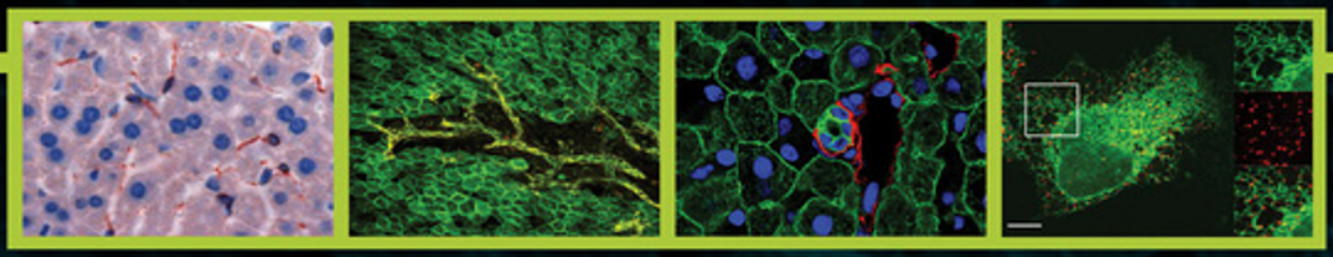
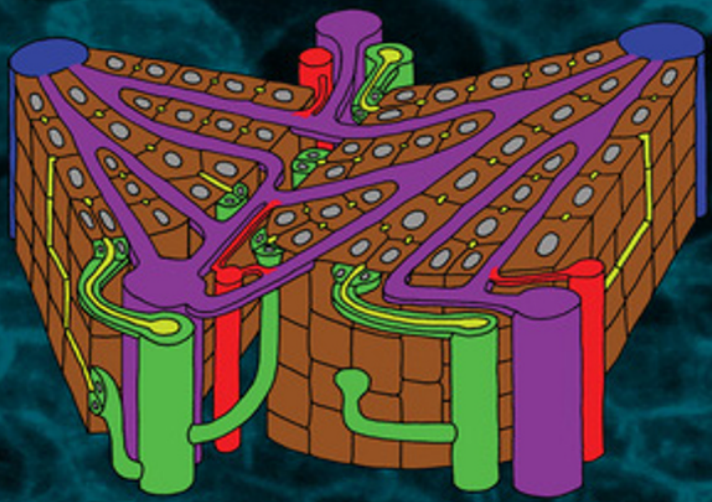


THE LIVER
BIOLOGY AND PATHOBIOLOGY

Sixth Edition



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The Liver

Dedication

This book is dedicated to Win Arias, whose enthusiasm, insight, and scientific rigor have served as an inspiration to several generations of investigators, providing the essential foundation and tools for building bridges between basic and clinical hepatologists as they elucidate together the mysteries of liver function in health and disease.

The Liver

Biology and Pathobiology

Sixth Edition

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Preface

The pace of discoveries in basic biomedical sciences and engineering and their application to diagnosis and treatment of liver disease continues to exceed greatly the expectations expressed in the Preface to the previous editions published in 1982, 1988, 1994, 1999, and 2009. Concomitantly, the challenge addressed by this book has not changed since first appearing in the Preface to the first edition over 30 years ago:

> *The amazing advances in fundamental biology that have occurred within the past two decades have brought hepatology and other disciplines into new, uncharted and exciting waters. The dynamic changes in biology will profoundly influence our ability to diagnose, treat and prevent liver disease. How can a student of the liver and its diseases maintain a link to these exciting advances? Most physicians lack the time to take post-graduate courses in basic biology; most basic researchers lack an understanding of liver physiology and disease. This book strives to bridge the ever-increasing gap between the advances in basic biology and their application to liver structure, function and disease.*

