

The Hepatic Vasculature and Its Response to Hepatic Injury: A Working Hypothesis¹

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Received November 16, 1976

The hepatic circulation is unique in that high volumes of low pressure blood flow are supplied through a dual venous and arterial circulation. This vascular supply is modulated both by the gastrointestinal vascular bed and an intrahepatic microcirculation. This complex vascular system is influenced by pathologic processes within the liver. Alterations in the hepatic circulation reflect hepatic metabolic adaptation and injury. It seems reasonable to assume that in some circumstances hepatic circulatory alterations are inappropriate, exaggerated or inadequate and contribute to the initiation or perpetuation of hepatic injury. This paper attempts to focus on evidence derived from studies of the normal and abnormal hepatic circulation that provide insights into hepatic circulatory responses and their role in the initiation and perpetuation of hepatic injury. A possible relationship of these vascular changes to pathologic processes within the liver is proposed. Ultimately, precise measurement and understanding of hepatic vasculature changes may allow appropriate intervention to offset injury or stimulate maximum effective repair.

INTRODUCTION

Study of the hepatic circulation has been based upon the inkling that the hepatic vasculature and its adaptive responses play a role in the initiation and perpetuation of hepatic parenchymal injury. In comparison to the histopathologic study of liver disease with its complex of intertwined aggressive and reparative factors and prolonged time course, the hemodynamic changes associated with liver disease provide an opportunity to observe rapidly evolving pathophysiology and test methods for determining prognosis, capacity for restitution and efficacy of therapeutic maneuvers in the entire living organ of man (Table 1) [1].

Our increasing appreciation of hepatic vascular physiology and the development of new technics for its study and manipulation in man make it appropriate to summarize selected data and attempt to generate potentially fruitful working hypotheses. Our aim is to define the anatomic and physiologic characteristics of the hepatic circulation that play a vital role in the evolution of liver disease and its consequence, portal hypertension, and to probe for delicate balance points from which critical forces may be shifted.

1. *Dual Hepatic Arterial and Portal Venous Circulation:* The hepatic sinusoid and its adjacent microvasculature is the site of complex anastomosis between the high pressure, low volume hepatic arterial inflow and the low pressure, high volume portal venous input. In prenatal life the hepatic artery alone supplies the liver. The gut is dormant and portal blood is shunted through the ductus venosus along with maternal umbilical venous blood into the vena cava and right atrium (Fig. 1). At birth the umbilical vein and ductus venosus close and the liver relies largely on portal venous

¹This article is the twelfth in a series entitled, "Seminars on Liver Disease," that have been presented as part of the Training Program in Liver Disease at the Veterans Administration Hospital, West Haven, Connecticut. Dr. Harold O. Conn, Professor of Medicine, Yale University School of Medicine and Director of the Training Program in Liver Disease, is guest editor.

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TABLE I
Pathologic Alterations of the Hepatic Circulation in Liver Disease

	Normal	Liver Disease
Macrocirculation		
1. Portal-hepatic venous pressure gradient (mm Hg) ^a	5	5-30
2. Volume flow (ml/min) ^b	1,500	400-800
3. Fractional contribution hepatic artery/portal vein (percent) ^c	33/67	90/10
4. Portal venous flow (percent) ^d	67	0-67
5. Extraction efficiency (percent extraction) ^e	83±15	31-60
6. Lymph production (percent blood flow) ^f	0.06	1.6
7. Extrahepatic leak (percent intracellular production) ^g	0.1	1-50
Microcirculation		
1. Autoregulation ^h		
a. Periodicity of lobular flow	Present	?
b. Synergistic arterial-portal flow ^d	Present	Impaired
2. Sinusoidal function ⁱ		
a. Permeability ^j	400,000 mole wt.	Reduced
b. Space of disse ^j	Small	Enlarged
c. Hepatocyte proximity ^j	Immediate	Distant
d. Numerical reduction (hepatocytes sinusoids) ^{k,l} ^{f,m}	No	Yes
e. Lobular gradient ⁿ	Intact	Distortion-shunts
f. Transit time ^o	Homogeneous	Increased-decreased
g. Sphincter function ^p	Yes	?

