

lites on the hepatic microvessels has barely started. Glucose infusion dilates the arterioles and renders their jets conspicuous during microscopic observation *in vivo* (206). McCuskey (36) has reported that adenosine and potassium are the chief metabolic dilators of the hepatic arterioles.

Secretory The early observation by Schwiegk (229) that an injection of sodium dehydrocholate produces an increase in HA blood flow together with the choleresis has been confirmed (230-232). This choleretic also dilates the arterioles (229, 233, 234). Sodium taurocholate and other natural bile acids are also choleretic (230, 231, 235). A direct link may thus be perceived between an increase in bile flow and sinusoidal perfusion (6, 236). Such regulation of intrahepatic blood flow and adjustment to momentary requirements of the parenchyma through the absorbed bile salts seem plausible, although a more detailed study is needed to establish a definite relationship.

Neurohumoral Stimulation of the hepatic nerves decreases liver volume, and as much as 50% of the blood in the liver may be expelled; this again proves the role of the liver as a blood reservoir (237). Regulation of flow occurs in the microcirculatory units mainly by the glycogenolytic hormones: glucagon, epinephrine (36), and possibly also secretin; the latter two dilate the arterioles and relax the precapillary sphincters. Glucagon causes an arterial pressure reduction in the pig of 7 to 11 mm Hg; the HA flow increases by 80% 2 min after administration, and by 58% in 10 min. The response to the drug is not modified by varying the anesthesia (238).

The portal contribution to the oxygen supply of the liver rises when the shunt vessels in the intestine (239) are dilated. The arteriolar smooth muscles and precapillary sphincters are very sensitive to stimulation by vasoactive substances circulating in the blood (240). Norepinephrine is released from the endings of the nerves supplying the splanchnic vessels; β receptors responding to circulating epinephrine are present in the splanchnic and hepatic vessels (241). Dopamine, the immediate precursor of norepinephrine, accounts for 95% of the catecholamine demonstrable in the liver. Norepinephrine has a strong vasoconstrictor effect on both the splanchnic and hepatic arteries. In a dose of 30-60 $\mu\text{g}/\text{min}$ given intravenously, it decreases total hepatic blood flow, although the hepatic arterial component is increased because of an elevation in systemic blood pressure (242). Epinephrine injected into a portal tributary has a vasoconstrictor effect; when administered directly into the HA it causes vasodilation; given intravenously to dogs it increases hepatic blood flow by augmenting its arterial component. Epinephrine administered by intravenous infusion to cats increases total hepatic blood flow with little change in hepatic arterial flow. Both epinephrine and norepinephrine are clearly vasoconstrictors in the perfused liver (243), because α receptors are also present in the hepatic vascular bed (242). The effect of epinephrine and norepinephrine depends on the dosage employed and on the route of administration.

Acetylcholine has been found in large amounts in the spleens of oxen and horses (243) but not in other species. The effects of acetylcholine on the

hepatic circulation are equivocal, and reproducible results are difficult to obtain. Acetyl- β -methylcholine dilates partly open arteriolar sphincters in the frog (244). One should keep in mind the absence of cholinergic innervation of the splanchnic and hepatic vessels and their lack of response to vagal neurectomy and stimulation. However, some workers (243) note an increase in hepatic arterial flow after the injection of 1-5 μg acetylcholine directly into the HA, which in the presence of circulating adrenaline showed a vasodilator effect. After an intravenous infusion of acetylcholine (60 $\mu\text{g}/\text{min}$) a marked vasoconstrictor effect occurs because of a drop in systemic blood pressure. This vasoconstrictor effect is exerted on the portal as well as the hepatic arterial vessels, and a drop in total estimated hepatic blood flow results.

In their classical experiment, Dale and coworkers (245) noted that histamine produces constriction of the smooth muscles of the hepatic veins, decreasing hepatic outflow and inflow of blood. This effect is dependent on the presence of the throttle muscles in the hepatic veins. The anatomy of these muscles is variable. Intra-arterial histamine evokes decreases in hepatic arterial vascular resistance and increases in hepatic portal vascular resistance. Intraportal injection of histamine through a transhepatic effect also decreases hepatic arterial resistance (246). Intravenous histamine injection is followed by a fall in systemic pressure in all species. These facts may explain the variable responses to histamine, ranging from increase (242, 247) to decrease in estimated hepatic blood flow and in HA flow (248, 249).

There is a decrease in portal flow following pituitrin injection (242, 250). Vasopressin, although it reduces portal pressure and flow, causes myogenic relaxation of the hepatic arterioles and increases the hepatic arterial flow (251-253). The increase in hepatic blood flow by Decholin (229), and to a minor degree by other bile salts, is caused mainly by augmented hepatic arterial flow (231, 233, 234).

