Spontaneous Reversal of Portal Blood Flow:

The Case For and Against Its Occurrence in Patients With Cirrhosis of the Liver

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Because of its presumed serious clinical significance, we made an analysis of the evidence for and against the occurrence of spontaneous reversal of portal flow in cirrhosis of the liver. We examined the evidence obtained from manometric studies, radioactive tracer studies, radiologic studies, and actual measurements of magnitude and direction of portal blood flow. Concerning manometric studies, we introduced a physical analysis, based on first principles, which demonstrates that the occluded portal pressures cannot be used to construct a hydraulic gradient for portal flow. Similarly, we examined the weakness of the evidence derived from radioactive tracer and radiologic studies and, in the latter, the drastically opposite results reported by different investigators. Finally, we found that actual measurements of magnitude and direction of portal flow provide impressive evidence against the occurrence of spontaneous reversal of portal flow in cirrhosis. We conclude that unless new and convincing evidence is provided, it may not serve the best interests of medicine and of our patients to continue accepting spontaneous reversal of portal flow in cirrhosis as if it were a proven phenomenon.

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SPONTANEOUS REVERSAL of portal flow implies that the portal vein delivers hepatic blood into the splanchnic bed instead of delivering splanchnic blood into the liver as intended in the orderly scheme of nature. This departure from the normal order has been predicated on the basis of the outflow tract obstruction prevailing in cirrhosis.[1,25,58] Under these conditions, the blood entering the liver through the hepatic artery would find it easier to exit the organ through the portal vein than through the normal route of the hepatic veins. The diverted hepatic blood would then fight its way against the incoming splanchnic flow and eventually reach the right heart via the collateral network.

Apparently, the need for a concept of spontaneous reversal of portal flow was created by some unexpected results observed after side-to-side portacaval anastomosis. At the time, it was becoming increasingly clear that this operation was not yielding the results originally predicted, i.e., decompression of the splanchnic bed and varices with preservation of some hepatic perfusion by portal blood. Quite the contrary, it was evident that while the lower limb of the shunt was effectively decompressing the splanchnic bed, its upper limb appeared to be draining hepatic blood into the inferior vena cava. The question immediately arose as to whether the hepatic arterial blood now leaving the liver through the shunt had had an opportunity to perfuse the hepatic cell or, if by taking the route of arterio-portal anastomoses, it had actually bypassed the sinusoidal bed. Primarily on the basis of measurements of hepatic oxygen consumption, two different camps of opinion were promptly formed.[28,37,38,44,54] In the meantime, the concept of spontaneous reversal of portal flow in cirrhosis proved to be a more convenient alternative for the dilemma. Here, the reasoning was that if a patient with advanced cirrhosis already had his portal flow spontaneously reversed before any surgical intervention, then the shunt would only complete the task initiated by nature,[57,58] and the matter of perfusion of the liver cell would become a moot question.

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At this writing, the concepts of outflow block in the formation of ascites advanced by Madden,[25] and of correcting this complication by simultaneous splanchnic and hepatic decompression pioneered by Welch[58] and McDermott,[26] appear to have become definitely established on their own merits. Therefore, it seems no longer necessary to advance hypothetical arguments to justify the rationale of the side to side shunt. Unfortunately, the hypothesis of spontaneous reversal of portal flow in cirrhosis[57] has survived on the basis of what, after all, may only be "circumstantial" evidence. Recently, the presence of alleged spontaneous reversal of portal flow has been reported to be associated with different mortality and morbidity after portacaval shunts performed during acute bleeding.[7] In this report we intend to examine in some detail the evidence available for and against spontaneous reversal of flow in the portal vein of patients with cirrhosis of the liver. For convenience, we will examine the evidence under four main subheadings: manometric studies, radioactive tracer studies, radiologic studies and actual measurements of magnitude and direction of portal flow.

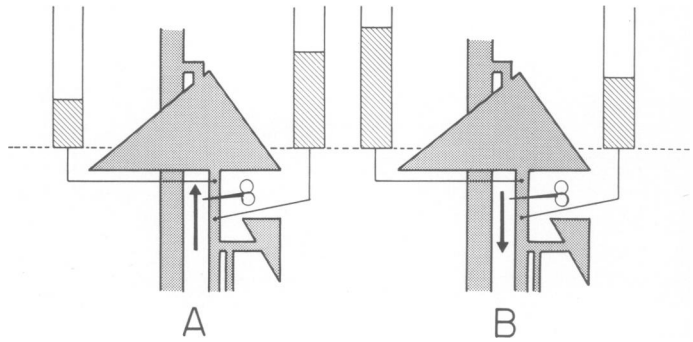


FIG. 1. Common interpretation of the significance of pressures measured on the hepatic and splanchnic sides of a clamp occluding the portal vein. (Redrawn after Conn[9]). A. When the pressure on the splanchnic side of the clamp (SOPP) is higher than the pressure on the hepatic side of the clamp (HOPP), the portal blood should flow into the liver in the normal fashion. Portal flow is then variously said to be forward, cephalad, hepatopetal, or antegrade. B. When the hepatic occluded pressure is higher than the splanchnic occluded pressure, the portal blood should flow out of the liver into the splanchnic bed. Now, the portal flow is said to be reversed, caudal, hepatofugal, or retrograde. (See Fig. 2 for a model that would be compatible with this interpretation.)

Manometric Studies

Measurements of pressure on the hepatic and splanchnic sides of a clamp occluding the portal vein have been used in the literature to support the presence of spontaneous reversal of flow in the portal vein of patients with cirrhosis of the liver. If the pressure on the hepatic side of the clamp were higher than either the free portal pressures or the pressure on the splanchnic side of the clamp, the blood, flowing from the higher to the lower pressure, would leave the liver through the portal vein and enter the splanchnic circulation.

In the previous reasoning, the unstated but necessarily implied assumption is that the pressure on the hepatic side of the clamp approximates the pressure in the sinusoids of the liver and that this approximation holds not only during the portal occlusion but also when the portal blood is flowing into the liver. That being the case, the difference between the hepatic occluded and the free portal pressure would become a true pressure differential or hydraulic gradient for flow in the portal vein.[27] Similarly, the difference between hepatic and splanchnic occluded portal pressures would become some sort of potential gradient for flow which has been designated as the "maximum perfusion pressure."[54,56,57] These concepts have become ingrained so deeply in our routine clinical thinking that even surgical residents react with surprise, and sometimes with hidden or overt indignation, to any attempt to question their validity. Frequently, such questioning is taken with the connotation of a challenge to the fundamental laws of nature. And yet, it is simpler to demonstrate the physical weakness of these hemodynamic concepts than to trace the oversimplifications which, explicitly or implicitly, were used to introduce them as legitimate expressions of valid laws of physics. In the next paragraphs we will attempt to examine these oversimplifications and some of their natural consequences.

