Liver Transplantation

The Cambridge—King's College Hospital Experience

Edited by

R. Y. Calne F. R. S.

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Preface

In 1963 Starzl performed the first orthotopic liver graft in man. He has now a series of more than 200 cases. Our own experience began in 1968 and we have performed 125 liver grafts. There are two further active programmes in Europe, in Hanover (under Professor Pichlmayr) where 54 patients have received transplants and Groningen (under Dr Krom) with 18 patients. Results in these four centres have slowly improved and a concensus of many aspects of the procedure would appear to have been reached. There is obviously a world-wide need for liver grafting and for those who are interested and hope to develop programmes, this book has been written.

The experimental background of liver grafting is the platform on which clinical application has been built. The orthotopic operation was pioneered independently by Moore *et al.* (1959, 1960) in Boston and by Starzl *et al.* (1959, 1960) in Denver. Study of the organ's and the recipient's ability to withstand the operation, methods of preservation, the pattern of rejection and immunosuppression have all been the subject of much experimental work which will be reviewed in this book. Liver grafts in all species are rejected less aggressively than other organs but in the pig and the rat, the difference between the liver, on the one hand, and other parenchymatous organs such as the heart, kidney and pancreas on the other, is remarkable. Much effort has been devoted in our department to discover the mechanisms involved in the protection of the liver from rejection and also the donor specific inhibitory immune response found in liver grafted recipients towards other grafts from the same donor origin.

Our clinical programme is a joint collaborative endeavour between the University of Cambridge Department of Surgery at Addenbrooke's Hospital and the Liver Unit, King's College Hospital, London, under Dr Roger Williams. Dr Williams' enormous experience of liver disease has been essential in the selection and management of our patients. He and his colleagues discuss first the indications, assessment and selection of patients for liver grafting, including a most important consideration, namely the timing of when to offer the patient an operation. They review the clinical results, long term follow-up and rehabilitation of patients.

The operation itself and immediate postoperative phase constitute the most important hurdle the patient has to overcome. This is an extremely formidable operative procedure in which major physiological disturbances are necessary and a single error at any stage is likely to lead to the patient's death. No other aspects of liver grafting can be successful without an adequate operation, so

considerable space is devoted to this subject, including the selection of a suitable donor, the donor operation, the anaesthesia and monitoring, the instruments required and the postoperative care. The details of the operation itself have evolved after many errors had been made. These have been described in the hope that our experience will be of value to others undertaking this operation. The present procedure is described in detail and whilst it is not claimed that this is the final answer, if the steps described are followed there is a good chance of a safe and satisfactory outcome.

Prevention of rejection is still of great importance in human liver transplantation. Until the last few years, Azathioprine and corticosteroids were the main immunosuppressive drugs, utilised in a manner similar to that in kidney grafting. The advent of Cyclosporin A provided us with an agent that will certainly permit reduced steroid dose and often no steroids are required at all. The drug, however, is nephrotoxic and can be hepatotoxic. Since many patients accepted for liver grafting have already compromised renal function, the use of a nephrotoxic agent can be dangerous. Cyclosporin A is more powerful and infectious complications are less common than with Azathioprine and corticosteroids. We therefore feel that this drug has an important part to play in improving the results of liver grafting, but there are pitfalls in its use that have to be avoided to obtain a satisfactory outcome.

The morphological appearances of rejection of the liver and other pathological changes in grafted livers that may complicate assessment are described. There is a discussion on the recurrence of the patient's original disease in the transplant.

We are grateful to all our colleagues who have contributed in the care of our patients in the development of liver grafting as a therapeutic reality. The procedure is time-consuming and requires the co-ordinated efforts of a dedicated team of doctors, nurses and technicians and above all courageous patients who are prepared to commit themselves completely to assist in their recovery and rehabilitation after this daunting procedure. For those who have recovered and returned to normal active life after liver grafting, the value of the operation is obvious. There have been many patients who have not had such a successful outcome, yet they have faced adversity with the same courage. Their suffering has contributed to knowledge that has helped the practice of liver grafting to become a worthwhile treatment.

Cambridge R.Y.C.
January 1983

Acknowledgements

I should like to thank all those who have contributed to this monograph, and all members of the Cambridge—King's College Hospital team. I thank, also, all my medical, nursing and technical colleagues who have contributed to the work and to the secretaries in the Department of Surgery who helped with the typescript.

