Emergency Portacaval Shunt: A Comparative Study of Shunt, Varix Ligation and Nonsurgical Treatment of Bleeding Esophageal Varices in Unselected Patients with Cirrhosis

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BLEEDING from esophageal varices is the most lethal form of gastrointestinal hemorrhage.9 In patients with cirrhosis, varix rupture is one of several serious complications responsible for the high mortality rate of this disease. Statistics accumulated during the past two decades indicate that only approximately one out of three cirrhotic patients who were hospitalized because of their first episode of bleeding varices left the hospital alive. 1, 3, 7, 13, 16, 24 Furthermore. substantial evidence suggests that, until recently, the survival rate of patients with varix hemorrhage had not changed significantly during the present century. If incidence and mortality are considered, it is apparent that the major unsolved problem in the management of portal hypertension concerns the emergency treatment of bleeding esophageal varices.

The underlying objective in the therapy of cirrhosis and its complications is improvement of liver function. In patients who bleed from varices, immediate control of hemorrhage and prevention of recurrent

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bleeding become additionally related objectives. While it is generally agreed that permanent protection against bleeding can be accomplished consistently only by some form of portal decompression, there is considerable uncertainty regarding the most effective means, if any, of obtaining immediate hemostasis. Among the many emergency measures used to control varix hemorrhage only three warrant serious consideration. These are the nonsurgical application of esophageal balloon tamponade and the surgical procedures of transesophageal ligation of varices and, most recently, emergency portacaval shunt. Nonsurgical treatment and varix ligation are followed by an elective portacaval shunt if the patient survives the bleeding episode. Are these forms of therapy beneficial? Do they significantly influence the survival of the bleeding cirrhotic population? How do they compare with each other? The answers to these questions are unknown or incomplete.

Several years ago we initiated a program aimed at evaluating emergency therapy. It was clear that the retrospective and selective features of most evaluations of clinical therapy represented serious shortcomings. The first of these defects was avoided by formulating a prospective study plan and obtaining the cooperation necessary for its

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uniform and rigorous application. The second shortcoming, that of patient selection. is an inherent feature of human studies in which an established, successful form of treatment is available, and often it cannot be eliminated. However, the experience of our institution prior to 1961 indicated that a mortality rate in excess of 80% was associated with every type of emergency therapy of varix bleeding, so that a successful treatment regimen did not exist. Moreover, it was apparent that sound criteria for the selection of patients for one or another type of management had not been established, either at our hospital or elsewhere. Accordingly, the program was designed to include every cirrhotic patient who entered our hospital with bleeding varices.

The application of this program to the evaluation of emergency nonsurgical treatment and of transesophageal varix ligation in unselected cirrhotic patients has been reported previously.¹⁷ This report describes the results of a prospective study of emergency portacaval shunt in 40 unselected patients with cirrhosis and varix hemorrhage, and compares the three forms of emergency therapy.

Material and Methods

Study Plan. The prospective program for the evaluation of emergency therapy of bleeding esophageal varices was initiated at Harbor General Hospital in 1961 and has been uniformly applied without change since. The evaluation of emergency portacaval shunt was conducted from 1962 to 1966. All members of the faculty and house staff were sent copies of the study plan, the program was discussed with many members of the staff, and copies of the protocol were posted in the emergency room, clinics and on the hospital floors. All potential patients were admitted to the Surgical Service and were managed there with the aid of consultants from other services.

Every patient who entered the hospital with upper gastrointestinal bleeding and suspected or known cirrhosis of the liver was considered a potential candidate and was included in the study. The patients were seen within minutes of entering the emergency room by a surgical resident on full-time emergency duty. The resident obtained the history, performed the first of several physical examinations, obtained specimens for diagnostic studies, ordered fresh blood, started the initial therapy and contacted appropriate other members of the house staff and faculty. Routinely, intravenous catheters were placed through cutdowns in each arm and an indwelling bladder catheter was inserted. When the patient's condition had stabilized following parenteral therapy, he was taken to the radiology department by a physician member of the team who remained in attendance throughout the roentgenologic studies and continued treatment. The diagnostic work up was completed within 6 hours of admission to the hospital, and often within 3 hours.

After completion of the diagnostic studies, a final decision was made regarding patient eligibility and was based on the demonstration of esophageal varices, the failure to demonstrate other lesions commonly responsible for upper gastrointestinal hemorrhage, and the presence of history, physical findings, and results of laboratory tests compatible with the diagnosis of cirrhosis of the liver. Eligible patients were subjected to a portacaval shunt within 8 hours of admission to the hospital.

Postoperatively, all patients received similar therapy. A prescribed battery of diagnostic studies was obtained at frequent intervals. Upon discharge, the patients were followed at regular intervals in the Surgical Outpatient Clinic.

It is to be emphasized that the study plan was uniformly applied to all patients. The author participated in the care and evaluation of every patient in the study. Patients. Fifty-two unselected cirrhotic patients were involved in the study initially. Twelve were judged ineligible for operation after the diagnostic work up showed that they were bleeding from lesions other than esophageal varices. Three of the 12 had a peptic ulcer and eight had gastritis. Roentgenograms and esophagoscopy failed to reveal esophageal varices in these patients. In nine of the 12 ineligible patients, percutaneous splenic manometry showed that portal hypertension was absent. The remaining 40 patients underwent emergency portacaval shunts.

During the 4 years of this study a number of additional patients underwent portacaval shunts. Eight were transferred to our institution after prolonged therapy at other hospitals or developed bleeding in the hospital on another service and were not brought to our attention until they received prolonged treatment. These patients were operated upon several days to several weeks after the onset of bleeding. A number of patients entered the hospital after recovery from an episode of varix bleeding and underwent an elective portacaval anastomosis. Finally, there were several individuals who had portacaval shunts for intractable ascites. None of these was included in the evaluation of emergency portacaval shunt.

Diagnostic Studies. The diagnostic studies included determinations of hemoglobin, hematocrit, white blood count, differential count, blood urea nitrogen, prothrombin activity, Bromsulphalein excretion, serum bilirubin, cephalin flocculation, thymol turbidity, serum glutamic oxaloacetic transaminase, serum proteins, and serum alkaline phosphatase. Confirmation of bleeding was obtained by aspiration of the stomach and by gross and chemical examination of the stool for blood. In 26 of the 40 patients who subsequently underwent operation blood gases and pH were measured, and in 31 patients serum electrolyte levels were determined preoperatively. All patients had chest roentgenograms and barium contrast upper gastrointestinal series after blood was removed from the stomach. Esophagoscopy and splenic manometry were performed in several instances when there was a question about diagnosis. All blood tests were repeated at frequent intervals after operation.