A good example of the current interpretation of the occluded portal pressures is given in Fig. 1 which has been redrawn from an illustration in a writing by Conn.[10] On the left side of Fig. 1, labelled A, two manometers are represented by reservoirs adjusted to a common datum plane given by the broken line. The level in the reservoir connected to the splanchnic side of a clamp occluding the portal vein is higher than the level in the reservoir connected to the hepatic side of the occluded portal vein. As the arrows near the portal vein indicate, the splanchnic blood should enter the liver in the normal manner. On the right side of the illustration (B), the level in the reservoir connected to the hepatic side of the occlusion is higher than that of the one connected to the splanchnic side of the occlusion. The arrow along the portal vein indicate that now the hepatic blood should flow out of the liver into the splanchnic bed. The apparent disarming logic of this reasoning can be immediately challenged. Although we have objected to the current abuse of the word "model" in medical writings,[35] we have nothing against its proper use and, therefore, will search for a model that would be compatible with the previous reasoning. Then, we will compare the model with reality to see if it can be considered an adequate representation of the true physical system under discussion.

Figure 2 shows a model compatible with the interpreta-

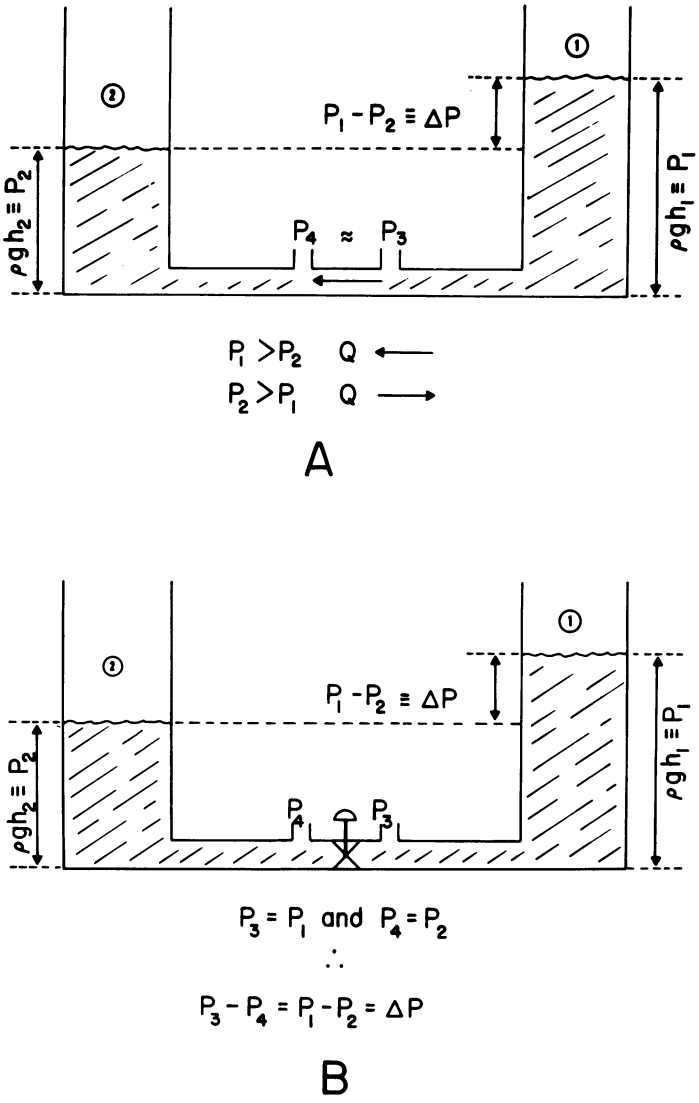


FIG. 2. A simplified model that would be compatible with the interpretation that the pressures on the hepatic and splanchnic sides of a clamp occluding the portal vein could be used to construct a hydraulic gradient for flow in the portal vein. A. Liquid flows from Reservoir 1 to Reservoir 2 through a smooth pipe of constant cross-sectional area. For constant density of the fluid (ρ) and consant acceleration of gravity (g), only the heights h_1 and h_2 determine the pressure in the reservoirs. The difference between these pressures is the hydraulic gradient for flow (ΔP). The direction of flow (Q), is a function of the relative magnitudes of P_1 and P_2. Pressures at two close points in the pipe (P_3 and P_4) are almost identical due to the short distance separating the points and to the absence of any narrowing or roughness of the pipe between them. Measurements at these points will not reflect the gradient for flow in the system. B. A valve has been closed between points 3 and 4 in the pipe and there is no flow in the system. If this model would be an adequate representation of the splanchnic-hepatic-collateral system in cirrhosis, closing of the valve would be equivalent to clamping the portal vein. Now points 3 and 4 are connected to their respective reservoirs by static columns of fluid and $P_3 = P_1$ while $P_4 = P_2$, then $(P_3 - P_4) = \Delta P$, the gradient for flow in the system. This model sustains the interpretation of the occluded portal pressures advanced in the literature (see Fig. 1). However, the model is not an adequate representation of the true physical system in cirrhosis. First, the model represents an open, gravity system and, second, the reservoirs do not have the outlets which in the real system are provided by the hepatic veins and the collateral network respectively.

tion of the occluded portal pressures given above. Essentially, the illustration shows two reservoirs (1 and 2) connected by a smooth pipe of constant cross-section. In Fig. 2A, flow is taking place from 1 to 2 on the basis that P_1 is greater than P_2. In this model, for fluids of constant density (ρ), submitted to a constant acceleration of gravity (g), only the height of the column of fluid (h) is required to define the pressure. The difference ($P_1 - P_2$) is the gradient for flow in the system (ΔP). With P_1 greater than P_2, the flow proceeds from 1 to 2 and ΔP is said to be positive. With P_2 greater than P_1, we have flow from 2 to 1, and ΔP is said to be negative. The difference between the pressure measured at two points closely located in the pipe (P_3 and P_4) is very small due to the proximity of the points and the absence of any narrowing of the pipe between them.

If one now occludes the pipe between the points where P_3 and P_4 are being measured, equivalent in this model to clamping of the portal vein, the points become connected to their respective reservoirs by static columns of fluid (Fig. 2B). These columns of fluid act as manometers or as extensions to any manometer connected to the points 3 and 4. Then, the difference between P_3 and P_4 would equal the difference between P_1 and P_2 and, therefore would equal the true gradient for flow in the system (ΔP). If this model adequately represents the splanchnic-hepatic-collateral system in cirrhosis, the difference between the occluded portal pressures would be a measure of the true gradient for flow in the system. However, as we will discuss later in more detail, the model does not represent the real system adequately, and we have the case of a correct analysis for a model which is not a correct representation of the real system. In other words, it is not the model but its selection that is incorrect in this scheme.