Molecular biology was not the only great wave in contemporary science, nor is it surely the last. Remarkable advances in genetics and various omics are increasingly linked with dynamic super-resolution light microscopy, which permits the study of cellular, molecular, and organ-based physiology at nano-levels. The expanding worlds of RNA structure and function, CRISPR-type gene editing, and chromatin biology coupled with single-cell and single-molecule genomic analyses are facilitating discoveries with great importance in organ physiology and medicine, including personalized diagnosis and treatment. Unexpected discoveries are certain to emerge from the ongoing bridge-building between chemical and physical structural analysis, engineered drug design, signaling networks, immune mechanisms and tolerance, the brain, and metabolic/digestive functions. Discoveries in these disciplines have already facilitated diagnosis, treatment, and improved clinical outcome of many liver diseases. Much more is undoubtedly yet to come.

This sixth edition contains new chapters that present major progress that has been achieved in research laboratories and clinics around the world. All other chapters have been completely revised and updated. Following the death of our colleague Nelson Fausto, Snorri Thorgeirsson became an Associate Editor. Previous editions included a section called "Horizons," devoted to extraordinary advances in areas of potentially major importance to the liver. Virtually all of these fields have rapidly expanded and become topics for later chapters. Sixteen new "Horizons" chapters are presented in this edition. One may safely predict that their impact on the field of hepatology will be considerable. As stated in the Preface to previous editions:

> *The amazing advance in science proceeds at an ever-increasing pace. The implications for students of liver disease are considerable. The authors and editors will have achieved our goals if the reader finds within this volume glimpses into the current state and future direction of our discipline and perspectives that lead to better understanding of liver function and disease.*

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Harvey J. Alter
James L. Boyer
David E. Cohen
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Allan W. Wolkoff

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PART ONE:
INTRODUCTION

1 Organizational Principles of the Liver

Peter Nagy[1], Snorri S. Thorgeirsson[2], and Joe W. Grisham[3]

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PRINCIPLES OF LIVER STRUCTURE AND FUNCTION

The liver is the largest organ of the mammalian body and has a highly versatile and complex function. Its specialized role is shown by the fact that, despite intense efforts, the activity of the liver cannot be replaced by artificial equipment. The liver participates in the maintenance of the organism's homeostasis as an active, bidirectional biofilter. It is classed as bidirectional because it filters the portal blood that transports nutritional and toxic compounds from the environment through the gastrointestinal tract and also filters the systemic blood (the body's own products, e.g. bilirubin), providing the only channel of the body, the biliary system, through which non-water-soluble substances can be removed. It is classed as an active filter because it rapidly metabolizes most nutritional compounds and neutralizes and prepares for removal toxic exogenous (xenobiotics) and endogenous (worn out) materials. Because of these major functions the liver is constantly exposed to intense microbiological and antigenic stimuli which require function of the innate and adaptive immune systems. These diversified functions are executed by a structurally complex, multicellular tissue with a unique angioarchitecture, and by the combined and integrated activities of the participants.

There are only two unique cell types in the liver – hepatocytes and biliary cells (or cholangiocytes). The hepatocytes are "the most valuable" parenchymal cells of the hepatic tissue. They do not constitute a homogeneous cell population. They are highly polarized cells (i.e. molecular specializations of the various surface membranes, including receptors, pumps, transport channels and carrier proteins) and their functions and to a certain extent morphology depend on their location in the parenchyma. This polarization makes the hepatocytes the logical center of the liver. In addition, they perform the most complex metabolic tasks of the mammalian organism.

