HEPATIC MICROCIRCULATORY CHANGES LEADING TO PORTAL HYPERTENSION

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In recent years, human cases suffering from portal hypertension without the symptoms and signs of cirrhosis have been reported with increasing frequency. The causes given for this hypertension range from tropical splenomegalies,[1,2] schistosomiasis,[3] congenital portal fibrosis,[4] sarcoidosis, myelogenic infiltration,[5] noncirrhotic portal fibrosis,[6] extra- and intrahepatic phlebosclerosis,[7] acute hepatitis and necrosis,[8–10] to centrolobular collagen deposition.[11]

Fatty liver is regularly quoted as an intrahepatic cause of portal hypertension. However, one finds in the literature very few cases of portal hypertension in which fatty metamorphosis of the liver is not associated with sclerotic lesions.[12,13]

It was therefore a great achievement for Dr. Leevy and his coworkers in 1958 [14] to prove convincingly that dietary therapy in severely fatty livers, even in the presence of slight sclerosis, reduces portal hypertension to such a degree that surgical intervention can be obviated.

For years we have been interested in the pathways of the hepatic microcirculation and their pathologic alterations. In a study of the fatty liver produced in mice by dietary means, we were able to demonstrate the progressive changes in the sinusoidal circulation that lead to portal hypertension.[15] In another study on young rats, we showed that the severe congestion and edema of the parenchyma occurring in toxic hepatitis after the ingestion of fulvine causes a drop in portal flow and a rise in portal pressure.[16]

Methods

Twenty mice weighing around 20 gm were fed a diet deficient in choline and low in proteins (Table 1) and were supplied with 15% $v/_v$ alcohol solution instead of drinking water.

In another experiment, 50 young rats received a single dose of fulvene (0.065 mg/gm/bw) by stomach tube after a 16–24 hour fast. The animals of both series were observed for a varying length of time before being subjected to direct *in vivo* observation of the hepatic microcirculation.

In Vivo *Transillumination of the Liver*

Mice and rats were anesthetized with Nembutal® (.06mg/gm/bw) and insufflated with pure oxygen under 10 mm water pressure through an indwell-

ing cannula in the incised trachea. The abdomen was opened and a plastic apron was slipped under the liver and the margins of the abdominal wound. The apron covered the intestines, preventing them from drying or cooling, and restored the intraperitoneal pressure.

Light for transillumination was obtained from a zirconium arc, and was transmitted to the microscope by a quartz rod slipped under the liver margin.[16] Observations were made at magnifications ranging from 12–200×. For color cinephotography, an Arriflex camera was mounted above the objective lens. The microscope and camera were attached to a steel bar, forming one rigid system. The rat was placed on a miniature operating table permitting micrometric movements and tilting in all directions.[16] To improve the photography at higher magnifications, the respiratory movements were eliminated by intravenous injection of tubocurarine (3μg/gm/bw). Observations on the same animal were carried out for up to 16 hours, and the animal was then sacrificed.

Portal pressure was measured by introducing a polyethylene catheter through the ileocolic vein into the portal vein of rats; a special instrument for cannulation of fine vessels without visual control was used.[16] In some rats the portal stem was cannulated directly. The pressure was determined in choline-deficient animals when the gross aspect of the liver was fatty. In fulvine-intoxicated rats, portal pressure was measured on the third day after the ingestion of fulvine. In some rats, the external iliac artery was employed for simultaneous measurement of the systemic arterial pressure. In severely intoxicated rats, however, the pressure could be determined in one vessel only because of the poor general condition of the animal.

Results

A brief glimpse of the normal hepatic microcirculation is mandatory in order to understand its pathologic change.

Normal Hepatic Microcirculation

In the *in vivo* transilluminated normal liver no hexagonal lobules, only acini [17,18] can be discerned.

The simple liver acinus of a mouse or rat (Figure 1) represents a small parenchymal mass, irregular in size and shape, arranged around an axis consisting of a terminal portal venule, hepatic arteriole, bile ductule, lymph vessels, and nerves which grow out together from a small triangular portal field. The simple liver acinus lies between two (or more) terminal hepatic venules ("central veins") with which its vascular and biliary axial channels interdigitate.

The area of a simple liver acinus is subdivided into three circulatory zones (Figure 2). The cells in zone 1 are situated close to the supplying (nutrient) vessels; they are bathed by fresh blood of the same composition as that in the supplying vessels, and they display a specific enzyme pattern.[19] The cells in zone 3, the circulatory periphery of the liver acinus, are supplied with blood that has already passed through the other zones; they contain enzymes different from those in zone 1.[19]

TABLE 1

R. R. M.-O-Diet	Percent
Alc. Ext. peanut	6
Soya proteins	2
L-cystine	0.1
L.-P. salts	1.0
Cellu-flour	3.0
Cornstarch	2.0
Sucrose	74.9
P.D.W. vit.	0.5
Corn oil	10.0
Regular A.D.E.	0.5