The model in Fig. 2 is not an adequate representation of the splanchnic-hepatic-collateral system in cirrhosis on two main counts: first, it represents an open, gravity flow system and, second, it does not provide for outlets to the reservoirs, i.e., hepatic veins outflow for the liver reservoir and collateral bed outlet for the splanchnic reservoir. If one would like to persist with the open gravity flow system and provide the necessary outlets for the reservoirs, one would obtain a model such as the one represented in Fig. 3. Here, the two reservoirs empty into a common third reservoir, the vena cava, by outlets which have a definite resistance. If we now occlude the pipe representing the portal vein between points 3 and 4, we note that P_3 and P_4 are no longer simple functions of the height of the levels of the reservoirs 1 and 2, but complicated functions of the pressure differentials between the various reservoirs, of the flow through the outlets, and of the resistance of the outlets. These relationships do not even include the pressure in the arterial reservoirs or the high arteriolar resistances which are

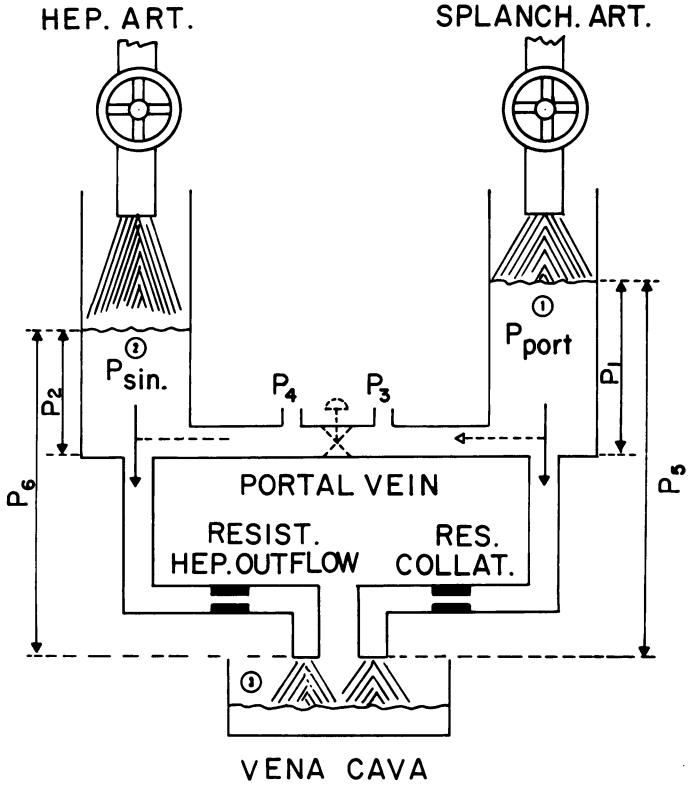
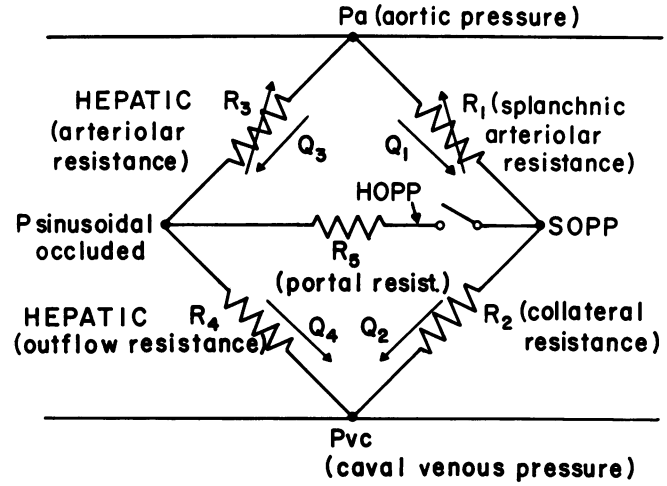


FIG. 3. A more realistic model of the splanchnic-hepatic-collateral system in cirrhosis. While still restricted by representing an open, gravity system, the model improves that shown in Fig. 2 by providing outflows to the reservoirs. The arterial inflows although shown refilling the reservoirs through high arteriolar resistances (heavy valves) will not be considered in a preliminary discussion. When the valve between points 3 and 4 in the pipe representing the portal vein is open, reservoir 1 (the splanchnic reservoir) divides its flow between the portal vein and the collateral outlet. In turn, reservoir 2 (the hepatic reservoir), empties the combined contributions of the hepatic artery and the portal vein into the vena cava through the resistance of the hepatic outflow. When the valve between points 3 and 4 is closed, flow through the transverse pipe (the portal vein) ceases but flow through the collateral and hepatic veins outlets continues. P_3 and P_4 are no longer simple functions of the height of the fluid in the reservoirs 1 and 2. Even disregarding the arterial pressure and the arteriolar resistances, P_3 and P_4 are still complex functions of the pressure differentials between the various reservoirs, of the outlet flows and of the resistance in these outlets (represented by black blocks). The arteriolar resistances, although not included in this discussion, are represented by adjustable valves to imply their ability for adjustments in short time scales. The hepatic outflow and collateral outlet resistances are represented by fixed resistances to indicate their capability for long term adjustments only. These adjustments may require months or even years as the cirrhotic process and the development of collaterals advance.



P = pressure R = resistance

Q = flow

HOPP = hepatic occluded portal pressure

SOPP = splanchnic occluded portal pressure

$$HOPP \approx P_{sin.\,occl.} = P_{vc} + (P_a - P_{vc})\,R_4/(R_4+R_3) \quad (1)$$

$$SOPP = P_{vc} + (P_a - P_{vc})\,R_2/(R_2+R_1) \quad (2)$$

FIG. 4. The splanchnic-hepatic-collateral system in cirrhosis represented by the Wheatstone bridge analogy proposed by Bradley.[3] Clamping of the portal vein, represented by the open switch in the circuit, turns the bridge into two parallel circuits, i.e., the hepatic artery-hepatic veins circuit, and the splanchnic-collateral circuit. Equations 1 and 2 show the determinants for the hepatic occluded portal pressure (HOPP) and for the splanchnic occluded portal pressure (SOPP). Note that in Equations 1 and 2, the pressure terms are the same for both circuits and, therefore, that the difference is given by the resistive terms. These resistive terms are simply the ratio of the outflow to the total resistance on each circuit. The value of these ratios are the only determinants for the pressure on either side of the clamp to be higher or lower than the pressure on the other side. The important conclusion is that the hepatic occluded portal pressure (HOPP) approximates the sinusoidal pressure only when portal flow is not taking place. The value of the sinusoidal pressure when portal flow is taking place, the only value relevant for the construction of a hydraulic gradient for portal flow, is very different and is given by a much more complicated mathematical expression which we introduced in our reference.[36] As in Fig. 3, the arteriolar resistances are represented as variable resistances to indicate their ability for short time scale adjustments. Similarly, the hepatic outflow and hepatic outlet resistances are represented by fixed resistors to indicate their usual inability for short time scale adjustments.

represented in the sketch by heavy valves. Actually, at this point, it is no longer possible to carry further the analogy of the open, gravity system without introducing grave complications. Therefore, we will resort to a more manageable electric analogy using the Wheatstone bridge model proposed by Bradley.[3]

If one restricts the analysis to steady flows, leaving apart considerations of inertances and variable compliances, it is possible to apply directly the equations for the bridge developed in the field of electrical engineering.[14] In a previous communication,[36] we introduced such analysis for the splanchnic-hepatic-collateral system in cirrhosis (Fig. 4). As a result, we showed that the conditions for the pressure on either side of the clamp to be higher or lower than that on the other side are independent of the magnitude and direction of the portal flow and are determined uniquely by the ratio of the outflow to the total resistance on each of two parallel

circuits, i.e., the hepatic artery-hepatic veins system on one side (Equation 1 in Fig. 4) and the splanchnic-collateral system on the other (Equation 2 in Fig. 4). These circuits have been made independent parallel circuits by clamping of the portal vein which removes the direct connection between them. The analysis also showed that when flow in the portal vein is not interrupted by a clamp, the conditions determining the free portal pressure and the unoccluded sinusoidal pressure are given by mathematical relationships drastically different from those determining the occluded pressures. Therefore, the sinusoidal pressure during occlusion is very different from the sinusoidal pressure during flow, a fact that precludes the use of the occluded pressures to construct a gradient for portal flow. This explains the clinical findings in two of our previous reports[6,36] where we found a complete lack of correlation between the differences in occluded pressures and the magnitude and direction of the portal flow in a series of 80 patients having all the necessary measurements. Actually, nine of these patients did have an hepatic occluded pressure which was higher than the free portal pressure or than the splanchnic occluded pressure. However, none of them had reversal of portal flow as assessed by direct measurements with the electromagnetic flowmeter. Two of these patients had stagnant flow and the remaining seven had forward flow into the liver measuring from 80 to 1116 ml/min. We will return to discuss the value of measurements with the electromagnetic flowmeter in the last section of this report.

