The mechanism of the high cardiac output is thought to be due to lowering of the systemic vascular resistance, analogous to an arteriovenous fistula. Sharpey-Schafer (1961) studied forearm dynamics in two patients, one of whom had a cardiac output of 15 litres per minute. He showed that while there was a formidable dilatation of peripheral arteries the veins were constricted. He suggested that the high central venous pressure was not due to heart failure, as the Valsalva manoeuvre showed that the heart was capable not only of reducing its stroke volume when the high filling pressure was reduced but of increasing it during the "overshoot" as in the normal subject, but that it was due to peripheral vasoconstriction in the presence of an increase in blood volume. Therefore, as well as peripheral arteriolar vasodilatation increasing the cardiac output, further driving of the heart would appear to occur because of the high filling pressure due to peripheral vasoconstriction. However, in congestive heart failure per se there is peripheral vasoconstriction (Wood et al., 1956).

In conclusion vitamin-B$_1$ deficiency as a cause of cardiovascular disturbance may be rare in this country, but its recognition is important because it is amenable to treatment (Wood, 1939). Haemodynamic and pyruvate metabolism studies are shown here to be extremely valuable in making the diagnosis.

We would like to thank Dr. Evan Jones and Dr. Raymond Daley for allowing us to study patients under their care, and Dr. R. D. Bradley and Dr. M. A. Branthwaite for their help and advice.

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**Medical Memoranda**

**Liver Transplantation in Man after an Extended Period of Preservation by a Simple Technique**

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Satisfactory function in a liver transplant is dependent on the availability of a homograft in which anoxic damage has been kept to a minimum. Ischaemic injury may be manifest by the development of uncontrollable bleeding during transplantation or progressive liver failure in the event of survival from operation. Since infusion of cold electrolyte solutions had hitherto provided only two hours of tolerable ischaemia, various complex methods of preservation have been evaluated experimentally (Marchioro et al., 1963; Mikaellof et al., 1965) and tried clinically (Starzl et al., 1965) in attempts to provide organs of good quality for transplantation. Utilizing low-flow perfusion with diluted blood, hypothermia at 4°C, and hyperbaric oxygenation, Brettschneider et al. (1967) obtained satisfactory function after 10 to 15 hours' preservation in dogs. This was the first successful ex-vivo perfusion system and was employed by Starzl et al. (1968) in seven patients, in all of whom good initial function was obtained.

These methods of providing a liver of good quality are complex, however, and may be difficult to organize. Recent reports have suggested that good liver function may still be obtained when the organ is removed after cessation of heart beat, provided it is cooled by infusion beginning within 15 minutes of death (Calne and Williams, 1968; Schalm, 1968). This report confirms the value of simple cooling by infusion and indicates, moreover, that satisfactory function may still be obtained after preservation for as long as five hours.

**Case Report**

A 52-year-old man was admitted to the Manchester Royal Infirmary on 3 January 1969 with painless obstructive jaundice of recent onset. On examination there were no abnormal physical signs apart from jaundice.

**Laboratory Investigations.**—Hb 92%, white blood count and differential normal, platelets 260,000/cu. mm. Serum albumin 4.3 g, globulin 2.9 g, bilirubin 14.8 mg/100 ml., thymol turbidity 0.6 unit, alkaline phosphatase 29 K.A. units/100 ml., serum aspartate aminotransferase 40 units/ml., serum alanine aminotransferase 85 units/ml. Blood sugar 125 mg./100 ml., blood urea and electrolytes normal. Prothrombin time one-stage (Quick) 13.5 seconds, fibrinogen 425 mg./100 ml. Coagulation studies did not show any abnormality. A chest x-ray film was normal but a barium meal revealed a deformed duodenal cap. A transhepatic cholangiogram showed gross dilatation of the intrahepatic bile ducts with complete obstruction at the porta hepatitis.

At laparotomy on 10 January an intrahepatic mass was palpable above the porta hepatis, with collapse of the extrahepatic biliary system. Choledochostomy, with the object of probing the hepatic ducts and possible biopsy of a presumed bile duct carcinoma, was unsuccessful. As a result of these findings, and in the presence of deepening jaundice, the patient was referred for consideration of a transplant.