Changes in the composition of blood gases reflect on the hepatic circulation: in mild hypoxia there is little change in hepatic blood flow, whereas in severe hypoxia with an oxygen saturation 50% less than normal there is a fall in estimated hepatic blood flow and the intrahepatic arterioles are constricted (242); no reactive hyperemia develops in the liver (223).

Hypercapnia always causes an increase in splanchnic vasoconstriction of arterioles and venous channels (254). Contraction of the spleen occurs by neural and neurohumoral factors. Greenway and co-workers (131) have paid attention to the even distribution of arterial blood in the liver lobes. Their conclusion that "nothing is known about possible interrelationships between drug effects on vascular and metabolic parameters" leaves the field wide open for further investigation.

PORAL CIRCULATION

The portal circulation carries blood from the gastrointestinal and splenic vascular bed. Portal flow depends on the pressure in the arterioles of these

vascular beds; pressure may vary as the smooth muscles of the microvessels display myogenic autoregulation (255). Increase in intra-abdominal pressure above 40 cm H₂O will decrease portal flow by 90% (256); this was demonstrated by angiography.

Rhythmic segmental, as well as tonic, contractions of the intestinal wall greatly influence blood flow within the bowel loops (257). The minute volume of portal flow increases with the rate of rhythmic intestinal contraction, but decreases with the duration of the tonic contraction. Food intake (258, 259) and the quality of food (for example, protein and carbohydrates) increase portal circulation (260). Another factor in intestinal and portal flow is the passive change in intramural pressure because of distension, which will influence intestinal circulation. As the distension increases, intestinal circulation decreases to complete cessation in the overextended obstructed bowel loop; this may eventually lead to necrosis of the bowel wall.

It is estimated that two-thirds of total hepatic blood flow is of portal origin. One may therefore expect that the blood bathing the parenchymal cells is derived mainly from the vessels supplying the gastrointestinal tract. It is evident that the osmolarity, hormones, and metabolites in the portal blood determine to a great extent the inner environment of the hepatocytes. However, oxygen content and P_{O₂} in the hepatic blood are greatly influenced by the corresponding values in the arterial blood. Because portal blood is venous and 70% saturated, with a P_{O₂} around 50 mm Hg, the "inner milieu" and P_{O₂} of the hepatocytes will therefore depend on the interplay and reciprocity of flow between HA and PV as established by earlier (261) and recent investigators (258, 262, 263).

Portal Pressure

Portal pressure depends primarily on the state of constriction or dilatation of the mesenteric and splenic arterioles and on the intrahepatic resistance, be it at the site of inflow or outflow from the liver. Normal hepatic arterial pressure is already greatly reduced within the sinusoids and has little influence on the portal pressure (264, 265). Hormones (e.g., epinephrine) dilate the mesenteric arterioles, thereby increasing portal pressure; vasopressin constricts the mesenteric arterioles and causes a drop in pressure (253, 266). Pathologic tissue changes in the liver raise portal pressure. In cirrhosis the pressure is increased because of augmented postsinusoidal resistance, caused mainly by fibrosis in zone 3 of the acini, where the outflow portion of the sinusoids is situated. The architecture of the gross vascular tree is distorted in addition, and the entire intrahepatic venous bed is significantly diminished. Presinusoidal and sinusoidal portal hypertension also occur, depending on the site of the increased hindrance factor (203). Portal hypertension can be reduced by diverting portal blood via a portacaval shunt into the inferior vena cava.

Regulation of Portal Flow

The intrahepatic portal vessels do not show pressure-induced autoregulation of flow (239). The PV does not differ in this respect from other venous vessels (267). The absence of smooth muscle fibers in the TPV wall (see page 16) eliminates autoregulation at the microscopic level. The muscular elements of the macroscopic portal venous branches, however, respond to stretch with myogenic activity (268).

Stimulation of the hepatic nerve plexus in cats causes an increase in portal pressure, but no change in portal flow; this response is well maintained during the entire period of stimulation (167). In rats (269), rabbits, guinea pigs, and cats, stimulation of the hepatic nerves or administration of adrenalin produces blanching of the peripheral parts of the liver, indicating restricted flow; portal flow is diverted toward the portions of the liver lobes that lie closer to the hilum. Thus, in states of circulatory distress the short-circuited portal blood returns faster via the hepatic veins into the systemic circulation. There is as yet no angiographic proof that similar shunting is present in the human liver.

Streamlined flow, as noted in the portal vein of restrained, anesthetized, and laparotomized rabbits, is not present in the human liver. During splenoprtography opacification of the liver is not segmental, i.e., it does not occur in the left liver lobe first, but in all lobes at once. ¹³¹I-labeled rose bengal was uniformly distributed in the liver of dogs following injection into spleen, small intestine, cecum, and colon (270, 271). Recently, however, streamlined flow in the human portal vein appeared to occur during the injection of ¹⁹⁸Au-labeled colloid into the ileocecal affluents of the superior mesenteric vein (272).

