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Liver transplantation

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Liver transplantation presents a surgical challenge that was first accepted by Moore and Starzl and their colleagues in the 1950s. They showed that a reproducible technique of orthotopic liver transplantation in the dog was possible. The successfully transplanted canine liver, however, was subject to rejection in much the same way as a kidney, and this process could be inhibited in a proportion of animals by treatment with the same immunosuppressive agents that prevent rejection of transplanted kidneys, namely azathioprine, corticosteroids and antilymphocyte serum.

In this paper I will attempt to review some of the work on experimental liver transplantation and discuss the background and current results of clinical liver allografting.

Technique

The liver may be transplanted in the normal position (orthotopic transplantation). This requires preliminary hepatectomy of the recipient but has the great advantage that the liver is easily accommodated and the vascular connection lie in a normal anatomical situation. Complications of kinking and obstruction from external pressure are unlikely to occur.

Alternatively, the liver may be transplanted in an abnormal situation (heterotopic, accessory or auxiliary transplantation). The advantage with this technique is that preliminary hepatectomy is not necessary, but the disadvantages are that it may be very difficult to accommodate a large liver satisfactorily in the abdomen and there may also be problems in providing satisfactory vascular inflow and outflow and bile drainage with the liver in an abnormal position.

Orthotopic transplantation

This was first described in the dog by Moore et al. (1959) and an alternative technique was described shortly afterwards by Starzl et al. (1960). Both groups of workers were faced with the difficulty of maintaining the life of the animal in the anhepatic state, while the vascular connections of the graft were being anastomosed to those of the recipient. It was found

that clamping the inferior V. cava and the portal vein was poorly tolerated by the dog. The intestines became congested and were liable to develop haemorrhages and if the animal survived the congestion of its intestines, when the portal vein was declamped it might die suddenly from the release of toxic metabolites from the congested bowel. Clamping the inferior V. cava resulted in impaired cardiac output which was often not tolerated. Methods were developed for shunting blood from the inferior caval system and the portal vein to the superior V. cava. MOORE et al. preferred direct shunting from the two vessels to the jugular vein: STARZL performed a temporary side-to-side porto-caval shunt by suture anastomosis and then inserted a cannula into the inferior V. cava and connected it to the jugular vein. Both techniques and modifications devised by other workers were successful, but there are certain disadvantages in liver transplantation in the dog; in particular, the hepatic veins in the dog are liable to go into muscular spasm, blocking the outflow of venous blood and causing congestion of the liver with haemorrhage and destruction of the liver parenchyma. Great care in handling the donor liver is necessary to prevent this. The portal venous blood of the dog is also quite often contaminated with pathogenic organisms which may lead to septicaemia following liver transplantation. The dog deprived of the synthetic functions of the liver for the short period of the operation may become deficient in coagulation factors and develop a marked haemorrhagic diathesis during and immediately after surgery which may result in exsanguinating haemorrhage.

A further complication of liver transplantation in the dog is acute gastric or duodenal ulceration with haemorrhage or perforation. This may be difficult to prevent. STUART et al. (1967) found that ulcers still occurred after vagotomy but total gastrectomy was successful. This is a very formidable procedure to add to the liver transplant. Despite these disadvantages it has been shown quite clearly that dog livers successfully transplanted will function. A similar technique to that used in the dog has been found suitable in the pig and in various primate species including the baboon and rhesus monkey. In the pig it is not necessary to shunt blood from the inferior V. cava although the portal shunt is desirable (Fig. 1). In the monkey, baboon, chimpanzee and man, no shunting is necessary.

Autotransplants in the dog suffer ischaemic damage which is partially reversible and the liver can maintain the animal in a satisfactory condition for long periods (STUART et al., 1967; ALICAN and HARDY, 1967). Allografted livers, however, are rejected after a few days of satisfactory function, and the animals usually die in the second week after operation. The liver parenchyma undergoes necrosis and becomes heavily infiltrated with mononuclear cells of a similar morphology to those seen in a rejected kidney. Treatment with steroids, azathioprine and antilymphocyte globulin may inhibit the rejection process in a proportion of animals. Azathioprine is, however, hepatotoxic and if given in large doses will cause bile stasis and liver cell necrosis. Animals with liver transplants will only tolerate about

