The Enterohepatic Circulation

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Derivation of the name

Enteron - Intestine (Greek)

Hepar - Liver (Greek)

16.1 Enterohepatic Circulation (EHC) - Definition

The circulation of bile acids, bilirubin, drugs, or other substances from the liver to the bile, followed by entry into the small intestine, absorption by the enterocyte and transport back to the liver. Recycling through liver by excretion in bile, reabsorption from intestines into portal circulation, passage back into liver, and re-excretion in bile [1].

16.2 Introduction

The purpose of this chapter is to provide insight into the functioning of the enterohepatic circulation (EHC) as it relates to the practice of clinical nutrition. The focus will not be on disease management; rather, it will be on ways in which improving the health and function of the tissues and organs of the EHC might be approached.

Health professionals, of any level of training or experience, are the intended audience. To be inclusive, the content may be helpful for those who aspire to become health professionals, those who want to understand human physiology in greater depth and anyone who is interested in learning how to create a better state of health. This chapter should help those with training in conventional Western medicine who employ a "mainstream" approach to healthcare, but who feel that there is more to patient care than they are equipped to deliver. It should help open channels of communication and new thought processes to investigate ways to deliver patient-focused healthcare and guide the practitioner to find a new group of like-minded professionals.

The foundation of what we do is basic science. Yet science is always growing. What we know now about the EHC is vastly different from what was known in 1923, the date of one of the earliest publications on the subject [2]. The role of the EHC in the recirculation and conservation of bile salts is foundational and was known from the beginning. But the awareness that the EHC also handles hormones, drugs, and other substances, both endogenous and exogenous, emerged over the next 40 years [3–8]. In the subsequent 50 years, these topics have been extensively studied and documented. The role of the EHC in the metabolism of xenobiotics (see below) began to emerge later. The first use of the term "xenobiotic" in the Medline database was in 1965 [9].

The term gut "microbiome" first appeared in 2002, and it became clear that colonization with healthy bacteria is critical for the normal structural and functional development, and the optimal function of the mucosal immune system [10]. Other areas of important research include the relationships between the microbiome, the gut-associated lymphoid tissue, the enteric nervous system, and the enteric endocrine cells in regard to their systemic effects [11, 12]. The metabolic effects of bile acids are also garnering increased attention [13, 14]. Thus, understanding of the functions of the EHC has increased dramatically over nearly 100 years, and we can only expect this to continue.

16.3 Overview

To refresh our understanding of the structure of the EHC, the following drawing and comments will provide an overview. The purpose of this section is to provide a basic, common understanding of the EHC as a system (Fig. 16.1).

16.4 Details of Microanatomy, Physiology, and Biochemistry

The following sections will present a much more detailed understanding of some of the individual components of the EHC, how they relate together, and how the EHC interacts with the rest of the body. This will help provide a framework for further study, and to provide a foundation for understanding why nutrition needs to be incorporated into the root of medical education. In one sense, nothing said here is new, but will aid in expanding understanding of nutritional therapies [15].

16.4.1 Portal Vein

The portal vein and its tributaries drain the entire intestinal tract from the gastroesophageal (GE) junction at the top of the stomach, all the way to the anus. This is a distance of 33 feet (11 yards) in the average adult. Through these veins, all the blood flowing from the stomach, small, and large intestines is carried directly to the liver. Veins, in general, carry blood toward the heart. In the case of the portal vein and its tributaries, the blood ultimately reaches the heart, but after being processed in the liver. This portal venous system is separate from and parallel to the systemic veins, which carry blood from all the other organs and tissues in the body directly to the heart.

16.4.2 Portal Tracts

In the liver, the portal vein branches like a large tree. The tiniest branches are called portal venules, which travel through the liver in a network of fibrous channels called portal tracts. In addition to the portal venules, the portal tracts carry tiny arterioles from the hepatic artery, which carry highly oxygenated blood directly from the heart. About 70% of the blood supply to the liver comes from the portal venules and so from the intestines, the remaining 30% from the hepatic arterioles (Fig. 16.2).

Also coursing through the portal tracts are bile ductules, which carry bile out of the liver; lymphatic channels, which

