Effect of Portacaval Anastomosis on Hypersplenism

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Leukopenia, thrombocytopenia, and hemolytic anemia occur commonly in advanced cirrhosis. Some investigators have reported that portacaval anastomosis (PCA) abolishes hypersplenism while others have not found PCA to be uniformly beneficial. We compared the frequency of hypersplenism before and after admission to a controlled investigation of the effects of PCA in 52 unoperated control subjects and 38 patients with patent PCA. The two groups were followed for an average period of 5½ years. On admission to the study leukopenia was present in about 2% of patients, thrombocytopenia in 6%, and hemolytic anemia in 4%. Splenomegaly was present in 48% and hypersplenism in 11%. After randomization splenomegaly disappeared more frequently in the shunted group. In addition, fewer patients with PCA developed splenomegaly for the first time after inclusion into the study than did unoperated control subjects. Leukopenia, thrombocytopenia, and hemolytic anemia, when present at inclusion into the study, disappeared with equal frequency in the shunted and unshunted patients, and appeared with equal frequency in both groups after randomization in previously unaffected patients. In no instance was hypersplenism clinically significant nor was splenectomy considered or carried out in any of these 90 patients. In additional uncontrolled studies we observed that therapeutic PCA did not affect hypersplenism differently from prophylactic PCA. We conclude that PCA has neither clinically nor statistically significant effects on hypersplenism.

Cirrhosis is frequently associated with leukopenia, thrombocytopenia, and hemolytic anemia, which are common manifestations of hypersplenism (1–9) (Table 1). Portacaval anastomosis (PCA), which reduces portal pressure, has been claimed by some authors to correct these hematologic abnormalities (10–14). Other investigators, however, have found the hematologic response to portacaval anastomosis to be ineffective, inconsistent, or transient (4–6, 15–17). Occasionally, hypersplenism has appeared or progressed after PCA (18). To date, there has been only one controlled investigation which has evaluated the effect of PCA on hypersplenism (7). In that report PCA was associated with the improvement of the hematologic abnormalities.

In the present study, the records of patients included in two randomized, controlled clinical trials of prophylactic PCA were reviewed (19). We compared the presence, type, and severity of hypersplenism in cirrhotic patients who were randomly selected to have PCA or to be unoperated control patients. Previous reports on the incidence of various "complications" of PCA have been published using a similar format based on these controlled investigations (20–22).

MATERIALS AND METHODS

All patients studied had been admitted to the West Haven Veterans Administration Hospital between July 1, 1958, and March 1, 1973. Inclusion in the two prophylac-

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TABLE 1. FREQUENCY OF HYPERSPLENISM IN CIRRHOSIS

Senior author and reference		*Year*	*No. patients with cirrhosis*	*Number (and percentage) of Patients*			
				Splenomegaly	*Hypersplenism*	*Leukopenia*	*Thrombocytopenia*
King	(1)	1929	72				14 (19%)
Morlock	(2)	1943	80				14 (18%)
Berman	(3)	1949	25	12 (36%)		5 (25%)	5 (25%)
McDermott	(4)	1961	237			47 (20%)	
Rousellot	(5)	1963	104				15 (14%)
Burchell	(6)	1968	63				7 (11%)
Felix	(7)	1974	277	189 (68%)	41 (15%)		
Buligesco	(8)	1975	172	158 (92%)	121 (70%)		
Hutson	(9)	1977	66		24 (36%)	23 (35%)	13 (20%)
Mutchnick*		1980	90	53 (59%)	21 (23%)	10 (11%)	13 (14%)
Total			1186	412/564 (73%)	207/605 (34%)	85/418 (20%)	81/500 (16%)

*Present study.

tic shunt studies required a histologic diagnosis of cirrhosis, an endoscopic diagnosis of esophageal varices, no prior hemorrhage from varices, the presence of overt ascites in the second study, but not in the first, portal venous pressure in excess of 200 mm H_2O in the first and in excess of 250 mm H_2O above the level of the portal vein in the second, and that the patients be considered reasonable risks for elective surgery.

During the 15-year period of investigation in which the two prophylactic shunt studies were carried out, 189 cirrhotic patients were considered for admission to these studies. Seventy-one were excluded for a variety of reasons and 118 were randomized. Sixty were randomly selected to be unoperated control subjects and 58 to have prophylactic PCA. In the former group five patients bled from esophageal varices and had therapeutic PCA within the first year after admission to the study. These five patients were exluded from the current investigation. Fifty-two of these 55 patients had serial hematologic examinations and comprise the *control group*.

