At the present time there is no evidence in this study that the incidence of peptic ulceration in shunted patients is significantly greater than in the medically treated controls.

Hypersplenism does not appear to affect survival among the patient groups studied. Although the mortality (55%) was high, it was evenly distributed. Cytopenia and splenomegaly can improve after shunting operation.

In conclusion, it is deduced from this controlled and randomized study of a selected group of 155 bleeding cirrhotic patients that portacaval shunts are the recommended therapy.

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Discussion

Dr. Charles Gardner Child (Ann Arbor): I support Dr. Jackson's evidence that portal decompression is a good operation for patients with cirrhosis of the liver whose survival is threatened by recurring variceal hemorrhage.

I also wish to make a plea, a plea which I have made many times before to national audi-

ences. Before we can achieve any kind of equanimity in reporting our results of portal decompression, we must define precisely the kinds of patients we are talking about as well as the kind of operation that has been performed upon them.

If you will bear with me, I would first like to emphasize that before we can talk about postoperative mortality in patients with cirrhosis we should define as accurately as possible their degree of hepatic functional reserve.

In this slide is displayed the first 3 months postoperative mortality amongst 143 patients with cirrhosis of the liver subjected to portal decompression for massive hemorrhage. These are then broken down into good risks (A), intermediate risks (B) and poor risks (C). The marked difference in postoperative mortality is obvious. Talking about these patients as a group is not satisfactory; we should be specific and indicate which group is under discussion.

Here is a slide in which this same population of patients is viewed in terms of survival. Again, it is obvious that the good risk patients live longer after portal decompression than do those in the intermediate and poor risk groups.

To me, and I hope to you, there is still something missing from these two sets of data—I have not told you what kind of operation was done on these patients. Look now at these same patients in terms of two different operations, the end-to-side portacaval shunt and the side-to-side shunt.

In the next slide are compared these two operations in good risk patients (group A). There is no significant difference in survival. Among patients of intermediate risk slide we begin to see evidence of a difference in survival at the end of 4 years. We are not yet sure of the statistical significance between these two operations in intermediate risks but have begun to suspect that the less the hepatic reserve the better is the side-to-side portacaval shunt.

My final slide is discouraging but there is now a statistically significant difference between the end-to-side and side-to-side shunt in poor risk (class C) patients with little hepatic reserve. We are now convinced that the poor risk patient should have both his liver and his splanchic bed decompressed.

In conclusion, I am convinced as is Dr. Jackson that there is a very real salvage by portal decompression in patients with portal hypertension and bleeding varices. I am also sure, however, that if we are going to achieve valid comparisons from hospital to hospital we must define more precisely than is now the custom the degree of hepatic dysfunction manifested by our patients and the kind of operations we are performing upon them. You will have observed, I am sure, that I have not mentioned hepatic encephalopathy. The reason for omitting this third variable of portal decompression is not complicated; we are not yet able to discuss this entity in terms of statistically significant figures.

Dr. Clarence Dennis (Brooklyn): I wish to express my thanks to Dr. Jackson and his associates for the privilege of reading the manuscript prior to the presentation of this rather superb study. I rise simply to offer information which might have helped the 49% of all dying patients who died in coma.

Specifically, I want to report the work of my colleague, Dr. Roland Janis Adamsons, in Brooklyn. [Slide] He has attempted to evaluate the thesis that decompression of the portal system should be possible without altering the hemodynamic relationships within the liver. In order to accomplish this end, he has performed a standard end-to-side portacaval shunt and added to it a side-to-end anastomosis of the gastroepiploic artery to the reopened umbilical vein, which, of course, empties into the left branch of the portal vein.

Performance of such a pair of anastomoses is appropriate only if there is a distinct drop in pressure in the portal vein on the hepatic side of a temporarily occluding clamp. The gastroepiploic artery was chosen after some study because it provides a flow sufficient to maintain the sinusoidal pressure at the level to which the liver has already accommodated, without the high elevations which have been shown by others to be so damaging after arterialization of the hepatic stump of the portal vein.

Of the 11 patients who have had this procedure, four were performed for massive hemorrhage after failure of conservative care, and seven for elective indications. [Slide] Of these seven, one had had a previous end-to-side shunt, but was suffering from encephalopathy. Both the encephalopathy and the ammonia tolerance tests have shown improvement, as indicated on this slide. The response to a 50 gm. protein meal shown by this slide before and after the arteriovenous shunt is representative of the entire series.

The remaining patients—six in number—had previously suffered massive bleeding, controlled without operation. There has been no operative or postoperative mortality in the first ninety days. There has been no postoperative encephalopathy, save in one patient whose shunt was demonstrated to become occluded 3 months after operation. He developed encephalopathy within 2 weeks of occlusion of the arteriovenous shunt, and died in coma within two months.