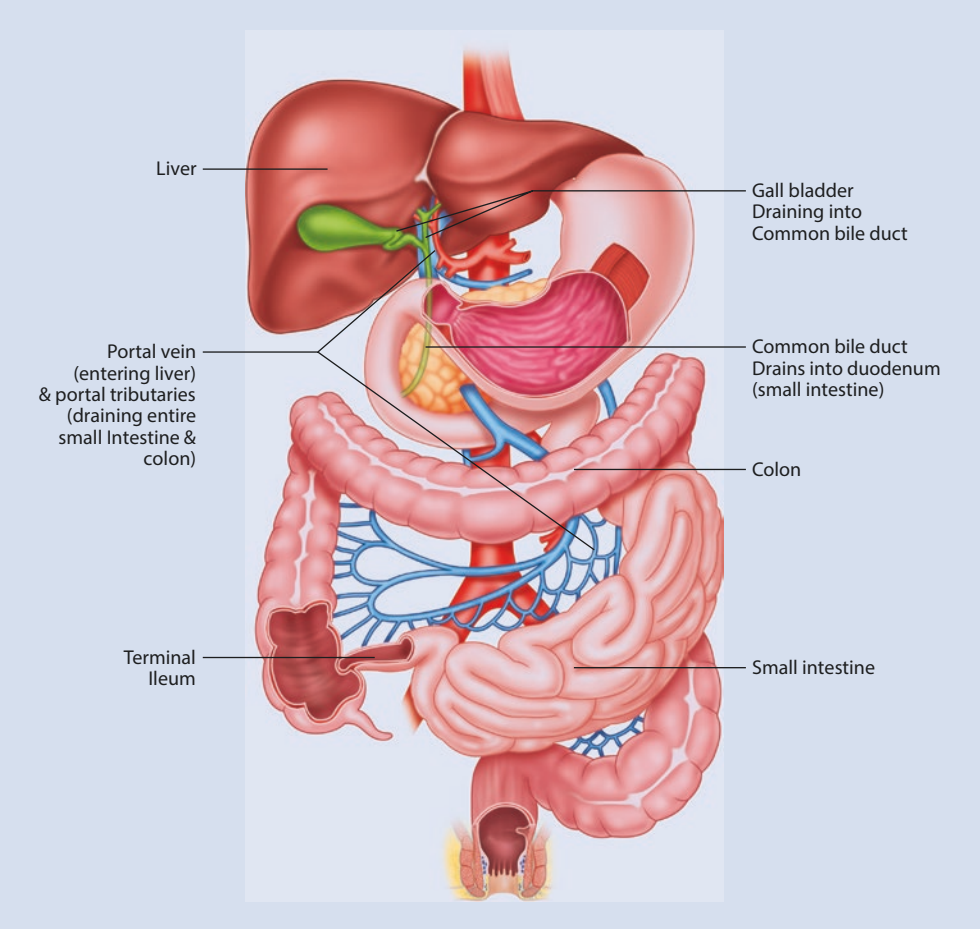

Fig. 16.1 (1) *Portal vein & portal tributaries*. Carries blood from the intestinal tract into liver; (2) *Liver*. Functions: nutrients synthesized into metabolic compounds transported and utilized by organs; detoxification processes; stabilization of blood glucose; synthesization of ATP; bile production; (3) *Bile ducts and gallbladder*. Bile, the main secretory product of the liver, is stored and processed in the gallbladder; (4) *Small intestine*. Duodenum: first part of the small intestine receiving bile and pancreatic enzymes; jejunum and ileum: second and third portions of the small intestine where digestion occurs; (5) *Terminal ileum*. Final 6 inches of the small intestine where 95% of the bile is absorbed and recirculated to the liver, historically the origin of the term enterohepatic circulation; (6) *Large intestine or colon*. The final five feet of the intestine where stool is concentrated, other metabolic processes occur, and the resulting feces are discharged through the anus; further absorption of bile also occurs, entering the portal circulation. (Adapted from [49]. With permission from Wolters Kluwer Health)

carry lymphatic drainage away from the liver; and branches of the autonomic nervous system, evidence of the input of the autonomic nervous system into functioning of the liver on a cellular level.

16.4.3 Liver/Hepatic Lobule

Viewed under light microscopy, the liver parenchyma consists primarily of a single cell type, the hepatocyte or liver cell. Hepatocytes occur in extensive sheets of cells with an essentially uniform appearance, which are interwoven with the hepatic sinusoids. (See section below) The classic unit of hepatocyte organization is called the hepatic lobule. This structure is composed of six portal triads and a central vein, and can be seen under the microscope. However, because the lobule is a three dimensional structure in vivo , the classic hexagonal lobular structure is seldom seen in photomicrographs of a 2-dimensional cut section.

Each lobule consists of an average of six portal tracts forming the corners of a hexagon made up of hepatocytes, with a central hepatic venule (CV) or terminal hepatic venule (THV) located approximately in the center. Blood enters through the portal tracts at the periphery of the lobule, flows into the sinusoids adjacent to the hepatocytes, is processed while traversing the sinusoid, and then empties into the central hepatic venule. The central hepatic venule is the smallest branch of the hepatic vein, which carries blood back to the heart.

16.4.4 Hepatic Sinusoids and Hepatocytes

Exiting the portal tracts, blood from the portal venules merges with blood from the hepatic arterioles and flows into a vast vascular web called the hepatic sinusoids, which extend throughout the liver (Fig. 16.3). Blood flow into the sinusoids is regulated by specialized tissues in the portal venules and hepatic arterioles as they emerge from the portal tracts. Hormones, autonomic nervous input, and other factors influence this sinusoidal blood flow. Part of the cell membrane of each hepatocyte (the basolateral membrane) is adjacent to a sinusoid. It is through this basolateral membrane that transport of molecules into the hepatocytes occurs for processing.

16.4.5 Interaction of Sinusoidal Blood with the Hepatocyte Basolateral Cell Membranes

In the sinusoids, the liquid part of the blood, the serum, bathes the basolateral membranes of the hepatocytes. These cell membranes are highly specialized to carry out specific

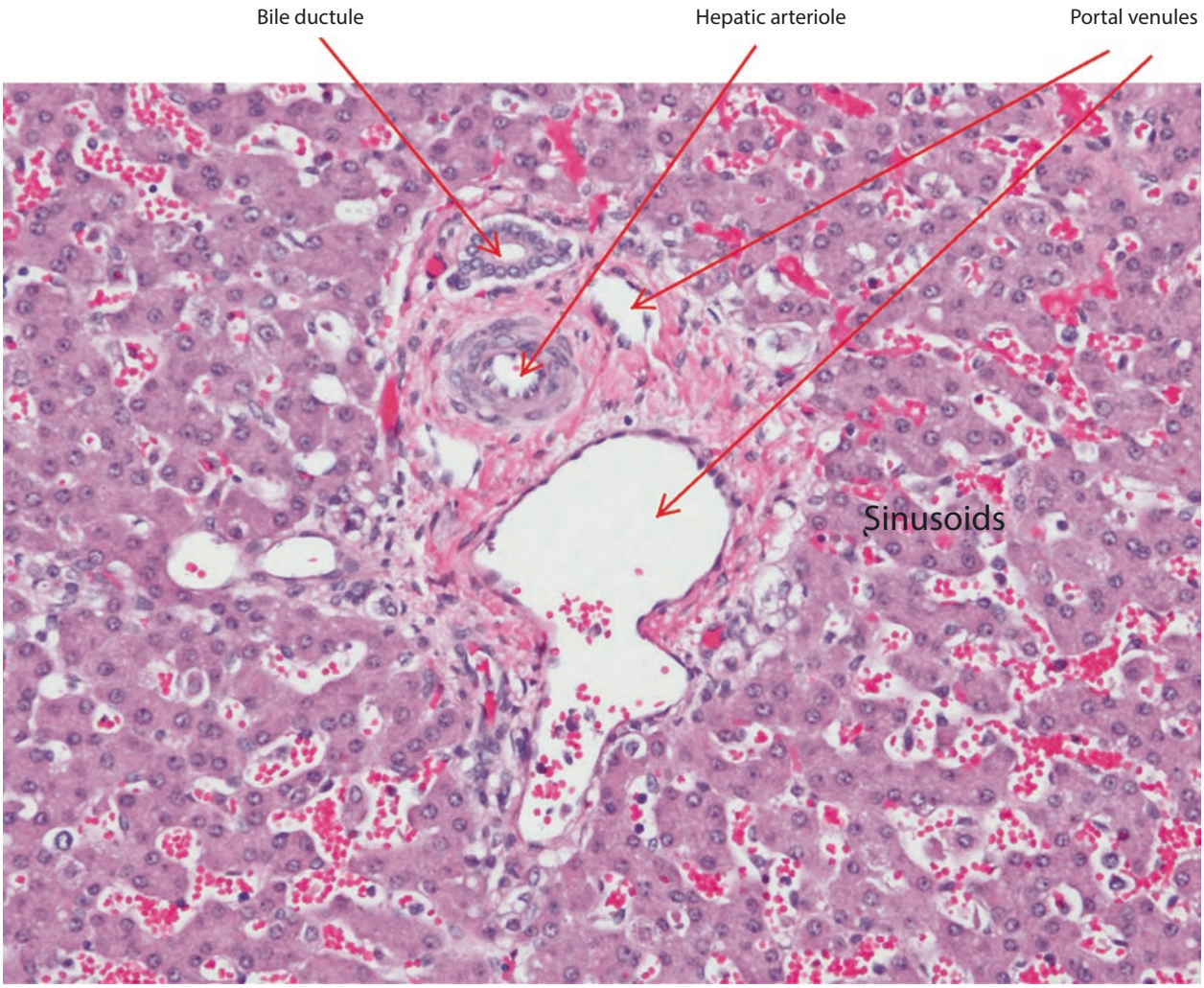

Fig. 16.2 (Portal tract photo) Portal tracts course in a vast network through the liver with the terminal branches of the portal venules carrying blood from the intestinal tract and hepatic arterioles carrying highly oxygenated blood from the heart. Portal blood mixes with hepatic arteriolar blood and flows into the sinusoids. Lymphatic channels and branches of the autonomic nervous system are not visible in this photomicrograph. The cells around the portal tract and adjacent to the sinusoids are periportal hepatocytes in which many synthetic and energy-producing steps occur. (Courtesy of Beverly B. Rogers MD, Emory University School of Medicine)