Physical Forces Modifying Hepatic Blood Flow

The liver moves with the diaphragm and is influenced also by the motion of the neighboring organs, intestines, and lungs. These mechanical factors produce shifts in the position of the hepatic vessels as well as in their filling. On the other hand, the blood content of the intraperitoneal organs will influence the intra-abdominal pressure. An experimental increase in intra-abdominal pressure causes a decrease in hepatic blood flow (256, 273). Gravity also affects hepatic blood flow; and orthostasis decreases estimated hepatic blood flow (274). Exercise causes changes in circulating blood volumes at the expense of the splanchnic circulation; consequently, the hepatic blood flow decreases because of splanchnic vasoconstriction (275, 276). These observations have initiated the introduction of prolonged rest in the therapy of patients with acute hepatitis.

It was commonly assumed that the phases of the respiratory cycle have their definite effects on emptying and filling the great splanchnic venous reservoir, thus increasing venous return during inspiration (277, 278). Deep

inspiration may reduce the luminal cross-section of the veins and impede the outflow of splanchnic blood (279-281). The modifying effects of respiration on splanchnic blood flow will depend on the forces active in the respiratory cycle (e.g., position, rate and depth of respiratory excursions, tone of diaphragm, abdominal wall muscles, intestinal filling).

As the "antechamber of the heart," the hepatic circulation is in a close relationship with the systemic circulation. This is most evident in pathologic circulatory states; for example, hemorrhagic hypotension (281a) and congestive heart failure.

In hemorrhagic shock splanchnic blood volume decreases to a greater extent in comparison to the loss in the total blood volume (282). Mesenteric arteriolar constriction occurs together with general vasoconstriction, but the hepatic arterioles have a tendency to dilate moderately and assure the oxygen supply of the hepatic parenchyma unless severe hypotension occurs.

In congestive heart failure the splanchnic vessels are constricted and estimated hepatic blood flow is reduced (283). There is passive distension of the splanchnic veins and the hepatic veins and venules are engorged. The trapping of blood in the venous reservoir may reduce the load on the failing heart. However, the large volume of blood in the abdominal veins can be easily displaced by increases in intra-abdominal pressure (forceful respiration, cough, defecation) and thrown—as a dangerous load—on the heart at any time.

Lymph Flow

The movement of lymph in mammals is caused by the *vis a tergo* of tissue turgor, by the position of the body and the limbs. Muscular activity, stretching, breathing, and variations in thoracic pressure are additional sources of energy for driving the lymph. The main function of the lymph is the collection and transport of large molecules, e.g., plasma proteins, particulate matter, tissue debris, bacteria, foreign substances, and tissue fluids. The liver lymph originates from the interstitial fluid in the spaces of Disse. These extend toward the limiting liver plates, and thus lymph fluid finds its way into the initial lymph clefts of Mall (106) situated in the portal spaces. Because of the permeability of the hepatic sinusoids to large molecules, the hepatic lymph contains 3%-5% protein, mainly albumin, thus approximating the protein content of blood plasma. Quantitative studies of hepatic lymph flow have been carried out by the Mayo group (284). They indicate that 80% of the hepatic lymph flow passes via the hilar lymphatics and cysterna chili into the thoracic duct. Hilar lymph flow is greatly increased in glycogenesis of the liver (285), in cirrhosis, and venoocclusive disease. Lymph flow increases when hepatic venous pressure is raised between 1 and 5 cm of H_2O above hilar interstitial pressure. The augmented flow parallels the rise in hepatic venous pressure (286). At the highest venous pressure induced, the protein composition of the lymph was almost identical to that of plasma. This is eas-

ily explained by the many communications of various and changing sizes (64) between the sinusoids and the spaces of Disse. Histamine in low doses increases hepatic lymph flow, its protein content, and specific gravity by changing the permeability of the endothelial cells lining the sinusoids (287).

There is a close connection between lymph flow and hepatic blood flow. Ligation of the thoracic duct and of the lymphatics at the hilum of the liver leads to a 30% decrease in total hepatic blood flow (288) because of stasis in the portal and the Disse spaces. The stasis leads to increased resistance in the arterial and portal vessels situated in zone 1 of the acinus. Ligation of the bile duct also increases the intrahepatic vascular resistance, but the maximal increase in tissue pressure occurs in zone 3; this causes an increased HA flow that overcomes the tissue pressure. Experimental production of acites by constriction of the inferior vena cava above the hepatic veins (289) blocks the efferent lymph vessels in the wall of the great vein. Experimental hepatic venous congestion or carbon tetrachloride poisoning in dogs and rats as well as liver cirrhosis in man lead to widening and increased permeability of the superficial and deep lymphatic vessels.

