PORTAL HYPERTENSION

Pancreatitis and Its Complications, edited by Chris E. Forsmark, 2004

Acute Gastrointestinal Bleeding: Diagnosis and Treatment, edited by Karen E. Kim, 2003

Inflammatory Bowel Disease: Diagnosis and Therapeutics, edited by Russell D. Cohen, 2003


Chronic Viral Hepatitis: Diagnosis and Therapeutics, edited by Raymond S. Koff and George Y. Wu, 2001

The past several years have seen a logarithmic increase in progress in the field of portal hypertension, both in clinical management as well as in pathobiology. For example, the implementation of beta-blockers in the primary and secondary prophylaxis of variceal hemorrhage and the establishment of endoscopic variceal band ligation in the management of acute variceal hemorrhage have become mainstays of clinical management of patients with portal hypertension. From a scientific standpoint, discoveries such as the elucidation of the hepatic stellate cell as a contractile sinusoidal effector cell and the understanding of nitric oxide as a key mediator of vascular responses have provided a cellular framework for the pathogenesis of portal hypertension. However, these discoveries and treatment advances are just the tip of the iceberg, with new therapies and pathogenic principles coming under scrutiny and likely to reach fruition in the years to come.

In this spirit, we hope that *Portal Hypertension: Pathobiology, Evaluation, and Treatment* will provide useful information for individuals actively engaged in the investigative aspects of portal hypertension, as well as clinicians who care for patients with portal hypertension throughout the world. The goal of this text is to provide scientific updates from leading portal hypertension researchers on key topics relating to the clinical and basic investigation of portal hypertension, as well as to provide input from leading portal hypertension clinicians regarding the revaluation and management of specific clinical circumstances relating to portal hypertension. We have garnered contributions from experts throughout the world, consistent with the global contributions that have been made in the field of portal hypertension.

We hope that the readership finds *Portal Hypertension: Pathobiology, Evaluation, and Treatment* useful as a reference as well as enjoyable as a cover-to-cover read!

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I

HISTORICAL PERSPECTIVE
The term portal hypertension or, more strictly, portal venous hypertension, refers explicitly to a pathologic elevation of pressure in the veins that carry blood from the splanchnic organs (including the spleen) to the liver. Implicit in the working definition of portal hypertension is the necessary condition that the rise in portal pressure is not simply a consequence of an increase in systemic venous pressure, as might occur with congestive heart failure for example, but is intrinsically part of an increase in the pressure gradient between the portal venous inflow to the liver and its hepatic venous outflow. Increased pressure in the hepatic veins from any cause, such as hepatic vein thrombosis, a suprahepatic inferior vena cava web, right heart dysfunction, constrictive pericarditis, or any other comparable anatomic and/or functional lesion, elevates portal pressure above its normal baseline value and can cause splenomegaly and ascites. Notwithstanding, without secondary structural changes in the liver, however subtle, portal pressure elevation that is solely caused by impaired hepatic venous drainage does not lead to the formation of esophagogastric varices and the other pathophysiologic complications of an increased portal–systemic pressure gradient that are discussed in detail in this book.

It is now self-evident that in health splanchnic blood percolates from the portal vein through low-resistance intrahepatic vascular channels (sinusoids) to the hepatic veins—but this was not always conventional wisdom. Ideas about the splanchnic and hepatic vascular architecture and blood flow have evolved over millennia (1), as have concepts of the nature of portal hypertension (2), although the time frame for the latter is only a couple of hundred years at most.

Recognition that the liver is a highly vascular organ dates back more than 30,000 yr to Paleolithic times, as shown by the remarkable cave art of prehistoric hunters found at Lascaux in Southern France (3) and at other sites. The ancient Egyptians also must have noticed the bloody content of the livers that they so carefully preserved for the next world, along with other vital organs of their departed nobility and deceased privileged
classes. Conversance with the vascularity of the liver was also common among people of antiquity in the Mediterranean basin and the Near East, who practised the now lost art of *haruspicy* or divination of the future by scrutinizing livers from sacrificed animals. Egyptian physicians, however, were the first to record a description of the hepatic vasculature that they thought consisted of four veins (4) but, like Diogenes, Hippocrates, and Aristotle in the 4th and 5th centuries BCE in Greece, and Galen in 2nd century CE Rome, they got it wrong. Aristotle was confused about the portal vein, for he thought that the vena cava supplied blood to the liver from above and that the liver and spleen were connected by veins to the right and left arms, respectively (5), permitting targeted phlebotomy for the ill *humors* of those organs. For Galen and his contemporaries and followers, in contrast, the liver was the “*fons venarum,*” the source of the major veins of the body and the “*sanguifactionis officina,*,” or the “factory of the blood,” the site of sanguification. Galen did recognize that veins from the mesentery entered the “*porta hepatis*” or gateway of the liver on its concave side (6), in his belief bringing digested food from the intestines to be converted into blood in the liver by “*(con)coction*” (*pepsis*), with separation of light, yellow bile that is excreted by way of the bile ducts and gallbladder and heavy, black bile that passes via the spleen to the stomach; the residue remained in the intestine to be voided. Galen reported the insightful view of Erasistratus of Chios, an Alexandrian scientist of the 2nd century BCE, who reasoned that there must be a labyrinthine system of channels in the liver connecting the portal vein to the vena cava (7), to allow the blood to pass through. In many respects, Galen was a bitter critic of his Alexandrian predecessor (8), who flourished 400 yr earlier (9) and who, with his contemporary Herophilus of Chalcedon (10), founded the Alexandrian school of anatomy that was based on dissecting human corpses. Galen disapproved of Erasistratus’s materialism and his dependence on morphology as the only indication of an organ’s function.

