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REVIEW

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Gut-liver axis

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Dedicated to Prof. Dr. med. W.F. Caspary on the occasion of his 60th birthday

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Abstract The gut and the liver are the key organs in nutrient absorption and metabolism. Bile acids, drugs, and toxins undergo extensive enterohepatic circulation. Bile acids play a major role in several hepatic and intestinal diseases. Endotoxins deriving from intestinal Gram-negative bacteria are important in the pathogenesis of liver and systemic diseases. Chronic liver diseases can influence gastrointestinal motility, which together with other factors may contribute to bacterial overgrowth and in patients with ascites to an increased risk of spontaneous bacterial peritonitis. Patients with end-stage liver disease frequently develop portal hypertension leading to varices, gastric vascular ectasia, and portal hypertensive gastroenteropathy. Several liver and biliary abnormalities are observed in patients with inflammatory bowel disease (primary sclerosing cholangitis, autoimmune hepatitis, cholelithiasis). The primary defect in hemochromatosis is located in the intestine, causing an inappropriate increase in iron absorption, and the liver is the site of earliest and heaviest iron deposition. Elevated transaminases are observed in many patients with celiac disease, and steatohepatitis frequently develops in patients with jejunoileal bypass and short bowel syndrome. Furthermore, the liver is the primary organ for metastasis of intestinal cancer. Many viral, bacterial, fungal, and parasitic diseases affect the intestine as well as the liver and the biliary tract.

Keywords Enterohepatic circulation · Bile acids · Motility · Portal system · Inflammatory bowel disease

Physiology

Nutrient absorption and metabolism

The essential function of the gut is to absorb nutrients, vitamins, minerals, and water as well as to serve as an excretory conduit for materials excreted in bile. The liver is the first organ which comes into contact with the various small molecules arising from digestion. Here nutrient delivery from the intestine is sensed, and this information is not only distributed to other organs but is also used to trigger an adaptation of liver function to augment the effective hepatic processing of nutrients [1, 2]. Several lines of evidence suggest metabolic cooperation between intestine and liver, for example, amino acids are not only translocated in the small intestine but are also metabolized to a varying degree [3].

Adaptation of liver function to enterally absorbed nutrients involves neural and endocrine mechanisms as well as direct substrate effects on liver parenchymal and nonparenchymal cells. Although gastrointestinal distension exerts some effect on hepatic blood flow, the well-preserved metabolic response of transplanted livers to a nutrient load argues against a major role of neural mechanisms and points to a superiority of endocrine and substrate-induced regulation. Current evidence suggests that changes in liver hydration in response to nutrients and hormones are an independent and potent signal which

helps to adapt metabolic liver function and gene expression to changes in intestinal absorption. Nutrient-induced cell swelling activates signal transduction mechanisms which produce an anabolic response; conversely, nutrition deprivation-induced cell shrinkage triggers a catabolic state [4, 5].

Gastrointestinal hormones and neurotransmitters

Many hormones, neuropeptides, and growth factors are synthesized in the intestine. Secretin, cholecystokinin, gastric inhibitory peptide, motilin, and substance P are found in the upper small intestine, while enteroglucagon, neurotensin, peptide YY, and substance P are found in the lower small intestine and colon. Neuropeptides are produced by the intrinsic nervous system of the gut. A biological function of these peptides in the liver and the biliary tract has been described for secretin (stimulation of bile secretion), somatostatin (inhibition of bile secretion), vasoactive intestinal polypeptide, bombesin (increase in ductular secretion), and cholecystokinin (gallbladder contraction, relaxation of the sphincter of Oddi). Glucose homeostasis and other metabolic activities in the liver are, however, regulated mainly by pancreatic hormones (insulin, glucagon) [6, 7].

Enterohepatic circulation of bile acids

During fasting the majority of bile acids are in the gallbladder. Cholecystokinin, which is released by intestinal endocrine cells after food ingestion, induces gallbladder contraction, which leads to a several-fold increase in intraluminal concentration of bile acids during digestion. Bile acids have multiple functions: (a) they induce bile flow by their osmotic effects and induce biliary lipid secretion; they solubilize cholesterol in bile, regulate their own biosynthesis from cholesterol by feedback inhibition, and are the water-soluble end-products of cholesterol metabolism; (b) bile acids promote lipid absorption and are essential for adequate absorption of fat-soluble vitamins; (c) bile acids bind multivalent metal ions and are likely to enhance their absorption [8–10].

The relative impermeability of the biliary and proximal small intestinal epithelium to conjugated bile acids maintains the concentration gradient established by active canaliculi. While the majority of lipids are absorbed in the proximal small intestine, bile acids are absorbed mainly in the terminal ileum. After absorption, bile acids are transported to and efficiently extracted by the liver and are promptly secreted into bile (enterohepatic circulation) [9]. Bile acids participating in the enterohepatic circulation are the primary bile acids (cholic acid, chenodeoxycholic acid) formed from cholesterol in the liver and the secondary bile acids (deoxycholic acid, lithocholic acid, ursodeoxycholic acid) formed from primary bile acids in the intestine by the action of intestinal bacteria. Hepatic conjugation of primary and secondary bile acids with taurine or glycine is highly efficient, and less than 1% of bile acids in gallbladder bile is present in unconjugated form [11]. Conjugation causes a significant increase in aqueous solubility of bile acids at the small intestinal pH and resistance to precipitation by divalent cations. About 25% of primary bile acids is deconjugated, most likely by bacterial enzymes in the terminal ileum or colon, absorbed partly in the distal intestine, and in the liver reconjugated and secreted into bile. Bile acids not absorbed from the terminal ileum pass across the ileocecal valve, enter the anaerobic environment of the cecum, and are metabolized by bacterial enzymes mainly to deoxycholic acid and lithocholic acid. Fecal bile acid loss equals hepatic biosynthesis (0.5–1.0 mmol/day) [12].

Immune system

The mucosal immune system is an important component of the normal physiological interaction between the host and food, viral, bacterial, and parasitic antigens in the intestinal tract. M cells within the follicle associated epithelium overlie Peyer's patches and allow vesicular transport of specific antigens to the underlying cells of the subepithelial dome area. Cells expressing MHC class II molecules are located here (macrophages, dendritic cells, B cells), which process and present the antigens to T cells. Peyer's patches represent the primary areas of antigen processing and the site of the generation of specific IgA immune responses [13]. After stimulation of T helper cells and IgA precursor B cells these cells migrate out of the Peyer's patches and enter the systemic circulation via mesenteric lymph nodes and the thoracic lymph duct. Maturation, differentiation, and activation occur while the cells are traversing through the lymphatic system. After subsequent circulation in the peripheral blood, mature activated T cells and B cells enter the intestine as specific effector cells ("mucosal homing"). Intestinally derived cells can also migrate to other effector sites of the mucosa-associated lymphoid tissue, such as the salivary glands, bronchus-associated lymphoid tissue, mammary glands, and female genital tract. Mucosal homing is not an antigen-trapping mechanism because antigen-reactive cells migrate to both antigen-exposed and nonexposed areas [14]. Recent evidence suggests that activated mucosal lymphocytes can recirculate and are not necessarily sessile once located back in the lamina propria [15].

The mucosal lymphoid tissue is highly compartmentalized and consists of intraepithelial lymphocytes which reside between intestinal epithelial cells and lamina propria lymphocytes which are separated by a basal membrane from the epithelial layer. Intraepithelial lympho-

cytes are a unique subset of T cells which are over 90% CD8-positive, while T lymphocytes in the lamina propria are mainly CD4-positive. IgA secreted by lamina propria plasma B cells is the predominant immunoglobulin class in the intestinal mucosa. As shown in mice, some IgA-producing B cells may be derived not from Peyer's patches but from the peritoneal cavity. Most of the lamina propria T cells provide helper function for immunoglobulin synthesis by plasma cells upon antigen challenge. Thus the immune cells in the mucosa are clearly specialized and carry out specific functions [16].

The uptake of antigen can result in a secretory IgA response on the intestinal mucosa, which can prevent the uptake of further antigen and mucosal damage, for example, by micro-organisms. Most of the IgA in the intestine is produced as a dimer and contains additional polypeptide chains, which may prevent rapid degradation by proteolytic enzymes. IgA can also bind antigen in the lamina propria or within intestinal epithelial cells and is then transported into the intestinal lumen, thereby contributing to the host defense. Alternatively, there may be stimulation of the humoral and the cellular immune system following the uptake of the antigen [17]. For most orally ingested dietary antigens, however, systemic tolerance is induced encompassing the level of humoral and cellular immune responses ("oral tolerance"). This tolerance is often associated with the generation of cytokine-producing suppressor T cells. The cytokines associated with active suppression are Th2 cytokines such as interleukin (IL)-4 and IL-10, as well as transforming growth factor (TGF)-β.