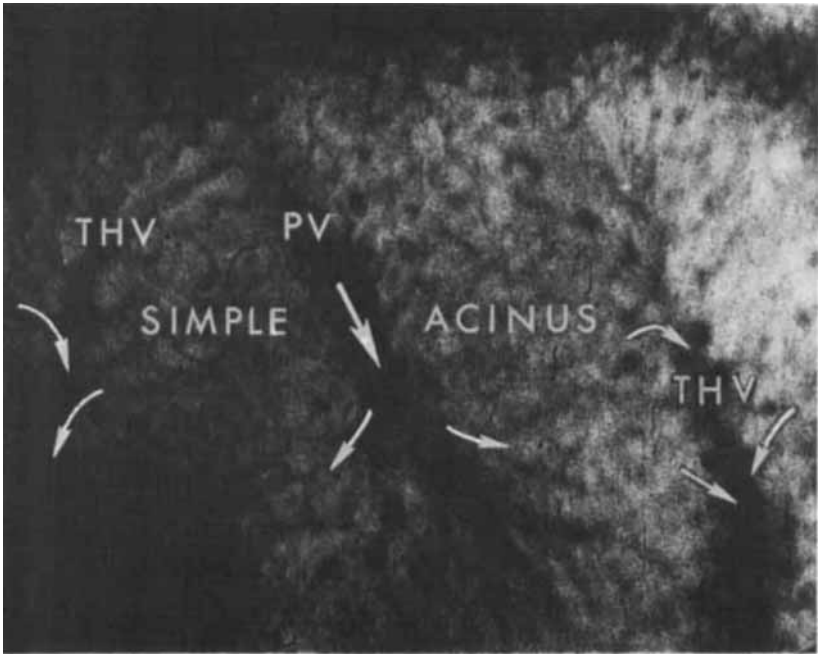

FIGURE 1. Transilluminated rat liver: simple liver acinus. The clump of parenchyma is organized around the terminal afferent vessels, bile ductules, lymphatics, and nerve plexus, and drained by two terminal hepatic venules. Abbreviations used: T.H.V. = terminal hepatic venule; P.V. = terminal portal venule. Enlarged 16 mm movie frame, i.e., cinephotomicrograph 385×.)

In a scanning view of the transilluminated liver of the mouse, with the respiratory movements eliminated by the injection of tubocurarine, one notices that the liver pulsates. One observes the superficial venous network interdigitat-

ing with the more deeply situated, hence less conspicuous, terminal and preterminal portal venous branches.

It is also evident that the axial vessel of the simple acinus is a branch of a larger vessel supplying a larger clump of parenchyma, the complex acinus.[18] The complex acinus is part of an acinar agglomerate organized around a still larger yet microscopic vessel. An agglomerate is usually composed of three complex acini.

The blood passes through the sinusoids—not in streamline flow—it advances in succussions through the entire capillary network of the acinus. Thus, the blood is shaken in the sinusoids as in test tubes and intermixes thoroughly with the fluid in the Disse's spaces before it empties into the terminal hepatic venules.

One can also study, *in vivo,* the arborization of the terminal portal venule into the sinusoids and distinguish several chararacteristic patterns, some of geometrical regularity. Frequently, one can find a direct transition of the terminal portal venule into the terminal hepatic venule, forming an intrahepatic anastomosis between the portal and caval system (FIGURE 3). The circulatory activity of the arterioles is intermittent and is best observed in the cross connections between the sinusoids in zone 1, i.e., close to the terminal portal venule. Through the intermittent opening and closure of arterioles and the varying

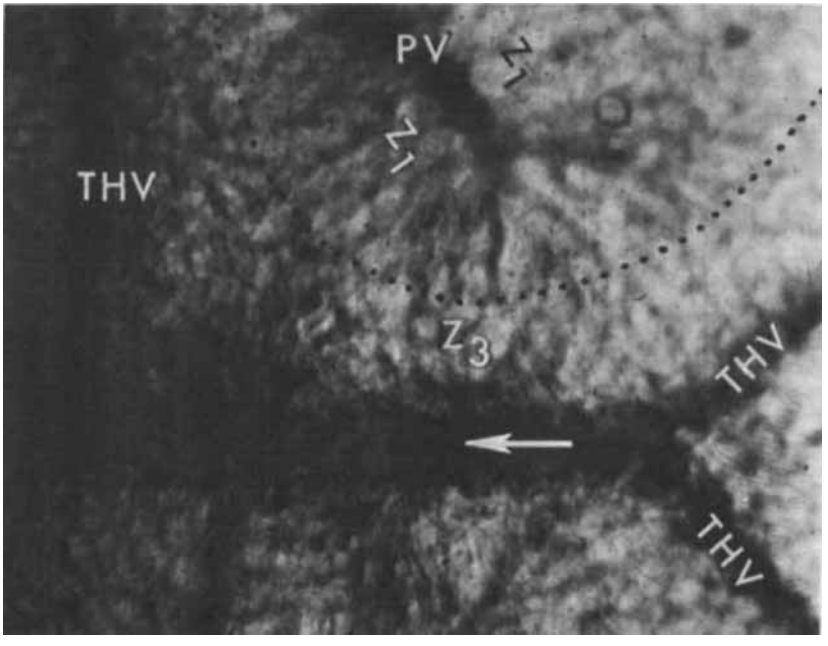

FIGURE 2. Circulatory zones in the liver acinus. Z_1 = zone 1: the area close to the afferent vessels receiving blood of the same quality as that in the afferent vessels. Z_3 = zone 3: represents the circulatory periphery of the unit; its cells are bathed by blood that has passed first through zones 1 and 2. (Cinephotomicrograph 385×)

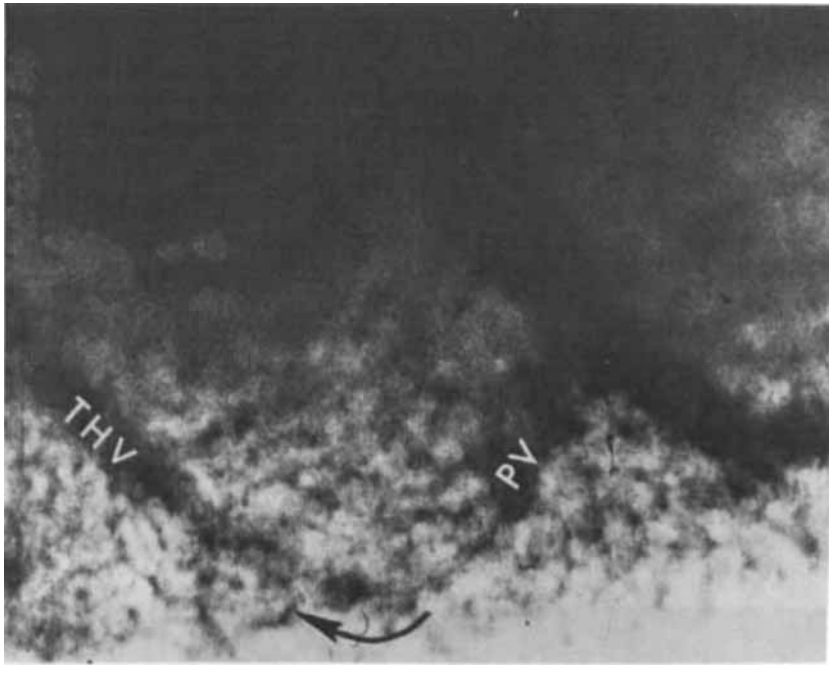

FIGURE 3. Portohepatic venous anastomosis in transiluminated liver edge of a mouse. The terminal portal venule arborizes into sinusoids; one of its branches joins directly with a terminal hepatic venule. (cinephotomicrograph 770×.)

force of their jets, the flow pattern, the O_2 content, and the pressure of portal blood are ever changing. The sinusoids empty their blood into hepatic venules, almost at right angles to their axes. Some sinusoids will gather into a small, stubby inlet venule (Daysach channel) prior to emptying. The terminal hepatic venules follow a straight course, join at acute angles, and form larger collecting venules which feed still larger superficial veins. Venous flow at this level appears to be continuous.

