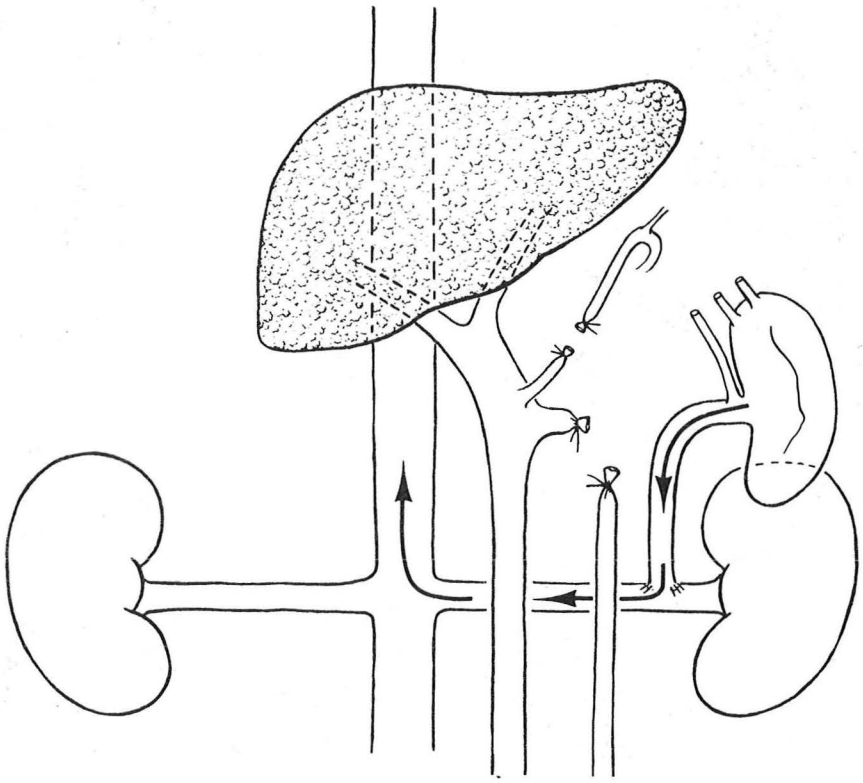
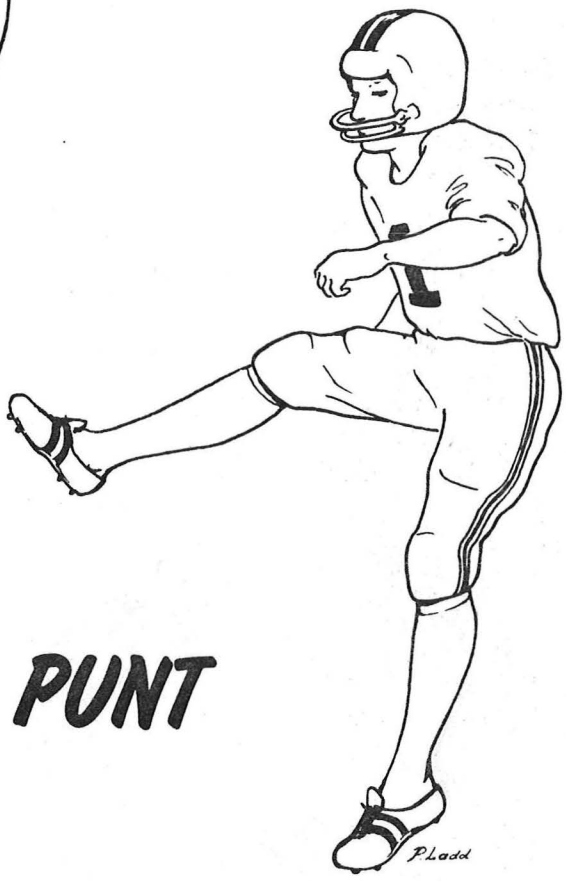
ESOPHAGOGASTRIC VARICES



SHUNT

OR

PUNT



Medical Grand Rounds

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Mark Feldman, M.D.

University of Texas
Southwestern Medical School

CONTENTS

PATHOGENESIS OF PORTAL HYPERTENSION AND ESOPHAGOGASTRIC VARICES

Each minute, 30-40% of the cardiac output flows through the liver into the inferior vena cava and right heart. Most (around 70%) of this blood enters the liver via the portal vein, while around 30% enters via the hepatic artery (1). When the incoming portal blood meets increased resistance to flow, portal pressure proximal to the site of increased resistance rises above the normal 5-10 mm Hg and portal hypertension is said to be present (2). Increased resistance to flow can occur in the heart (congestive heart failure, constrictive pericarditis), in the hepatic veins (Budd-Chiari Syndrome), in the liver parenchyma (cirrhosis with regenerative nodules) or in the portal vein itself (portal vein thrombosis). On rare occasions, portal hypertension can result not from increased resistance to flow but from increased sphlancnic flow per se, as in patients with splenic arteriovenous fistulas.

When portal venous pressure rises (for any reason), naturally-occurring anastomoses between the high pressure portal system and the low pressure systemic circulation enlarge, as blood flow follows the path of least resistance (3). These natural portal-systemic anastomoses include:

a) retroperitoneal veins, especially draining parts of the spleen, colon, and pancreas, which join with renal, adrenal, or veins in the posterior abdominal wall;

b) paraumbilical veins, which join with branches of the systemic circuit in the anterior abdominal wall;

c) inferior hemorrhoidal branch of the inferior mesenteric vein, which joins the middle and inferior hemorrhoidal branches of the internal iliac vein around the lower rectum;

d) coronary (left gastric) and short gastric veins, which anastomose in the lower esophagus with branches of the azygos and hemiazygos system and which can give rise to varices.

In some patients with portal hypertension, the first three pathways are so efficient that esophagogastric varices never develop (4-6). Estimates for the incidence of varices in cirrhosis range from 12-90%, with an average figure of 60% (6,7,8).

In less than half of patients with portal hypertension and varices, variceal hemorrhage occurs. Presumably, in these patients natural portal-systemic anastomoses are unable to reduce portal pressure enough to prevent bleeding. This is the type of patient who is likely to undergo

surgical decompression of varices by creating an unnatural communication ("shunt") between the portal vein (or a major tributary) and a large systemic vein, usually the inferior vena cava or renal vein. Examples of such patients are presented below.

Case 1 This 57 year old man was admitted to the Dallas VA in 11/78 because of hematemesis and melena. He had ingested large amounts of alcoholic beverages for several years. In 2/78 he had had hematemesis and was admitted to another hospital. Esophageal varices were found at endoscopy. In 5/78 he had melena for a few days, but he sought no medical attention. On admission to the VA in November, blood pressure was 90/60 and fell to 60/0 upon sitting. Other than mmelena the remainder of the examination was normal.

Hematocrit was 32%, BUN 24, bilirubin 0.6 mg%, SGOT 26 and serum albumin 3.5 gm%. He was given antacids, intravenous vasopressin and 5 units of blood. Bleeding ceased but soon recurred. Endoscopy showed large esophageal varices, high gastric varices and active bleeding from the fundus of the stomach. Four more units of blood were given. Vasopressin infusion was increased from 0.2 to 0.4 u/min and bleeding again stopped. The next day he was taken to the operating room where cirrhosis and chronic pancreatitis were found. An end-to-side portacaval shunt was performed (see Appendix for schematic description of this operation). He was discharged 16 days later and has done well for the past three months.