Morphological and phenotypical data indicate that liver sinusoids contain a heterogeneous population of lymphocytes, of which large granular lymphocytes are only one element. Flow cytometry studies on isolated cells have shown that human liver-associated lymphocytes differ phenotypically from peripheral blood lymphocytes. The former are characterized by a threefold increase in the percentage of cells presenting the CD56 antigen, a natural killer cell marker, an increase in the percentage of CD8-positive cells, and a decrease in the percentage of CD4-positive cells [18, 19]. Liver sinusoids also harbor γ/δ T cells which express a T cell receptor repertoire which differs from that found in peripheral blood lymphocytes from the same patients, suggesting site specificity. Liver-associated lymphocytes also express a lymphokine-activated killer activity against natural killer cell resistant cell lines, whereas no such activity is detected in peripheral blood lymphocytes from the same patients. They differ, both quantitatively and qualitatively, from peripheral blood lymphocytes in the expression of cellular adhesion molecules. Precise mechanisms of their homing or in situ differentiation must still be elucidated [19].

Bile and biliary epithelium also appear to have active immunological roles in both innate and adaptive immune responses. Bile is actively involved in the transport of immunoglobulin to the intestine [20], while biliary epithelial cells secrete chemokines and cytokines and serve to localize the immune response by expressing critical cell adhesion molecules. Evidence suggests that biliary epithelial cells also function as professional antigen-presenting cells and, in the process, contribute to the modulation of inflammatory reactions [21].

Pathophysiology

Role of bile acids in hepatic and intestinal disease

In bile acid malabsorption, increased concentrations of bile acids in the colonic lumen cause secretory diarrhea by a cyclic AMP dependent mechanism [22]. In addition, bile acids can also damage mast cells in the colonic submucosa, causing discharge of inflammatory mediators that in turn might induce colonic secretion [23]. Bile acid sequestrants (e.g., colestyramine) are administered either to decrease the return of bile acids to the liver or to lower the intraluminal concentration of bile acids. Constipation frequently results when the aqueous concentration of bile acids in the colonic lumen is decreased by administration of bile acid sequestrants.

Interruption of the enterohepatic circulation of bile acids leads to a decreased concentration of bile acids in the hepatocyte, increased cholesterol 7α-hydroxylase activity, increased bile acid biosynthesis, and an equivalent increase in cholesterol biosynthesis (up to 20-fold) [24]. Inhibition of cholesterol biosynthesis by hydroxymethylglutaryl–coenzyme A reductase inhibitors, however, causes relatively little change in bile acid metabolism [25].

Bile acids may suppress bacterial growth in the small intestine and bacterial translocation to mesenterial lymph nodes [26]. The reduced bile acid secretion in patients with cirrhosis may contribute to an increase in the intestinal bacterial colonization. In an animal model oral bile acid administration decreased bacterial translocation [27].

Bile acid cytotoxicity has been observed with isolated hepatocytes and intestinal cell monolayers [28]. In animal models bile acid cytotoxicity has been shown for the gastric mucosa [29]. In the perfused colon deoxycholic acid and chenodeoxycholic acid induce concentration-dependent destruction of the epithelial surface that is evidenced by a marked increase in colonic permeability [30]. Cholic acid is considerably less cytotoxic than deoxycholic acid and chenodeoxycholic acid, while ursodeoxycholic acid is not toxic [23].

Disturbances in the enterohepatic circulation of bile acids are as follows:

- Defective biosynthesis from cholesterol
- Defective biliary secretion or obstruction to bile flow (cholestasis)

– Defective ileal absorption
– Defective hepatic biotransformation
– Ectopic deconjugation
– Defective interorgan flow

Metabolic defects have been described for the biosynthesis from cholesterol, in nuclear biotransformation steps, and side-chain biotransformation steps [31–34]. Defective biliary secretion or obstruction of bile flow (cholestasis) leads to up-regulation of ileal transport, thereby further contributing to bile acid retention [35]. Inappropriate retention of chenodeoxycholic acid and deoxycholic acid conjugates is likely to cause hepatocyte damage. In complete cholestasis, secondary bile acids cannot be formed. Bile acids accumulate in the hepatocyte, undergo sulfation and glucuronidation after amidation, reflux from the hepatocyte and are excreted in the urine [36]. Bile acid biosynthesis and cholesterol biosynthesis are reduced. In patients with loss of ileal absorptive function because of resection or inflammatory disease and in patients with primary bile salt malabsorption [37–39] the increased hepatic synthesis of bile acids leads to a new steady state with increased amounts of bile acids passing into the colon. The clinical consequences of a colonic excess of bile acids depends on the complex biotransforming activity of the bacteria and can cause secretory diarrhea [28, 40]. In patients with large ileal resection the increased bile acid synthesis cannot compensate for the increased loss, and hepatic bile secretion decreases. Thus the intraluminal bile acid concentration becomes too low to achieve micellar solubilization of the products of fat digestion. Unabsorbed fatty acids pass into the colon, where, as with bile acids, they induce secretory diarrhea (“fatty acid diarrhea’) [24]. In addition, unabsorbed fatty acids may form calcium soaps and lead to increased absorption of oxalate and hyperoxaluria and an increased risk of oxalate nephrolithiasis [28]. Detective biotransformation with low biosynthesis of cholic acid has been described in patients with liver cirrhosis [41]. Increased bile acid deconjugation occurs in the stagnant loop syndrome and may cause an intraluminal bile acid deficiency [24]. An altered interorgan flow of bile acids has been described in several conditions. In patients with celiac disease the bile acid pool is increased due to impaired gallbladder function [42]. Whether the intraluminal bile acid deficiency contributes significantly to fat malabsorption in patients with reduced mucosal surface is unknown. In some patients with cholesterol gallstones the input of deoxycholic acid from the colon is increased and causes increased biliary cholesterol secretion and induces the formation of gallstones [43, 44]. The effect of cholecystectomy on the enterohepatic circulation is of minor importance; daily total bile acid secretion is unchanged. In patients with gastrocolic fistula bile acids may be deconjugated prematurely by bacteria in the small intestine or malabsorbed because of loss into the colon. In patients with liver cirrhosis there are multiple defects such as portal systemic shunting, defective hepatic uptake, impaired bile acid synthesis, and reconjugation [24].

Enterohepatic circulation of drugs and toxins

Many exogenous substances are secreted into bile and undergo some degree of enterohepatic cycling. These include commonly used drugs (e.g., morphine, warfarin, indomethacin, glycosides), several antimicrobial agents (e.g., clindamycin, rifampicin, erythromycin, metronidazole, ampicillin, ceftriaxone, doxycycline), radiocontrast media, and potentially toxic heavy metals. Interruption of enterohepatic circulation can be used in patients with toxic drug levels [45]. α-Amanitin, a toxic substance from *Amanita phalloides* which potently inhibits DNA-dependent RNA polymerase II [46], undergoes extensive enterohepatic circulation. In addition to specific treatment (penicillin G, silybinin), the interruption of the enterohepatic circulation through continuous bile aspiration (nasobiliary or nasoduodenal tube) and repeated administration of activated charcoal is most important [47, 48].

Cooperation of intestine and liver in xenobiotic metabolism

The intestinal epithelium contributes significantly to the metabolism of xenobiotics, especially if they are ingested orally. Almost the complete spectrum of phase I and phase II reactions which take place mainly in the liver can also be accomplished by the gut [49, 50]. The variable and low oral bioavailability of cytochrome P3A substrates (cyclosporin, verapamil) is caused to a considerable extent by the wide intra- and interindividual variation in the activity of the intestinal enzymes [51, 52]. Furthermore, drug metabolism by the intestinal microflora contributes to the pharmacological profile of various drugs. The metabolism of orally administered drugs can result in pharmacodynamic changes, and the hydrolysis of biliary drug conjugates is responsible for the enterohepatic circulation of drugs [53, 54].

Interaction between intestine and liver in hepatic encephalopathy

Hepatic encephalopathy is a complex neuropsychiatric syndrome that may occur in such diverse clinical situations as inherited errors of the urea cycle, acute or chronic liver disease, and spontaneous or iatrogenic portosystemic venous shunting. The clinical manifestations of this syndrome range from subtle abnormalities detectable only by psychometric testing to coma. The accumulation

of unmetabolized ammonia is considered to have an important role in the pathogenesis. In addition, a number of other possible mechanisms have recently been proposed, including production of false neurotransmitters, increased inhibitory neurotransmission mediated by γ-aminobutyric acid, activation of benzodiazepine receptors by ligands of endogenous origin, altered cerebral metabolism, and disturbed activity of Na^+/K^+-ATPase. Decreased activity of urea-cycle enzymes due to zinc deficiency and the deposition of manganese in the basal ganglia may also contribute to hepatic encephalopathy [55].