^a Viallet A, Joly J, Marleau D, et al: Comparison of free portal venous pressure and wedged hepatic venous pressure in patients with cirrhosis of the liver. *Gastroent* 59:372-275, 1970

^b Shaldon S, Chiandussi G, Guevara A, et al: The estimation of hepatic blood flow and intrahepatic shunted blood flow by colloidal heat-denatured human serum albumin labeled with I¹³¹. *J Clin Invest* 40:1346-1354, 1961

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^p McCuskey RS: A dynamic and static study of hepatic arterioles and hepatic sphincters. *Am J Anat* 119:455-478, 1966

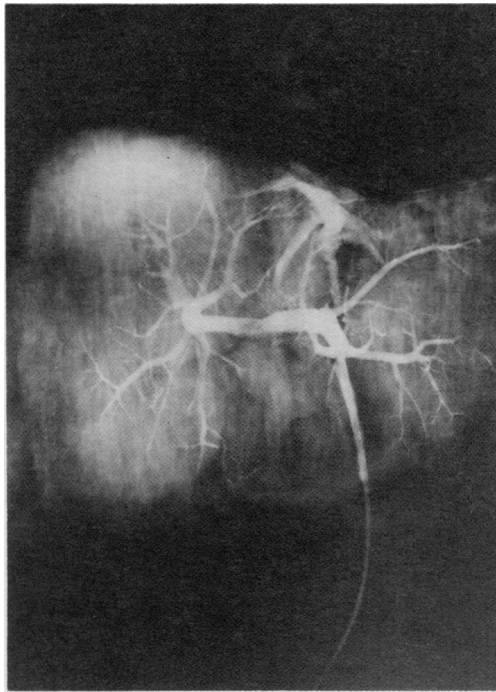


FIG. 1A. X-ray of a 50% barium sulfate suspension injected through the umbilical vein into the portal venous system of an adult human liver at post-mortem. After removing the liver from the body the suprahepatic vena cava and the portal vein were ligated. A probe was passed through the umbilical vein across the left branch of the portal vein through the ductus venosus into the vena cava. In life, this potentially patent channel is closed by sphincters at the umbilical-portal, ductus venosus-portal and ductus venosus-vena caval junctions.

flow [2]. From then on portal venous blood supplies approximately two-thirds of the hepatic blood flow and hepatic arterial blood the remainder. The hepatic artery retains the capacity to compensate for changes in portal flow and constitutes an important variable in hepatic vascular function [3]. Recent attempts to modify metabolic function in the liver by diverting portal venous flow in patients with glycogen storage disease [4] or hyperlipidemia [5] and ligation of the hepatic arteries in patients with hepatic cancer [6] emphasize the ability of the normal liver to tolerate acute loss of either hepatic arterial or portal venous flow without immediate disability. It is suspected, however, that such major changes in quantity or quality of flow may result in functional derangements that may become clinically apparent months or years later. The dual character of the hepatic circulation permits all or a portion of the liver to sustain itself through either the hepatic artery or portal vein and allows adaptation to diverse extrahepatic vascular and intrahepatic pathologic events. The precise metabolic and morphologic consequences of these alterations remain to be elucidated.

2. *Low Resistance Hepatic Venous and Sinusoidal Systems:* Resistance to flow from portal venous to hepatic venous vessels through hepatic sinusoids is remarkably low. In normal man the pressure gradient from portal vein to hepatic vein is less than 5 mm Hg at blood flow rates of 1500 ml per min [7,8]. A 1 mm Hg change in portal-hepatic venous pressure gradient would accommodate a 20% (\pm 300 ml/min) change in blood flow if hepatic vascular resistance were unchanged. Thus, large changes in

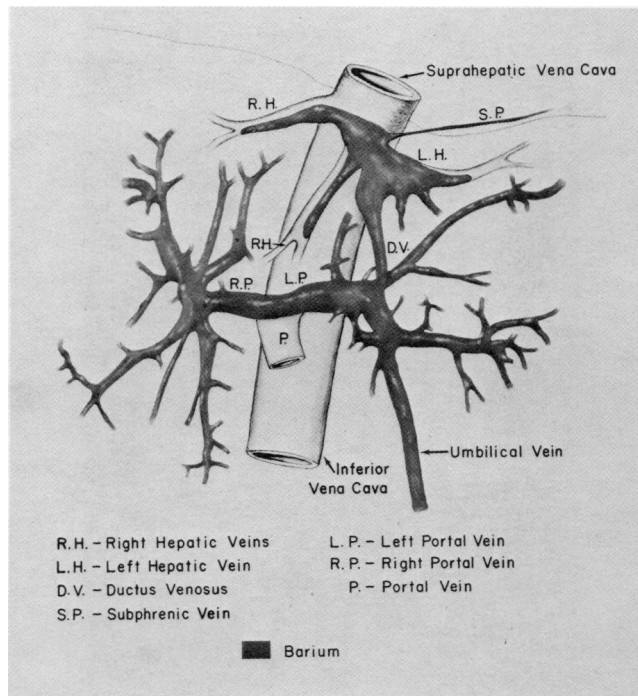


FIG. 1B. Drawing of barium radiography showing the umbilical vein and ductus venosus in an adult human liver at post-mortem.