Case 2 A 57 year old man with a history of alcoholic excess for 20 years was admitted because of hematemesis. Examination showed ascites and icterus. Endoscopy showed large esophageal varices. Pitressin, 3 units of blood, and 2 units plasma were given. Bleeding stopped. Bilirubin was 4, SGOT 160, albumin 3.3, prothrombin time 13.8 seconds. Five days later he rebled and continued to bleed despite intravenous pitressin, a Sengstaken-Blakemore tube and 14 units of blood. Emergency portacaval shunt and liver biopsy (showing alcoholic hepatitis and micronodular cirrhosis) were performed. Pressure

in portal vein fell from 36 to 23 mm Hg after the shunt. Postoperatively he developed respiratory failure and hepatic encephalopathy and 2 weeks later he had a rebleed from varices and died.

Case 3 A 69 year old man developed postransfusion hepatitis after a total hip replacement in 1975. In March, 1977 he developed hematemesis and ascites. Workup revealed esophageal varices and postnecrotic cirrhosis. In September, 1977 hematemesis recurred. Bleeding varices were seen at endoscopy and in hospital he rebled from varices. An end-to-side portacaval shunt was performed as an emergency. Preshunt portal pressure was 41 mm Hg and fell to 20 mm Hg postshunt. Bleeding has not recurred. However, he has been re-admitted to the hospital seven times (once for three months) for recurrent hepatic encephalopathy.

One patient did well; the second continued to bleed and died; and the third has been free of bleeding but has spent a great deal of his life in the hospital for disabling encephalopathy.

It is of some interest that our patients were treated a century after the first portal-systemic shunt operation was performed. The major purpose of this Grand Rounds is to review the history, rationale and efficacy of shunt surgery for esophagogastric varices with particular emphasis on newer operations and on the current dilemma that internists and surgeons are facing.

HISTORY OF PORTACAVAL SHUNTS

Prior to 1877, it was believed that interruption of portal venous inflow to the liver was rapidly fatal (9). In that year a Russian physiologist named Nikolai Eck disproved this theory by ligating the portal vein and performing a side-to-side portacaval shunt in 8 dogs (10). Most animals lived normally for 2 to 7 days after surgery before dying of infection or intestinal obstruction. One vigorous dog lived happily in Eck's laboratory for 2 1/2 months before running away ("lost to followup!"). In his publication, Eck stated that he would like "to determine whether it would be possible to treat some cases of mechanical ascites by means of forming such a fistula". Before he could perform further studies, however, he was drafted. When Eck returned to civilian life his interests had turned to sanitation and geology.

Eck's fistula operation was adopted in Pavlov's laboratory, and soon it became apparent that Eck's fistula dogs usually developed neurological symptoms after ingesting large quantities of meat (11). This syndrome was referred to as "meat intoxication" and continues to be a distressing complication of portal-systemic shunts.

Around the turn of the century, the first operations in man for complications of portal hypertension were performed. The earliest procedure was an omentopexy (12). This operation involved suturing omentum to the scarified parietal peritoneum and was designed to develop collateral circulation between the portal circulation and the systemic circulation.

In 1903, a French surgeon named Vidal (13) described the use of omentopexy "to counteract the hematemesis...(and) to diminish the pressure in the portal system, the important factor in ruptured varices". Almost by accident, Vidal performed the first portacaval shunt in man as described below.

> Antione, 34 years. Alcoholic cirrhosis for 8 months. Ascites of moderate severity and hematemesis which has been almost without remission for 7 weeks and which has, little by little, drained the patient. I recommend an omentopexy and I operated near the end of June, 1903.
>
> I discovered that the omentum is an indurated mass. For this very good reason it is impossible to draw it down for fixation. I decided therefore to put into practice the old procedure proposed by Eck, a portacaval anastomosis.

Then Vidal described the operation, which was actually an end-to-side modification of Eck's procedure.

He continues:

> After the 14th day the patient received nourishment, but all absorption of "albuminoides" provoked a very severe intoxication. Enema of sugared milk (given). By October, hematemesis had not recurred, but ascites had reappeared. Nevertheless, the general state remained fairly satisfactory until very recently - the sudden appearance of repeated shaking chills, profuse

> sweating, alternating coma and delirium and death in 48 hours.
>
> What occurs with resumption of alimentation? Elaboration of "albuminoides" in the digestive tract has produced an abundant production of ammoniacal substances which are toxic for the organism when the liver is no longer there to guard against this danger and transform them into urea and other waste products. The subject must return to the almost exclusive absorption of fats and hydrocarbons. This is a principal danger to total [portal] exclusion. When hematemesis demands a diminution of pressure in the portal system recourse should be to less major operations.

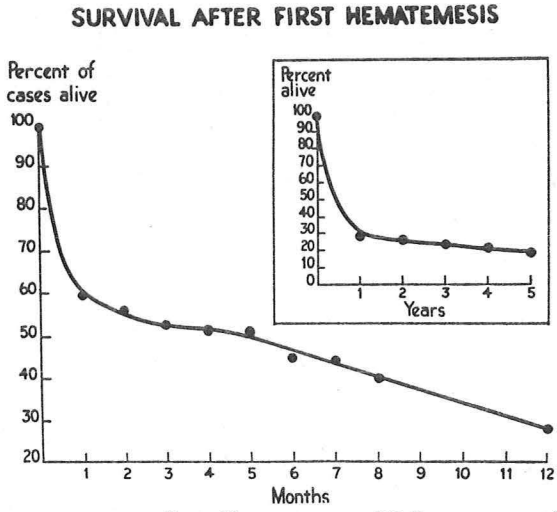
In this remarkable report Vidal recognized the advantages (cessation of bleeding) and hazards (encephalopathy and death) of end-to-side portacaval shunts. The analogy between a milk sugar enema and our current use of lactulose is striking. Based upon experience with one case, Vidal abandoned the operation because apparent risks outweighed benefits. Except for isolated instances, portal-systemic shunts were not attempted for the next forty years (13).

NATURAL HISTORY OF CIRRHOSIS AND ESOPHAGEAL VARICES

In the nineteenth and early part of the twentieth century little was known about the prevalence, natural history and pathogenesis of esophageal varices and variceal bleeding. Although Vidal thought that hematemesis in his cirrhotic patients was due to increased "portal tension", it wasn't until 1937 that portal hypertension was confirmed by direct measurement in five cirrhotic patients (14).

Around this time, Ratnoff and Patek reported their classical study of 386 patients with Laennec's cirrhosis conducted between 1916-1938 (15). They made the observation that more than 60% of cirrhotics died within a year of their first symptoms of disease. A substantial number of patients, 115 (30%), developed gastrointestinal bleeding (presumably from varices although this was not proven in all cases), and as shown in Figure 1, only 30% of these bleeding patients survived a year. This study therefore indicated that the diagnosis of cirrhosis carried a

grave prognosis, especially if hemmorhage occurred. Publication of these dreadful statistics in 1942 was one factor which led to a reassessment of portal-systemic shunts for the prevention of variceal bleeding in cirrhosis.



SURVIVAL AFTER THE FIRST HEMATEMESIS IN 106 PATIENTS WITH LAENNEC'S CIRRHOSIS

Fig. 1

Subsequent studies (16-18) have for the most part confirmed Ratnoff and Patek's findings. For example, Baker et al in 1959 followed 115 cirrhotic patients who had varices on esophagoscopy but who had not yet bled (17). Interestingly, in many patients varices decreased in size or disappeared despite no specific therapy. They found that only 33 (29%) of patients bled during an average follow-up period of 3 years. Only 26% of those who bled survived for a year compared to 68% of the entire group of 115 patients.

In 1968 Powell and Klatskin reported on 283 patients with biopsy-proven cirrhosis (19). Only 24% developed hematemesis (presumably from varices) during a followup period of at least 5 years. They found that 50-60% of patients who bled survived one year, compared to more than 80% one year survival for all patients. Although they found better survival rates than earlier studies (15-18), the presence of bleeding remained ominous.

