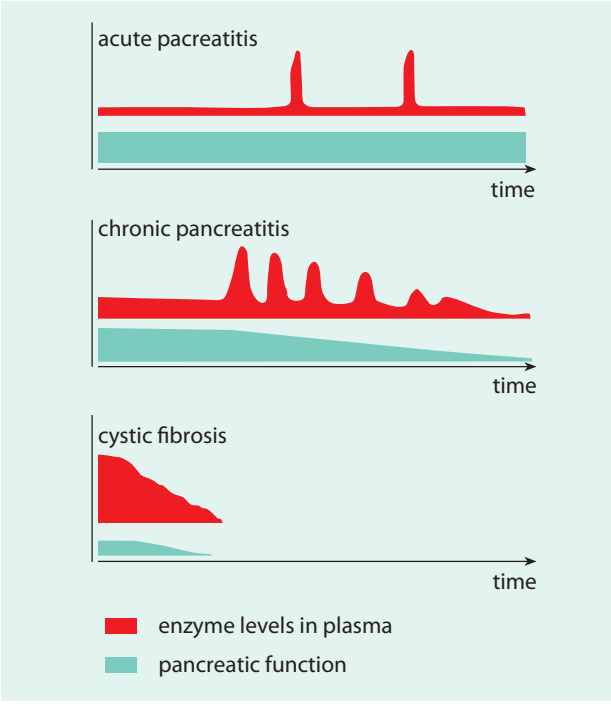

Fig. 7.22.: Plasma enzyme levels and the functional pancreas tissue in acute pancreatitis, chronic pancreatitis and cystic fibrosis.

Compression of ducts: Tumors, scarring and cysts cause repeated and lasting occlusions and promote the development of chronic pancreatitis.

States of prolonged hypersecretion: Overproduction of gastrin, secretin, CCK, VIP, or their defective removal in cirrhosis of the liver enhances the danger of chronic pancreatitis.

Hyperlipoproteinemias: High VLDL or chylomicron levels promote the disease. Diets rich in fat serve in deteriorating the condition.

Smoking: Smoking increases the risk of the development of the disease and speeds up the progression of chronic pancreatitis.

Genetic factors: A role for genetic factors may be conjectured from the finding that among individuals belonging to the "O" blood group the incidence of chronic pancreatitis is higher. Cystic fibrosis and many of the hyperlipoproteinemias are also genetically determined, and they are often combined with chronic pancreatitis. The gene mutation of PRSS1 (cationic trypsinogen) is accompanied by chronic pancreatitis with an 80% penetrancy and autosomal dominant transmission. Some mutations of SPINK1, CTRC, CEL, CFTR genes also increase the risk of development of chronic pancreatitis.

PATHOMECHANISM, CONSEQUENCES

In occluded segments of the ducts, the ductal pressure is high. Enzymes are squeezed out to the interstitium, where they become activated and cause smaller tissue injuries with fibrotic tissue production, as a general feature of chronic inflammation. In the perivascular region, there are stellatum cells of high fat and vitamin-A content, and these provide the basis of the progression. These cells can be activated by alcohol or acetaldehyde, and by oxidative stress, cytokines, growth factors (IL-1, IL-6, TNF-α, transforming growth factor and/or platelet derived growth factor), which derive from the macrophages and monocytes of chronic inflammation. Upon activation, lipid droplets are lost from the cytoplasm of stellatum cells, and the cells take up the appearance of fibroblasts and move towards the periacinar region. The TGF-β1 growth factor (perhaps also the IL-10, interferon-γ and the connective tissue growth factor) plays an outstanding role, by inducing collagen and fibronectin production, it has a strong fibrogenic effect. The periacinar fibrosis inevitably leads to fibrotic transformation of the entire pancreas and to the loss of functional arrangement of the acini. In this process, the role of stellatum cells is

similar to that of the Ito cells in the formation of hepatic cirrhosis (ch. 7.6.1.7.)

The fibrotic connective tissue accumulating in the vicinity of the ducts causes further narrowing, while the ductal epithelium cells are also transformed. The connective tissue spreads towards the injured tissues, it cicatrizes, and compresses the nerves, which explains the ***pain*** involved. Large meals may deteriorate the condition, as seen in the duodenal secretin and CCK stimulation of the production of pancreatic juice, and this acutely worsens the situation. Notably, **se-lipase** and **se-amylase** are particularly high in such cases. Later, the acinar cells atrophize, resulting in a lower amount of enzymes considered in the use of intestinal digestion, and eventually, chronic **complex malabsorption syndrome** develops. Small, yet frequent meals can slow down, but rarely stop the progression, even without presence of the original causing factor.

Consequences: The loss of body weight and diarrhea can be explained by the complex *maldigestion* and consequent *malabsorptio*n syndrome, and the resulting pain is due to the compression of nerves of the fibrotic tissues. Malabsorption particularly strongly affects fats, however, even this will be great only when lipase activity drops below 10% of the normal, although medium-chain fatty acids can still be absorbed. Malabsorption of carbohydrates is the latest step, without particular symptoms. The lack of lipase in the presence of bile does not seriously affect the absorption of fat-soluble vitamins. However, vitamin B_{12} deficiency may develop since, due to the lack of trypsin with consequently poor protein digestion, the vitamin may bind to non-digested proteins instead of the intrinsic factor. Protein loss of the body is late in starting, however, it is significant, resulting in a decreased absorption of the intake, enteral protein loss by the non-reabsorbed enzymes and an increased protein catabolism, all of which serve in providing an explanation.

The lability of glucose metabolism at the beginning implies a decreased glucose tolerance, and, later the endocrine functions are also lost and absolute insulin-deficient *diabetes mellitus* develops, which resembles 1DM (but secondary, ch. 9.2.2.), except that now the glucagon production is also lost.

7.6. DISORDERS OF THE HEPATOPORTAL SYSTEM

7.6.1. LIVER FUNCTIONS AND THEIR DISORDERS. HEPATIC COMA

More than 1000 individual liver functions are studied throughout various groups. Such groups include the following important ones: 1) The role of the liver in intermediary metabolism 2) The liver's role in vitamin metabolism and storage 3) Detoxification by the liver 4) Bile production 5) Additional functions, such as salt and water balance, immune functions, hematologic functions and endocrine functions.

7.6.1.1. INTERMEDIARY METABOLISM IN LIVER DISEASES

Carbohydrates:
The most fundamental source of glucose supply for the body is typically attributed to the liver, even following food intake (the liver takes up the consumed glucose from the portal vein, the liver stores it and releases other glucose from glycogen to the plasma: in experiment, isotopically labeled glucose was consumed, unlabeled released). In liver diseases, either hypoglycemia or hyperglycemia may occur. Hypoglycemia is predominant in severely acute or chronic end-stage disturbances including alcohol intoxication, when glyconeogenesis from pyruvic acid cannot take place, (lactate from anaerobic glycolysis in state of pseudohypoxia cannot be converted to pyruvate). In other cases, the liver cannot take up glucose due to the portal shunting of blood, resulting in diabetoid glucose tolerance tests or even high fasting glucose levels may be observed. Despite the diabetes-like tendency, the insulin levels are also high, and the insulin-antagonist hormones (GH, glucagon, cortisol) may be elevated, since the liver cannot bind, metabolize, or eliminate them.

Protein/amino acid metabolism:
In general, the normal protein synthesis decreases in liver damage (e.g. albumin, coagulation factors and/or transport-proteins), although eventually an increase may be seen (e.g. acute-phase proteins), in which the plasma level of hepatic enzymes increases (e.g. alkaline phosphatase in cholestasis, gamma-glutamyl-transpeptidase /GGT/, AST and ALT transaminases). Catabolism of certain proteins is also reduced (e.g. the catabolism of plasminogen-activator protein is low, resulting

in enhanced fibrinolysis, and vasodilatory peptides are also poorly metabolized). Abnormal proteins may be produced (dysfibrinogenemia and/or alpha-feto-protein). Since the urea synthesis decreases, the plasma ammonia level is elevated.

The damaged liver cannot take up aromatic amino acids, therefore the level of these amino acids, when compared with the branched-chain versions, increases. The abundance of aromatic amino acids is important in the synthesis of false transmitters.

Lipids:
The fat content of the pathological liver is elevated from 5% up to 50% (hepatic steatosis). The most obvious cause of this is the lowered production of protein synthesis, and the production of small amounts of abnormal apoproteins. In the blood, cholesterol-rich abnormal lipoproteins appear (e.g. LPX in biliary congestion), which incorporate into the membrane of red blood cells, thereby decreasing their membrane resistance and causing a tendency for hemolysis. Levels of plasma lipoproteins are elevated, and type-III hyperlipoproteinemia is characteristic. The only regulated method to eliminate cholesterol is through the liver, however, this is disrupted in liver damage. Transformation of cholesterol to bile acids (cholic acid, chenodeoxycholic acid), conjugation with taurine/glycine may be disrupted, or excretion of bile acids may be low, thereby the only regulated way of cholesterol elimination becomes insufficient.