Among the 58 patients randomized to have PCA, eight refused surgery, four died shortly after surgery, one had unsuccessful surgery, and five were subsequently found to have thrombosis of the shunt. Thirty-eight of the 40 with patent PCA had serial hematologic examinations and comprise the *prophylactic shunt group*. During this same period an additional 39 cirrhotic patients bled from esophageal varices and had therapeutic PCA which were subsequently shown to be patent. These patients all had serial hematologic studies and comprise the *therapeutic shunt group*. The therapeutic shunt group is included as a clinically relevant reference group. Statistical analyses, however, are limited to the two randomized groups.

Virtually all patients in the investigation were seen in the Liver Out-patient Clinic by members of the Liver Research Laboratory staff. They were seen at three-month intervals or as often as was indicated clinically and were admitted annually for more complete evaluation. As indicated previously, the great majority of these patients had alcoholic cirrhosis, but there was no significant difference in alcohol consumption during the follow-up period between the control and prophylactic PCA group (19).

At the time of the annual evaluation the following routine laboratory tests were performed: hematocrit, white blood cell count, platelet count, blood smear for morphology of erythrocytes and differential analysis of leukocytes and, usually, the hemoglobin concentration and reticulocytes. A conventional battery of "liver function" tests and the concentrations of BUN, glucose, serum electrolytes, iron and iron-binding capacity, and blood ammonia were also measured. The physical findings, including the presence or absence of a palpable spleen were recorded. Examinations for palpability of spleen were done by two investigators independently. ^{99m}TC-sulfur colloid scans were performed when ascites, obesity or other factors interfered with the physical examination.

Patients were classified as having anemia, leukopenia, thrombocytopenia, and/or hypersplenism. Measurements made during admission for hemorrhage, infection, or other disorders that might affect the hematologic values were excluded. Anemia was defined as a hematocrit of <36% and was classified as hemolytic, iron deficiency-blood loss, macrocytic-dietary deficiency, or "other." Hemolytic anemia was defined as chronic normocytic anemia associated with reticulocytosis and erythroid hyperplasia of the bone marrow and confirmed by shortened red cell survival (^{51}Cr-labeled erythrocytes half-life <25 days). Leukopenia was defined as <4000 leukocytes/mm^3. Thrombocytopenia was defined as <100,000 platelets/mm^3. Hypersplenism was defined as the presence of splenomegaly plus leukopenia, thrombocytopenia, or hemolytic anemia of unknown cause or any combination thereof. Splenomegaly was defined as a palpable spleen and/or extension of the spleen below the costal margin on anterior and left lateral liver-spleen colloid scans.

Data were analyzed at the time of admission to the studies and annually thereafter during the follow-up period, which was 54.7 ± 7 months in the control group, 54.5 ± 7 months in the prophylactic shunt group, and 59.9 ± 7 months in the therapeutic shunt group. The number of patients available for study at annual intervals progressively declined due to death or loss to follow-up. At two years the data are based on approximately half and at five years on one fourth of the original groups. Statistical

TABLE 2. CLINICAL FEATURES AT TIME OF ADMISSION TO STUDY

Groups	*No. of patients*	*Age (years)*	*Duration of cirrhosis (months)*	*Endoscopic magnitude of esophageal varices (1+ to 4+)*	*Radiologic presence of varices (%)*	*Portal venous pressure (mm H_2O)*
Control	52	47	29	2.2+	60	347
Prophylactic shunt	38	49	18	2.2+	66	332
Therapeutic shunt	39	50	32	2.6+	87	387

techniques used in these investigations were Student's *t* test, paired and unpaired, χ^2 tests, and *t* tests for proportions. The patients in the prophylactic shunt investigations, which accepted patients from 1958 to 1973, gave informed consent for randomization into this study and for follow-up studies. Hematologic measurements were made using standard clinical laboratory methods.

RESULTS

At the time of inclusion in the study, the control and prophylactic shunt groups were similar in age; in the type, severity, and duration of cirrhosis; and in the clinical and laboratory manifestations of cirrhosis and portal hypertension (Tables 2 and 3). The only statistically significant difference between the randomized groups was the higher serum albumin concentration in the prophylactic shunt group. The explanation for this difference is not known. Hematologically, the control and prophylactic shunt groups were similar at that time (Table 4). In addition, the cumulative survival curve was similar for the two groups (Figure 1).

During the average period of follow-up of $4^1/_2$ years, there was no significant difference in the prevalence of hypersplenism in the two groups. Hemolytic anemia, which had been present at accession in four patients in the control group (8%), disappeared in all four (Figure 2). Hemolytic anemia appeared during the follow-up period in two additional patients. It had not been present at randomization in any patients in the prophylactic shunt group, but appeared in three patients after PCA. None of these differences is statistically significant. In the therapeutic shunt group one patient (3%) had hemolytic anemia at inclusion. It persisted after PCA in this patient and developed in seven additional patients (18%).