The drawings were by Mrs. Marcia Thorburn and Dr. Jaime Arias and photographs by the Departments of Medical Illustration at Addenbrooke's and King's College Hospitals.

Cambridge R.Y.C.

Dedication

To our courageous patients who have undergone liver grafting.

Contents

Part I

Experiments in Animals

1

Experimental Background

R. Y. Calne

The first report of a technique that would enable experimental transplantation of an extra liver in an abnormal situation was by Welch (1955). The extra liver was accommodated in the lower abdomen with the portal vein being supplied by systemic blood from the inferior vena cava of the recipient and the hepatic artery anastomosed to an iliac artery. Venous drainage was via the inferior vena cava and the gall-bladder was drained into the duodenum. Since that time there have been many reports of a variety of techniques for the grafting of a liver into an heterotopic site, with or without removal of the recipient's own liver (Starzl, 1969a; Gugenheim *et al.*, 1981). A very important consideration if the recipient's own liver is left *in situ* is that there will be metabolic competition between the donor and recipient livers that will always result in the donor liver being severely compromised, leading to gross atrophy, unless the animal's own liver is deliberately damaged or most of it removed. Between 1965 and 1975 there was a spirited controversy as to whether the donor liver was discriminated against because it failed to receive heterotopic factors from the portal vein or because its blood supply was deficient (Starzl, 1969a). Many ingenious experiments were devised in an attempt to resolve the debate, but it now appears that a number of factors operate, and that these are not mutually exclusive (Starzl, 1969b). The allografted liver is subjected to an immunological reaction because it is a foreign graft; if, in addition, its total blood supply is curtailed, it will suffer further. Starzl *et al.* (1973) have shown that insulin and other hepatotrophic factors coming from pancreatic venous drainage are important in the maintenance of a normally functioning liver. If an auxiliary liver is transplanted into a patient dying from parenchymatous liver disease, this can restore him to health since, under these circumstances, it is the diseased liver that is compromised and the donor liver will get a fair share of hepatotrophic factors, which cannot be utilized by the diseased liver. If rejection can be controlled and the donor liver is adequately vascularized, it can function well. The difficulty with transplantation of accessory livers is, however, technical. There is little room in the abdomen for a large, irregular organ such as the liver, which must lie in a position that can permit adequate

inflow of blood to the organ and unimpaired venous drainage. There must also be access for free drainage of bile to avoid ascending cholangitis. If all these requirements are fulfilled, there is still a danger that the extra liver will, by reason of its bulk, impair movement of the diaphragm and lead to respiratory tract infection, a hazard to which the patient is in any case sensitive after major upper abdominal surgery and chemical immunosuppression.

If a surgically reliable technique of extra liver grafting were developed, it would have obvious value in non-malignant parenchymatous cirrhotic diseases. There would be no place for it in the treatment of malignant disease in which the liver must be removed. However, a completely new field might be exploited, namely accessory liver transplantation to restore essential enzymes in patients with fatal debilitating enzyme deficiency diseases. It is in these cases that the likelihood of competition between the grafted liver or lobe of liver and the patient's own liver, which would otherwise be functioning well, would be likely to lead to irreversible atrophy of the donated organ.

The transplantation of an accessory liver is an important tool in the study of liver physiology and also of the phenomenon of the liver's lack of susceptibility to rejection, which in pigs and certain rat strain combinations