Changes in Hepatic Microcirculation through Progressive Fatty Metamorphosis

Changes in the microcirculation of the liver were observed in mice from 48 hours up to 4½ months after being on a diet deficient in choline and drinking 15% alcohol.

Within 48 hours, fat droplets appear in zone 3 of the liver acinus at the cell membrane facing the sinusoids (FIGURE 4). As the fat droplets accumulate, they also occupy zone 2.

In a week's time, the cells close to the axial afferent vessels (zone 1) are free of fat while the area around the terminal hepatic venules (zone 3) is

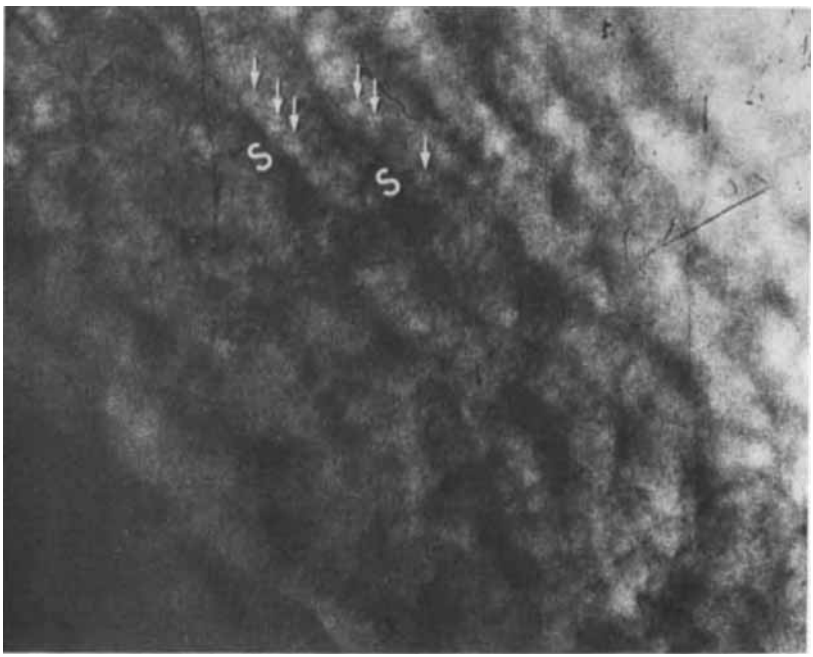

FIGURE 4. Transilluminated liver of a mouse on a choline-deficient diet and alcohol for 48 hours. Tiny fat droplets (↙) lie close to the cell membrane facing the sinusoids (S). (Cinephotomicrograph 770×.)

replete with fat (FIGURE 5). At 100× magnification, the cells filled with fat surround two terminal hepatic venules downstream to their junction (FIGURE 6). A similar site viewed at 200× magnification (FIGURE 7) shows the fat droplets occupying the base of the cells that adjoin the sinusoids and the site of the openings of the sinusoids into the terminal hepatic venules.

After four weeks, the margin of the transilluminated liver changes its color from dark brown to the color of milk chocolate. The scanning of the liver margin at 12× magnification shows a faint vascular pattern, as if it were out of focus; the sinusoids are indistinct, since they are compressed by the bulging fatty cells. At higher magnification (100×), one sees that fat has also accumulated in the cells of zone 1, i.e., close to the axial afferent vessels supplying the liver acini (FIGURE 8). The accumulation of fat in zone 1 is typical of a diet deficient in protein and amino acids. The diet we used, besides being deficient in choline, was deliberately low in protein, to hasten the pathologic changes in the liver. The patterned branching of the terminal afferent vessels into the sinusoids is replaced by random ramification of irregular sinusoids; at a certain moment an isolated arteriole opens up with intermittent circulatory activity. The accumulation of fat in zone 3 is very marked, and the incompressible fat droplets indent the walls of the draining venules (FIGURE 9). At such magnification (200×), one sees the bizarre shapes impressed upon the sinusoids by the intracellular fat globules. The sinusoidal diameter is reduced in width, and

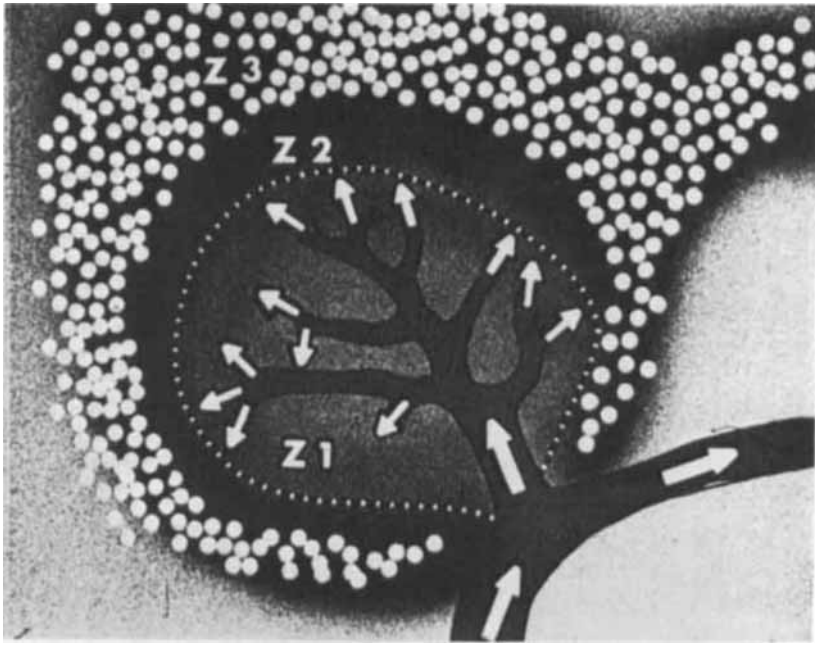

FIGURE 5. Schematic outline of a simple liver acinus and its three circulatory zones. The direction of afferent blood flow and the vasculature are shown in zone 1 only. Fatty change (white dots) occurs mainly in the hepatocytes of zone 3 during the first week of the choline-deficient diet.

the blood has to fray its way against increased resistance to flow. Under similar magnification, the terminal hepatic venules in zone 3 do not follow a regular straight course but curve their way between wavy shorelines formed by cells bulging with fat (FIGURE 9).