After the fall of Rome in 476 CE, and with it the decline of Greco-Roman civilization and learning, there were no advances in understanding the anatomy and function of the liver, nor indeed anatomy in general, until the Renaissance dawned one thousand years later. Throughout the Dark Ages, from the 5th to the 10th century CE, and even in the latter half of the Middle Ages, the views and schemes of Aristotle and Galen were preserved in the East in the Byzantine Empire and in the Arabic (Islamic) culture. In the West, with its religious preoccupation with death and salvation, the soul was more important than the body in which clerics and philosophers sought its haven. The graphic demonstrations of bodily structures by Leonardo da Vinci in the 15th century (11) and Andreas Vesalius in the 16th century (12) exemplified the revival of interest in anatomy but it was not until William Harvey’s publication in 1628 of his discovery of the circulation of the blood (13) that the Galenic perspective of the vasculature of the liver was seriously challenged. Harvey reasoned that if blood could pass through a dense organ like the liver, from the portal vein to the vena cava, seemingly without any local propulsive force, then blood could surely flow through the delicate spongy lungs driven by the contractions of the heart’s right ventricle. Yet it took a mere 1900 yr before Erasistratus’s hypothesis of transhepatic blood flow was conclusively proved empirically by Francis Glisson (1597–1677) (14), then Regius Professor of Physic at Cambridge, cofounder of the Royal Society, and one-time President of the Royal College of Physicians of London. Using an ox bladder attached to a syphon, such as was used in those days to administer enemas, Glisson injected “warm water, coloured with a little milk” into the portal vein of a fresh human cadaver, and found that the liver blanched when all the blood in it was expelled. With this demon-
stration, Glisson not only vindicated Erasistratus and his theory of intrahepatic vascular channels, but he also provided direct proof for Harvey’s assertion that blood flows through the lungs, because the milky contrast passed sequentially through the right heart, the lungs, and the left heart into the systemic arterial circulation.

The structural proof of Harvey’s theory and of Glisson’s functional demonstration of a connection between arteries and veins—and, in the case of the liver, of a low-resistance pathway between portal and hepatic veins—was made possible by Marcello Malpighi’s landmark microscopic identification of capillaries that he first saw in the lung of a living frog (15). Following the discovery by Wepfer, in the latter half of the 17th century, of lobules or acini in the liver of the pig (16), a finding confirmed by Malpighi in many other species (17), one would have expected that the fundamental anatomic hepatic unit would have been well authenticated and universally agreed upon by now, but it has not (1). Kiernan, using only a hand lens and a quicksilver injection technique, distinguished triangular spaces containing minute branches of the hepatic artery, portal vein, and bile duct, in other words portal tracts or triads, at the periphery of classic hexagonal lobules (18). Elias, using elegant three-dimensional (3D) microscopic reconstructions (19), confirmed Hering’s original layout of one-cell-thick hepatocyte plates separating and bordering vascular spaces (20), which many authors continued to call capillaries. Later, Minot (21) distinguished the smallest blood vessels in the liver by the term “capilliform sinu-soids” (later, plain sinusoids) because of their unique endothelial structure and associated perisinusoidal cells, an arrangement that was later fully elucidated and is well recognized today. It has yet to be settled whether the once popular acinus of Rappaport (22) or the more current hepatic microcirculatory unit of Ekataksin (23), or some other model, will be universally accepted as the ultimate morphofunctional unit of the liver. Irrespective, in health, the sinusoidal system that connects portal and hepatic veins, which Malpighi originally identified (17), constitutes a low-resistance vascular pathway. It follows that any derangement of sinusoidal structure or venous drainage that is likely to increase resistance to blood flow through the liver may thereby initiate portal hypertension.

