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Hepatic Blood Flow: Morphologic Aspects and Physiologic Regulation

A. M. RAPPAPORT*

Department of Physiology and Liver Laboratory, Department of Internal Medicine,
Sunnybrook Medical Centre, University of Toronto, Toronto

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Dedicated to Hans Popper on his 75th birthday.

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Hepatic circulation is essential for the survival and function of the hepatic cells. It is integrated into our systemic circulation and is a simile of cosmic motion in our body, as was pointed out three centuries ago (1). Blood flow, through its ultimate exchange with the tissues, illustrates the *continuous change* of the morphe, although it may appear motionless to our senses. Science and philosophy have long since demonstrated that motion is the essence of all organic and inorganic things and processes (2).

Indeed, it is the pre- and postnatal changes of the circulation that determine size (3, 4), shape (5), and structure (6) of the liver.

FUNCTIONAL ANATOMY OF THE HEPATIC VASCULAR BED

Development of the Hepatic Vessels

The hepatic diverticulum arises from the duodenum in a 4-week-old embryo. The entodermal cells grow into the mesoderm of the septum transversum, which is permeated by a capillary plexus. This plexus receives the omphalomesenteric and umbilical veins and drains via the hepatocardiac veins into the heart. The growing cords of liver cells gradually fill in the proximal portion of the omphalomesenteric venous lakes, break them up into a maze of small channels, the *sinusoids*, and these ramify through the substance of the liver. The proximal stubs of the omphalomesenteric veins persist to form the *hepatic veins*. The remainder of the cardiac portion of the right omphalomesenteric vein evolves into the right hepatic vein. Distal to the liver mass, the paired omphalomesenteric veins bringing blood from the yolk sac and the evolving gastrointestinal tract are retained; they form transverse anastomoses in front of and behind the developing duodenum. Later, the omphalic portion of the veins regresses with the disappearance of the yolk sac, and the mesenteric portions persist with the growth of the intestines. The *portal vein* (PV) develops out of the paired venous trunks by dropping out the original left channel cephalic to the middle anastomosis and the original right channel caudal to the anastomosis. Thus the S-shaped curve of the portal vein trunk behind the duodenum is formed. Anomalies of the PV, especially the cavernoma, are in the majority of cases caused by early thrombosis and recanalization (7). The left umbilical veins join the sinusoids and the left lobar branch of the portal vein. Thus, in the embryo the bulk of the nutrients coming from the placenta via the umbilical vein reaches the liver first, before distribution to other organs. A similar pattern exists in the adult, with the liver being first to receive the nutrients absorbed from the intestines.

The *hepatic artery* originates from the paired ventral segmental arteries; they fuse and are reduced to the midline arteries of the foregut. Ventral anastomoses of the esophageal and celiac trunks form the gastric and hepatic artery.

In the evolution of the liver the ingrowth of tridimensionally budding liver cords into the omphalomesenteric venous plexuses along biliovascular axes is the basic event that will determine the vascular and lobular structure and function of the liver. The interdigitation of glandular structures (8) on the one hand, and of afferent and efferent vessels on the other hand, is the main determinant of the acinar lobulation of the parenchyma. Interdigititation of afferent and efferent vessels, if regular, may mimic a hexagonal design, which gave rise to the misconception of a hexagonal lobular unit in the liver.

Extrahepatic Distribution of Hepatic Vessels

Portal Vein The valveless portal vein is an afferent nutrient vessel of the liver, and in this sense there is an analogy between the portal vein and the pulmonary artery. Reeves et al. (9) compare the lung lobule with its central pulmonary arterial inflow to the liver acinus with its portal venular axis. The latter carries blood from the entire capillary system of the digestive tract, spleen, pancreas, and gallbladder (Figure 1). In recent years more frequent operations on the portal vein have led to new investigations of its anatomy (10, 11). It has been found constant in its length but extremely variable in its tributaries. The PV results from the confluence of the following veins.

The *splenic vein* (0.94 cm in diam) commences with five to six branches that return the blood from the spleen and unite to form a single nontortuous vessel (Figure 1, no. 11). In its course across the posterior abdominal wall it grooves the upper part of the pancreas, from which it collects short tributaries (Figure 1, no. 11a). It can be visualized preoperatively by splenopertitoneal angiography (12, 13). It runs close behind the neck of the pancreas where it joins the superior mesenteric vein at a right angle. Because of its nearness to the vessels of the left kidney, the splenic vein can be anastomosed with the renal vein. Its tributaries are the short gastric veins (Figure 1, no. 13), the pancreatic veins (Figure 1, no. 11a), the left gastroepiploic vein (Figure 1, no. 12), and the inferior mesenteric vein.

The *inferior mesenteric vein* (Figure 1, no. 14) (0.24 cm in diam) returns blood from the superior and the inferior left colic and the superior rectal veins.

The *superior mesenteric vein* (Figure 1, no. 5) (0.78 cm in diam) is second in diameter to the portal vein and well suited for anastomosis with the caval system. It carries blood from the veins of the small intestine (Figure 1, no. 6), the cecum (Figure 1, no. 8), the ascending colon (Figure 1, no. 9), and the transverse colon (Figure 1, no. 10). The confluence of the mesenteric and splenic veins forms the portal trunk behind the neck of the pancreas. The *portal trunk* (Figure 1, no. 4), approximately 5.5 to 8 cm long and about 2 cm in diam, also receives the rootlets of the superior pancreaticoduodenal vein, some accessory pancreatic veins, the pyloric vein, the left gastric (coronary) vein (Figure 1, no. 18), and the cystic vein. Usually there is an upper segment of the portal trunk, averaging 5 cm in length, that is devoid of major branches (10). Here surgical dissection can be started without danger of hemorrhage. The most troublesome tributary of the portal trunk is the left gastric (coronary) vein (Figure 1, no. 18). It runs upward along the lesser curvature of the stomach, where it receives some esophageal veins. With progressing cirrhosis of the liver these enlarge to form varices that are apt to produce fatal hemorrhage. The portal trunk runs in the hepatoduodenal ligament in a plane dorsal to the bile duct and the hepatic artery and divides into two lobar branches before entering the portal fissure. The right lobar branch (Figure 1, no. 19), short and thick, receives the cystic vein. The left lobar

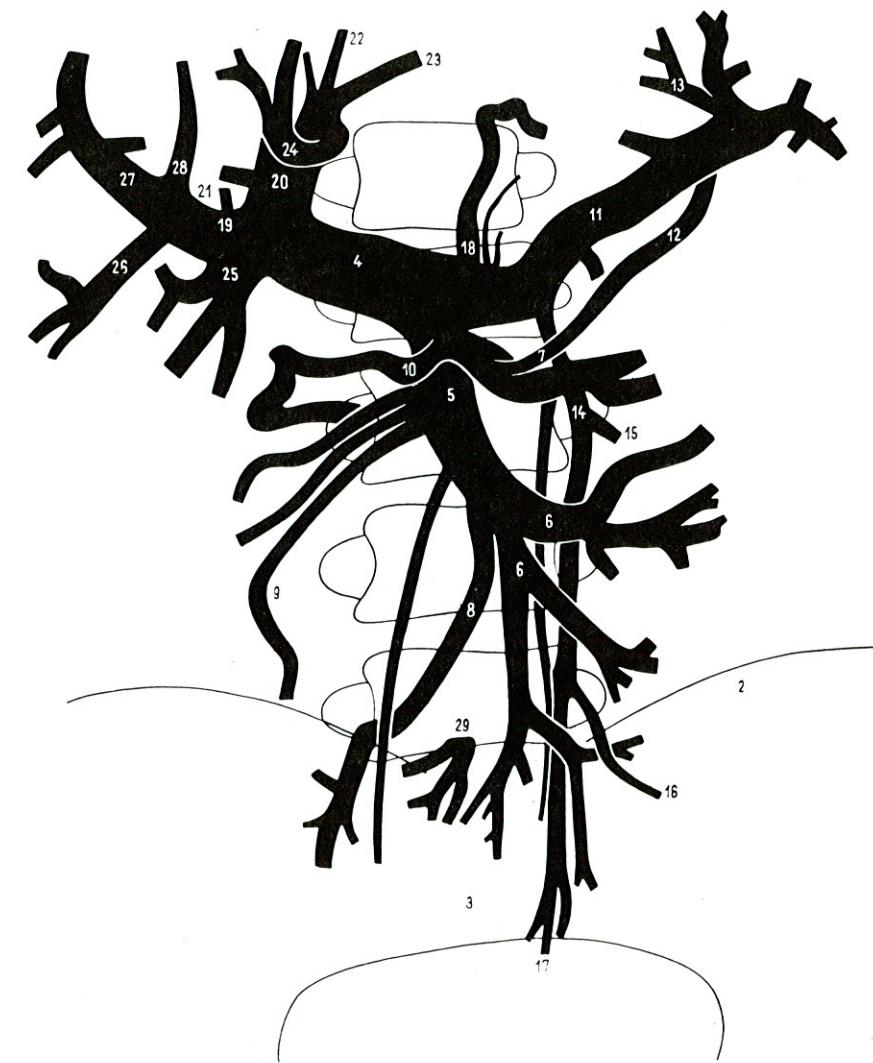


Figure 1. The portal vein and its branches (anteroposterior view). A multiplicity of splanchnic veins, each of them carrying a variety of products from a different area, join together to form the portal vein and its lobar branches. 1. Lumbar vertebra. 2. Wing of the ilium. 3. Sacrum. 4. Portal vein. 5. Superior mesenteric vein. 6. Jejunal and ileal veins. 7. Right gastroepiploic vein. 8. Ileocolic vein. 9. Right colic vein. 10. Middle colic vein. 11. Splenic vein. 11a. Pancreatic vein. 12. Left gastroepiploic vein. 13. Short gastric veins. 14. Inferior mesenteric vein. 15. Left colic vein. 16. Sigmoid veins. 17. Superior rectal veins. 18. Left gastric vein. 19. Right branch of portal vein. 20. Left branch of portal vein. 21. Caudate branches, V₁. 22. Left superior branch, V₂. 23. Left inferior branch, V₃. 24. Transverse part, V₄. 24a. Umbilical part. 25. Inferior anterior branch, V₅. 26. Inferior posterior branch, V₆. 27. Superior posterior branch, V₇. 28. Superior anterior branch, V₈. 29. Cannula in jejunal vein. From Luzsa, G. (1974). *X-ray Anatomy of the Vascular System*. Butterworths & Co., Toronto.

branch (Figure 1, no. 20), longer and smaller, is joined by the umbilical vein (ligamentum teres) and the associated paraumbilical veins. It connects by the venous ligament (ductus venosus Arantii) with the inferior vena cava. The left lobar branch gives branches to the quadrate lobe and also to the caudate lobe before entering the liver at the left end of the porta hepatis.