After 4½ months, the liver edge looks milky. This color is due to the decrease in circulation at this peripheral part of the organ; a sinusoid can barely be seen with the scanning lens (12×). An isolated, superficial stellate venule overlying this barren area still carries blood, probably from more deeply situated vascular networks.

It should be noted that the tissue observed under the microscope represents zone 3 of the acini located at the surface of the liver. The tract of liver tissue adjacent to the milky liver edge has a mottled appearance. Under the scanning lens, it is seen to be due to an accumulation of dark cells containing ceroid.

Another region of the same liver viewed at 35× magnification is characterized by a total absence of normal hepatic structure (FIGURE 10). It looks like a devastated field: instead of regular liver cords subdivided evenly by cell membranes, there are only bulky cells replete with fat. Like boulders, they surround depressed areas formed by shrunken dark cells that contain ceroid (C in FIGURE 10). Blood flow is markedly reduced in this area. There are odd arterioles and efferent terminal vessels; lone sinusoids are often seen through

FIGURE 6. Transilluminated liver of a mouse on a choline-deficient diet and alcohol for 6 days. Fat has accumulated in large (white) droplets in the cells of zone 3 (Z_3) close to the terminal hepatic venules (T.H.V.) and to their confluence. (Cinephotomicrograph 1000×.)

the large fat drops as through a round window. These sinusoids run beneath the superficial cells in a circuitous way, displaying winding shorelines, but one can hardly determine where the sinusoids originate or where they empty.

High magnification (200×) of an area in which circulation is still visible shows the bloodstream in the collecting venules to be fast and riding like a conveyor belt over the fat blebs of the adjacent cells bulging into the lumen.

At a similar magnification, one can also see fatty cysts, i.e., Hartroft's [20] lipodiastemata (FIGURE 11). One of them was of such magnitude that the 16 mm film frame could not encompass it. The cysts are surrounded by drawn out, narrow sinusoids through which a fine thread of blood still passes. They illustrate well the impediment and distortion of the normal sinusoidal circulation which is presented here for comparison (see FIGURE 1).

Changes in Hepatic Microcirculation after Toxic Hepatitis Induced through the Ingestion of Fulvine

Fifty rats were transilluminated hourly after the ingestion of a single dose of fulvine. The phases of the developing hepatitis were described in detail

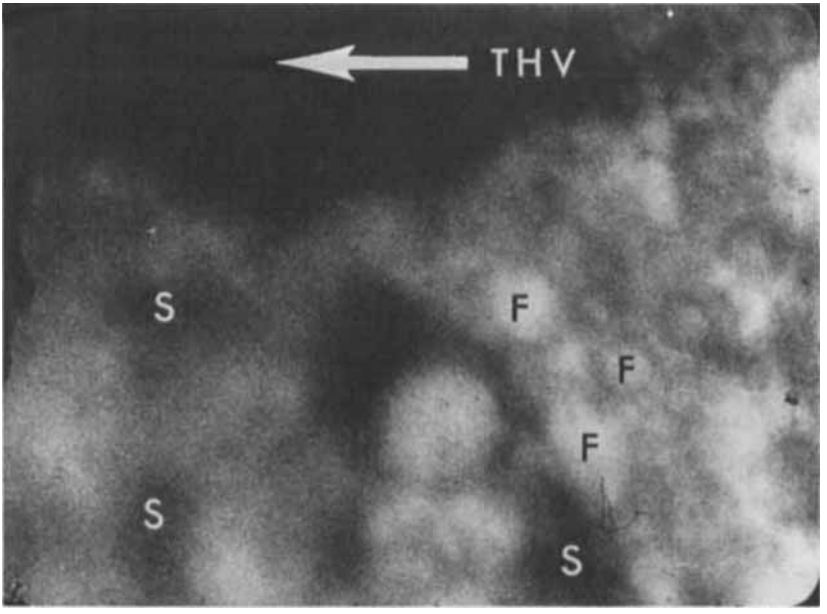

FIGURE 7. Transilluminated liver of a mouse on a choline-deficient diet and alcohol for 8 days, under high magnification. Cells at the periphery of the acinus contain fat droplets (F); some large droplets lie close to the cell membrane adjoining the sinusoids (s). Numerous intracellular fat droplets in the right half of the picture (i.e., toward the periphery) compress the sinusoids which can no longer be distinguished. (Cinephotomicrograph 2000×.)

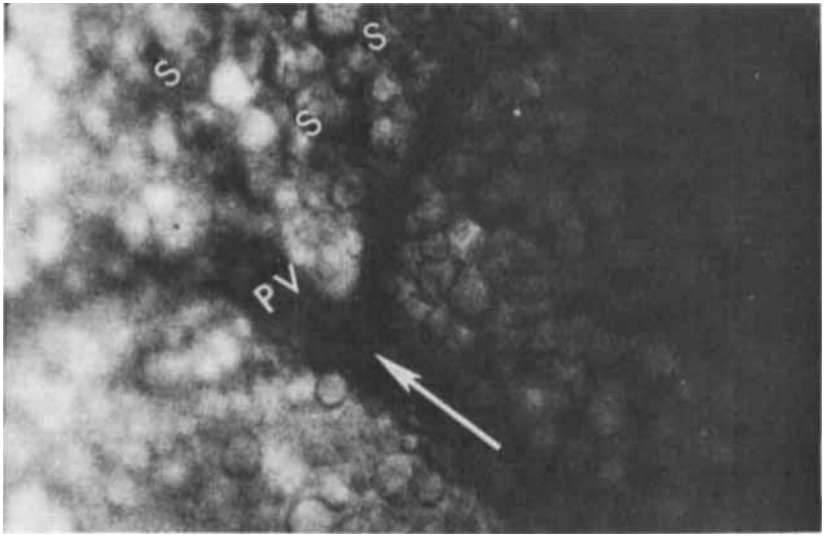

FIGURE 8. Transilluminated liver of a mouse on a choline-deficient diet and alcohol for 4 weeks. Fat droplets are present in the cells of all zones; some lie close to the axial terminal portal venule. Note the irregular course of the narrowed sinusoids (S) in the upper center of the picture. (Cinephotomicrograph × 500.)