7.6.1.2. METABOLISM AND STORAGE OF VITAMINS

Primarily, the fat-soluble vitamins A and D, together with the water-soluble folic acid and vitamin B_{12} are possessed in greater quantities in the hepatic storage. Regarding the release of vitamin A, the liver must also produce a transport protein (retinol binding protein, ch. A6.2.4.1.), since, without this, the vitamin accumulates within the cells and thereby induces cell injury. The Ito-cells which store vitamin A, have a central role in the development of cirrhosis (ch. 7.6.1.7.). In reference to the role of hepatic 25-hydroxylase enzyme, liver function is also required for producing the active form of vitamin D. The most important function in which vitamin K plays an important role is in the effective production of coagulation factors within the liver. Although vitamin K has no hepatic storage, its action requires the existence of intact hepatocytes.

7.6.1.3. DETOXIFICATION IN THE LIVER

Most fat-soluble substances and waste products are eliminated by the liver. They enter the hepatic cells through passive transport. Within the cell, they first bind to Y and Z proteins (ligands), and then are metabolized with the aid of cytochrome P-450, and conjugated by taurine or glycine, to become water-soluble. Although the metabolites may eventually have higher toxic actions when compared to the original substance, the conjugated form can be quickly emptied into the intestine through active biliary excretion. In the case of water-soluble substances, the hepatic detoxification does not necessitate conjugation, thus, their metabolites can be excreted partly by the bile, or in a smaller extent, they re-enter the circulation to be renally excreted.

Disorders of hepatic detoxification may originate from disturbances of hepatic circulation, from abnormalities of blood-to-hepatocyte transport, from disorders of IC metabolization, or from too slow excretion. In the case of slow detoxification, the toxins and their metabolites are present in the hepatocytes for a sustained period of time, thereby induce cellular injury, necrosis, and finally, cirrhosis.

The most important groups of substances to be detoxified and/or metabolized and excreted by the liver include the following: 1) ammonia, 2) alcohol, drugs, xenobiotic substances, which are in competition and mutually impede one another's metabolism, and, 3) bilirubin and the bile acids.

Detoxification of ammonia:
Originating from the highly toxic ammonia, with the aid of CO_2, the intact liver produces urea in the urea cycle (Fig. 5.15.). Urea is a water-soluble weak toxin and after being released from the liver to the circulation, it is excreted by filtration in the kidney. Ammonia appears in the circulation from various sources, including deamination of proteins, metabolism of renal glutamine, and mainly bacterial breakdown of proteins in the gut. In liver failure, detoxification by the urea pathway becomes ineffective, ammonia accumulates and its strong toxic effects appear primarily in the central nervous system and contribute to the development of hepatic encephalopathy. In portal hypertension (ch. 7.6.3.), the ammonia originating from the guts avoids the liver, and through shunt vessels it enters the systemic circulation, ultimately explaining the portal encephalopathy.

Detoxification of alcohol:
Alcohol is detoxified by its transformation in the liver. Any alcohol not transformed by this method will remain in the circulation to be removed through the kidney.

In plasma levels exceeding 50 mg/ml, the maximal hepatic ethanol metabolism is about 10 g/hour (supplying about 7 kcal/g), and the excess is removed by the urine. The alcohol, although it alone does not cover the daily energy need, in cases of otherwise sufficient nutrient supply may serve as a substantial excess of calories (causing a form of obesity). Of course, this is not the case, if and when the nutritional intake is lower, as it is in most chronic alcoholics.

The ethanol → acetaldehyde → acetate transformation (and in competition with this, also the methanol → formate transformation) is catalyzed by the alcohol dehydrogenase enzyme, the microsomal ethanol oxidizing system (MEOS) and the peroxisomal catalase enzyme (Fig. A5.1.). Acetaldehyde is very toxic (formate is even more so), a fraction of which can enter circulation where they bind to albumin and remain in the circulation for a sustained period of time, causing damage throughout various organs, apart from the liver. The formate is more toxic and its removal is far slower. In the course of alcohol metabolism, short life-time free radicals are also produced, which have characteristically severe damaging effects. The ethanol-methanol competition explains that, as seen in methanol intoxication, administration of ethanol may help: more acetaldehyde, but less formate is produced and in the meantime a greater amount of the water-soluble methanol can be renally emptied and its toxic effect remains far less severe. Some alcohol-dehydrogenase activity can already be demonstrated within the stomach.

The velocity of these hepatic processes is determined primarily by the amount of NAD (NAD takes up the hydrogen from alcohol-dehydrogenation) and by the speed of re-oxidating the produced NADH. The re-oxidation (NADH to NAD) causes reduction of other substances, thereby more pyruvate is transformed to lactate and due to the low pyruvate level the capacity of gluconeogenesis decreases; simultaneously, the fat synthesis increases and oxidation of fatty acids decreases. During this process, lactic acidosis and hypoglycemia (and hyperlipemia often with ketosis) may develop (Fig. A5.1). If the amount of pyruvate is small, well before the need of such detoxification, the NADH increase is more pronounced, the alcohol metabolism is slower (more remains in aldehyde form) and its toxicity is higher. This is seen in fasting states, and this explains how, in contrast to common beliefs, it is not a fat-rich diet but a carbohydrate-rich diet which may suppress the toxicity of alcohol.

Within the Indian culture, and in the population of the Far-East, and also in women of any race, the transformation of the aldehyde form is slower (particularly in the stomach), and this likely explains their greater sensitivity to alcohol intoxication among these groups. In acute alcohol action the activity of MEOS and the production of cytochrome P-450 are responsible for detoxification of alcohol and other xenobiotics – these are in competition and the process is slow. In chronic alcohol-effect the cytochrome P-450 greatly increases, the detoxification is faster and the severity of the toxic effects decreases. In acute alcohol action, this results in enhanced effects of other toxins and substances (drugs and xenobiotics, which should be detoxified by the same cytochrome P-450 way), or in the presence of other toxins, the toxic effect of alcohol is stronger (Fig. A5.2.). In contrast, as seen in chronic actions of alcohol, the elimination of both the alcohol and xenobiotics (drugs) may be faster or other drug interactions can be expected (e.g. faster elimination of drugs used in medicine, or weaker and diminished drug action, e.g. narcosis at surgery becomes difficult).

Detoxification and excretion of bilirubin and bile acids:

The normal se-bilirubin (5-17 μmol/l) is primarily unconjugated, albumin-bound (=indirect) form: the size of this molecular-complex does not allow its filtration through the glomerular capillaries. Other substances, including salicylate, sulfonamide, etc. compete for albumin, and they may prevent albumin-bilirubin binding of bilirubin and the free unconjugated bilirubin is highly toxic. As little as less than 10% of bilirubin is in direct form (i.e. conjugated with a polar group, e.g. glucuronic acid), and this fraction consists of small, water-soluble molecules. Although these small molecules could be filtered by the glomeruli, as long as their amount is normal, they are rather secreted from the liver cells (where they are produced) and excreted by the bile to the guts, and either they enter into the enterohepatic circulation or exit the body along with the feces. If direct bilirubin is still elevated somehow in the plasma, it is excreted by the kidney. In case of its prolonged elevation,

a portion binds covalently to the albumin and either remains within the circulation for a sustained period of time, or becomes deposited into the interstitium. This bilirubin may cause tissue injury, similarly to the case in which the still unconjugated bilirubin is "freed" from albumin in case of excessive amount of indirect bilirubin.

The process of detoxification involves an uptake of bilirubin by hepatocytes, its conjugation within the cells (mainly by glucuronic acid), and its secretion from the hepatocyte to the bile and intestine. Some of it is reabsorbed from the gut in the form of UBG: the enterohepatic circulation, and presence of some se-bilirubin may be necessary due to its antioxidant and free radical scavenger properties. Bile acids (cholic acid and its derivatives) are produced in the liver originating from cholesterol, and they are secreted in a conjugated form along with glycine or taurine, to participate in the enterohepatic circulation, similarly as seen in case of bilirubin (97% of cholic acid derivatives are reabsorbed in the chylomicron fraction). The reabsorbed UBG and bile acids are secreted again, ensuring the possibility in which their daily secretion is higher when compared with their daily production. In case of obstruction of the biliary tract, it is not limited strictly to bilirubin, but bile acids are also retained, and their level increases in the circulation or, similarly to direct bilirubin, they accumulate within the tissues, in which they excite non-specific nerve endings – this explains and substantiates itching seen in jaundice.

Steps of bilirubin metabolism:

- Hemoglobin (= Hb, from older, red blood cells and erythroid forms, the globin and Fe dissociate)
- Hem (origin: Hb, myoglobin, hem-containing enzymes, cytochromes); and, it may be further transformed into high NO-affinity hem-oxidase, which of course, increases during stress
- Biliverdin (produced in the RES with some levels of CO)
- Bilirubin (upon biliverdin reductase effect, and the transport into hepatocytes)
- Bilirubin glucuronide (in liver cells upon glucuronyl transferase effect; in newborns it is still defective), it is secreted by the bile, and with minimal regurgitation in sinusoids
- Urobilinogen group (UBG: produced in intestine, and generally returns to the liver through enterohepatic circulation, and once again, re-converted to direct bilirubin and secreted. Small amount avoids the liver, enters the circulation, then onto the glomeruli, eventually to be filtered into urine
- UBG derivatives and stercobilins that remain within the gut (5%) are emptied by the feces

Disorders of bilirubin metabolism, ***hyperbilirubinemias*** *(Fig. 7.23.)*

General causes include an enhanced hem degradation, low hepatic uptake, disorders of glucuronation, and these lead to an accumulation of indirect bilirubin. Secretion abnormalities of the glucuronated form lead to changes in the level of direct bilirubin. In prehepatic disorders (e.g. hemolysis) the indirect, and in the posthepatic versions (e.g. gallstone) the direct bilirubin accumulates within the plasma, while in generalized dysfunctions of liver cells (e.g. hepatitis) the changes appear in a combined form (liver cell dysfunction results in a decreased hepatic uptake and glucuronation, what elevates indirect bilirubin, while the concurrent abnormality of secretion elevates the direct form).