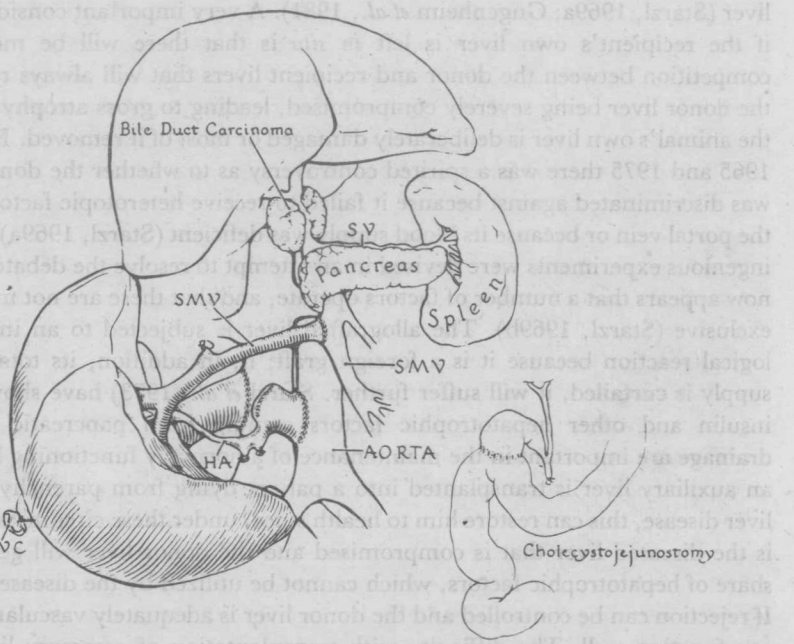

FIG. 1.1. *Fortner's technique of accessory liver transplantation. The extra liver is implanted into the right side of the abdomen. SMV = superior mesenteric vein; SV = splenic vein; HA = hepatic artery; IVC = inferior vena cava. (From Fortner, J. G.* et al. *(1973).* Surgery **74**, *739).*

can be particularly striking (see Ch. 5) (Calne *et al.*, 1969; Kamada *et al.*, 1981). Experiments have so far failed to give a conclusive answer as to whether an extra liver has the same immunosuppressive effect as one orthotopically transplanted after the removal of the animal's own liver. An answer to this question is important, since it is unlikely that the immunosuppressive effect of a liver graft could be utilized without transplanting a vascularized liver, unless it were quite clear that an accessory liver has the same effect as an orthotopically grafted organ.

The longest surviving recipient of a functioning extra liver graft was a patient reported by Fortner *et al.* (1977) who survived for 5 years. The technique they used is shown in Fig. 1.1. Most other workers have had dismal results with extra liver grafts and progress in clinical liver transplantation has been virtually confined to the orthotopic operation. However,

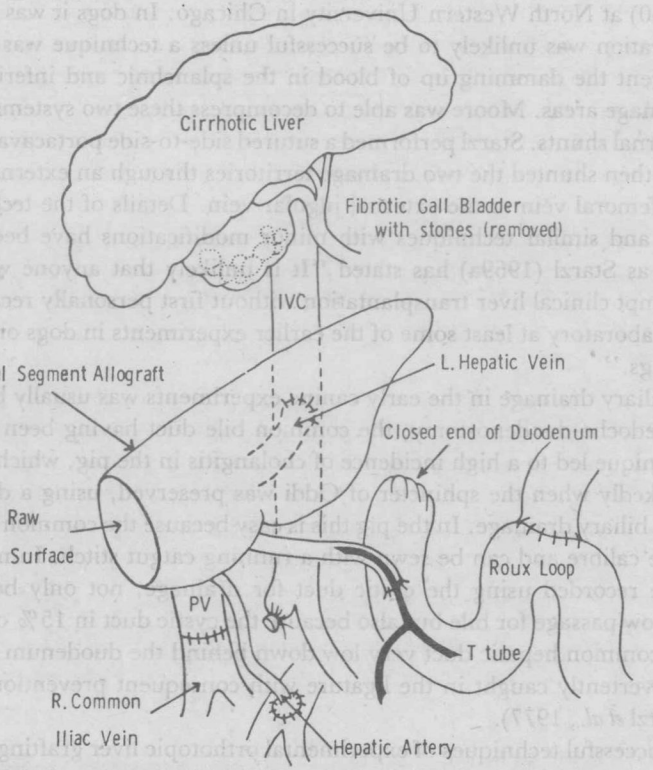

FIG. 1.2. *Left hepatic lobe accessory liver graft. Portal inflow is from the distal end of the right common iliac vein. The hepatic artery with Carrel patch is anastomosed to the right common iliac artery. The left hepatic vein is anastomosed to the infrarenal vena cava (IVC). The common bile duct draining the left hepatic duct is anastomosed to the side of a long Roux loop. The anastomosis is splinted with a T-tube brought out through the Roux loop. The cut raw surface points infralaterally. The lobe fits comfortably below the patient's own fibrotic, shrunken liver. PV = portal vein.*