Most episodes of hepatic encephalopathy in patients with chronic liver disease are due to a clinically apparent precipitating event which is frequently related to the intestine. For example, septicemia and bacterial peritonitis, typically with Gram-negative, colonic-type flora, develops within 48 h in about one-half of patients with Child-Pugh class C cirrhosis who have an acute gastrointestinal hemorrhage [56]. Current concepts in the treatment of hepatic encephalopathy focus mainly on the reduction of production and absorption of ammonia. The intestinal production of ammonia can be reduced by restricting the intake of dietary protein and inhibiting urease-producing colonic bacteria [55]. Both dietary and endogenous ammoniagenic substrates are removed from the intestinal lumen by the osmotic cathartic action of nonabsorbable disaccharides such as lactulose and lactitol. The daily dose should be titrated to result in two to three soft, acidic (pH <6) stools daily. As well as having a cathartic effect, lactulose lowers the colonic pH as a result of the production of organic acids by bacterial fermentation. The decrease in pH creates an environment that is hostile to the survival of urease-producing intestinal bacteria. Furthermore, acidification of the colonic secretions not only reduces the absorption of ammonia by nonionic diffusion but also results in the net movement of ammonia from the blood into the bowel lumen [55]. In addition to ammonia produced in the intestinal lumen, ammonia generated in the stomach by urease-producing *Helicobacter pylori* has recently been suggested to contribute substantially to blood ammonia levels and to precipitate or exacerbate hepatic encephalopathy in patients with cirrhosis [57]. However, the efficacy of eradication therapy has not yet been confirmed in large controlled trials.

Endotoxins

Because of its rich supply of blood sinusoids and direct access to bacteria and their derived components, for example, lipopolysaccharides (endotoxins) brought by the portal circulation, as well as the presence of resident macrophages (Kupffer cells) and their derived cytokines [tumor necrosis factor (TNF), IL-1]), the liver is a target organ for neutrophil influx in the acute phase of an inflammatory response. Liver injury after lipopolysaccharide (LPS) exposure is associated with morphological and functional changes and induces an acute inflammatory response with early accumulation of neutrophils [58, 59]. These polymorphonuclear leukocytes might cause injury by release of reactive oxygen metabolites, proteases, and other enzymes from the granules [60, 61].

The systemic inflammatory response syndrome is frequently initiated by bacterial infection where bacterial cell wall components (LPSs) are recognized by the immune system and cause an overshooting inflammatory response. The toxicity of these substances is due to the release of inflammatory mediators in the host and may result in multiorgan failure including lungs, kidneys, bowel and the liver [62, 63]. LPSs from Gram-negative bacteria act on different populations of macrophages and endothelial cells, which express and release various proinflammatory cytokines such as TNF-α, IL-1β, IL-8 and granulocyte-macrophage colony stimulating factor as well as anti-inflammatory factors such as IL-10, TGF-β and the acute-phase protein IL-6 to counterbalance overshooting activation [64]. LPS also promotes bacterial translocation from the gut, resulting in further augmentation of endotoxemia [65]. In addition to activated macrophages, natural killer cells and T lymphocytes release the proinflammatory cytokine interferon-γ during bacterial infection [66], which itself enhances the LPS-induced release of TNF and IL-1 by macrophages [67]. Secondary to the release of TNF, arachidonic acid release and its metabolism to prostaglandins, thromboxane, and leukotrienes are initiated and cause chemotaxis, broncho- and vasoconstriction, and capillary leakage [68, 69]. The fall in blood pressure in septic shock is largely due to cytokine-induced release of nitric oxide (NO) in response to LPS. However, NO reduces organ injury in various models of septic organ failure and shock, including endotoxin-induced liver damage [70, 71]. The role of TNF-α is pivotal. This cytokine alone elicits all the pathophysiological alterations observed in endotoxic shock [72–74]. In animal models LPS-induced TNF release leads to hepatocyte apoptosis followed by widespread necrosis and enzyme release from the liver. Whether other receptor-ligand systems that control hepatocyte apoptosis (CD95/CD95L, WSL-1/Apo-3, TRAMP) are also modulated by LPS is unclear [75].

Evidence suggests that alcohol favors production of Gram-negative bacteria, thereby increasing endotoxin production [76]. Alcohol increases membrane permeability of the gut to macromolecules such as endotoxin [77], which activate Kupffer cells to release cytokines (e.g., TNF-α), prostaglandins, and free radicals [78]. These molecules stimulate hepatocyte metabolism of oxygen and alcohol, leading to hypoxic conditions and free radical generation and may induce neutrophil activation, endothelial lesions, increase permeability of sinusoids, and disturb microcirculation [79–81]. Thus, intestinal effects

of alcohol may contribute to the pathogenesis of alcoholic liver disease by causing cellular damage extending to hepatocyte necrosis, inflammatory infiltrates of neutrophils and deposition of collagen.

Plasma endotoxin levels are elevated in patients with chronic liver disease and increase with the progression of Child-Pugh grades in patients with liver cirrhosis [82, 83]. Endotoxemia, together with a failure to inactivate endotoxins, has been suggested to possibly aggravate the clinical course of patients with chronic liver disease [84]. In both peripheral and portal circulation endotoxemia is closely related to in vitro thrombin generation, suggesting also a role for endotoxemia in activating the clotting system [85–87].

LPS increase microvascular permeability in many organs, including intestine and liver. Under physiological circumstances the continuous production of NO by the Ca^{2+}-dependent constitutive NO synthase (NOS) isoenzyme in the vascular endothelium (eNOS) protects against endotoxin-provoked acute microcirculatory damage [88, 89]. It is thought that a Ca^{2+}-independent inducible isoenzyme of NOS (iNOS) plays a role in inflammatory bowel disease (IBD), the expression of iNOS being detected in the inflamed bowel of patients with ulcerative colitis [90, 91]. Indomethacin leads to the induction of iNOS in the jejunum in association with the development of jejunal microvascular injury. Broad-spectrum antibiotics inhibit the development of iNOS activity and reduce intestinal inflammation following challenge, thus suggesting that induction of iNOS following administration of nonsteroidal anti-inflammatory drugs involves local transmigration of gut bacteria [92].

Based on the pharmacological findings with NOS inhibitors, the overproduction of NO has been suggested to contribute to the hyperdynamic circulation in patients with cirrhosis and portal hypertension [93]. The excessive synthesis of NO may result from the expression of a Ca^{2+}-independent iNOS, which may be triggered by the elevated circulating levels of LPS found in cirrhotic patients [82, 94]. Furthermore, induction of NOS has been shown to be associated with microcirculatory damage in the liver and with direct cellular toxicity in hepatocytes [95, 96].

Endotoxins have been shown to play an important role in the pathogenesis of sepsis-associated cholestasis and, in addition to lipid overload and nutrient deficiencies, of total parenteral nutrition-associated jaundice [97]. The endotoxin-induced release of TNF-α and other cytokines mainly from Kupffer cells causes a profound down-regulation of hepatocellular bile formation [98, 99]. Impaired bile flow and the reduced enterohepatic circulation of bile acids predispose to the formation of sludge in the gall bladder of patients receiving total parenteral nutrition [97]. In endotoxemia basolateral transport may exceed the canalicular transport, which consequently could lead to intracellular accumulation of potentially toxic compounds [100].

Gastrointestinal dysfunction in liver disease

Gastrointestinal symptoms (nausea, vomiting, diarrhea) are common in patients with advanced liver disease. Symptoms may be related to (a) gastrointestinal functional alterations that develop as a consequence of the underlying liver disease; (b) the associated etiological factors for the liver disease, such as alcohol; (c) the effects of therapeutic interventions, for example, sclerotherapy; and (d) the result of complications of portal hypertension. Forms of gastrointestinal dysfunction in liver disease include:

- Impaired motility
- Bacterial overgrowth
- Spontaneous bacterial peritonitis
- Portal hypertension
  - Varices
  - Portal hypertensive gastropathy
  - Gastric vascular ectasia
  - Portal hypertensive enteropathy
  - Portal hypertensive colopathy

Motility

Most studies suggest that gastric emptying is delayed in patients with advanced liver disease and is correlated with upper gastrointestinal symptoms [101, 102]. The pathogenesis of impaired antroduodenal motility is unclear. Gastric emptying seems not to be related to gastric colonization with *H. pylori*, elevated portal pressure, ascites, or hepatosplenomegaly [103, 104]. Recent studies show that gastric emptying is related to blood glucose levels [105]. Thus, future studies investigating the etiology of impaired gastric emptying in patients with end-stage liver disease should focus also on metabolic parameters and factors leading to liver disease and autonomic dysfunction such as alcohol consumption.