Increased hemolysis → indirect hyperbilirubinemia: The hepatocyte functions are enhanced, thus, more direct bilirubin is produced and excreted to the guts. The color of the feces is darkened (pleiochromic), more UBG is formed and from the enterohepatic circulation a larger quantity inevitably escapes the liver, causing elevation of the urinary UBG level. There is no bilirubin in the urine. Jaundice develops due to the accumulation of indirect bilirubin within the plasma.

Occlusion of the biliary tract → direct hyperbilirubinemia: The normally produced direct bilirubin is not forwarded to the guts, but due to a back-leak from the broken biliary canaliculi, it returns to the plasma. The feces is colorless (acholic) and it contains fat. No UBG is formed in the guts, therefore, there is no UBG in the urine, however, large amounts of direct bilirubin are present. Jaundice develops due to the accumulation of direct bilirubin within the plasma. Painless yet physically detectable (by touch) cholecyst with jaundice (Courvoisier sign) suggests bile duct occlusion due to a tumor in the head of the pancreas.

In hepatic injury: The liver cannot take up the normal amount of indirect bilirubin, can produce even less direct bilirubin from this, even this cannot be excreted to the guts, however, a portion of it returns into the circulation. Jaundice develops due to direct+indi-

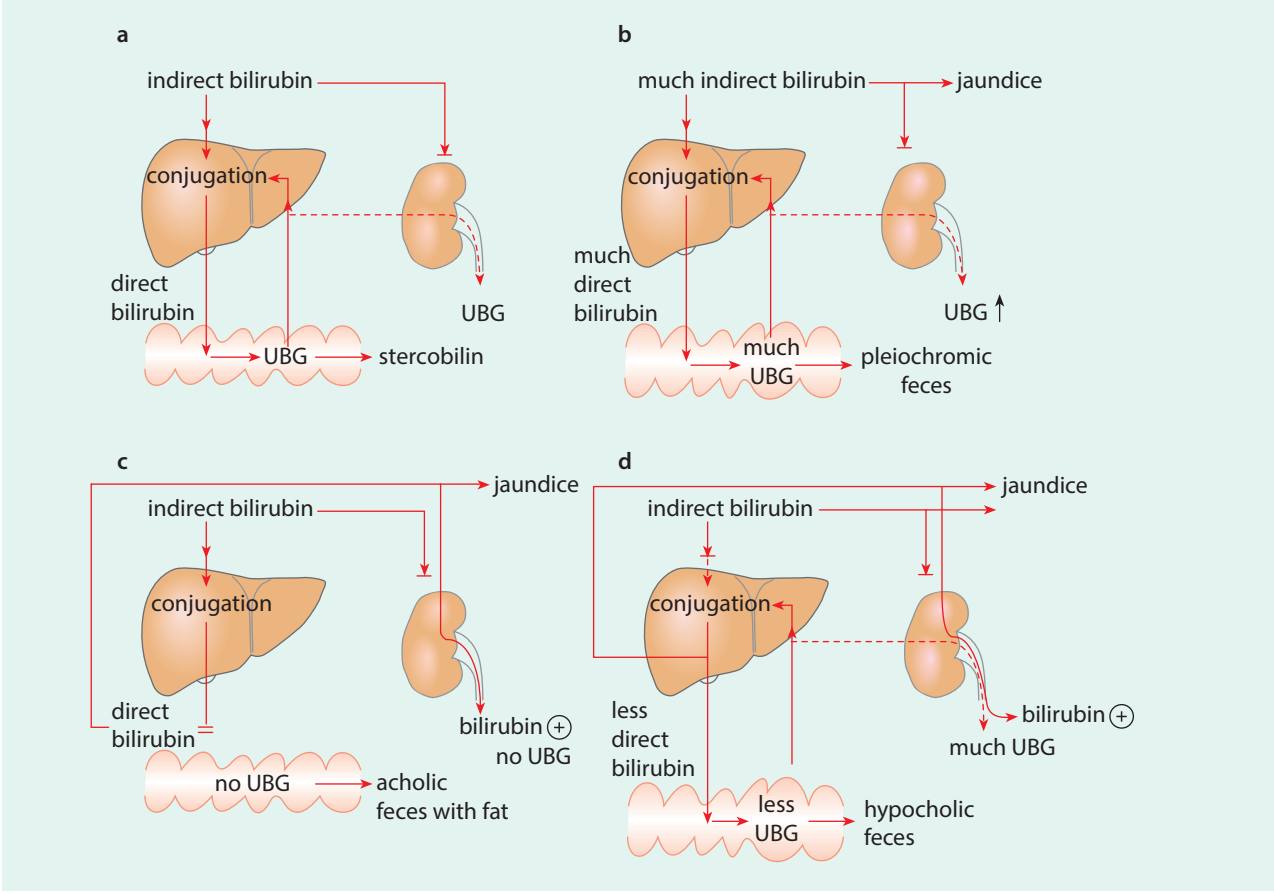

Fig. 7.23.: Bilirubin metabolism and its pathological changes. a: normal process, b: hemolytic jaundice, c: posthepatic obstruction, d: generalized liver damage.

rect hyperbilirubinemia. Less bilirubin reaches the gut, therefore, the color of the feces is lighter and contains fat. Less UBG is formed, however, the reabsorbed UBG cannot be re-converted to bilirubin by the hepatocytes and more UBG escapes the liver than normally, and appears in the urine. The urine also contains (direct) bilirubin in addition to UBG.

Shunt-hyperbilirubinemia: Although the life expectancy of red blood cells does not diminish, the signs of hemolytic anemia are present, as seen in leukemia and/or pernicious anemia.

Icterus neonatorum: In addition to the increased hemolysis of fetal Hb, the enzymes of glucuronation do not yet function efficiently (barbiturates are able to activate these enzymes). Indirect bilirubin can pass the blood-brain-barrier, the free bilirubin (released from the albumin) is extremely toxic for the brain.

Gilbert's disease: The transport of biliary pigments through the plasma to the hepatocyte is not sufficient, and the glucuronation is disrupted.

Glucuronyl transferase inhibition: Pregnandiol of maternal milk inhibits glucuronation within the liver cells.

Crigler-Najjar syndrome: Due to insufficiency of the transferase enzyme, the conjugation of bilirubin cannot be activated (according to severity, types I and II are known).

Dubin-Johnson syndrome: Purging the conjugated bilirubin from the liver cells is defective, although there is no obstruction among the bile ducts.

Rotor syndrome: Insufficient purging of conjugated bilirubin from the liver cells.

Intrahepatic cholestasis: Drug-induced, pregnancy-related, postoperative cholestasis, or hepatitis, biliary cirrhosis are the most frequent causes.

Obstruction of biliary bract: Stone, obstruction, lymph gland, and other possibilities of compression. The most frequent cause of painless icterus is due to obstruction at the pancreatic head as a consequence of a local tumor.

The genuine yellow shade of color seen in jaundice (= icterus) may vary in consideration of the origin of the disease. In parenchymal jaundice (hepatitis), red tint appears (rubinicterus), in hemolysis a bright yel-

7.2. table

Comparison of forms of jaundice

	Prehepatic	Hepatic	Posthepatic
main cause	hemolysis	parenchymal damage	obstruction of bile-ducts
se-bilirubin (indirect)	↑↑	↑	N
se-bilirubin (direct)	N	↑	↑↑
urine bilirubin (direct)	–	+	++
urine UBG	↑↑	↑↑	–
feces colour	↑	↓	–
feces fat	–	↑	↑↑

low shade (flavinicterus) is characteristic. Obstruction results in a greenish tint (verdinicterus), which is characteristic and if it is long-lasting, as seen in tumors, a darkened "icterus melas" may develop. The shade intensity is dependent partially upon the accumulated pigments, and partially upon skin circulation.

