Portal Hypertension
Pathobiology, Evaluation, and Treatment

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Humana Press
PORTAL HYPERTENSION

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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 esophageal 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
Reuben and Groszmann

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 “*sanguificationis 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 “*concoction*” (*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 sinusoids” (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 “askiTēs” (ασκiTηξ), itself derived from “askos” (ασκοξ), 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 Medusae (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, Sengstaken, 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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