Leukopenia, which had been present in one patient in the control group at the time of inclusion (2%), disappeared during follow-up (Figure 2). It appeared in eight additional patients during the period of follow-up (16%). Leukopenia had been present in one patient in the prophylactic shunt group (3%) and disappeared after shunt surgery in this patient. It appeared in four additional patients after PCA. None of these differences is statistically significant. In the therapeutic shunt group leukopenia was present at inclusion in two patients (5%). It disappeared after PCA in both, but appeared in four other patients thereafter (11%).

Thrombocytopenia, which was present in two patients in the control group at the time of randomization (4%), disappeared in both (Figure 2). It appeared in six additional patients (12%). In the prophylactic shunt group thrombocytopenia was present at randomization in three patients (8%). It disappeared in two and persisted in one. It subsequently developed in six additional patients

TABLE 3. MEAN LIVER FUNCTION TESTS AT TIME OF INCLUSION IN STUDY

Group	*Total serum bilirubin (mg/100 ml)*	*Thymol turbidity (MacLagan U)*	*Serum alkaline phosphatase (Bodansky U)*	*Serum GOT (RF U)*	*Serum albumin (g/100 ml)*	*Serum globulin (g/100 ml)*	*Prothrombin time (%)*
Control	1.5	3.9	5.2	45	2.8	4.3	79
Prophylactic shunt	1.3	3.9	4.8	38	3.1*	4.2	82
Therapeutic shunt	1.9	3.2	4.9	34	2.8	3.9	68

*$P < 0.01$ (mean between Control and Prophylactic shunt groups).

TABLE 4. HEMATOLOGIC FINDINGS AT ADMISSION TO STUDY

Group	No.	Hematocrit (%)	RBC ($\times 10^6$/mm^3)	Hemoglobin (g/100 ml)	Reticulocytes (%)	WBC ($\times 10^3$/mm^3)	Platelets ($\times 10^5$ mm^3)	Serum iron (μg/100 ml)	Iron-binding capacity (μg/100 ml)	Direct serum bilirubin (mg/100 ml)	Indirect serum bilirubin (mg/100 ml)	Granulocytes (%)
Control	52	38.7	3.6	11.4	2.1	7.7	2.1	102	303	0.8	0.8	65
Prophylactic shunt	38	39.4	3.7	12.1	2.1	7.1	1.8	96	305	0.5*	0.7	65
Therapeutic shunt	39	33.4	3.7	11.1	1.8	8.2	1.9	117	397	0.8	1.1	69

*$P < 0.05$ (mean between Control and Prophylactic shunt groups).

(16%). None of these differences is statistically significant. In the therapeutic shunt group one patient (3%) had thrombocytopenia at inclusion. It persisted after PCA in this patient and developed in three additional patients (7%). The times of appearance of hemolytic anemia, leukopenia, or thrombocytopenia in the control and prophylactic shunt groups are shown in Figure 3.

Splenomegaly, which was present in 23 patients in the control group (48%) at randomization, disappeared in 8 patients during follow-up (Figure 4). Splenomegaly appeared in 10 additional patients, 34% of those at risk. Splenomegaly, which was present in 20 of the patients in the prophylactic shunt group at randomization (53%), disappeared in 8 of them. After PCA splenomegaly appeared in two of the patients at risk (11%). Splenomegaly disappeared with about equal frequency in the two groups, but previously undetected splenomegaly appeared more frequently in the control than in the prophylactic shunt group. This difference did not quite achieve statistical significance ($P < 0.07$). In the therapeutic shunt group splenomegaly was present in 18 patients (46%) at inclusion. After PCA it disappeared in 7 of them, but persisted in 11. Splenomegaly appeared after PCA in 5 additional patients.

Hypersplenism, which was present in 5 patients in the control group at randomization, disappeared in all 5 afterward (Figure 4). It appeared in 11 other patients during follow-up (21%). In the prophylactic shunt group hypersplenism was present at randomization in five patients and disappeared in four of them. It appeared in nine additional patients during follow-up (24%). None of these differences is statistically significant. In the therapeutic shunt group