functions, and these functions vary as the blood flows through the sinusoids. As with cell membranes throughout the body, the basic hepatocyte cell membrane structure consists of molecules called phospholipids. Cholesterol is also a vital membrane component. Membranes are highly structured, yet fluid and flexible. Studding the membranes are hundreds of different types of transport channels, usually constructed from proteins, which allow molecules to move in and out of the hepatocytes in coordinated fashion.

Interactions of serum molecules with the basolateral cell membrane transport channels are not haphazard or random. As with cell membranes anywhere in the body, enzymes which comprise the transport channels seem to have a specific affinity for molecules they transport based on many factors, including pH, electrostatic forces, molecular size and folding (S Finnegan, Research on lactase and carbohydrase enzymes (Lactaid and Beano), Quality Control Director, Body Bio Corporation, personal communication, 2016; R Silva, Emeritus Professor of Chemistry, California State University Northridge, personal communication). In other words, interactions between serum molecules with the basolateral membrane of hepatocytes are not simply random collisions. There are dynamic and specific interactions which direct individual molecules to their corresponding transport channels so the processes of hepatic metabolism can proceed in orderly fashion. Other aspects of the sinusoidal anatomy (fenestrated endothelial cells, space of Disse, Kupffer cells, stellate cells, and others), although fundamental and vital, will not be discussed here, and the reader is referred to texts to expand knowledge.

16.4.6 Metabolic Zonation/Organization of Hepatocytes by their Function

The first article on metabolic zonation was published by Katz and Jungermann in 1976 [16]. Techniques have since been developed whereby the hepatocytes adjacent to the portal tract (periportal hepatocytes) and those adjacent to the cen-

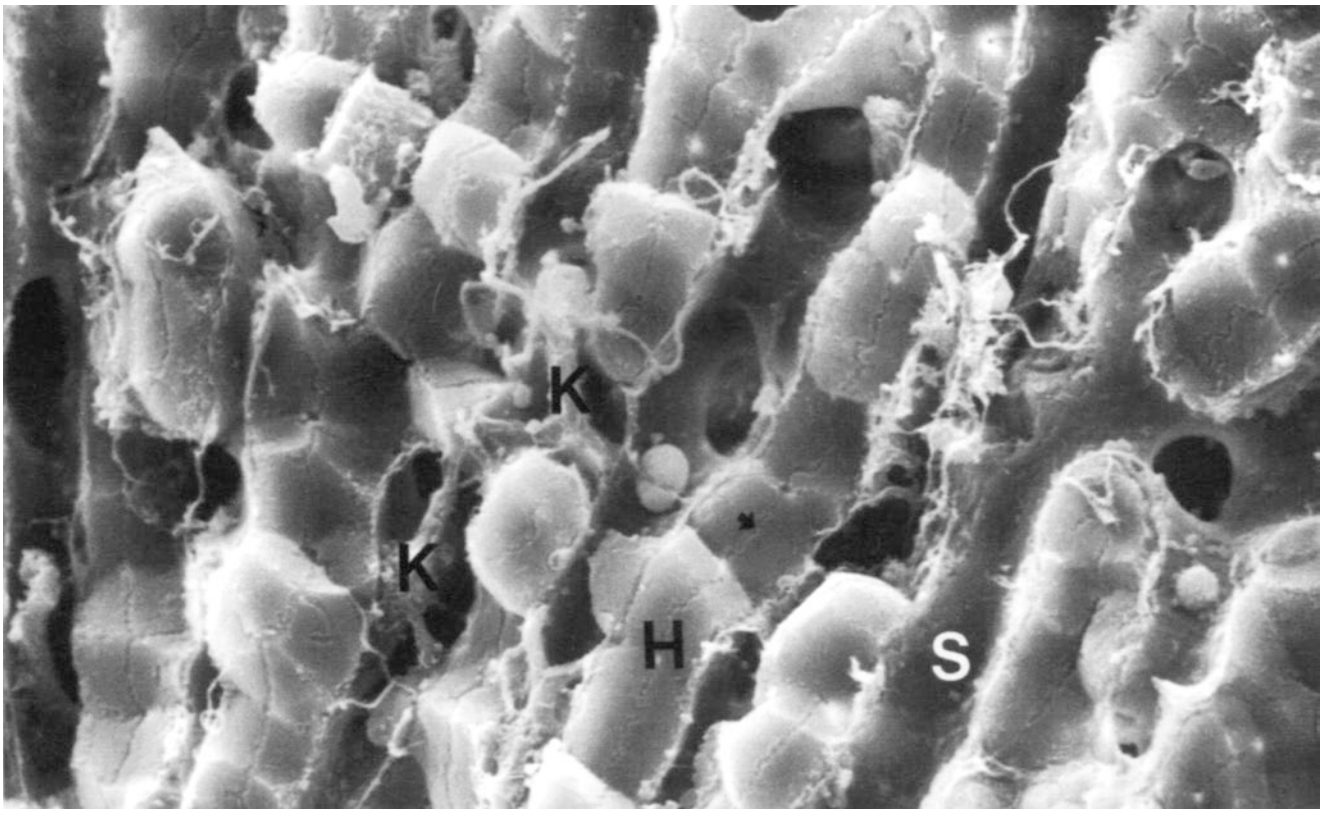

Fig. 16.3 (Sinusoid photo) Scanning electron micrograph showing rows of hepatocytes (H) adjacent to hepatic sinusoids (S) with bile canaliculi visible as small, winding grooves visible on the surface of some of the hepatocytes. (The cells designated K are kupffer cells, and are not discussed here.) (Reprinted from Schiff et al. [50]. With permission from Wiley)

tral vein (perivenular hepatocytes) can be isolated from one another, and their properties studied [17]. The hepatocytes in a liver lobule vary in their function, depending on their position along the path from the portal tract to the central venule. The generally uniform appearance of the liver under light microscopy does not accurately depict the highly specialized and tightly regulated functions of different hepatocyte populations (Fig. 16.4).

