different treatments. Saunders carries out an exchange transfusion routinely if the patient remains in deep coma after 24 hours. In another personal series (from the Hospital Beaujon, Clichy) the results were quite different.¹⁶ Between 1952 and 1969 77 patients with severe viral hepatitis were seen, of whom 75 were in coma. Of 56 patients treated conservatively 13 survived, whereas there were no survivors in the 21 treated by corticosteroids, exchange transfusion, cross circulation, or hyperbaric oxygen. However, it is again quite likely that the more severe cases were treated by the more active measures. In the F.H.F.S. study of 101 patients in whom no treatment procedures were undertaken 10% survived,⁴ while 24% of 166 patients lived in whom exchange transfusions were done.

Thus no firm conclusions can be drawn about the value of exchange transfusion in the management of fulminant hepatic failure. Indeed the preliminary results in the first randomly allocated and controlled trial of exchange transfusion in fulminant hepatitis shows a higher mortality in the treated group.¹⁷

References

- ¹ Trey, C., and Davidson, C. S., in *Progress in Liver Diseases*, ed. H. Popper and F. Schaffner, vol. 3. New York, Grune and Stratton, 1970.
- ² *British Medical Journal*, 1970, 4, 255.
- ³ Trey, C., et al., *New England Journal of Medicine*, 1968, 279, 798.
- ⁴ Trey, C., Lipworth, L., and Davidson, C. S., *Gastroenterology*, 1970, 58, 306.
- ⁵ Sharpstone, P., Medley, D. R. K., and Williams, R., 1971, *British Medical Journal*. To be published.
- ⁶ Williams, R., and Toghill, P. J., *Postgraduate Medical Journal*, 1968, 44, 173.
- ⁷ Polli, E., Porro, G. B., and Maiolo, A. T., *Lancet*, 1969, 1, 153.
- ⁸ Parkes, J. D., Sharpstone, P., and Williams, R., *Lancet*, 1970, 2, 1341.
- ⁹ Saunders, S. J., Bosman, S. C. W., Barnard, C. N., and Terblanche, J., *Present Concepts*, 1969, vol. 2. No. 7.
- ¹⁰ Read, A. E., Laidlaw, J., McCarthy, C. F., *British Medical Journal*, 1969, 3, 497.
- ¹¹ Samson, R. I., Trey, C., Timme, A. H., and Saunders, S. J., *Gastroenterology*, 1967, 53, 291.
- ¹² James, I. M., et al., *Lancet*, 1969, 2, 1106.
- ¹³ Almeida, J. D., and Waterson, A. P., *Lancet*, 1969, 2, 983.
- ¹⁴ Goertz, G., Weinbren, H. K., and Williams, R., 1971, to be published.
- ¹⁵ Saunders, S. J., 1970. Personal communication.
- ¹⁶ Rueff, B., and Sicot, C., Presented at the 5th Meeting of the European Association for the Study of the Liver, Berne, 1970.
- ¹⁷ Redeker, A. G., personal communication.

Haemostasis in Fulminant Hepatic Failure

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In fulminant hepatic failure the general reduction in protein synthesis by the liver leads to a fall in the plasma concentration of many clotting factors¹, which is often sufficient to cause spontaneous bleeding. The concentration of clotting factors can sometimes be maintained, and bleeding prevented, by the transfusion of blood or blood products, but even this may be unsuccessful owing to an abnormally rapid loss of the transfused factors. Patients with hepatic coma have a fast clearance of fibrinogen,² and indirect evidence suggests that platelets and coagulation factors other than fibrinogen are also involved in a process of intravascular coagulation.

Intravascular Coagulation

Many patients with fulminant hepatic failure show mild thrombocytopenia when platelet production is active. At the same time circulating fibrin degradation products are often increased.³ Hence the increased clearance of fibrinogen is probably due to consumption by coagulation in the blood stream. This "disseminated intravascular coagulation," "consumption coagulopathy," or "chronic defibrination," is seen in many states when blood comes into contact with damaged cells.³ In fulminant hepatic failure the stimulus probably comes from blood in contact with damaged liver cells.

Perhaps the most cogent argument in favour of intravascular coagulation, and the importance of its recognition, lies in the fact that heparin given to the patient tends to return fibrinogen clearance to normal. Such intravascular coagulation must throw an extra strain on the already overtaxed production capacity of the liver for clotting proteins. When their hepatic synthesis is severely reduced clotting factors can be

increased only by transfusions of fresh or fresh frozen plasma, but their effect will last longer if heparin is given at the same time.

Probably all patients in hepatic coma may be assumed to have intravascular coagulation, though proof is difficult to obtain. The thrombin clotting time is prolonged when early breakdown products of fibrin or fibrinogen digestion are increased in the circulation, when the fibrinogen concentration is very low, or when circulating anticoagulants such as heparin are present. If the latter can be excluded, then a thrombin clotting time of 5 sec. or more longer than that of the control normal plasma is a typical finding of intravascular coagulation states.

Causes of Bleeding

The usual one-stage clotting tests—prothrombin time and partial thromboplastin time—do not indicate consumption directly but represent the balance achieved between production and loss of clotting factors. Together these simple tests cover the activity of almost the whole range of coagulation factors. The two tests are usually prolonged to a similar degree in hepatic coma but isolated readings are little guide to the risk of bleeding. Associated precipitating factors may have an important role—including damage to vessels (oesophageal varices, peptic ulcer, acute gastric erosions or surgical wounds) and a blood urea over 100 mg/100 ml. Bleeding, when it occurs, is often from the gastrointestinal tract, sometimes with skin purpura, and resembles the bleeding found in acute renal failure.

Current Approach to Management

Vitamin K is given to ensure that synthesis of clotting factors is not prevented by failure to absorb this vitamin. The one-stage clotting tests are repeated daily. Patients with very

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.

References

- ¹ Ratnoff, O. D., *Medical Clinics of North America*, 1963, 47, 721.
- ² Rake, M. O., Flute, P. T., Pannell, G., and Williams, R., *Lancet*, 1970, 1, 533.
- ³ Merskey, C., Johnson, A. J., Kleiner, G. J., and Wohl, H., *British Journal of Haematology*, 1967, 13, 528.

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 perfusion⁸ 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 shunt¹³ 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

FIG. 1—Circuit for extracorporeal perfusion of the 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.