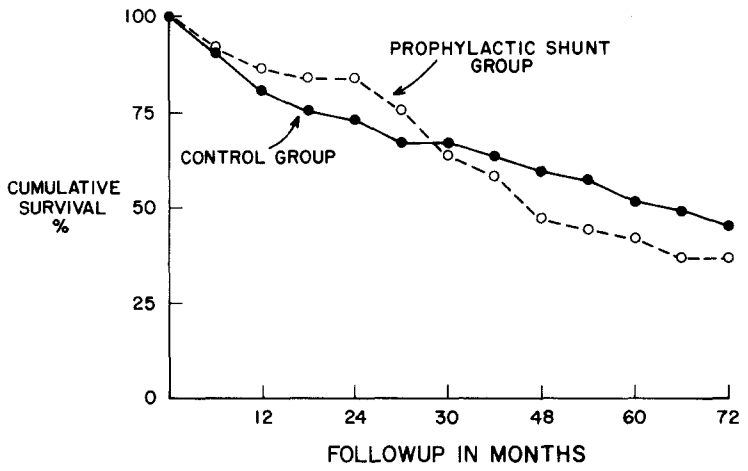

Fig 1. Cumulative survival in control and prophylactic shunt groups. Cumulative survival is plotted for the 52 patients in the control group (solid circles and solid line) and the 38 patients in the prophylactic shunt group (open circles and dashed line). There are no statistically significant differences in cumulative survival.

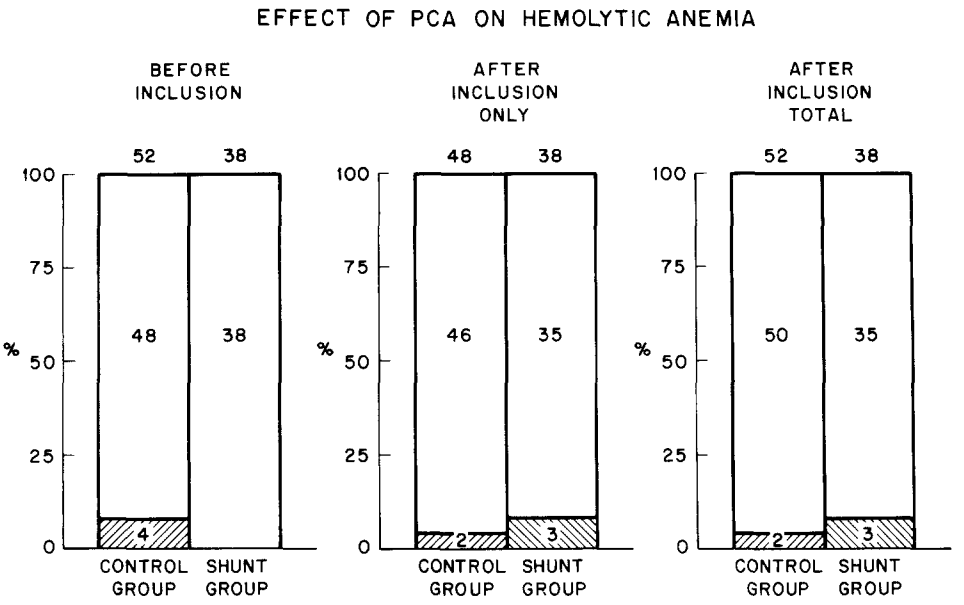

Fig 2a. Effect of portacaval anastomosis on hemolytic anemia. The bars on the left of each pair depict the 52 patients in the control group and the bars on the right the 38 patients in the prophylactic shunt group. Cross-hatched areas indicate the percentage of patients with the hematologic abnormality and the clear portion of the percentage of patients without the abnormality. The numbers indicate the number of patients. The pair of bars on the left compares the groups at the time of admission to the study. The pair of bars in the center indicates the development of hemolytic anemia in patients who did not have hemolytic anemia at the time of admission. The pair of bars on the right shows the overall prevalence of hemolytic anemia after admission, including those patients in whom hemolytic anemia that was present before randomization persisted plus those patients in whom hemolytic anemia developed *de novo* after randomization. None of the differences between the control and prophylactic shunt groups is statistically significant.