While the hepatic lobule describes structure, the concept of the liver acinus, first put forth by Rappaport [18], is related to hepatocyte function. Periportal hepatocytes have a higher oxygen content and perform different metabolic functions compared to perivenular hepatocytes. Rappaport called the periportal area, Zone 1, the perivenular area, Zone 3, with Zone 2 representing the intermediate area between Zones 1 and 3 [17, 18].

In their study on the microvasculature of the liver, Matsumoto and Kawakami found the organization of the vascular flow through the sinusoids is reflected in the precise detail seen on the microscopic level [19]. What might otherwise seem like a random flow of blood from the portal venules and hepatic arterioles into the liver parenchyma via the sinusoids is, in fact, a highly structured hemodynamic process which feeds the blood flow through the sinusoids in an organized fashion, with the resulting effluent flowing into the central hepatic venules [19, 20]. The results of their findings are congruent with the acinus concept, with periportal and perivenular hepatocytes performing different functions.

Zone 1 (Z1) is more highly oxygenated than Zone 3 (Z3) [17]. Many details of metabolism in Z1 and Z3 have been identified (Fig. 16.5), but there is much yet to be discovered. The details of this metabolic zonation can vary from time to time. Some of the driving forces have been identified, including oxygenation, pH, hormones, nutrients, metabolites, cytokines, and molecules called morphogens, the most well-known of which is named Wnt (beta) catenin, [17].

In summary, at the microscopic level of function, the complex processes of hepatic metabolism are proceeding and constantly adjusting to both what is delivered from the portal circulation and to inputs from the rest of the body, including hormonal signals and those from the autonomic nervous system.

16.4.7 Functions of the Liver

The liver is the most potent synthetic factory in the body and a significant organ for waste processing and disposal. See Table 16.1 for a summary of some of the important functions.

16.4.8 Xenobiotics

The term "xenobiotic" is derived from two Greek words, *xenos* meaning foreign or strange, and *bios* meaning life.

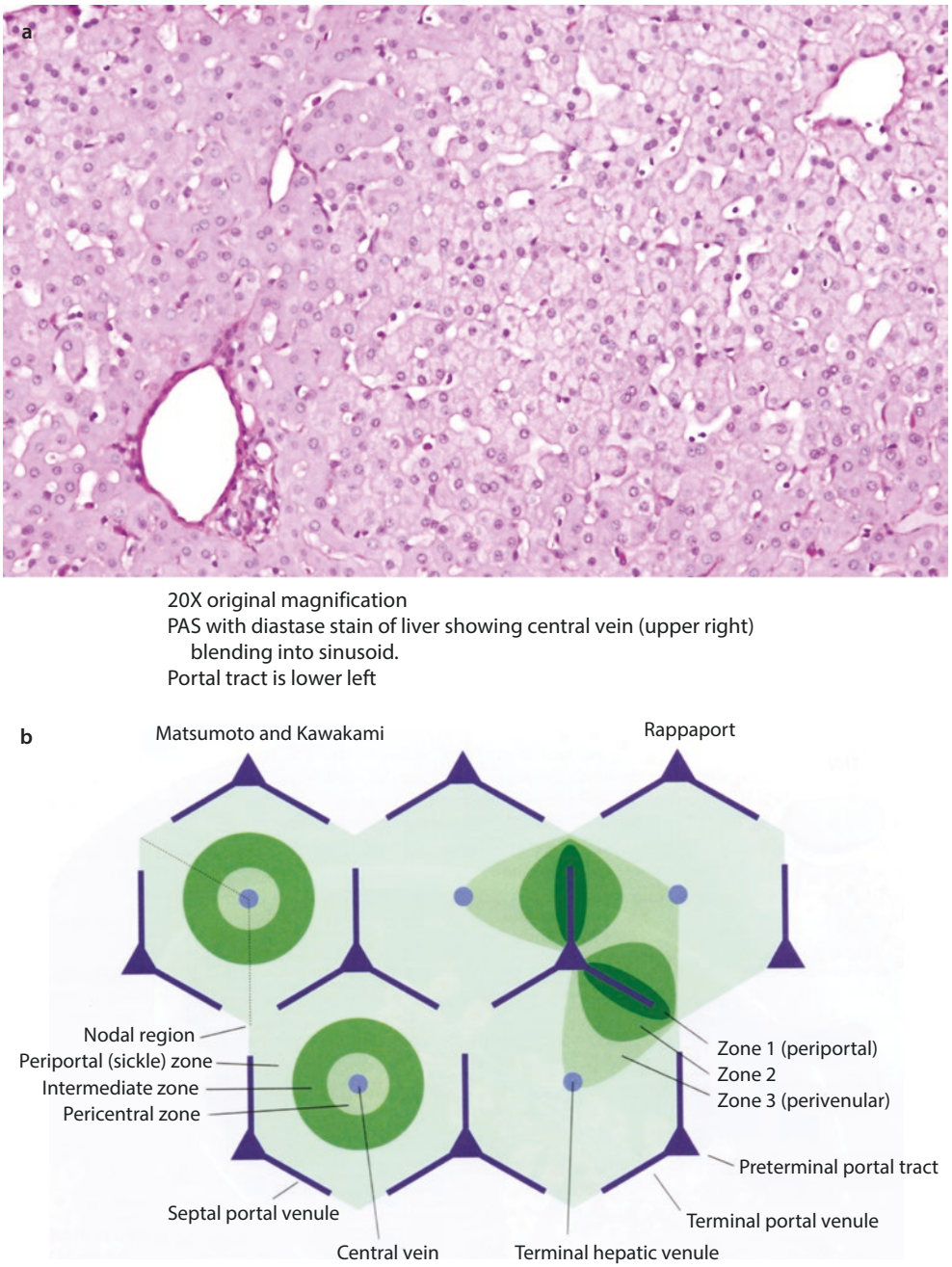

Fig. 16.4 [Hepatic lobule photomicrograph (**a**) and drawing (**b**)]. (**a**) Photomicrograph: Portal tract (lower left) and central venule (upper right) with sheets of hepatocytes interspersed with the intervening vascular sinusoids. Blood entering the liver through the portal tract flows into the sinusoids where it is processed and flows out of the liver through the central venule. Hepatic lobules typically consist of six portal tracts. (**b**) Diagram: Depiction of five classic hepatic lobules. Triangles correspond to portal tracts, from which blood flows to centrally located central venules; detailed microvascular work of Matsumoto and Kawakami contribute to concept of the hepatic acinus proposed by Rappaport; metabolic functions occur in these hepatic lobular structures. (**a**) (Courtesy of Beverly B. Rogers MD, Emory University School of Medicine). (**b**) (Reprinted from Schiff et al. [50]. With permission from Wiley)

Xenobiotic can be defined as a chemical compound foreign to a given biological system. With respect to animals and humans, xenobiotics include drugs, drug metabolites, and environmental compounds such as pollutants that are not produced by the body. In the environment, xenobiotics include synthetic pesticides, herbicides, and industrial pollutants that would not be found in nature [21]. For further information see ▶ Chap. 13.