Initial Therapy. Posterior pituitary extract in a dose of 20 units diluted in 200 ml. of dextrose solution was administered intravenously over a 15- to 20-minute period to every patient shortly after admission. Blood transfusions were started usually within 45 minutes of admission and always within 90 minutes. At least 2,000 ml, of the transfusion volume consisted of fresh blood donated less than 12 hours prior to administration. The stomach was irrigated with iced saline solution via a nasogastric tube and, after completion of the roentgenographic studies, the barium was evacuated and 60 ml. of magnesium sulfate and 4 Gm. of neomycin were instilled in the stomach through the tube. Two saline enemas, each containing 4 Gm. of neomycin, were administered preoperatively. Therapeutic doses of vitamins K, C, and the B complex were given intravenously along with a hypertonic glucose solution containing appropriate amounts of electrolytes to correct acid-base abnormalities. No patient was treated with esophageal balloon tamponade.

Portacaval Shunt Operation, All 40 patients were operated upon within 8 hours of entering the emergency room. Twentyunderwent side-to-side portacaval anastomoses and 15 were treated by endto-side shunts. Prior to undertaking the study it was agreed that the choice of shunt would be left to the surgeon except when portal pressure determinations indicated reversal of portal flow and made a side-toside shunt mandatory. With the exceptions of five cases in which this stricture applied, and a few instances in which an end-toside anastomosis was performed because the liver contained a large caudate lobe, the type of shunt selected was largely a reflection of the personal preference of the operating surgeon. The shunts were designed to measure 2 to 3 cm. in widest diameter.

Anesthesia in all cases consisted of a combination of nitrous oxide-oxygen, intravenous demerol and small quantities of a muscle relaxant. Eleven patients, selected at random, were operated upon under hypothermia of 30 to 31° C., which was induced by surface cooling in a tub of ice water according to our previously described technic.¹⁷

All operations were performed through a long right subcostal incision, with the patient in the oblique position. The electrocautery was used liberally for dissection and hemostasis. Pressures in the portal vein (free and occluded) and inferior vena cava were measured with a saline manometer by direct needle puncture before and after performance of the shunt. A liver biopsy was obtained in each case. Lavered closure of the wound with interrupted sutures was used uniformly, as were heavy wire retention sutures. Ancillary procedures included a cholecystectomy for chronic calculous cholecystitis in three patients, and a pyloroplasty for an active duodenal ulcer in one patient. Operations were performed by four members of the faculty and several senior residents.

Postoperative Treatment. Following operation the patients were managed in the intensive care unit for at least a week, and then in the general care area. Therapy initiated preoperatively was continued. Nasogastric suction was maintained until there was evidence of the resumption of gastrointestinal activity. Neomycin in a dose of 1 Gm. every 4 hours was continued for a week. Intragastric magnesium sulfate and enemas containing neomycin were given daily for 3 days. Alkalosis was corrected with parenteral ammonium chloride and large doses of potassium chloride. Hyper-

tonic glucose solutions containing vitamins and appropriate amounts of electrolytes were administered intravenously until oral feedings became possible. The oral diet, at first liquid and then solid, consisted of an ulcer regimen containing 200 mg. of sodium and 20 Gm. of protein per day; the protein content was gradually increased until the patient could tolerate unlimited quantities. Delerium tremens was treated with parenteral magnesium sulfate, a tranquilizer, 50% glucose solutions and vitamins. Hypothermia was used to control high fever. Particular attention was given to supportive measures such as tracheal suction, frequent turning, a high humidity atmosphere, and an adequate supply of oxygen.

The patients were discharged from the hospital with instructions to continue an ulcer diet and antacid therapy. Restrictions of sodium and protein intake were individualized.

Follow Up. Patients were followed at regular intervals in the Surgical Outpatient Clinic. In the spring of 1967, detailed evaluations of the survivors were conducted at Harbor General Hospital. The author and his associates examined every patient except three who had moved away. These three were seen by local physicians and the status of each was reported to us. Therefore, 100% follow up was achieved. Autopsies were performed on every patient who died.

Results

Characteristics Of Patients and Their Bleeding (Table 1). The results concern 40 patients who underwent emergency portacaval shunts. Ages ranged from 33 to 65 years with a mean of 49 years. Twenty-eight were men and 12 were women. Thirty-eight were Caucasians and two were Negroes. All had a history of chronic alcoholism. Twenty-six had consumed large quantities of alcohol during the 24 hours prior to the onset of bleeding

TABLE 1. Characteristics of 40 Patients Treated by Emergency Portacaval Shunt

:	Number of Patients	Percent of Group		Number of Patients	Percent of Group
Age			Hepatomegaly	38	95
30–39	7	18	Splenomegaly	38	95
40-49	14	35	Jaundice	23	58
50-59	14	35	Ascites	17	43
60–65	5	13	Encephalopathy		
Sex			On admission	8	20
Male	28	70	Previous episodes	5	13
Female	12	30	Varices on X-ray	40	100
Bleeding episode			Hemoglobin of 11 Gm./100		
First	26	65	ml. or less	28	70
Second	9	23			
Third or more	5	13			
Alcoholic cirrhosis on biopsy	40	100			

and nine of these continued to drink alcohol after the onset of varix hemorrhage. Seven patients had abstained from alcohol for 1 to 3 weeks prior to their bleeding episodes and seven others had not consumed alcohol for 6 months or more before hospitalization.

Thirty-nine of the 40 patients vomited blood and 38 had gross blood in their stools. All had gross blood in aspirated stomach contents. The time from the onset of bleeding at home to the start of the shunt operation in 39 patients ranged from 4 to 72 hours and averaged 25 hours. One patient bled intermittently at home for 3 weeks. Within the above time range, there was no correlation of time lapse with survival. The time lapse from admission to the emergency room to the start of the shunt operation ranged from 3 to 8 hours and averaged 5.8 hours.

Twenty-six patients (65%) were bleeding for the first time, nine patients (23%) had experienced one previous episode of gastrointestinal bleeding, four patients (10%) had had two previous bouts of hemorrhage, and one patient (3%) was bleeding for the fourth time.

Admission hemoglobin levels ranged from 4.8 to 14.2 Gm./100 ml., with a mean of 9.7 Gm./100 ml. Twenty-eight patients

(70%) had hemoglobin levels of 11 Gm. /100 ml. or lower. Admission hematocrits ranged from 12 to 44% and averaged 29%. Thirty-one patients (78%) had hematocrits of 34% or less.