Toxicity of bilirubin:
Jaundice is only deposition of several forms of bilirubin within the interstitium which is easily observed by the color of the skin and the sclera (plasma bilirubin exceeding 40 μg/l). Although the hem-oxidease, NO and CO may improve the local tissue circulation, and in small quantities, the bilirubin acts as a free radical scavanger, in larger concentrations the pigment is toxic. Damage is caused primarily by the unconjugated free bilirubin, which can cross the weak blood-brain barrier (or it is „freed" after passing the BBB) and, as seen in neonates (particularly in hypoxic-septic neonatal infants), it can cause yellow discoloration of the basal ganglia = Kern-icterus (der Kern = nucleus, stone). The lipophilic bilirubin binds to phospholipid membranes of the cells and it inhibits membrane-based enzymes and blocks mitochondrial functions. This leads to disorders of the synaptic transmission, to EEG abnormalities, and eventually to severe retardation of the development. In adults, the barrier functions are better, and the direct bilirubin-oxidase enzyme is also operant, thus, the peril, or risk – regarding the brain – is diminished. However, bilirubin may damage other cells. Bilirubin has a role in the development of biliary cirrhosis (damages the liver parenchyma), and in the renal tubular cells, too, are sensitive to bilirubin. In covalent binding, the bilirubin may accumulate in the interstitium and may cause tissue damage. Some symptoms of jaundice, such as undue itching, are likely far better explained by the similar accumulation of bile acids.

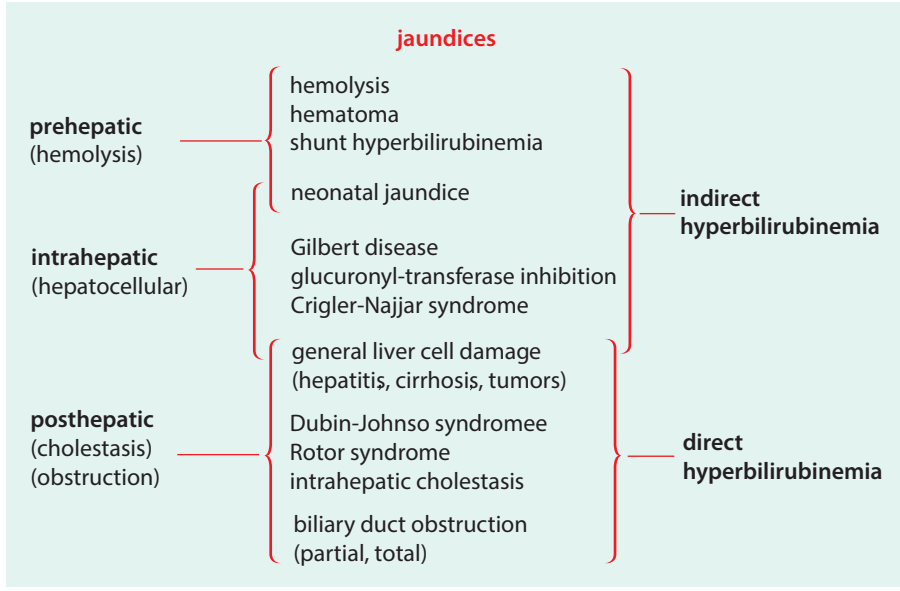

Fig. 7.24.: Classification of forms of jaundice.

7.6.1.4. DISORDERS OF BILE FORMATION.

Bile produced by the liver is a suspension containing bile acids (cholic acid derivatives, together with cholesterol), bilirubin, lecithin (and phospholipids) and elec-

trolytes, and its quantity is proportional primarily with the amount of bile acids. The produced bile enters the small bowel during food intake, otherwise it is stored and concentrated within the gallbladder. Secretin enhances the secretion, primarily due to the bicarbonate and electrolytes, while mainly CCK stimulates the purging of the bile. The role of lecithin is mainly to keep the bile-acid-coated cholesterol particles in a micellar type suspension, without this the cholesterol forms crystals, which means the basis of stone formation.

Role of the bile:

1. Bile acids attach to the fat (and fat-soluble vitamin) particles of nutrients by their lipophilic parts, while their hydrophilic part allows maintenance in a water-phase (=detergent action), what is a basic precondition of digestion and absorption of lipids and fat-soluble substances. The conjugated bile acids are reabsorbed, primarily from the ileum, by an active form (later on the liver secretes them once again, through enterohepatic circulation) and only a few percentage eventually enters into the colon. Once inside the colon, bacteria deconjugate them, and what little free bile acids arrive here, now physiologically excite the colon to enhance water secretion and promote fecal propulsion (free bile acids derived from premature bacterial deconjugation excite the small bowel, while too much conjugated bilirubin entering the colon cause excessive deconjugation and excitation of the large bowel). The bile acids are reabsorbed from the guts and are secreted once again to repeat their detergent action.
2. Regarding the bile, bilirubin, cholesterol, and other sterane-structure compounds, drugs, xenobiotics, toxic substances can all be excreted, i.e., the bile-secretion possesses a similar excretory role as noted in the kidney (aiming at mainly the lipids and fat-soluble substances). The bilirubin (UBG) and cholesterol levels can be utilized once again with the aid of the enterohepatic circulation.

Disturbances of bile production are characteristic regarding hepatic damage, while disorders of purging and emptying the produced bile originate from extra- and intrahepatic obstructions, and lead to cholestasis. The absence of bile is followed by the malabsorption of fats and fat-soluble vitamins, however, the detoxifying functions are also impaired (the detoxified end-products cannot be emptied). More bile is produced and emptied in the conditions of high secretin levels or CCK activity. As seen in ”short bowel syndrome”, an increased amount of conjugated bile acids enters the colon, and here they will be deconjugated, generally evoking diarrhea.

In bacterial overgrowth of the small bowel, the bile acids are already deconjugated at this level, and the result excites the small bowel and enhances its secretory function, while the deconjugated bile acids cannot fulfill their roles in absorption of lipids.

7.6.1.5. OTHER LIVER FUNCTIONS

Endocrine disorders: Normally, insulin, glucagon, secretin, CCK, steroid-hormones (estrogen!) are at least partly inactivated in the liver (steroids are excreted by the bile), therefore their metabolism decreases in the course of liver damage. In such cases, the amount of gonadotropic hormones decreases in both sexes, therefore, hypogonadism is frequent. In males, the high level of non-inactivated estrogens and prolactin may cause feminization (gynecomastia, testicular atrophy).

In liver failure, some vasodilatory substances (glucagon, NO, CGRP, VIP, substance P, ANP) are not inactivated, thus, they accumulate and cause systemic and pulmonary vasodilation (contributing to hepatorenal and hepatopulmonary syndromes). The ammonia level increases, excites the respiratory center, consequently leading to hyperventilation and hypocapnia, contributing to the peripheral vasodilatation and brain vasoconstriction.

Abnormalities of salt- and water-balance: Many of these aspects characteristically originate from the portal congestion and the formation of ascites generally attributed to chronic liver diseases, however, the relative hypovolemia due to vasodilatory substances and the consequent hypotension are also important. The skin vasodilation may be so pronounced that the skin temperature increases. While the portal veins are rather overfilled, there is hypovolemia in the systemic circulation. The salt and water balance abnormalities feature endocrine causes, too (relative increase of RAAS function, deficient activity of natriuretic factors), and these cause salt and water retention. The insufficient RAAS effect often leads to hyponatremia (hypotonicity), what is likely explained by the consequent activation of ADH secretion and pure water retention. The oliguria is partially explained: due to the decreased arterial volume, the renal perfusion decreases, particularly in the cortex. Later this will sufficiently explain the ”hepatorenal syndrome”.

7.6.1.6. HEPATIC ENCEPHALOPATHY, HEPATIC COMA

Hepatic encephalopathy which develops in severe generalized liver failure is a complex neuropsychiatric syndrome including asterixis (liver flap, flapping tremor), EEG abnormalities, depression and confusion. The disorders of consciousness and vigilance grow worse in a pattern of waves, inevitably reaching the most severe, fatal state of coma with the complete loss of consciousness. The explanation is likely found in the metabolic and detoxification dysfunctions of the liver, which affect the overall function of brain cells.

Its cause may be a ***hepatocellular lesion*** (cirrhosis, hepatitis, hepatic tumor, toxins /CCl_4, halothane, mushroom poison, alcohol, INH = isoniacide antituberculotic/, intra- or extra-hepatic cholestasis, hereditary disorders /mucoviscidosis, α_1-antitrypsin deficiency, glycogenoses/, herbal toxins), and/or ***portal encephalopathy*** (portal hypertension, due to porto-caval shunts toxins avoid the liver, ultimately reaching the brain in higher concentration).

Pathomechanism of hepatic encephalopathy (Fig. 7.26.):

1. *Dysfunctions of the blood-brain barrier*
   - Non-specific elevation of permeability, the crossing neurotoxins inhibit the Na^+/K^+ ATPase enzyme, and this causes brain cell dysfunction
   - Non-specific transport-processes are increased, e.g. more short-chain fatty acids (SCFA) enter the brain, but they cannot be broken down (β-oxidation is not present in the brain), and the accumulating SCFA are toxic
   - Specific transport of aromatic amino acids (Phe, Tyr, Trp) increases (in contrast to the branched-chane ones which are metabolized in the muscles), these should be utilized and transformed by the liver, however, they now accumulate. Originating from a part of the aromatic amino acids, abnormal catecholamine-like substances (false neurotransmitters, e.g. phenylethanolamine, octopamine) are produced, which disallow the binding of the normal transmitters. In other cases, real transmitters are overproduced (serotonin).