The major complications of portal hypertension, notably ascites and to a lesser extent variceal hemorrhage, were recognized long before their pathogenesis was understood. Ascites is mentioned in the most ancient of medical texts, i.e., the papyrus Ebers of Ancient Egypt (25) and the Ayurveda of the Hindu tradition (26), both dating from as early as 1500–1600 BCE and both offering remedies for accumulation of abdominal fluid that the Hindus call Jalodara (26). In Central America, at about the same time, the Ancient Mayans knew of the association between tense ascites and umbilical herniation, which they vividly depicted in the clay figurines of the time. The term ascites first appeared in English in the late 14th century as aschytes, and was taken from the Greek word for dropsy “askiTes” (ασκιΤες), itself derived from “askos” (ασκος), an ancient Greek word for a leather bag or sheepskin that was used for carrying water, wine, oil, and so on. Whereas the Old Testament blamed ascites on adultery (27), Hippocrates knew of its seepage from the liver and its poor prognosis (28). Erasistratus almost solved the pathogenesis of ascites when he argued that “the water cannot accumulate… in any other way than from narrowness of the blood vessels going through the liver,” (29) which, as usual, invited scorn from his nemesis Galen. In contrast to the ample documentation available of the history of ascites and its treatment through the ages (29–31), relatively little has been written before the modern era about varices and variceal hemorrhage in patients with cirrhosis or portal vein occlusion.
In patients with portal hypertension, esophagogastric varices were undoubtedly common but their discovery in life would have been almost impossible before the advent of radiology and endoscopy. Even in death from variceal hemorrhage, collapsed luminal varices are difficult to identify at autopsy. Bleeding from esophageal varices was described with certainty in France (32) and America (33) in the mid-19th century, and a little later by Osler (34). Yet, in 1860, Friedrich Theodor von Frerichs, who is widely regarded as the founder of modern hepatology, considered variceal bleeding to be a rare complication of cirrhosis and hemorrhoids to be infrequent (35), even though he and others (35–37) ably demonstrated, by injection opacification, an extensive portal collateral circulation in cirrhosis, including the legendary caput Medusæ (35) and congestive splenomegaly (35).

If we ignore the hypothesis proposed by the German physician and chemist Georg E. Stahl (1660–1734) that congestion of the portal vein, so-called abdominal plethora, is responsible for most if not all chronic illness (38), then the concept of portal hypertension can be considered to have been introduced at the turn of the 20th century by Gilbert and Villaret in Paris, who also coined the term that we use today (39). Gilbert and Weil had shown previously that pressure in ascitic fluid was high in patients with cirrhosis (40), in which setting they inferred that portal venous pressure must be high too (39). However, the next obvious deduction was not made, namely, that the cirrhotic liver must be responsible in some way for portal pressure elevation and its many consequences, including splenomegaly. What followed instead was the classic error of confusing cause with effect, as the enlarged spleen was thought to be the cause and not the result of the portal pressure elevation. This conclusion was based on the faulty reasoning of the renowned Florentine physician and pathologist Guido Banti (41), whose erroneous hypothesis was not accepted by his colleagues in Europe but was supported for the longest while by none other than the most respected physician of the day in Britain and America, William Osler (42,43). Banti reasoned that in patients with splenomegaly, anemia, and leukopenia [so-called splenic anemia (44) or Banti’s disease], the spleen was damaged by a toxin (45) and, in turn, the splenopathy injured the liver and caused cirrhosis in a syndrome he labeled hepatosplenopathy (46) (later called Banti’s syndrome). Osler later withdrew his support for the notion that a primary splenic disorder causes portal hypertension but not before surgeons, from Harvey Cushing to William Mayo, removed the offending spleens with gusto, despite recurrent hemorrhage and late mortality (41). Other surgeons performed omentopexy, producing decompressing portosystemic collaterals by sewing the omentum to the peritoneum (47). Despite its obvious shortcomings, Banti’s theory held sway from the 1880s to the 1950s, until the weight of evidence from pathologic, radiologic, hemodynamic, and surgical shunt studies laid to rest the legend of hepatosplenopathy (41,48–53).

The rejection of Banti’s hepatosplenopathy hypothesis cleared the way for less enigmatic solutions to the pathogenesis of portal hypertension. Plausible, testable mechanistic explanations were lacking for the perplexing association between cirrhosis and esophagogastric varices (54), as were more rational treatments than splenic amputation. To answer these needs, one of the arguably most significant contributions came from the extensive anatomic, pathologic, and liver-perfusion studies reported by a young New Zealander trainee in pathology and surgery at the Mayo Clinic, Archibald McIndoe (55). McIndoe—who later found fame in Great Britain, during World War II and its aftermath, for his innovative plastic and reconstructive surgery on severely burned and injured airmen, other service personnel, and civilians—concluded from the results of his experiments that portal hypertension was a result of vascular obstruction in the cirrhotic liver (55). Banti’s “for-
ward flow hypothesis” was thus replaced by McIndoe’s “backflow” phenomenon. McIndoe also suggested that portal hypertension could be ameliorated by the use of the portocaval fistula devised by the Russian surgeon, bureaucrat, and engineer, Nicolai Vladimirovich Eck, working in St. Petersburg 50 yr earlier (56). Whipple, Rousselot, Blakemore, Sengs- taken, and many other surgeons at Columbia University in New York City and elsewhere pioneered a mainly surgical approach to decompression of the portal venous system (41), which will be discussed and updated later by Dr. Michael Henderson (Chapter 16) as will nonsurgical shunts, the radiologic counterparts, by Dr. Rajiv Jalan (Chapter 17).