Despite conflicting data on small bowel motility in patients with chronic liver disease are reported, slowing of transit seems evident in patients with liver cirrhosis [106, 107]. Reduction in small bowel motility, however, is not correlated with Child-Pugh score. Hepatic encephalopathy may influence small bowel transit, as transit time improves following treatment [107]. An effect of portal hypertension on myoelectric activity of the small intestine has been described in a portal vein ligation rat model, suggesting that such alteration is the cause of impaired small bowel motility [108]. However, this hypothesis was not confirmed in a different model [109]. When motility patterns result in a delay of normal migrating motor complex activity, an increased risk of small intestine bacterial overgrowth and a further decrease in small bowel function may result.

Bacterial overgrowth

The prevalence of small intestinal bacterial overgrowth (SIBO) in patients with chronic liver disease is high (20–75%). The presence of SIBO may be related to the severity of the liver disease, but not to the underlying cause [110]. In the pathogenesis of SIBO in patients with chronic liver disease, reduced gastric acid secretion, luminal IgA deficiency, malnutrition, and impaired intestinal motility may be relevant. Treatment of cirrhotic patients with prokinetic drugs accelerating small intestine transit time may decrease bacterial overgrowth in the jejunum. Small bowel bacterial overgrowth causes malabsorption of cobalamin (vitamin B_{12}), carbohydrate, fat, and protein. Carbohydrates are degraded intraluminally and fat malabsorption results from bacterial deconjugation of bile acids. Protein depletion probably results from a combination of decreased mucosal uptake, intraluminal degradation, and antibiotic-reversible protein-losing enteropathy. SIBO may aggravate liver disease by hepatic accumulation of phlogistic bacterial cell wall polymers (peptidoglycans), overproduction of toxic bile acids such as lithocholic acid, and an increased toxic effect of alcohol due to formation of acetaldehyde [111, 112].

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is a life-threatening complication of decompensated cirrhosis. The incidence of SBP is increasing in patients with poor liver function and low ascitic fluid protein concentration. Among patients with SBP 70% are in Child-Pugh class C, and among patients with Child-Pugh class C more than 70% are likely to develop an episode of SBP within 1 year [113, 114]. Because bacteria are difficult to culture from ascites, cases of culture-negative neutrocytic ascites (>250/µl) are also considered as SBP. Gram-negative bacteria of enteric origin can be demonstrated in 70% of cases with positive cultures [114, 115]. In contrast to secondary bacterial peritonitis, anaerobes are rare in SBP. Bacterial translocation to mesenteric lymph nodes is an important initial step in the pathogenesis of SBP. This process is facilitated by impaired intestinal motility, small bowel bacterial overgrowth, and impaired function of the intestinal immune defense [116, 117]. Bacteremia may result from infected mesenteric lymph nodes via the thoracic lymph duct, and may be prolonged due to an impaired reticuloendothelial system, portosystemic shunts, and reduced opsonic and phagocytic activity in serum of patients with advanced chronic liver disease. Low protein ascites with reduced concentrations of opsonins and complement and impaired function of neutrophils is prone to bacterial colonization and SBP [115, 118]. Passage of enteric organisms from the bowel lumen to the peritoneal cavity through the intestinal wall has never been clinically or experimentally demonstrated. Direct bacterial migration into the ascites is also considered unlikely because SBP is in general a monomicrobial infection. Gastrointestinal bleeding facilitates intestinal bacterial overgrowth and is thereby associated with bacteremia and SBP. The incidence of bacteremia is further increased by endoscopic intervention (sclerotherapy, ligation) [119]. Antibiotic treatment (second- and third-generation cephalosporins, quinolones) of SBP is mandatory. Oral administration of norfloxacin is as effective as intravenous cefotaxime in uncomplicated SBP [120]. Several studies have shown that prophylactic antibiotic treatment decreases the probability to develop SBP after gastrointestinal bleeding and recurrence in patients who recovered from a SBP episode [121, 122].

Portal venous system

Patients with end-stage liver disease frequently develop portal hypertension due to both an increase in vascular resistance and splanchnic blood flow. The increased resistance to portal venous blood flow can be related to prehepatic, intrahepatic, and posthepatic sites. Prehepatic and posthepatic portal hypertension are caused by obstruction of the portal and hepatic veins, respectively. Intrahepatic portal hypertension may be the result of anatomic alterations in the hepatic lobule with secondary compression of portal venules, sinusoids, and hepatic venules, and functional derangement of the intrahepatic microcirculation. The hyperdynamic splanchnic circulation is the result of vasodilatation and plasma volume expansion.

Varices

Formation of portal-systemic collaterals begins to develop when portal pressure reaches levels above 12 mmHg and is one of the main consequences of portal hypertension [123, 124]. The most common and clinically significant collaterals are those that form gastroesophageal varices. Nonselective β-adrenergic blockers and nitrates are applied for the prevention of first variceal hemorrhage. Pharmacological therapy (somatostatin, vasopressin), endoscopic therapy (sclerotherapy, ligation), surgical decompressive shunts, and interventional shunts (transjugular intrahepatic portosystemic shunts) are used in various combinations to treat patients with acute variceal bleeding. Because the risk of recurrent hemorrhage is high, endoscopic, pharmacological, interventional radiological, and surgical techniques are used for secondary prevention [125–127].

Portal hypertensive gastropathy

The term portal hypertensive gastropathy (PHG) defines gastric mucosal changes (nonspecific redness, mosaic pattern, discrete or confluent red spots, hemorrhagic gastritis) observed in patients with portal hypertension [128–130]. Dilatation of mucosal vessels without inflammatory changes is histologically consistent with PHG, but several studies have found no correlation between endoscopic and histological findings [131–133]. It has been shown in animal models that the portal hypertensive gastric mucosa is more susceptible than normal gastric mucosa to injury when exposed to aspirin [134], bile salts [135], alcohol [136], and endotoxins [137], but not from *H. pylori* infection [138]. In the pathogenesis of PHG the question of reduced mucosal perfusion with congestion or increased perfusion without congestion remains unsettled. Conflicting data between the association of PHG and serum gastrin, glucagon, and prostaglandins have been reported [139]. Recent studies suggest that enhanced production of nitric oxide plays an important role in the vasodilatation and vascular hyporeactivity observed in patients with portal hypertension [140, 141]. Impaired mucosal defense mechanisms and mucus secretion may be additional pathogenetic factors [142]. PHG is clinically significant because it is a frequent cause of nonvariceal bleeding in portal hypertensive patients. In patients who have undergone endoscopic eradication of gastroesophageal varices PHG may deteriorate.

Gastric vascular ectasia

Severe PHG must be distinguished from gastric vascular ectasia (watermelon stomach syndrome), which also occurs in patients with liver cirrhosis and portal hypertension [143]. The watermelon stomach syndrome has distinct pathological findings of capillary dilatation, intravascular fibrin thrombi, and fibromuscular hyperplasia of the lamina propria [144]. While PHG responds to portal decompression, gastric vascular ectasia should be treated by endoscopic coagulation.

Portal hypertensive enteropathy

In patients with portal hypertension, endoscopic and histological changes consistent with congestion in the duodenum, jejunum, and ileum have been described. Compared with PHG, the prevalence of portal hypertensive enteropathy is low and clinically less important [128, 145].

Portal hypertensive colopathy

Portal hypertensive intestinal vasculopathy may involve the colon and presents as rectal varices or portal hypertensive colopathy. Anorectal varices are portosystemic collaterals that usually occur 4–5 cm above the anal verge in up to 40% of patients with portal hypertension. These must be distinguished from hemorrhoids, which do not occur more frequently in patients with portal hypertension [146, 147]. In approximately 50% of portal hypertensive patients macroscopic evidence of portal hypertensive colopathy is present. Histological examination of the mucosa shows edema and capillary dilatation with minimal inflammation. Several studies have reported no correlation between the severity of liver disease and the presence of portal hypertensive colopathy [148, 149]. In many patients coexisting PHG is present.