An important functional distinction is that molecules absorbed from the small intestine and transported to the liver can be viewed as either "nutrients" or "xenotiobitcs". A nutrient molecule, once it reaches the liver, does not require further breakdown or processing to be used metabolically. Examples of nutrients include amino acids from proteins, monosaccharides from complex carbohydrates, and cholesterol. In the hepatocyte, nutrients can be used in synthesis of macromolecules (building blocks for the body), metabolized through the electron transport chain to produce ATP, and for other purposes.

A xenobiotic, on the other hand, must undergo a process called biotransformation. The products of biotransformation are excreted from the liver in the bile, or in a minority of cases, sent into the systemic circulation, where some accumulate in other organs including the brain, liver, lung, fat, kidney, and/or bone (See ◘ Table 16.2).

16.4.9 Where Are Xenobiotics Found?

We are exposed daily to many harmful environmental chemical toxicants. The Centers for Disease Control and Prevention

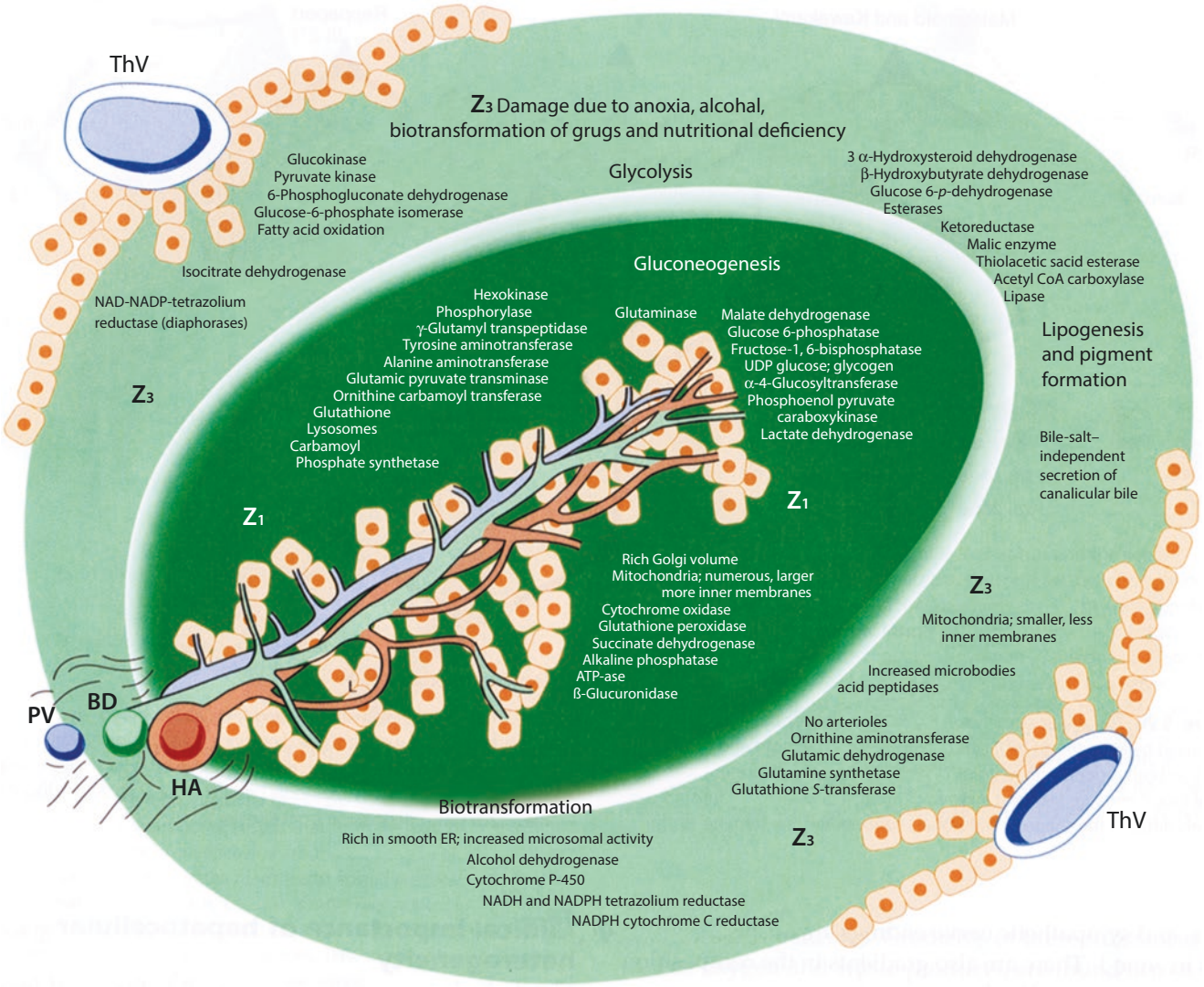

Fig. 16.5 (Schiff Z1 and Z3 characteristics) Diagram depicting some of the known metabolic processes occurring in Zone 1 (periportal) and Zone 3 (perivenular) of hepatic lobules. Zone 1, biosynthetic and energy producing processes; Zone 3, biotransformation enzymes which metabolize xenobiotics. Blood flowing from the portal tracts is first exposed to the hepatocytes in Zone 1, periportal areas, ultimately reaching Zone 3, the perivenular hepatocytes. (Reprinted from Schiff et al. [50]. With permission from Wiley)

(CDC) lists 265 environmental chemicals, many of which were shown to be present not just in the environment, but in the tissues of individuals studied [22]. It would be profitable for the reader to access the CDC report and scan through it to get a sense of the vast number of xenobiotics modern humankind is exposed to and understand this report gives only a partial listing. The report details xenobiotic exposures that may be present from multiple sources, including air, water, food, skincare products, and cleaning chemicals, and from a vast number of industrial sources that find their way into homes and the environment.

16.4.10 A Few Examples of Problems Caused by Xenobiotics

One of the first papers linking the harmful effects of environmental chemical exposures with fetal development was diethylstilbestrol which showed the exposed individual's subsequent risk in the development of vaginal cancer [23]. Subsequently, a consensus statement from the Wingspread Conference in 1991 began with this statement, "We are certain of the following: A large number of manmade chemicals that have been released into the environment, as well as a few natural ones, have the potential to disrupt the endocrine system of animals, including humans" [24]. One important approach to mitigating the problem of harmful xenobiotic exposures is addressing the liver's biotransformation enzyme systems, through which they are processed.