Since the site of bleeding was not always established definitively in any of these early studies, it is likely that some patients were bleeding with varices, but not from varices. This phenomenon is well-documented in the literature (20,21) and an example is given in Table 1.

Table 1

Endoscopic Findings in Patients With Active Upper Gastrointestinal Hemmorhage and Varices (from Reference 20)

Number with varices	492
Bleeding from varices	139 (28%)
Gastritis, duodenitis	197 (40%)
Peptic ulcer	117 (24%)
Mallory-Weiss syndrome	48 (10%)
Unknown or miscellaneous	11 (2%)

In seven other articles (see ref. 21, Table 3), the incidence of variceal bleeding in patients with upper gastrointestinal hemorrhage and known varices ranged from 19% to 56%. Thus, the 30-50% one year survival rate for known cirrhotics with hematemesis may not be an accurate reflection of survival related only to variceal bleeding.

Recently, I reviewed the records of the last 19 cases of variceal bleeding documented by endoscopy at the Dallas Veterans Hospital. Twelve of the 19 (63%) patients have died, all in less than a year. Seven (37%) have survived and have been followed for 1 month to 1 year. It should be noted that 6/7 patients treated medically (87%) are dead, whereas 6/12 (50%) patients treated surgically are dead. However, better risk patients went to surgery. These data indicate how lethal variceal bleeding can be, even in the 1970's.

THE REBIRTH OF SHUNT SURGERY

By 1945 the soil was ripe for an aggressive approach to variceal bleeding secondary to portal hypertension. In that year, Whipple and Blakemore (22,23) ushered in the modern era of shunt surgery by describing their results with splenorenal and end-to-side portacaval shunts (see Appendix). In their early reports, it appeared that the incidence

of hemorrhage had been markedly reduced, although their studies had no matched controls. In the next several years, dozens of reports appeared in the surgical literature exalting the "new" operation. These studies used for comparison with shunt patients either historical controls (e.g. those of Ratnoff and Patek) or patients who refused or did not qualify for surgery. Looking back at this era, Grace et al observed that the more uncontrolled the series, the more enthusiastic about the operation was the author (24). It seemed axiomatic that a reduction in variceal bleeding had to be associated with improved survival, since variceal bleeding was the cause of death in one-third of cirrhotics (18,19). The operation was adopted quickly at medical centers throughout the world.

However, by the 1950s a few skeptical surgeons began expressing reservations about portacaval shunts (8,16,25). For example, Nachlas (8) critically reviewed published data on all surgical treatments for portal hypertension and concluded that neither omentopexy, splenectomy or portal-systemic shunts were of proven value. He called for the performance of controlled clinical trials using medically-treated patients.

Around this time Hallenbeck et al reported their experiences with shunting (portacaval and splenorenal) and nonshunting procedures (splenectomy, with or without omentopexy) in a large group of cirrhotic patients, almost all of whom had bled (26,27). Their results are shown in Table 2.

Table 2

	Splenectomy (n=73)	Splenorenal Shunt (n=64)	Portacaval Shunt (n=42)
Survival at 7 yrs(%)	46	45	37
Severe chronic Encephalopathy(%)	0	5	25
Rebleeding(%)	66	25	24

Their conclusion -- that patients who undergo splenectomy do at least as well as shunted patients -- was a serious blow to shunt enthusiasts. Subsequently, Hsu (28) confirmed Hallenbeck's findings. His results are summarized in Table 3.

Table 3

	Splenectomy (n=64)	Portal-Systemic Shunt (n=49)
Operative mortality(%)	9	10
Survival at 7 years(%)	68	46
% of Deaths due to Variceal Hemorrhage	63	22
% of Deaths due to Hepatic Failure	11	57

Although shunting prevented bleeding, there were increased deaths from hepatic failure in the shunted group.

Since splenectomy in cirrhosis reduces portal venous inflow by approximately 40% (22) and may therefore reduce portal pressure, it is hard to know from these data whether splenectomy is as good as a portal-systemic shunt, or as bad. However, the studies do indicate (although operations were not done randomly) that shunted patients bleed less, flap more and live no longer than splenectomized patients.

Besides suggesting that portal-systemic shunts prevent bleeding and pointing out the need for controlled clinical trials using medically treated patients, the early work on portacaval shunt surgery made one other important contribution. This related to prognosis based upon various preoperative clinical and laboratory parameters. In 1942 Ratnoff and Patek had observed that survival after variceal hemorrhage was more likely in the absence of ascites, jaundice and encephalopathy (15). Child later (29) applied these and other criteria to patients about to be shunted with great ability to predict outcome (Table 4).

Table 4: Child's Criteria

Child's Group	A	B	C
Bilirubin (mg%)	<2	2-3	>3
Albumin (gm%)	>3.5	3-3.5	<3
Ascites	None	Easily Controlled	Poorly Controlled
Neurological disorder	None	Minimal	Advanced
Nutrition	Excellent	Good	Poor

Child found that all 48 "A" patients survived the portacaval shunt operation; that 42 of 46 (91%) of "B" patients survived; but that only 16 of 34 (47%) of "C" patients lived for a month after the portacaval shunt. Long-term survival also correlated with Child's grouping. Other workers have for the most part confirmed Child's findings and it is probably the best and most widely used classification at the present time (30).

CONTROLLED CLINICAL TRIALS

To this point we can say that no more than one of three cirrhotics with varices will experience a variceal bleed. If they do bleed the short term (one year) mortality is as high as 70%. Also, we can now predict reasonably well (using Child's criteria) who can survive a shunt operation. Who then should undergo a shunt procedure? Prior to the performance of the controlled trials which I am about to describe, answers to this question would frequently have been: (a) shunt any cirrhotic patient with portal hypertension whether or not they have varices (31); (b) shunt any cirrhotic patient who has varices but has not yet bled (prophylactic shunt) (32); or (c) shunt any cirrhotic patient with varices who has bled (therapeutic shunt).

PROPHYLACTIC SHUNTS

Since the short term mortality of the first variceal bleed is so high, it had been suggested that a shunt should be performed prophylactically once varices were diagnosed (32). Three randomized studies using medically-treated patients as controls were initiated in the late 1950s and early 1960s (33-35). All but a few patients had biopsy-proven cirrhosis and all had esophageal varices that had never bled. Patients were considered acceptable surgical risks. Certain patients were excluded, e.g., patients with severe non-hepatic disorders, such as emphysema (33), women, and men older than 65 years (35). Most patients received end-to-side portacaval shunts, with a few receiving side-to-side portacaval shunts or splenorenal shunts (see Appendix).

In Table 5 the mortality rates in the studies are given. Note that the New Haven study had two parts - Part I (1958-1963) included any cirrhotic with varices and Part II (1965-1970) included only cirrhotics with varices and ascites.

Table 5

Study Group	Ref	N	Mortality Rate (%) Control	Shunt	P
New Haven I	33	55	57	80	NS
New Haven II	33	41	45	42	NS
BILG	34	50	42	46	NS
VA Cooperative	35	95	28	51	< 0.02

Average followup ranged from 5-8 years in these studies. It is apparent that the portacaval shunt was not associated with improved survival. In fact, in the largest study (35) the shunted group fared significantly worse than the control group. Patients who were randomized to portacaval shunt but refused surgery (shunt group RSN) survived longer than those who accepted the operation (Fig. 2).