HEPATIC MICROCIRCULATION: ITS HEMODYNAMICS

The microcirculatory network of the liver is subdivided into units. The *microcirculatory hepatic unit* is the result of an ingenious modification of AV anastomoses at the microscopic level (Figure 7), with the arterioles having the function of additional injection pumps (290). The arterioles, 15-100 μm wide, have even at their smallest diameter the wall vested with one layer of smooth muscle cells and unmyelinated nerve fibers; some arterioles at the transition into their capillaries form precapillary sphincters. Arterioles and capillaries, after forming a periductular plexus, empty into the sinusoids at the site of their origin from the TPV into the latter (Figures 2 and 7).

The study of the hemodynamics of the hepatic microcirculation is at its very beginning stage for two reasons:

1. There are only scant and as yet unconfirmed reports on direct measurements of pressure and flow in the microvessels of the liver, the pressure being around 50 mm H_2O in the TPV and 10 mm H_2O in the THV (122, 123, 291).
2. We are still without an orientation in hepatic microcirculation because of the retention of the concept of a hexagonal liver lobule, a structure that has no microcirculatory unity (292).

However, from the clinical data on pressure in the portal and hepatic veins (PV, 200 mm H_2O ; wedged hepatic venous pressure, 80-100 mm H_2O) a tentative presentation of the forces governing the microcirculation of the liver is possible. The hepatic arterioles lie deeper under the liver surface than the TPV and THV, and pressure in them has not been determined as yet. One

has to distinguish between arterial capillaries originating from the periductular arteriolar plexus and the terminal arterioles branching off larger arterioles. The latter (Figure 7, no. 1) bypass the periductular arterial plexus and empty, with gushing pulsations, directly into sinusoids in zone 1, or less frequently into the TPV (124). No arteriolar activity can be observed outside zone 1 (36, 37). Because there are no structural differences between the hepatic and any other arterioles (e.g., the mesenteric), one is justified in assuming that the hepatic arteriolar pressure is at the same level as in the other arterioles; i.e., 30–35 mm Hg (400–500 mm H₂O). The question of how portal blood with low pressure can pass into sinusoids that are receiving arterial blood under pressure eight times as high, is explained through the following mechanisms:

1. Reduction of arteriolar pressure in the periductular capillary plexus; the capillaries arising from this plexus empty their blood with reduced pressure into the sinusoids.
2. An immediate drop to sinusoidal or to portal venular pressure at the opening of the arterial capillaries into the sinusoids or TPV, with the energy of pressure being transformed into velocity and acceleration of the blood flow. Ligation of the HA causes a decrease in velocity of erythrocytes (293).
3. Intermittent closure of arterioles and arterial capillaries, noted in the *in vivo* transilluminated liver (39, 43, 124), facilitates the entry of portal blood into the sinusoids that become shielded from arterial pressure (Figure 8); portal blood then flows because of the pressure gradient between TPV and THV (60–250 mm H₂O → 50 mm H₂O). When the arterioles open again, the *vis a tergo* on the portal venous columns of blood is increased, and they are swept ahead toward the THV, at the same time exerting (through interconnecting sinusoids) a Bernoulli effect on neighboring sinusoidal areas (207) (Figure 8).

Intermittent opening and closing of arterioles, their capillaries, and precapillary sphincters (44) are events regularly recorded in the cinematographic study of the normal microcirculation (124); it is not limited to the short interconnecting sinusoids (122), nor is it a sign of anoxia or disturbed flow (291). This inherent random rhythmicity in the microcirculatory flow pattern is part of the intrinsic tendency of an organ to maintain an overall constant blood flow despite changes in arterial perfusion pressure. The rhythmicity is not dissimilar to that observed in mesenteric capillaries (211); the microvessels of the liver, an outgrowth of the foregut, also participate in this particularity.

The pressure readings (122) obtained by lateral micropuncture of the TPV and THV (50 and 10 mm H₂O, respectively) indicate a further substantial venous pressure loss occurring during the passage of blood through the wide and multibranched sinusoids. No micropuncture of a hepatic sinusoid