In view of the discussion above, the findings recently reported by Charters et al.[7] remain in need of an explanation. These authors reported clinical correlations with the values of the occluded pressures and the presumed direction of the portal flow in patients operated during acute bleeding. However, from a purely statistical frame of reference, their conclusions seem difficult to justify. When they state that encephalopathy on admission was more common in patients with presumed reversal of flow, they give an incidence of 27% versus 17% in patients with presumed forward flow. If a contingency table is prepared according to the statistical makeup of the group, a test of significance renders a value of $\chi^2 = 1.822$ which for one degree of freedom yields the non-significant value of $P < 0.32$. Similarly, the difference in survival was not significant at the 5 per cent level ($P < 0.08$). Finally, the incidence of encephalopathy in the survivors, given as 23% for the patients with presumed reversal of flow versus 12% in those with presumed forward flow is statistically not significant ($\chi^2 = 0.108$ and no value of P can be computed). In reality, the data of Charters et al. show that their division of clinical results into patients having presumed reversed portal flow and into patients having presumed forward portal flow is hardly justifiable because a separation based on random selection would have a high probability of yielding the same results. In other words, both groups might have been extracted from a common group.*

Irrespective of the lack of correlation between the values of the occluded portal pressures and the magnitude and direction of the actual portal flow, the fact remains that Charters et al. did find a higher incidence of reversed pressure differences in their acutely bleeding patients. Without access to their raw data, one may only speculate that a sudden decrease in the outflow collateral resistance may have rendered a transiently higher incidence of reversed pressures. Such a decrease in collateral resistance may have resulted from the opening of a wide rent, at the site of bleeding, in the collateral circuit. In turn, this decreased in collateral outflow resistance may have lowered temporarily the resistive ratio in Equation 2.

The fact that the values of the differences between the occluded sinusoidal and splanchnic pressures do not determine the magnitude or direction of the portal flow should not be taken as a statement that true spontaneous reversal of flow cannot occur in this vessel. Using the Wheatstone bridge analogy one can derive the conditions for the unoccluded sinusoidal pressure to exceed the portal pressure. Essentially, these conditions require a much larger hepatic outflow resistance than the resistance in the collateral bed. Since the difference between the unoccluded sinusoidal and the free portal pressure is a true pressure differential or hydraulic gradient for flow, there would be spontaneous reversal of portal flow whenever the unoccluded sinusoidal pressure exceeds the free portal pressure. This condition must not have existed in any of the patients in our study. Apparently, the value of the hepatic outflow resistance was not sufficiently large in our patients with cirrhosis to produce spontaneous reversal of portal flow. Conversely, its value should be very large in Budd-Chiari syndrome with almost complete obstruction of the outflow tract. This might be the reason why true spontaneous reversal of portal flow appears to occur in this syndrome.[16,40,43,47]

On the basis of our analysis and clinical measurements, we conclude that there is no justification for the claims of spontaneous reversal of portal flow in cirrhosis reported in the literature if the claims are based solely on the presence of an hepatic occluded portal pressure which is higher than either the free portal or occluded splanchnic pressure.

Radioactive Tracer Studies

The studies of Longmire et al.[24] in 1958, are often quoted in the literature as proof of spontaneous reversal

*For the case of the incidence of encephalopathy in the survivors, the use of the χ^2 statistics may be questioned because there is an expected frequency lower than five. However, any attempt of correction, for example the Yates correction, makes the results even less significant.

of portal flow in cirrhosis. Careful reexamination of the protocol of the studies shows, once more, that the evidence for spontaneous reversal might be more "circumstantial" than definitive.

These authors inserted catheters in the splanchnic-hepatic system of patients about to undergo side to side portacaval shunts. One catheter was located in a peripheral mesenteric vein, another was advanced into the main trunk of the portal vein well cephalad to the site of the intended anastomosis, and a third catheter was threaded into the hepatic artery through one of its branches. Injecting radioactive tracer into the peripheral mesenteric vein and sampling from the cephalad catheter in the portal vein, they detected the passage of a large bolus of radioactivity. This was interpreted as forward portal flow carrying the peripherally injected tracer into the liver. However, injecting into the hepatic artery and sampling, again, from the cephalad portal vein, the authors noted that some radioactivity "may be immediately detected" in the portal blood. This time the interpretation was that some backflow of hepatic arterial blood into the portal vein may have been taking place. Now, these interpretations are mutually exclusive, i.e., the first injection shows forward flow while the second injection shows reversed flow. It might be argued that in living systems there are occasions where diffusion of substances do occur against hydraulic, chemical or electrical gradients. However, this requires mechanisms of active transport with elaborate use of energy. Such is the case of the transport of ionic calcium into the sarcoplasmic reticulum during muscular relaxation. Here, the transport is achieved against a gradient of concentration through the energy yielding splitting of ATP.[23] An equivalent process is described by the formalism of the thermodynamics of irreversible processes as "incongruent" diffusion.[17,42] There are many "pumps" of this sort operating in living beings, but few would claim such sophisticated mechanisms to explain the diffusion of a modest radioactive tracer against the incoming portal flow. A simpler explanation could be that the suction exerted by the cephalad catheter resulted in some sampling of sinusoidal blood rightly containing isotope. This is conceivable if one compares the order of magnitude of the suction created by a sampling syringe with that of the small pressures prevailing in the portal-sinusoidal system. In a group of 23 patients with cirrhosis, Reynolds compared the values of the sinusoidal pressure using hepatic vein wedged measurements and of the portal pressure measured simultaneously through the recanalized umbilical vein.[45] He found that the sinusoidal and portal pressures were almost identical, a fact that shows the very small resistance existing between the portal vein and the sinusoids.

After constructing the side to side shunt, Longmire and associates repeated their series of injections. The results were now reversed, i.e., the portal cephalad samples showed little or no radioactivity after mesenteric peripheral injection and large radioactivity after hepatic arterial injection. The radioactivity after hepatic arterial injection was measured as several times larger than that detected before constructing the portacaval shunt. The probably correct interpretation was that now the mesenteric blood was diverted into the vena cava through the lower limb of the shunt while the upper limb, acting as an accessory outflow tract, was carrying hepatic blood away from the liver.

The results of the important studies of Longmire and associates indicate that reversal of flow does take place in the hepatic limb of a side to side portacaval shunt. However, it is highly improbable that they could be construed as proof of spontaneous reversal of portal flow in cirrhosis.