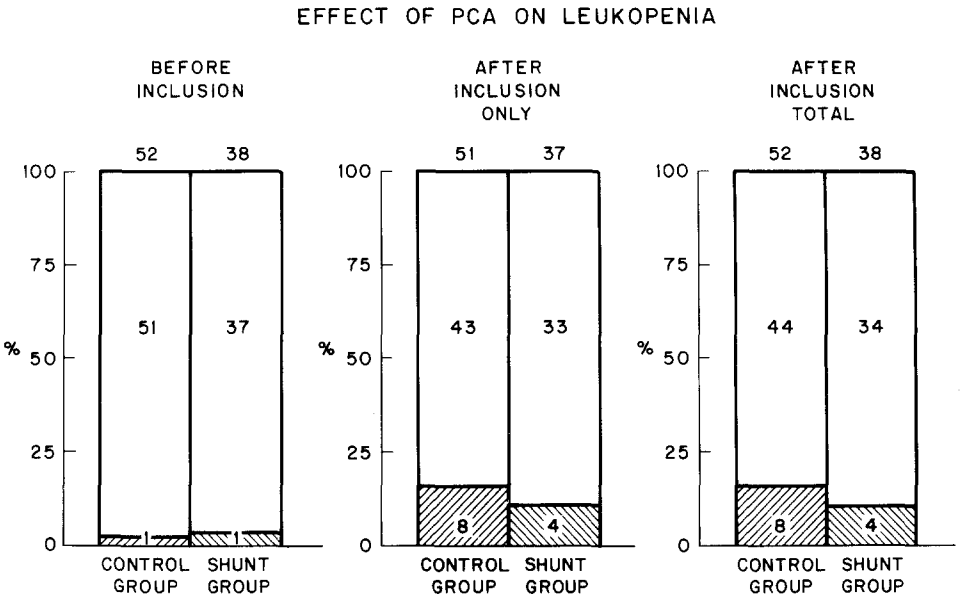

Fig 2b. Effect of portacaval anastomosis on leukopenia. None of the differences between the control and prophylactic shunt groups is statistically significant.

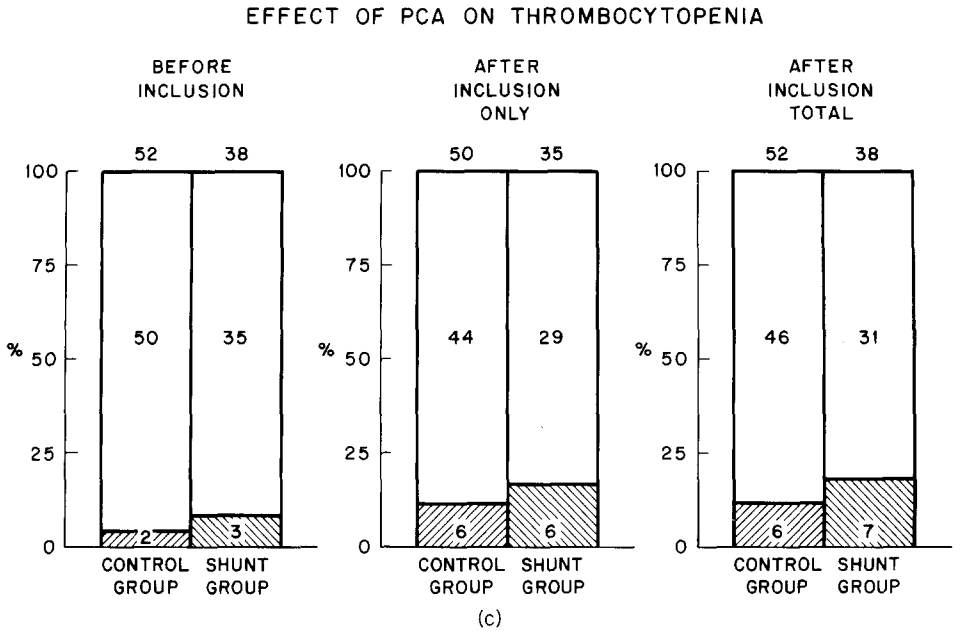

Fig 2c. The effect of hemolytic anemia on thrombocytopenia. None of the differences is statistically significant.

hypersplenism was present in two patients (5%) at inclusion. It disappeared after PCA in one and persisted in the other. Hypersplenism appeared in 8 additional patients subsequently (22%). The patterns observed in the therapeutic shunt group were qualitatively and quantitatively similar to those in the prophylactic shunt group.

The mean values for the hematocrit, white blood cell count, and platelet count in the 6-year period following randomization are shown in Figure 5. The mean hematocrit values tended to increase during the period of follow-up in both the control and prophylactic shunt groups, but at no time are the differences between the groups significant statistically. The mean WBC and platelet counts in the two groups remained relatively constant throughout the period of observation, and none of the differences between the control and prophylactic shunt groups is statistically significant.

The mean total and unconjugated serum bilirubin levels, serum iron concentration, iron-binding capacity, and reticulocyte counts remained relatively constant and were not significantly different in the control and prophylactic shunt groups throughout the period of follow-up.