16.4.11 Biotransformation

In the liver, xenobiotics, that is any molecules not treated as a nutrient, are processed through the biotransformation enzymes [25]. These biotransformation enzymes are located

Table 16.1 Important functions of the enterohepatic circulation and the liver

Proteins (including albumin), lipids (fats, including cholesterol) and complex carbohydrates are synthesized and transported out of the liver
Production of ATP, the principle energy storage molecule in the body, via the electron transport chain
Bile acids formed and secreted into the biliary system; also perform metabolic functions within the hepatocytes
Glucose homeostasis occurs in the balance between gluconeogenesis (formation of the storage molecule glycogen) and glycolysis (release of glucose from glycogen)
Foreign substances (xenobiotics) are metabolized, mostly into nontoxic substances, which can be secreted into the bile or sent to long-term storage depots elsewhere in the body
Important communication functions carried out by hormones and the autonomic nervous system

Table 16.2 Classes of xenobiotics

Food additives
Pharmaceuticals
Environmental pollutants, including many categories of synthetic molecules
Heavy metals
Genetically modified foods; unless the GMO modifications produce nutrients, which are native to the human body, these foods fall into the category of xenobiotics

almost exclusively in the perivenular hepatocytes, Z3, in the liver acinus. Most xenobiotics are fat-soluble, serve no useful physiological purpose, and must be eliminated from the body. In most situations, this occurs in a two-step process.

Phase I biotransformation (detoxification) occurs in the smooth endoplasmic reticulum of the perivenular hepatocytes. Most commonly, once a xenobiotic molecule enters the hepatocyte, it encounters the cytochrome P450 enzymes, which convert the molecule into a highly energetic intermediate. These intermediates are then metabolized by Phase II biotransformation enzyme pathways. The names of these pathways are sulfation, glucuronidation, acetylation, methylation, amino acid conjugation, and glutathione conjugation [25].

The majority of the products of Phase II enzymatic reactions are secreted into the bile. A small percentage of the excretory products from the hepatocyte do not go into the bile; they are secreted back through the basolateral membrane into the sinusoid, from which they enter the systemic circulation and are carried to other organs and tissues. This most likely represents the pathway by which heavy metals (lead, mercury, cadmium, etc.) reach and are ultimately stored in other organs, such as the brain, kidney, lung, bone, and the liver itself. Please see ► Chap. 13 for more in-depth discussion.

16.4.12 Cytochrome P450 Genes and Enzymes

The cytochrome P450 enzymes (CYP 450) are numbered to indicate a specific group within the gene family, a letter indicating the gene's subfamily, and a number assigned to the specific gene within the subfamily. A specific CYP gene codes for the corresponding CYP enzyme. As of 2012, there were 57 human CYP enzymes, each with its specific propensity to metabolize certain categories of xenobiotics [25–27]. One example would be CYP 450 2D6, which is one of the cytochromes responsible for metabolizing hypertensive drugs. Another is CYP 450 2E1, which plays a role in the hepatotoxicity of acetaminophen. There has been extensive research into the CYP 450 genes and enzymes, and there are extensive references regarding the CYP 450 enzymes and xenobiotic metabolism [24, 26, 28, 29].

16.4.13 Single-Nucleotide Polymorphisms

Where there are genes, there are gene mutations. These mutations code for altered proteins with varying structures and activities. A common form of gene mutation is the single nucleotide polymorphism (SNP), in which a single nucleotide in a gene is changed, which may result in altered enzyme function. There are extensive publications on the effects of these polymorphisms on disease patterns and susceptibility and drug metabolism [30, 31]. There are more than 6000 review articles in the PubMed database detailing polymorphisms and their clinical effects.

In summary, if a healthy biologic system depends on the normal function of its enzyme systems, mutated genes and altered enzymes may have adverse effects on health. These consequences may vary from inconsequential to devastating. Perhaps nowhere else in the human body is the problem with mutated genes and altered enzymes more prevalent than in the liver's biotransformation enzyme systems, which critically impact xenobiotic transformation. Also important to understand is that while the biotransformation systems in the liver are vast, they are not infinite. If our purpose is to create health, the focus should be on feeding the system substances that are nutrients, not xenobiotics, and allowing the pathways in the liver to function as efficiently as possible. This requires optimizing nutrient intake and minimizing exposure to unnecessary xenobiotics. Improving the function of Phase II biotransformation in an individual patient should serve to eliminate, or to ameliorate the adverse health effects of many harmful xenobiotics.

16.4.14 Bile and the Biliary System

Bile is secreted from each hepatocyte into the bile canaliculus through a secretory process requiring energy [13]. Figure 16.5 shows a bile canaliculus as it travels along

adjacent hepatocytes on its way to the bile ductule in the portal tract. The bile ductules merge into the bile duct system, which transports bile out of the liver. Bile then flows down the common bile duct and through the sphincter of Oddi into the second part of the duodenum, where it mixes with intestinal content and begins its multifaceted function.

When there has not been a recent meal, the sphincter of Oddi is tightly closed, and the bile is diverted into the gallbladder. However, the gallbladder is more than a simple storage compartment. It concentrates bile and performs other important functions. When food is eaten, hormones, including cholecystokinin (CCK), are released, which cause gallbladder contraction, relaxation of the sphincter of Oddi, and a bolus of bile is released into the duodenum.

Bile is a micellar liquid. This means that the lipids/fats (cholesterol, phospholipids) and proteins secreted by the hepatocytes, when they reach a certain concentration in the bile, spontaneously form into round or cylindrical transport structures, which are carried in the ionic transport solution of the bile into the duodenum. Some molecules are carried in the micellar component of bile, some in the aqueous or liquid component. Bile contains bile acids which are essential to normal fat digestion, and have other metabolic properties. Bile is a potent antioxidant, and carries products from hepatic biotransformation out of the liver [32].

16.4.15 Small Intestine

The small and large intestines can be seen as the main digestive organs of the body (Fig. 16.6). The small intestine includes the duodenum, jejunum and ileum for a combined length of about 25 feet. The large intestine or colon is about 5 feet long. In the small intestine, proteins, carbohydrates, fats, vitamins, minerals and trace elements are processed, and the products of digestion are absorbed through the intestinal wall.

The inner lining of the small intestine contains circular folds called plicae, the surface of which is studded with leaf-or-finger like projections called villi. Enterocytes, the absorptive cells in the small intestine, make up 90% of the cells lining the villi [33]. The apical surface of each enterocyte faces the intestinal lumen and is itself further folded into microscopic tubular structures called microvilli. Because of the plicae, villi and microvilli, the absorptive surface of the small intestine which is exposed to food and other ingested material is vastly increased - about the size of a tennis court in an average adult.