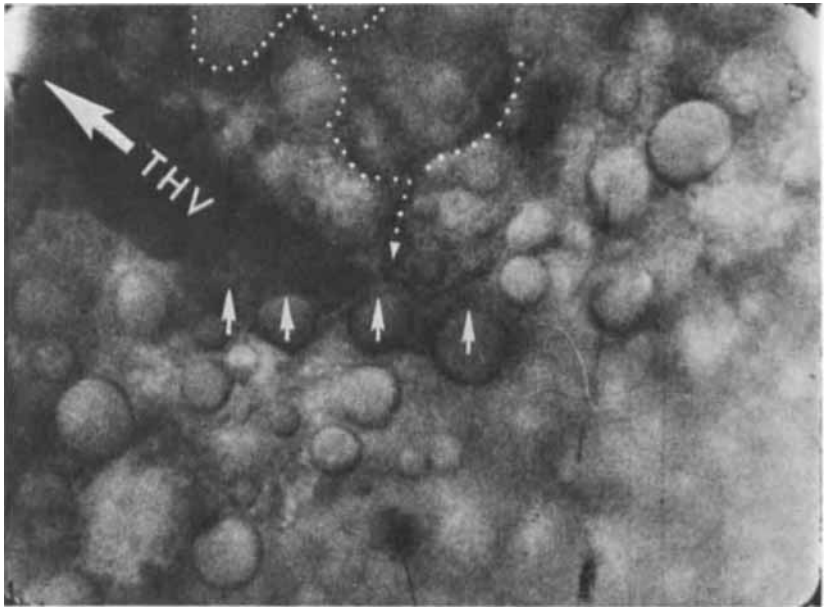

FIGURE 9. Peripheral portion of the liver acinus of a mouse on a choline-deficient diet and alcohol for 4 weeks, under high magnification. Many fat droplets encroach (↑↑↑) upon the lumen of the terminal hepatic venule. In the lower half of the picture, the entry of the sinusoids into the T.H.V. cannot be seen, since they are compressed by the fatty cells. Note wavy shorelines of the sinusoids narrowed by intracellular fat droplets (upper half). (Cinephotomicrograph × 960 approx.)

elsewhere.[16] The main features leading to increased impediment of portal flow were: (1) Progressive sludging of blood in the sinusoids and in the afferent and efferent terminal venules led to rouleaux formation, and eventually microthrombi blocked the narrowed sinusoidal bed. (2) The enlarged and edematous parenchymal cells gradually narrowed the sinusoidal network. Twenty-four hours after the ingestion of fulvine, many sinusoids were totally compressed. This gave the transilluminated tissue a pale appearance. At the liver margin entire acini were devoid of circulation, and they appeared watery and transparent because of the edema (FIGURE 12). (3) There was engorgement of the liver with blood that could not pass through the many sinusoids narrowed by edema and plugged with microthrombi, especially in the acinar zone 3 (FIGURE 13).

Portal pressure was measured in the ileocolic vein of 10 rats on the third day after the ingestion of fulvine; the values ranged between 200–300 mm of physiologic saline solution. In five such rats, the systemic arterial pressure as determined in the left iliac artery was between 80–100 mm Hg.

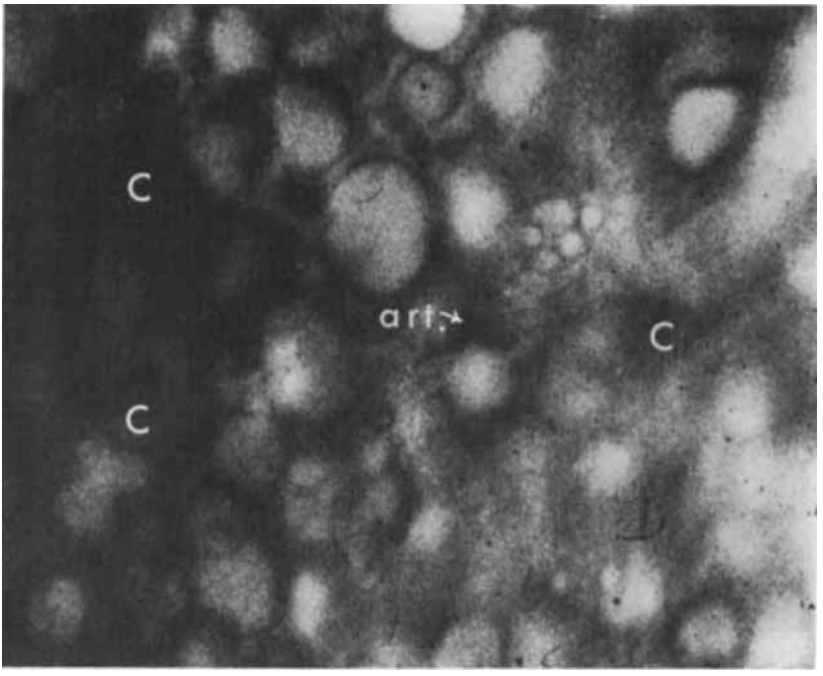

FIGURE 10. Transilluminated liver of a mouse on a choline-deficient diet and alcohol for one month. Normal sinusoidal pattern has disappeared; light prominent spots are fat globules; dark depressed areas (c) consist of cells filled with ceroid. A lone arteriole (art.) is active. (Cinephotomicrograph × 750.)