The abandonment of Banti’s hypothesis does not mean that forward flow is discredited as a contributory factor in portal hypertension. Patients with advanced liver disease have long been recognized to exhibit the physical signs of a hyperdynamic circulation (57,58). Whereas many possible mechanisms have been proposed for the hyperdynamic circulatory state seen in cirrhosis and portal hypertension (59), central to the syndrome is arterial vasodilatation in both the splanchnic and peripheral vascular beds (60–62), which will be analyzed and explained by Dr. Didier Lebrec (Chapter 4). Despite normalization of resistance to portal blood flow as a result of portal–systemic collateralization, elevated portal pressure is not abolished but persists, now being maintained largely by the hyperdynamic increase in portal blood flow. Thus, the hyperdynamic portal inflow and not only the resistance provides the impetus for preserving an elevated portal venous pressure. In other words, the backflow phenomenon gives way to and/or is augmented by forward flow, as shown well in experimental animal models (60,63).

Parenthetically, one must concede that Banti’s ghost still stalks from time to time, especially but not exclusively in the case of patients with hematological causes of splenomegaly who also have portal hypertension and varices (64). Hematologists and others have argued that the increased blood flow from a grossly enlarged spleen meaningfully contributes to, or can even cause, portal pressure elevation, in much the same way as the hyperdynamic circulation of cirrhosis does and can occur in the extreme case of splenic arteriovenous fistula (65). This argument is often used to justify splenectomy, which can be hazardous by causing portal and/or mesenteric thrombosis (66–69), possibly because of the thrombogenic effect of a temporary slowing of portal blood flow (70), in the presence of vessel wall injury and thrombocytosis. In cirrhotic patients undergoing distal splenorenal shunt surgery there appears to be no correlation between spleen size and estimated sinusoidal pressure, and direct measurement intraoperatively shows no reduction of portal pressure with splenic vein clamping (71). In patients with certain hemologic disorders, portal hypertension is either the result of a subtle change in sinusoidal structure (72), hepatic fibrosis (73), or portal vein lesions with the secondary development of other liver lesions such as nodular regenerative hyperplasia (72). Whether laparoscopic splenectomy (74), which is being used increasingly in cirrhotic patients to alleviate thrombocytopenia (75), will prove less hazardous than open splenectomy remains to be seen as portal thrombosis has already been reported in patients with splenomegaly who undergo laparoscopic splenectomy (75).

The final stop in this historical romp through portal hypertension is to review the introduction of portal pressure measurements in humans, for investigational and clinical purposes. Portal pressure had been measured directly intraoperatively since the 1930s at least (52,77). The introduction of hepatic vein catheterization in 1944 for blood sampling (78) was preparatory to the earliest efforts at hepatic venous pressure measurement and sinusoidal pressure estimation by Friedman and Weiner (79) and Myers and Taylor (80) in
1951, and Paton et al. in 1953 (81) using an occlusion (wedged) technique, which was preferred to both abdominal wall vein (82) and splenic pulp (83) puncture. While the precise role of wedged hepatic venous pressure measurements in routine clinical practice is still being debated (84), the importance of making the measurements correctly cannot be over-emphasized (85) lest the technique fall into disrepute because of inadequate performance.

In this introductory chapter, we have shown that the history of the discovery and investigation of the hepatic vasculature and portal hypertension is a colorful and illustrious one in hepatology and in medicine in general. The remainder of this volume will build on this historical account by providing explanations of the pathophysiology of portal hypertension and its complications, clinically and experimentally, with data ranging from studies in conscious humans to minutiae at the cellular and molecular levels, and embracing the most modern and rational approaches to therapy. The Ancient Egyptians, Mayans, Hindus, Greeks, Romans, and others will surely applaud our progress with the organ once considered to be the “seat of the soul.”

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II

PATHOBIOLOGY AND EXPERIMENTAL PROGRESS IN PORTAL HYPERTENSION
Anatomy and Vascular Biology of the Cells in the Portal Circulation

Massimo Pinzani, MD, PhD
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REFERENCES

INTRODUCTION

Portal hypertension occurring during the natural course of liver cirrhosis is a consequence of the increased intrahepatic resistance to portal flow. For a long time, this phenomenon has been ascribed only to the profound changes of liver tissue angioarchitecture consequent to the progression of the fibrogenic process. However, studies performed during the last decade have demonstrated that there is also an increased vascular tone that could be modulated to a certain extent by pharmacological agents. The aim of this chapter is to provide general information on the anatomy of the portal systems and on the regulation of vascular tone in this specific vascular district and in the splanchnic circulation. Information about the collateral circulation that becomes relevant in the case of portal hypertension is also provided.

