Discussion

Dr. Eric W. Fonkalsrud (Los Angeles): We have also had an interest in determining the nature of the humoral factor produced by hepatic ischemia since animals that have orthotopic liver transplants usually experience a marked degree of hypotension once the new graft has been revascularized in the recipient. If one takes the hepatic venous effluent from a newly revascularized canine orthotopic liver transplant and transfuses this blood into another normal dog, one produces a moderate degree of hypotension in the second dog within a matter of a few moments as is shown on this slide.

In additional studies in our laboratory using a canine model similar to that which Dr. Vargish described today, the hepatic inflow was occluded for 2 hours and then the liver was revascularized. The initial hepatic venous effluent was then transfused to a second normal recipient in increments of 100 cc. Simultaneously a like amount of blood was removed from the second dog in order to maintain a constant blood volume. A rather prompt decrease in the arterial blood pressure occurred in the normal dog receiving the transfusion. Surprisingly, the portal venous pressure decreased transiently in the recipient dog after the transfusion. The central venous pressure also decreased transiently. The arterial pH serum potassium and other electrolytes were monitored closely, and cultures of the hepatic effluent did not grow pathogenic organisms. It was therefore concluded that some vasoactive substance was released into the hepatic venous effluent following hepatic revascularization similar to that which Dr. Vargish and his associates have described today.

More recent studies in our laboratories have shown that blood from the hepatic vein of a transplant following revascularization when transfused to a normal dog produces a more mild and transient hypotension that when it is transfused into a dog that has experienced some degree of hepatic ischemia itself. When the blood was transfused to dogs that had been subjected to 30 minutes of hepatic ischemia, severe shock ensued and several of these dogs died.

Further studies have suggested that metabolic inhibitor drugs including cortisone, chlorpromazine, phenoxybenzamine and similar drugs, when given to a dog that is subjected to a period of hepatic ischemia, reduces the severity of the hypotension produced by the hepatic venous effluent. One might conclude that hepatic ischemia produces hepatocyte autolysis, which may be demonstrated by electron microscopy. One may initially demonstrate an increase in intracytoplasmic free lysosomal enzymes, following which the same lysosomal enzymes may be shown to increase in the circulation to extremely high levels which approximates the time when the dog develops profound shock.

In conclusion I would like to ask Dr. Vargish if he and his associates have had any experience with the use of vasodilators or other metabolic inhibitors in their animal preparation and whether they might postulate if such drugs might effect the renal blood flow. Furthermore our studies and those of many other investigators have questioned whether the dog is a suitable animal model to study hepatic ischemia and its influence on the circulatory system. Perhaps the primate model might be a better choice.

Dr. Thomas E. Starzl (Denver): It seems to me that there are several possible mechanisms by which kidney function can be depreciated by bad liver function. One hypothesis, compatible with Dr. Vargish's observations, is that the damaged liver releases some kind of substance which actually harms the kidney.

A second hypothesis is that biologically active substances which are normally detoxified by the liver cannot be gotten rid of and as a consequence there is injury of the kidney. Vasopressor materials might be examples.

A third possibility is that in hepatic failure there is an absence or deficiency of the liver-produced renin substrate which is of influence in determining the patterns of intrarenal blood flow distribution. This last theory is that of Berkowitz and Miller (Surg. Forum, 23:342, 1972).

I do not know that we have any crucial evidence to support any one of these possibilities in preference to the others, but I would like to say that we have carried out orthotopic liver transplantation in several patients who have had extremely advanced renal failure as part of the hepatorenal syndrome. After successful liver transplantation there was recovery of renal as well as hepatic function. The three most completely studied cases are just now being written up for publication.

In all three of these patients, the BUN's were 100 mg./100 ml. or greater. It took from 4 to 10 days after liver transplantation before there was relatively complete recovery of renal function.

In one of these three patients, renin and renin substrate were measured repeatedly. Prior to the liver transplantation, a deficiency of renin substrate was documented as well as an excess of circulating renin. These same conditions have been described by Berkowitz and Miller as essential for the development of the renal failure of the hepatorenal syndrome. After operation, the concentrations of these substances returned to normal. Recovery of the kidneys was delayed for several more days after that.

I think our observations are consistent with the renin substrate hypothesis as the essential beginning point for a redistribution of blood flow in these kidneys and then secondary renal failure, although, of course, other interpretations could be placed on these findings.

Dr. T. Vargish (Closing): We did not note a fall in blood pressure in our experiments with cross transfusion and we were very conscious of this fact. We interpreted this as having two explanations: one, that as mentioned, our dogs had normal livers and were detoxifying whatever vasoactive substance was being transfused and second, that possibly this substance was being bound in the infused kidney. This is supported by our evidence that the contra-lateral kidney does not demonstrate as marked a change in renal function.

In reference to some of Dr. Starzl's comments about the etiology of this material, we are presently doing work in evaluating the effect of portal vein blood in a similar preparation. While our results are inconclusive at the present time, it seems to us that we are showing no real change in renal function in these kidneys.

We agree with Dr. Starzl on the possibility that renin substrate depletion may well be the explanation and this would certainly coincided with our findings. We have noted electrolyte changes in the effluent that we have collected, although the potassium, which really concerned us, was only elevated slightly in the area of 5.5 milliequivalents per liter in the studies we have done. We have also been interested in the pH of this fluid and it has ranged in the area of 6.9 to 7.2. Normal blood which has been altered to the pH of 6.9 however, has had no effect when infused in our kidney model.