DISCUSSION

Pressure in the vascular system is usually expressed as a result of flow × resistance to flow: $P = F \times R$. With an increase in flow or in peripheral resistance, the pressure will rise. The difficulties in measuring hepatic blood flow, or its arterial and portal component, and the interplay between the two streams as a possible cause of raised portal pressure are intriguing subjects. I would like to touch on a few points only. The simultaneous measurement of hepatic arterial and portal flow with electromagnetic flowmeters is still not reliable because of interference between the magnetic fields of the probes placed close to each other. Furthermore, the estimated total inflow into the liver does not indicate how much of the measured blood passes through its sinusoids and how much is bypassed through intrahepatic shunts. The interplay between arterial and portal flow is intermittent, as illustrated in FIGURE 14. It shows how the arterial blood under high pressure and the intermittent activity of arteriolar sphincters help to move the portal blood through the sinusoids.[21] Recently we have been able to reproduce in a glass model of the hepatic microcirculation the many possible combinations of opened or closed arterial and

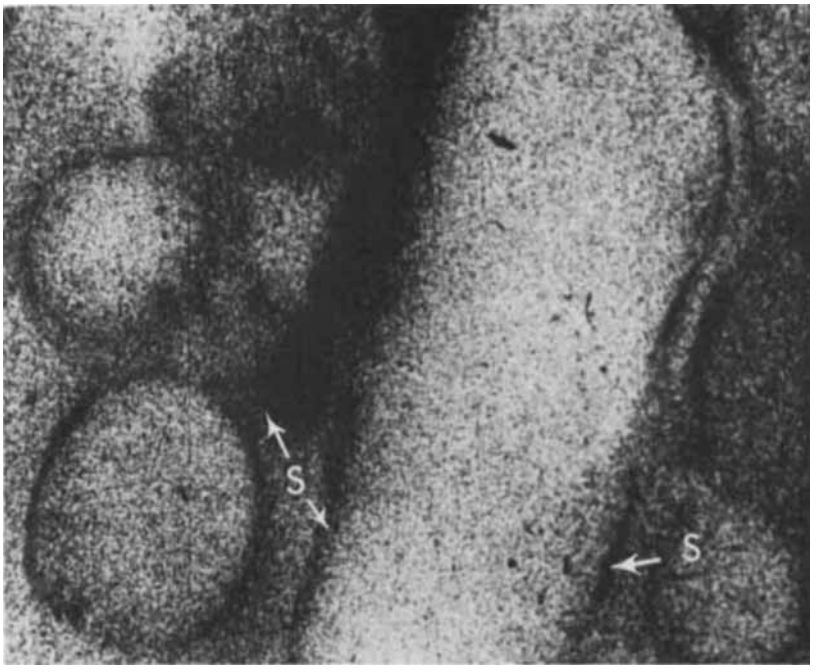

FIGURE 11. Transilluminated liver of a mouse on a choline-deficient diet and alcohol for 4½ months. A large fatty cyst occupies entire width of the microscopic field. The sinusoids (S) around the cyst are distorted and compressed. There are several fat globules adjacent to the cyst. (Cinephotomicrograph × 2500.)

portal inlet channels and of the sinusoidal outlet sphincters.[22] Continuous flow in the sinusoids results from the random intermittency in the activity of the inlet- and outlet-sphincters.

With some imagination, one can visualize the entire hepatic vascular net unfolded into a vast web, ¼ mm thick. Its finest vascular branches empty into the sinusoidal ditches that irrigate the fertile brown soil. Under the microscope, one sees how arterial blood jets intermittently into some of the sinusoids while the portal blood wells up in others. This activity shifts from area to area. Shifting of the blood flow patterns with varying speeds was also noted in gross circulatory studies by Birtch and coworkers.[23]

The intermittent activity of arterioles and terminal portal venules accounts for the great adaptability of the intrahepatic circulation to the multiple metabolic functions of the hepatocytes, and there must surely be a fine control mechanism of quantity, blood pressure, and of blood content in oxygen and nutrients. We are as unaware of this mechanism as Galen was of the general circulation of blood. Further, more complete investigations of afferent and efferent hepatic blood flow, the content in gases and metabolites of the blood, and an open mind to newer interpretations of normal hepatic structure and function may help us to understand their distortion—the pathology.

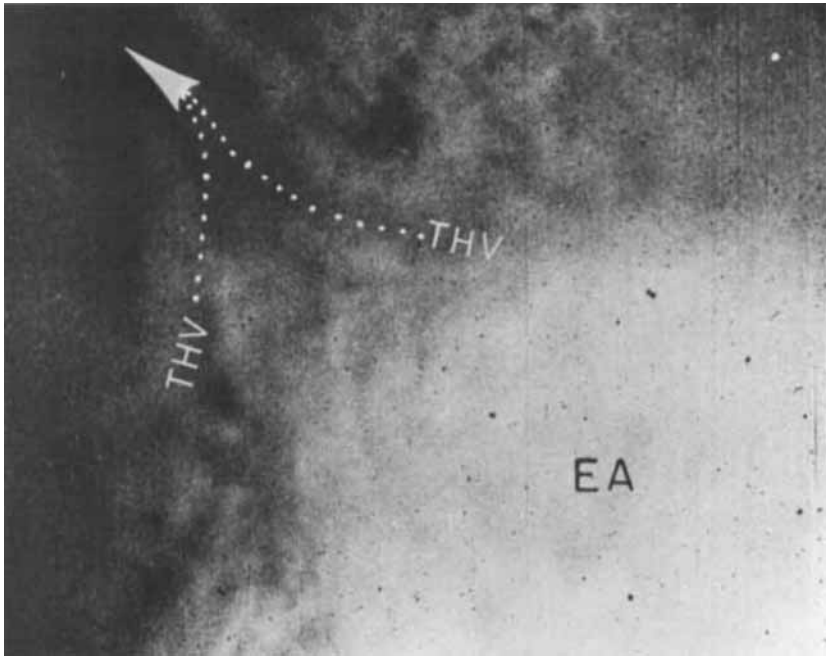

FIGURE 12. Transilluminated rat liver 24 hours after ingestion of fulvine. The edematous liver acinus (EA), delimited by two terminal hepatic venules (THV), is completely devoid of microcirculation. There is congestion in the remainder of the liver. (Cinephotomicrograph 800×.)