has been accomplished to date. Wedged hepatic venous pressure transmits arterial (rather than portal) venous pressure from the sinusoids (294); also, pulsatory oscillations are noticed in the pressure tracings (295, 296). From the measured pressure difference between TPV and THV one may assume that sinusoidal pressure is very low, between 10 and 20 mm H₂O. The puzzling 40% drop in pressure in the sinusoidal bed has been explained by the passage through sphincters. Their presence is asserted by some authors (39, 297) but denied by others (42, 201). Recently, the pressure drop in the sinusoids has been ascribed to the porosity of their endothelium (56). The intermittent activity of the arterioles and of the endothelial inlet and outlet gates of the sinusoids (298) alters the movement of plasma from and into the sinusoids. Outward motion of plasma occurs on opening of the arterioles, narrowing of the sinusoidal outlets, or a rise in hepatic venous pressure. With a small rise in sinusoidal pressure the filtering of plasma through the fenestrated endothelium will continue because the tissue colloid osmotic pressure is thereby not modified. Inward movement of plasma, of interstitial tissue fluid, and of metabolites into the sinusoidal lumen is facilitated by narrowing of the sinusoidal inlet gates, constriction of the arterioles, and widening of the sinusoidal outlets. The intermittent emptying of the arterioles into the sinusoids and their junction under various angles allows rapid altering of direction, rate, and velocity of sinusoidal flow. This anatomic arrangement tends to diminish the natural concentration gradient that exists between the portal and hepatic venous end of the sinusoids, thus upsetting unidirectional flow. This together with the pulsatile motions in the sinusoids may ensure a thorough mixing of arterial and portal blood and expose all the hepatocytes to a plasma of a more uniform composition (299).

Regulation of the Microcirculation

Regulation of hepatic microcirculation occurs mainly via the arterioles through nervous stimulation, hormones, metabolites, and bile salts. The regulation of portal flow by the TPV is practically nil, because their walls have no smooth muscles (300). Still, they can adjust their width to the volume flow that is determined by constriction or dilatation of the splanchnic arterioles. Stimulation of the hepatic plexus has a transient vasoconstrictive effect on the arterioles. Glycogenolytic hormones (glucagon, adrenalin) relax the arteriolar sphincters, and the swift current of arterial blood moves glucose quickly out of the liver. Increased arterial flow also provides an arterial P_{O₂} necessary for raised metabolic activity, i.e., for gluconeogenesis and ATP formation. One can foresee that other gastrointestinal hormones (for example, secretin and gastrin), which increase flow in the HA and in the bile ducts, affect the microcirculation too. The contractility of the smooth muscles of the arterioles and precapillary sphincters depends further on the arterial P_{O₂}. Decrease in P_{O₂} will affect the most peripheral parts of the affer-

ent vasculature, the arterioles, first; lack of oxygen makes their smooth muscles relax and blood flow increases (301).

The literature has been examined in an attempt to evaluate the role of metabolically linked chemicals in the local regulation of blood flow. Nucleotides and some of the intermediary metabolites of the Krebs cycle in double concentration in the perfusate decrease vascular resistance in kidneys and muscles. Two or more chemicals may act simultaneously; however, the dominant chemicals are not the same in all organs (240). In the liver intermediary and end products of metabolism (lactate, pyruvate, adenosine, ATP, CO₂) will cause relaxation of the vascular smooth muscles (36). Ingested electrolytes brought in by the portal vein (302) may cause tissue hyperosmolarity that leads to an increase in blood flow (303). Changes in the firing rate and transmembrane potential, as well as the slow spread of excitation from cell to cell, have been noticed in smooth muscles when in a state of hyperosmolarity (304). Increase in concentration of K⁺ and H⁺ ions in the interstices of vascular smooth muscles may also modify blood flow by relaxing the smooth muscle cells of the vasculature (36, 305). Recent experiments producing local change in the pH around arterioles of the brain surface have demonstrated that their diameter is increased by a low pH and that the microvessels will constrict when the perivascular tissue is rendered alkaline (306). Many of these observations, although made in vascular areas outside the liver, will lead to new *in vivo* investigations of the factors regulating flow in the hepatic microcirculation.

Intestine and liver have more precapillary muscles than other organs; therefore, myogenic control prevails and it responds especially to rises in sinusoidal and venous pressure. It is also assumed that the reciprocal relationship between portal and arterial flow is based on myogenic control. A drop in PV flow results in a decrease in sinusoidal pressure that elicits the diminution in precapillary muscular tone, which in turn leads to increased HA flow (211). Increase in diameter of mesenteric arterioles during a drop in arterial pressure has been measured *in vivo* in cats (307). In the liver, however, the extent of the arterioles and their diameter cannot be gauged *in vivo* because only their openings into the sinusoids can be seen.

Bile Salts The fact that the arterioles of the excretory bile ductules are situated upstream from the sinusoids (Figure 7) indicates a certain dependence of sinusoidal flow on a prepositioned biliary filtering arrangement. It was compared to the excretory apparatus in the kidneys (46). The afferent arterioles enter the wall of the bile ductules and form the periductular arterial plexuses, from which arise the efferent arterioles; the latter empty into the straight sinusoids that run along the outside of the liver cell plates containing the excretory biliary capillaries. The observation *in vivo* of the arteriolar openings in zone 1 shows a distinct difference in circulatory activity between arterial capillaries of the periductular plexus that empty into the sinusoids (Figure 7, no. 1) and those that bypass the plexus and deliver their

blood in strong pulsating jets directly into sinusoids and their TPV (Figure 7, no. 2). There is a direct link between food digestion, absorption, and hepatic microcirculation (308). Such regulation of intrahepatic blood flow and adjustment to momentary requirements of the parenchyma through the absorbed bile salts has been discussed (see p. 30).