The cholangiocytes form the channels that constitute the biliary system, which drains the parenchyma and guarantees the permanent flow of the bile, a highly toxic solution. Cholangiocytes also modify the composition of the bile and, in case of adverse conditions, can participate in repair mechanisms. These liver cells could not carry out their specific functions, of course, without the support of several "communal" cell types, which are highly adapted to the special function and architecture of the liver. The endothelial cells of the parenchyma have a unique fenestrated structure and various different subpopulations can be distinguished. There are several subpopulations of hepatic myofibroblasts as well. In addition to their mechanical functions the myofibroblasts can store special substances (e.g. vitamin A in stellate cells) and are a major source of growth factors and cytokines. The Kupffer cells are the resident macrophages in the liver. In addition to filtering the blood, they perform their traditional immunregulatory function. The presence of almost all subtypes of lymphocytes and dendritic cells makes the liver the largest organ of the immune system. The mesothelial cells of the Glisson capsule are, beside their mechanical function, an important source of lymph production and can contribute to the generation of other hepatic cell types. The features of the hepatic extracellular matrix are unique. The components of the basement membrane are present around the sinusoids in an "unstructured" fashion, and cannot be detected by electron microscope, yet they can perform certain functions.

Another fundamental feature of liver organization is its unique vascular pattern. Two afferent vessels supply blood to the liver: the portal vein and the hepatic artery. The blood of the portal vein, having already "drained" the stomach, gut, pancreas, and spleen, is reduced in oxygen and pressure, and is

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enriched in nutrients and toxic materials absorbed from the alimentary tract and in viscerally generated hormones and growth factors. The arterial blood of the hepatic artery has systemic levels of oxygen, pressure, and composition. The major function of the hepatic artery is to supply the peribiliary vascular plexus, the portal tract interstitium, the hepatic capsule, and the vasa vasorum of major vessels. In some species, the hepatic artery forms anastomosis with the branches of the portal vein, but even then this blood also ends up in the sinusoids. The blood of the liver is collected by one efferent draining system, the hepatic or "central" veins, which reach the systemic circulation via the inferior vena cava. The sinusoids form a very special vascular system, which is interposed between the afferent and efferent vessels. The large number and capacity of the sinusoids and the special arrangement of the supplying vessels provide a large volume of blood at a high flow rate via the large vessels with high compliance and capacity. At the same time the sinusoids are perfused with blood at low pressure and flow rate. These arrangements (i.e. low flow, specifically fenestrated (perforated) endothelial cells, and the lack of the structured basement membrane) provide an especially efficient communication between the blood and hepatocytes. This is well illustrated by the pathological condition of liver cirrhosis, when the changes in hemodynamic condition (i.e. the "capillarization" of the sinusoids) disrupts this communication, resulting in severe dysfunction of the liver.

Bile acids and their enterohepatic circulation are another good example of the cumulating functions. The bile acids are synthetized in the hepatocytes by a complex biochemical process that requires 16 different enzymes, which are further modified by the gut microbiota. The primary physiological function of the bile acids is to convert lipid bilayers into micelles. This makes possible the excretion of important waste products from the blood. The bile acids also emulsify elements of the food in the gut and aid their absorption. In addition, bile acids act as signaling molecules, synchronizing the cooperation of the liver and gut.

The different types of cells and vessels mentioned above can operate only if they are organized in a well "designed" structure. The most widely studied and analyzed morphological and functional unit or module of the liver is the hepatic lobule. The popularity of this structure for studies can be partly explained by the fact that lobules are outlined nicely in some species (pig, camel, bear) by connective tissue septa, and can therefore be easily recognized on the two-dimensional histological sections commonly used in structural studies. The idealized lobule has a polygonal (usually hexagonal) shape. The terminal branch of the hepatic vein (central vein) is in the center of the lobule while the corners are occupied by the "portal triads." The components of the triad are the interlobular bile ducts and the terminal branches of the portal vein and hepatic artery. The blood carried by these afferent vessels is distributed by the inlet venules and arteries along the virtual "vascular septa." This vascular frame is filled up columns (or sheets in three-dimensional space) of the hepatocytes constructed as "plates" arranged in a radial fashion. The hepatic plates are separated by the similarly distributed sinusoids. The blood runs in a centripetal direction from the vascular septa to the central vein. The vascular septa secure the mixing of the portal venous and arterial blood and the more-or-less equal supply to the sinuses. The bile produced by the hepatocytes runs in a centrifugal direction in the bile canalicules formed by neighboring hepatocytes and is collected by the interlobular bile ducts of the portal triads. There is thus a countercurrent between the flow of the blood and bile at lobular level.