hepatic flow may occur with little change in portal pressure [8]. When one considers that the accuracy of pressure measurement in man is ± 1 mm Hg, it is apparent that large changes in hepatic vascular resistance may go undetected.

3. *Complex Acinar Microcirculation:* In lower animals transillumination studies of the hepatic circulation in vivo demonstrate that at any instant only a fraction of the total number of hepatic acinar vascular units are actively perfused. Some acini are dormant with stagnant sinusoids while adjacent vascular units are actively perfused and presumably, are also active metabolically, as uptake and excretion proceed. The functional role of the acinar rest period is obscure. Periods of active perfusion are complex. Blood progresses through individual sinusoids in a series of succussions that mix the formed and fluid elements and expose the sinusoidal surface and its large pores to a perfusate of continually changing composition. Periodic spurts of hepatic arterial blood from lateral and branch vessels accelerate sinusoidal transit and add red cells rich in oxygen [9]. A gradient of nutrient concentration along the sinusoid determines the metabolic activity, oxygen availability and susceptibility to injury of the individual acinar zones of Rappaport (Figs. 2,3). Zone 1, adjacent to the portal inflow and high in nutrients and oxygen, is most active metabolically. It is protected from some types of injury, particularly ischemic, and is the site of regenerative activity. In Zone III, at the acinar periphery, hepatocytes are living in a marginal environment of limited nutrients and oxygen, bathed in excrement. Zone III is highly susceptible to ischemic and toxic injury. Zone II is in an intermediate position anatomically, functionally, and in susceptibility to certain types of injury [9].

4. *Interplay of Portal Venous and Acinar Microcirculation in Liver Injury:* The portal venous network is highly branched and responds with rapid changes in the

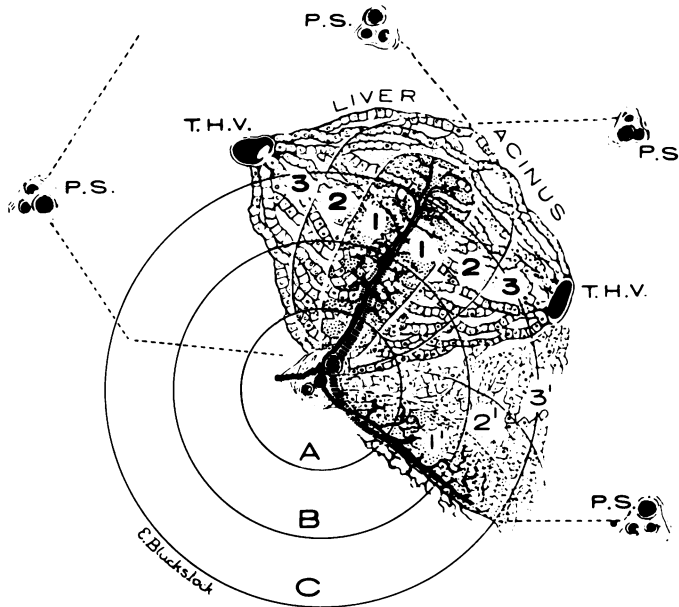


FIG. 2. Hepatic acinar vascular zones as described by Rappaport. Zone I is adjacent to the portal space (P.S.) and vascular inflow. Zone II holds an intermediate position. Zone III is at the vascular periphery of the acinus adjacent to the terminal hepatic vein (T.H.V.). (Courtesy of A.M. Rappaport, University of Toronto School of Medicine).

magnitude and direction of flow to small changes in metabolic activity, tissue pressure and probably hepatic arterial flow [10]. In disease states this diversity of flow patterns could allow the diversion of portal blood from damaged areas of increased resistance to less injured areas of lower vascular resistance. This marked vascular response to cellular injury and the complexity of hepatic acinar blood flow pattern may explain the spotty lobular pattern of many types of hepatic injury as observed through the extended time frame of histopathology. Acute severe hepatic injury could cause cessation of individual acinar blood flow by impeding both the sensitive portal and more resistant arterial flow.