Severity of Liver Disease. All 40 patients had cirrhosis of the liver proven by biopsy and believed to be of the alcoholic type on the basis of history and gross and microscopic pathology. Every patient had some or all of the common clinical stigmata characteristic of alcoholic cirrhosis. Thirty-eight patients (95%) had hepatomegaly; the two patients with a small liver failed to survive. Thirty-eight patients (95%) had a palpable spleen.

Twenty-three patients (58%) had jaundice on physical examination and this observation was confirmed by determinations of serum bilirubin. Seventeen patients (43%) had clinically detectable ascites confirmed at operation. Eight patients (20%) presented clear evidence of encephalopathy ranging from stupor to confusion, slurred speech and asterixis. An additional five patients had a documented history of previous episodes of encephalopathy, but no signs of this disorder on admission. Thus, 33% of the patients suffered from encephalopathy at some time. Thirty-three of the 40 patients (83%) had one or

TABLE 2. Results of Preoperative Liver Function Tests in 40 Cirrhotic Patients

	Mean	Range	Comment
Serum bilirubin (mg./100 ml.)	3.5	0.4 -12.7	Elevated in 27 patients (80%)
Prothrombin (% of normal)	39	14-79	Below 50% in 30 patients (75%)
Bromsulphalein retention (%)	43	21-100	Above 30% in 32 patients (80%)
Alkaline phosphatase (K.A. units)	14	4–36	Abnormal in 13 patients (33%). Not meaningful.
Serum albumin (Gm/100 ml.)	3.8	2.6 -4.9	Below 3.0 Gm.% in 6 patients (15%). Not meaningful.
Thymol turbidity (units)	7.0	1.2 -18.4	Above 7.0 units in 12 patients (30%). Not meaningful.
SGOT (units)	67	20 –215	Above 100 units in 5 patients (13%). Not meaningful.
Liver index*	2.9	1.3 - 4.0	Above 3.0 in 23 patients (58%) 2.0-2.9 in 13 patients (33%) Below 2.0 in 4 patients (10%)
Arterial pH (26 patients) (units)	7.49	7.40- 7.62	Alkalosis with pH 7.50 or above in 13 patients (50%)
Serum potassium (31 patients) (mEq./L.)	3.4	2.0 - 4.7	Below 3.8 mEq./L. in 21 patients (68%)

^{*} Liver index was calculated by averaging the weights assigned to various laboratory values as follows:

	0	1	2	3	4
Bilirubin	<1.0	<1.5	<3.0	<5.5	>5.5
Prothrombin	>80	61-80	41-60	21-40	<21
Bromsulphalein	<4	<10	< 20	< 30	30 or>

more of the three serious complications of cirrhosis at the time of hospitalization, and four patients had jaundice, ascites and encephalopathy concurrently.

Esophageal varices were demonstrated roentgenographically in all 40 patients. In addition, one patient was reported by the radiologist to have a distorted duodenum and one patient was reported to have a "questionable duodenal ulcer."

In our experience, liver function tests which are most consistently abnormal and of greatest help in evaluating patients with cirrhosis are prothrombin activity, Bromsulphalein excretion and serum bilirubin (Table 2). All patients had depressed prothrombin activity ranging from 14 to 79% of normal and averaging 39%. Three-fourths of the patients had a prothrombin time below 50% of normal. All patients had a markedly impaired capacity to excrete Bromsulphalein, with retention of

dye 45 minutes after injection ranging from 21 to 100% and averaging 43%. Thirty-two patients (80%) had retention levels above 30%. It should be noted that Bromsulphalein excretion was determined only after the blood volume had been restored and the blood pressure was in the normal range. The total serum bilirubin levels ranged from 0.4 to 12 mg./100 ml. with a mean of 3.5 mg./100 ml. Twenty-seven patients (80%) had elevated levels; in 24 these exceeded 2.0 mg./100 ml. and in seven patients the serum bilirubin was above 5.5 mg./100 ml.

Analysis of results of other liver function tests in many cirrhotic patients during the past 6 years has indicated that these are often of little value in the assessment of the severity of the disease or in the selection of patients for operation. In this series of 40 patients, serum alkaline phosphatase was abnormally elevated in

33%, serum albumin levels were below 3.0 Gm./100 ml. in 15%, thymol turbidity was significantly elevated in 30%, and SGOT was above 100 units in 13% of the group. The results of these studies showed no correlation with the results of the three important liver function tests, with the clinical staging of the disease, with the pathologic evaluation of the liver, or with survival.

In an attempt to simplify and render more useful the data obtained from a battery of liver function studies. McDermott 12 suggested the use of a liver index calculated on the basis of weights assigned to various values in each of five tests. We have used this method in the past, but more recently we have modified it to include only the levels of prothrombin activity. Bromsulphalein retention and serum bilirubin. The results of serum albumin and alkaline phosphatase determinations have been eliminated from the calculations for the reasons given above. A liver index of 0 indicates normal hepatic function and an index of 4.0 indicates decompensated. terminal disease; indices between 0 and 4 presumably reflect varying degrees of hepatic dysfunction. The liver index in this group of 40 patients averaged 2.9 and ranged from 1.3 to 4.0. Twenty-three patients (58%) had a liver index of 3.0 or above and only four patients had an index below 2.0.

In 26 patients, blood gases and pH were determined preoperatively (Table 2). Thirteen (50%) had an arterial blood pH of 7.50 or higher. The alkalosis was usually of the metabolic type. Serum potassium levels were measured on admission in 31 patients. They ranged from 2.0 to 4.7 mEq./L. with a mean of 3.4 mEq./L. Twentyone patients (68%) had hypokalemia with a level below 3.8 mEq./L. Twelve of the 13 patients with a blood pH in the alkalosis range had an associated hypokalemia.

Control of Hemorrhage. Thirty-five of the 40 patients (88%) stopped bleeding following the administration of posterior pituitary extract. Since all patients were operated upon within several hours of receiving Pituitrin, it was not possible to evaluate the prolonged effects of the drug. However, five of the 35 who responded initially resumed bleeding during the induction of anesthesia or during operation. In five patients, bleeding was not influenced by posterior pituitary extract.