FUNCTIONAL ANATOMY OF THE LIVER

Macroanatomy

The liver is a continuous sponge-like parenchymal mass penetrated by tunnels (lacunae) that contain the interdigitating networks of afferent and efferent vessels [1]. The adult human liver weighs from 1300 to 1700 g, depending on sex and body size. It is relatively small compared to other species (2% of the body weight) – in rat and mouse the liver is 4–5% of the body.

In most mammalian species the liver is multilobed, the individual lobes reflecting the distribution of the major branches of afferent and efferent blood vessels. In contrast, the human liver parenchyma is fused into a continuous parenchymal mass with two major lobes, right and left, delineated only by being supplied and drained by separate first- and second-order branches of the portal and hepatic veins. Right and left lobes are topographically separated by the remnants of the embryonic umbilical vein (the falciform ligament), but this landmark does not locate the true anatomic division. Anatomically, the medial segment of the left lobe is located to the right side of the falciform ligament, centered on the anterior branches of the left portal vein. Interdigitation of first- and second-order branches of the portal and hepatic veins produces eight macrovascular parenchymal segments centered on large portal veins and separated by large hepatic veins [2]. Hemodynamic watersheds or fissures separating afferent and efferent macrovascular segments permit the surgical resection of individual or adjacent segments.

Liver transplantation and surgery has reached such a complexity, however, that the traditional eight-segment scheme is no longer sufficient. Detailed histological and imaging investigations have revealed that the number of second-order branches given off by the left and right portal veins is much higher, and the mean of their number is 20, leading to the "1–2–20" concept of portal venous segmentation [3]. The recognition of the watershed septa between the variable actual segments is helped by intraoperative imaging techniques in real operative situations.

Microanatomy

Normal liver function requires the unique arrangement of basic components of hepatic tissue: portal vein, hepatic artery, bile duct, hepatic vein, and hepatocytes. These form in two-dimensional sheets the above-mentioned hepatic (classical of Kiernan's) lobules. Profiles of portal tracts and hepatic veins of various sizes are a prominent feature of liver histology [4–6]. Smaller branches of the afferent and efferent vessels (together with their stromal components) predominate in tissue sections taken from peripheral, subcapsular locations, whereas tissue sections taken from more proximal areas nearer to the hilum contain larger vascular structures [6]. These vascular/stromal elements are contained in tunnels (lacunae) that penetrate the

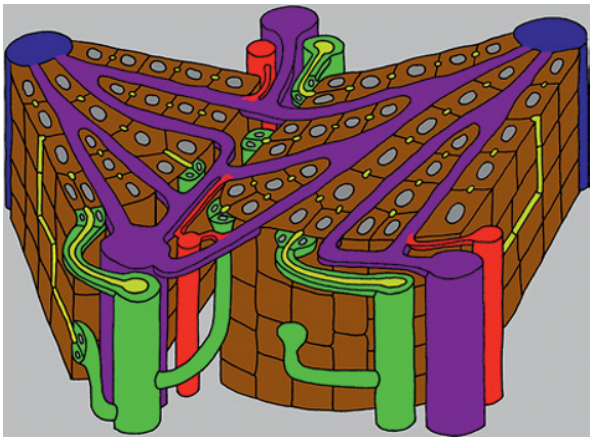

Figure 1.1 Schematic drawing of the organization of blood vessels (arteries, red; portal veins, purple; central veins, blue; bile ducts, green; lumen of the biliary channels, including bile canaliculi, yellow) in two adjacent lobules of human liver. One sixth of a lobule is visible on the right and one third of a lobule is visible on the left. A terminal portal venule, arteriole, and bile ductule (canal of Hering) are present in the vascular septum between the lobules. The arteriole is connected directly to the sinusoids or enters the inlet venule. Bile is drained over the whole surface of the lobule. Arterioles and bile ductules are not present in the vascular septum in rodents. The bile is drained through canals of Hering connected to hepatocytes of the limiting plate. The arterioles anastomose with the portal system at higher level as well. Courtesy of Sandor Paku, Semmelweis University, Budapest, Hungary.