The second factor determining pressure is peripheral resistance. Data have been accumulated on the impediment on portal inflow and on outflow from the sinusoids—the presinusoidal and postsinusoidal blocks. As can be seen in the figures of the microcirculation in the fatty liver, severe distortions of the shape of the sinusoids is brought about by the accumulation of fat in the parenchymal cells. Instead of running in straight lines from the terminal, afferent vascular axes towards the terminal hepatic venules (the so-called "central veins"), the sinusoids wind their way between boulders of fat that curve and lengthen the course of the fine vessels. At the same time the wavy, irregular shorelines of the sinusoids form narrows (Fig. 9) through which the blood can pass only under higher pressure. Thus, the increased hindrance factor $\left(\frac{1}{r^4}\right)$ in the formula of resistance $R = \frac{8\eta l}{\pi r^4}$ is the main cause of sinusoidal hypertension. In addition, the arteriolar activity is more conspicuous in the fatty liver, thus increasing the supply of arterial blood under high pressure to the sinusoids.

In rats with toxic hepatitis after ingestion of fulvine the sinusoidal flow observed *in vivo* reveals extensive narrowing of the sinusoids. The vascular

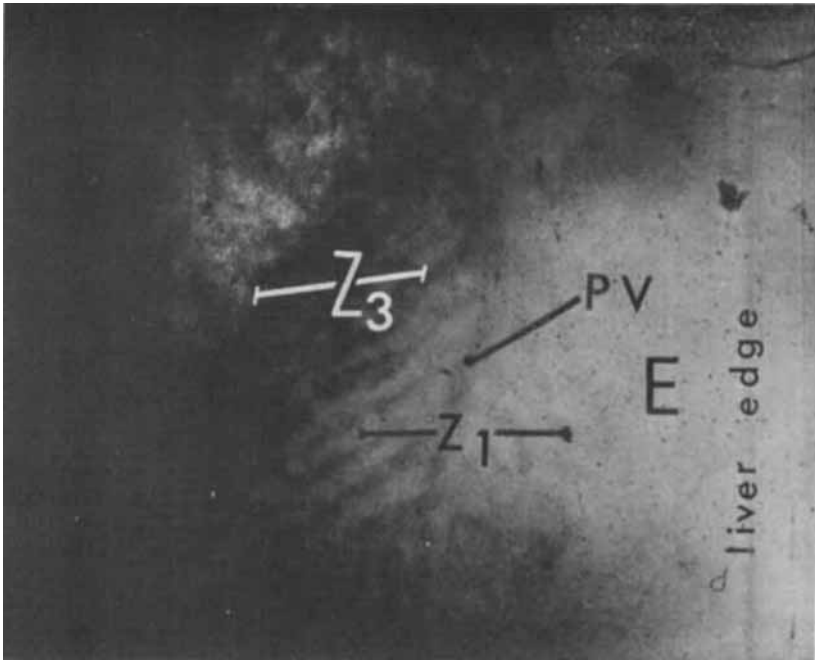

FIGURE 13. Transilluminated rat liver 40 hours after ingestion of fulvine. Through overlaying edematous tissue (E) one still sees granular flow in the terminal portal venule and in the sinusoids of zone 1. Peripheral zone 3 (Z_3) is completely blocked by microthrombi. (Cinephotomicrograph 450×.)

network is compressed by the edema of the adjacent cells and the blood flow is diminished. Such observations were made by Himsworth [24] in histologic sections, and his concept that ischemia of the parenchyma leads ultimately to cell death has now been confirmed *in vivo*. These phenomena are pronounced in zone 3, the circulatory periphery of the acinus. In addition to the narrowing of the sinusoids in acute toxic hepatitis with increase of peripheral resistance to flow, we note also a variety of changes in the viscosity of blood (factor η in the formula of resistance), ranging from a slight stickiness of the blood cells a few hours after the ingestion of fulvine to a clumping of erythrocytes seven hours after the start of the experiment.

Eventually, microthrombi form in the sinusoids; some break up and their debris are diverted into still open sinusoids through which blood moves in a thick paste. Others reform and become sessile in the narrowed sinusoids where flow has ceased. The efferent parts of the sinusoids are mainly affected; the outflow of blood from the sinusoids into the terminal hepatic venules (T.H.V.) is blocked and the liver becomes congested. Recent experiments by Potvin [25] have demonstrated that arterial inflow almost doubles in the experimentally congested liver. Thus, narrowing of the sinusoids, increased viscosity of blood, and greater arterial inflow are all present in toxic hepatitis and lead to portal hypertension.

