abnormal results for these tests may not bleed and blood transfusion is not entirely free from risk. Hence no transfusion is given to correct the defects unless certain positive indications are present—such as daily deterioration in test results; damage to blood vessels; and if bleeding has occurred.

The amount and type of transfusion fluid to be used follows the generally accepted principles for the management of a haemorrhagic diathesis. Calculated amounts are given and the tests repeated to ensure their efficiency. Deficiency of factor V is usually added to deficiencies of the more stable factors, II, VII, IX, and X, which are dependent on vitamin K for their synthesis, and hence fresh frozen plasma is used rather than stored blood or plasma. Platelet concentrates may be required. For patients who are bleeding freshly collected whole blood or fresh frozen plasma with red cell concentrates can be used. Intravenous infusion of heparin, starting at 2,000 units every six hours, is begun whenever transfusion is indicated, in an attempt to reduce the utilization of clotting factors. If the thrombin clotting time exceeds 100 seconds the dose is reduced, for the risk of bleeding due to heparin is then very great. Special attention must also be given to the management of the renal failure, for this creates an additional reason for the bleeding which is so often the immediate cause of death in these patients.

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Pig Liver Perfusion and Other Methods of Temporary Liver Support

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Liver failure, while including a deficit of excretion, also includes a failure of synthesis, and though a suitable dialysis membrane could cope with the first, it would be unlikely to rectify the second. Hence the best form of temporary support for a patient in liver failure is considered to be the circulation of the patient's blood through an intact functioning liver.

Possible Methods of Temporary Liver Support

To connect a patient to an additional functioning liver (Fig. 1) the new liver may be set up in an extracorporeal perfusion chamber, or left in situ, when treatment will take the form of full cross-circulation between the patient and the owner of the functioning liver. Animal species that have been used in the former include pigs,[1-5] calves,[6] baboons and monkeys.[7] These livers will function while being perfused with human blood for up to ten hours. If the human blood chosen is completely compatible with that of the patient, connection of the liver to the patient's circulation becomes a practical possibility. Human livers for extracorporeal perfusion[8] are obtained from cadavers and are superior to a liver from other species since they may function satisfactorily for 35 hours or more.[7] Treatment of a patient in liver failure by means of a functioning liver in situ has been accomplished by cross-circulation with another human[9 10] and also with a baboon.[11 12]

Extracorporeal Perfusion

In Britain a regular supply of disease-free pigs or calves is simple, but that of baboons or monkeys would be more difficult. After careful hepatectomy hepatic cellular function is protected during ischaemia of the liver by cooling with infusion of a suitable cold solution into the portal vein and later the hepatic artery. The cooled animal liver is then set up in a perfusion circuit. The perfusion chamber, filled with normal saline, allows the liver to be perfused evenly without any part of the liver resting on a firm surface. The perfusing fluid is fresh blood compatible with the patient's blood.

Most reported series of connexion of a patient to an extracorporeal perfusion circuit describe the use of an arteriovenous Quinton-Scribner shunt[13] in the same way as it is used in dialysis. Nevertheless, we find that a double cannula introduced into the inferior vena cava via a small cut-down over the saphenous vein can consistently achieve flows of up to 500 ml/min.

Before the patient is connected to the liver, the perfusion is allowed to run for 30-60 minutes to assess the function of the liver. Clinically we find sufficient information of perfused liver function is given by bile flow and the appearance of an evenly perfused liver surface. This period before connexion to the patient also allows the pH of the perfusate to be adjusted, since this tends to be low owing to the unavoidable slight ischaemia of the liver during hepatectomy.

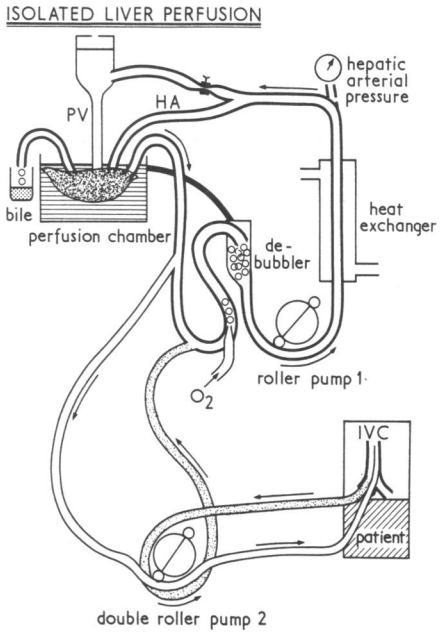

FIG. 1—Circuit for extracorporeal perfusion of the liver.

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RESULTS

Whether the animal is the pig[14] or the calf,[6] the patient may be brought out of coma regularly, but long-term survival is disappointing; as much by reason of the nature of the disease, as by complications of this treatment. The longest reported treatment of hepatic coma by means of extracorporeal perfusions is that of G.M. Abouna and his co-workers,[7] where after 16 perfusions over a two-and-a-half-month period the patient died before a suitable donor for liver transplantation became available.