parenchymal mass [4]. The hepatocytes arranged in plates fill in the space between the portal tracts and hepatic veins (Figure 1.1). The hepatic plates form brick-like walls (muralia) of hepatocytes one cell (one brick) thick. The first hepatocytes of the hepatic plates form a virtual barrier between the periportal connective tissue and the liver parenchyma called a limiting plate.

The blood vessels and their investments of connective tissue provide the soft, spongy liver with its major structural support, or "skeleton." Larger afferent vessels, portal veins, and hepatic arteries are contained together with bile ducts in connective tissue – the portal tracts – which are continuous with the mesenchymal components of the liver's mesothelium-covered surface capsule (Glisson's capsule). Portal tracts also contain lymphatic vessels, nerves, and varying populations of other types of cells, such as macrophages, immunocytes, myofibroblasts, and possibly hematopoietic stem cells (see [7] and references therein). The collagenous investment of the efferent vessels is less robust and lacks large numbers of adventitious cells.

The hepatic artery is distributed to the tissues of portal tracts, the liver capsule, and the walls of large vessels [4–6]. In portal tracts arterial branches form a capillary network (the peribiliary plexus) arborized around bile ducts [8, 9]. Efferent twigs from the peribiliary plexus empty into adjacent portal veins in rat and mouse but not in human and hamster [10]. The portal vein supplies blood to the parenchymal mass through the so-called inlet venules [9, 11].

In histological sections of mammalian liver, afferent and efferent vessels interdigitate regularly in an approximate ratio of 5–6 portal tracts for each profile of a hepatic vein, to form a pattern of cross-sections of portal tracts and hepatic veins separated by parenchyma [5, 6]. Most of the cross-sectioned portal tracts contain preterminal hepatic venules. These vessels represent the seventh- to tenth-order branches from the hilar portal vein in large mammals, such as humans. These small portal tracts and hepatic (central) veins penetrate the parenchyma in nearly parallel orientations about 0.5–1.0 mm apart. The portal inlet venules are very short vessels with no smooth muscle in their walls. They branch from preterminal and terminal venules at points on the circumference of the lobules at about 120 radial degrees (triradial branching) and penetrate the parenchyma together with terminal arteriolar branches approximately perpendicular to and midway between two adjacent terminal hepatic venules [5, 6]. During their course through the parenchyma portal inlet venules break up completely into sinusoids, which are oriented more or less perpendicularly to the veins. Because they are hardly larger than sinusoids, the inlet venules are not conspicuous in humans and other mammals that lack a definite connective sheath around them. However, in adult swine their course through the parenchyma is clearly marked by connective tissue.

Capillary-size sinusoids occupy the smallest and most numerous tunnels (lacunae) in the parenchymal mass [4]. Unlike capillaries elsewhere, liver sinusoids are composed of endothelial cells that are penetrated by holes (fenestrae) and lack a structured basal membrane [12], features that allow free egress of the fluid components and solutes of the perfusing blood. For example, tagged albumin has access to a space in the liver that is about 48% larger than the sinusoidal volume, in contrast to other tissues in which capillary space and albumin space are nearly the same [13]. In favorably oriented histological sections, more or less parallel, longitudinal profiles of sinusoids alternate with hepatic plates [14]. A narrow cleft, called the space of Disse, separates sinusoids from hepatocytes located in adjacent hepatic plates [12, 15]. At their proximal (portal venous) ends, sinusoids are narrow and somewhat tortuous, whereas their middle and distal (hepatic venous) portions are larger and straighter [9, 16, 17]. Sinusoids and hepatic plates are disposed radially around the draining hepatic veins and extend directly to the supplying inlet venules [17].