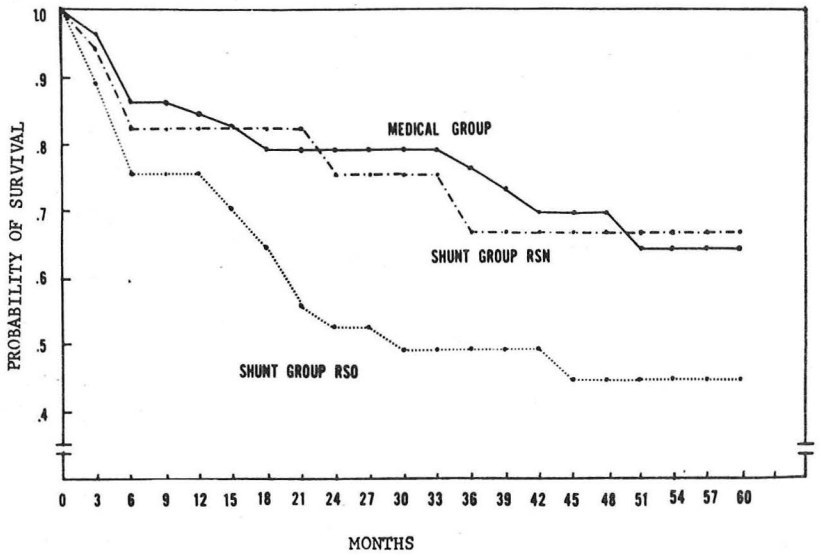


Fig. 2

In the tradition of Harold Conn, a chief investigator in the New Haven studies, I have taken the liberty of combining studies to look at causes of death in these patients (Table 6).

Table 6

	Control	Shunt
Bleeding Varices(%)	35	5
Hepatic Failure(%)	18	41
Surgery(%)	-	16
Non Variceal Bleed(%)	20	13
Other(%)	27	25
Total	100	100

Shunting markedly reduced mortality from variceal bleeding but increased deaths from hepatic failure. Moreover, 9 patients (8% of the shunt group) died as a result of the surgery despite being a fairly selected group. This accounted for 16% of the deaths in the shunt groups.

Not only did the shunt not prolong life, but it increased the likelihood of a patient developing hepatic encephalopathy in all three series. For example, in the New Haven series 29% of control patients and 45% of shunted patients developed encephalopathy (often after a bleed or precipitated by medications). In one of five patients in the shunt group, moreover, encephalopathy was chronic, spontaneous and recurrent, whereas this syndrome was not seen in the control group. In the VA study 20% of control patients compared to 38% of shunted patients developed encephalopathy ($P < 0.05$).

From these studies we can conclude that prophylactic shunting is of no benefit to cirrhotic patients with varices -- in fact, it is detrimental.

ELECTIVE THERAPEUTIC SHUNTS

Three studies of the therapeutic shunt have been published to date (36-38). These studies all have had two major problems with experimental design. First, variceal bleeding was not always documented (diagnosis was often made by exclusion). As mentioned earlier, this is likely to be a grave error. Some patients may have been shunted because they had bled from gastritis or a Mallory-Weiss tear. A second shortcoming

is that medically-treated patients in these studies were often subsequently shunted if they rebled and their survival was included with medically-treated patients. Obviously, this confounds data analysis.

Nevertheless, these studies came to similar conclusions: (1) Survival curves were not significantly different in shunted and control groups; (2) surgical mortality was 5-10%; (3) shunted patients had less bleeding, but more encephalopathy. A combined survival curve (39) from these three studies is shown below (Figure 3).

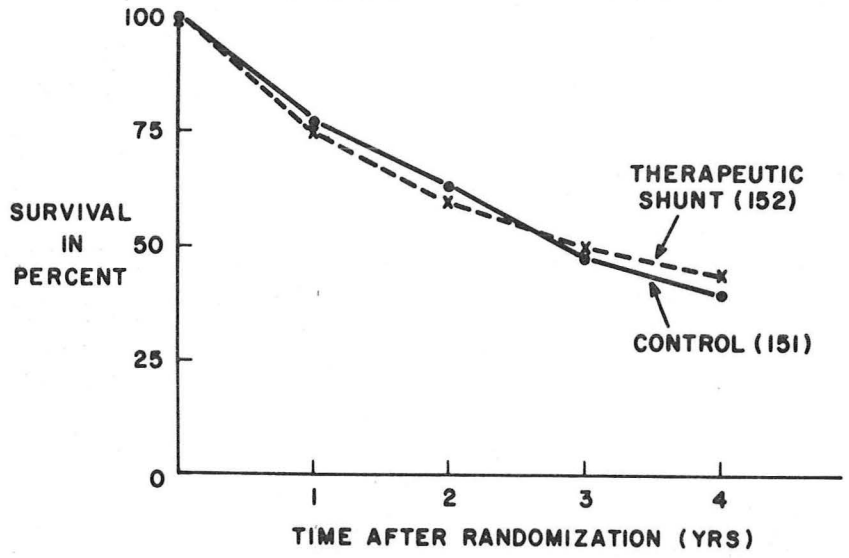


Fig. 3

A fourth ongoing study from Los Angeles has found similar results (40). It is of interest that a preliminary report of this study was published in 1974 (41). At that time survival appeared to be improved in the shunted group ($0.05 < P < 0.1$). This trend has disappeared with more patient entries and with time.

In summary then, portal-systemic shunts are very effective in preventing hemorrhage, but the price is hepatic failure and encephalopathy. Two questions are naturally raised. First, why does the portacaval shunt accelerate hepatic failure? And second, can better operations be designed, operations which continue to protect against variceal bleeding, but which do not induce encephalopathy?

PORTACAVAL SHUNT AND HEPATIC FAILURE

It must first be stated that hepatic failure and encephalopathy are not synonymous. For example, patients with idiopathic portal hypertension or with extrahepatic portal obstruction frequently develop encephalopathy ("meat intoxication") after portacaval shunts for bleeding, although their hepatic function is normal (42).

As long ago as 1920 it was recognized by Rous and Larimore that interruption of portal venous inflow led to liver atrophy (43). These workers speculated that the portal blood may contain substances which are trophic for the liver. In 1953, Child et al (44) reported that the ability of the liver to regenerate following a partial hepatectomy was impaired in Eck fistula dogs. However, this regenerative capacity could be restored toward normal by perfusing the liver with systemic blood via the inferior vena cava (portacaval transposition). Child concluded that the quantity of blood presented to the liver and not the quality (portal versus systemic) was important in hepatic regeneration.

Most investigators interpreted the work of Child and of others (45-46) to indicate that a reduction in total hepatic blood flow accounted for liver failure seen in patients after portacaval anastomosis. This led to the concept that portal diversion was dangerous and that some portal venous flow must be preserved with shunting procedures in order to prevent liver failure.

After the conventional end-to-side portacaval shunt, hepatic blood flow usually decreases, with an average reduction of 40% (47-49). This fall in total blood flow occurs despite the fact that there is usually a variable increase in hepatic arterial inflow after creation of a portacaval shunt. The increase in hepatic arterial inflow is thought by some to be important for survival. For example, Burchell et al measured at laparotomy the increase in hepatic artery flow that occurred at the

time of portacaval shunt (50). They found, that patients who had had hepatic artery flow increments greater than 100 ml/min after the portacaval shunt was constructed survived significantly longer and had less encephalopathy than a group who had an increment of less than 100 ml/min. Thus, the ability of the hepatic artery to increase flow may protect the liver and influence outcome. However, this correlation between increased hepatic artery flow and survival may have been a manifestation of severity of cirrhosis with scarring rather than truly a protective effect of enhanced hepatic blood flow.