Wedge pressures are routinely determined in the hepatic vein before and after operation. Dr. Adamsons has been remarkably successful, in that the mean of the postoperative pressures is within 2 cm. of water of the mean of the preoperative pressures. Flow data indicate that this procedure can maintain total hepatic blood flow and sinusoidal pressure at preshunt levels.

The postoperative course has been smooth in all eleven patients, and no patient is suffering from ascites or encephalopathy on unrestricted protein intake.

Apparently this procedure is efficacious in avoiding at least some of the undesirable metabolic sequelae of the standard portal decompression.

Dr. Ronald A. Malt (Boston): The enormous amount of data in the complete manuscript, and the objectivity with which Dr. Jackson and his

colleagues have analyzed it sets a new standard in this area, and I am afraid that the rest of us who are interested in portal hypertension are going to have to work a lot harder just to try to keep up with it.

The results of even a smaller number of patients [slide] entered in the randomized prospective Boston interhospital liver group study, under the direction of Frank L. Iber, offer confirmation of some of the data that Dr. Jackson has presented; although there was no difference in the medically treated and the surgically treated patients to start with, after 3½ years there is a 56% survival in patients with end-to-side anastomoses versus a 20% survival in those who were medically treated. The difference is significant at the 0.05 probability level.

In contradistinction the side-to-side data at the end of 3½ years are not different from those of the control group, thus confirming our clinical impression at the Massachusetts General Hospital that patients in general do better with an end-to-side rather than with a side-to-side portacaval.

I have one question that perhaps Dr. Jackson's data might help to answer. Since there are inevitably a certain number of patients with bleeding gastritis who will be included in the therapeutic group because of our inability to distinguish between bleeding gastritis and bleeding varices preoperatively, is there any indication that lowering the portal pressure will also reduce the bleeding from gastritis?

DR. W. DEAN WARREN (Miami): I had not intended to discuss this paper, but it raised several important points, and I would like to comment briefly and ask a question.

First, it pointed out the danger of portacaval shunt therapy as a combination of immediate mortality, which in itself is quite significant, and what we refer to as delayed hepatic death. This can occur any time from a few weeks to a few years after the shunt is completed.

As you know, we have devised a new procedure in Miami in an attempt to offset this hepatic deterioration. This operation is a selective distal splenorenal shunt, and I would just like to point out at this time that we have twenty-three patients who have been followed for up to 4½ years, and have had only one questionable case of encephalopathy. This was drug-induced and cleared immediately in that period of time. We brought this patient into the hospital for restudy about 4 years after operation. Immediately postoperation she had had an hepatopetal flow in the superior mesenteric and portal veins, with portal venous blood perfusing the liver. At the time of restudy subsequent to a morphine-induced, transient encephalopathy, she was found to have reversed her portal flows, that it had become hepatofugal.

We knew that this would happen sooner or later because it happens in nonshunted patients; it's just a question of how often, and we don't at this time have an answer. However, the incidence of encephalopathy has apparently been greatly lowered by the use of selective distal splenorenal shunt, with maintenance of portal venous flow to the liver.

Postprandially, portal venous blood can carry as much as eight times the concentration of nitrogenous materials (which are implicated in the precipitation of true portal systemic encephalopathy) as will arterial blood, so I don't think a simple arterialization is going to be the final answer.

Finally, there is an interesting feature of Dr. Jackson's study that he did not comment on. That is the difference between the prophylactic shunt series and the therapeutic shunt series. Although on obvious answer for the better results in the surgical group in the therapeutic series is higher incidence of rebleeding in the control group. However, there was an increased postoperative survival in the therapeutic shunt group as compared to their data with prophylactic shunts.

I would like to ask him if he thinks this is a factor of selection, based on survival of a hemorrhage, or could it be related to an old theory of ours. That is, sudden complete portal diversion in a patient with good portal venous flow to the liver preoperatively will cause a greater change than seen in the patient who has very little portal flow to be diverted.

A Class A patient, for instance, seems to deteriorate to a more severe degree if he has lost a large amount of portal flow from the liver.

DR. EDWARD B. PERRIN (Closing): As biometrician for this study, I am always pleased to be able to discuss matters of the design of clinical trials and the analysis of such trials with my surgical and medical colleagues. I especially appreciate the privilege extended to me today in allowing me to speak.

I have, briefly, just a couple of points I want to emphasize with respect to the study just presented. As Dr. Jackson mentioned, there are two kinds of departure from protocol, if you wish to call it that, in this study, that is, two subgroups of patients generated within the study which deviate somewhat from the original randomly assigned shunt or medical therapy groupings.

As you may recall, we randomized 78 patients into the shunt group and 77 into the medical group. Of the 78 shunt-randomized patients, only 67 actually received the shunt. Eleven of the 78 were not shunted, the primary reason being refusal of surgery by the patient. The first problem which confronts the biostatistician then is: Is this group of eleven different in some important fashion from the remainder of the 78 on whom shunts were performed?