In addition, because of the many studies performed in animal models and isolated and cultured hepatic cell, attention will be paid to the biology of these cells and to the relative pathophysiological implications. In particular, hepatic stellate cells, now regarded as liver-specific pericytes, are likely to play an important role in the progression of portal hypertension because of their active role in the deposition of fibrillar extracellular matrix and of their contractile properties. In this context, several vasoconstricting agonists, whose expression is increased in fibrotic liver, may play a role in inducing contraction...
of hepatic stellate cells as well as of other resident cells characterized by contractile ability. The features of different vasoactive agents will be analyzed and their potential involvement in physiological and pathological conditions thoroughly discussed.

ANATOMIC CONSIDERATIONS OF THE NORMAL PORTAL CIRCULATION

A portal venous system is defined as one beginning and ending in capillaries. The name “portal vein” derives from the notion that it is the gate into which the splanchnic circulatory system is connected to the liver (porta = gate). The name portal vein is applied to the venous system that originates in the capillaries of the intestine and terminates in the hepatic sinusoids. Nutrients absorbed from the gastrointestinal tract, in addition to hormones such as glucagons and insulin released by the pancreas, are directly delivered to the liver in high concentrations.

Embryology of the Portal System

The portal venous system originates from the two vitelline and the two umbilical veins. The vitelline veins, which drain blood from the yolk sac, intercommunicate in the septum transversum, at which point the liver sinusoids and lobules develop. The extrahepatic portal system develops primarily from the left vitelline vein (which is later joined by the splenic vein to form the portal vein), whereas the intrahepatic portal circulation originates from the umbilical veins. In addition, the left umbilical vein communicates with the venous sinus connecting with the inferior vena cava, thus allowing a large quantity of blood to bypass the liver in the fetal circulation. Soon after birth, the umbilical vein is obliterated and the normal adult circulation is established. Despite this complexity in the development of the portal system, only very few congenital anomalies of the portal venous system are observed.

Gross Anatomy of the Portal System

The portal vein is a vessel collecting the venous blood of the abdominal part of the alimentary tract, spleen, pancreas, and gallbladder to the liver. The portal vein begins at the level of the second lumbar vertebra, just behind the neck of the pancreas as an upward continuation of the superior mesenteric vein after this vessel has been joined by the splenic vein. The superior mesenteric vein (0.78 cm in diameter) is primarily formed by all the veins draining the small bowel, with significant further contributions of the ileocolic, right colic, and middle colic veins. It runs in the root of the mesentery, in front of the third portion of the duodenum to merge with the splenic vein. The splenic vein (0.94 cm in diameter) originates with five to six branches that return the blood from the spleen and unite to form a single nontortuous vessel at the splenic hilum and join near the tail of the pancreas with the short gastric vessels to form the main splenic vein. This vein proceeds transversally, close to the hilum of the left kidney, in the body and head of the pancreas, receiving numerous tributaries from this latter portion of the pancreas. The left gastroepiploic vein joins the splenic vein near the spleen, and the inferior mesenteric vein (0.24 cm diameter), collecting blood from the left part of the colon and rectum, usually enters its middle third. Occasionally (one-third of subjects) the inferior mesenteric vein enters directly into the superior mesenteric vein or at its junction with the splenic vein. On its way to the porta hepatis, the portal vein trunk receives (in some variants) the superior pancreaticoduodenal
vein (with right gastroepiploic vein) and the right gastric (pyloric) veins. The left gastric (coronary) vein joins the portal vein at its origin 50% of the time, and it joins the splenic instead of the portal vein in the other 50% of subjects. Coronary vein runs upward along the lesser curvature of the stomach, where it receives some esophageal veins.

The portal system carries all the blood from the alimentary tract to the liver and, thus, in the normal subject all of the above-named veins have blood flow directed toward the liver. The segment of the portal vein after the last afferent branch runs in the hepatoduodenal ligaments (the free edge of the lesser omentum) in a plane dorsal to the bile ducts and the hepatic artery. This segment extends for approx 6–8 cm before entering the liver and it is 1–1.2 cm in diameter. The portal vein is not provided with valves, so the pressure is transmitted freely back to the afferent branches. The portal vein pressure normally ranges between 5 and 10 mmHg (depending on the method of measurement). Normal fasting hepatic blood flow is approx 1500 mL/min. The best available estimates in humans indicate that about two-thirds of the total hepatic blood flow and about one-half of the oxygen consumption are supplied by the portal vein, whereas the remainder is supplied by the hepatic artery. This dual hepatic blood supply makes the liver rather resistant to hypoxia. Accordingly, ligation of the portal vein does not cause hepatocellular necrosis. Similarly, accidental ligation of the hepatic artery or its major branches does not necessarily lead to hepatic failure. The portal trunk divides into two lobar veins before entering the portal fissure. The right lobar branch, short and thick, then receives the cystic vein. The left lobar vein is longer than the right and consists of a transverse and an umbilical part. The latter is the remainder of the umbilical parts. The recanalized umbilical or parau- bumilical veins arise from the umbilical portion of the left portal vein and pass through the round ligament to the anterior abdominal wall, where they may become evident, in the presence of portal hypertension, in the umbilical varices.