A potential method for augmenting hepatic blood flow after portacaval shunt is to arterialize the portal vein stump. This technique can prevent hepatic atrophy in dogs (51) and has been employed in man (52). The right gastroepiploic artery is attached to the hepatic end of the ligated portal vein via a saphenous vein graft. Early results are encouraging but uncontrolled. One of 18 patients died from the operation. None of the 17 survivors has developed encephalopathy on unrestricted protein intake during short followup period (mean 15 months). Lengthier followup, more patients, and control groups will be necessary before this operation can be accepted.

Initially, it was hoped that the side-to-side portacaval shunt would preserve some portal flow and prevent liver damage. However, the reverse appears to be the case (49,53). With this operation the portal vein becomes a low-resistance outflow tract from the liver and "steals" blood from the hepatic artery. Other shunt procedures have been designed to preserve hepatic blood flow. These include splenorenal, mesocaval (superior mesenteric artery-inferior vena cava), portarenal and mesorenal shunts, with or without Dacron "H" type interposition grafts (see Appendix). Although these shunts may preserve portal flow to varying degrees in dogs without portal hypertension (54), there is little evidence that portal flow is maintained in cirrhotic patients (55). Therefore, these operations are probably not superior to the end-to-side portacaval shunt as far as maintaining hepatic blood flow is concerned (56).

Even if <u>total</u> hepatic blood flow could be maintained with a given shunt, it is possible that liver damage might still occur if putative "antiatrophic factors" in portal blood are diverted away from the liver by the shunt operation. Candidates for antiatrophic factors include pancreatic and gut hormones (which are presented to the liver in high concentrations prior to their entry into the systemic circulation), and various absorbed nutrients. Recently, Starzl and his associates in Colorado (55,58) have shown convincingly that insulin prevents the hepatic atrophy which follows construction of an Eck's fistula in dogs (Figure 4).

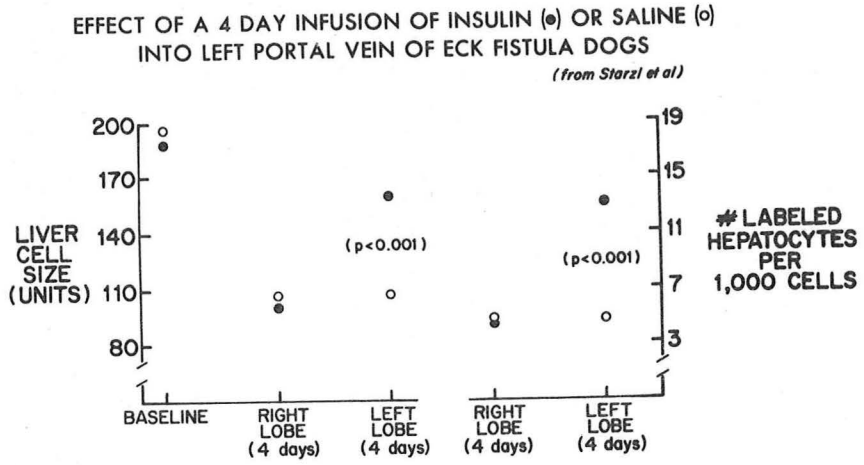


Fig. 4

Insulin or saline (control) was infused into the left branch of the portal vein for four days after the portavacal shunt. There was atrophy of hepatocytes in both right and left lobes after four days when saline was infused. Insulin prevented atrophy and increased hepatocyte proliferation in the left lobe. The insulin dose did not affect peripheral blood glucose levels. These data suggest that insulin is one, and perhaps the major factor which prevents hepatic atrophy. (Incidentally, glucagon had no trophic effect.)

Recently, at a symposium on hepatotrophic factors in Sweden (59), Blumgart attempted to quantitate the relative importance of blood flow versus trophic factors on liver atrophy and regeneration following portal diversion. He performed a portacaval transposition in rats. This operation did not change total hepatic flow (measured by ^{85}Krypton clearance); nevertheless the liver atrophied significantly. However, when partial hepatectomy was subsequently done in these animals, the liver could regenerate normally. He concluded that liver atrophy after portal diversion is not a result of a decrease in absolute liver blood flow and is therefore probably a result of deprivation of trophic substances in portal blood. On the other hand, liver regeneration appears to be independent of a direct supply of portal venous blood.

It is now generally agreed that loss of trophic factors (especially insulin), and not decreased blood flow is the major cause of liver atrophy after portal venous diversion (60), although loss of trophic

substances and a decrease in total blood flow may be additive. A corollary of this observation is that a shunt operation which preserves portal venous (and insulin-rich pancreatic venous) flow to the liver may induce less hepatic atrophy and encephalopathy than total portal diversion procedures, such as portacaval shunts.

NEWER OPERATIONS MAINTAINING PORTAL VENOUS INFLOW

By the early 1960s several surgeons were beginning to see the handwriting on the wall. The portacaval shunt traded one problem (bleeding) for another (liver failure). At the University of N. Carolina, shunts were abandoned. Instead, patients underwent variceal ligation, splenectomy and vagotomy (61). Although encephalopathy was prevented, hemorrhage was still common and mortality rates (operative and long-term) were high.

In 1967 Warren, Zeppa and Fomon (62) introduced a new procedure - the distal splenorenal shunt (see Appendix). A similar operation was later suggested by Britton (63). This operation was designed to selectively decompress gastroesophageal varices while preserving portal venous flow to the liver. This type of shunt has recently been referred to as a "selective", as opposed to a "total" shunt.

In the operation, the esophagogastric-splenic circulation is separated from the high pressure portal-mesenteric circulation by ligating the coronary (left gastric) vein, the pyloric (right gastric) vein, and the right gastroepiploic vein. Since the portal venous system is valveless, esophagogastric venous blood will flow retrograde into the short gastric veins and spleen (which are preserved in this operation) and then into the splenic vein. This gastrosplenic circuit is converted into a low pressure circuit by performing a end-to-side anastomosis between the distal splenic vein and the left renal vein. Other collateral vessels between the portal system and systemic circulation (e.g. the umbilical vein) are also ligated in order to preserve as much hepatic blood flow as possible. By ligating the distal splenic vein, some pancreatic venous blood (from the body and tail) bypasses the liver, but blood from the head and neck of the pancreas reaches the liver via the superior mesentric or portal vein (64).

The goals of this operation seem to have been accomplished (65,66). Portal pressure (and presumably portal flow) remain high while pressures in the spleen and splenic vein fall. Varices usually disappear (66,67) and bleeding is rare. Liver failure and encephalopathy are extremely uncommon. Survival curves are more impressive than any previously published protacaval shunt series (Fig. 5) (68).

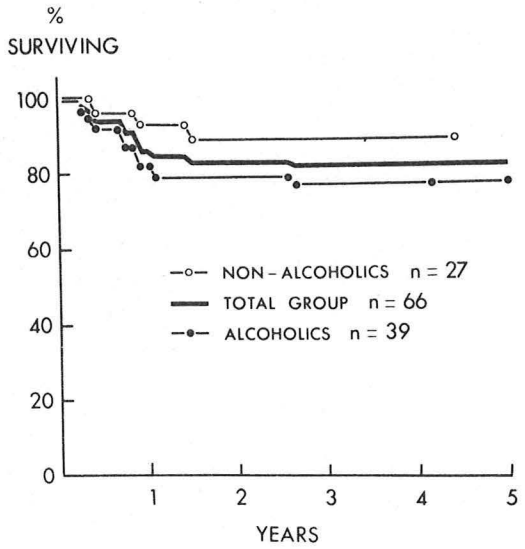


Fig. 5

However, before jumping on the bandwagon, some caveats are appropriate. First, the operation is technically difficult, even for surgeons skilled in vascular surgery on the portal system. For example, the splenic vein must be dissected off the pancreas and this is especially difficult if the pancreas is diseased. Eight of the first 15 patients on whom Warren et al operated died shortly after surgery (65). This has gradually improved with increased experience, and surgical deaths in Warren and Zeppa's hands are now unusual. Secondly, patients were highly selected (see below) and meticulously cared for. And third, long term followup data are limited. From the portacaval shunt series, we know that the death rate accelerates at around 4 years post-shunt. Whether this will occur following Warren's shunt remains to be seen.