Recent experiments with selective destruction of the hepatocytes of zone 1 or zone 3 by Gumucio and co-workers (308a) led to the conclusion that the periportal hepatocytes are bathed with blood that contains a high concentration of bile salts. These cells transport the largest amount of bile salts into the canalicular of the acinus. Hepatocytes located in zone 3 contribute predominantly to the secretion of the bile salt-independent fraction of canalicular water. In further experiments perfusing the liver with [¹⁴C]taurocholate via the portal vein, the authors demonstrated the concentration gradient of bile salts from zone 1 to zone 3. They also showed that a single dose (15 μmol/100 g of body wt) of sodium taurocholate unduly raises the concentration of bile salts within the zone 1 portion of the sinusoids and selectively damages the periportal cells (308b). More research in this direction is to be expected. The connection between hepatic microcirculation and biliary excretion is also evident from the effect of glucagon (309, 310) and theophylline (311) on bile secretion. Although it is reported that both increase bile flow in dogs and man by enhancing the biological activity of cyclic AMP (312), it is well known that these drugs are also potent dilators of hepatic arterioles and that the Po₂ of bile is greater than that of portal blood and close to the arterial Po₂ (313). Secretin infused into the hepatic artery causes increased watery bile flow, suggesting an effect on the periductular arteriolar network (314, 315) similar to that on pancreatic blood vessels (316). Recent experiments with intravenous infusion of secretin demonstrated mesenteric arteriolar dilation and increase in PV flow. Thus the periductular arteriolar network is instrumental in the dilation as well as in the concentration of the organic constituents of bile (317). The intimate connections between hepatic microcirculation and biliary secretion in the same clump of parenchyma demonstrate again the structural, microcirculatory, and secretory unity of the acinus, the functional unit of the liver.

Drugs Any drug entering the liver is liable to have an effect on the microcirculation. Some of these were discussed under neurohumoral regulation of arterial flow (p. 30). However, our experience with a systematic testing of *in vivo* microcirculatory effects of commonly used drugs, even of those specifically used in liver ailments, is very limited. We have some knowledge about vasoactive substances. Norepinephrine and dopamine cause hepatic arteriolar constriction by direct interaction with α-adrenergic receptors in vascular smooth muscle (318). Acetyl-β-methylcholine chloride dilates partly open arteriolar sphincters (244); its inhibition of adrenergic neurotransmission concurs with its direct relaxatory effect on arterial smooth muscle (319). Vasopressin, although constricting the mesenteric and

splenic arterioles and reducing portal flow, causes myogenic relaxation of the hepatic arterioles and increases arterial flow (251, 252, 320) and oxygen tension in the hepatic tissue (253). A four- to fivefold increase in arterial flow to the liver follows the injection of parathyroid hormone (0.6 I.U./kg of body wt) in dogs (321). Prostaglandin (PGE) reduces arterial resistance through a local action on the arterial wall of mice, and this occurs even in the denervated vessels or after β -adrenoreceptor blockade (171). Extensive pharmacodynamic studies of the hepatic circulation have been done by Greenway and Stark (239) and I refer the reader to their detailed review.

Experimental Alteration of Hepatic Blood Flow

Alteration of hepatic blood flow was born out of the clinical need to cope with lethal esophageal bleeding due to portal hypertension (322). Pawlow and his co-workers (323) used it as an experimental tool for the study of the role of portal venous blood in hepatic ammonia metabolism. These experiments laid the foundation for the concept that hepatic coma is primarily caused by faulty ammonia detoxication (324).

Because the HA was at that time considered a vessel with a minor role in liver function, the Eck fistula was also carried out as a means of excluding the liver from the general circulation. The goal of total devascularization of the liver was achieved later, after combining the total portacaval shunt with ligation of all branches of the hepatic artery (160, 191). By properly staging this procedure, all signs of reversible or irreversible hepatic coma could be reproduced in dogs. The procedure for producing fatal coma by devascularization of the liver has only recently been rediscovered (325) and is now the common experimental model for the study of hepatic coma (326-328).

Since the observations by Mann (329) that diversion of portal blood from the liver leads to atrophy of the organ, much thought has been given not only to the quantity but also to the quality of blood the liver is deprived of after shunting away the portal flow (330). The reversed Eck fistula (328), portacaval transposition (331), and the most recent experiments by Starzl and co-workers (332, 333) created new models for the study of this problem. It is generally agreed that the hepatotropic substances present in portal blood are primarily hormones, the most important among them being insulin. Recent experiments with portacaval shunting in rats (334) demonstrated that the presence of portal blood is necessary to maintain the biotransformation of drugs and of hepatic cytochrome P-450.