I have examined this question carefully, and it turns out that, in reality, this self-selected group is not different in any significant way from the 67 who did get shunted. This is, of course, of primary importance, because if they were different from the others in some relevant variable their elimina-

tion from the shunt-randomization group might have introduced an important of bias. In fact, the experience of this nonshunted group following the beginning of treatment, which was the same as that given the medical group, was very similar to that in the medical group.

The second group of patients which presents special problems is one which occurs later among those patients that were assigned medical therapy. As you may recall, 50 of 77 patients in the medical group rebled. The question then became: How should these patients be treated after the rebleeding episode? Should they be shunted or should they be maintained on the protocol of medical treatment only? As a statistician, you can imagine that my first response was to suggest a second randomization at this point. There would, in fact, be good reason for a randomization here since we would like to know the effect of the shunt on the survival of these rebleeding patients. Treatment assignment by a random procedure would provide the means for a legitimate comparison of the shunt and nonshunt therapies after rebleeding. Any other method of treatment assignment would not guarantee the lack of bias in the composition of the comparison groups.

Despite its theoretical advantages, randomization of rebleeders was not attempted in this study since it was not felt to be appropriate by the investigators. The treatment of the 50 rebleeding medical group patients was left to the local investigator's option. In actual fact, 26 of those were shunted and 24 were not shunted.

It should be emphasized that it is very difficult to make direct comparisons between these groups of shunted and nonshunted rebleeders, because we have no guarantee, since the operation was done at the discretion of the individual investigator, that these two groups were comparable before treatment. I would caution you, therefore, to be very careful in making inferences from comparisons between these two groups.

Although I did want to point out the origin of these two slightly aberrant groups that you saw identified in the flow chart which Dr. Jackson presented, I do not wish to overemphasize their importance to the study itself. I think, in fact, ther may be no way of avoiding completely the occurrence of these particular groups of patients in a study of the surgical treatment of esophageal varices. Surgical refusals will continue to occur despite one's best efforts and local option at critical points in patient treatment is an important safeguard in a clinical trial of this nature.

If anything, I think this study illustrates that with a large enough series and proper design considerations you can generate sufficient information on the major questions at issue, can employ reasonably straightforward analysis, and do not necessarily get hamstrung by minor unexpected complications, with the consequence that the resulting data has the happy property of possessing both statistical and medical significance.

DR. FRANCIS C. JACKSON (Closing): We have been well aware of Dr. Child's classification of liver disease since the beginning of the study. I might say that we have not assigned our patients into his classification, although this was done in a small emergency series which appeared in this month's *Annals of Surgery* (March).

From that experience we do agree that one can be more selective when one utilizes his technic of utilizing both the laboratory and the clinical signs of liver failure.

I don't at the present time have any answer as to which is a better shunt, the side-to-side shunt or the end-to-side shunt. As a matter of fact, there seems to be some contradiction, in the sense, that the side-to-side shunt which functions perfectly, would dearterialize the liver. Why these patients do better, therefore, is most confusing. On the other hand, Dr. Dennis points out that arterializing the liver in an ingenious operation may have a better prognosis, also for reasons that are not apparently clear. I think, however, that his operation may very well bear more watching.

With regard to Dr. Malt and the Boston Interhospital Liver Group's ("Bilge") series, we have worked very closely with Tom Chalmers, and also with Dr. Child, and we are awar of their experience—which has shown the same results, incidentally, as our prophylactic series (i.e., the portacaval shunt is not recommended in the established cirrhotic who has never bled.)

With regard to the presence or absence of bleeding from gastritis, we did find this in a number of cirrhotic patients at the time of autopsy. We did not identify it during the period of the study, and I cannot say, other than on theoretical grounds, whether it frequently accompanies bleeding varices. The presence of gastritis in the setting of portal hypertension does seem to be a very difficult situation, and obviously increases, the possibility of hemorrhage.

We did notice, incidently—and it is reported in this series, that bleeding from all sources occurs frequently in these patients.

Now, Dr. Warren, of course, presented his ingenious operation, to this group a number of years ago. It has intrigued us. We also used him as an advisor to our study. When I approached him, and I asked, "Dean, would you allow us to randomize your operation?" he replied, "Oh, my God, no!"

And so all I can say at the present time is that we still need to determine in a controlled study whether or not his procedure (the distal splenorenal shunt) does prevent encephalopathy over the long run.

In conclusion I would like to give credit in these studies to our veteran patients. In both the "Bilge" series (the original report) and, certainly, in our current report they have indeed contributed much. As the retiring chairman of a cooperative study, I feel very strongly that it has been much easier for me to deal with recalcitrant patients than to deal with recalcitrant investigators.