Hepatic Artery (HA) The HA (Figure 2, no. 4), along with the left gastric and splenic arteries, is a branch of the celiac axis. At its origin the HA is called the common hepatic artery. After giving off two branches, the gastroduodenal artery and the right gastric artery, the common hepatic artery becomes the proper hepatic artery, which in turn divides into the right (Figure 2, no. 5) and left (Figure 2, no. 6) hepatic arteries to supply the corresponding lobes of the liver. A branch of the right hepatic artery is the cystic artery (Figure 2, no. 9), supplying the gallbladder in 30% to 40% of the cases. The anatomy of the arterial supply to the liver is, however, highly variable. From studies on 200 cadavers, Michels (14) demonstrated that the textbook anatomy was found in only 55% of the cases. The right and left branches of the HA are joined to one another via subhilar arterial arcades (15-17) that can contribute to collateral circulation.

In human angiograms one finds three types of HA (single, double, or multiple), of celiac, mesenteric, or mixed origin (18). Michels found a total of 26 possible collateral pathways (14), of which 10 basic routes were anatomic variations of the HA arising from the left gastric and superior mesenteric vessels. These variations should be taken into account when measuring the contribution of the proper HA to total hepatic blood flow.

The liver is a segmental organ like the lung. "Each HA is an end artery with a selective distribution to a definite area of liver and cannot be sacrificed without resultant necrosis of liver tissue" (14). A line extending from the gallbladder fossa inferiorly to the inferior vena cava superiorly is the dividing line separating the right and left hepatic arterial fields (19-21).

Hepatic Veins (HV) The hepatic veins are enveloped by the coronary ligament and empty into the inferior vena cava (Figure 3, no. 4), which lies in the groove of the posterior surface of the liver.

An upper group of three major hepatic veins, right (Figure 3, no. 5), middle (Figure 3, no. 10), and left (Figure 3, no. 12), empty into the inferior vena cava. They drain three hepatic venous segments, which interdigitate and overlap the portal segments (right, Figure 3, nos. 22, 23, 24, 25; left, Figure 3, nos. 19, 20; and middle, Figure 3, nos. 17, 18, 21).

The *left hepatic vein* drains the left lobe. It is composed of two major radicles: an upper one (Figure 3, nos. 13, 14) coming from the upper half, and a lower one (Figure 3, no. 15) from the lower half of the territory they drain.

The *middle hepatic vein* carries blood from the central parts of the liver, i.e., from areas irrigated by the right and the left lobar portal branches (Figure 3, nos. 17, 18). The middle vein (Figure 3, no. 10) sometimes unites with

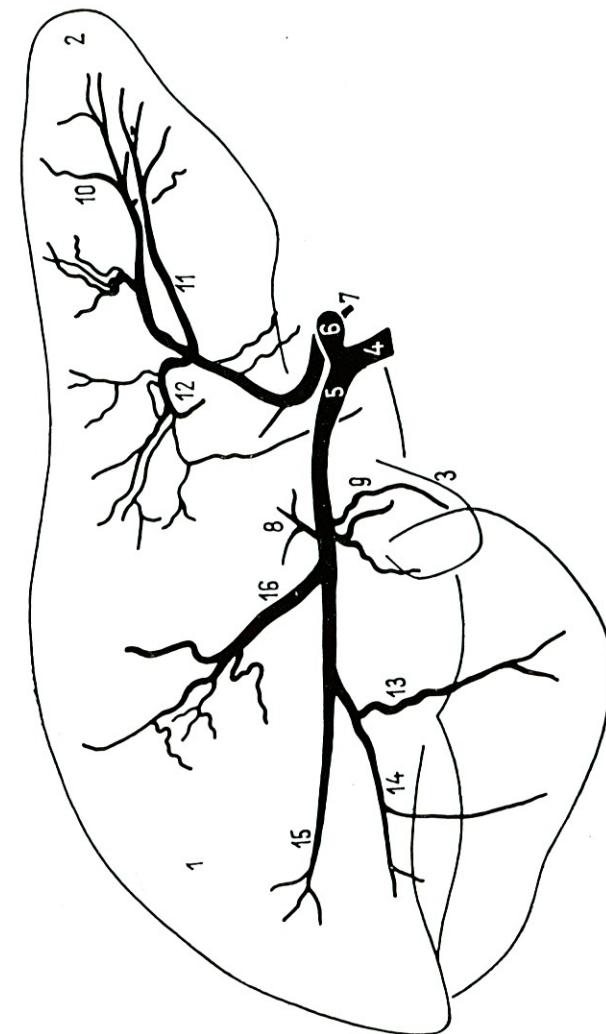


Figure 2. The hepatic artery and its branches (anteroposterior view). Arterial blood is evenly distributed to the parenchyma of all liver lobes. 1. Right lobe. 2. Left lobe. 3. Gallbladder. 4. Hepatic artery. 5. Right branch. 6. Left branch. 7. Left accessory hepatic artery. 8. Artery of caudate lobe, A₁. 9. Cystic artery. 10. Superior lateral segmental artery, A₂. 11. Inferior lateral segmental artery, A₃. 12. Medial segmental artery, A₄. 13. Inferior anterior segmental artery, A₅. 14. Superior posterior segmental artery, A₆. 15. Superior anterior segmental artery, A₇. 16. Superior posterior segmental artery, A₈. From Luzsa, G. (1974). *X-ray Anatomy of the Vascular System*. Butterworths & Co., Toronto.

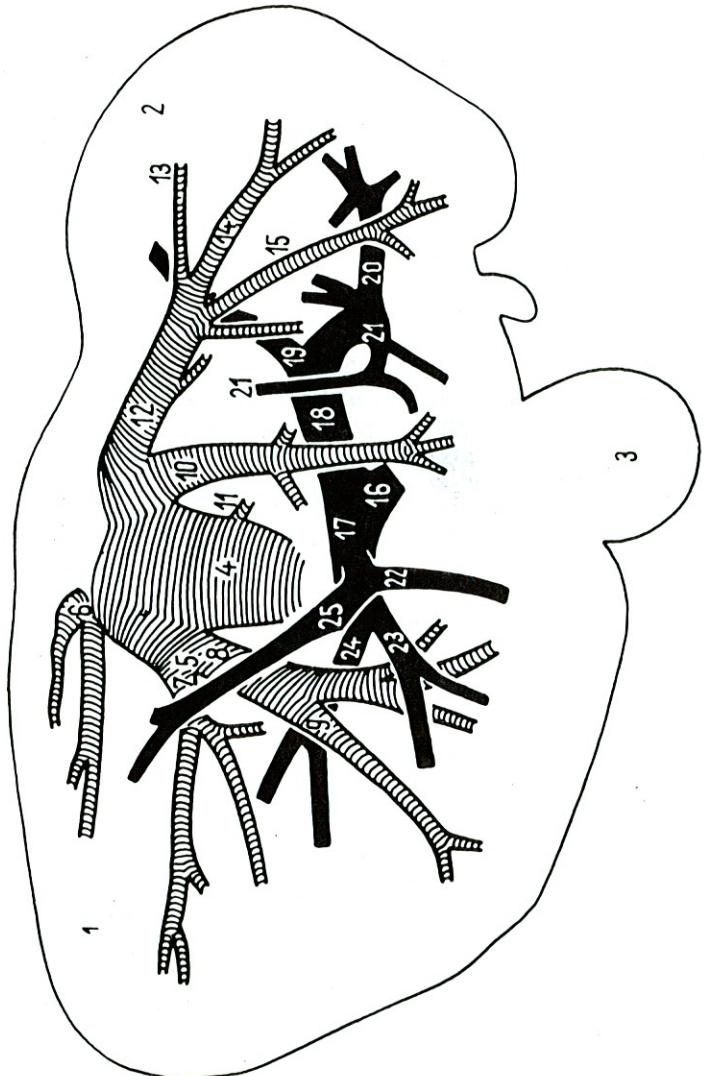


Figure 3. The portal vein and its efferent branches (black), and the hepatic veins (crosshatched) (craniocaudal view). The right and left hepatic veins spreading their branches in a fingerlike way deep into the lobar parenchyma and interdigitate with the intrahepatic portal branches. 1. Right lobe of liver. 2. Left lobe of liver. 3. Gallbladder. 4. Left lobe of liver. 5. Inferior vena cava. 6. Right superior hepatic vein. 7. Posterior intermediate hepatic vein. 8. Left superior hepatic vein. 9. Middle hepatic vein. 10. Caudate hepatic vein. 11. Superior branch. 12. Left branch. 13. Transverse branch. 14. Portal vein. 15. Superior root. 16. Inferior root. 17. Right branch. 18. Left branch. 19. Superior branch. 20. Inferior branch. 21. Superior posterior branch. 22. Inferior anterior branch. 23. Inferior posterior branch. 24. Superior anterior branch. 25. Superior posterior branch. 26. Caudate branches. V₁. From Luzsa, G. (1974). X-ray Anatomy of the Vascular System. Butterworths & Co., Toronto.

the left hepatic vein (Figure 3, no. 12) to form a short common trunk before emptying into the vena cava.

The right hepatic vein (Figure 3, no. 5) drains the territory to the right of the Sérégé gallbladder-caval line. Smaller veins empty above and below the group of the three major hepatic veins into the vena cava. They drain blood from around the gallbladder, from the caudate process (Figure 3, no. 11), from the posterior portal segment (Figure 3, no. 6), and from the lateral portion of the anterior portal segment in the right liver lobe.