Hepatic and biliary injury in patients with gastrointestinal disease

Liver and biliary abnormalities are common in patients with IBD, celiac disease and in patients with jejunoileal bypass or short bowel syndrome. In genetic hemochromatosis the inappropriate increase in the absorption of dietary iron is associated with progressive liver disease. Cystic fibrosis, another autosomal recessive disease, affects many organs, including the intestine, liver, and the biliary system. Hepatic and biliary injury in patients with gastrointestinal disease are:

- Inflammatory bowel disease
  - Primary sclerosing cholangitis
  - Autoimmune hepatitis
  - Cholelithiasis
- Celiac disease
  - Mild steatosis, inflammation, and fibrosis
- Hemochromatosis
  - Iron deposition, inflammation and fibrosis, liver cirrhosis, hepatocellular carcinoma
- Cystic fibrosis
  - Steatosis, fibrosis, cirrhosis
  - Sclerosing cholangitis
  - Microgallbladder
  - Cholelithiasis
- Jejunoileal bypass
  - Steatohepatitis
- Short bowel syndrome
  - Steatohepatitis
- Intestinal cancer
  - Metastasis

Ulcerative colitis and Crohn's disease

Diseases of the liver and bile ducts are the most common extraintestinal conditions associated with IBD. Hepatic granulomas are frequently found in patients with Crohn's disease, but these patients usually do not develop pro-

gressive liver disease [150]. Fatty liver occurs in approximately 40–45% of patients with IBD. The presence of fat alone does not appear to be associated with progressive hepatic damage, but progression to fibrosis may occur when fatty liver coexists with inflammatory lesions. The etiology may in part be related to treatment of IBD (e.g., corticosteroids) and malnutrition [151]. Amyloidosis of the liver is rare among patients with IBD and occurs particularly in those having Crohn's disease with fistula and perianal disease. The pathogenesis is unknown but is presumed to be secondary to chronic inflammation. If progressive, the disease is fatal. Controlled data for specific therapy of amyloidosis in patients with IBD are not available [152]. In patients with Crohn's disease a hyperdynamic mesenteric circulation has been described. However, splanchnic blood flow does not reflect the clinical or biochemical activity of the disease but appears to be linked to maximum bowel thickness and anatomical location [153]. The clinically most relevant extraintestinal conditions in patients with IBD comprise primary sclerosing cholangitis, autoimmune hepatitis, and cholelithiasis.

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is characterized by fibrosis and inflammation of the intra- and extrahepatic bile ducts [154, 155]. The key lesion in the histopathology is pleomorphic and fibrous-obliterative cholangitis, characterized by an "onion-skin" type of periductal fibrosis around intralobular and septal bile ducts, with degeneration and atrophy of the epithelial lining and eventual replacement of the bile duct by a fibrous cord. PSC is the most common hepatobiliary disorder associated with IBD. The prevalence of PSC in patients with IBD has been estimated to be about 5%, and approximately 75–90% of PSC patients have associated IBD, most commonly ulcerative colitis [151, 156]. The pathogenesis of PSC remains unknown; however, two lines of evidence suggest a genetic component. The first is the familial occurrence of PSC and ulcerative colitis [157], and the second is the association of PSC with certain human leukocyte histocompatibility antigens, specifically HLA-A1, HLA-B8, HLA-DR3, HLA–DR13, HLA-DR52a, and HLA-DQ2 [157–160]. HLA-B8 occurs in 60% of PSC patients, compared with 25% of normal controls [161]. The prevalence of DR3, DR13, and DR52a is approximately twice as high in patients with PSC as in controls [159, 160]. A negative association of DR4 with PSC was found in several studies [159, 160]. DR4 has also been described as a marker for rapid disease progression in some studies [160, 162]. A novel strong genetic susceptibility to PSC was found to be associated with the TNF genes, located in class III of the HLA region [163, 164].

Although it is tempting to consider portal bacteremia, absorbed colonic toxins, and toxic bile acids as a cause of PSC, evidence to support these as causes are sparse. Experimental and clinical data support an expanding role for the intestinal flora in the initiation or perpetuation of gut inflammation [165, 166] which share some similarities to the pathogenesis of PSC [164]. Indirect evidence supports the hypothesis that bacterial chemotactic peptides and/or lactoferrin undergo enterohepatic circulation and may represent a pathogenetic link between IBD and PSC [167].

Currently the pathogenesis of PSC is believed to be most closely linked to alterations in immune regulation. Abnormalities in cell-mediated immunity include enhanced autoreactivity of suppressor/cytotoxic T cells from peripheral blood to class II major histocompatibility antigens, aberrant expression of class II antigens on biliary epithelium, inhibition of leukocyte migration in the presence of biliary antigens, and presence of activated T cells associated with bile duct destruction [158, 168–171]. A causative role for these lymphocytes in the bile duct lesions has been suggested by reports of increased expression of intercellular adhesion molecule (ICAM)-1 on biliary epithelium and increased level of ICAM-1 in the circulation in patients with PSC [172, 173]. ICAM-1 is a member of the integrin family of leukocyte adhesion molecules that mediate leukocyte adherence to target structures and to other immune cells. Normal bile ducts do not express ICAM-1; expression of ICAM-1 is strongly associated with bile duct damage [172]. Abnormalities in humoral immunity include high prevalences of circulating anti-colon antibodies, antinuclear antibodies, and anti-neutrophilic cytoplasmic antibodies (up to 80%) in patients with PSC [174–176].

The natural course of the disease varies considerably and is not related to the activity of the ulcerative colitis. In the largest series of PSC patients, with a mean follow-up of 6 years, median survival from the time of diagnosis was 11.9 years [177]. Cholangiocarcinoma is a common complication but difficult to diagnose in patients with PSC and may occur in up to 20–30% of patients. The PSC patients at highest risk for the development of cholangiocarcinoma are those with long-standing ulcerative colitis and those with liver cirrhosis [178]. In addition, an increased risk of colonic dysplasia and aneuploidy leading to increased risk of colonic cancer has been suggested for PSC patients with ulcerative colitis in several [179–181] but not all studies [182].

Most controlled trials found the treatment of PSC with D-penicillamine, colchicine, or methotrexate not to be associated with clinical benefit or with biochemical or histological response [183–185]. Ursodeoxycholic acid therapy has minimal impact on preventing disease progression and prolonging survival or time to liver transplantation [186]. For patients who have a dominant stricture of the biliary tract, endoscopic balloon dilatation of the stricture is frequently effective in alleviating jaundice

and pruritus, and decreasing the frequency and severity of bacterial cholangitic episodes. Survival has been shown to be improved by treatment with ursodeoxycholic acid and endoscopic dilatation of major duct stenoses [187]. Proctocolectomy appears to have no effect on the clinical course of PSC, and it therefore should not be considered a therapeutic option for the treatment of PSC [188]. Patients with liver cirrhosis undergoing proctocolectomy with the construction of an ileal stoma are at risk of developing peristomal varices [189]. Pouchitis may occur more frequently in patients with associated PSC after ileal pouch-anal anastomosis for ulcerative colitis. Pouchitis is not related to the severity of liver disease but may reflect an altered fecal bile acid pool. Liver transplantation must be considered for patients with end-stage PSC. The results of liver transplantation in PSC patients are good (80–85% 3-year survival); however, recurrence of PSC in the hepatic allograft may occur [190]. Furthermore, the risk of developing colorectal carcinoma may be increased in liver-transplanted patients with ulcerative colitis [191, 192]

Autoimmune hepatitis

Diagnosis of autoimmune hepatitis in patients with IBD requires exclusion of stricturing of the intra- and extrahepatic biliary tree by cholangiography. The prevalence of autoimmune hepatitis in patients with IBD has been shown to be between 15% and 20% and the prevalence of ulcerative colitis in patients with autoimmune hepatitis around 15% [151, 193]. The pathogenesis of autoimmune hepatitis associated with IBD remains poorly defined. An increased frequency of HLA-A1, HLA-B8/-DR3, and more recently HLA-DR4 in older and Japanese patients and IgG heavy-chain Gm a^+x^+ alleles suggests that susceptibility to autoimmune hepatitis is genetically determined. The occurrence of decreased serum complement components and decreased peripheral blood T suppressor cell activity in patients and first-degree relatives provides additional support for inherited susceptibility. The disease is characterized by periportal and portal inflammation, with piecemeal and bridging necrosis [194, 195]. Antinuclear antibodies, anti-smooth muscle antibodies, anti-liver-kidney-mitochondrial antibodies and others or a variety of combinations can be detected in serum of almost all patients [151]. With few exceptions, antibody titers are not correlated with disease activity. Furthermore, all autoantigens identified so far, except the asialoglycoprotein receptor, are localized to intracellular organelles but not the plasma membrane, where they can be recognized by autoantibodies and/or antigen-specific T cells.

Increased immunoglobulin secretion in patients with autoimmune hepatitis has been attributed to an abnormality in regulatory T cell function. Indeed, decreased concanavalin A induced and antigen-specific T suppressor cell activity in patients and first- and second-degree relatives has been reported. However, the relationship between increased immunoglobulin secretion and decreased T cell suppressor activity is undefined. Peripheral blood mononuclear cells from patients with autoimmune hepatitis are capable of mediating cytotoxic activity toward xenogeneic, allogeneic, and autologous hepatocytes in vitro. The mononuclear cell subpopulation responsible for peripheral blood cytotoxic activity is a non-T cell that expresses Fc receptor for IgG. T cell cytotoxic activity appears to be less important. However, the functions of peripheral T cells may not directly reflect the function of liver T cells. T cell clones derived from the liver of patients with autoimmune hepatitis are predominantly CD4 positive. As with peripheral blood T cells, liver T cell clones are also sensitized to the asialoglycoprotein receptor and liver-kidney-mitochondrial antigen [196].