**Liver Transplantation.**—Transplantation was undertaken on 22 January when a donor Liver became available. Both donor and recipient were O positive blood group. On lymphocyte (tissue) typing there were two major and two minor incompatibilities and no pre-existing cytotoxic antibodies were detected.
Donor Procedure.—The donor was a 60-year-old man with rheumatic heart disease who had undergone an open heart procedure on the previous day. Death occurred at 11.00 hours and hepatectomy began 10 minutes later. On opening the abdomen, a cannula was inserted into the superior mesenteric vein and an infusion of Hartmann’s solution (4°C) begun. The hepatic artery was also cannulated and similarly infused. The hepatectomy proceeded uneventfully and was completed by 11.40 hours, when the liver was removed, placed in a bag of normal saline at 4°C, and surrounded with ice chips. About 800 ml. of Hartmann’s solution, containing 1,600 i.u. of heparin, had been infused through the portal vein and hepatic artery by the time the hepatectomy was completed. The hepatic artery and superior mesenteric vein were then infused slowly with a plasma solution at 4°C containing glucose, procaine, and bicarbonate, and this was continued throughout the preservation period.

Recipient Operation.—This procedure was begun at 12.45 hours. The abdomen was opened through a bilateral subcostal incision. Hepatectomy proceeded uneventfully and was completed by 15.00 hours without the need for any venous bypasses during the anhepatic stage. The donor liver was then sewn in orthotopically. The portal vein and hepatic artery anastomoses were completed by 16.00 hours. The liver appeared to perfuse well, though remaining darkish in colour, and there was an insignificant amount of bleeding from the anastomoses. On re-examination of the hepatic artery anastomosis at this time no pulsation was felt distally. Two further attempts to effect a satisfactory anastomosis were unsuccessful owing to friability of the arterial wall, and finally the proximal splenic artery was mobilized and anastomosed end-to-end to the donor hepatic artery (17.00 hours). Biliary drainage was achieved by anastomosing the common bile duct end-to-side to the duodenum over a Portex T-tube. The patient recovered consciousness immediately after the end of the procedure and was returned to the ward in good condition, having received 6 pints (3.4 litres) of blood.

Macroscopic examination of the recipient’s liver confirmed the presence of a tumour measuring by 3 by 2 cm., situated at the junction of the main hepatic bile ducts, which proved to be a well-differentiated intrahepatic cholangiocarcinoma histologically.

The subsequent clinical course is shown in Fig. 1 up to the time that death occurred on the 11th postoperative day. Immuno-suppression consisted of azathioprine, steroids, and antilymphocyte globulin (A.L.G.) and was begun at the time of transplantation. The immediate postoperative course was uneventful and excellent clinical and biochemical progress was maintained over the first four days. Although the serum aspartate and alanine aminotransferase (S.G.O.T. and S.G.P.T.) values were markedly raised on the day after operation, they fell rapidly over the next few days. On the fifth day, however, there was clinical and biochemical evidence of deterioration which was thought to be due to cholangitis. Regression continued and on the 10th day leakage of bile was noted from the wound. On exploration the gall bladder and common bile duct were found to be necrotic. The hepatic artery had thrombosed. The liver, though swollen, appeared viable apart from several small infarcts, the largest of which was in the left lobe. The gall bladder was removed and the common hepatic duct anastomosed to the jejunum with a Roux-en-Y. The patient died six hours later.

At necropsy all the anastomoses were patent except for the hepatic artery, which was thrombosed. The right lobe of the liver appeared normal apart from a few discrete areas of necrosis 1–2 cm. in diameter. In the left lobe there was a large infarct measuring 10 by 5 cm. and there were also smaller areas of necrosis which were patchy in distribution. Related to the large infarct was a thrombosed intrahepatic branch of the portal vein.

Histological studies of the right lobe showed some centrilobular necrosis with preservation of the reticulin framework. The liver architecture was otherwise well preserved. The portal tracts were moderately infiltrated with mononuclear cells. The liver cells appeared healthy (Fig. 2), apart from those in the centrilobular areas. In the left lobe the general pattern was similar to that found on the right side, apart from the areas of necrosis. There was no evidence of infection throughout the liver. The hepatic artery showed some intimal hyperplasia which began at the site of anastomosis and was present throughout its branches.