Intrahepatic Distribution of the Hepatic Vessels

The topography of the vascular and biliary structures within the liver has been studied by Hjortsjö (22, 23) and by Elias and Petty (24). Bilbey and Rappaport (19) have reinvestigated the gross intrahepatic distribution of portal vein, hepatic artery, and hepatic veins. For the illustration of these vessels line drawings made after angiograms of the human liver are used (25).

Portal Vein The portal trunk divides in the portal fissure into the left (Figure 1, no. 20) and right (Figure 1, no. 19) hepatic lobar branches. The left branch is longer than the right and consists of transverse (Figure 1, no. 24) and umbilical parts (Figure 1, no. 24a). The latter is the remainder of the left umbilical vein. It has a longitudinal course (Figure 1, no. 23) and continues into the round hepatic ligament. Thus a bend is formed between transverse (Figure 1, no. 24) and umbilical parts of the left lobar branch (Figure 1, no. 20). The paraumbilical veins, important hepatofugal collaterals within the falciform ligament, spring from the umbilical part of the left portal branch.

The injection of multicolored vinylite acetate into the vascular branches and the biliary ducts accessible in the porta hepatis has demonstrated that the liver can be divided into gross and microscopic segments according to the distribution of the major supplying and efferent vascular and biliary branches (19). The outline of the vessels (Figure 1), according to the gross segments of the liver they service, summarizes the nomenclature for the intrahepatic branches of the portal vein. Each segment depends on its major vessel for blood supply. There is no anastomosis between the macroscopic branches, but abundant intercommunication exists at the level of the sinusoids.

Hepatic Artery Thorough knowledge of the intrahepatic segmental arterial supply and of the topography of the intrahepatic branches is important in radiology, surgery, and pathology of the liver. The straight intrahepatic arterial branches seen in the young become tortuous in older individuals (17). The major arterial rami (Figure 4) do not parallel the corresponding portal and biliary channels, although the smaller branches do (Figure 5). The tridimensional growth of the intrahepatic vessels and bile ducts is favored by the hemispherical shape of the hepatic surface, which molded itself into the space under the cupola of the right hemidiaphragm (26). The

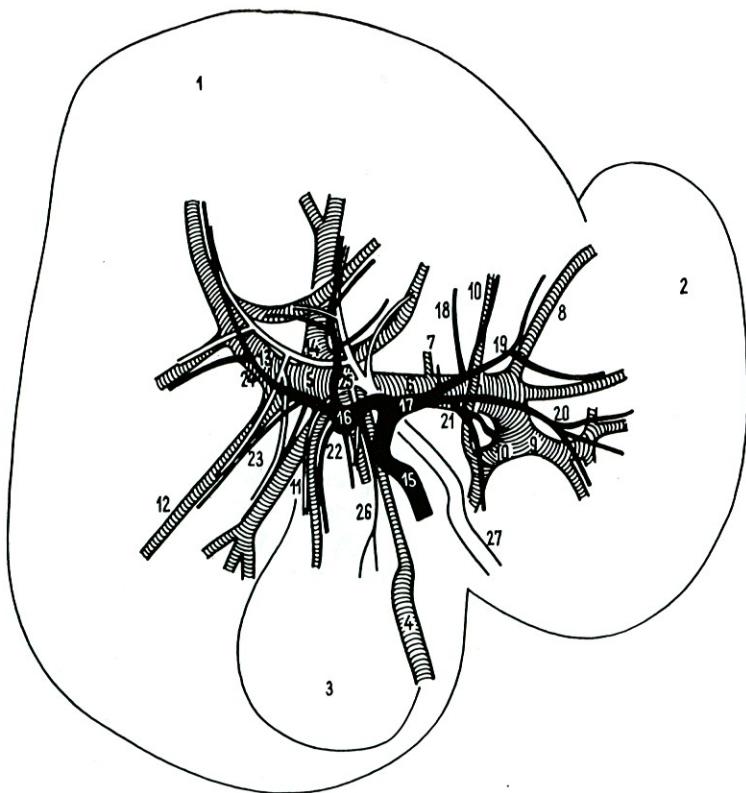


Figure 4. The portal vein (crosshatched), hepatic artery (black), right hepatic duct (white), and their branches (craniocaudal view). The large branches of HA, PV, and bile duct take an individual intrahepatic course; only their small branches run parallel to each other. 1. Right lobe of liver. 2. Left lobe of liver. 3. Gallbladder. 4. Cannula in portal vein. 5. Right branch of the portal vein. 6. Left branch of the portal vein. 7. Caudate branches, V₁. 8. Superior branch, V₂. 9. Inferior branch, V₃. 10. Pars transversa, V₄. 11. Inferior anterior branch, V₅. 12. Inferior posterior branch, V₆. 13. Superior posterior branch, V₇. 14. Superior anterior branch, V₈. 15. Cannula in hepatic artery. 16. Right branch of the hepatic artery. 17. Left branch of the hepatic artery. 18. Artery of caudate lobe, A₁. 19. Superior lateral segmental artery, A₂. 20. Inferior lateral segmental artery, A₃. 21. Middle segmental artery, A₄. 22. Inferior anterior segmental artery, A₅. 23. Inferior posterior segmental artery, A₆. 24. Superior posterior segmental artery, A₇. 25. Superior anterior segmental artery, A₈. 26. Cystic artery. 27. Cannula in right hepatic duct. From Luzsa, G. (1974). *X-ray Anatomy of the Vascular System*. Butterworths & Co., Toronto.

intrahepatic arterial branches of macroscopic size have a strong circular smooth muscle layer and a well developed elastica interna (27). In the intima of the human HA one can also find sphincter pads formed by scattered bundles of longitudinal smooth muscle fibers connected with the circular smooth muscle layer (28). Contractions of the sphincters regulate blood flow to macroscopic areas (lobar segments) as well as to large microscopic structural units. The slender intrahepatic arterial rami usually run parallel to the intra-

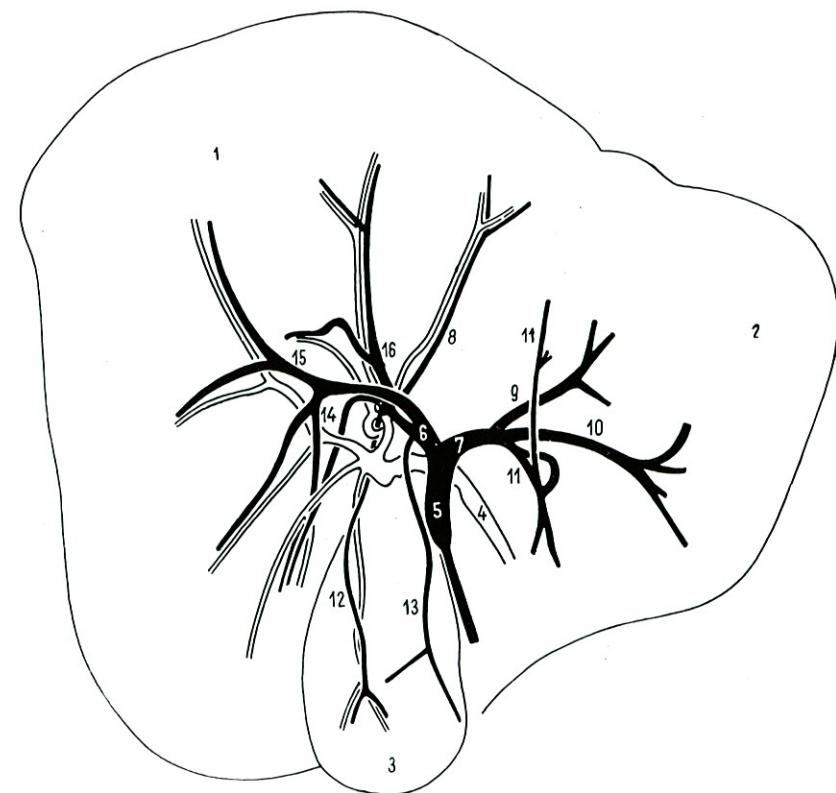


Figure 5. The hepatic artery, the right hepatic duct and their branches (craniocaudal view). The close anatomical relationship between arterial branches and the small bile duct branches is evident. The left hepatic duct and its branches are not shown. 1. Right lobe of liver. 2. Left lobe of liver. 3. Gallbladder. 4. Right hepatic duct. 5. Hepatic artery. 6. Right branch. 7. Left branch. 8. Artery of caudate lobe, A₁. 9. Superior lateral segmental artery, A₂. 10. Inferior lateral segmental artery, A₃. 11. Medial segmental artery, A₄. 12. Inferior anterior segmental artery, A₅. 13. Cystic artery. 14. Inferior posterior segmental artery, A₆. 15. Superior posterior segmental artery, A₇. 16. Superior anterior segmental artery, A₈. From Luzsa, G. (1974). *X-ray Anatomy of the Vascular System*. Butterworths & Co., Toronto.

hepatic bile ducts (Figure 5). The microscopic arterial twigs run close to the corresponding portal branches of microscopic size, thereby assuring a supply of arterial blood along with portal venous blood.