2. *Dysfunctions due to neurotoxins*
   - *Ammonia:* Ammonia (NH_3) is detoxified by the urea cycle of the liver (Fig. 5.17.). In liver failure, this does not function normally. The accumulating ammonia excites the respiratory center and induces respiratory alkalosis. Due to alkalosis, a greater portion of ammonia enters the intracellular (IC) compartment, where it accumulates in the form of ammonium-ion (NH_4^+). Here it binds to the α-ketoglutarate, therefore, this can no longer participate in the energy producing TCA cycle. As a consequence, Na^+/K^+ ATPase deficiency develops, accompanied by cellular swelling. Glutarate is transformed to glutamate, and the excitatory glutamic acid to glutamine by binding to ammonia. Ammonia also promotes an influx of aromatic amino acids to the brain, to form false transmitters. The respiratory alkalosis is coupled with hypocapnia, what, in turn, causes vasoconstriction and oxygen deficit in the brain.
   - *Toxins of synergistic action:* These are derived from the guts. Mercaptans (gut bacteria produce these from methionine and sulfur-containing amino acids, and following absorption from the gut, the liver's role is to detoxicate them), phenol-derivatives, short-chain fatty acids (SCFA – in brain no β-oxidation!), all potentially cross the blood-brain barrier, resulting in damaged brain functions.

3. *Changes of brain metabolism:* Inhibition of the TCA cycle diminishes glucose utilization of the brain. From another perspective, acute liver failure may cause hypoglycemia due to lack of gluconeogenesis. Both may lead to insufficiency of the brain energy supply.

4. *Anomalies of neurotransmission:*
   - False neurotransmitters are produced from aromatic amino acids, and bind to benzodiazepine receptors (BZD-antagonist flumazenyl attenuates the symptoms).
   - Serotonin (from Trp): as its level increases, it prevents noradrenaline binding to its receptors.
   - GABA (inhibitory): increased activity of its neurones (GABA is derived from the gut, the sick liver cannot eliminate it, and the high permeability of the blood-brain barrier allows more to enter the brain).
   - Glutamate (excitatory): as its level decreases, coupled with ammonia it is now transformed to glutamine.

5. *Cellular and other changes:* Brain cells have energy deficit, they are swollen, and they lose potassium.

Free radicals (from disordered metabolism) injure them. The respiratory alkalosis is accompanied by renal acidosis and hypokalemia, hypovolemia, hypotonicity – all may potentially develop, and these cause unfavorable changes in the functions of brain cells.

Factors provoking a coma associated with hepatic injuries:

- High protein-(NH_3)-load (alimentary protein, eventually blood plasma enters the GI tract from a ruptured esophageal varix)
- Electrolyte imbalances (hypokalemia, alkalosis and hypoxic lactate-acidosis)
- Drugs (narcotics, diuretics /hypovolemia, hyponatremia and hypokalemia/)
- Other causes (infection, surgery and direct hepatic lesions)

7.6.1.7. GENERALIZED LIVER INJURIES. LIVER STEATOSIS. CIRRHOSIS. ASCITES. HEPATORENAL SYNDROME. HEPATOPULMONARY SYNDROME

Primary symptoms characteristic to generalized liver damage:

Basically, the liver has a marvellous regenerating capacity, provided it is not damaged simultaneously by various mechanisms. In early animal experiments a big portion of the liver was removed, but soon it was regenerated and within a short interval a practically normal liver was seen again. (Later on, this made liver transplantation possible: the donor was not endangered). After repeated removals altogether more liver mass was removed than the original amount, the still remaining liver stucture was somewhat altered, but the functions were maintained, although with higher vulnerability. This physiological regeneration capacity was diminished or altered in case of simultaneous damage by hepatotoxic agents – in these cases the liver structure and function were more severely damaged.

In clinical practice, upon liver damage, depending on the type and action time of the damaging factor, various abnormalities may appear:

- Size and consistency of the liver changes (as seen in hyperacute necrosis, it may be smaller and soft, while in chronic hepatic disease, it is first enlarged, later rather cumbersome, unyielding, and the gradually shrinking liver is all entirely characteristic)
- Jaundice (cf. bilirubin metabolism and detoxication, ch. 7.6.1.3.)
- Fluid-retention, ascites (retention may happen without ascites), hypovolemic signs on the arterial side
- Portal hypertension (it may occur also with a normal liver, if and when the portal vein is compressed/occluded)
- Encephalopathy (from mildly disturbed behavior to coma)
- Generalized wasting (malabsorption and lost appetite), in which, this often emphasizes the severity of the simultaneous ascites or hypalbuminemic edema
- Coagulation abnormalities and vitamin deficiencies
- Anomalies due to the defective detoxifying function

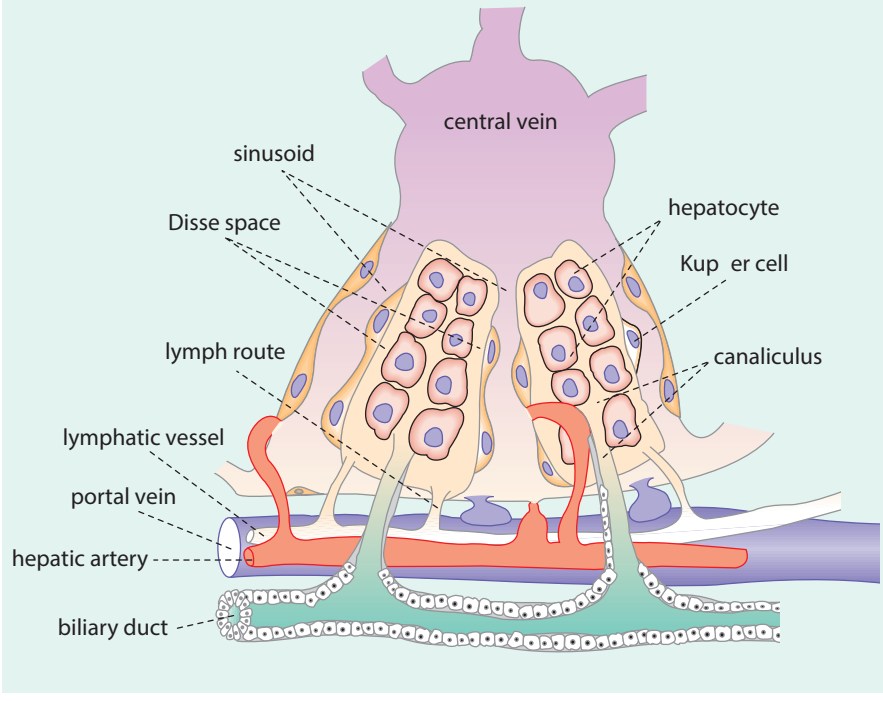

Fig. 7.25.: From the structure of the liver, the development of portal hypertension and ascites is understandable. Ito cells are located between the endothelium underneath the Kupffer cells and the hepatocytes, in the Disse-space.

Process of generalized liver damage

In the clinical practice a severe acute injury (atrophia hepatis flava), primary necrosis of liver cells acutely leads to a decrease in liver size (yet, still in the form of a soft texture), next, to functional insufficiency and inevitably, coma.

In less acute or definitely chronic processes, usually ***steatosis*** develops first, associated with hepatomegaly. Later, the injury initiates a local ***inflammatory*** process. Finally (with a contribution of Kupffer cells and lymphocytes) "regenerative" processes are initiated, in which fibroblasts and myofibroblasts extremely proliferate (of which, the perisinusoidal Ito-cells containing lipids and vitamin-A possess a distinctive role: upon the effect of cytokines and growth factors, they are transformed into collagen-producing myofibroblasts). This is the basis of proliferation of the connective tissue, followed by scar formation and shrinkage, eventually destroying the liver structure (Fig. 7.19.) and by contraction of the former increased liver size, referred to as ***cirrhosis***. From one perspective, cirrhosis causes further deterioration of liver functions: it compresses the intrahepatic veins (central veins and sinusoids), thereby it inhibits forwarding the blood from the portal vein resulting in ***portal hypertension*** (Fig. 7.22.). The intrahepatic obstruction of blood flow leads to the development of ***ascites***, while the concomitant disorder of salt and water balance and its circulatory consequences (redistribution of cardiac output) contribute to the development of ***hepatorenal syndrome***. The accumulation of vasodilatory substances (lack of their destruction by the liver) explains the generalized (also pulmonary) vasodilatation, the decrease of arterial pressure, and, in some cases, the development of ***hepatopulmonary syndrome***.

Development of cirrhosis

1. Preinflammatory phase:
Due to the inflammatory agent, the hepatic β-oxidation and breakdown of lipids are suppressed, together with the protein/apoprotein synthesis. The cells are unable to release lipids as lipoproteins, and steatosis may develop (the fat content of the liver may increase from 5% to 50%). Simultaneously, the fat uptake of the liver cells increases (obesity, glucocorticoid effect, diabetes, lasting starvation and hepatic wasting, all enhance the mobilization of fat from fat tissue). The fat content of Ito-cells is also elevated. These cells also contain leptin and other cytokines, which are bound primarily to receptors of the Kupffer cells (fix macrophages), partly to those of endothelial cells and serve in activating them. The lipids accumulated in hepatocytes induce further parenchymal damage and these, together with the cytokines, induce an inflammatory process with free radical (ROS) formation. Abnormal lipoproteins may enter circulation from the liver, and secondary hyperlipidemia, dyslipidemia are characteristic.