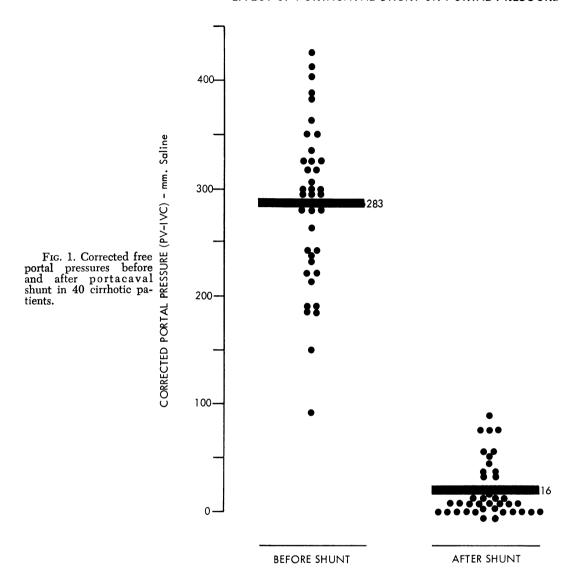
The emergency portacaval shunt stopped the gastrointestinal bleeding in every patient. None subsequently bled from esophageal varices, and none bled from any other cause for at least 72 hours following operation.

The total volume of blood transfused from the time of admission to one week postoperatively, including that given during operation, averaged 4,168 ml. and ranged from 1,500 to 8,000 ml.

The estimated operative blood loss ranged from 300 to 6,560 ml. and averaged 2,277 ml. Thirty-two patients (80%) had a blood loss of 3,100 ml. or less during operation, and 21 patients (53%) had a blood loss of 2,000 ml. or less. The time required to perform the operation, from making the skin incision to completion of the skin closure and termination of anesthesia, averaged 3.8 hours and ranged from 2.2 to 8 hours. Thirty-one of the 40 operations were accomplished in 4 hours or less and only two operations required more than 5 hours. Both of these patients survived. Every operation involved detailed pressure determinations, a layered closure of the large incision with interrupted sutures, and placement of retention sutures. No unusual emphasis was placed on speed of operation.

Operative Pressures (Table 3 and Fig. 1). All patients had portal hypertension with free portal pressures ranging from 280 to 536 mm. saline. When corrected by subtraction of the inferior vena cava pressure level, they ranged from 92 to 422 mm. The hepatic occluded portal pressure was

EFFECT OF PORTACAVAL SHUNT ON PORTAL PRESSURE



high in 33 of the 40 patients, an indication that outflow resistance was great and that the liver received most of its blood supply from the hepatic artery. In five patients, the hepatic occluded portal pressure was higher than the free portal pressure indicating spontaneous reversal of portal flow; four of these five patients had ascites.

Following portacaval shunt the portal pressure ranged from 104 to 340 mm. (0 to 90 mm. corrected), with a mean of 213

mm. (16 mm. corrected). Because of the extended position of the patients, vena cava pressures were often quite high so that consideration of corrected pressures is particularly meaningful. In 36 of the 40 patients the pressure gradient across the shunt was 50 mm. or less and in no patient did the gradient exceed 90 mm.

Postoperative Complications (Table 4). Twenty-three of the 40 patients (58%) developed hepatic coma following operation.

TABLE 3. Operative Pressures in 40 Cirrhotic Patients

	Before Shunt-mm. Saline			After Shunt-mm. Saline				
	M	ean	Ra	ınge	M	ean	R	ange
	Actual	Cor- rected*	Actual	Corrected*	Actual	Cor- rected*	Actual	Corrected*
Free portal	423	283	280–536	92-422	213	16	104-340	0-90
Hepatic occluded portal**	361	233	122-538	32-366	-			
Splanchnic occluded portal	473	348	361-730	206-602		_	_	
Inferior vena cava	140		50-320	_	197		110-330	

^{*} Corrected pressures were obtained by subtracting inferior vena cava pressure.

** 5 patients had spontaneous reversal of portal flow.

Coma usually appeared during the first 7 to 10 days. Six of the 23 survived. There was no relationship between the development of hepatic coma in the immediate postoperative period and the subsequent occurrence of symptoms of hepatic encephalopathy or of protein intolerance.

Delerium tremens developed in 18 patients (45%). Seven of the 18 survived.

Twenty-four of 28 patients (83%) in whom blood gases and pH were measured had alkalosis as indicated by a pH of 7.50 or higher. Eleven of the 24 survived. Sixtynine per cent of the patients had hypokalemia and 85% of those with alkalosis had an abnormally low serum potassium level.

Eight patients (20%) developed a peptic ulcer in the immediate postoperative period and only one of these individuals survived. Ulcers were located in the stomach

TABLE 4. Early Postoperative Complications in 40 Patients Treated by Emergency Portacaval Shunt

	Number of Patients		Per cent with this Complication Surviving
Hepatic coma	23	58	26
Delerium tremens	18	45	39
Alkalosis (determined in 29 patients)	24	83	46
Peptic ulcer Gastric Duodenal	8 6 2	20	13 17 0
Rebleeding Gastric ulcer Hepatic failure diathesi Unknown cause	7 5 s 1 1	18	17 20 0 0

alone in six patients, in the duodenum alone in one patient, and in both the stomach and duodenum in one patient. Five of the six patients with ulcers confined to the stomach developed bleeding, and both patients with duodenal ulcers experienced perforation and peritonitis. An additional patient had an active duodenal ulcer at the time of operation and developed complications several months later. It is tempting to attribute the striking incidence of ulcer to the portacaval shunt. However, it should be pointed out that in six of the eight patients, ulcers were located in the stomach, were superficial, and developed in desperately ill individuals who were close to death. It would seem justifiable to consider the possibility that equally sick and debilitated individuals without portacaval shunts would develop similar stress ulcers.

Seven patients (18%) bled from the gastrointestinal tract in the postoperative period; two survived. In five of the seven patients the bleeding was due to the development of a gastric ulcer during the second or third postoperative week. One patient bled massively from an undiscovered source on the third day after operation. The bleeding was not controlled by esophageal balloon tamponade and, therefore, was presumed not to originate from a ruptured varix. After 24 hours bleeding stopped and did not recur during 3½ years

of observation. Finally, one patient had bleeding from the nose, mouth, gastrointestinal tract, urinary tract and skin on the third postoperative day as a manifestation of a coagulation abnormality associated with liver failure.

Almost all patients developed chemical evidence of further impairment of liver function soon after operation. Serum bilirubin rose in 86% of the patients, reaching a peak during the first or second postoperative week. The level of serum bilirubin was of limited prognostic value. Nine patients reached a level of 10 mg./100 ml. or higher and four survived. The highest level observed in a survivor was 25 mg./100 ml. Serum albumin declined in 65% of the group; the lowest levels were observed during the second week after the shunt. Prothrombin activity decreased in 47% of the patients during the first or second postoperative week. Bromsulphalein retention increased in only 21% of the patients and the other liver function tests showed changes in but a few individuals. With the exception of a progressively rising serum bilirubin exceeding 15 mg./100 ml., none of the chemical changes correlated with survival.