Diversion of blood flow and metabolic activity to the more intact acini might provide an efficient reserve of hepatic function for the organism acutely and could stimulate the relatively less injured areas to undergo hypertrophy and hyperplasia until a remodeling process is complete and adequate hepatic mass is restored. In the long run this valuable acute response might be detrimental and perpetuate hepatic injury since injured areas deprived of portal flow and the accompanying hepatotropic nutrients [11] may fail to survive injury or, if surviving the acute injury, come to atrophy as other acinar units gain a permanent vascular advantage.

The damaged liver liberates substances that stimulate collagen synthesis [12]. Reduced local perfusion may limit removal of these factors and dispose to irreversible fibrosis.

Blood is shunted through hepatic vascular segments when injury, failure of repair and fibrosis reduce the hepatocyte population [13,14]. Less injured areas hypertrophy, regenerate, and attempt to increase their fractional metabolic and vascular role. In this proposed sequence of events the hepatic vascular and metabolic adaptive response that preserves adequate function and allows restitution of hepatic functional mass after acute injury leads to the formation of a heterogeneous organ with areas of

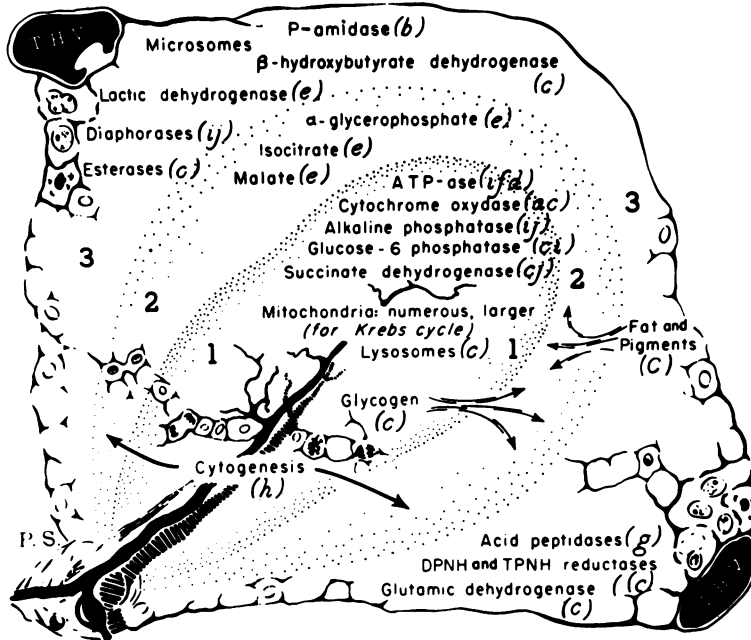


FIG. 3. Metabolic areas of the hepatic acinus defined in terms of enzymatic patterns and metabolite accumulation. Varied relationships to acinar blood flow result in metabolic variation within the lobule which in turn determine enzymatic activity and sites for production and storage. (Courtesy of A.M. Rappaport, University of Toronto School of Medicine).

hypertrophy and hyperplasia interspersed with atrophic and destroyed (collapsed) acini with adjacent fibrosis. If the process were severe, cirrhosis would be the result. This working hypothesis emphasizes the role of vascular and blood flow mediated metabolic processes in the perpetuation of acute liver injury and the development of hepatic cirrhosis. It implies a need for intervention at the outset of acute liver injury to maintain maximum portal venous perfusion (pressure) that could remove potentially toxic products and supply nutrients and hepatotropic factors to stimulate repair at the acinar level even when overall hepatic functional deficit may appear modest and immediate survival of the organism is not in doubt. This hypothesis provides a potential mechanism whereby empiric metabolic therapy (corticosteroids) could favor restitution of hepatic architecture by increasing metabolic activity and acinar blood flow [15,16].

5. Acinar Concept of Rappaport Applied to Chronic Hepatic Injury: In the normal human liver increased volume of blood flow could be accommodated by recruitment of additional acinar units and reduced flow by a reduction in the number of functioning acinar units through prolongation of the individual rest periods. In this situation, the concept of hepatic vascular resistance as the simple function of mean input pressure divided by blood flow rate is untenable, and comparisons between the normal liver with surplus functional mass and the heterogeneous diseased liver are presumptive at best.