2. Inflammatory phase:
The production of free radicals (ROS) is highly evident in the injured liver parenchyma. This contributes to transformation of fat and vitamin A-storing Ito cells into myofibroblasts by elimination of their fat content. The myofibroblasts proliferate and produce a connective tissue matrix and enzymes for its breakdown and transformation (the matrix production prevails during reconstruction after the breakdown). Additionally, they produce cytokines, which activate Kupffer cells. From the activated Kupffer cells, increasing amounts of TNF-α, IL-1, IL-6, TGF-β (transforming growth factor), PDGF (platelet-derived growth factor), FGF (fibroblast growth factor) are released, and their levels are continuously increasing, thereby further enhancing the inflammation, matrix production and reconstruction. The matrix and the collagen it contains tightens the sinusoids and enhances sinusoidal resistance and pressure. The sinusoidal endothelium cells are damaged, and their fenestration increases. The fenestration allows translocation of proteins, inflammatory and growth factors, blood cell forms, platelets and their products (serotonin, PDGF) into the Disse space and the interstitium. The hepatocyte function may still prove acceptable (as long as at least 20% of parenchyma is intact), however, hyperlipidemia can already be demonstrated.

3. Postinflammatory (fibrotic) phase:
The majority of Ito cells has been transformed to myofibroblast, and, they are active even without the stimulatory effect of Kupffer cells. They presently do not contain fat or vitamin A, however, they produce an immense quantity of matrix (collagen, hyaluronic acid, proteoglycan, fibronectin). In this phase, aggressive connective tissue proliferation and liver tissue transformation characterize the damaged liver. A contraction of collagen fibers leads to lobular cirrhosis with irreversible damage of the parenchyma and fibrotic transformation, the histological picture is hardly recognizable. Elevation of γ-GT (γ-glutamyl-transpeptidase, GGT) from injured liver cells implies characteristic laboratory data which correlates suitably with the severity of the damage.

The role of Kupffer cells and leptin is verified by the findings in which, following gadoliniumchlorid ($GdCl_3$) damage to the Kupffer cells and as seen in leptin-deficient animals, the CCl_4-cirrhosis proved difficult to exert. In other experiments, the interfering RNA of vitamin A connected liposomes (this blocks heat-shock-like proteins) are taken up to the Ito cells, together with vitamin A, thereby the activity of Ito cells has been normalized, the collagen production ceased, and residual resolution of the fibrotic fibers was found.

Development of ascites:

Ascites is an intraperitoneal fluid accumulation. Minimal value is thought to exceed 25 ml, however, when it is certainly detectable, the volume is at least 1.5 liters. Through percussion, U-shaped hypogastric/lower abdominal dullness can be detected, which changes corresponding to the position of the body. In the case of larger amounts (even exceeding 10 liters) there is a preponderance of abdominal distension, in which the fluid can be pushed from one side to the other.

Three basic factors support of its development, including a higher hydrostatic pressure in the abdominal capillaries, hypoproteinemia, and defective lymphatic drainage.

Even a small elevation in the pressure within the intrahepatic veins leads to the production of ascites. This may appear in cirrhosis, however, possibly without the occurrence of cirrhosis, as seen in posthepatic obstructions. Due to the fenestration of the sinusoids, they are freely permeable for proteins, what explains the formation of ascites. Largely due to this permeability, within the Disse space the protein content and oncotic pressure are equal to that in the plasma of sinusoids, and these vessels do not follow the pathways of fluid movement witnessed in other capillaries (cf. Starling forces, according to which the fluid moves from or into the capillaries according to the relationship between the intra- and extra-capillary hydrostatic and oncotic pressures). In the liver, the oncotic pressure bears no distinctive role, and a small (1-2 mmHg) elevation in sinusoid hydrostatic pressure implies a prompt increase of high protein concentration fluid movement into the Disse space, furthermore, onto the lymphatic vessels. In the case of suitable lymph flow, this causes no immediate problem, however, even a slightly elevated lymph flow may not be able to carry all excess lymph to the cysterna chyli. As a result of such dynamic insufficiency of lymphatic vessels, the excess appears as droplets of exsudate containing high protein content upon the surface of the liver, dripping into the peritoneal cavity. This high protein-content intraperitoneal fluid allows fluid extravasation from the mesenterial capillaries (the high pericapillary oncotic pressure "sucks" fluid from the mesenterial capillaries in which the hydrostatic pressure is high). In cases of generalized hypoproteinemia, ascites formation is far easier accomplished, as more fluid exits the mesenterial capillaries. Since the final source of ascites fluid is the plasma, ascites cannot develop without causing decrease in intravascular volume and inducing secondary hyperaldosteronism (RAAS activation), but the intravascular space remains below the normal level (hypovolemia, except for the congested portal system). The lasting hyperaldosteronism tends to cause hypokalemia and metabolic alkalosis. Since even the hyperfunctional RAAS cannot normalize plasma volume, the hypovolemia enhances the ADH production and due to lasting ADH excess, free water is absorbed, thus, hyponatremia and hypotonicity develops.

In cases of portal hypertension (e.g. cirrhosis, portal vein thrombosis, congestive heart failure, constrictive pericarditis forms), the ascites fluid contains an immense quantity of protein, its albumin concentration exceeds that of the se-albumin (>11 g/l difference), however, the difference is much smaller in many other forms of ascites (without portal hypertension: peritoneal carcinomatosis, peritoneal tbc, pancreatic ascites, ileus, serositis, nephrosis, etc.).

Phases of ascites formation:

1. Preascites: splanchnic and peripheral arterial vasodilation, low effective arterial volume, hypotension. The volume regulation requires salt and water retention.
2. Ascites formation and hypovolemia. Portal hypertension. Congestion in GI tract, kidney hypoperfusion, low intravascular volume, further RAAS activation, high ADH-secretion. The apparent vicious circle allows the continuous re-fabrication of ascites.
3. In cirrhosis, the total blood volume may be higher, causing overfilling regarding the venous perspective, but not the arterial one.

PRINCIPLES OF TREATING ASCITES:

- Fluid removal by cannulation, slowly (cave! – too rapid a loss of fluid/protein, a fast decline in the intraperitoneal pressure causes circulatory abnormalities, resulting in release of the compressed abdominal vessels, and their dilation followed by distributive shock)
- Diuretic treatment and protein replacement

- Immersion: higher outer hydrostatic pressure may promote a backflow of ascites to ECV and vascular space
- LeVeen shunt: cannula with a valve from abdominal cavity to v. cava inferior

Hepatorenal syndrome (HRS)

In the beginning, the decline in effective circulating volume (arterial hypovolemia) induces a decrease in GFR, oliguria, prerenal azotemia, notably, without any structural change of the kidney. The kidney is intact, and it may be considered for succesful transplantation.

Later in HRS the lasting hypovolemia and more severe renal hypoperfusion may cause some tubular hypoxia and damage, consequently leading to hyposthenuria and further fluid loss – with ascites this is implying a vicious circle regarding plasma volume. Toxic substances further enhance the constriction of renal vessels (thromboxane, leukotrienes, PAF), while systemic vasodilatory substances (PGE, PGI, kallikrein/kinin and NO) indirectly worsen the renal perfusion by causing systemic hypotension. Azotemia, metabolic acidosis and uremia often develop. At this stage, the tubular cells already possess morphological damage (ATN), resulting in a kidney which cannot be considered for transplantation.

HRS develops in about 20% of liver failure, and it features a high mortality rate. Factors provoking its development include serious bleeding, strong diuresis, rapid draining of ascites and, inevitably, sepsis.

Hepatopulmonary syndrome (HPS)

Interestingly, it was only two decades ago when it was described how pulmonary functions may exhibit abnormalities in chronic liver failure. Although very rarely, pulmonary hypertension was found, yet every sixth patient (every third in consideration of those lined up, awaiting surgery) exhibited hepatopulmonary syndrome (HPS). In these patients, many without primary cardiopulmonary disease, the arterial pO_2 measured at least 15 mmHg below the alveolar tension, while small vessels of the lung exhibit various disorders, and, the normal 15 μm diameter of pulmonary capillaries is 4-6-times greater (50-80 μm). The hypoxemic hypoxia can be explained partly due to the shunt-circulation (portal anastomoses to the pulmo-