Radiologic Studies

Five primary radiologic methods have been used to attempt a demonstration of spontaneous reversal of flow in the portal vein of patients with cirrhosis: 1) retrograde injection of contrast medium from the "wedged" hepatic vein position; 2) portal injection through catheterization of the umbilical vein; 3) splenic portography; 4) selective hepatic arteriography; and 5) hepatic intraparenchymal deposition of contrast medium.

Retrograde Injection of Contrast Medium from the Wedged Hepatic Vein Position

Warren et al.[55–57] and Viamonte et al.[53] have most persistently reported the occurrence of spontaneous reversal of portal flow in cirrhosis on the basis of their observations following hepatic vein "wedged" injection of contrast material. In this technic, the opaque medium is introduced under pressure through a catheter wedged into a small hepatic vein branch and forced, in retrograde fashion, into the sinusoids and the portal venules. According to these authors, more advanced degrees of cirrhosis with smaller portal blood inflow would facilitate the retrograde injection and the visualization of the portal branches. If the main trunk of the portal vein is visualized, the flow in this vessel is said to be retrograde, i.e., the portal blood would be flowing out of the liver into the splanchnic bed. Visualization of the coronary system and varices would further affirm the presumption of spontaneous reversal of portal blood flow. Conversely, it would be very difficult to force contrast material into the portal vein system of normal subjects having large portal inflows.

Opposite findings have been reported by Ney[39] who showed that the contrast medium could be forced into the main portal vein of normal subjects, by Britton[4] who found that very little pressure is required to force contrast material into the portal trunk of most patients with

cirrhosis, and by Smith[49] who found a greater incidence of this forced retrograde filling of the portal system in patients with early cirrhosis. Perhaps the report of Smith et al. contains the most damaging evidence against the ability of these forced, retrograde injections to demonstrate, without artifacts, the presence of spontaneous reversal of portal blood flow. Their communication includes a patient who showed what was considered a most typical pattern of presumed spontaneous reversal of portal flow during the wedged hepatic vein injection and who, at operation, was found to have a forward flow of 480 ml/min as measured by the electromagnetic flowmeter. In our own studies,[46] we found a patient with such extensive retrograde filling of the portal system after hepatic vein wedged injection, that true spontaneous reversal of portal flow in cirrhosis appeared to have been confirmed. However, during measurements with the electromagnetic flowmeter, the patient was found to have forward portal flow into the liver measuring 165 milliliters per minute. Finally, Smith et al, also studied 11 patients after side to side portacaval anastomosis. Despite the fact that most of these patients are known to have reversal of flow in the hepatic limb of the shunt, none of them showed evidence of such reversal during hepatic vein wedged injections.

The conflicting findings reported by different authors, occasionally being one hundred and eighty degrees out of phase, cast serious doubts on the occurrence of spontaneous reversal of portal flow in cirrhosis when only evidence from hepatic vein wedged injection is brought in its support. The conflicting findings should not be unexpected in a method which is based on the retrograde injection of contrast. If the material is forcefully backed up to the level of the junction with the coronary vein, at the point where the splanchnic flow divides between the portal vein and the collateral bed, the medium would easily take the route of gastroesophageal varices and this needs not imply that the portal flow had spontaneously reversed its direction in the absence of the forced injection.

Even accepting the reports of Warren and associates as proof of the validity of the hypothesis of spontaneous reversal of portal flow in cirrhosis, the evidence would still be sparse. We had difficulties keeping our arithmetic straight while sorting out the patients repeatedly included in their various reports. Within these difficulties, we were able to identify only six patients having presumed reversal of portal flow in the reports published between 1963 and the present writing.

Portal Injection Through Catheterization of the Umbilical Vein

Kessler and associates[18] have reported on this method. They catheterized the umbilical vein and injected 40 ml of 75% contrast material at 125 psi. This is followed by complete flooding of the portal vein and varices. However, when the injection ceases and the portal inflow resumes, the dye stained portal blood is observed to perfuse the liver in the normal manner. They also noted that in some patients the flooding was more intense and was not followed by the forward hepatic perfusion with radiopaque portal blood. They interpreted these findings as indicating the presence of spontaneous reversal of portal flow which prevented the entrance into the liver of the radiopaque blood. Although this explanation is plausible, an equally convincing case could be made for these patients having stagnant flows, a condition that we have reported to occur in eight per cent of portal flow measurements in patients with cirrhosis.[6,32,36]

At any rate, the technique of flooding the portal vein devised by Kessler et al. has shown the lack of hepatic perfusion that could be interpreted as indicating spontaneous reversal of portal flow in only two patients with cirrhosis in a series of 150 examined by them. In a later report,[19] they have increased the number of patients with cirrhosis studied by this method to 232 patients. They also added refinements of the technic which should lead to a better demonstration of spontaneous reversal of portal flow in these patients. However, they do not include any new patients with this condition in this later report.

Splenic Portography

During the early experience with this method, lack of visualization of the portal vein was interpreted as the result of either anatomic obstruction of the portal vein or of spontaneous reversal of portal blood flow. In the case of the presumed reversal of flow, the blood exiting the liver through the portal vein would prevent the contrast material from entering the vessel and outlining its contour.[20] Increasing use of splenic portography, which in our group surpassed the 1000 patient mark before being partially replaced by selective arteriography, showed that most cases of non-visualized portal vein were associated with an anatomically patent vessel. Moreover, no reversal of flow could be found in the patent vessels. We have devoted an entire report to the examination of this problem,[5] and have evaluated the lack of justification for making a diagnosis of spontaneous reversal of portal flow based on non-visualization of this vessel during splenic portography. In that report we included direct measurements of portal flow in 14 patients with cirrhosis and non-visualized portal vein during splenic portography. Three of these patients had stagnant flow while the remaining 11 had forward flows averaging 400 ± 324 (S.D.) ml/min. More recently, we have retabulated our data and provided guiding diagrams of the hemodynamic patterns associated with non-visualization of the portal vein during splenic portography.[46] However, the possibility of associating non-visualization with spontaneous reversal of portal flow is revived from time to time and