The shrinkage of functional hepatic mass during the evolution of liver disease may

be conceptualized as a progressive reduction in the number of functional acini. Initially reserve units are lost. With disease progression, a point is reached where adequate hepatic function can be maintained with fewer acini by increasing the period of activity and reducing the rest interval. With increased demands or a further reduction in tissue mass, blood flow per unit increases. This increased acinar metabolic and vascular activity may achieve a steady state and provide adequate hepatic function. A further increase in demand or further hepatic injury would lead to decompensation when increased blood flow or competition between substrates yielded reduced, rather than increased hepatocyte extraction from sinusoidal blood and accentuated overall hepatic metabolic inadequacy [17]. Alternatively, the continuous demand for acinar function, both vascular and metabolic, could in itself prove injurious, and a vicious circle of hepatic injury and reduced hepatic function develop.

Although the consequences of disordered hepatic vascular function and reduced tissue mass both lead to the final common pathway of reduced metabolic function, the causes of and remedies for each of these disorders differ. Reduced hepatic perfusion in the extreme of hypovolemic shock or congestive heart failure may severely compromise even the normal liver [18]. The complete loss of portal venous flow and presumed hepatotropic pancreatic factors which accompany portacaval shunt and pancreatic extirpation for cancer may prove lethal in the presence of normal hepatic morphology [19]. The cirrhotic liver may be more susceptible. The cirrhotic patient, whose hepatic vascular pattern is already grossly deranged, may not tolerate abrupt diversion of portal flow by portacaval shunt [20,21]. A similar, but less dramatic, decline in hepatic function may accompany the stress of anemia or hypovolemia. Indeed, the enormous increments in serum transaminase in patients with compromised hepatic blood flow indicate abrupt damage to the cells of Zone III. Anemia forces the diseased liver with reduced blood flow and limited capacity for oxygen extraction into a more hypoxic state. Partial compensation through increased oxygen extraction occurs [22], but undoubtedly hepatocytes in the marginal environment of Zone III will suffer. Reserve hepatic function is compromised and hypertrophy or regeneration limited.

6. *Potential Role of Portal Perfusion Pressure in Acinar Function:* Portal venous pressure is directly proportional to blood volume [23]. Hypovolemia reduces portal pressure. Hepatic blood flow may also be reduced indirectly through reduction of cardiac output or its splanchnic fraction following direct changes in splanchnic hemodynamics [24]. Here is a mechanism whereby hepatic perfusion pressure and hepatic blood flow are linked to blood volume. In the relatively passive hepatic sinusoidal bed, changes in perfusion pressure may alter both volume and distribution of portal flow (see section 4). Reduced perfusion favors flow through low resistance paths and divorces high resistance areas from portal inflow, forcing them to rely more on hepatic arterial perfusion with its lesser content of nutrients and hepatotropic factors. Conversely, higher portal perfusion pressures might expand the area of portal perfusion and encourage hypertrophy, hyperplasia, and survival of marginal hepatocytes and acini.

In the presence of esophagogastric varices with the accompanying risk of hemorrhage, an excessive increase in vascular volume with its attendant increase in portal pressure presents a hazard. This risk must be balanced against the need in the individual patient for an optimal hepatic environment to encourage improved cellular function and regeneration. Blood volume and portal pressure should, ideally, be monitored during clinical management and an appropriate balance achieved [23].

7. *Portal-Systemic Collateral Venous Network:* The prominent portal-systemic

collateral venous network of portal hypertension arises from preformed vascular anastomoses at sites where the portal and caval systems are embryologically juxtaposed. Rarely an anomalous situation exists where the portal vein or one of its tributaries terminates directly in the caval system. Fine existing portal systemic collaterals are expanded by increasing portal pressure [25]. With long-standing, severe portal hypertension an increasing quantity of portal venous flow is diverted into these collaterals and bypasses the liver to enter the systemic circulation [26]. In advanced cirrhosis most of the portal blood is shunted around the liver [26]. Since portal flow constitutes 20% or less of cardiac output, the mixing of portal blood with systemic blood deprives the liver of the opportunity to extract nutrients in full concentration, and forces it to do so only after they have been diluted fivefold. Furthermore, specific metabolites such as tryptophan or insulin, present in low concentrations in portal blood, may be lost to the liver completely when they are altered or utilized by competing tissues. The loss of this "first pass" phenomenon is, in a sense, the loss of a golden metabolic opportunity.