Three of the 40 patients (7%) developed wound infections postoperatively.

Early Survival. Patients who both survived 30 days and left the hospital were considered early survivors. Twenty-one of the 40 patients fulfilled the requirements of this definition, an early survival rate of 53%. Nineteen patients died, fifteen from liver failure. Two patients died from massive bleeding from gastric ulcers which precipitated hepatic decompensation. One patient died from peritonitis due to perforation of a duodenal ulcer. Finally, the cause of the sudden death of one patient was not apparent, but autopsy revealed thrombosis of an end-to-side shunt.

Autopsies revealed a widely patent shunt in all but one patient.

Long-Term Survival. Twenty-one early survivors have been observed for up to 50 months. Four have died and 17 are alive. a long-term survival rate to date of 43%. All but one of the current survivors have lived for over a year since operation. Three have lived for 4 years, six for over 3 years, and 11 for over two years. One patient died 4 months postoperatively from complications associated with a second operation for a bleeding duodenal ulcer which had been present for several years and was observed at the time of the portacaval shunt. This man was considered a good risk patient. The other three patients resumed drinking large quantities of alcohol and died from liver failure 3 months, 14 months and 25 months, respectively, following the shunt procedure. All three had advanced cirrhosis prior to the shunt with liver indices above 3.0, jaundice and previous episodes of ascites and encephalopathy. Of all survivors, they were the ones who could least afford to resume drinking alcohol. Autopsies in the four patients showed widely patent shunts.

Six of 21 early survivors (29%) resumed ingestion of large quantities of alcohol following discharge from the hospital. Three have died, and three have failed to develop improvement of liver function. Two additional patients, both in good health, have consumed occasional small quantities of beer since discharge. Thirteen patients (62%) deny ingestion of alcohol at any time since operation.

Two of the early survivors have had gastrointestinal bleeding since discharge. Both bled from a duodenal ulcer, one 3 months postoperatively and the other 7 months after the shunt; both required ulcer operations. One (described previously) died and the other has had no subsequent bleeding. Thus, of the initial group of 40 patients, nine or 23% have had gastrointestinal bleeding at some time since operation. Seven (18%) bled from a peptic ulcer, one bled from the dyscrasia associated

with liver failure, and the cause of bleeding in one is unknown. None is believed to have bled from esophageal varices. Four of the 40 (10%) died as a direct result of the bleeding.

Since discharge from the hospital, six of 21 early survivors (29%) have had clinical jaundice. Four patients, described above, developed jaundice in association with terminal liver failure. One had jaundice with an episode of hepatic coma but now has none. One patient developed jaundice following ulcer surgery but now has a normal serum bilirubin. None of the 17 survivors has jaundice.

Ascites has not developed in any of the 21 early survivors. Five patients have had pedal edema, but in four it has been mild and occasional.

Five of the 21 early survivors (24%) have had encephalopathy at some time since discharge. Four of the five had encephalopathy prior to performance of the portacaval anastomosis. Two patients, described previously, developed encephalopathy terminally. One patient had an episode of hepatic coma following alcohol ingestion one month after discharge but now is free of symptoms. One patient developed encephalopathy immediately after ulcer surgery, but at present has no evidence of this disorder and tolerates unlimited quantities of protein. One man with an end-to-side shunt, has chronic, incapacitating encephalopathy which requires restriction of protein intake. Thus, of the 21 early survivors, only one (5%) has chronic encephalopathy clearly attributable to the portacaval shunt. All other instances of encephalopathy have occurred in patients who had encephalopathy prior to construction of the shunt, and in association with a severe insult to the liver, such as ingestion of large quantities of alcohol or a major abdominal operation. It is noteworthy that two survivors who had encephalopathy before operation have had no post-shunt difficulties.

Of the five patients who have had encephalopathy at some time since discharge, three had a side-to-side anastomosis and two had an end-to-side shunt. Ages of these patients ranged from 38 to 55 years with a mean of 45 years; the age of the patients without nervous system symptoms averaged 50 years. Three survivors were over 60 at the time of operation and none has had encephalopathy. Therefore, there was no evidence that the type of shunt or the patient's age influenced the incidence of encephalopathy.

As mentioned previously, two of 21 early survivors (10%) have had a duodenal ulcer with bleeding. None of the other survivors has had symptoms of peptic ulcer disease. Thus, of the initial group of 40 patients, 10 or 25% have had a peptic ulcer. In one patient, the ulcer was present before the shunt while in the other nine it was a post-shunt development. Ulcers developed in the immediate postoperative period in eight patients, and were clearly superficial gastric erosions of the "stress" type in six. Only one patient in the group of 40 developed a new chronic ulcer following the shunt.

Sixteen of the 17 current survivors have undergone recent physical examinations. In all, the liver has decreased in size. In three it is no longer palpable, in 12 it is markedly smaller, and in four it is moderately smaller than it was preoperatively. The spleen is no longer palpable in 14 of the 16 patients. Thirteen of the 16 have no muscle wasting and in only one patient has muscle wasting increased. Three of the 21 survivors (14%) have developed uncomplicated incisional hernias.

Liver function tests have been performed recently in 15 of the 17 current survivors. Compared to the levels obtained prior to the shunt procedure, 60% of the patients have an increase in prothrombin activity, 73% have a lower serum bilirubin, 67% retain less Bromsulphalein, and 60% have a higher serum albumin. The mean liver

index is 1.8 compared to a mean preoperative index of 2.6 for this group. Eighty per cent of the patients have a lower liver index. All in all, in 11 of the 15 patients (73%) hepatic function has improved significantly, in one it has improved slightly, in one it has not changed, and in two patients (13%) it has become worse than before the shunt operation.

Excluding the four patients who died, all of whom were hospitalized terminally, 13 of the 17 survivors have not required subsequent admissions to the hospital because of liver disease. Four patients have been hospitalized at some time, one for treatment of a duodenal ulcer, one for treatment of delerium tremens, and two for treatment of hepatic coma. Thus, 13 of the original 21 survivors (62%) have managed to stay out of hospitals.

Two of the 21 survivors did not live sufficiently long to obtain gainful employment. Of the 12 remaining men, one has died, eight are employed and three are of retirement age and have not worked either before or since operation. The work status was not altered by the operation in any of the surviving male patients when compared to the status one year preoperatively. The work status of the seven women has been more difficult to evaluate. One has died, four do regular housework, and two do little housework. Only one does less housework than she did preoperatively. When asked to compare their capacity for work with their preoperative capacity, 53% of the patients believed their capacity was the same or greater, and 47% thought their capacity had decreased. The factor of increasing age was ignored.