DISCUSSION

Hypersplenism is a common manifestation of portal hypertension. It was found in 11% of cirrhotic patients with esophageal varices at the time of inclusion in two investigations of prophylactic PCA. Hypersplenism in these patients was not significantly affected by the creation of a PCA. The hematologic abnormalities disappeared with about equal frequency in the patients with and without PCA. Furthermore, about 10% of patients who had not previously had hypersplenism developed hemo-

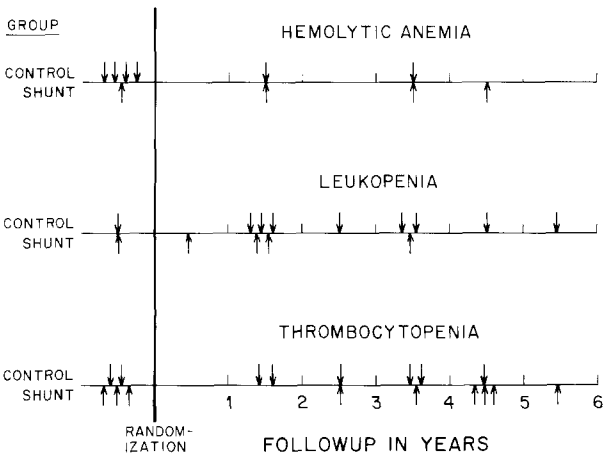

Fig 3. Time of appearance of hypersplenism. Top, hemolytic anemia. Each case of hemolytic anemia is represented by an arrow which indicates the approximate time at which hemolytic anemia was first noted. The control group is depicted by arrows above the time line and the prophylactic shunt group by arrows below the time line. Middle, leukopenia. Bottom, thrombocytopenia. The time of appearance is similar for the control and prophylactic shunt groups for each type of hypersplenism.