EFFECT ON COAGULATION DISTURBANCE

Frequently a perfused liver which is functioning well biochemically will deplete the patient's blood of platelets, worsen the prothrombin and clotting times, and produce severe bleeding.[5] This platelet sequestration within the liver appears to be related to endothelial damage in the sinusoids occasioned by slight ischaemia during hepatectomy[15]; a minor degree of endothelial damage has a more notable effect than minor damage to the liver cells. There is no reported method of predicting which liver will cause this platelet depletion. Our studies[16] suggest that if the fall in radioactive fibrinogen is pronounced in the early part of the perfusion, the liver is likely to cause platelet depletion and a consumptive coagulopathy if connected to a patient, and should therefore be discarded as unsuitable as a therapeutic tool.

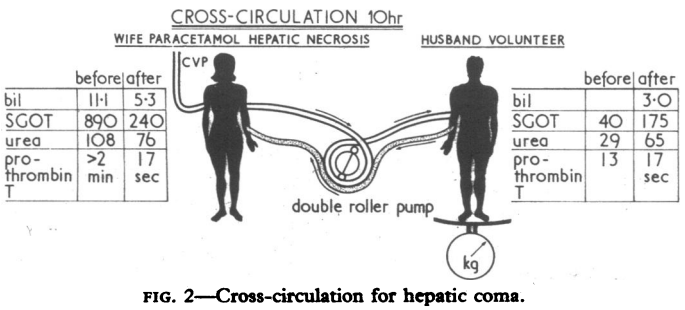
DEVELOPMENT OF SERUM ANTIBODIES

A further complication of connecting an animal liver repeatedly to a patient is that the patient may become sensitized to the animal protein. In six liver perfusions where we used six normal calves in the place of patients[17] we were able to show circulating porcine protein by immunodiffusion on Ouchterlony plates in four of the calves up to 14 days after perfusion. None of these calves developed antibodies to this protein, however, either after perfusion or after a secondary challenge with injected pig-liver extract. J. C. Norman and his colleagues[3] have reported the absence of antibody response after multiple perfusions in his patients up to 18 days after perfusion, so that it is likely that the same species could be used repeatedly at least during 18 days for the same patient.

Cross-circulation

When hepatic coma is not due to an infective agent or to malignant disease, a further method of bringing the patient's blood into prolonged contact with a normal liver is cross-circulation with a volunteer partner who has compatible blood.

A young woman who took 35 g of paracetamol because her husband had left her, developed hepatic necrosis and coma on the sixth day, with considerable haemorrhagic complications in many systems. Her husband, who happened to be of the same blood group, volunteered to help in any way, and agreed to cross-circulation when the position was explained to him. Fig. 2 shows the set-up for the ten-hour cross-circulation. Both had their blood pressures monitored with, in addition, continuous monitoring of central venous pressure in the patient and body-weight in the partner.



	before	after
bil	11·1	5·3
SGOT	890	240
urea	108	76
pro-thrombin T	>2 min	17 sec

	before	after
bil		3·0
SGOT	40	175
urea	29	65
pro-thrombin T	13	17 sec

FIG. 2—Cross-circulation for hepatic coma.

Cross-circulation is not without complications in the partner, and J. M. Burnell and his colleagues[10] have reported the following observations in four partners used in treating three patients in hepatic coma: fever, a fall in platelets, and a delay in the return of liver function tests to normal in two partners.

D. M. Hume and his co-workers[12] have shown that if a baboon has its blood washed out by Ringer-lactate under hypothermia and then replaced by human blood, it will live normally for five to seven days before the human red cells undergo haemolysis. During this time the baboon may be used as a partner in cross-circulation for hepatic coma. Of four patients three were improved by the method of treatment; one was sufficiently improved to leave hospital. S. J. Saunders and his colleagues[18 19] have also reported one case treated in this way, and their patient recovered from her coma but died at 52 days of a cause seemingly unrelated to her liver disease.

Possible Use of Liver Transplantation

We have not yet carried out a transplant in a patient with fulminant hepatic failure due to acute hepatic necrosis, since a donor organ has never been available at the appropriate time—in other words, when a patient could not be maintained any longer by supportive therapy or temporary liver support as described above. Transplantation carried out for fulminant hepatitis would, of course, carry considerable risk of hepatitis to the surgical team. We have had experience of transplantation in a boy of 17, with a history of subacute hepatic necrosis of six months' duration, whose liver showed large areas of necrosis but with regenerating nodules, which were nevertheless inadequate to prevent the occurrence of deep coma. From being unresponsive to painful stimuli before operation, to lucid conversation on the day following transplantation, is a dramatic indication of the effectiveness of this form of treatment. We have also had two other patients with chronic encephalopathy due to cirrhosis who showed an equally striking improvement in the clinical state. In one of these the electroencephalogram, which had shown gross changes of low voltage theta activity, returned to normal during the seven to ten days following transplantation.[20]

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