According to the distribution of major portal vein branches, so-called segmental branches, the liver can be divided into functional segments. Each segment depends on its major vessel for blood supply. The right branch of the portal vein is usually less than 3 cm long and runs more vertically. It divides into anterior and posterior branches, which supply the anterior and posterior parts of the right lobe. Each of these vessels divides again into superior and inferior branches. The left lobar vein gives branches to the quadrate lobe and to the caudate lobe, before entering the parenchyma at the left end of the porta hepatitis. A separate branch may arise near the bifurcation to supply the caudate lobe. The vein is then joined by the obliterated umbilical vein as it turns medially. The terminal part of the vessel continues into segment IV, which it supplies with ascending and descending branches. In addition to the main portal vein and its branches, the liver receives other veins from the splanchnic circulation, the so-called parabiliary venous system of Couinaud. This highly variable plexus includes several veins that arise from the pancreaticoduodenal or pyloric veins and drain into the portal vein or directly into hepatic segments, especially segment IV. This plexus provides examples of the metabolic effects of proximity to an insulin source. Veins arising from the pancreatic region would carry blood with high insulin levels and pyloric veins would carry low-insulin blood. The anatomy of these veins could explain some examples of focal fatty liver and focal fatty sparing, in fact, insulin determines the ability of the liver to accumulate triglycerides (1).

The other vessel supplying the liver is the hepatic artery. About one-third of the total hepatic blood flow is supplied by the hepatic artery. The common hepatic artery is the second major branch of the celiac axis. It runs to the right along the upper border of the
pancreas in the context of the right gastropancreatic fold, which conducts the artery to
the medial border of the hepatoduodenal part of the lesser omentum. It ascends in front
of the portal vein in 91% of subjects and to the left of and behind the bile duct in 64%
of cases. It divides into the left and the right hepatic arteries to supply the corresponding
hemilivers. Although the left and right hepatic arteries are end-arteries, they often anas-
tomose within the hilar tissue (2). The right and left hepatic arteries each divide into two
arteries that supply the right anterior and posterior sections and the left medial lateral
sections, respectively. Another branch, the middle hepatic artery, arises from the left or
right hepatic artery and supplies the quadrate lobe. The cystic artery arises from the right
hepatic artery in the upper part of the Calot triangle (formed by the cystic duct, common
hepatic duct, and inferior surface of liver) (3).

Portal Collateral Circulation

The portal system has numerous collaterals that interconnect with the systemic circu-
lation. When portal pressure rises above 10 mmHg potential portosystemic collaterals may
develop. Formation of collaterals is a complex process involving the opening, dilation,
and hypertrophy of preexisting vascular channels. It is possible that active neoangiogen-
esis is involved in the formation collateral vessels (4). The sites for the development of
portal collateral vessels are those areas where veins draining into the portal system are in
immediate juxtaposition to veins draining into the superior or inferior vena cava. Collat-
erals vessels could be classified into three embryological groups: (1) junction of absorptive
and protective epithelium (gastroesophageal and hemorrhoidal plexuses); (2) obliterated
fetal circulation (umbilical or paraumbilical veins in round and falciform ligaments); and
(3) organs derived from the gastrointestinal tract that became retroperitoneal or adhere
to the abdominal wall because of pathologic process (portorenal plexus, veins of Retzius,
surgical stomata, and other interventions connecting portal bed with the ascending lum-
bar azygos, renal, and adrenal veins).

The most important sites for the development of portosystemic collateral vessels are:
(1) esophageal submucosal veins, supplied by the left gastric vein and draining into the
superior vena cava through the azygos vein; (2) paraumbilical veins, although normally
nonfunctional, can serve as an anastomosis between the umbilical part of the left portal
vein and the hepigastric veins of the anterior abdominal wall that drain into the superior
or inferior vena cava, and in special circumstances may form caput medusae at the um-
bilicus (Cruveilhier–Baumgarten syndrome); (3) rectal submucosal veins, supplied by the
inferior mesenteric vein through the superior rectal vein and draining into the internal
iliac veins through the middle rectal vein; (4) splenorenal shunts, in this case venous blood
may be carried to left renal vein, either directly or by way of the diaphragmatic, pancre-
tic, or gastric veins; (5) short gastric veins communicate with the esophageal plexus. Mor-
over, within the cirrhotic liver, there is significant collateral flow in small veins that con-
nect branches of the portal and hepatic veins (5).