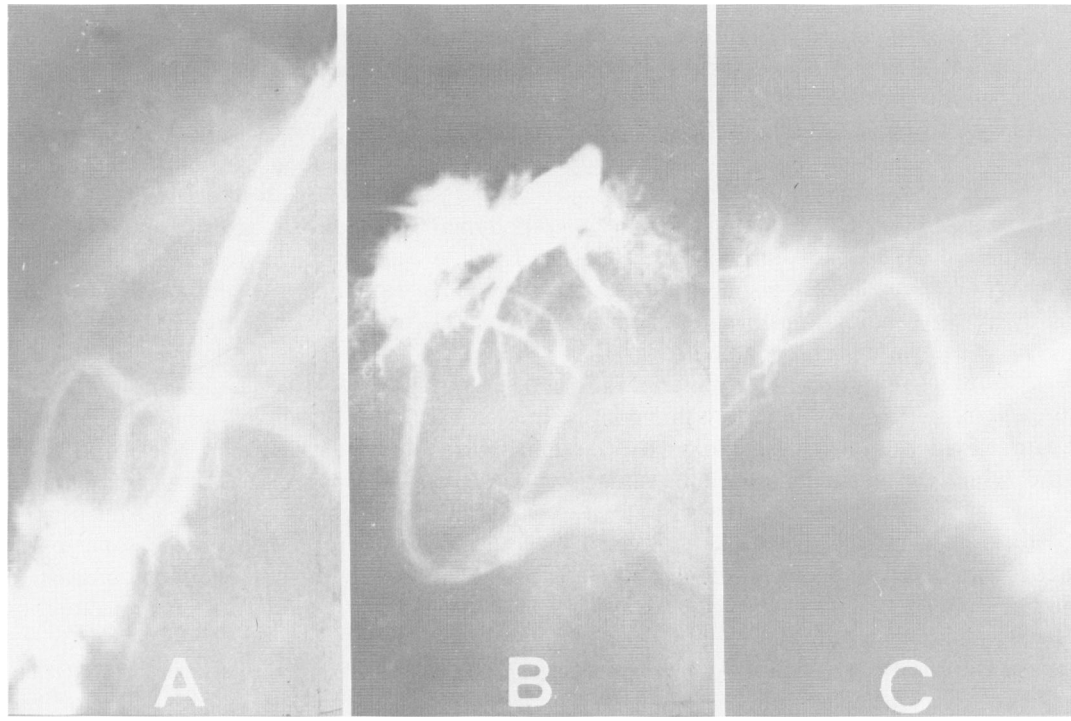


FIG. 5. Intraparenchymal deposition of contrast medium into the liver of three patients with cirrhosis submitted to side to side portacaval shunt. A. In this patient, the pool of contrast material is drained by a large hepatic vein and by the hepatic limb of the side to side shunt acting as an accessory outflow tract. B. In this patient the hepatic limb of the shunt appears to have become the primary outflow tract. C. As in B, the hepatic limb of the shunt takes a primary role as an outflow tract for the liver.

reintroduced as an accepted truth.[15] Had it not been for these periodic revivals, this section would have been omitted in the present report.

Selective Hepatic Arteriography

This is, perhaps, the most physiological method to assess the presence of a suspected spontaneous reversal of portal blood flow. The contrast material is injected into the hepatic artery. The hepatic arteriolar resistance dissipates the arterial pressure in the normal fashion and also dissipates any excess pressure resulting from the injection of the medium. The dye stained hepatic arterial blood perfuses the sinusoids and is collected by the outflow system, normally the hepatic venules and veins. In case of reversal of portal flow, the portal venules, the portal veins and even the main portal trunk would be removing the dye from the sinusoids. Boijsen and Ekman[2] have demonstrated this to be the case after splenorenal shunt. In their patient, the contrast medium injected into the hepatic artery escaped the liver through the portal vein, traversed the splenic vein and emptied through the shunt into the systemic circulation. In our own studies using hepatic arteriography,[46] we have seen this reversal of flow to take place in the hepatic limb of a side to side portacaval shunt.

Selective hepatic arteriography has also shown spontaneous reversal of portal blood flow in patients with Budd-Chiari syndrome. Pollard and Nebesar[40] observed the contrast injected into the hepatic artery to exit the liver via the portal vein in two patients with bilateral obstruction of the outflow tract. They also observed retrograde flow in one lobe obstructed by veno-occlusive disease into the portal branch of the normal lobe. There, the forward direction of flow was resumed. Ruzicka and Rossi[47] also reported reversal of portal flow after hepatic artery injection in one patient with Budd-Chiari syndrome.

Hepatic artery selective angiography has about the best opportunity to show reversal of portal flow, either following some type of side to side shunt or, spontaneously, in association with bilateral or unilateral veno-occlusive disease. Considering the extensive use of this method, it is remarkable that there are no reports, to our knowledge, indicating spontaneous reversal of portal flow in cirrhosis. Pollard and Nebesar[40] go as far as to state that, except for veno-occlusive disease, they have never seen spontaneous reversal of portal flow in any conditions studied by them in 30 patients.

Intraparenchymal Hepatic Deposition of Contrast Medium

In 1963[31] we introduced the clinical use of the intraparenchymal deposition of contrast medium in the liver of patients with hepatic cirrhosis. This clinical application was preceded by extensive experimentation in small[29] and large[30] laboratory animals. At the time, we were searching for more physiological methods of studying the altered hemodynamics of patients with hepatic cirrhosis. Three somewhat unexpected results emerged

from the clinical application of this method: 1) the visualization of the efferent lymphatic system of the liver in patients with cirrhosis and ascites; 2) the visualization of the hepatic limb of a side to side shunt acting as an accessory outflow tract; and 3) the recognition by others (16) that the method was the "only truly diagnostic study" for Budd-Chiari syndrome.

The capability of the method of intraparenchymal deposition of contrast medium to demonstrate retrograde flow in the hepatic limb of a side to side portacaval shunt is shown by the radiographs of the three patients grouped in Fig. 5. The plate corresponding to the first patient (A) shows how a pool of contrast material is formed in the parenchyma of the liver and how this pool is drained by hepatic venules into large hepatic veins and by portal venules into the hepatic limb of the shunt and into the vena cava. Figure 5B shows another patient in whom the hepatic limb of a side to side shunt acts as an outflow tract for the liver, and Fig. 5C shows similar findings in another patient.

In Budd-Chiari syndrome, bilateral or unilateral, intraparenchymal deposition has shown either total backflow into the splanchnic bed or partial retrograde flow into the healthy lobe.[8,16,43,44]

In addition to our original report,[31] we have further increased the number of our observations[34] which at present number 184 patients with cirrhosis and portal hypertension.[46] In this rather large series of patients with cirrhosis submitted to intraparenchymal deposition of contrast material, we have not found a single instance of spontaneous reversal of portal blood flow. The report of Ramsey and Britton[43] on 15 additional patients does not include any cases of spontaneous reversal of portal flow, and none is found in the reports of the English[8,9] or French[21] investigators who used intraparenchymal deposition of contrast as a method of investigation. Nevertheless, the method is not free of false positive results. In one of our patients with cirrhosis (see Fig. 7 in our reference 5), the intraparenchymal deposition forced contrast medium back into the main portal vein and mesenteric bed, thus simulating the occurrence of spontaneous reversal of portal flow. On high speed motion pictures taken on the same patient, it was shown that when the injection of contrast medium ceased, portal flow resumed its normal direction and the dye stained portal blood perfused the liver. At operation, measurements with the electromagnetic flowmeter indicated that the patient had a forward portal flow into the liver measuring 90 ml/min (see flow recordings also in Fig. 7 of our reference 5). Price et al.[41] in an article devoted mainly

TABLE 1. *Magnitude and Direction of Portal Blood Flow Measured by Various Methods in 273 Patients with Hepatic Cirrhosis and in 21 Normal Control Subjects*

		Electromagnetic Flowmeter					
		Patients with Cirrhosis		Normal Controls		Post Side to Side Shunt	
Authors	Year	Forward Flow	Reversed Flow	Forward Flow	Reversed Flow	Forward Flow	Reversed Flow
Schenk, McDonald, and Drapanas[47]	1962	5	-	9	-	-	-
Ferguson[12]	1963	11	-	-	-	-	-
Moreno, Burchell, Rousselot, *et al.*[31]	1967	85†	-	6	-	4*	9
Price, Vorhees and Britton[40]	1967	21	-	-	-	-	2
Fauvert[11]	1967	52	-	-	-	-	-
Leger, Lenriot, Gorin and Lemaigre[20]	1970	9	-	-	-	-	-
Smith[49]	1973	18	-	-	-	-	-
Burchell, Moreno, Panke and Nealon[6]	1974	145†	-	-	-	-	-
Moreno, Burchell, Reddy, *et al.*[35]	1974	153†	-	-	-	-	-
Subtotals		269	-	15	-	4*	11
		Electromagnetic Velocity Probe					
Strandell, Delin, Erwald, *et al.*[51]	1973	1	-	-	-	-	-
		Computer Analysis of High Speed Cineangiography					
Sovak, Soulen and Reichle[50]	1971	3	-	6	-	-	-
Grand Totals		273	-	21	-	4*	11

*Small magnitude.
†Cumulative series.