With these caveats in mind, I would like to review the results of a recently published randomized controlled trial by Warren's group (55). Unfortunately, the distal splenorenal shunt was randomized against a total (non-selective) shunt rather than against medical therapy. This was because the authors believed (in my opinion erroneously) that therapeutic shunts enhance survival, and that a medical group would have been unethical. Forty-eight patients with biopsy-proven cirrhosis and at least one previous episode of upper gastrointestinal bleeding (requiring more than 2 units of blood) were studied. It is not stated how many of the 48 patients had had more than one bleed prior to entry. Mucosal lesions

such as gastritis and Mallory-Weiss tears were not excluded in all patients. Other criteria for for admission were no current ascites and no "appreciable" parenchymal lesions and inflammation on liver biopsy (the presence of alcoholic hepatitis is thought by some (69), but not by others (70), to adversely influence survival after a portacaval shunt). Finally, on preoperative angiography patients had to have suitable venous anatomy for shunting and have evidence of hepatopedal portal flow on the venous phases of superior mesenteric and splenic arteriography. Obviously, if a patient preoperatively has hepatofugal portal flow there is no reason to perform a shunt designed to preserve portal venous inflow to the liver.

Therefore, this represented a highly selected group of good risk (mostly Child's A) patients. Patients were randomized as follows:

Table 7

Warren Shunt	Number	Number and Type of Total Shunts	
Randomized to	24	Mesorenal Dacron "H" graft	14
Performed in	22	Mesocaval Dacron "H" graft	5
Total Shunt		Splenorenal Dacron "H" graft	3
Randomized to	24	Portacaval	1
Performed in	24	Splenocaval	1
			24

It is apparent that: a) Warren's shunt could not be performed because of technical difficulties in 2 of 24 (8%) of the patients so randomized (even though they had been selected as ideal candidates angiographically); b) the total shunt group received not one and the same, but several different operations, the choice depending on the surgeon's decision at surgery.

Patients had been followed, on the average, a little more than 2 years at the time of publication. Results are shown in Table 8.

Table 8

	N	Operative Deaths	Total Deaths	UGI Bleed	Encephalopathy
Warren shunt	22	1	6	3	1
Total shunt	24	1	6	3	10

The only statistically significant difference between the groups was the incidence of encephalopathy. They defined encephalopathy as an altered state of consciousness which was chronic and recurrent and not precipitated by drugs (including alcohol), gastrointestinal hemorrhage, or post-transfusion hepatitis. It is not stated that encephalopathy was diagnosed by a physician who was blinded to operative treatment. The authors did state that encephalopathy was always recognized by family members or associates.

As shown in Fig. 6, the authors also found that the development of encephalopathy correlated inversely with the ability to synthesize urea after intravenous amino acid loading.

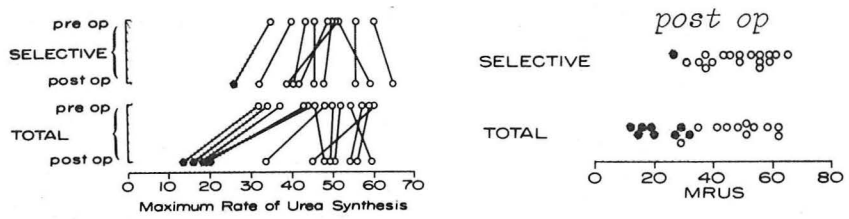


Fig. 6

From Figure 6 (left) we can see that, preoperatively, the maximum rate of urea synthesis (MRUS) ranged from around 34 to 60 mg urea nitrogen synthesized per kilogram per hour$^{0.75}$ and that the two groups had similar values. Post-operatively, the MRUS fell to less than 20 in 5 patients (Figure 6, right), all of whom developed hepatic encephalopathy (shown as solid circles). These 5 encephalopathic patients were all in the total shunt group. All 26 patients whose postoperative MRUS was greater than 33 remained free of encephalopathy.

It is not fortuitous that a low MRUS correlates with hepatic encephalopathy since an important function of the liver is to synthesize urea from ammonia via the Krebs-Henseleit (K-H) urea cycle (Figure 7).

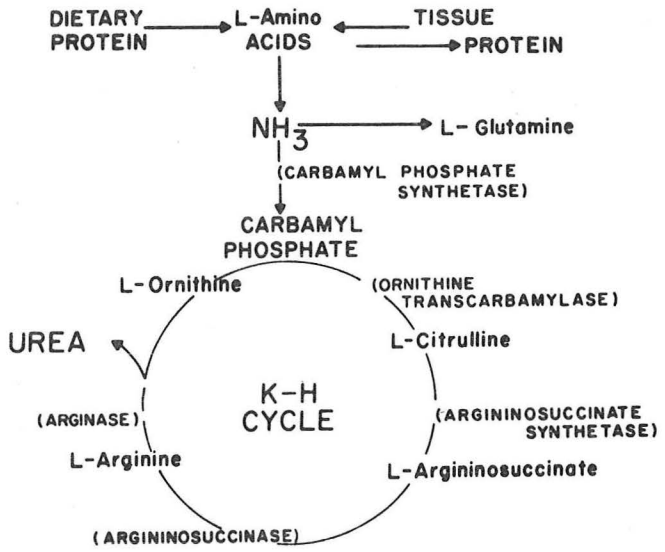


Fig. 7

Impairment of this cycle by a portal-systemic shunt would reduce urea production from nitrogenous substrates and could lead to hyperammonemia and dietary protein intolerance.

There is experimental evidence in animals that selective shunts lead to less liver damage than nonselective shunts (71,72). For example, Reichle et al (72) found that urea cycle enzyme activities were markedly reduced in dogs after total (portacaval) shunts. Although levels of these enzymes also fell after distal splenorenal shunts, reductions were not as dramatic. Moreover, ammonia tolerance after a protein meal was impaired in the portacaval group, but not in the distal splenoreal shunt group.

These authors also found the liver atrophied less after distal splenorenal than after portacaval shunt:

Table 9

	Liver weight (gm) 8 Weeks After Operation	
Sham Operation	545 ± 31 }	P < 0.01
Distal splenorenal shunt	227 ± 9 }	P < 0.01
End-side portacaval shunt	154 ± 16	

Liver biopsies in distal splenorenal shunt dogs were normal, whereas fat accumulation was prominent after portacaval shunt. Although these studies in noncirrhotic dogs cannot be directly compared to results in patients with liver disease and portal hypertension, the data suggest that the distal splenorenal shunt leads to less liver "damage" (decrease in urea cycle enzymes, atrophy, fatty change) than portacaval shunts and less encephalopathy.

There is other biochemical data which supports the concept that the Warren shunt is less harmful to the liver than a total (nonselective) shunt (73). Yamoaka found that ligation of the left portal vein leads to a compensatory increase in liver mitochondrial phosphorylase activity in the right (non-ligated) lobe. This increased activity precedes DNA synthesis and regenerative activity and is dependent upon insulin. These workers evaluated whether the compensatory rise in mitochondrial phosphorylase activity in the nonligated lobe would still occur after a Warren shunt or a total (splenocaval) shunt:

Table 10

	Phosphorylase Activity‡ in Nonligated Lobe at 2 days
a) Control(n=5)	50.8 ± 2.5
b) Portal branch Ligation Alone (n=7)	75.4 ± 4.6
c) Portal branch Ligation and Warren Shunt(n=4)	73.4 ± 3.6
d) Portal branch Ligation and Splenocaval Shunt(n=4)	36.2 ± 4.1

(‡ mμM ATP synthesized/mg mitochondrial protein/min)

Total (splenocaval) shunt impaired the phosphorylase response (and presumably energy generation and DNA synthesis), whereas the Warren shunt permitted a compensatory increase in phosphorylase which occurred after portal ligation.