Figure 2 shows the predicted survival rate of this group of patients calculated according to the actuarial or life-table method.^{2, 4, 8} All but one of the current survivors have lived for more than a year. The patient who has been followed for just short of a year is doing well, and the liberty has been taken of including her in



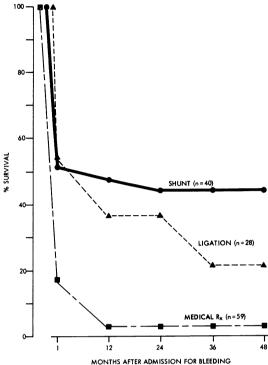


Fig. 2. Cumulative survival rates of the three treatment groups calculated by the life-table method.

the 1-year survival group. The predicted 4-year survival after emergency portacaval shunt is 43%. Because of the small sample, this prediction must be interpreted with caution.

Factors Which Might Have Influenced Survival. With the aid of our computer facility, all data obtained in this study were analyzed to determine which preoperative and operative factors, if any, influenced survival. The influence of each factor separately, and of various combinations of factors was determined. It was hoped that information would be obtained which would help to select patients for operation. It should be emphasized that analysis was limited by the size of the study group and the array of data provided by 40 patients who did not represent, by any means, the spectrum of cirrhosis. The results of analysis are presented in Table 5.

TABLE 5. Evaluation of Factors Which Might Have Influenced Survival

Factor	Pa- tients	Sur- vival %	Significance
Age			
30-39 60-65	7 5	71 60	None
Sex			
Male Female	28 12	46 67	None
Bleeding episodes			
First Third or more	26 5	62 60	None
Jaundice			
Present Absent	23 17	48 59	None
Encephalopathy			
Present Absent	8 32	25 59	None
Ascites			
Present Absent	17 23	24 74	p < 0.01
Jaundice, encephalopathy,			
Ascites All three present	4	0	Sample too smal
All three absent	9	78	cample too smar
Individual liver function tests		_	None
Liver index			
>3.4 3.0–3.4	7 16	14 63	Significant only
<2.4	10	60	at upper extreme
Alkalosis			
Present Absent	13 13	31 69	p < 0.05
	13	09	
Hypothermia Used	11	45	None
Not Used	29	55	140110
Type of Shunt			
End-to-Side Side-to-Side	15 25	47 56	None
Portal Pressures (Free, oc- cluded hepatic, maxi- mum perfusion pressure)	_	_	None

The only clinical factor which influenced survival significantly was the presence of ascites at the time of admission. Addition of jaundice or of encephalopathy to ascites had no greater influence on survival than ascites alone. The occurrence of ascites, jaundice and encephalopathy together was uniformly fatal, but the number of patients with all three complications was too small to permit a statistical conclusion. It should be emphasized that the ascites in these patients was of the unstable variety and probably was a manifestation of liver deterior

oration. Application of the results of this analysis to all patients with ascites, and particularly to those with long-standing stable ascites who are in relatively good condition, would seem unwarranted.

The only laboratory finding which had a significant influence on outcome was the presence of alkalosis on admission. Our recent experience indicates that alkalosis, and the related hypokalemia, are manifestations of advanced hepatic disease and nutritional depletion.

Results of liver function tests, considered individually or together, were of little help in predicting survival. Liver index correlated with mortality only at the upper extreme, in which case clinical evaluation alone would have permitted a prediction of outcome.

The lack of influence of the type of shunt on survival and on the postoperative sequelae was of particular interest. Table 6 shows a comparison of the results of end-to-side and side-to-side shunt. The side-to-side shunt appeared superior on all accounts, but the differences were insignificant. We were unable to confirm the suggestion that side-to-side shunt is followed by a greater incidence of encephalopathy and of deterioration of liver function.^{20, 28}

Finally, our previous experience with operative hypothermia plus its failure to influence survival in the present study suggest that this adjunct is of little or no value.

Comparison of Emergency Shunt, Varix Ligation, and Nonsurgical Treatment. Our earlier evaluation of transesophageal

Table 6. Comparison of End-to-Side and Side-to-Side Shunt

	End-to- Side	Side-to- Side
Number of patients	15	25
Early survival—%	47	56
Long-term survival—%	33	48
Encephalopathy in survivors—%	29	22
Liver index in survivors	1.7	1.8

TABLE 7. Comparison of Emergency Portacaval Shunt, Varix Ligation, and Medical Treatment

	Me	dical Treatme		_		
	Study Group	Prestudy Group	Combined Group	Varix Ligation	Emergency Portacaval Shunt	
Number of patients	14	45	59	28	40	
Age Range Mean Sex	33-64 48	32–67 50	32–67 50	34–63 48	33–65 49	
Male Female	$10(71\%) \ 4(29\%)$	30(67%) $15(33%)$	40(68%) $19(32%)$	$21(75\%) \\ 7(25\%)$	$28(70\%) \ 12(30\%)$	
Type of cirrhosis Alcoholic Post-hepatitic	14 (100%) 0	$42(92\%) \ 3(7\%)$	56 (95%) 3 (5%)	28 (100%) 0	40(100%) 0	
Bleeding episode First Second Third or more	$10(71\%) \\ 2(14\%) \\ 2(14\%)$	29 (64%) 10 (22%) 6 (13%)	39 (66%) 12 (20%) 8 (13%)	$ \begin{array}{c} 18(64\%) \\ 6(21\%) \\ 4(14\%) \end{array} $	26(65%) 9(23%) 5(13%)	
Time-Admission to Operation Range (hours) Mean (hours)	_	_	_	3–8 6.2	3–8 5.8	
Jaundice	6(43%)	19 (42%)	25 (42%)	16(57%)	23 (58%)	
Ascites	4(29%)	20 (44%)	24(41%)	14(50%)	17 (43%)	
Encephalopathy on admission	2(21%)	12 (27%)	15(25%)	7 (25%)	8 (20%)	
Liver Index Range Mean	1.3-3.7 2.8	13.–4.0 2.8	1.3–4.0 2.8	1.3-3.7 2.8	1.3-4.0 2.9	
Admission hemoglobin 11 Gm./100 ml. or Less	14(100%)	27 (60%)	41 (70%)	20(71%)	28(70%)	
Varices shown preop., at operation, or at autopsy	14(100%)	42 (93%)	56 (95%)	28(100%)	40(100%)	
Volume of blood transfused (mean)—L.	7.0	7.2	7.2	4.2	4.2	
Early survival (30 days and left hospital)	2(14%)	8(18%)	10(17%)	15 (54%)	21 (53%)	
Four-year survival	2(14%)	0	2(3%)	6(21%)	17(43%) (predicted)	