Considering the large number and varied types of ingested substances presented to the lining of the small intestine, and the large surface area involved, the small intestine performs a monumental task of identifying toxins and pathogens, digesting nutrients, maintaining the barrier function of

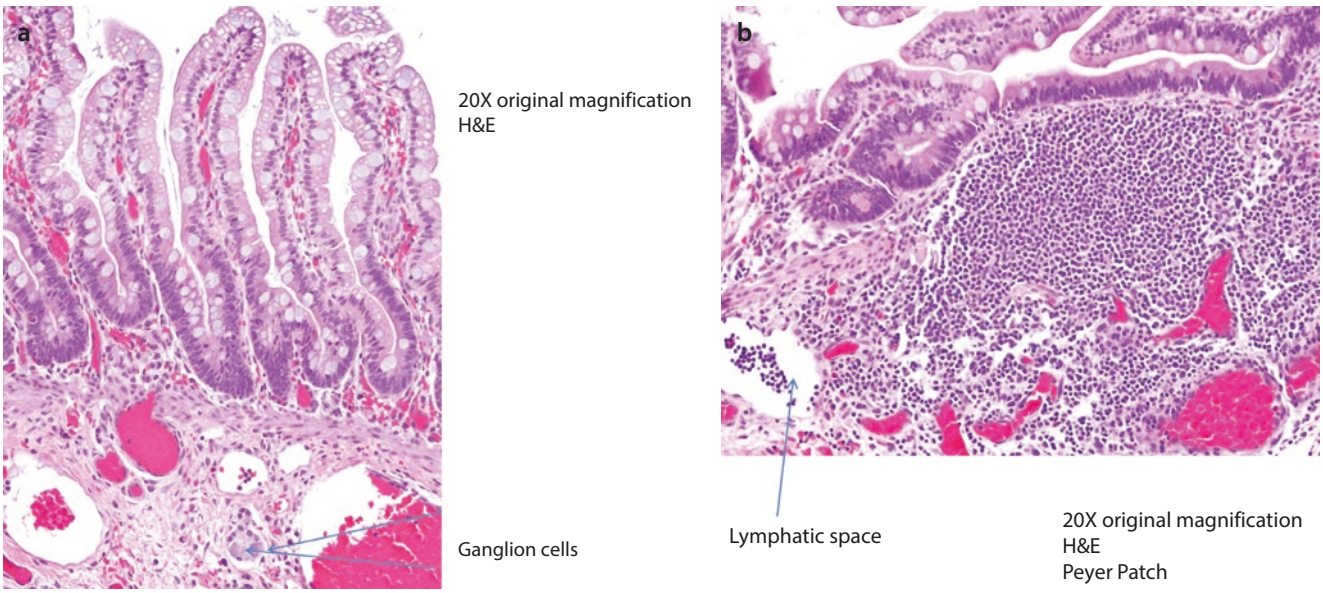

Fig. 16.6 Aspects of small intestine lining. (**a**) Photomicrograph of villi lining the mucosal surface of the small intestine. The predominant cell type is the enterocyte, through which nutrients and xenobiotics pass. Approximate surface area of the small intestinal lining in an adult is that of a tennis court, indicating the immense task of the enterocytes in distinguishing what should and should not be allowed to enter the submucosal space, and hence the portal circulation. Everything swallowed passes through the stomach into the small intestinal lumen, goes through processes of digestion, interacts with microbiome, and is sorted and evaluated, to determine if it will be allowed into the body or not. (**b**) Photomicrograph of submucosal lymphoid tissue known as a Peyer's patch, part of the GALT (gut-associated lymphoid tissue). Note lymphatic channels, and the capillaries which lead into the portal venous drainage. Fibers of the extensive enteric nervous system (the largest concentration of nervous tissue outside the central nervous system, and so called the "second brain" by some) are not visible in this exposure. Enteric endocrine cells (EEC), part of the intestinal lining, are likewise not specifically distinguished. (Courtesy of Beverly B. Rogers MD, Emory University School of Medicine)

the intestinal wall, and choosing which substances to allow to pass into the portal circulation.

16.4.16 Microbiome/Metabolome

After partially digested food from the stomach combines with bile and pancreatic secretions in the second part of the duodenum, it then passes into the jejunum and encounters the microbiome. In an average adult, the microbiome is four to five pounds of microorganisms which live in the lumen of the small and large intestines [34–37]. The microbiome begins to form immediately after birth. An infant's first stools are meconium, which is essentially digested amniotic fluid; cultures taken of meconium in healthy infants are sterile. Within a few days after delivery, microorganisms can be grown in culture. These microorganisms originate from the breast, skin, and secretions from the birth canal. Breast feeding promotes growth of *Bifidobacteria*, which have been associated with the healthy nature of stool flora in infants [38].

Bifidobacteria are well-known to be one of the more common probiotic species in the microbiome [38]. In adults, if the microbiome consists of healthy probiotic bacteria, such as *Lactobacillus*, *Bifidobacteria*, and others, this contributes significantly to healthy intestinal function and thus to the overall health of the individual. The microbiome assists in nutrient metabolism, protection against pathogens, processing of antigens and presenting them to the individual's immune system, processing of xenobiotics, and maintenance of a healthy barrier function of the intestinal wall [35]. However, if the constituents of the microbiome are pathogenic, the normal function of the microbiome is altered. The composition of the microbiome is affected by diet, antibiotics, stress, and other factors.

The term "Metabolome" refers to the multiple metabolic processes associated with the microbiome. There are more than 3000 articles referencing the metabolome, the first of which appeared in 2000 [39].

16.4.17 Enteric Nervous System

An important part of overall intestinal function is nerve cells in the wall of the small intestine forming a separate and intricate enteric nervous system (Fig. 16.7). There are multiple neuron types in multiple locations. These neurons communicate from one part of the intestine to another and back and forth with the central and autonomic nervous systems. There is bidirectional information flow between the ENS and the CNS and between the ENS and the sympathetic prevertebral ganglia [11, 12].

Sensory distress from the enteric nervous system can lead to symptoms such as nausea, bloating and pain. But most of the sensory signals from the intestine are not consciously perceived. The enteric nervous system has been called the second brain [40] because of its many functions and its vast numbers of neurons. There are more neurons in the enteric nervous system than anywhere else in the body except the central ner-