Hepatic Veins. Since catheterization of the hepatic veins for the determination of hepatic blood flow and portal pressure has become a standard procedure (29, 30) and guided catheterization of the hepatic veins has permitted their radiography (31-34), a brief outline of the intrahepatic branches of these veins may be useful. The intrahepatic course of the valveless veins is straight and simple. Their small branches are in direct contact with the hepatic parenchyma. They are named after the segments of the liver they drain (see legend to Figure 3). There are some anastomoses among the various

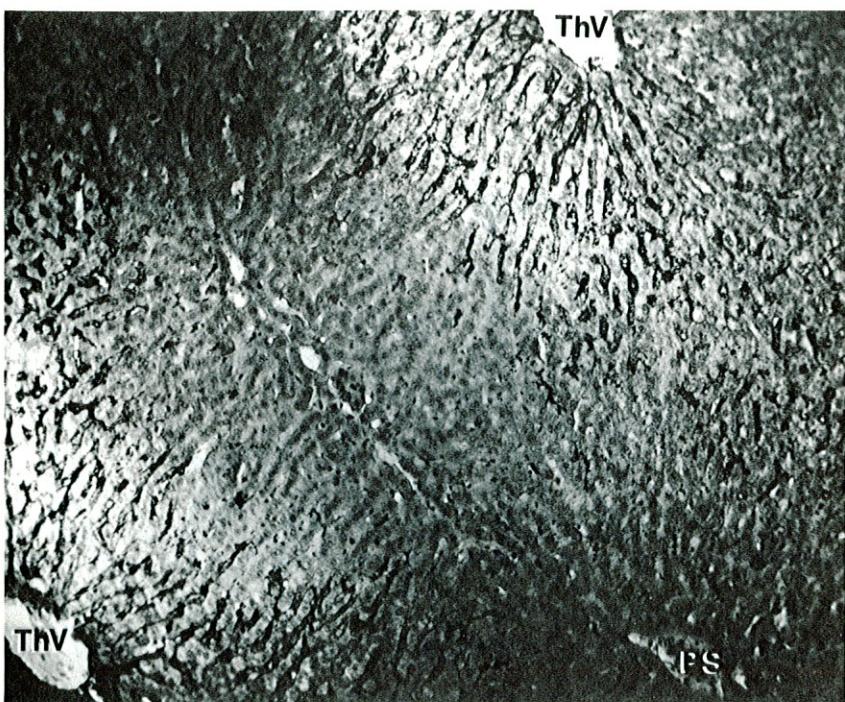


Figure 6. Acinar unit in the liver of a rabbit. The area clear of India ink is centered around the axial channels that grow out from a small portal space (PS) and are the dividing line between two hexagonal fields. The unit extends into the two adjacent hexagonal fields, the terminal hepatic venules (ThV) of which are seen in the left lower and right upper corner. (Modified after Rappaport, A. M., Borowy, Z. J., Lougheed, W. M., and Lotto, W. N. (1954). *Anat. Rec.* 119:11.) ($\times 100$ approx.)

branches of the hepatic veins. Normally no communication exists between the hepatic veins and the portal venous system, except via the sinusoids.

There is a definite spatial relationship between the branches of the hepatic veins and those of the portal vein and the hepatic artery. The branches of the hepatic vein interdigitate with the afferent vessels (Figure 3). This architectural arrangement is maintained up to their finest ramifications (Figure 6). A uniform and quick drainage from all parts of the liver is thereby accomplished. The regular interdigitation of the terminal radicles of the hepatic veins (Figure 6, terminal hepatic venules—the "central" veins) with the tridimensionally arranged terminal afferent channels brings about a hexagonal pattern in the parenchyma at microscopic level. The distance between two terminal hepatic venules is equal to the width of one liver acinus (Figure 6). This distance is halved by the perpendicularly running pair of afferent axial vessels and the terminal bile ductule of the acinus (Figure 6). Thus the veins are found to be situated at the periphery of the structure they drain, an arrangement that corresponds to the rule in vascular anatomy.

Terminal (Axial) Branches of Afferent Vessels, Sinusoids, and Radicles of Hepatic Veins

Hepatic Artery The terminal branches of this vessel supply all of the structures in the portal tracts and the parenchyma. There is general agreement that the arterioles and arterial capillaries join the terminal portal venules and the sinusoids in the periportal zone 1 only; no arteriole enters zone 3 (Figures 7, 8, and 9) (35-38). Indeed, two blood streams flow into a firmly encapsulated organ under quite different pressures and the question as to how the portal blood streams uphill against arterial pressure is not fully answered. It is believed that sluice mechanisms raise one stream to the level of the other by means of sphincters (39) at the junction of arterioles and arterial capillaries with portal venules and sinusoids. There are also sphincters at the outlets of the sinusoids into the peripheral venules. Sphincter activity has been observed by several workers (40-43), but the information about the histologic features of these sphincters is recent (44). McCuskey describes them as consisting of reticuloendothelial cells (36). These cells, when contracting their microfilaments, bulge with their nuclear region into the vascular lumen and narrow it.

According to Hale's clear review (45), the distribution of the terminal (axial) branches of the hepatic artery may be divided into: 1) a general plexus within the portal tract, 2) a special capillary plexus surrounding the bile ducts (peribiliary plexus), and 3) the arterial capillaries emptying directly into the sinusoids. The general plexus supplies the structures within the portal tract, except for the terminal branches of the bile duct. The plexus capillaries have an open network woven around the contents of the portal space, and send branches into the radial or peripheral sinusoids (38).

The peribiliary plexus consists of a close network around the bile ducts up to their terminal branches. These capillaries play an important role in secretion (46), absorption and concentration of bile, regeneration of hepatic parenchyma, and collateral arterial circulation of the hepatic tissue (47). Branches of this plexus pass into radial (48) and peripheral (49, 50) sinusoids, and through capillary connections join the portal vein. These capillaries form the "internal roots of the portal vein" (48, 49, 51). Their presence has been confirmed through microscopic observation of the intrahepatic circulation *in vivo* (40, 41, 43).

Arterioles and Their Junctions (Figure 7) The intralobular arterioles running freely through the hepatic parenchyma were described by earlier workers (52) and more recent investigators (53). We have repeatedly observed *in vivo* periportal activity of hepatic arterioles in zone 1 only (41). A clear and detailed electron microscopic study under low magnification of the various anastomotic ways of the hepatic arterioles with the sinusoids and portal venules in the rat has been published by Burkel (44). The structural complexity of the arterioportal junctions indicates multiple possibilities for

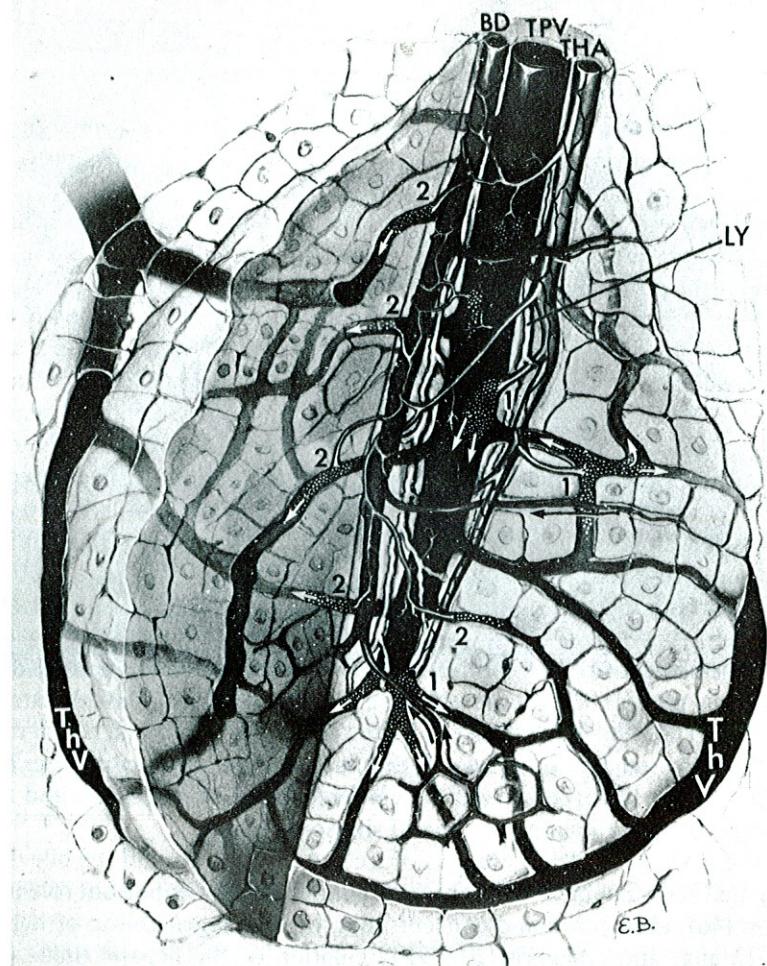


Figure 7. Microcirculatory hepatic unit. The unit consists of: a) the terminal portal venule (TPV) with the sinusoids branching off it and forming a glomus; and b) the hepatic arteriole (THA) lacing with its branches a plexus around the terminal bile ductule (BD). The arterioles empty either directly (1) or via the periductular plexus (2) into the sinusoids and TPV. The sinusoids run along the outside of cell plates and cords, inside of which are the capillaries of the secretory and excretory systems of the liver. The glomus of sinusoids is drained by at least two terminal hepatic venules (THV). Ly = lymphatics. (From Rappaport, A. M. (1973). *Microvascular Research*. Courtesy of Academic Press, Inc., New York.)

the hepatic artery to regulate the flow of arterial and portal blood into the acini. An understanding of the regulatory mechanisms is essential for the solution of many circulatory problems of hepatic physiology (54), pathology, and therapy.