Not everyone agrees that the Warren shunt is a panacea. Tyler et al in Lund, Sweden (74) reported on 25 patients who had undergone a slightly modified distal splenorenal shunt (74). Operative mortality was 16%. In all survivors studied, portal vein inflow was decreased postoperatively compared to preoperative flow and in 6 patients hepatofugal developed rather soon after surgery. They also found that of 10 additional patients who died during the fairly short follow-up period (less than three years), liver failure was a major contributing factor in 8. This study indicates that not all patients do as well as Warren and Zeppa's patients.

Another new operation besides the Warren shunt needs to be mentioned (75,76). Inokuchi in Japan is able to anastomose the coronary (left gastric) vein to the inferior vena cava end-to-side using a saphenous vein graft (Appendix). In addition, a splenectomy is done and the short gastric veins are ligated to reduce collateral circulation to the varices. Pressure in the coronary vein falls and varices disappear, whereas portal pressure is maintained. Results in 100 cases are encouraging (3% operative mortality, 10% rebleeding, 78% five year survival, and no encephalopathy). None of their cirrhotics were alcoholics, however. This procedure is unlikely to be adopted for widespread use in this country because it is technically difficult.

FINAL COMMENTS AND GUIDELINES

At the present time, I would suggest the following approach to the patient known to have esophagogastric varices.

1) If the patient has never bled from his varices, he is not a candidate for any kind of portal-systemic shunt. The patient should be advised to stop drinking alcohol. If he does, he will have a better prognosis (19).

2) If the patient is seen with active upper gastrointestinal bleeding, the site of bleeding should be documented as soon as possible by endoscopy. At least half of such patients will be found to be bleeding from sites other than varices. These latter patients are not candidates for shunts.

3) If the patient is actively bleeding from varices, attempts should be made to stop the bleeding medically. This has been reviewed recently in Grand Rounds by Dr. Peterson. Ice water lavage is sometimes sufficient. If not, (unless the patient has coronary insufficiency) intravenous vasopressin (Pitressin) should be used in a dose of 0.2 to 0.4 units per minute. This is probably as effective as vasopressin via the superior

mesenteric artery and avoids catheter-related complications (77). If vasopressin fails, either a Sengstaken-Blakemore or Linton tube can be used (with caution) to tamponade the varices. In most cases (perhaps 85%) bleeding will cease with usual measures. Overtransfusion must be avoided since this may increase portal pressure (78) and the risk of rebleeding.

4) If the patient does not stop bleeding with these measures (or has several episodes of rebleeding in hospital), the mortality rate, with or without surgery, is high. Therapeutic choices include:

a) Continued Medical Therapy. Published data suggests that only 1/4-1/3 of such patients will survive if treated medically (79). However, medical therapy of bleeding varices may be improving in the near future. Procedures such as injection of varices with sclerosing agents through an esophagoscope (an old treatment reborn!) and transhepatic catherization and obliteration of the coronary vein are being used successfully in some centers (80,81,82). Also, intraarterial vasopressin may occasionally work when intravenous vasopressin has failed (83).

b) Emergency Portacaval Shunt. Between 25 and 60% of patients survive this operation (79). Some survivors go on to live several years. Although there are no controlled data, this approach is thought by many surgeons to be superior to current medical therapy (84-85). As nonoperative (medical) therapy improves with time, emergency shunts may be used less and less frequently.

c) Emergency Transabdominal (or Transthoracic) Ligation of Varices. This procedure is an expedient and direct way of stopping bleeding (87). Since rebleeding is common, most would favor a definitive shunt in the survivors of the first operation once they are stable. The data supporting this approach are skimpy at best.

d) Esophagogastrectomy. This is largely reserved for children or adults in whom a shunt cannot be constructed (88).

Ultimately, the decision is made together with the surgical consultant.

The choice will depend on 1) the condition of the patient (Child's "C" patients rarely survive a shunt); 2) the rapidity of bleeding; 3) the familiarity of the surgeon with the above operations and 4) the wishes of the patient and family.

5) A difficult decision concerns the patient who had bled once from varices and then stops bleeding. Shunt or punt? Unfortunately, there is no simple answer to this question. I advocate the following approach which is based more upon clinical instinct than knowledge from the literature that this is correct.

a) Follow the patient initially. Some patients will never rebleed. Varices may even disappear as collateral circulation develops or as fatty infiltration and alcoholic hepatitis resolve (17,89,90).

b) If the patient does rebleed and if he is Child's "C", I would again treat him medically and not recommend a shunt.

c) If the patient rebleeds from varices (either in hospital or later) and is a good risk patient (Child's "A" or perhaps "B"), I would then discuss in detail with the patient and his family the shunt dilemma and ask if they are willing to consider surgery. It is crucial that the patient understands the facts: that bleeding can be expected to be prevented, that prolongation of life cannot be guaranteed and that the operation itself can be lethal at least 10% of the time. If the patient is willing to consider surgery, the next steps should usually include: 1) liver biopsy to confirm cirrhosis and to help rule out active, severe liver disease and hepatoma; and 2) arteriography to be certain that vessels are patent and of sufficient size for shunting. The following case is an example of why this approach is necessary.

> W.S. is a 69 year old man admitted to the Dallas VA Hospital in 1978 with hematemesis and melena. He had consumed large amounts of alcohol for several years. In 1973 he had had surgical drainage of multiple hepatic abscesses (B. fragilis). In 1977 he developed weakness and dizziness. Hematocrit was 22% and the stool was guaiac positive. He was found to have esophageal varices, deformity of the duodenal bulb and a small adenomatous colonic polyp, which was removed. Liver-spleen scan showed diffuse hepatocellular disease, splenomegaly and shunting of isotope to the bone marrow. He was treated with iron and antacids and the hematocrit increased to and stayed at 48%. He remained well until the day of admission. Physical examination revealed only orthostatic hypotension, splenomegaly and melena. Hematocrit was 31%. Endoscopy revealed large esophagogastric varices. Active bleeding appeared to emanate from a gastric varix in the fundus. Four units of blood were given as was intravenous vasopressin. The bleeding ceased. Bilirubin was 0.6 mg%, SGOT 58, serum albumin 4.2 gm% and prothrombin time was normal. Serum amylase was either normal or slightly elevated on several occasions.

> Surgical consultants felt he was an ideal candidate for a distal splenorenal shunt (documented variceal bleeding; Child's "A"), However, a subsequent liver biopsy was normal! Then angiography showed splenic vein obstruction, gastroesophageal varices, marked collateral circulation around the spleen to retroperitoneal veins, and a patent portal vein. That evening he had another episode of hematemesis requiring two units of blood. At laparotomy splenic vein thrombosis secondary to chronic pancreatitis was found. The portal vein pressure was only 8 mm Hg. Splenectomy and ligation of markedly enlarged short gastric veins and gastroepiploic veins were performed and he recovered uneventfully.
>
> Splenic vein thrombosis can cause regional venous hypertension and esophagogastric varices (91,92) which are curable by splenectomy. It would have been a grave error to perform a portal-systemic shunt in this patient.