Frequently patients with autoimmune hepatitis have evidence of other autoimmune diseases such as thyroiditis and sicca syndrome. The activity and prognosis of chronic hepatitis do not seem to be correlated with the extent of involvement or the severity of IBD. Patients with autoimmune hepatitis associated with IBD should be treated with corticosteroids and/or azathioprine in an attempt to relieve symptoms, improve biochemical parameters and histology. Overlap syndromes of autoimmune hepatitis and PSC may exist [194].

Cholelithiasis

Up to 35% of patients with Crohn's disease develop gall stones [197, 198]. Recent studies have established that bilirubin levels are increased in bile of patients with Crohn's disease. Evidence suggests that the lack of functional ileum causes increased colonic bile salt levels which solubilize unconjugated bilirubin, prevent calcium complexing, and promote bilirubin absorption and enterohepatic cycling [199]. The prevalence of cholelithiasis is not associated with disease extent or the site of previous intestinal resection [200]. This, together with the finding of normal cholesterol saturation of bile in patients with Crohn's disease [201, 202], indicates that these patients may develop pigment stones rather than cholesterol stones [200]. A high incidence of cholelithiasis is also observed in patients with PSC and ulcerative colitis [203]. Chronic cholestasis is known to predispose to the formation of cholesterol gallstones, and biliary stasis associated with bacterial cholangitis predisposes patients to the development of pigment stones, which are most often found in patients with PSC.

Celiac disease

Elevated serum aminotransferase levels have been reported in about 40% of adults [204, 205] and in 54% of

children [206] with celiac disease at the time of diagnosis and may represent the only finding of silent disease [207, 208]. In a series of 140 consecutive patients with chronic elevation in serum transaminases of undetermined origin, 13 (9.3%) were positive for anti-gliadin and anti-endomysium antibodies [209]. Celiac disease was confirmed by duodenal biopsy. After gluten-free diet, serum ALT and AST levels returned to normal in all patients but one [209]. Similar results have been reported by Volta et al. [210] in a smaller series of comparable patients. Liver histology in these patients shows uncharacteristic changes such as variable degrees of mild steatosis, fibrosis, and inflammation [209]. Liver cirrhosis has been observed in single cases [211, 212]; however, in these series patients were not tested for anti-HCV antibodies. Logan et al. [213] described four patients with PBC and celiac disease who responded to a gluten-free diet by normalization or amelioration of the small intestinal biopsy specimens. The liver disease, however, remained unchanged. The pathophysiological mechanism(s) of liver abnormalities in celiac disease are unknown but may represent a common response to an underlying autoimmune response, responsible both for the intestinal and hepatic lesions [212].

Hemochromatosis

Genetic hemochromatosis is an autosomal recessive disorder in which an inappropriate increase in the absorption of dietary iron is associated with accumulation of this metal within liver cells and in other sites of the body. The genetic defect has been localized on chromosome 6 in proximity to the histocompatibility leukocyte antigen (HLA)-4 locus and is now termed *HFE* gene. The HFE gene product is a 343 amino acid residue type I transmembrane glycoprotein that is homologous to class I MHC proteins and interacts with the class I light-chain β_2-microglobulin [214]. In populations of northern European origin about 65–95% patients with clinical hemochromatosis have a single amino acid mutation (Cys-282–Tyr). A second mutation at position 63 (His-63–Asp) increases the relative risk of developing hemochromatosis in individuals who are heterozygous for the Cys-282–Tyr mutation [214, 215]. HFE interacts with the transferrin receptor, thereby diminishing its affinity for iron-bound transferrin [216, 217]. The Cys-282–Tyr mutated protein, however, does not interact with the transferrin receptor and does not decrease the affinity of the transferrin receptor for iron-bound transferrin and may therefore facilitate iron uptake into cells. It has also been shown that the soluble transferrin receptor and HFE tightly bind at the basic pH of the cell membrane but not at the acidic pH of endosomes or other intracellular vesicles [218]. This pH dependence suggests that HFE enters the cell along with the transferrin-transferrin receptor complex and then dissociates from this complex in acidic intracellular compartments. Immunohistochemical analyses have located HFE in the intracellular portion of small intestinal cells in the deep crypts, preferentially in the duodenum. These cells, however, have previously not been implicated in the regulation of iron absorption.

Uptake of iron by mucosal cells involves several steps: (a) presentation of chelated iron to the cell surface, (b) binding and translocation across the apical membrane of the mucosal cell, (c) intracellular transport, and (d) release at the basolateral site of the plasma membrane [219, 220]. Iron can be transported via the portal vein to the liver by binding to low molecular weight chelating molecules. This nontransferrin bound iron may be taken up by the hepatocytes by a membrane iron transport system similar to the one in apical membranes of mucosal cells. Transferrin-bound iron is taken up by hepatocytes and other cells by the transferrin receptor endosomal pathway [221, 222]. Intracellular iron storage proteins are ferritin and hemosiderin, which are of particular importance in the liver [223, 224].

The liver is the site of earliest and heaviest iron deposition. Other clinical complications include B-cell damage, abnormal skin pigmentation, arthropathy, cardiomyopathy, and pituitary hypogonadism [225]. It remains unclear why certain organs are particularly affected by excessive iron accumulation. Laboratory, clinical, and histological signs of liver disease are observed in most patients with hemochromatosis. The presence of liver cirrhosis is closely associated with the amount of mobilizable iron and with the liver iron concentration [225]. Hepatocellular carcinoma develops in about 30% of cirrhotic patients, even after removal of excess body iron stores by phlebotomy [225, 226]. From the pathophysiological localization of the genetic defect in hemochromatosis it is self-evident that venesection therapy (phlebotomy) must be continued in all patients following orthotopic liver transplantation for hemochromatosis-related end-stage liver disease.

Cystic fibrosis

Cystic fibrosis is another common autosomal recessive disease in the white population. The primary molecular defect, the reduced expression of the cystic fibrosis transmembrane conductance regulator (CFTR), leading to a chloride secretory defect, is present in all epithelial cells of endodermal and mesodermal origin and has been described in sweat glands, airway epithelium, intestine, and pancreas. The gene encoding for the 1480 amino acid CFTR is located on chromosome 7. Mutated CFTR is retained in the endoplasmic reticulum and becomes subsequently degraded and not inserted into the apical plasma membrane [227].

The clinical phenotype of cystic fibrosis in the intestine is related to the decreased secretion of chloride ions and fluid and the sticky mucous covering the enterocytes. In particular the colon is a common site of serious complications, such as rectal prolapse, distal intestinal obstruction, and intussusception. Furthermore, an increase in colonic strictures after use of high-dose pancreatic enzymes has been reported [228]. The most common liver and biliary diseases associated with cystic fibrosis are steatosis, fibrosis/cirrhosis, microgallbladder, cholelithiasis, and sclerosing cholangitis. Plugging of the intrahepatic bile ducts with inspisated secretions is thought to play an important role in the pathogenesis. Ursodeoxycholic acid has been used in the treatment of gallstones and pathological liver function in patients with cystic fibrosis. Findings regarding the effect on gallstones have been contradictory, and the effect on liver function tests has been shown to be dose-dependent, with an optimum at about 20 mg/kg body weight [229, 230].

Steatohepatitis in patients with jejunoileal bypass and short bowel syndrome

Theories regarding development of hepatic steatosis center around increases in fatty acid supply to the liver or alterations in the synthesis and secretion of lipoproteins. Alcohol and its metabolites are common causes of hepatic steatosis. Alcohol does not appear to affect intestinal absorption of lipids or lipoprotein synthesis. It does increase lipolysis in peripheral adipose tissue, resulting in an increased delivery to the liver. Alcohol also increases fatty acid synthesis by decreasing the NAD to NADH ratio and damaging mitochondria. Ethanol inhibits the tricarboxylic acid cycle, resulting in increased production of acetate that can be used as substrate for fatty acid synthesis [231]. Various forms of nonalcoholic hepatic steatosis can be differentiated etiologically as due to metabolic and nutritional causes, drugs, and infections. The differentiation from alcohol-induced hepatic steatosis is primarily based on an absence of a significant alcohol history [232].

Jejunoileal bypass

One of the most pronounced and reproducible forms of nonalcoholic steatohepatitis syndrome is that produced by jejunoileal bypass operations for obesity [233, 234]. Changes are generally seen within 6 months after surgery in the liver, ranging from asymptomatic steatosis to steatohepatitis with liver failure. Patients having jejunoileal bypass operation for approximately 5 years have significant increases in hepatic steatosis, inflammatory cell infiltrates, and fibrosis. Some patients develop liver cirrhosis [235, 236]. The explanation for the fat accumulation and liver disease is not clear. It is not simply a result of increased fatty acid mobilization from adipose tissue. Dieting and other forms of obesity surgery do not cause these changes. Also, changes can be improved or prevented with the use of antibiotics, suggesting that factors resulting from bacterial overgrowth in the excluded loop (e.g., endotoxins) are likely to be responsible [237]. In addition, patients with jejunoileal bypass are hypoproteinemic and may have decreased ability to form lipoproteins for transport of triglyceride from the liver [238]. The metabolic complications associated with the operation led to a National Institutes of Health consensus development conference, at which the consensus was that the operation should stop being performed, and the call for a moratorium eliminating the performance of the operation was issued in 1978 [239]. Reversal of the bypass procedure can reverse the changes in the liver [231].