Three-dimensional reconstruction of the interlobular zone revealed the existence of a small vessel in this plane, the vascular septum, that serves as a starting pool for intralobular sinusoids. This is a hemodynamic barrier, a "watershed" between the two neighboring lobules. This "interlobular" septum contains connective tissue matrix in pig, camel, bear, etc. and outlines the lobules nicely; it also exists in a rudimentary form in human liver [18].

The bile – the excretion product of the hepatocytes – is collected and transported in bile canaliculi, which are formed by the apical sides of two adjacent hepatocytes in the hepatic plate. The network of canaliculi is drained into the interlobular bile ducts through interface structures called canals of Hering. These are intermediary structures constructed partly by hepatocytes or cholangiocytes (Figure 1.2). Since these structures are the primary candidates to harbor the hepatic stem cell compartment, they are the subject of intensive investigations [19]. The distribution of canals of Hering shows variation among different species. They are characterized by a distinct ($EMA^-/CD56^+/CD133^+$) immunophenotype in humans, leave the periportal space and spread into the parenchyma along the rudimentary interlobular septa, and thus do not enter into the hepatic lobule [18].

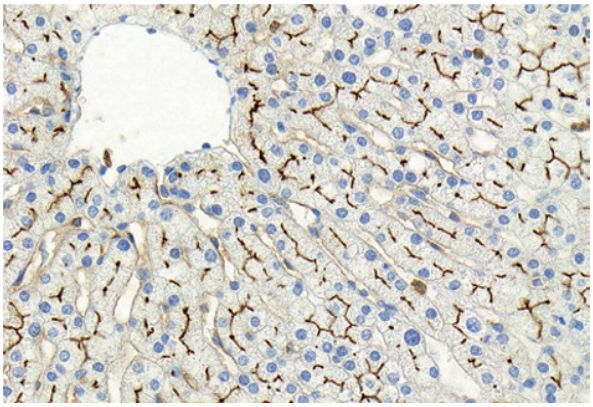

Figure 1.2 Normal human liver stained for CD10. The hepatocytes form trabeculae, 1–2 cells thick, radiating from a central vein. CD10 is expressed on the canalicular domain, indicating the polarization of the cells. Courtesy of Sandor Paku, Semmelweis University, Budapest, Hungary.

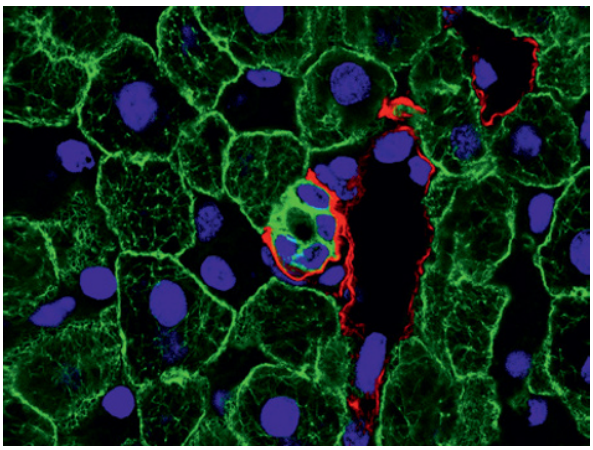

Figure 1.3 Normal rat liver stained for pankeratin (green) and laminin (red), the nuclei are labeled by TOTO (blue). There is a cross-section of a canal of Hering beside a small portal vein. The cytoplasm of the cholangiocytes is strongly positive for keratin and these cells are outlined by laminin (basement membrane) but basement membrane is absent at the pole where the ductile is connected to an adjacent hepatocyte. Courtesy of Sandor Paku, Semmelweis University, Budapest, Hungary.