Partial shunting of portal blood into the inferior vena cava often produces hepatopetal blood flow and increases the size of small portal venous rootlets between the patent portacaval anastomosis and the porta hepatis into large venous affluents (335).

Arterialization of the Liver via the Portal Vein This surgical intervention is carried out to compensate for the diminished quantity of blood flow to the liver after portacaval shunting. Cohn and Herrod in 1952 (336), after

performing an end-to-side Eck fistula, connected the proximal portal stump of the portal vein with a venous graft to the aorta. The liver increased in size and its hepatocytes were stuffed with glycogen; regeneration after a partial hepatectomy was more rapid (337). Recently this experimental procedure has found its application in the wake of a portacaval anastomosis for alleviating portal hypertension in cirrhotics. It is aimed at improving hepatic perfusion and ammonia metabolism (338). However, distension of the portal vein, vasculitis, thrombosis, and changes in liver structure and function are complicating factors that can be explained by the action of the pressure the arterial jet exerts on the walls of vessels adjusted to nonpulsatile venous flow. Furthermore, arterial blood is delivered to the sinusoids without first passing through microvessels endowed with a strong muscular coat capable of reducing arterial pressure to capillary pressure. Damage to the hepatocytes and severe hepatic fibrosis are the common sequelae of portal arterialization; such lesions have been described in earlier experiments by Schilling (339).

Occlusion of the Hepatic Veins Experiments altering the hepatic venous flow grew out of the desire to better understand the dynamics of portal hypertension and its most common complication, ascites.

Since the observations by Budd (340), and later by Chiari (341), of the occlusion of hepatic veins in humans, investigators have tried to reproduce the veno-occlusive disease and its sequelae in experimental animals. A number of plant alkaloids that induce hepatic venous thrombosis have been studied (342-344) and were found to be causes of venous occlusion. Experimental surgical obstruction of the hepatic outflow tract has been attempted by various procedures (345, 346); they cause hepatic, splenic, and splanchnic venous engorgement, greatly increase hepatic lymph flow, and concomitant back pressure on the kidneys. Orloff and co-workers (347) surgically produced engorgement of the hepatic veins without caval obstruction. If the animals survived long enough, they developed copious ascites (348), which is initiated when liver lymph (with its high protein content) leaks from the hilar lymphatics and causes peritoneal transudation of extracellular fluid to maintain osmotic equilibrium. Plasma albumin appears in thoracic duct lymph earlier than ascitic fluid albumin; therefore, the former derives from the plasma of the hepatic sinusoids (349). In early cirrhosis also the permeable sinusoids are the major source of the augmented lymph flow in the thoracic duct (350). Ascites albumin turns over completely in 2-7 days whereas 40% to 80% of total ascitic fluid volume enters and leaves the peritoneal cavity each hour (351). However, some authors attribute more importance to the Na^+ ion than to the plasma proteins (352) in the formation of ascites.

Portacaval Transposition Child and associates (331), in order to study liver regeneration in dogs, devised the procedure of portacaval transposition. It consists of transecting the inferior vena cava (IVC) and the PV and

joining the caudal end of the IVC to the rostral end of the PV; the caudal end of the PV is anastomosed with the rostral end of the IVC. The volume of blood flowing each minute through the IVC is similar to the portal volume flow per minute; thus, a congestion of the hepatic vascular bed does not occur. A variety of gastrointestinal, physiologic, and biochemical phenomena were studied with this model. Gastric hypersecretion occurs after portacaval transposition in dogs that had previously undergone the formation of total gastric pouches. The nervous phase of their gastric secretion was excluded by vagal denervation (353). This augmented flow of gastric juice is caused by some gastric secretory hormone(s) produced by the intestines that escape efficient inactivation or excretion by the liver, now bypassed by the portal blood carrying these hormones. Starzl and co-workers (354) noted that portacaval transposition caused a glycogen depletion of the normal dog liver. They successfully carried out this operation on an 8-year-old child who had a deficiency of the amylo-1,6-glucosidase enzyme with hepatomegaly and hypoglycemia; all symptoms abated postoperatively. Riddel and associates (285) used this surgical procedure in a child suffering from glycogenosis of the liver due to lack of the enzyme glucose-6-phosphatase. Results were good, and postoperatively the patient's physical and mental development improved greatly.