varix ligation and of nonsurgical treatment of bleeding esophageal varices in unselected patients with cirrhosis was conducted in a manner identical to that used in the evaluation of emergency portacaval shunt. Our previous report concerned 15 patients who underwent varix ligation and 14 who were treated medically.¹⁷ The varix ligation study was continued until 28 patients were treated. In addition to the two previous study groups (ligation and medical treatment), a retrospective analysis was

conducted of a third group of 45 unselected patients all of whom received modern medical therapy, including esophageal balloon tamponade and measures to prevent and combat hepatic coma, prior to initiation of the study. A comparison of the three forms of treatment is presented in Table 7. Because the characteristics, treatment regimens and outcome were similar in the study and prestudy medical treatment groups, the two have been combined into a single group of 59 patients.

The data indicate that the three types of treatment were evaluated in comparable patients. The results of surgical management were strikingly different from those of nonsurgical therapy. The amount of blood required during the first week of hospitalization in the ligation and shunt groups was similar and averaged 4.2 L. In contrast, the volume of blood required by the patients who were treated medically averaged 7.2 L. Early survival rates following the two forms of operative therapy were almost identical (54 and 53%) and were about three times greater than the survival rate resulting from nonsurgical treatment. The difference was highly significant (p < 0.001). Compared to medical therapy, long-term survival, both actual and predicted by the life-table method, was significantly greater following both types of surgical management (p < 0.001). The emergency portacaval shunt resulted in a long-term survival rate which was twice as high as that produced by varix ligation, but the samples were too small to permit a valid statistical comparison. Figure 2 shows the cumulative survival rates up to four years after therapy in the three treatment groups.

The comparison of the three types of emergency therapy is subject to several criticisms. First, treatment regimens were not evaluated at the same time, and the potential defect in comparing nonconcurrent groups is apparent and has been emphasized by others.^{6, 8} It could be argued that the overall care of patients with varix hemorrhage improved progressively with time as experience was gained so that a bias was introduced against medical treatment and in favor of emergency shunt. However, the yearly survival rates in the two surgical treatment groups were lowest in the last years of each study and, if anything, showed a downward trend throughout. For example, the survival rate in the first year of the emergency shunt study was 60%, while in the fourth year it was 47%.

Second, the major component of the combined medical therapy group consisted of patients who were treated before the study program was initiated and were analyzed in retrospect. Criticism of this aspect of the comparison is certainly valid. However, the results in the small study group subjected to nonsurgical management were strikingly similar to those in the larger prestudy medical treatment group. Moreover, the long-term survival rate was similar to that in a recently reported study of unselected cirrhotic patients.⁵

Finally, the most important criticism of this comparison concerns the number of patients being compared. Although 82 patients were involved in the study program and 127 patients were included in the analysis, the number of patients in each group was insufficient to warrant firm conclusions. The predictions regarding survival must be considered with reservations.

Discussion

It is generally agreed that the portalsystemic anastomosis represents the definitive treatment of portal hypertension and esophageal varices. Numerous studies have shown that a technically satisfactory portacaval shunt will permanently solve the problem of bleeding in the majority of patients. 10, 11, 15, 22, 26 The obvious potential advantage of the emergency shunt is that, unlike other forms of treatment, it can be expected to provide both immediate and prolonged control of varix hemorrhage. However, for many years it has been doubted that patients with cirrhosis could tolerate the performance of an operation of this magnitude under emergency circumstances, in the face of hemorrhage. For this reason, many stop-gap measures have been devised for the temporary control of varix bleeding in the hope that it might be possible to prepare patients deliberately for an elective shunt under stable conditions. Unfortunately, this hope has been realized too infrequently. The first objective of our study, was to determine the capacity of critically ill cirrhotic patients to withstand an immediate shunt operation. This determination was undertaken without expectations that operative treatment would be successful.

The results of the present study indicate that the emergency portacaval shunt was tolerated at least as well as any other form of management. That operation was performed in unselected patients, many of whom had advanced and complicated liver disease, adds meaning to the results. These findings provide support for the recent observations of several other workers which suggest that emergency shunt therapy is worthwhile.

Mikkelsen ¹⁴ performed an emergency portacaval shunt in 37 selected private and indigent cirrhotic patients, 35 of whom were bleeding from varices. The early survival rate was 65%, and the 3-year survival rate in those who were eligible for evaluation was 33%. All 18 patients who were considered to be good risks survived the operation, which led Mikkelsen to the important conclusion that emergency operation was as safe as elective shunt in such patients.

Wantz and Payne ^{25, 26} subjected 34 selected patients with varying types of cirrhosis to emergency portacaval shunt, either as the treatment of first choice or because of failure of response to tamponade. Fifty-nine per cent of the patients survived the operation. Twelve of 13 with mild or moderate liver disease lived. The authors concluded, that in the absence of advanced disease, emergency shunt should be performed without initial attempts at non-operative control of bleeding.

Ekman and Sandblom evaluated emergency portacaval shunt in 30 selected cirrhotic patients who were admitted to their hospital after initial treatment at other institutions. Seventeen patients were operated on because of continuing hemorrhage, and 13 underwent operation two to 21 days

after bleeding had stopped. Eighty per cent of the patients survived the operation and 53% were alive seven months to 8½ years postoperatively. The authors recommended emergency operation in patients who failed to respond to conservative therapy. Similar results and conclusions based on studies in smaller groups of patients have been reported by others. 18, 19, 21, 23, 27 While it is not valid to compare the results of the present study with those of other workers, particularly because of the factor of selection, the survival rates are both similar and encouraging.

The second objective of the present study was to compare the results of emergency portacaval shunt with those of transesophageal varix ligation and nonsurgical treatment. These comparisons had several shortcomings, particularly those resulting from small sample size and nonconcurrent evaluation, so that further studies are clearly necessary. Nevertheless, the superiority of emergency shunt over medical treatment in producing both early and long-term survival appears striking. Moreover, the survival rate following emergency shunt in this study is significantly greater than the survival rates of medical treatment reported by other workers.

The results of emergency shunt appeared to be better than those of varix ligation. The predicted 4-year survival rate following shunt was twice as high as that following ligation. However, the small number of patients in the shunt group who have been observed for 4 years makes the prediction uncertain. At the same time, it seems obvious from the almost identical early survival rates following the two operations that the ligation group will have a lower long-term survival rate than the shunt group. Early survivors of varix ligation must face the risk of an elective portacaval shunt or, if they refuse a second operation, the risk of almost certain recurrent hemorrhage.