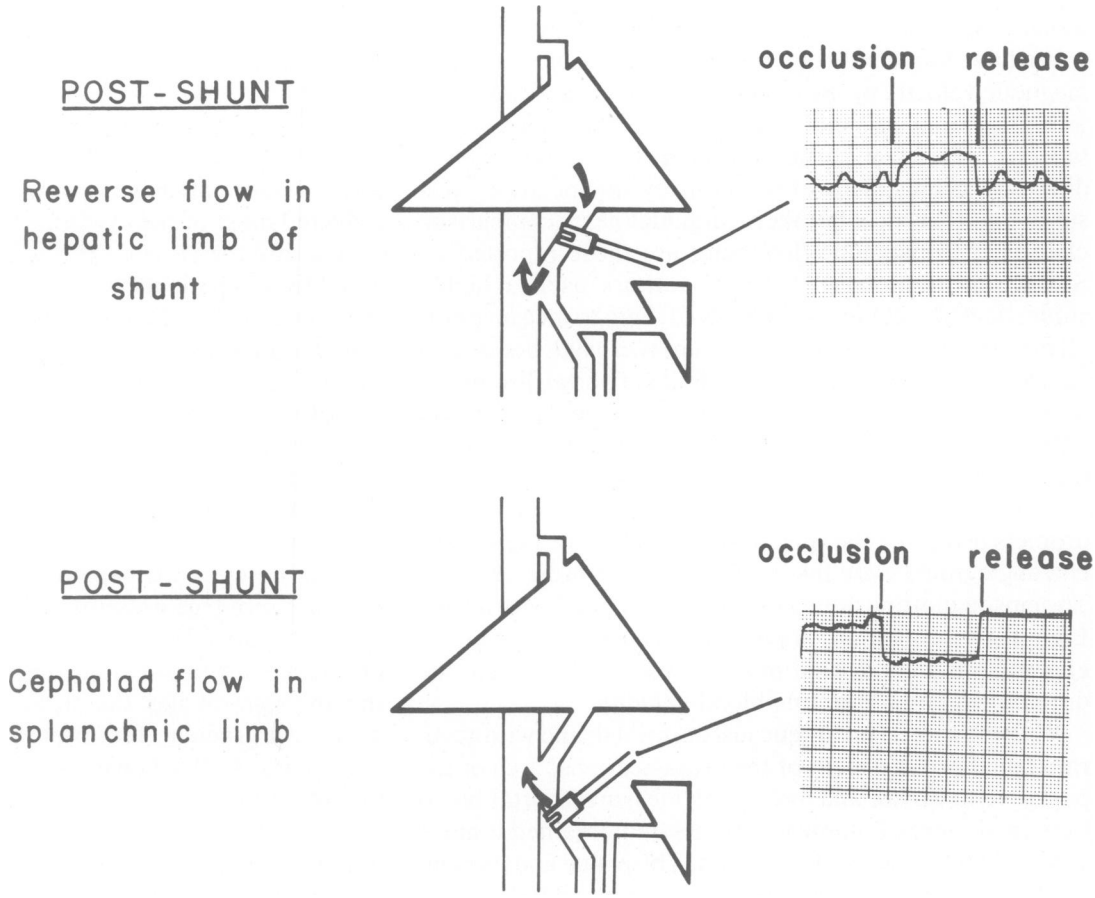


FIG. 6. Recordings with the electromagnetic flowmeter in one patient with cirrhosis after completing a side to side portacaval shunt. Note the ability of the flowmeter to measure retrograde or reversed flow in the hepatic limb of the shunt and forward or cephalad flow in the splanchnic limb.

to electromagnetic flowmeter studies, reported one patient with cirrhosis apparently showing spontaneous reversal of portal flow during intraparenchymal injection. Unfortunately, the authors did not provide electromagnetic flowmeter measurements in this uniquely interesting patient.

Actual Measurements of Magnitude and Direction of Portal Vein Flow

In a rather extensive review of the literature which includes the 12 year period between 1962 and the present writing, we have been able to collect measurements of magnitude and direction of portal flow in 294 human subjects. Of these subjects, 273 were patients with cirrhosis of the liver and portal hypertension and 21 were normal control subjects (Table 1). There was no single instance of measured spontaneous reversal of flow in the portal vein, although such reversal of flow was detected and measured in the hepatic limb of a side to side portacaval shunt in 11 patients.

Electromagnetic flowmeters, most frequently of the square wave type of Denison and Spencer,[11] were used in 284 subjects including 269 patients with cirrhosis and 15 normal control subjects. These flowmeters detected reversed flow very clearly when such reversal was present, i.e., after side to side portacaval shunt. Figure 6 shows tracings of flow obtained with one such instrument. After a side to side portacaval shunt, flow takes place in the retrograde direction in the hepatic limb of the shunt and in the forward direction in the splanchnic limb. Note the clear upward and downward deflection from zero line in the case of forward and retrograde flow respectively. At this point, we would like to correct an error frequently made when quoting the article by Price et al.[41] on measurements using flowmeters. The article is quoted as reporting three patients with spontaneous reversal of portal flow in cirrhosis. Actually, in two of the patients, the reversed flow was measured after side to side portacaval shunt, and did not occur spontaneously. In the remaining case, spontaneous reversal of portal flow was diagnosed by the method of intraparenchymal deposition of contrast medium and was not measured with the flowmeter. We have referred to this patient before,in the section of radiologic studies.

Before concluding the discussion of measurements of magnitude and direction of portal vein flow using electromagnetic flowmeter, it is only fair to point out that in the report of Smith et al.[49] there is mention of one patient with cirrhosis who appeared to have spontaneous reversal of portal flow as detected by the electromagnetic flowmeter. Unfortunately, the authors did not measure, or did not

report, the magnitude of such flow. This patient appears not to have been included in a later report by Smith.[50]

We have found only one report on the use of an electromagnetic velocity probe in the portal vein of a patient with cirrhosis,[52] and we include this patient as showing no spontaneous reversal of portal flow as measured by a slightly different technic. However, the truly independent measurements that could be taken as a guideline for comparison of the electromagnetic flowmeter are those reported by Sovak and associates.[51] These authors used a highly sophisticated technic which allowed them to measure portal flow in awake patients. This point is crucial, because of the frequent questioning of the validity of portal flow measurements at operation, with patients under anesthesia. After recannulating the umbilical vein several days prior to the measurements, Sovak and associates injected droplets of oily contrast medium at the hilum of the spleen. As the droplets traversed the splenic and portal veins, high speed cineangiograms were taken. The film was projected on a Thompson plotting table connected "on line" with a Linc Eight digital computer. A polynomial curve, derived from experiments in hydraulic models, was used to relate the droplet velocity to the true blood velocity.