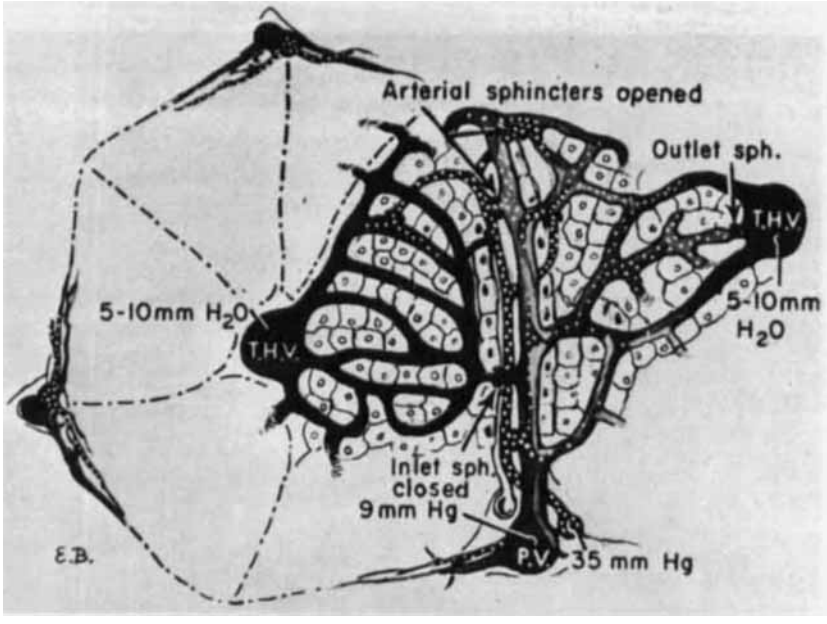

FIGURE 14. Microcirculation in a liver acinus. The pressure in the terminal portal, arterial, and hepatic venous branches is indicated. In the left half of the figure an opened arteriolar inlet sphincter admits arterial (white, dotted) blood into the sinusoidal area, primarily filled with portal (black) blood; outlet sphincters around the terminal hepatic venule (T.H.V.) are open. In the right half of the figure all arteriolar-portal and arteriolar-sinusoidal sphincters have opened, admitting blood and thus raising the pressure in all the sinusoids to arteriolar level. Opening and closing of sphincters occur in an intermittent rhythm. One outlet sphincter at the junction of a sinusoid with the terminal hepatic venule is closed.

SUMMARY

There is a sinusoidal type of portal hypertension in addition to the pre- and postsinusoidal variety; it is due to an increased resistance to blood flow through the sinusoids. This type of hypertension occurs in the fatty liver and in toxic hepatitis. The normal *in vivo* microcirculation of the mammalian liver is briefly presented for a better understanding of the microcirculatory changes leading to sinusoidal portal hypertension. The normal hepatic microcirculation is characterized: by a flow pattern outlining acini (no hexagonal lobules are ever seen); by a sinusoidal network connecting terminal afferent and efferent vessels in straight lines; by intermittent circulatory activity of inlet venules and arterioles that yields a sinusoidal flow with pulsatory and respiratory succussions.

The accumulation of fat in the hepatocytes of choline-deficient mice drinking alcohol distorts the microcirculatory pathways. The sinusoids increase

in length and are narrowed by the fat droplets bulging into their lumen. Thus, the hindrance factor $\frac{1}{r^4}$ in the formula of peripheral resistance is increased. Also, the circulatory activity of the arterioles is augmented in the markedly fatty liver. The aformentioned factors lead to portal hypertension.

Toxic hepatitis induced in rats by a single ingested dose (.065 mg/gm/bw) of fulvine (*Crotalaria fulva*) results in an increased resistance to sinusoidal flow: edema of the hepatocytes develops early and narrows the sinusoids. Seven hours later the sticky blood cells clump; in another five hours microthrombi form and block the sinusoids at their exit (zone 3). Around the 24-hour mark, edema compresses the sinusoids and entire acini at the liver margin become ischemic. The viscosity of blood increases further, and a paste of erythrocytes winds slowly through a few patent sinusoids. Congestion of the parenchyma increases during the following 24 hours, making further *in vivo* observation of the mircrocirculation impossible. Portal pressure rises from 110 mm (normal) to 260 mm of physiologic saline solution on the third day of toxic hepatitis.

Acknowledgment

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DISCUSSION OF THE PAPER

DR. SHERLOCK (*The Royal Free Hospital, London, England*): I was particularly interested in your view that sphincters, intralobular sphincters, might be responsible for telling the blood sinusoids or helping to. Dr. Brown has already

mentioned species differences particularly with muscular hepatic veins in dogs in which we know the difficulty.

The question I wanted to ask is do you have any anatomical basis for these sphincters? What species have it, and what species do not?

DR. RAPPAPORT: The question of sphincters along the arterioles is a loaded one. We hoped that we will get our answer from electronmicroscopy, but the electron microscope has not provided it; however, one should not be disappointed. We know that in any capillary bed of any circulatory area there is intermittent closing and opening of the capillaries. The Frenchmen have a descriptive name for it, they called it "le coeur capillaire." What actually moves the capillaries, one does not know; even today we have no contractile cells definitely demonstrated in the capillary walls. The same situation exists in the case of the liver, but I am convinced that circulatory activity, arteriolar and venular, is intermittent, and observe it all the time *in vivo* in the rat, the mouse, the rabbit, and the frog. I couldn't see it in the liver of the dog; its liver is too thick and cannot be transilluminated; the human liver is even less accessible to *in vivo* transillumination.

DR. GORESKY (*University of Montreal, Montreal, Can.*): I am delighted to see Dr. Rappaport's picture. He has shown me why there is such an apparent distribution in the times of transit through the liver. It is distributed at cross-lobules, as well as within a lobule.

I think the intermittency that he alludes to is intermittency in a different sense than I had intended to use the word. I have visualized intermittency to mean on and off. What he is showing is a variation from large to small, but I see a continuation of flow within a lobule, so that the philosophy varies along the length and the transit time varies along the length, within a lobule and between lobules. I really think there is nothing incompatible between what he has seen and certain arguments that I have put out.

DR. IBER (*Lemuel-Shattuck Hospital, Boston, Mass.*): Dr. Rappaport, in your movies and discussion, I was not completely clear on how much change you observed in the arterial radicle input into the sinusoid. In one illustration you did allude to this change. Would you repeat your general finding in your two models in regard to what the arterial participation was in the sinusoidal model, or was there no change in these two examples? I want to know if the only changes you observed were in the venous component of flow through the sinusoid. Or did you observe evidence in these two models of increase or more persistency of the arterial twig input of blood into the sinusoids that were arterialized?

DR. RAPPAPORT: Are you talking about the model, or about our observations *in vivo*.

DR. IBER: The observations *in vivo*.

DR. RAPPAPORT: The observations *in vivo* show intermittent activity in arterioles. They hit the eyes most strongly because the blood is coming in jets. But you can see the closing and opening of inlet sphincters around inlet venules, and also the shutting off of some sinusoids by sphincters at their outlet into the hepatic veins.

This activity goes on with such great rapidity that one showing of a film does not make it clear to the onlooker. After we have looked at a film 20 times, and we have taught ourselves to look away from this turning jet of

blood, and our eye focuses on other sites, we will soon notice either a change in velocity or greater disturbance of flow by a jet coming or by another dying down. Thus, intermittency in capillary flow is a general phenomenon, although the liver surface under small magnification shows only rivulets of blood flowing in the sinusoids continuously.