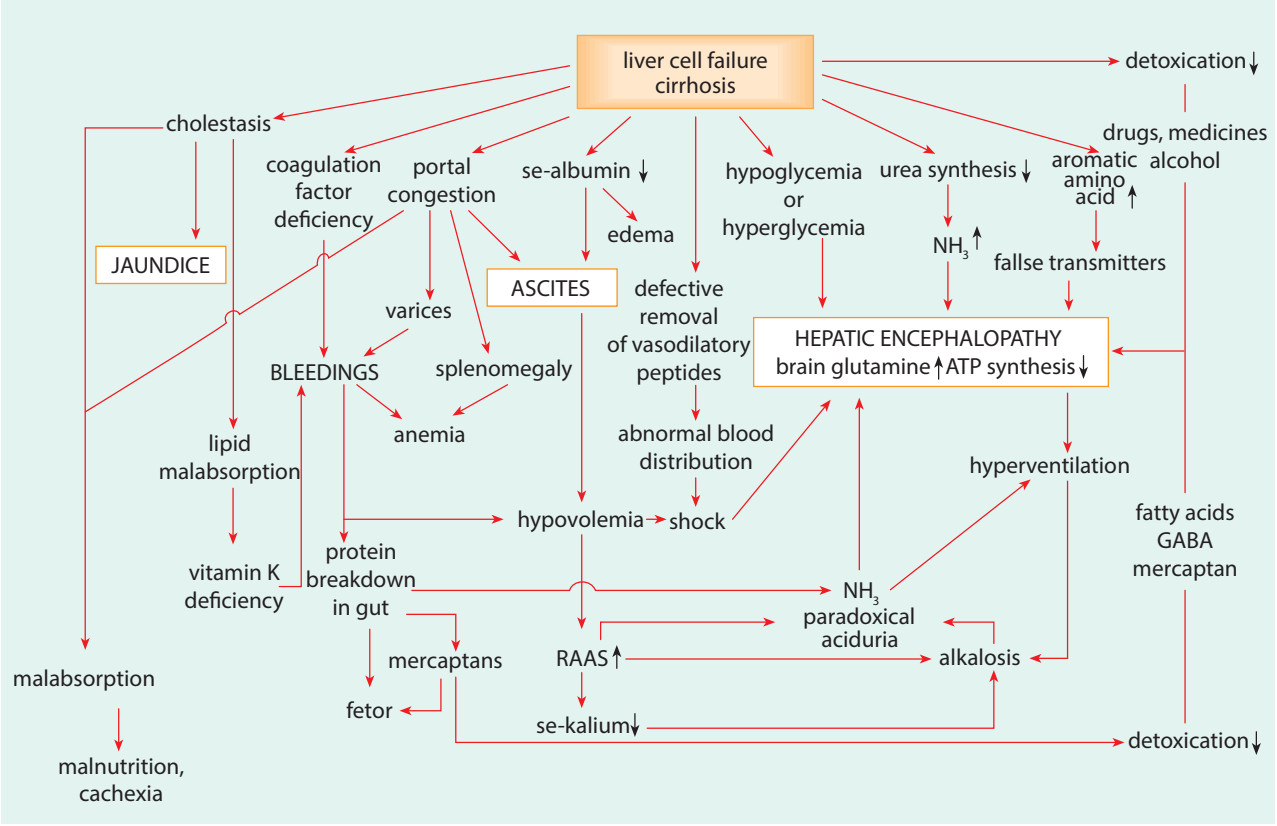

Fig. 7.26.: Pathomechanism of complex consequences of hepatic failure with or without cirrhosis.

nary vein, or a shunt within the lung), however, it may be more important that in the dilated pulmonary vessels oxygen reaches only the marginal blood, i.e. the diffusion cannot oxygenate all the perfusing blood. Due to such diffusion disorder (ch. 3.3.), even 100% oxygen inhalation cannot secure normal arterial pO_2. Disproportional ventilation and/or perfusion contributes to the hypoxemia, although at some regions the perfusion may even decrease as compared with ventilation. At the same time, as seen in cirrhotic patients, hyperventilation is frequent (ammonia excites the respiratory center) and this attenuates the hypoxia, until the ascites-induced elevation of the diaphragm begins inhibiting the abdominal (diaphragmatic) ventilation. The dilation of pulmonary vessels, or capillaries, is explained by vasodilatory humoral factors (glucagon, NO, partly CGRP, VIP, substance P, ANP, etc.), and these cannot be effectively neutralized by the diseased liver. The hypoxemia is not proportional to the severity of liver failure, however, cyanosis, dubbed fingers, etc., may call attention to the lasting hypoxemia and HPS. This results in partial respiratory failure: hypoxia, but no rise (rather a decrease) in pCO_2.

Complex picture of liver failure
The connections and interactions are demonstrated in Fig. 7.26.

7.6.1.8. BASELINES OF INVESTIGATING LIVER FUNCTIONS

- the same function should be examined by the implementation of several rounds of tests
- several functions should be examined
- the tests must be repeated
- the tests may be evaluated but only in unison with the clinical signs

Bilirubin level measuring
Measuring se-enzyme levels:
- aminotransferase enzymes: AST (GOT), ALT (GPT)
- alkaline phosphatase
- gamma-glutamyl-transpeptidase (γGT, GGT)

Measurement of se-proteins
- albumin
- globulins
- coagulation factors (I, II, V, VII, IX, X), prothrombin-time
- pseudocholinestherase: offers a glimpse regarding the protein-synthesizing capacity of the liver

Se-ammonia level
Se-lipoproteins
Pigment excretion probes (bromsulphalein test)

7.6.2. DISORDERS OF BILE SECRETION. GALLSTONE FORMATION (cholelithiasis)

The role of bile has been effectively explained in ch. 7.6.1.4. Additionally, canalicular secretion and bile quantity are dependent upon stimulation by secretin, gastrin, CCK and vagal impulses (these influence primarily the water, electrolyte and bicarbonate contents). In biliary canaliculi, the secretion is determined essentially by the production of bile acids, which is influenced by food intake. The daily production of bile acids is 500-700 mg. Although the bile acid content of the body is 2.5-4.0 g, the daily secretion (15-35 g) obviously exceeds this, with the aid of enterohepatic circulation. Regarding this, the most important preconditions include the integrity of the small bowel, intact liver and normal portal pressure.

The secreted bile enters the small bowel only during food intake, otherwise it is stored and thickened within the confines of the gallbladder. Accordingly, a disorder of bile secretion (cholestasis) may occur when liver functions are compromised, however, also in the obstruction of intra- or extra-hepatic biliary ducts (e.g. anticoncipients, steroids or mechanical obstruction and, the appearance of a stone, compression and inflammation of the ducts, etc.). Consequences of cholestasis include biliary congestion, generalized liver cell injury, jaundice and malabsorption and malnutrition.

Gallstone formation (cholelithiasis)

In the thickened accumulation of bile originating from the gallbladder, the cholesterol level reaches such high concentrations that its solution becomes supersaturated and precipitates in the form of crystals, particularly in the presence of a ”nucleation factor” (e.g. detached epithelial cells). Any further stone formation occurs in the vicinity of this nucleus. In practice, the ratio of cholesterol-lecithin-bile acid is decisive in the initiation of stone formation. Bile acid, lecithin deficiency or excess cholesterol (diet and obesity) promote stone formation. Most frequently seen is the pure cholesterol stone, however, there are smooth, colored bilirubin

stones (and pigmented stones in the case of increased Hb breakdown). Ca^{++} may be incorporated into these stones. Stones containing a large quantity of Ca^{++} are produced by mechanisms independent of cholesterol, and they often feature a textured, rough surface.

Predisposing factors for cholesterol stones are estrogenes (females, oral anticoncipients, pregnancy), obesity, fat-rich foods, old age, loss of bile salts (e.g. resection of terminal ileum, chronic diarrhea, inhibition of enterohepatic circulation), insufficient purging of the gallbladder (e.g. 1DM, parenteral nutrition, slimming diet, yo-yo syndrome, notably, without feeding the bile remains within the gallbladder and thickens), a broken duct (e.g. pregnancy). Pigment stones include hemolysis, bile congestion and biliary infection. Additionally smaller pigment stones may be formed within the choledochus, and they tend to cause infection, however, infection in itself promotes stone formation.

Consequences include the appearance of "silent" stones or stones which reportedly cause relatively minor complaints (dyspepsia, meteorism, nausea and dull pain beneath the rib-line). The most severe acute complaint is the biliary colic (colicky pain accompanied by nausea, vomiting, collapse by reflex, and paralytic ileus). If the symptoms are accompanied by fever, the likeliehood of an ascending infection is great. Small stones may eventually enter the bowel, may become dislodged in the duct (causing obstruction-type jaundice), and become dislodged in the papilla Vateri (acute pancreatitis!). Larger stones generally remain in the gallbladder, excite the wall, cause repeated infections, and in the long run, may lead to the development of a gallbladder tumor.

7.6.3. PORTAL HYPERTENSION (CONGESTION)

Normally, the pressure difference between the portal vs. hepatic veins measures at or about 3-6 mmHg. The perfusion of the large amount of portal blood through the liver towards the v. cava inferior may be partially blocked, and, in such cases, the pressure difference exceeds 10 mmHg. Consequently, throughout the entire system of the portal vein (splanchnic areas) a congestive elevation in pressure develops, and this is best defined as portal hypertension.