With the careful technique just described, and with accurate biplane assessment of the cross-sectional area of the portal vein, Sovak and associates measured portal blood flow in six normal control subjects and obtained a mean value of 1160 ± 243 (S.D.) ml/min. This value and its standard deviation are of the same order of magnitude as our measurements with the electromagnetic flowmeter in normal subjects: 1299 ± 246 (S.D.).[32] What is more remarkable, they found respiratory oscillations amounting to 20% of the total normal flow, which is exactly the amount we reported with the electromagnetic flowmeter.[32] During inspiration they found that the velocity of the portal flow decreased to 5 cm/sec while during expiration the flow accelerated to 26 cm/sec. It was precisely this type of alternation which led us to formulate our early, two-chamber, hepatic valve model of respiratory regulation of systemic and splanchnic venous return.[33] Finally, Sovak et al. found further confirmation of our findings in cirrhosis. In their patients with this disease, the respiratory oscillations grew to become a substantial portion of the total flow. We had reported these oscillations to reach 40, 50, 80 and even 100% of the total flow in cirrhosis. The latter amounts we found in patients with stagnant flow showing only to and fro oscillations synchronous with the respiratory cycle. The Sovak et al. counterparts for these extreme cases were one patient in whom forward flow took place only during inspiration, and another patient, who showed only to and fro motions synchronous with respiration.

The unusually close agreement between two completely different methods of measuring portal vein flow, i.e., electromagnetic flowmeter measurements during anesthesia and computer analysis of high speed cineangiography in awake patients, increases our confidence in our findings, and in those of others using flowmeters, who failed to demonstrate spontaneous reversal of portal flow in cirrhosis.

Discussion

In a rather extensive review of the literature, we have collected most of the evidence that could be mustered to build a case for the occurrence of spontaneous reversal of portal flow in patients with cirrhosis of the liver. We have examined such evidence under four different headings: manometric studies, radioactive tracer studies, radiologic studies and actual measurements of magnitude and direction of portal blood flow.

The manometric evidence, as presented, has only the value of indirect evidence which requires accepting the assumption that the differences in pressure between the hepatic and splanchnic sides of a clamp occluding the portal vein, or between the hepatic occluded and the free portal pressure, are true pressure differentials or hydraulic gradients for portal flow. The lack of correlation between these differences in pressures and the measured portal flow, were the first signs of alert that these differences, after all, may not be true gradients for flow in the portal vein. The further demonstration that hepatic occluded pressures higher than the splanchnic occluded or the free portal pressure, can still coexist with significant forward portal flows added more doubts to the validity of the fundamental assumptions used to support the argument of the occluded portal pressures. We have been able to demonstrate by a theoretical analysis based on first principles, and by clinical measurements, that the hepatic occluded pressure approximates the sinusoidal pressure only during occlusion of the portal vein, but that it is quite different from the sinusoidal pressure in the absence of occlusion of the portal vein. Since the latter is the relevant quantity to construct a gradient for portal flow, the argument for using the hepatic occluded pressure becomes considerably weakened. Furthermore, reports in the literature correlating these differences with clinical results, are difficult to reconcile with simple statistical treatments.

Evidence from radioactive tracers studies make a good case for reversal of flow in the hepatic limb of a side to side portacaval shunt, but provides little if any evidence of spontaneous reversal of portal flow in cirrhosis.

Forced retrograde injection of contrast material into the portal system performed from the wedged hepatic vein position, has been proposed as proof of spontaneous reversal of portal flow in cirrhosis. Different investigators have reported completely opposite results. There are at least two patients in the literature who showed what was considered evidence of spontaneous reversal of portal flow during forced wedged hepatic vein injection but who were demonstrated to have significant forward flow during measurements with the electromagnetic

flowmeter. Even accepting the validity of the findings of the most decided advocates of the technic of wedged hepatic vein injection, we have been able to find in their reports only six patients with presumed reversal of portal flow in cirrhosis during the period between 1962 and this writing.

Flooding of the portal vein with contrast material injected through the recannalized umbilical vein is normally followed by a washout which ends in hepatic perfusion by the dye stained portal blood. If this does not occur, the presumption of spontaneous reversal of portal blood flow is commonly advanced. Besides the fact that stagnant portal flow, which is found in 8% of patients with cirrhosis, would render the same results, the incidence of this presumed reversal of portal flow has been reported in only two patients with cirrhosis.

Non-visualization of the portal vein during splenic portography has been shown to coexist not only with patent portal veins, but also with forward direction in portal flow. Our own evidence denies reversal of flow in portal veins non-visualized during splenic portography but found to have forward flow when it was measured with the electromagnetic flowmeter.

Selective hepatic arteriography would be an ideally physiological means of demonstrating spontaneous reversal of portal flow. Indeed, it has been used successfully to demonstrate such spontaneous reversal in patients with Budd-Chiari syndrome, as well as reversal of flow in the hepatic limb of a side to side portacaval shunt. However, we have been unable to find a single report of spontaneous reversal in cirrhosis by the use of this technic.

In a large series of patients with cirrhosis submitted to hepatic intraparenchymal deposition of contrast medium, there is one false positive case of spontaneous reversal of portal flow which was negated by direct measurements of forward flow with the electromagnetic flowmeter. Another patient who was reported as showing a pattern compatible with spontaneous reversal of portal flow during intraparenchymal deposition of contrast medium was not submitted to the challenge of direct measurements with the electromagnetic flowmeter.

Actual measurements of magnitude and direction of portal flow in 273 patients with cirrhosis collected in the literature have shown no incidence of spontaneous reversal of portal blood flow. Results using electromagnetic flowmeters in patients under anesthesia have been confirmed by methods using computer analysis of high speed cineangiography in awake patients. There is, on the other hand, one isolated report of reversed direction, no magnitude indicated, of portal blood flow in cirrhosis. The authors of this article do not clarify the reasons for omitting the magnitude of this reversed flow in their report while including the magnitude of a forward portal flow in another patient.

Conclusions

In summarizing the data collected in this report, we cannot avoid the conclusion that the evidence for spontaneous reversal of portal flow in cirrhosis is weak and sparse. In our own personal judgement, the strongest support for this hypothesis derives from one patient whose direction of portal flow is said to have been found reversed during flowmeter determinations which did not include a report of the magnitude of the flow. What might be more important, there is no instance in which the presumed spontaneous reversal of portal flow has been confirmed by two independent methods of demonstration.

On the other hand, the evidence against spontaneous reversal of portal flow in cirrhosis seems to be overwhelming on both, qualitative and quantitative terms.

In the light of the findings discussed, and unless new and convincing evidence can be brought into the picture, we fail to see how we can serve the best interests of medicine in general and of our patients in particular by prolonging a debate concerning the clinical significance of an unproven phenomenon whose occurrence has been postulated, at best, on the basis of mere circumstantial evidence.

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