The Gastroesophageal Junction

The normal venous anatomy of the gastroesophageal junction and of the lower esophag-
gus is particularly relevant to this introductory chapter. Studies of Vianna et al. docu-
mented four distinct zones of esophageal venous drainage (from distal to proximal): (1)
the gastric zone, which extends for 2–3 cm just below the gastroesophageal junction. This
is the junctional zone between the stomach and lower oesophagus. Veins from this zone
drain into the short gastric and left gastric veins. (2) The palisade zone extends 2–3 cm superiorly from the gastric zone into the lower esophagus and represent the watershed between the portal and systemic circulation. (3) The perforating or transitional zone extends approx 2 cm further up the esophagus above the palisade zone. Here, the organized longitudinal structure is lost, with veins looping and forming a network. The main feature of this zone is represented by the presence of perforating veins through the muscle wall of the esophagus linking the submucosal and paraesophageal venous plexuses that are tributaries of the azygos venous system. These perforating veins run circumferentially around the esophageal wall. In portal hypertensive patients, dilated perforating veins become incompetent and allow retrograde blood flow from the paraesophageal to the submucosal veins. This associated with the turbulent flow caused by pressure changes as a result of the respiratory movements, coughing and stretching may contribute to formation and dilation of varices. (4) The truncal zone is 8–10 cm long and is characterized by four of five longitudinal veins in the lamina propria. In this zone, perforating veins penetrate from the submucosa at irregular intervals to the external esophageal venous plexus.

In summary, venous drainage from the gastric fundus and the lesser curvature is directed inferiorly to the portal vein. In the palisade zone, there is to/from flow that is probably respiration dependent. The perforating veins connect the intrinsic and extrinsic esophageal plexuses. Flow in the truncal zone is inferior to the perforating zone. In conclusion, the perforating, transitional zone is the “critical area” for variceal rupture. Indeed, varices tend to be bigger and to form “nodules” at the distal end of the esophagus, at the level of the perforating veins (6).

**Structure and Function of the Splanchnic Vasculature**

The splanchnic circulation consists of those vascular beds perfused by the celiac, superior and inferior mesenteric arteries, and the portal vein. The organs perfused by the splanchnic vasculature receive about 25% of cardiac output and account for about 30% of total body oxygen consumption under resting conditions. Functional and/or structural changes in arterioles, capillaries, and venules can initiate or perpetuate an elevated portal pressure (e.g., dilation of arterioles, passive occlusion of capillaries, and active constriction of hepatic venules). The structural and functional characteristics of the microvasculature of the stomach and small and large intestine are very different from those of the liver. First, splanchnic capillaries are much less porous than the hepatic sinusoids and have a well-defined basement membrane. Although most splanchnic capillaries are fenestrated, the estimated pore size, 3.7 to 12 nm in radius, is between 50 and 100 times lower than that of the hepatic sinusoids. A very little amount of the total protein oncotic pressure may pass across a splanchnic capillary membrane; consequently, any increase in filtration in the splanchnic capillaries is quickly counterbalanced by an increase in the oncotic pressure difference between capillary lumen and interstitial space. In addition, there is evidence that the intestinal microvasculature autoregulates the capillary pressure and capillary filtration coefficient. There are significant differences between the intestinal and hepatic interstitium in terms of compliance; in fact, considerable interstitial fluid can accumulate without causing any major changes in interstitial pressure. Moreover, the intestines have a very efficient lymphatic system to remove interstitial edema. In normal conditions, approx 20% of the fluid absorbed by the small intestine is carried out to the general circulation by the lymphatics (7).
Under basal conditions, splanchnic arterioles are partially constricted, and have the
capacity to either further constrict or dilate. This arteriolar smooth muscle tone is the
sum of multiple factors that tend to either relax or constrict vascular smooth muscle. A
variety of metabolic end-products (e.g., adenosine), some endothelium-derived substances
(e.g., nitric oxide), and certain neurotransmitters (e.g., acetylcholine) are known to relax
arteriolar smooth muscle and produce vasodilation. Important vasoconstrictors influences
on splanchnic arterioles include some circulating agents (e.g., angiotensin II), certain
endothelium-derived substances (e.g., endothelin), and some neurotransmitters (norepinephrine).
These factors can alter the contractile state of arteriolar smooth muscle either
by acting directly on vascular smooth muscle (e.g., metabolic mediators) or by stimulat-
ing endothelial cells to release vasoactive agents that act on the underlying adjacent
vascular smooth muscle (e.g., acetylcholine). Hypoxia, in terms of reduced oxygen deliver-
ry or increased oxygen demand, can lead to changes in arteriolar tone and consequent
changes in blood flow. This effect appears to be mediated by terminal products of oxida-
tive metabolism, such as adenosine, and tissue oxygen tension ($pO_2$) and appear to be
one of the principal mechanisms of postprandial hyperemia. In fact, when tissue $pO_2$
falls or extracellular adenosine concentration rises, arterioles dilate. Normally, splanchn-
ic arterioles are exquisitely sensitive to acute changes in intravascular pressure. Vascu-
lar smooth muscle of splanchnic arterioles contracts intensely in response to stretch (induc-
ing a sudden elevation in portal pressure). The intense dilation of arterioles observed in
chronic portal hypertension likely reflects the accumulation of vasodilators [e.g., increased
nitric oxide (NO) production, increased blood levels of glucagons] that overcome intrin-
sic myogenic vasoconstrictor factors (8).