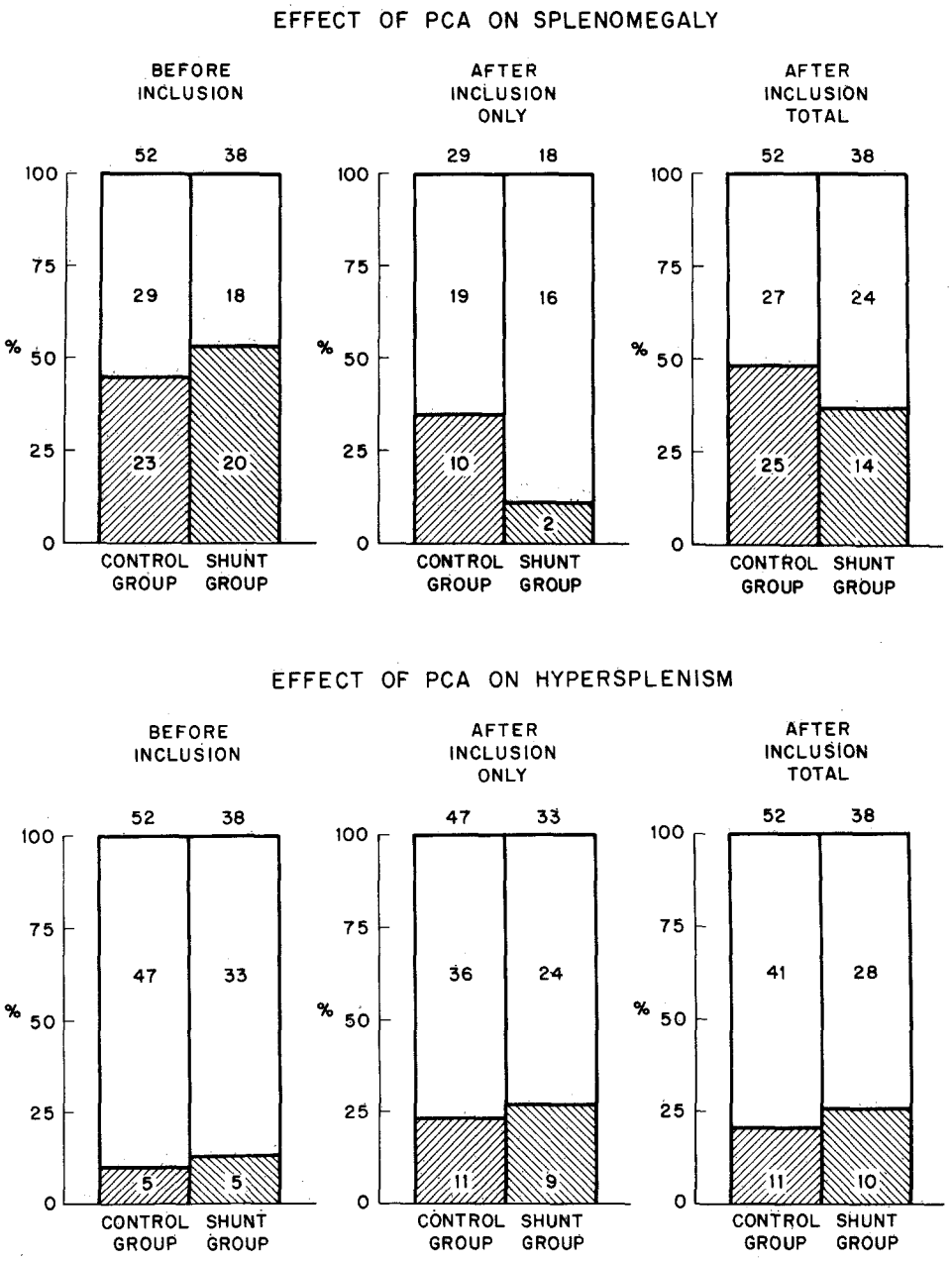

Fig 4. Effect of portacaval anastomosis on splenomegaly and hypersplenism. The figure is organized in the same manner as Figure 2. Top, splenomegaly. Bottom, hypersplenism. Although splenomegaly developed less frequently after inclusion in the prophylactic shunt group than in the control group, this difference is not statistically significant.

lytic anemia, leukopenia, and/or thrombocytopenia during a period of prolonged follow-up whether or not the patients had had a PCA.

These findings are at variance with the only other controlled investigation of PCA in which hypersplenism was monitored. Felix and his associates found that 38 of their 277 randomized patients (14%) had hypersplenism at the time of accession (7). They presented data on 35 of these 38 patients who survived for one year. Unfortunately, they supplied no information about the 239 patients who had not had hypersplenism before randomization. Furthermore, they presented data about these 35 patients for only their first year in the study.

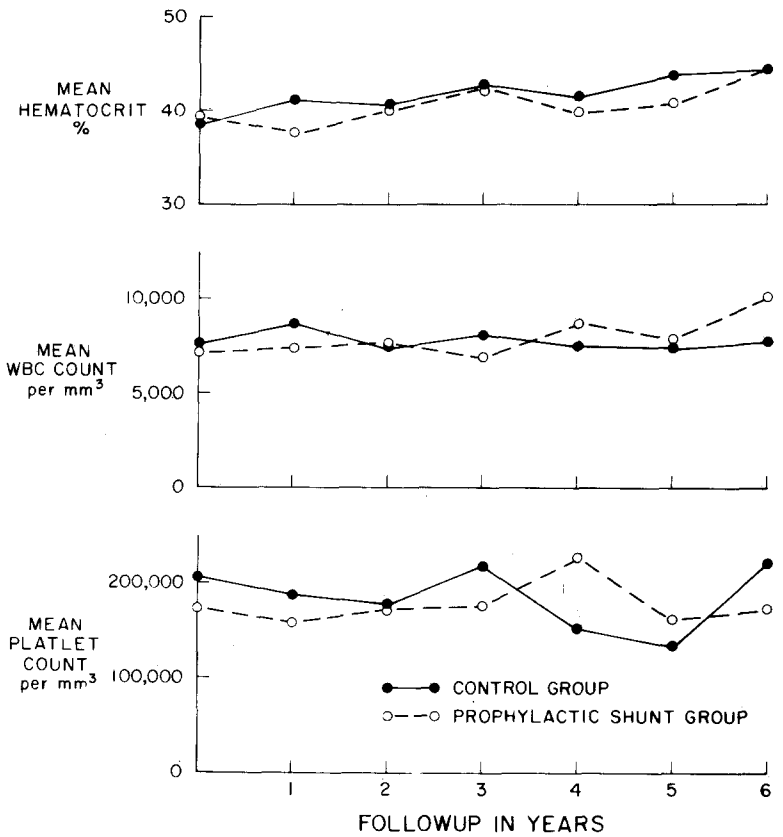

Fig 5. Mean values of hematocrit, white blood cell count, and platelet count in control and prophylactic shunt groups. Top, hematocrit. Mean hematocrit levels, which tended to increase over the period of follow-up, do not differ significantly in the two groups. Middle, leukocytes. The mean number of WBC remains constant in both groups. Bottom, platelets. The mean platelet counts, which remain relatively constant in the two groups, do not differ significantly from each other.

A comparative tabulation of their data and ours is shown in Table 5. They found that splenomegaly, leukopenia, and thrombocytopenia persisted or tended to increase in the unshunted control group. In almost half of the shunted patients, however, splenomegaly disappeared and leukopenia and thrombocytopenia reverted to normal.

Our study, too, showed that the prevalence of splenomegaly, leukopenia, and thrombocytopenia increased during the follow-up period in the control group. In the shunted patients with hypersplenism, splenomegaly, leukopenia, and thrombocytopenia frequently disappeared, but leukopenia and thrombocytopenia often appeared in others, sometimes several years after the shunt had been constructed.