Although portal systemic collaterals do not usually divert a sufficient volume of portal flow to reduce portal pressure in cirrhosis [27], occasionally a large collateral circulation will reduce portal pressure to near normal levels [28]. This may be a consequence of an unusually large collateral capacity for flow diversion. The capacity for diversion of portal flow through preformed collaterals is determined not only by the diameter, length and tortuosity of the collaterals, but by the resistance to flow at the stoma where the portal and caval vessels join. Presumably, these junctions are usually small and restrictive. The diameter of portal collaterals is proportional to the height of portal pressure [7]. Current evidence suggests that the quantity of portal flow diverted is not a simple function of portal pressure, since cirrhotic patients with similar portal pressures have widely differing quantities of portal flow traversing the portal vein [26]. It would, therefore, appear that additional factors influence the capacity of collaterals to divert portal flow. Perhaps, sustained, severe portal hypertension forces anastomotic stomata open. On the other hand, the size of these connections may be determined at their embryological formation as are the collateral vessels themselves [25]. In that case, different individuals would have differing capacities for diversion of portal flow from the liver.

8. *Potential Influence of Portal-Systemic Collateral Flow on the Evolution of Liver Injury:* At the extremes of a hypothetical continuum, the patient with small high resistance anastomoses between portal and caval beds would retain portal flow to the liver despite the presence of portal hypertension. The maintenance of portal perfusion would favor hepatic regeneration and hypertrophy by continuing to supply the damaged liver with concentrated nutrients and hepatotropic factors. This situation could favor the development of the large cirrhotic liver (hypertrophic cirrhosis). On the other hand, the presence of a high volume portal-systemic collateral runoff would deprive the injured hepatic parenchyma of portal factors and intensify the consequences of hepatic injury. A small cirrhotic liver largely supplied by arterial blood (atrophic cirrhosis) might result [29].

Current surgical approaches to the control of bleeding from esophagogastric varices emphasize the preservation of portal flow to the liver [30]. In fact, these technics may increase the portal fraction of hepatic blood flow since they include the intentional interruption of large portal-systemic collateral vessels [31]. Sophisticated angiographic technics also allow selective obliterative thrombosis of large portal-systemic collaterals by percutaneous or umbilical venous routes to reduce the risk of variceal hemorrhage and redirect portal nutrients and hepatotropic factors to the

liver [32]. The potential importance of portal flow to the liver emphasizes the subtle but possibly detrimental effects of diurectic induced hypovolemia and its accompanying reduction in portal pressure [33]. In addition, the current popularity of parenteral alimentation detracts from the essential unique consequences of the portal route of hepatic nutrition [34].

The quantity and quality of hepatic perfusion is intimately related to the maintenance of hepatocellular mass and function. In acute liver injury we aim to stimulate restoration of parenchymal mass around an intact vasculature. To protect the damaged organ and encourage maximum function, adequate stimuli for regeneration and cellular hypertrophy must be supplied. Portal venous blood is unique in providing these stimuli in the form of as yet poorly defined hepatotropic factors and high concentrations of exogenous and gut derived nutrients [35,36]. It, therefore, seems reasonable to assume that in liver disease maintenance of adequate portal flow to the liver is required if maximum function be preserved. Diversion of portal flow from individual acini and the liver as a whole recapitulates the prenatal state (Table 1), in which the liver is deprived of digested nutrients [37].

The quantitative validation of these hypotheses will require the measurement of hepatic arterial and portal fractions of hepatic blood flow, portal-systemic collateral flow, functional hepatic parenchymal mass [29] and the response of these factors to the manipulations proposed. There are numerous other factors active in the initiation and perpetuation of hepatic injury. Nevertheless, these other pathogenetic mechanisms may be modulated by the hepatic vascular response to hepatic injury.

CONCLUSION

The anatomic and physiologic characteristics of the hepatic circulation influence the severity and consequences of hepatic injury. An understanding of the evolution of hepatic vascular changes in liver disease may provide methods for estimating the magnitude of liver injury and predicting its course. Where the inherent hepatic vascular response is inappropriate or injurious, specific therapeutic countermeasures may be possible.

ACKNOWLEDGEMENT

I wish to acknowledge the encouragement of Dr. Harold Conn who stimulated the writing of this paper and to thank Dr. A.M. Rappaport for his kind contribution of Figs. 2 and 3 and the development of the acinar concept of hepatic physiology on which the majority of the thinking in this paper is based. I also wish to express my appreciation to Miss Rubell Smith for her excellent secretarial contribution.

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