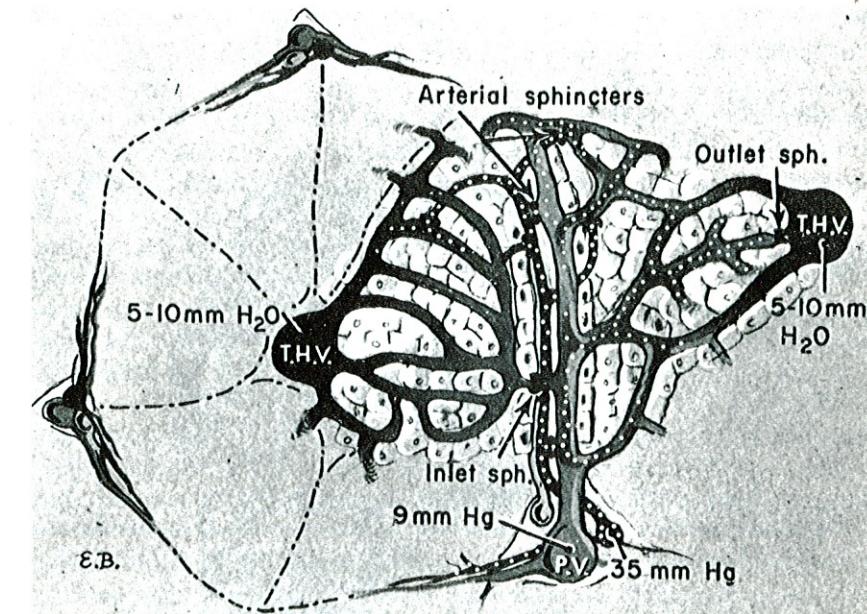


Figure 8. Microcirculation in a liver acinus. The acinus is shown in its relation to the hexagonal design. The pressure in the terminal portal, arterial, and hepatic venous branches is indicated. Note in the upper left half of the figure an opened arteriolar sphincter that admits arterial (white dotted) blood into the sinusoidal area filled primarily with portal (black) blood. The outlet sphincters around the left terminal hepatic venule (THV) are open. In the right half of the figure arteriolar-portal and arteriolar-sinusoidal sphincters (arrows) have opened, admitting blood and thus raising velocity in all the sinusoids. PV = portal vein. (From Rappaport, A. M. and Knoblauch, E. (1967). In Vanderbroucke et al. (eds.), *Liver Research*. Courtesy of *Tijdschrift voor Gastro-enterologie*, Antwerp.)

Portal Vein Elias (50) introduced a distinctive nomenclature for the finer intrahepatic ramifications of the portal vein. His differentiation into "conducting" and "axial distributing" veins, although possible only when these vessels are seen in longitudinal section, is very suitable for practical purposes. Serial sections of conducting veins reveal the regular branching out of venules to supply periportal cuffs of tissue. Thus the conducting veins also distribute blood quite regularly to neighboring tissue. Similar observations were made by Daniel and Prichard (55). In contrast, however, the axial distributing vein (50) is a terminal branch of the portal vein and is situated in the axis of an acinar unit whose sinusoidal glomus it supplies with its arborizing inlet venules. These venules show sphincterlike activity that regulates the amount of portal blood in the sinusoids (56).

Terminal Portal Venules (TPV) These are easily recognized in the microscopic slide. Their cross-sections are found in the smallest round or oval portal spaces; in a longitudinal section of the TPV the sinusoids branching from it can be seen easily. Preterminal portal branches—the axial vessels

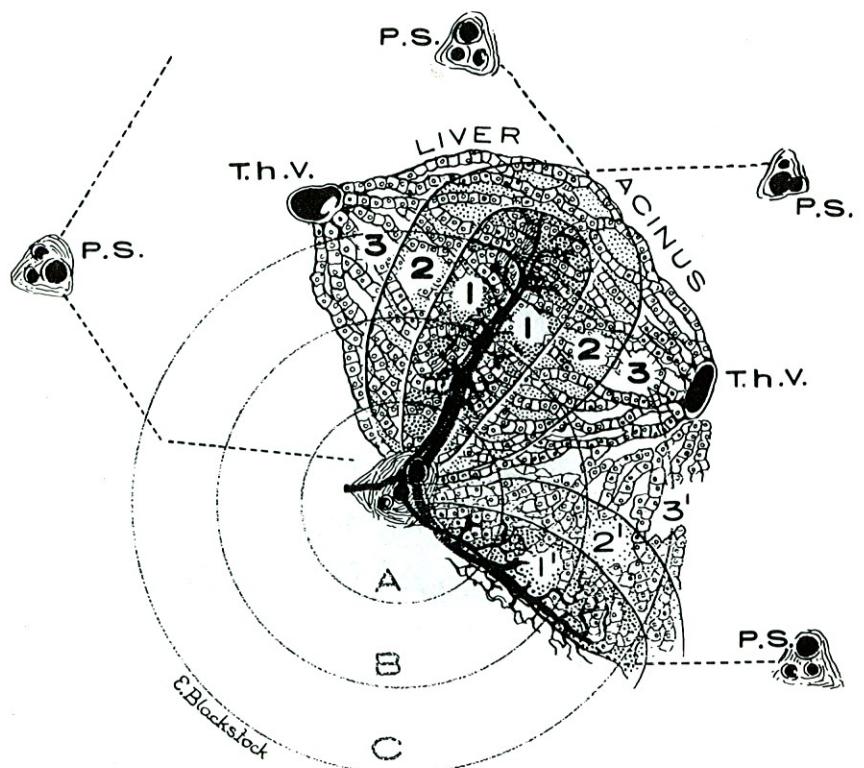


Figure 9. Microcirculatory zones in a simple liver acinus. The acinus occupies adjacent sectors of neighboring hexagonal fields. Zones 1, 2, and 3, respectively, represent areas supplied with blood of first, second, and third quality with regard to oxygen and nutrients. The zones center around the terminal afferent vascular branches, terminal bile ductules, lymph vessels, and nerves and extend into the triangular field from which these branches crop out. Zone 1', 2', and 3' designate corresponding areas in a portion of an adjacent acinar unit. The afferent vascular twigs empty into the sinusoids of zones 1 and 1' only. The circles B and C around a portal space of any size and shape indicate circulatory areas erroneously called "peripheral." The commonly called periportal zone A contains parenchyma belonging to zones 2 and 3. True periportal cells are seen in zone 1, close to the nutrient terminal portal venule. PS = portal space; THV = terminal hepatic venule. (Modified from Rappaport, A. M., Borowy, Z. J., Lougheed, W. M., and Lotto, W. N. (1954). *Anat. Rec.* 119:11.)

of complex acini—lie in small *triangular* portal spaces. The terminal portal venule is 50–70 μ long with an inner diameter of 15 to 35 μ ; its wall is formed by an endothelial lining and a basement membrane but has no smooth muscle cells. Regulation of blood flow through TPV is inefficient and is possible only through alternate swelling and shrinking of large endothelial cells at the entry into the sinusoids (36).

Sinusoids These hepatic capillaries are unique in their thin endothelial syncytial lining, large Kupffer cells, and fat-storing Ito cells (57, 58). The phagocytic endocytes (the Kupffer cells) are attached to the endothelial plasmidium and spread their stellate processes through the capillary lumen

toward different points of the wall where they anchor (59). Besides their role in the production of bilirubin, they are the scavengers of the circulatory canal system, clearing it of particulate matter, old erythrocytes, microthrombi, bacteria (60), and debris, which they engulf. The littoral cells and Kupffer cells are seen in the electron microscope as a discontinuous layer (61, 62) of endothelium composed of cells of various types (58, 63). Some are very thin and extend over three or four parenchymal cells; others are thicker, up to 5–6 μ . Their overlapping cytoplasmic lamellae are separated from each other by narrow passages, *fenestrae*. The fenestrations of the endothelium permit easy passage for blood plasma with its protein macromolecules, lipids, and lipoproteins (64) into Disse's spaces that communicate with the tissue spaces at both ends of the sinusoids (65). Sinusoids are primarily venous capillaries of the liver; they are 250 μ long and 7–15 μ wide; 90% of their length is lined by an endothelium that has no basement membrane. Their porosity is of chief hemodynamic importance because the low hydrostatic pressure (2 to 3 mm Hg) is not appropriate for a quick exchange between blood plasma and hepatic cells (56). The width of the sinusoids can increase to 180 μ when necessary. This change in caliber is caused by contractility, an exquisite feature of these capillaries, the structural elements of which have not been fully investigated. Thus, the microscopic feature of the function of the liver as a "venesector and blood giver of the circulatory system" (66) is disclosed. There is also tonic contractility (40), which helps to regulate the amount of flow through a vascular area. Groups of sinusoids shift their work asynchronously. The circulatory activity spreads simultaneously to those sectors of neighboring hexagonal fields that are adjacent to the active axial vessel. This phenomenon can be explained as circulatory activity of single acini (Figure 6).

Terminal Hepatic Venules (THV) The structure of these radicles of the hepatic venous system is not different from that of the TPV. The THV are surrounded by fewer pericytes, fibroblasts, and reticular fibers, and by a small tissue space; the hepatocytes lie close to their wall. Abrupt transition from capillaries to such large vessels as the THV (the so-called central veins) is unusual in vascular anatomy. The majority of the sinusoids empty individually into terminal hepatic venules. These venules are also the drainage centers of several outlet venules of groups of sinusoids, the "sluice channels of Deysach" (67). Collecting venules are surrounded in some species by sphincters at their site of junction with the preterminal hepatic venules into which they short-circuit a certain amount of sinusoidal blood when needed. However, microphotos of the different phases of uranin secretion *in vivo* (68) further demonstrate that different acini around a THV also empty into collecting venules that they border. The absence of a limiting plate around the THV indicates that the surrounding tissue is not unified, but belongs to several structural units.

The walls of the intrahepatic venous branches have contractile elements (69, 70). In dogs and guinea pigs, the smooth muscles in the wall of the he-

patic veins contract during shock (71). The presence of muscle fibers in dogs and man was described by early workers (72, 73) and demonstrated later by Popper (74), who found that an inversely proportional rate of flow is possible in the hepatic veins and in their mural lymphatics.

The interdigitating relationship between the branches of the hepatic vein and the portal vein that is observed in the gross specimen is maintained at microscopic level between terminal branches of these veins. The terminal (axial) branches of the portal vein and of the hepatic artery run mainly perpendicular to the radicles of the THV that they surround (Figure 8).