Comparison of these two investigations may not be valid. More than half the patients in the VA Cooperative Study (7) had therapeutic PCA after surviving hemorrhage from varices. Such patients have more severe portal hypertension and a much worse prognosis than those who have not yet bled from varices (23), such as those we studied with prophylactic PCA. Buligesco et al have suggested that hypersplenism may be a late manifestation of portal hypertension (8). Perhaps hypersplenism in patients with more advanced cirrhosis responds differently to PCA than it does in patients with earlier cirrhosis. The fact that we observed similar results in our patients with both prophylactic and therapeutic PCA makes this explanation less likely. Our finding of a higher prevalence of hypersplenism and of the delayed appearance of hypersplenism in patients with PCA reflects in part our longer follow-up (up to six years) compared to theirs (one year).

Another possible explanation for the difference in our results and those of Felix et al may be found in the studies of Schreiber (15). He studied 60 cirrhotic

TABLE 5. COMPARISON OF DATA OF FELIX ET AL (7) AND MUTCHNICK ET AL

Group	*Splenomegaly*			*Leukopenia*			*Thrombocytopenia*		
	No. of patients	*No. on inclusion*	*No. at one year*	*No. of patients*	*No. on inclusion*	*No. at one year*	*No. of patients*	*No. on inclusion*	*No. at one year*
Felix et al (7)									
Control	17	14	16	17	14	15	7	6	7
Shunt	18	18	11	18	17	9	9	9	4
Mutchnick et al									
Control	52	23	25	52	1	8	52	2	6
Shunt	38	20	14	38	1	3	38	3	7

patients with portal hypertension and esophageal varices who underwent therapeutic PCA. A large majority of these patients (79%) had evidence of hypersplenism. Creation of a PCA usually resulted in an immediate but transient increase in the concentrations of the formed elements of the blood. Mean numbers of leukocytes, platelets, and reticulocytes increased within minutes after the shunt was opened and often reached peak levels within two hours. Leukopenia, which was present in 78% of the patients before the shunt, was rarely found two days afterward and was uncommon for the first two weeks after shunt surgery. By one month postoperatively, however, the percentage of patients with leukopenia had returned to preoperative levels. From two to five years post-PCA, the percentage of patients with leukopenia was greater than before shunt surgery. The percentage of patients with thrombocytopenia was the same postoperatively as preoperatively from one month onward, although the number of patients studied was too small for meaningful measurements. The changes in the erythrocytes were not so overt. In a group of 18 patients in whom serial measurements were made, the number of reticulocytes increased dramatically after PCA. The mean percentage of reticulocytes was twice as high one month postoperatively as it had been preoperatively, but by two years postoperatively it had returned to baseline levels. The change in reticulocytes was not accompanied by compatible changes in red cell counts or in hemoglobin concentration. Splenomegaly disappeared in over 90% of the patients after the shunt and did not recur. None of these changes was still evident a year or more after PCA, except for the reduced spleen size.

Schreiber's data show, as do ours, that the overall prevalence of hypersplenism or its component syndromes is not decreased from preoperative levels by PCA. Furthermore, they demonstrated that a decrease in the formed elements of the blood persists for only several weeks or months. Conceivably, the improvement in hypersplenism reported by Felix et al may represent this transient phenomenon.

Finally, our data show that in the cirrhotic patients we studied, ie, candidates for prophylactic PCA, hypersplenism is neither a frequent nor a serious problem. In none of the patients in our controlled clinical trials was hypersplenism clinically significant. No leukopenic patient developed recurrent bacterial infections or required prophylactic antibiotic therapy to prevent such infections. No thrombocytopenic patient exhibited spontaneous bleeding that could be attributed to decreased numbers of platelets. No patient had hemolysis severe enough to require transfusions. In no patient was splenectomy seriously considered to correct hypersplenism. In fact, the only patient who had clinically significant hypersplenism was a patient who developed acute hemolytic anemia immediately after a therapeutic PCA and who required splenectomy to control the hemolysis.

It seems clear that PCA does decrease portal hypertension and splenic size. One would expect, therefore, that hypersplenism would be improved by PCA. Indeed, a number of anecdotal observations show correction of hypersplenism after this operation (10–14). Our controlled investigation of prophylactic PCA, however, fails to confirm this expectation.

The present investigation, in which patients are randomly allocated to treatment and control groups, like previous studies of the effect of PCA on peptic ulcer (20), portal-systemic encephalopathy (21), and hemosiderosis (22), demonstrates the necessity for a randomly selected control group in assessing the complications or benefits of therapeutic measures.

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