Causes and forms:

- Prehepatic (e.g. thrombosis, compression of v. portae)
- Intrahepatic (mostly due to cirrhosis)
- Posthepatic (e.g. v. hepatica or v. cava inferior obstruction and/or narrowing, including right-sided heart failure)

Consequences:

1. The amount of splanchnic blood increases, particularly following feeding. In contrast, the non-splanchnic volume decreases (hypovolemic symptoms and the possibility of hypoperfusion of some tissues). Secondary hyperaldosteronism is to be expected (even in the absence of ascites). Hypovolemia induces mobilization of vasoconstrictor substances, the renal blood flow decreases, the renal excretory functions decrease, *ad absurdum* prerenal azotemia may develop even in the presence of a morphologically intact kidney (hepatorenal syndrome). Hypovolemia also enhances the excretion of ADH, what results in hypotonicity.
2. Splanchnic congestion causes splenomegaly (high hemolysis and pancytopenia), disorders of gut motility, malabsorption, and the tendency for mesenterial thrombosis (due to slow circulation).
3. Ascites formation, if and when the obstruction is at the level of, or beyond the sinusoids (postsinusoidal).
4. Vascular disorders: through collateral vessels, the blood flows from the portal vein to the inferior vena cava, since blood flow through the liver is difficult. The most important collaterals are in the esophagus, retroperitoneum, periumbilical regions (caput Medusae[5]), and the rectum. Largely, due to the thinness of the wall of the collateral vessels, severe bleedings may occur due to a rupture of the varicosities (cf. possible coagulation abnormalities).
5. The blood originating from the mesenterial system escapes the liver through the collaterals (shunts), and substances originating from the guts (e.g. ammonia, particularly following protein-rich food) may cause transient disturbances of brain dull, disoriented, morose: **portal encephalopathy**. GABA originating from the gut contributes to the encephalopathy. Drug-effects may also change, due to defective liver functions. The enterohepatic circulaton of substances is also affected.

[5] Medusa: a monster from Greek mythology (Gorgo): in place of curly hair, snakes writhe upon her head.

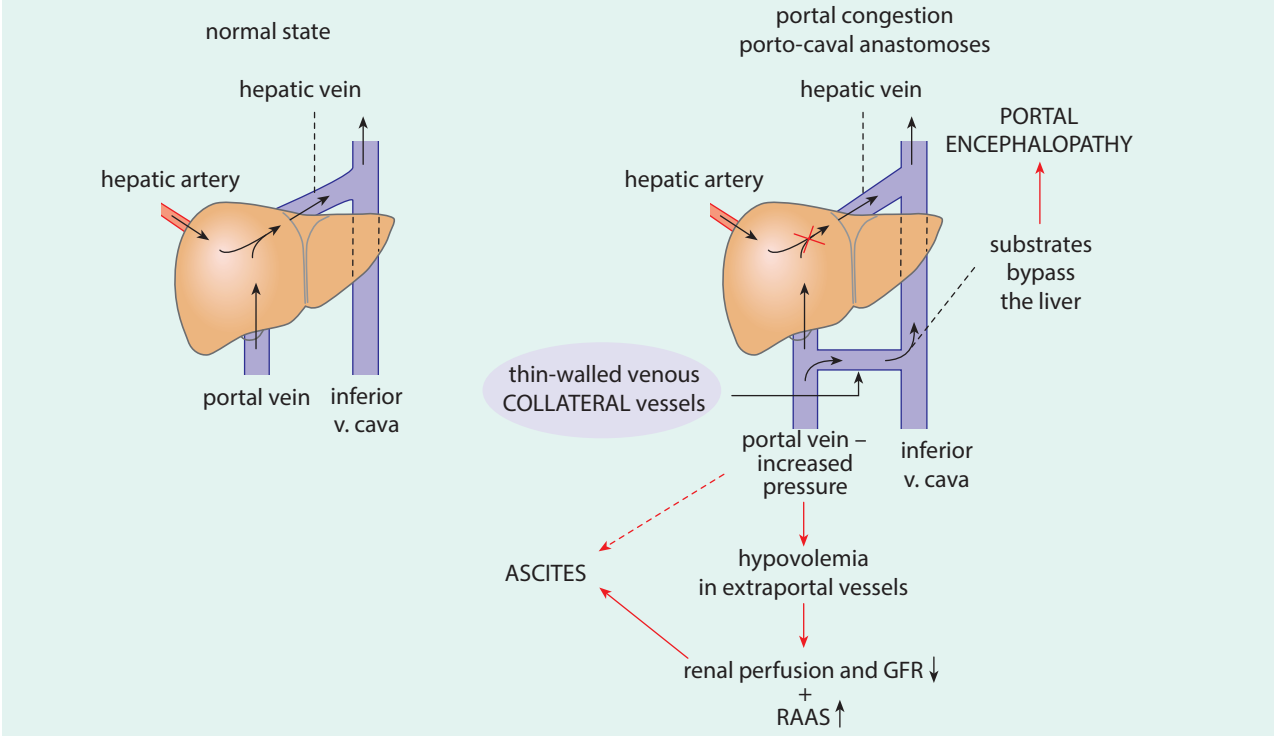

Fig. 7.27.: Development and consequences of portal congestion, porto-caval anastomoses.

7.7. AGE-RELATED CHANGES IN THE GASTROINTESTINAL FUNCTIONS

The age-related changes of GI system functions are basically related to changes in circulation (consequently secretion and absorption) and motility.

The distribution of cardiac output changes with age, even at rest, strongly limiting the perfusion of the GI tract. This is more pronounced if the distribution has to be altered (e.g. in stress situations or during muscular activity). Perfusion may remain critically low when, specifically the perfusion of the GI system should be enhanced (e.g. postprandial states), as seen in such cases in which abdominal angina (GI hypoxia) may develop. In other cases, postprandially, any increase of GI perfusion occurs at the expence of other organs, thereby for instance, following a more substantial food intake, an orthostatic collapse or even acute coronary syndrome may develop (the necessary increase of cardiac output requires the enhanced effort of the myocardium without improving its oxygenation). Most severely, the intestinal villi are affected by the hypoperfusion-induced ischemia, and, consequently lead to the appearance of absorption disorders. The secretory functions are affected only in the most severe forms. However, among seniors, the ischemia often causes dangerous mucosal injury, e.g. in the stomach, and in the form of large bleeding, stress-ulcer (or rather acute erosion). The ischemia makes mucosal regeneration far more difficult, not only in the stomach, but in the entire length of the enteral system. Ischemia of the bowels mostly manifests as non-obstructive mesenterial ischemia or as ischemic colitis. On the basis of a lasting effect, repeated ischemia may cause degenerative abnormalities, mucosal atrophy, atrophic gastritis, and this possibly explains how among seniors, achylia gastrica and consequent pernicious anemia can often easily and unexpectedly develop. Defective absorption must be considered regarding the utilization of nutrients, e.g. the dietary protein need may be somewhat higher among seniors, however, the absorption of drugs may also change with age.

Anomalies of motility were explained first by weak muscles, but now innervation disorder is considered. This may affect the entire system, from dysphagia, esophagus motility, GERD, including the decreased gastric motility, a tendency for obstipation, even atonia ventriculi or paralytic ileus may occur. Obstipation or subileus is more often observed in seniors, and the slower peristaltic movements easily result in bacterial overgrowth, followed by malabsorption and recurrent

diarrhea. With the process associated with aging, diverticulosis and its consequences become more frequent (50% at age 80-y). Similarly, it is equally important to note the higher freqency of intestinal inflammatory processes, polyposis and tumors. The prolonged enteral transit time and consequent malabsorption, coupled together with innervation abnormalities of the rectum and a certain level of immobilization may explain the occurrence of either feces impactation or fecal incontinence.

Acute enteral disorders may develop with non-GI origin, e.g. vomiting is characteristic for myocardial infarction of inferior location. In other cases, GI diseases may develop among the elderly without symptoms, e.g. appendicitis without pain or any characteristic sign of the disease.

With aging, some substrate-specific malabsorptions become more frequent, such as the amount of lactase which decreases with age, while lactose-intolerance is more frequent. Lurking behind the generalized malabsorptions often stands a decreased exocrine pancreas function, one in which seniors are often more sensitive to dietary imbalances. This may be explained by circulatory or autoimmune pancreatic disorders, however, the endocrine functions are usually not affected.

Liver functions are generally not affected for a long period of time, if and when they still are, it is due to chronic arterial hypoperfusion and centrilobular hypoxia. Among the very aged individuals cirrhosis-like fibrotic changes were occasionally found without any cause for cirrhosis, likely due to age-related generalized increase of fibrotic fibers. Hepatic elimination of drugs may prove defective among seniors, and in the hepatocytes abnormal proteins may accumulate. The storing function of the liver may also be affected, and this may also contribute to the more frequent occurrence of perncious anemia. More frequent is the appearance of cholelithiasis, as the bile composition is altered and the purging of the gallbladder is slower.

Further readings

Harrison's Principles of Internal Medicine. I., II., 19th Edition, McGraw-Hill, 2015.

Hawkey CJ, Bosch J, Richter JE, Garcia-Tsao G, Chan FKL (Eds.): Textbook of Clinical Gastroenterology and Hepatology, John Wiley & Sons, 2012.

Testoni PA, Colombo M, UNIGASTRO (Eds.): Handbook of Gastoenterology and Liver Diseases, Edizioni Minerva Medica – EGI, Milan, 2016

Yamada T: Principles of Clinical Gastroenterology, John Wiley & Sons, 2011.

Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powell DW (Eds.): Textbook of Gastroenterology, 5th Edition, Blackwell Publishing, 2008.