The third objective of the present study

was to establish sound criteria for selection of patients for operation. It was hoped that the study of unselected patients, some of whom had far-advanced disease, would clearly demonstrate the contraindications to operative therapy. This hope was not fully realized. While the extremes of the cirrhosis spectrum were easy to identify as contraindications, key selection factors or combinations of factors in patients who were not clearly in the terminal stages of their disease were not obvious. For example, most workers would agree that patients with concurrent encephalopathy, ascites, jaundice and severe muscle wasting have little chance of surviving with any type of treatment and should not undergo operation. All four such patients in this study died. At the same time, 25% of all patients with encephalopathy survived, 48% of all patients with jaundice survived, 43% of patients with a serum bilirubin above 5.5 mg./100 ml. survived and 24% of patients with ascites survived. Unless these abnormalities were present together, there was a definite possibility of surviving the operation and the chances of living were clearly greater with operative therapy than with medical treatment. The presence of unstable ascites or of alkalosis, while not contraindications to operation, appear to be factors which warrant particular attention in evaluating patients for emergency shunt. It is obvious that further studies involving many more patients are necessarv to establish selection criteria.

In recent years, almost all reports of large series of portacaval shunts have described a disturbing frequency of postshunt encephalopathy or hepatic coma.¹⁰, ¹¹, ¹⁵, ²⁰, ²², ²⁶ The incidence has been sufficiently high to raise the question of whether the neurologic disability might not outweigh the benefits derived from protection against hemorrhage. However, the terms encephalopathy and hepatic coma include a variety of ill-defined nervous disturbances most of which have no direct re-

lationship to ammonia intoxication or the shunting of portal blood into the systemic circulation. Rather, they often appear to be a result of hepatic cell failure. While it is possible that the diversion of portal blood from the liver sometimes produces hepatic damage, factors unrelated to the shunt, such as operative trauma, infection, and resumption of alcohol are certainly equally or more important in many cases. Although five of the 21 early survivors in this study developed encephalopathy at some time after operation, in four patients it followed a severe hepatic insult and, in addition, had been present preoperatively. Only one patient developed chronic, shuntrelated encephalopathy that was influenced by protein intake, an incidence of 5%.

Several additional findings of interest resulted from this study. The immediate control of bleeding by Pituitrin therapy in 88% of the patients suggests that this agent can usually be used in place of esophageal balloon tamponade for obtaining initial hemostasis, provided early operation is planned. The abstinence from alcohol practiced by two-thirds of the survivors is a contradiction to the frequent report that most of these patients resume heavy drinking. There is little question that a return to chronic alcoholism is the most important factor influencing long-term survival. The significant improvement in liver function observed in three-fourths of the long-term survivors provides evidence that the portacaval shunt does not usually or necessarily affect hepatic function adversely. Finally, the frequency with which the survivors established an active and productive life following operation suggests that there is much to be gained by an intensive effort to develop effective emergency therapy.

The results of the present investigation lead us to question the well-established concept that nonoperative, nondefinitive treatment of varix hemorrhage provides the opportunity to stabilize and improve the underlying liver disease so that an elec-

tive shunt will be possible. Examination of the mortality rate associated with medical treatment reveals that over three-fourths of the patients died before reaching the point of stability. Analysis of the mechanisms responsible for death shows that rebleeding and infection often precipitated the hepatic failure which ended life. Moreover, ignoring the tremendous risk of dving early, is there evidence that the patient who undergoes an emergency shunt with a restored blood volume and in the absence of pneumonia is less stable than he would be one or two months later? To the contrary, Mikkelsen 14 and Wantz and Payne 26 reported identical mortality rates following emergency and elective shunt operations in patients with moderate liver disease. The mortality rates in patients with advanced cirrhosis are high under both emergency and elective circumstances. The results of the present study can only be interpreted as indicating that early and definitive control of bleeding profoundly influenced survival. While further experience is necessarv to draw firm conclusions, it would appear that emergency portacaval shunt is the most effective measure available for the treatment of bleeding esophageal varices.

Summary

A prospective study of emergency treatment of bleeding esophageal varices in unselected patients with cirrhosis has been conducted. Forty unselected, adult patients with moderate to advanced alcoholic cirrhosis and bleeding varices were subjected to an emergency portacaval shunt within 8 hours of admission to the hospital. Fiftyeight per cent had clinical jaundice, 43% had ascites and 20% had encephalopathy at the time of admission. Almost all patients had severe hepatic dysfunction and hypokalemic alkalosis was present in onehalf of the subjects in whom blood gases and pH were measured. Intravenous posterior pituitary extract temporarily controlled the bleeding preoperatively in 88% of the group.

Every patient had portal hypertension. Fifteen had an end-to-side portacaval anastomosis and 25 had a side-to-side shunt, both of which reduced the portal pressure markedly and controlled the bleeding in every case. Postoperatively, 58% developed hepatic coma, 45% had delerium tremens, 83% had alkalosis, and 20% developed a peptic ulcer.

Twenty-one of the 40 patients recovered from operation, an early survival rate of 53%. Three-fourths of the postoperative deaths were due to hepatic failure. Except for one patient who has been observed for just short of a year, the survivors have been followed for from 13 to 50 months. Seventeen are still alive and the predicted 4-year survival rate calculated by the lifetable method is 43%. Liver function has improved significantly in 73% of the survivors and most have established active and useful lives. Two-thirds of the survivors have abstained from alcohol.

Analysis of potentially influential preoperative and operative factors showed that only the presence of unstable ascites and of hypokalemic alkalosis affected the outcome. Survival of significant numbers of patients with one or another of the serious manifestations of cirrhosis suggested that, except for obviously decompensated cirrhosis with concurrent jaundice, ascites and encephalopathy, there are no clear contraindications to operation.

Results of emergency portacaval shunt have been compared with those obtained in our previous prospective studies of medical treatment and of varix ligation. In comparable patients, both forms of operative therapy produced an early survival rate which was 3 times greater than that resulting from medical management. The four-year survival rate after emergency shunt was significantly greater than the survival rate with the other types of treatment.

Results of this study suggest that early and definitive operative control of varix hemorrhage provides the cirrhotic patient with the greatest chance of surviving. Although studies involving larger numbers of patients are clearly necessary, it would appear that the emergency portacaval shunt is the therapy of choice for most cirrhotic patients who bleed from esophageal varices.

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