THE MICROCIRCULATORY HEPATIC UNIT

The microcirculation is the most active part of the hepatic circulation inasmuch as it regulates nutrition and function of the parenchyma and its supporting tissues. It is the result of the total merging of the hepatic arterial and portal streams in a common delta. However, the arterial blood with its high pressure does not drop like a great waterfall into the large sinusoidal bed with its low pressure level; it does not dissipate its energy at once. The stream in the hepatic artery breaks up into as yet uncounted rivulets, each of them passing through an arteriole. The arteriole becomes the center of a microvascular glomus around which the acinar parenchyma is organized. Thus the microcirculation of the liver is organized into *units* in which pressure and flow are primarily under arteriolar control. The microcirculatory hepatic unit (Figure 7) is structured around the terminal hepatic arteriole that eventually twines itself as a plexus of arterial capillaries around the terminal bile ductule. The arterial capillaries empty into the sinusoids at the site where they branch off from the TPV. The sinusoids form a glomus around the axis of arterial and portal terminal vessels and empty at their peripheral end into at least two THV, which interdigitate with the two axial vessels and the terminal bile ductule(s). The anatomical features important for the dynamics of the hepatic microcirculation are the smooth muscle cells around the larger arterioles and, to a lesser degree, the precapillary sphincters. The large endothelial cells at the entry and exit of the sinusoids and arterial capillaries, by the activity of their intracellular microfilaments, may act as the adjusting "microscrews" of sinusoidal flow.

The arterioles of the largest size (100μ in diam) have an elastica interna, a media of a double layer of smooth muscle cells, and a thin adventitia containing unmyelinated nerve fibers. The terminal arterioles ($20-50 \mu\text{m}$ in diam) have no elastica interna, only a single layer of smooth muscle cells richly supplied with unmyelinated nerve fibers. The arterioles continue into capillaries that form the peribiliary (periductular) arterial plexus and eventually join the sinusoids (Figure 7, no. 2). The capillaries originate at right angles to the axis of the arterioles; here, for a distance of 30μ , some of them have their walls surrounded by strong smooth muscle cells forming precapil-

lary sphincters (75). The arterial capillaries are lined by a nonfenestrated endothelium.

Role of the Hepatic Arterioles in the Functional Organization of the Hepatic Parenchyma

In the fetus, hepatic arterial flow is extremely low (76-78). At birth the circulatory activity of the HA is augmented. The hydrostatic pressure and Po_2 gradients between the afferent and efferent terminal vessels of the liver increase and an organization of the hepatic parenchyma around the arterioles takes place. Parenchymal clumps cluster like berries on the stalks of the supplying vessels and were named "liver acini" by Malpighi as early as 1666 (79).

Simple Liver Acinus (Figure 6) The simple liver acinus is defined as a microscopic parenchymal mass, *irregular* in size and shape, arranged around an axis consisting of the terminal hepatic arteriole, portal venule and bile ductule, lymph vessels, and nerves, which grow out together from similar preterminal structures in a small triangular portal space (80, 81). The acinus lies between two or more THV (Figure 6), i.e., the "central veins" with which the acinar vascular and biliary axis interdigitates. The interdigitation at the microscopic level of terminal branches originating from three triangular portal spaces around one THV may create a vascular pattern resembling a hexagon (Figure 8). A simple liver acinus is subdivided into three circulatory zones surrounding the supply vessels like layers of a bulb. Cells in zone 1, in proximity to the arterioles, are bathed by blood closer in composition to arterial than to portal venous blood. The cells in zone 3, into which no arteriole enters (35, 37, 82, 83) are most distant from their own supplying vessels, as well as from those feeding adjacent acini (Figure 9). Hence, zone 3 is situated at the microcirculatory periphery of the acinar unit and receives blood that has already exchanged gases and metabolites with the cells in zones 1 and 2. Cells in zone 3 are most sensitive to damage through anoxia, ischemia, congestion, and nutritional deficiency (84). Zone 2 represents a dividing layer of tissue that joins either zone 1 or zone 3, depending on the changing dominance of hepatic arterial flow in the individual acinus. The cross-section of a portal space harboring the axial structures of a simple acinus is *round* and small (around $100 \mu\text{m}$).

Periarteriolar Metabolic Areas The changeover from the fetal to the neonatal circulation establishes different microenvironments in the circulatory zones (85). Cytologic (86), enzymatic, and biochemical changes in the liver have been demonstrated in the perinatal period (87-89).

From the data collected in the literature on histochemistry and enzymology (26, 85) (tabulated in Figure 10), it is evident that in the hepatic microcirculatory unit (56) there is metabolic organization closely related to the direction of blood flow (94) and the arteriolar supply. As the arterioles deliver their blood into the beginning of the sinusoids in zone 1, the tissue Po_2 in this

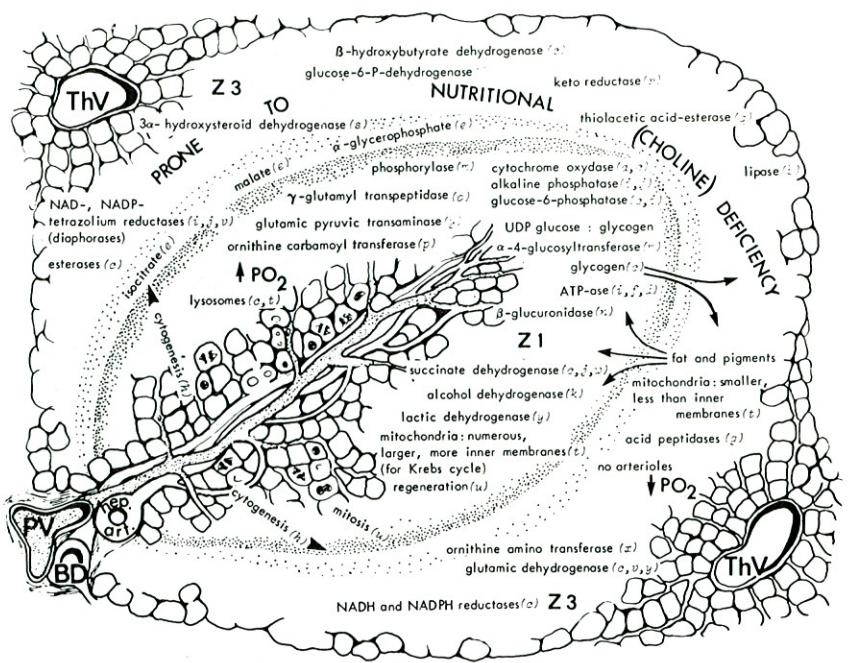


Figure 10. Metabolic areas in the acini. Specific enzymic activities indicate predominant metabolic functions in each of the microcirculatory zones of the acinus. The references in parentheses indicate the corresponding source: *a* = (366); *b* = (102); *c* = (62); *d* = (367); *e* = (368); *f* = (369); *g* = (370); *h* = (99); *i* = (371); *j* = (372); *k* = (373); *l* = (374); *m* = (93, 94); *n* = (375); *o* = (376); *p* = (377, 377a); *q* = (378); *r* = (379); *s* = (380); *t* = (381); *u* = (382); *v* = (383); *w* = (384); *x* = (385); *y* = (386). PV = portal vein; THV = terminal hepatic venule; BD = bile ductile; hep. art. = hepatic arteriole; *Z*₁ = periportal area; *Z*₃ = microcirculatory periphery. (From Rappaport, A. M. (1975). Anatomic considerations. In L. Schiff (ed.), *Diseases of the Liver*, Chap. I. Courtesy of the J. B. Lippincott Co., Philadelphia.)

area is closer to arterial tension than in zone 3. In the proximity of the THV the PO_2 is rather venous. Direct measurement of the tissue PO_2 gradient has been carried out by Kessler (90, 91). A periportal-perivenous redox potential gradient has been observed by Quistorff and Chance (92) in the normoxic rat

liver. Enzymatic activities resulting in glycogen formation (93–95) prevail in zone 1, where the tricarboxylic cycle is most active. Rat liver glycogen synthetase is strongly stimulated by cellular carboxylic acids, which are intermediates of glycolysis and of this cycle (96). Recently Jungermann and Sasse brought evidence that the gluconeogenic compartment in rat liver is formed by hepatocytes of zone 1, whereas the glycolytic liponeogenic liver cells are predominantly in zone 3 (95). Sasse et al. (97) studied the zonal distribution of enzymic activity of glucose-6-phosphatase, glycogen synthetase, and glycogen phosphorylase in the hepatic parenchyma and in the single cell population of fed and fasted rats. They came to the following conclusion: "Hepatocytes from the one and the same physiological state have a different outfit of active enzymes and of cell constituents and thus probably different functions." Zone 1 is the most active area of protein synthesis (98); this is also the prime area of cyrogenesis (99), especially during regeneration (100). In the rat with normal hepatic circulation, the activity of γ -glutamyltranspeptidase is limited to the highly arterialized zone 1. Arterialization of the liver by diverting portal blood distributes the activity of the enzyme over all zones of the acinus (101). The functional dependence on arterial supply of this enzyme is instrumental in the detoxication of drugs.

In zone 3, enzymic activity of lipid (102), steroid, drug, and pigment metabolism is dominant. Recently, Guder et al. (103) and Van Waes and Lieber (104) have underlined the importance of glutamic dehydrogenase activity in zone 3. Substantial changes in the microcirculation, however, may lead to alterations in the usual enzymatic pattern of the adult liver. The diagrammatic outline of the enzymatic activities in Figure 10, therefore, should not be considered as a static map of metabolic functions; it is rather to be thought of as a dynamic state during normal hepatic microcirculation (56, 93). Necrosis of the parenchymal cells in one zone leads to a shift of the enzymatic activity toward the healthy cells of the neighboring zone (70).

Deductions made from experimental reversal of intrahepatic blood flow in dogs in an attempt to prove the independence of the enzymic topography from the direction of intra-acinar blood flow are not valid. The "reversed liver" does not receive portal blood at all, and the venous caval blood flows in a direction opposing the arterial stream (26), thereby wiping out the microcirculatory flow pattern and its delicate pressure and PO_2 gradients from afferent to efferent vessels.

Complex Liver Acinus The arterioles forming the axes of three simple liver acini are offsprings of a parent arterial branch contained in a small triangular portal space. The triangularity of the portal space is due to the cross-section of the arterial, portal, and bile duct canals branching out in a three-directional way (105). The common origin of the arterioles provides a certain microcirculatory unity between the three acini; together they form the microscopic hepatic unit of next higher order, the complex acinus (81). Constrict-

tion or dilatation of the parent branch will decrease or increase, respectively, the arterial flow through all simple acini constituting the complex acinus.