Short bowel syndrome

Short bowel syndrome can be defined as a malabsorption syndrome that results from extensive intestinal resection. In general, the severity of malabsorption in short bowel syndrome depends on five factors: (a) the extent of resection with consequent loss of absorptive surface area, (b) the site of resection with loss of site-specific transport functions (e.g., bile acid malabsorption) and gastrointestinal hormone synthesis, (c) the presence or absence of the ileocecal valve, (d) the sequential adaptation of the remaining intestine, and (e) possible residual disease in preserved bowel. Severe malnutrition may lead to fatty infiltration of the liver. The most likely mechanism is decreased synthesis of lipoproteins, which results in decreased export of lipids from the liver [240, 241]. The risk of developing cholesterol gallstones in the short bowel syndrome has been estimated to be as high as 30% [242]. The risk may be even higher in patients on long-term parenteral alimentation because of decreased gallbladder emptying and development of sludge [243].

Liver metastasis in intestinal cancer

The most frequent organ location of distant metastasis in cancer is related to organ tropism and the first capillary bed encountered by the circulating cells. In general, metastatic colonization of small intestinal and colorectal cancer occurs primarily in the liver. Circulating cancer cells that develop into metastasis must undergo a series of steps, including adherence, interaction within the hepatic microvasculature, and migration. Intrinsic features of tumor cells, for example, proteolytic enzymes, adhesion molecules, and a number of liver host factors, for example, hepatocyte growth factor, may have important

roles in the development of metastases [244]. Hepatic metastasis from colorectal cancer are most often asymptomatic, detected either synchronous at the time of primary cancer diagnosis or metachronous during follow-up after resection of colorectal cancer. Therapeutic options comprise surgical resection, systemic chemotherapy, and several regional treatment modalities [245].

The risk of extracolonic adenocarcinomas is increased in patients with hereditary nonpolyposis colorectal cancer. In addition to a higher incidence of endometrium, urogenital, gastric, and pancreatic tumors, an increased risk of developing bile duct carcinoma is established in families with hereditary nonpolyposis colorectal cancer [246]. No common association with hepatobiliary abnormalities has been observed in polyposis syndromes. Patients with familial adenomatous polyposis syndrome frequently develop adenomas or adenocarcinomas of the ampulla of Vater, and in patients with Peutz-Jeghers syndrome the risk of polyps or cancer of the biliary tree and gallbladder may be increased [247, 248].

Infectious diseases affecting intestine and liver/biliary tract

Several viral, bacterial, fungal, and parasitic diseases can affect both the gastrointestinal tract and the liver and biliary tract. Infectious diseases affecting intestine and liver/biliary tract include:

- Viral disease: hepatitis A virus, hepatitis E virus, cytomegalovirus, herpes simplex virus, adenovirus, enterovirus, human immunodeficiency virus
- Bacterial disease: pyogenic hepatic abscesses (*Klebsiella*, streptococci, *Escherichia coli*, staphylococci, *Pseudomonas*, *Bacteroides*, *Proteus*, clostridia); infectious diarrhea with hepatic manifestation (*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Leptospira*, *Mycobacteria*, *Tropheryma whippelii*)
- Fungal disease: *Candida*, *Aspergillus*, *Histoplasma*, *Coccidioides*
- Parasitic disease: protozoa (*Entamoeba histolytica*, *Toxoplasma gondii*, coccidia, microsporidia); schistosomes, *Fasciola hepatica*, *Clonorchis* and *Opisthorchis*, *Ascaris lumbricoides*, *Echinococcus*

Viral disease

Acute infection with enterically transmittable hepatotropic viruses, such as the hepatitis A and E virus, can be associated with nausea, vomiting, and diarrhea. Replication of hepatitis A virus in intestinal epithelial cells has not been observed, except under experimental conditions when animal models were immunosuppressed with prednisolone [249, 250]. Hepatitis A virus is released from infected hepatocytes into the biliary tree via bile canaliculi. The presence of hepatitis A virus in bile during acute infection explains the presence of the virus in stool [251]. Similarly, hepatitis E virus can be detected by immune electron microscopy in feces of patients with acute hepatitis E [252]. Other viruses involved in hepatic and intestinal inflammation include cytomegalovirus, herpes simplex virus, adenoviruses, and enteroviruses. Cytomegalovirus can also be detected in the gallbladder mucosa and may cause acalculous cholecystitis and papillary stenosis [253]. In general, infection of the liver and the intestinal tract by these viruses indicates disseminated disease and is typically observed in immunocompromised individuals.

The human immunodeficiency virus (HIV) has been detected in hepatocytes by in situ hybridization. Hepatic macrophages and endothelial cells express the CD4 surface molecule, which serves as the receptor for HIV. However, no characteristic biochemical or pathological abnormalities accompany the presence of HIV within hepatocytes in vivo [254, 255]. Enteric HIV infection may lead to mucosal atrophy; a close relationship between mucosal T cells and enterocyte proliferation and maturation has been suggested [256, 257].

Bacterial disease

Pyogenic hepatic abscesses

Most pyogenic hepatic abscesses are caused by infection originating in the biliary or intestinal tract. Infection in the liver can extend (a) through the bile ducts (e.g., choledocholithiasis, malignant biliary obstruction), (b) via the hepatic artery (e.g., subsequent to hepatic artery embolization), (c) by way of the portal vein (e.g., appendicitis, diverticulitis), (d) by direct extension, (e) from blunt or penetrating trauma, or (f) cryptogenically. Multiple hepatic abscesses frequently result from massive sepsis, for example, in bacterial endocarditis. Organisms isolated most frequently from pyogenic liver abscesses include *Klebsiella*, streptococci, *Escherichia coli*, staphylococci, *Pseudomonas*, *Bacteroides*, *Proteus*, and *Clostridium* [258]. In general, treatment requires percutaneous drainage in combination with antibiotics and, if applicable, endoscopic drainage of the biliary tree.

Infectious diarrhea with hepatic manifestation

Most organisms ingested are suppressed by gastric acid and subsequently by the bile. Another key element in maintaining a sparse flora of the upper bowel is forward propulsive motility. Finally, the microflora maintains stability of the normal populations by producing its own antibacterial substances which normally prevents implanta-

tion of pathogens. Some pathogens causing infectious diarrhea can also affect the liver.

Liver and gallbladder involvement is common in patients with typhoid fever [259]. Unrecognized typhoid hepatitis is associated with a high mortality. *Salmonella* causes hepatic dysfunction by direct tissue invasion, liberation of cytotoxins and/or endotoxemia [260]. Some patients become chronic carriers of nontyphoidal *Salmonella* (usually harbored in the gallbladder) as a consequence of either symptomatic or asymptomatic infection [261]. *Shigella* infection which causes scattered ulcerations in the small and especially in the large bowel with mucopurulent and bloody diarrhea is rarely associated with liver disease [262]. Infections with *Campylobacter* spp. are common causes of diarrhea and may be complicated by, for example, cholecystitis [263]. *Yersinia enterocolitica* is an important intestinal pathogen that causes a spectrum of clinical illnesses from simple gastroenteritis to invasive ileitis and colitis together with mesenteric adenitis. Pathogenic mechanisms include the ability to invade epithelial cells, proliferation within the follicles of Peyer's patches and spread into the lamina propria as well as the production of a heat-stable enterotoxin. After systemic dissemination, enteropathogenic *Y. enterocolitica* typically establishes an infection in spleen, liver, and lungs. Liver function tests are frequently abnormal, and liver abscesses occur more frequently in patients with hemochromatosis or secondary hemosiderosis, which may be related to the fact that *Yersinia* is an iron-dependent bacterium [264–266]. Severe leptospirosis (Weil's disease) can affect the liver and the intestine. In more than 50% of cases leptospirae can be identified in liver biopsy specimens. The pathogenesis of the jaundice is suspected to be due to a subcellular defect in bilirubin metabolism; hemolysis can also play a role. Gastrointestinal bleeding is felt to be caused by an underlying vasculitis [267, 268].

Any region of the gastrointestinal tract or the liver can be involved with tuberculosis. Liver involvement in generalized miliary tuberculosis is well recognized but may also occur in patients with pulmonary or intestinal tuberculosis. *Mycobacterium avium complex* is the most common opportunistic pathogen found on liver biopsies in patients with acquired immunodeficiency syndrome (AIDS). Hepatic involvement occurs in the setting of disseminated disease. Cholestasis may be caused from microscopic obstruction of small biliary ductules by granulomas [269–271].