The interlobular bile ducts are lined by a single layer of cuboidal cholangiocytes (Figure 1.3). They anastomose and unite larger septal and hilar branches. The connective tissue around the largest biliary branches contain peribiliary glands which also secrete into the biliary tract (Figure 1.4).

Teutsch and coworkers [20, 21] analyzed serial sections of rat and human livers to reconstruct the three-dimensional structure of hepatic tissue. Although there were differences between the two species, the basic arrangement was similar. The reconstruction revealed primary "modules," which constructed a more complex "secondary" module. The integration was based on a common drainage by branches of the hepatic veins and supplying portal veins, and the modules were covered by continuous vascular septa. The primary modules correspond to the two-dimensional hepatic lobules. Quite a substantial variation in the shape and size of the modules was found, which provides morphogenetic plasticity to construct the whole organ. This

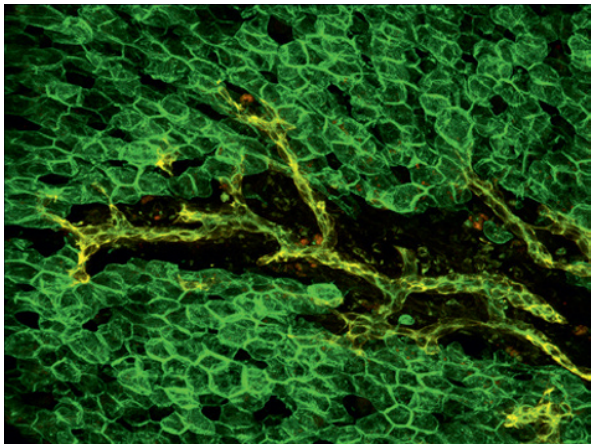

Figure 1.4 Normal human liver stained for pankeratin (green) and keratin 7 (red). The dark lane in the center represents an interlobular vascular septum. The double positive (yellow) biliary ductules have several connections with the limiting hepatocytes but do not enter into the lobules. Courtesy of Sandor Paku, Semmelweis University, Budapest, Hungary.

modular arrangement can improve the interpretation of lesions, especially in pathologically altered livers, but it is certainly not easy to transform the two-dimensional observations into three-dimensional space.

Functional unit of the liver

The concept of the primary functional unit of the liver has been the subject of debate for more than 350 years since its description by Wepfler in 1664 [22]. The first and most widely accepted traditional unit of the liver is "Kiernan's lobule" [23], as described earlier. This is the efferent microvascular segment, being the smallest unit of parenchyma that is drained of blood by a single efferent (terminal hepatic or central) vein. It is quite easy to identify it, especially in species where they are outlined by connective tissue. The major criticism of the concept is that the terminal afferent vessels through the vascular septa contribute to the blood supply of adjacent lobules, and therefore the lobule cannot be a "basic functional unit." Rappaport defined the basic unit as the compartment of the hepatic parenchyma supplied with blood by a single terminal portal vein and called this unit the "liver acinus" [24]. Now we know that this unit is also supplied by a single terminal branch of the hepatic artery. The simple acinus is a parenchymal mass around a portal tract and it is drained by more hepatic venules. The acinus is subdivided into three zones, based on the distance from the portal vein. The distribution of these areas fits to the functional zonality of the hepatic parenchyma. Pathological lesions (e.g. steatosis or necrosis) also often follow this zonal pattern, which made this unit attractive. However, this zonality did not correspond perfectly to the distribution of enzyme activities and the hepatic modules described by Teutsch [20, 21] were also not compatible with the concept of the acinus.

Matsumoto and his colleagues [6] investigated the angioarchitecture of the human liver on thousands of serial sections, distinguishing conducting and parenchymal portions of the portal venous tree. A cone-shaped parenchymal portion (primary lobule) was defined which was supplied by a terminal portal venule.