Lymph Vessels of the Liver

In the human liver there is a well developed subserous lymphatic network. The deep lymphatic channels run in the portal tracts where they are visible as the spaces of Mall (106), especially when serous exudation is present. The lymphatics surround the branches of the hepatic artery and the portal vein up to their finest ramifications and extend to their endothelial lining. The lymphatics are also connected intimately with the biliary tree. The injection of Chicago blue into the clamped choledochus against the direction of bile flow, under 310 mm H₂O pressure, makes the dye appear immediately in the hepatic lymph vessels (107). The lymph from these vessels is drained toward the lymph nodes at the hilum of the liver. The lymphatics surrounding the tributaries of the hepatic veins are frequently overlooked; they run along the walls of the tributaries of the hepatic veins and drain into the nodes around the inferior vena cava. The wall of the lymphatic capillaries is formed of spindle-shaped, scallop-shaped, and irregular endothelial cells; neither pericytes nor a basement membrane are present. Slits between the endothelial cells can constrict or dilate (108). Lymph capillaries have not been detected between the parenchymal cells. In 1890 Disse (109) put forward the theory that lymph spaces exist between the longitudinal fibers surrounding the hepatic sinusoids and that the walls of these clefts consist of a structureless fine ground substance and fine fibrils. These findings were denied by later investigators (106, 110). Electron microscopy, however, has revealed a continuous tissue space along the sinusoidal linings that terminates at the limiting plates. A direct connection between the Disse spaces and the lymph vessels in the terminal portal fields has not yet been demonstrated (111). One may also assume that some lymph percolates from the veins into the lymph vessels of the surrounding connective tissue.

Morphological Overview

In conclusion, when considering the overall morphological view of the affluents and road beds of the hepatic circulation we have presented, one has to bear in mind that the two rivers feeding the microcirculatory delta of the liver come from quite different areas. The one carries the life-giving goods of our atmosphere, and in the other primarily floats the goods of mother earth harvested on the peaks and valleys of the mucosal ridges in our intestinal regions. The hepatic sinusoidal delta into which both empty is arranged tridimensionally; if it were flattened in two dimensions it would cover a yet undetermined number of square meters. From these microvascular channels with their well controlled sluices the two united streams, after having been thoroughly mixed with each other, purified, and enriched with liver

"goodies" (112), empty through three to five venous arms into the large caval bay that will carry their bloody waters into the pounding cardiac surf. From there they will flow on and around myriads of sacs in the bubbly atmosphere where they spread out anew into vascular deltas. Finally, after having merged with other streams they will get into the heaviest breakers lashing against the stoney wall of the left heart, which will project their blood again onto the heights of pressure of one merged large mountain stream. The multiple and powerful falls of this stream will provide sufficient energy to drive the currents back to the regions they had just passed seconds ago, thereby completing a circular image of flow: the circulation.

Science, however, in its attempt to understand such repetitive events in our body, must turn to abstract and quantitative views on the motions of vital fluids in our organism in order to evolve the laws of circulatory physiology. But, function cannot be grasped without the framework of a structure that carries the functioning. Thus the preceding detailed knowledge of the vascular system of the liver, its structural variety, and differentiation will help us in the interpretation of unexpected and anticipated complexities of the hepatic circulation.

Measurement of Hepatic Blood Flow

The vascular network of the liver is interposed between the gastrointestinal and systemic circulation. It has often been called the antechamber of the heart because it collects all gastrointestinal and splenic blood via the portal vein and delivers it to the right heart. Each minute, a fifth of the cardiac output of blood passes through the huge vascular network of the liver. Although the hepatic vessels are accessible only by invasive procedures, the desire to determine minute flow in them dates back to the experiments by the anatomic Hyrtl in 1864 (113). Since that time many techniques have been developed for the quantitation of blood flow to the liver. According to Bradley (114) they can be classified as follows.

Direct Methods Direct methods are fraught with surgical trauma: anesthesia, opening of the peritoneal cavity, and preparation or section of vessels are necessary. These methods have yielded a lot of information about liver blood flow in various species. The older techniques—using Stromuhr, Thermostromuhr (115), internal calorimetry (116), the rotameter (117), or the collection method (118) (now made possible in humans with the help of a double balloon catheter [33])—are now supplanted by the electromagnetic flowmeter (119). This instrument can be calibrated for the measurement of absolute flow in humans (120); its flow probes, fitting the vessels tightly, can be implanted and left in situ to be used in the unanesthetized animal (121). The electromagnetic flowmeter has been employed for measuring hepatic blood flow in patients during operation. Another direct method is the transillumination of the exposed liver in small animals; besides the live aspect of the structure of hepatic parenchyma and microvessels (40), it conveys pat-

terns of microcirculatory change (42). It permits the microcannulation of the terminal hepatic vessels (122-124) and measurements of pressure, velocity, and volume flow in microscopic areas (125). These data are quite different (123) from those obtained in livers of small animals perfused primarily through the portal vein for metabolic studies (126, 127). Indeed the importance of pulsatile arterial perfusion has been demonstrated recently in larger animals, e.g., pigs (128). Radiologic visualization of the state of filling of the arterial and portal system and their collaterals (129) has also been used to evaluate the blood flow. The results, however, are uncertain. Angiography of the arterial, portal, and hepatic venous trees has now become a standard clinical procedure for the assessment of the abnormal pathways of circulation in various hepatic diseases (130). The liver, similar to the lungs, harbors 5% of the total blood volume; hepatic blood volume determinations, however, are not given full importance in the investigation of the metabolism of the liver. Pioneers of microcirculatory studies (43) have pointed out that not all the microvessels are in circulatory activity at all times. The *storage phase*, they claimed, should permit a closer exchange of metabolites between blood and parenchyma. Therefore, one notes shifts between circulatory activity and rest in macroscopic vessels also (131). Circulatory rest might also signify great metabolic activity in the particular area. Unfortunately, determination of hepatic blood volume plethysmographically is relegated to animal experiments only; this requires laparotomy, isolation, and fixation of the organ, which make results doubtful. Radioisotope labeling of plasma (132) has been helpful in overcoming these difficulties.

Indirect Methods The indirect methods are subdivided into three main procedures: 1) clearance and extraction technique, 2) single injection technique, and 3) dilution technique.

Clearance and Extraction Technique This technique is based on the Fick principle (133). It permits the calculation of blood flow through an organ if the amount of substance infused and removed exclusively by this organ each minute is known. Catheterization of the hepatic vein and sampling of its blood are required in order to establish the concentration difference of the substance between the artery supplying and the vein draining the liver. The substances most often used in liver blood flow studies are brom-sulphalein (BSP) (29) and indocyanine green (Cardio-Green) (134-137).

$$\text{Estimated hepatic blood flow} = \frac{R}{P - H(1 - HCT)}$$

where R = total dye removal rate (mg/min); P = arterial concentration of dye; H = hepatic vein concentration of dye; and HCT = peripheral venous hematocrit. A critical evaluation of the clearance and extraction technique has been presented by Winkler et al. (138).

Single Injection Technique With this technique one computes the change in plasma concentration over time following the intravenous injec-

tion of a single dose of a test substance, cleared by the liver only (139). When it is completely cleared from the blood and the concentration in the hepatic vein is at zero, an elimination curve is obtained. Blood flow can be calculated provided 1) the disappearance follows a simple decay function:

$$C_t = C_0 e^{-kt}$$

where C_0 = the initial concentration, C_t = the concentration at time t , and k = the disappearance constant; and 2) the plasma volume of distribution (V) is known. Clearance is then equal to the product of V and k , since k represents the fraction of volume of the test substance completely cleared. The value for V commonly used is the total plasma volume. Based on the efficient phagocytic activity of the reticuloendothelial (RE) cells situated in the liver, radioactive particulate matter has been used as a test substance; for example, ^{32}P -labeled chromium phosphate (140), radioactive gold (^{198}Au) (141), and heat-denatured plasma albumin labeled with ^{131}I (142). Phagocytic removal depends mainly on blood flow delivering the particles to the RE cells, which prefer the larger particles ($> 100 \text{ \AA}$). From 80% to 100% of a single dose of the above substances accumulates within the liver and spleen, yielding a disappearance curve that can be resolved into simple experimental functions. The label is an ideal test material, which allows the following of changes in plasma radioactivity by external monitoring; it eliminates invasive methods and prolonged infusions. It seems that data obtained with ^{198}Au come closest to those obtained by the direct electromagnetic method (143). When indocyanine green (ICG) is used in the single injection technique, it requires catheterization of an artery and of hepatic veins. Although there was good correlation between the flow data obtained with ICG and the direct electromagnetic flow measurements in normal states, the ICG method underestimated the actual flow by about 30% following experimental hemorrhage (144) and by 20% in septic shock (145), both in dogs.

Dilution Technique The indicator-dilution technique is based on the hydraulic principle that the volume flow within a moving stream may be determined by its ability to dilute a known amount of indicator measured with respect to time. In case of liver blood flow one determines the dilution of a known quantity of tracer substance within the hepatic circulation over a measured period of time (146). Human serum albumin (HSA) labeled with ^{131}I when injected into the spleen travels as a "bolus" into the liver. The amount actually injected and diluted within the hepatic blood flow can be calculated as the product of peripheral blood flow radioactivity at equilibrium (10 min after injection) and the total blood volume determined separately. This value is then divided by the value for hepatic venous activity, established either by external recording or by repeated collection of hepatic venous blood samples. However, several factors (e.g., nonuniform mixing and recirculation) make this method yield uncertain results. Recently, the methods of Ketty-Schmidt used in the measurement of cerebral blood flow

have been adapted to the determination of hepatic blood flow. Lipid soluble and highly diffusible radioactive isotopes such as ^{133}Xe and ^{85}Kr are used in the measurement of blood flow through an organ (147). Their fast diffusion establishes an instantaneous equilibrium between blood and tissue concentration of the gas. The removal of the gas is directly proportional to the blood flow, and the activity of the isotope as it disappears from the organ can be detected by an externally placed detector. In a homogeneously and constantly perfused tissue the disappearance rate is calculated using the equation for a monoexponential clearance function:

$$C_t = C_0 \cdot e^{-kt}$$

where C_0 and C_t indicate the concentration of the tracer in the organ at times 0 and t , respectively. The logarithm of the concentration of the tracer diminishes in relation to time and k is expressed by the following mathematical relationship:

$$k = \frac{\ln 2}{t_{1/2}}$$

where $t_{1/2}$ = the time in minutes during which the concentration of the tracer has declined to half its given value. Assuming that the gas leaves the tissue of the liver via the blood, only flow of blood can be calculated by the formula flow = $k \cdot S \cdot 100$. In this formula S stands for the tissue-blood partition coefficient of the tracer divided by the specific weight of the tissue (148). If, instead of one, there are several tissues homogeneously perfused, then a composite elimination curve will be registered that can be resolved into a number of components (149). Various routes for administration of ^{85}Kr and ^{133}Xe have been used (150-154). In recent years substances have been injected into the PV via a catheter placed in the umbilical vein and reaching the left lobar portal branch. This procedure, permitting the study of portal flow in man without laparotomy (155, 156), is now being used more frequently in the clinic. However, there are many methodological problems in the measurements of hepatic blood flow (157) that are under continuous investigation. The term "estimated hepatic blood flow" (29) is still justified.