**Fig. 2.—**Histological section of liver. (H. and E. X460.)

**DISCUSSION**

The cause of death appears to have been liver failure secondary to hepatic artery thrombosis. We believe there is evidence to suggest that the liver would have continued to function satisfactorily if the artery had not thrombosed.

Clinically and biochemically initial liver function was excellent in spite of the prolonged preservation period. The absence of a bleeding diathesis and the immediate return of consciousness after operation indicate prompt resumption of function following revascularization.

More critical indices of liver function are provided by the haematological studies. In general the changes noted have been reported in other series (Groth et al., 1969; Flute et al., 1969). There was a pronounced increase in factor VIII levels (Calne et al., 1968), and though this substance may also be produced...
in other organs in man, it provides some evidence of liver function. Other liver-dependent coagulation factors, as measured by the prothrombin time (one-stage and two-stage), were well maintained. There was also evidence of the development of a hypercoagulable phase as suggested by the slow fall in fibrinogen, increasing factor VIII levels, and thrombocytopenia. Antilymphocyte globulin, however, was also being administered and fibrin degradation products were not measured.

Although the histological appearances are difficult to evaluate in terms of function, it was considered that in the absence of arterial thrombosis the liver would have been expected to survive. There was only moderate evidence of rejection as indicated by mononuclear cell infiltration.

In conclusion, satisfactory function has been demonstrated in a human liver allograft after prolonged ischaemia, protected by the simple method of core-cooling in situ and infusion of a preservative solution. Whereas experimental evaluation of this technique in the dog provided only three and a half hours of safe ischaemia (Schalm, 1968), this interval may apparently be extended in man.

We wish to thank Mr. N. C. Keddie, under whose care the patient was first admitted, for referring the case for transplantation. We are indebted to Dr. A. G. Burch, of the Peter Bent Brigham Hospital, Boston, Mass., for the supply of antilymphocyte globulin. We are grateful to Professor K. A. Porter, of St. Mary's Hospital Medical School, London, for his opinion on the histological studies. Our thanks are also due to the many members of the medical and nursing staff who were involved, and to Dr. Robert Ollerenshaw, of the department of medical illustration.

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REFERENCES


Sudden Death after Exertion in Apparently Healthy Boy

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It was taught, and perhaps still is, that the normal heart cannot be overtaxed. That this idea may need revision is suggested by the following case.

CASE REPORT

A 15-year-old Glasgow boy scout had been perfectly well during the few weeks before his death on 8 May 1965. In particular, there was nothing to suggest a recent infection. On the morning of his death he had taken part in an athletic meeting at his school, but apparently had not unduly tired himself. He had had a light lunch before going to Aberfoyle to start a 12-mile (19-km.) walk to Rowardennan in the company of other boy scouts. He was one of a group of three and had forged well ahead of his companions by running. He had left the course, but it was impossible to attract his attention, and he ran into some woods which were crossed by deep drainage trenches. The effort required to make progress across such terrain must have been considerable. About eight miles (13 km.) from the start the other runners caught up with the boy, who complained of cramp in his legs and was unable to run any further. He soon collapsed, and his companions, realizing that he was unwell, tried to get help. When a farmer arrived the boy was dead.

Necropsy.—The body was that of a well-built adolescent male. There was intense cyanosis of the fingers and ears. The skull was normal, the dura was not tight, and the venous sinuses were clear. The brain weighed 1,415 g. and was completely normal when sectioned serially after fixation. Apart from an area of melanosis of the leptomeninges at the second and third cervical segments, the spinal cord was normal. There was a small quantity of clear yellow fluid in the pericardial sac. The heart, which weighed 290 g., showed dilatation of both ventricles, the right more than the left, but there was no structural abnormality. The myocardium, endocardium, and valves were normal. The coronary arteries were normal. The aorta was not hypoplastic and the carotid arteries were normal. The pleural cavities were clear, but the main air passages contained a considerable quantity of frothy blood-stained fluid. The mucosa of the trachea and main bronchi was very congested. The lungs together weighed 750 g. and were slightly oedematous. The alimentary tract was normal, apart from a haemorrhagic area in the gastric mucosa. The liver and pancreas

FIG. 1.—Many fibres were bright red—evidence of damage—and appear dark. There was no inflammatory exudate. (Cresyl violet and acid fuchsin. × 320. Green filter.)