Norepinephrine, angiotensin II, and vasopressin are estimated to account for more than
two-thirds of basal splanchnic vascular tone. Norepinephrine generally elicits a profound,
yet transient, reduction in splanchnic blood flow. Increased tissue levels of adenosine
during vasoconstriction-mediated arterioles escape from norepinephrine-mediated vaso-
constriction. On the contrary, vasopressin and angiotensin II cause a sustained reduction
in splanchnic blood flow. Glucagon attenuates the splanchnic vasoconstrictive response
induced by catecholamines, vasopressin, and angiotensin II through a downregulation
of receptors and/or postreceptor mechanisms such as impairment of second-messenger
activation in splanchnic vascular smooth muscle. A wide variety of hormones and pep-
tides produced within the alimentary tract are capable of altering splanchnic blood flow
when infused into arterial blood. Somatostatin and neuropeptide-Y are locally produced
peptides that exert potent vasoconstrictor actions. Vasoactive intestinal polypeptide, sub-
stance P, cholecystokinin, and gastrin are examples of gastrointestinal peptides that dilate
splanchnic arterioles and increase blood flow.

Splanchnic organs exhibit an intrinsic ability to regulate local blood flow by modulat-
ing the tone of arterioles. Two examples of intrinsic vasoregulation are pressure-flow auto-
regulation and functional (postprandial) hyperemia. Pressure-flow autoregulation is the
ability of an organ to maintain its constant blood flow when arterial pressure is reduced.
This regulatory mechanism depends on metabolic or myogenic-mediated dilation of arte-
 rioles at lower intravascular pressures. However, pressure-flow autoregulation of splanchn-
ic organs is not as potent and precise as in other vascular beds such as the heart, the
brain, and the kidneys. Nevertheless, this autoregulation is improved in the postprandial
phase (increased metabolic demand), when arterioles become more sensible to reductions
in arterial pressure. Postprandial hyperemia has recently received much attention as a
potential cause of rapid elevation in splanchnic blood flow and portal pressure that may lead to variceal formation, dilation, and explosion (9, 10). Splanchnic vasodilatation and hyperemia is caused by the interaction of intrinsic (change in arteriolar transmural pressure and/or increase in vasodilator tissue metabolites) or extrinsic mechanisms (autonomic nervous system especially noncholinergic vagal reflexes) and the effect of nitric oxide, gastrointestinal hormones and peptides (gastrin, cholecystokinin and glucagons), autacoids (histamine, serotonin), osmolality, and prostaglandins. The relative contribution of these different factors is influenced by the composition of the meal (i.e., long-chain fatty acids appear to be the most potent stimulus) and the preprandial metabolic status of the affected organ.

**Nerves**

The liver is predominantly innervated by two plexuses, the anterior and the posterior, which communicate with each other. The anterior plexus surrounds the hepatic artery and is made up of fibers from the celiac ganglia and anterior vagus nerve. The posterior plexus surrounds the portal vein and bile duct and is formed from branches of the right celiac ganglia and posterior vagus. The vast majority of nerve fibers terminate in plexuses in the adventitia around hepatic arterioles and venules. Small fibers from these plexuses then end on smooth muscle cells in the media of these vessels. Within the liver cell plate, the majority of nerve fibers are observed in periportal regions. Some of the nerve fibers terminate on endothelial cells in the smallest hepatic arterioles, near the space of Disse, on Kupffer cells, and on hepatic stellate cells (HSC).

Hepatic innervation can be distinguished in extrinsic and intrinsic. The extrinsic innervation of the liver is constituted by: (1) efferent sympathetic nerve fibers and parasympathetic nerve fibers; these play a role in regulating the metabolic load of hepatocytes, hemodynamic and biliary motility; (2) afferent fibers, which are thought to be involved in osmo- and chemoreception. At the hilus, amyelic fibers from the anterior and posterior plexuses enter the liver mainly around the hepatic artery. The intrinsic innervation is composed of fibers (mostly adrenergic, but also cholinergic and peptidergic) mainly associated with vascular and biliary structures in the portal spaces (11). Certain fibers enter liver lobule where they form a network around hepatocytes and extend into the sinusoidal wall, sometimes reaching the centrilobular vein. Some neuropeptides have been identified, such as vasointestinal peptide, neuropeptide Y, substance P, glucagon, and calcitonin gene-related peptide. Stimulation of sympathetic fibers causes an increase in vascular resistance and a decrease in hepatic blood volume.

**The Hepatic Portal Tree**

Segmental branches of the portal vein split dichotomously into equal sized branches, constituting a tree of conducting vessels that terminate in venules having an inner diameter of about 400 µm. Each branch of the afferent vessels is essential for proper function because it supplies blood to a specific area. There are few, if any, anastomoses that could provide collateral circulation if a major branch is impaired. In other words, the first portion of the portal system is merely conductive up to the branching into preterminal portal venules with an inner diameter of 80–40 µm. This latter portion appears to be the main site of the constrictive response of the portal tree to various constrictive stimuli and, as such, the main mechanism for controlling blood distribution within the liver. Further downstream, the so-called terminal portal venules are endothelial tubes surrounded by