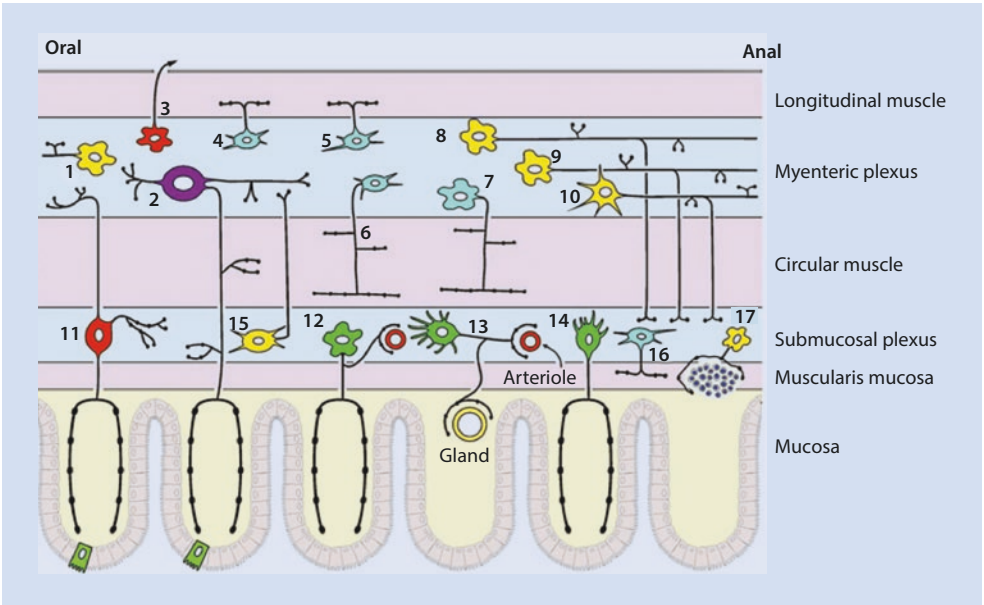

Fig. 16.7 Neurons found in small intestine defined by function, cell body morphology, chemistry, neurotransmitters, and projections to targets. Neuron types: (1) ascending interneurons; (2) myenteric intrinsic primary afferent neurons (IPANs); (3) intestinofugal neurons; (4) excitatory longitudinal muscle motor neurons; (5) inhibitory longitudinal muscle motor neurons; (6) excitatory circular muscle motor neurons; (7) inhibitory circular muscle motor neurons; (8) descending interneurons (local reflex); (9) descending interneurons (secretomotor and motility reflex); (10) descending interneurons (migrating myoelectric complex); (11) submucosal IPANs; (12) non-cholinergic secretomotor/vasodilator neurons; (13) cholinergic secretomotor/vasodilator neuron; (14) cholinergic secretomotor (non-vasodilator) neurons; (15) uni-axonal neurons projecting to the myenteric plexus; (16) motor neuron to the muscularis mucosa; (17) innervation of Peyer's patches not illustrated, motor neurons to enteroendocrine cells. (Adapted from Furness [51]. With permission from Wiley)

vous system. A number of commonly used phrases reflect this plentiful innervation of the GI tract, and its function in interacting with the central and autonomic nervous systems: "I knew it in my gut," "I had a gut instinct," or "the bowels of compassion."

16.4.18 Gut-Associated Lymphoid Tissue

The small intestine has the job of sorting out whether molecules presented to its lining cells are friend or foe, as everything ingested is not an ideal nutrient. Some substances can trigger allergic reactions while some are frankly toxic. Some molecules may be a known nutrient, but trigger the immune system to develop an autoimmune disease, the most well-known being celiac disease and the reaction to gluten/gliadin proteins [41].

The lining of the small intestine serves as a barrier between the outside world (ingested substances) and the body. This is called the intestinal barrier function, or the intestinal firewall [42]. Sometimes the function of the lining of the small intestine in forming a barrier to the outside world is compromised in various ways. Molecules may translocate or leak through the mucosal membrane by alternate pathways and can end up in the intercellular space below the mucosal lining enterocytes. This leads to increased intestinal permeability (referred to by some as "leaky gut") [43].

When non-nutrient molecules pass through the intestinal lining, the gut-associated lymphoid (GALT) system is stimulated. In the small intestine, GALT resides throughout the intestinal wall in vast numbers of microscopic collections of lymphoid tissue. In the distal small intestine and colon, these cell clusters occur in larger structures called Peyer's patches.

16.4.19 Enteric Endocrine Cells

There are more hormones produced in specialized cells of the small intestine than in any other organ in the body [44, 45]. Hormones are messenger molecules that convey various messages between cells, between different parts of the small intestine, and between the small intestine and other organs.

16.4.20 Terminal Ileum

The last 6 inches of the small intestine are structurally different from the rest. This segment is called the terminal ileum. Vitamin B12 is absorbed at this location [46]. In this segment, about 95% of the bile, which has remained inside the intestinal lumen to perform its functions, is reabsorbed and returned to the liver through the portal circulation. This absorption and recirculation of bile was the origin of the name "entero-hepatic circulation".

16.4.21 Large Intestine

The large intestine, or colon, begins in the right lower abdomen in a bulging pouch called the cecum. The terminal ileum empties into the cecum through the ileocecal valve (IC). The structure of the IC is such that it prevents reflux of contents from the cecum back into the ileum. The colon is approximately 5 feet long, and digestion and nutrient absorption are essentially complete by the time the intestinal contents enter the cecum. There is a vibrant microbiome in the colon [47, 48], and no doubt there are many metabolic functions yet to be clarified. One main role of the colon is reabsorption of water and electrolytes, preparing the stool to be passed from the body through the anus.

16.5 Conclusion

Based on the structure and function of the EHC, the ingestion of proper nutrients, possessing a healthy microbiome, maintaining an intact intestinal barrier function, and keeping exposure to xenobiotics to a minimum, the whole EHC system will function as it was designed. However, if the microbiome is unhealthy, if the intestinal barrier function allows toxic molecules to be taken up, or if there are insufficient nutrients or an overload of xenobiotics, the system will not function well. This is a reasonable place to begin in patient care. Using this paradigm and approach, patient care becomes conceptually simple: restore a healthy microbiome, restore a healthy intestinal barrier function, ensure delivery of proper and optimal amounts of nutrients, take into account biochemical individuality, and minimize harmful xenobiotics. The goal becomes identifying ways in which function deviates from this norm and taking steps to restore normal function. This is a vastly different approach from waiting until an identifiable disease develops and is diagnosed, then treating that disease with medication and/or surgery. In many cases the approach discussed above, based on correcting altered function, deals with the problem long before it forms.

Integrative nutritional care use is the closest approach to returning to the roots of human physiology and biochemistry and allowing these principles, along with patients' needs, to guide practice. In this approach, nutritional principles are applied first, along with other principles of a healthy body. Other healthcare disciplines are included in the treatment process as they are found to be useful; none are excluded. The conversations may include naturopaths, chiropractors, herbalists, nutritionists, homeopaths, acupuncturists – anyone who seems to have something to offer. At times, pharmaceuticals are needed. From the author's observation, integrative nutritional therapy is not just a new buzz-word or catch-phrase. It is not a new discipline, to be replaced at some point by another. It represents the closest paradigm found leading to understanding the principles of human physiology and allowing the use of nutrition to emerge from

that awareness. Integrative and functional nutrition properly applied leaves room for any approach, any discipline that has something to offer. With knowledgeable guidance and patient motivation, an immense amount can be accomplished.

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