Arterial Flow

The role of the hepatic arterial circulation has been considered for centuries to be of minor importance for the function of the hepatic parenchyma; it was supposed to supply only the connective tissue and gallbladder. Generations of surgeons in the preantibiotic era, however, dreaded accidental injury to the HA during operations, because it was followed by death in at least 50% of the cases (158). When an experimental procedure was devised for the successful ligation of each of the branches of the hepatic artery with the animal surviving (159, 160), it became possible to evaluate the contribution of arterial flow to hepatic function.

Arterial Pressure and Volume Flow The mean pressure in the HA under anesthesia is generally quoted at around 100 mm Hg. The resistance in the HA bed is 30-40 times that in the portal venous bed. The arterial blood passes through a long path of fine, muscular resistance vessels before entering the wide sinusoids. Circulatory phenomena resulting from this junction (see pages 13-14) cannot be mechanically explained as the interposition of a slow-flowing stream into the path of a fast one (161).

Separate measurements of the arterial and portal contributions to total hepatic blood flow have been made (155, 156, 162-164). The hepatic arterial bed shows pressure-induced autoregulation (165, 166). The basal tone of the resistance vessels is minimal at 80 mm Hg and increases as arterial pressure rises (167).

Interactions between the Hepatic Artery and the Portal Vein There is physiologic evidence of intrahepatic mixing of portal and arterial blood (168) and for a one-way HA-to-PV flow (39, 169-173). Experimental alterations of portal flow yielded various results. In some studies an increase in HA flow is associated with a decrease in portal flow (166, 174-176); others note little or no change (177-179). Differences in the findings may be attributed to experimental design with perfused liver (180, 181) failing to slow a compensatory increase in HA flow. However, when these types of preparations were not employed HA flow increased when PV flow was reduced (120, 181-183), e.g., during hemorrhage. The HA can deliver 65% of total liver blood flow (184, 185) under these circumstances. Also, hepatic arterial flow doubled after the formation of a side-to-side portacaval shunt (186).

Increased PV pressure in the liver causes increased constriction of the hepatic arterioles. The effects are most marked at portal pressure below 10 mm Hg (187), a reaction attributed to a myogenic control mechanism (166). Occlusion of the HA seemed to cause small and transient decreases in portal pressure, but the results are not uniform (165, 188, 189). The injudicious clinical application of these observations led to the surgical treatment of portal hypertension by ligation of the HA, with unfortunate results (190, 191). The hepatic arterioles react with vasoconstriction to increases in hepatic venous pressure, and arteriolar resistance may double when the pressure in the hepatic veins rises to 10 mm Hg (187, 192). However, arterial flow still manages to pass through the experimentally congested vascular network of the rabbit liver (193). In perfusion experiments, one finds (194) that during nonpulsatile perfusion the vascular resistance is increased by 115% as compared with pulsatile perfusion, a fact to be taken into consideration because in the majority of experimental liver perfusions nonpulsatile perfusion pumps are used. Resistance rises progressively with increases in perfusion rate. The increases in resistance are proportionately of greater magnitude than those in blood flow, thereby demonstrating autoregulation in the arterial system and, to a lesser degree, in the portal vein (195).

The arteriolar constriction following a rise in arterial, portal, or hepatic venous pressure is considered to be a myogenic reaction to a rise in trans-

mural pressure across the arteriolar wall (196-198), which enhances the rhythmic activity of the smooth muscle cells in the vessel wall.

Role of the Hepatic Artery Lautt (197, 198) has suggested that there is a reciprocity between hepatic arterial and portal venous flow for the purpose of reducing fluctuations in the clearance of substances such as drugs. The hepatic artery also regulates parameters affecting oxygen uptake, but oxygen extraction by the hepatic parenchyma is relatively constant because the structure of the normal microcirculatory pathways does not permit short-circuiting of oxygen from arterial or portal blood into the hepatic venules. Direct studies of the role of arterioles in the hepatic microcirculation have been made using the transillumination technique first introduced by Knisely (199) in the United States, Löffler (200) in Germany, Maegraith et al. (201) in Britain, Rappaport et al. (41, 202, 203) in Canada, Chenderovitch (204) and Caroli in France, Hanzon (205) in Sweden, and Nakata (122) in Japan.

The hepatic arterioles are constricted effectively by smooth muscle elements (41, 44). The angle at which arterioles and arterial capillaries join the sinusoids (9, 36, 206) determines the direction of blood flow through the sinusoids, the mixture of portal and arterial blood, and, thus, the oxygen saturation (41, 207). Our own in vivo observations show a marked slowing of flow after the HA has been occluded. With PV occlusion there is an incomplete circulatory block (204) since the hepatic arterioles continue to deliver blood.

Control of Hepatic Arterial Flow

Neural The hepatic plexus receives fibers from the celiac plexus, the vagi, and the right phrenic nerves; and it forms a thick coat around the HA. The origin and distribution of these fibers have been investigated by Ungváry et al. (208). The splanchnic arteries have an outer nerve plexus in the adventitia, a plexus between the adventitia and the media, and another plexus within the muscular media. No parasympathetic plexus to spleen, dorsal root, or sympathetic vasodilator nerve fibers to splanchnic vessels are present. Dilatation of these vessels is due to diminished vasoconstriction tone. Stimulation of vagal fibers produces no obvious change in intrahepatic resistance (209). Reflex responses occur within the hepatic vasculature. The first observations by Burton-Opitz (210) that stimulation of the plexus causes an increase in pressure in the HA and a marked reduction in flow in dogs have been confirmed (178). Following these changes there is reactive hyperemia; α -adrenergic receptors (176, 178) mediate these effects; and phenoxybenzamine blocks the receptors. Reactive hyperemia involves a combination of metabolic and myogenic mechanisms and an increase of metabolites (CO_2 , lactate, pyruvate, adenosine) and of osmolarity (H^+ and K^+ ions) in the stagnant blood during occlusion of the vessel. The hyperemia is greater after a longer occlusion. The repayment of flow debt is inversely proportional to the duration of vascular occlusion. Myogenic and metabolic factors are less active with venous than with arterial occlusion (211). Stimu-

lation of the hepatic nerves in the cat 1 hr after the blockade causes a vasodilatation, which in turn is blocked by propranolol, indicating the activation of β -adrenergic receptors (212). In cats there is an autoregulatory escape and return to control levels within 4 min in spite of maintained stimulation (167, 213). Accumulation of vasodilator metabolites may be the cause of this escape. After sinoaortic denervation in dogs there is a transient increase in hepatic arterial resistance, indicating that the HA takes only a minor part in the adjustment of systemic blood pressure changes (214). The HA easily evades nervous control. Although diminished HA flow could not be demonstrated in exercising dogs (215), there is a definite reduction in hepatic blood flow and splanchnic blood volume in man during muscular exercise (216-218). The regulation of intrahepatic flow takes place at the microvascular level. The rate of flow in the TPV is determined by the state of constriction or dilatation of the mesenteric, splenic, and gastric arterioles. Caliber changes in the TPV are adjustments to decreased volume flow in the microvessels, caused by constriction of the mesenteric arterioles or by changes in shape and volume of the endothelial cells at both ends of the sinusoids. The arterioles are richly supplied with unmyelinated nerve fibers and respond to sympathetic stimulation with a transient constriction. Expansion of the portal venous lumen elicits a "veno-motor" reflex (219); i.e., arteriolar constriction proximal to the site of venous distension. Mesenteric arteriolar constriction has been observed by Selkurt and Johnson (220) during an elevation of portal pressure; however, this could also be explained on the basis of myogenic autoregulation (221).

Elevated hepatic venous pressure may also induce reflex constriction of the hepatic arterioles (187). Traction on the mesenteric vessels produces in man and in experimental animals a fall in arterial pressure, provided the nerve supply is intact (222, 223). Traction is usually avoided by the careful surgeon during operation on the intestines. Splanchnic nerve stimulation causes transient hypertension (224). Heating or chilling the skin, a rise in carotid sinus pressure, or stimulation of the central end of the cut sciatic nerve all elicit changes in the splanchnic and hepatic vasculature (225).

Metabolic Although metabolism and circulation of an organ are interdependent, little is known about the relationship between hepatic arterial flow and hepatic metabolic rate (114). However, metabolites flowing into the sinusoidal network via the PV can have a "transhepatic" effect on the arterioles opening into these channels (226). Hopkinson (215) showed that during a 32% increase of total hepatic flow following a meat meal HA blood flow remains unchanged. However, in dogs an 87% increase in hepatic arterial flow is noted after an infusion of amino acids (227). Hypoxia does not affect HA flow; hypcapnia causes constriction of HA, and hypercapnia causes dilatation of HA. These data confirm earlier findings with hypercapnia; also, alkalosis caused by hyperventilation results in a decrease of hepatic arterial pressure and flow (228). The study of the effects of metabo-