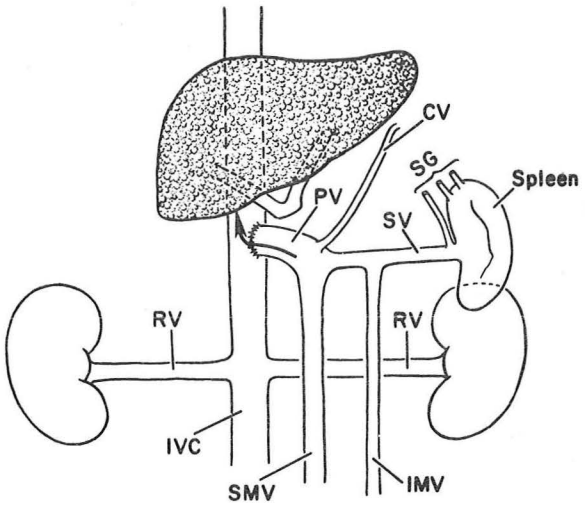
If angiography shows suitable anatomy and liver biopsy confirms cirrhosis with no active hepatitis or cancer and if the patient is still willing, I would then refer the patient to a surgeon skilled in performing the distal splenorenal shunt or the coronary-caval shunt. It would be ideal if that surgeon were engaged in a randomized trial using medically-treated patients as a control group (I know of no such ongoing study, however). Obviously, this represents a very select group of patients who are likely to die of variceal hemorrhage and much less likely to die of hepatic failure or from the operation.

Now that I've said what I do, it may be instructive in closing to see what others do. Harold Conn, in New Haven, made the following statement in 1974 (39):

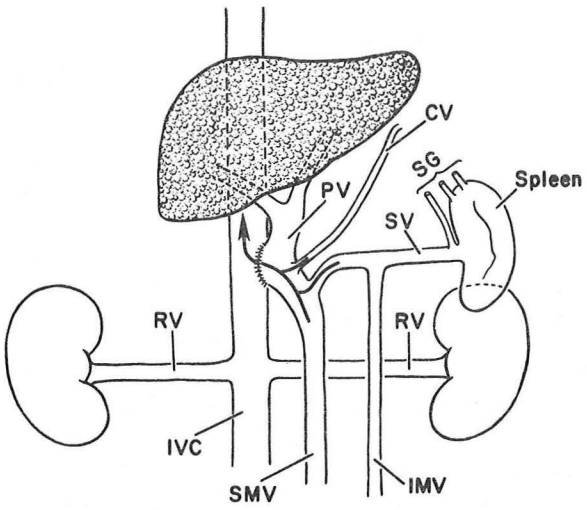
> If I, for example, were bleeding from esophageal varices, I should like to be treated at an academic institution, preferably one where a controlled investigation was in progress. I would try to meet the criteria for inclusion, since the prognosis of those who do is much better than those who do not. I would fervently hope to be selected - randomly, of course - for the operative group. Then, in light of previous findings, and with faint heart, I would refuse surgery.

APPENDIX

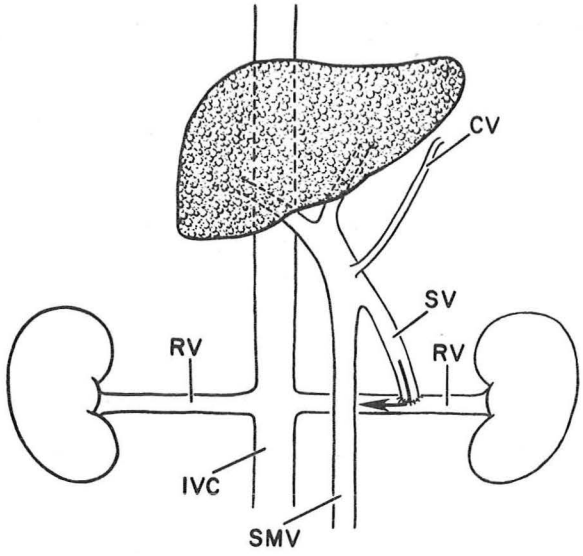
Schematic diagrams of six commonly used portal-systemic shunt operations. Abbreviations are as follows: PV = portal vein; CV = coronary (left gastric) vein; SV = splenic vein; SG = short gastric veins; IMV = inferior mesenteric vein; SMV = superior mesenteric vein; RV = renal vein; IVC = inferior vena cava. For simplicity, several smaller branches of the portal venous system have been omitted (see Ref. 64).



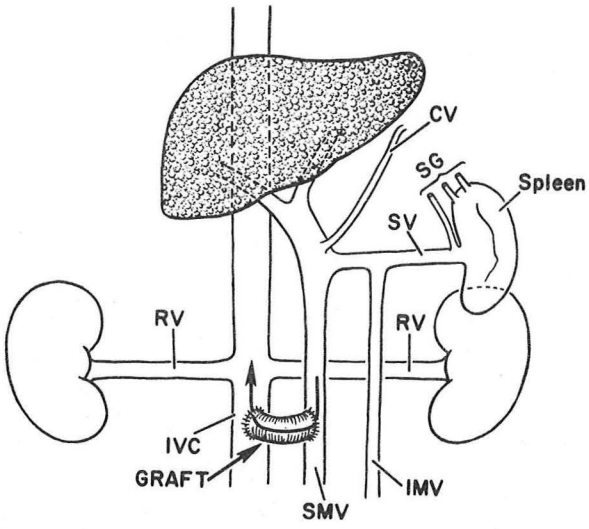
END-TO-SIDE
PORTACAVAL SHUNT



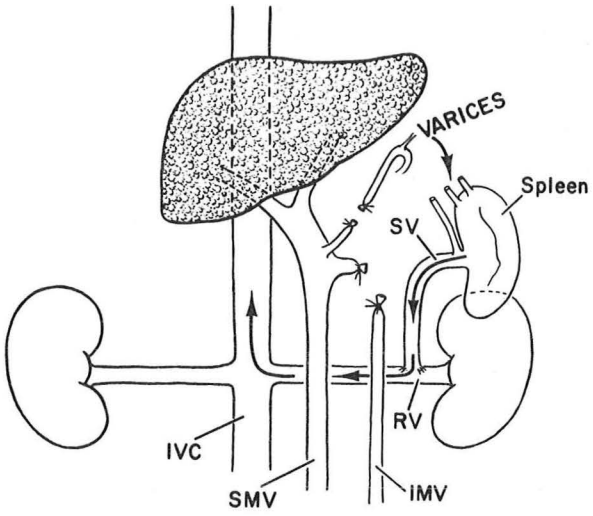
SIDE-TO-SIDE
PORTACAVAL SHUNT



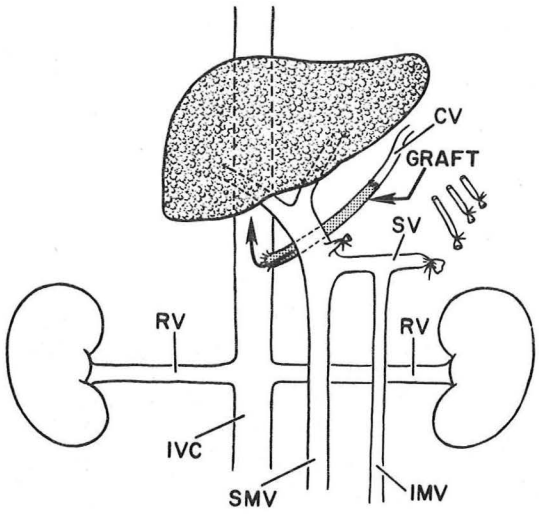
SPLENORENAL SHUNT



MESOCAVAL INTERPOSITION SHUNT
("H" GRAFT)



DISTAL SPLENORENAL
(WARREN) SHUNT



CORONARY (LEFT GASTRIC)-CAVAL SHUNT
INCLUDING SPLENECTOMY

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