Whipple's disease is an uncommon systemic disease caused by *Tropheryma whippelii*. Infiltration of the small intestine with periodic acid–Schiff positive macrophages is specific. Sarcoidlike granulomas have been noted in the small intestine as well as in other tissues including the liver and may precede more diffuse infiltration by macrophages. Lymphatic dilatation and fat accumulation in the extracellular spaces of the lamina propria probably reflect lymphatic obstruction caused in mesenteric lymph nodes. Macroscopically the bowel wall appears thickened and edematous. Malabsorption is a leading clinical feature, but extraintestinal and systemic symptoms may even precede gastrointestinal complaints. Long-term antibiotic treatment is mandatory [272, 273].

Fungal disease

The presence of *Candida* in the small intestine is particularly frequent in immunosuppressed and immunocompromised patients. When antibiotic therapy is instituted, *Candida* overgrowth and diarrhea can occur. The liver is usually involved only in patients with disseminated disease [274, 275]. *Aspergillus* is also an enteric pathogen in immunosuppressed patients and can manifest with gastrointestinal bleeding [276]. Disseminated *Aspergillus* can invade the liver, causing cholestasis and abscess formation. Histoplasmosis may manifest as a diffuse colitis with large ulcerations, as a mass, or as serosal disease in association with peritonitis and can also cause hepatic infiltration [277, 278]. Coccidioidomycosis of the gut is rare and, as with histoplasmosis, occurs in the context of systemic infection. Liver involvement appears to be more common than luminal disease [279].

Parasitic disease

Protozoal disease

Entamoeba histolytica is a cause of dysentery, colitis, and amebic liver abscess, whereas *E. dispar* has clinically never been associated with disease [280]. Infection by *E. histolytica* is ubiquitous, and most infected individuals are healthy carriers. To initiate symptomatic infection, trophozoites present in the bowel lumen, penetrate the mucosal layer, and adhere to the underlying mucosa. Initial steps in tissue invasion may be aided by the release of proteases from trophozoites, which are capable of degrading extracellular matrix components. A pore-forming peptide named amebapore is considered an essential part of the amebic cytolytic machinery [280]. Hepatic abscesses are the most frequent complication of invasive amebiasis. The portal vein is regarded as the major route of ameba invasion from the intestine to the liver; however, in same cases a peritoneal route must be considered. Antiamebic antibodies are important in the differential diagnosis of liver abscesses. In contrast, microscopy of stool specimens or aspirated content of the abscess for the identification of trophozoites or cysts are of little value. Metronidazole is the drug of choice and drainage should be considered only when a considerable risk of rupture or an association with pyogenic infection is suspected [281–283].

Oocysts of *Toxoplasma gondii* in soil, water, or contaminated meat are ingested and mature in the intestinal tract of humans to become sporozoites, which penetrate the intestinal mucosa, become tachyzoites, and circulate systemically, invading a wide array of cells. Hepatic involvement has been observed in severe, disseminated infection, which in general occurs in immunocompromised patients. Treatment consists of a combination of pyrimethamine and sulfadiazine, plus folic acid to minimize hematological toxicity [284, 285]. Other protozoal diseases (malaria, leishmaniasis) may affect the liver, but usually not the intestine or vice versa (giardiasis).

Spore-forming protozoa (coccidia: *Isospora belli*, *Cyclospora cayetanensis*, *Cryptosporidium parvum*; microsporidia: *Enterocytozoon bieneusi*, *Septata intestinalis*) have been increasingly identified as intestinal pathogens, especially in patients with AIDS. The clinical spectrum varies from mild, nonspecific changes, mild to severe diarrhea, to necrotizing enterocolitis. Coinfection of the biliary tract has been noted in cyclospora, cryptosporidia, and microsporidia infection. In AIDS patients cryptosporidiosis is commonly associated with sclerosing cholangitis, acalculous cholecystitis, and papillary stenosis [286, 287].

Schistosomiasis

Schistosomes begin their life cycles with the passage of eggs by adult females that live, paired with male worms, in the mesenteric or vesical venous beds. Viable eggs erode through the intestinal or bladder mucosa, are passed in feces or urine, hatch in water, and infect an intermediate snail host. Snails shed the infectious stage for humans, free-swimming ceracariae, which have the ability to penetrate human skin and transform into immature worms. The worms mature as they traverse the venous, pulmonary, and systemic circulation and home on their species-specific target vessels to start egg production [288]. The majority of schistosomal liver disease is caused by infections with *Schistosoma mansoni* and *S. japonicum*. Liver disease results from entrapment of eggs that are not excreted but instead lodge in portal venules, which leads to granuloma formation, portal tract inflammation and fibrosis. Complications of advanced hepatic schistosomiasis are related to the development of presinusoidal portal hypertension. Detection of schistosome eggs in the stool is the most useful diagnostic method for identification of active infection. The drug of first choice is praziquantel, effecting a parasitological cure in about 90% of patients [289, 290].

Fascioliasis

Fasciola hepatica resides in the bile duct and may remain viable for more than a decade. The worms produce eggs that are passed in feces, hatch in water, and infect a snail intermediate host. Snails release a cercarial stage of the parasite that contaminates aquatic plants ingested by humans. When ingested, transformed metacercariae penetrate the intestine, traverse the peritoneal cavity and liver capsule, and burrow through the liver parenchyma for several weeks while maturing and cause necrosis infiltrated by an intense eosinophilic inflammatory response. Finally, they enter the bile ducts to become mature adults and complete the cycle [291]. Atypical manifestations of acute fascioliasis may result when penetration of the ductal system causes hemobilia or abscess formation. Immature worms that fail to migrate into the liver can produce ectopic masses or abscesses. Large number of mature worms in the ductal system may precipitate episodes of acute biliary obstruction and cholangitis. Stool examination for eggs is useful only in chronic disease and may be negative when egg output is intermittent. Clinical symptoms, characteristic history, eosinophilia, and serological tests usually provide the diagnosis. Bithionol is the drug with the highest reported efficacy [292, 293].

Clonorchiasis and opisthorchiasis

Clonorchis sinensis, *Opisthorchis viverrini*, and *Opisthorchis felineus* reside in bile ducts and are acquired by individuals who eat raw fish containing infective metacercaria. Infected patients excrete eggs that hatch in water and pass through snail and fish stages to infect new humans and animals. Ascending the common bile duct and attached to intrahepatic bile duct epithelium, the life span of male and female adult worms achieves 10 years or more. The bile ducts that harbor adult worms can show dilatation, irregular thickening, and adenomatous epithelial hyperplasia. The risk of developing cholangiocarcinoma is significantly increased in infected patients. Praziquantel is the medical treatment of choice [294, 295].

Ascariasis

Ascaris lumbricoides infection occurs through the ingestion of embryonated eggs contaminating food or water. The larvae emerge from the ova in the duodenum, from which they migrate through the epithelium of the small bowel into the portal venous system and pass through the liver into the lungs. Subsequently the larvae break through the pulmonary capillaries into the alveoli and migrate up the bronchial system to the pharynx, where they are ultimately swallowed. Back in the small intestine, they develop into adult males and females. Large masses of worms may produce intestinal obstruction, perforation or penetration. Parasites in the appendix may

lead to appendicitis, and those in the common bile duct, to obstructive jaundice or pancreatitis. The diagnosis is mainly based on finding eggs, adult worms, or larvae. Mebendazole, albendazole, and pyrantel pamoate are effective for medical treatment [296, 297].

Echinococcosis

Infection with *Echinococcus granulosus* or *E. multilocularis* occurs by eating material contaminated with eggs excreted by infected animals. The eggs penetrate the intestine and reach the liver via the portal vein. The parasite normally multiplies as a larval scolex stage within cysts in the solid organs of herbivores or rodents that have consumed excreted eggs. Consumption of the cyst-containing viscera of these animals by new canines completes the cycle. Humans are accidental hosts for a cystic intermediate stage. Hydatid liver cysts caused by *E. granulosus* are fluid-filled structures delimited by a parasite-derived membrane that contains germinal epithelium that buds viable scoleces. The cysts formed in *E. multilocularis* infection are less well delimited. They tend to invade the liver parenchyma and seed adjacent organs and structures with scoleces and daughter cysts [298, 299]. No fecal eggs are present in human hosts. Clinical symptoms, characteristic imaging features, eosinophilia, and serological tests are diagnostic. Mebendazole and albendazole are the current standard for medical therapy. Surgical resection of hepatic *E. granulosus* cysts is recommended. Laparoscopic evacuation and ultrasound-guided percutaneous drainage of hepatic hydatid cysts have also been reported to be safe and effective [300, 301].

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