Ligation of the Hepatic Artery Experiments with ligation of the HA were started because of the need to understand the frequent fatal results following accidental ligation of the HA during operations on the biliary structures or on the upper gastrointestinal tract. As far back as 1905, Haberer (355) demonstrated the decisive role hepatic arterial collaterals play in the survival of the animal after HA ligation. Experiments by Narath (356), who attempted to join the central stump of the transected HA to the PV in order to supply the liver with arterial blood, failed. Successful ligation of the hepatic artery proper and of all its branches in dogs treated with antibiotics was carried out in our laboratory in 1948 (357). The story of this research (358) is an interesting example of the vagaries an experimental procedure passes through until the results become clear-cut. The essential findings (359) are as follows:

1. Death after ligation of the HA can be prevented in dogs treated with antibiotics.
2. The fate of the liver after ligation of HA depends to a large degree on the extent of preformed collateral arterial channels as well as on the anomalies of the origin of the hepatic artery.
3. Necrosis cannot be prevented by antibiotics; these do, however, diminish the bacterial invasion of the affected areas and the resulting inflammation and abscess formation (360).
4. No grave deficiency in hepatic metabolism is detectable after ligation of the HA; the formation of albumin is reduced, that of globulin is increased (361), and the hepatocytes are depleted of glycogen (362).

5. Thus, the possibility of investigating the liver lacking its arterial supply has been added to the studies of the liver deprived of portal blood, as described by Von Eck (322, 363, 364). The knowledge about the missing functions of the HA gained in the portal-venous liver has been summarized in a recent review article and I refer the reader to it (365).

SUMMARY

The study of the morphology of the hepatic circulation has given evidence that the liver consists of a large vascular delta formed by the confluence of the portal and arterial streams. Their arms, which subdivide the delta into lobar areas, start to run parallel and close to each other when they are still visible to the naked eye. Dwindled down to microscopic size, they become the scaffold of the parenchymal cell masses nestling between the microvessels. The arterioles, as they merge with the sinusoidal and portal channels, assume the role of organizing the microcirculation into units. These units are the vascular core of the structural and functional liver acini. It has now been demonstrated beyond doubt that a Po_2 gradient exists in the hepatic vessels and tissues, decreasing from the site of the arteriolar rivulets joining the venous stream toward the site of their common egress via the terminal hepatic venules. The gradient permits the subdivision of the microscopic vascular units into three microcirculatory zones, each of them creating an appropriate microenvironment for specific enzymic and metabolic activity. The microcirculatory shifts in arterial flow from tide to ebb will cause change in the activity of the zones. These are essentially *dynamic* subdivisions of the metabolic activity in the large liver swamp. Here also start the tiny rivulets forming a green river, the bile stream, that runs in the opposite direction to the portal and hepatic arterial flow. It is to be expected that the quantity and quality of bile carrying important products back to the gastrointestinal area for digestion and absorption of fat are influenced by the tides in portal and arterial flow. All in all, it is evident that vascular morphology is the visual aspect of the dynamic blood flow, thus permitting us to perceive its functional orderliness, and to study the circulatory physiology in the hepatic delta. Means of measurement of hepatic blood flow have been reviewed and its methodological problems have been discussed. It was found that the term "estimated" hepatic blood flow is still justified. Also the relationship between hepatic blood flow and metabolism is not yet clear-cut.

The role of the arterial and portal components of the hepatic circulation has been analyzed. There is a reciprocal relationship between arterial and portal volume flow; it is effectuated by the state of constriction or dilation of the mesenteric and hepatic arterioles, both under myogenic control. Portal blood delivers directly to the hepatocyte all water-soluble substances absorbed from the intestines or produced in the intestinal walls. The hepatic artery maintains an appropriate Po_2 gradient between the acinar zones and flow of blood against increased tissue resistance; it assures a steady clearance

of blood-borne substances, e.g., hormones and endogenous products. Regulation of arterial flow is less neural than neurohumoral; metabolites and bile salts exert additional effects on blood flow. Phases of respiration, intra-abdominal pressure, and intestinal contraction and relaxation, as well as gravity and exercise, are modifying forces of the hepatic circulation.

Lymph flow is intimately connected with the circulation since it provides an additional means of egress from the liver of protein-rich plasma fluid and tissue fluid. Lymph flow is greatly increased in states of impeded blood flow through the liver.

The hepatic microcirculation, representing with its terminal vascular bed the closest relation between blood flow and hepatocytes, has been outlined. The microanatomy of the microcirculatory hepatic unit with its zonal distribution of the pressure and Po_2 gradients has been presented. Intermittent changes in portal and arteriolar flow exert their dynamic effects on the enzymatic and metabolic activity of the hepatocytes. However, the randomness of these changes provides an overall steady perfusion with a mixture of blood well adjusted to the activity of the liver cells. The arterioles have a preponderant role in the regulation of the microcirculation. Endowed with unmyelinated nerve fibers and smooth muscles forming precapillary sphincters, they respond well to neural stimulation, the action of hormones, vasoactive substances, metabolites, and bile salts, and assure the adaptive and vital functions of the liver cell.

Experimental alteration of hepatic blood flow, such as portacaval anastomosis, ligation of the HA, total devascularization of the liver, occlusion of the hepatic veins, and portacaval transposition, have added to the understanding and therapy of liver diseases caused primarily by derangements of the hepatic circulation.

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