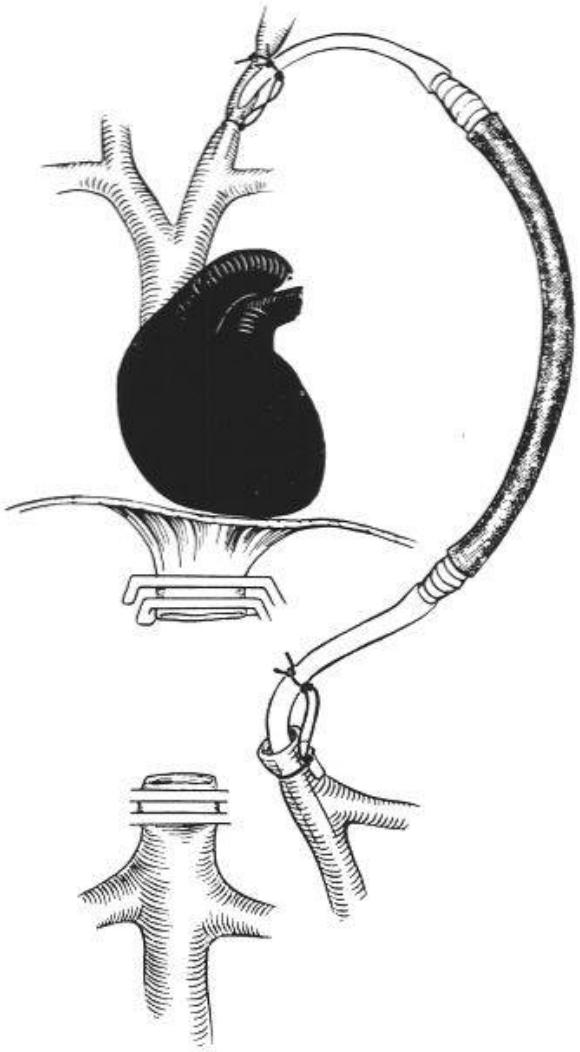

Fig. 1. Shunt technique of portal vein to jugular vein for orthotopic liver transplant in the pig.

half the dose of azathioprine that can be given to dogs with kidney allografts.

The insertion of the dog's liver orthotopically is straightforward. The V. cava above the liver is anastomosed to that of the recipient with a running silk stitch. The posterior wall is sutured from within the lumen of the vessel, the anterior wall from outside. The portal vein is anastomosed end-to-end with a similar stitch and when this anastomosis is completed the liver can be perfused with portal blood and external shunting of portal blood is no longer necessary. The hepatic artery is anastomosed end-to-end to the animal's own hepatic artery or a Carrel patch of aorta with the origin of the coeliac artery can be anastomosed to the aorta of the recipient. The infrahepatic IVC is joined end-to-end to that of the recipient with a running stitch. The common bile duct is ligated just above the duodenum and the gall bladder anastomosed to the duodenum of the recipient.

Fig. 2. Diagram of accessory liver transplant in the pig. The common bile duct and suprahepatic V. cava are tied. The fundus of the gall bladder is anastomosed to that of the recipient. The portal vein and infrahepatic V. cava are anastomosed end-to-side to the respective vessels in the recipient. A segment of aorta with the coeliac artery is anastomosed to the side of the recipient aorta.

Heterotopic transplantation

A large variety of heterotopic techniques have been described. They have been reviewed by STARZL et al. (1966) and I do not intend to go into them in detail. It has been found that if the liver has been deprived of portal blood it will not function normally and if an auxiliary liver is in competition with the donor's own liver it will atrophy rapidly, particularly if the donor's own liver has a direct portal blood supply that is denied the accessory liver. Accessory livers can be transplanted in the abdomen or pelvis. The technique that we utilise in the pig is shown in Fig. 2. This works very well provided the donor liver is smaller than that of the recipient. The anastomosis of gall bladder to gall bladder prevents ascending infection and cholangitis since bile from the transplant drains through the recipient's own common duct.

Prevention of ischaemic liver damage and liver preservation

The liver is exquisitely sensitive to ischaemic damage and if left at 37° C without perfusion for more than 15 min irreversible damage is likely to occur. This can be inhibited by cooling the liver: if the liver is cooled within 15 min of death of the donor, by perfusion with innocuous fluids via the

portal vein, and then kept cold in a preservation fluid consisting of plasma with bicarbonate and dextrose, satisfactory preservation can be achieved for three to four hours both experimentally and clinically (SCHALM, 1968; CALNE and WILLIAMS, 1968). Longer preservation requires complicated continuous perfusion apparatus with oxygenation and refrigeration. BRETTSCHNEIDER et al. (1968), using hyperbaric oxygen and continuous hypothermic perfusion, have been able to obtain consistent 8-hour preservation of dog livers with no detectable deterioration of the organs during that period. Any perfusion system, however, has the potential dangers of mechanical failure and bacterial contamination.

Immunological aspects

Livers have been allografted in the dog, rat, pig and rhesus monkey with and without immunosuppression, and pig-to-baboon and other primate species, liver xenografts have also been performed.

In summary, the results are as follows. The dog and the rat reject a liver in the same way that they reject a kidney, rapidly and aggressively, usually within 7–14 days after grafting. The salient features of rejection are cellular infiltration and liver cell necrosis (McBRIDE et al., 1962; STARZL et al., 1966; LEE and EDGINGTON, 1968). In a small series of rhesus monkey allografts, typical rejection similar to that seen in the dog occurred in three animals and the fourth, after a transient jaundice lasting two or three weeks, is in excellent health six months after orthotopic liver transplantation without receiving any immunosuppressive drugs (CALNE et al., unpublished observations). The pig tolerates liver allografts exceedingly well, in marked contrast to the active rejection of skin and kidney grafts (CALNE et al., 1967a, b, 1969). Moreover, a porcine liver allograft will prevent rejection of a kidney allograft from the same donor and will slow the process of rejection of donor skin. This phenomenon does not depend on hepatectomy of the recipient since accessory livers also have the same property. The pig is capable of rejecting a liver if previously sensitised and although in our own experience first-set liver rejection has never been severe or rapid, quite marked rejection has been observed by other workers using slightly different techniques and different pigs. The immunosuppressive effects of porcine liver allografts can be very marked. Our longest survivor with an orthotopic liver graft was 18 months when she had a litter of nine normal piglets. She died from intestinal obstruction shortly after her pregnancy. The liver appeared normal at autopsy. The longest survivor after bilateral nephrectomy and hepatectomy with an orthotopic liver and kidney transplant from the same donor is nearly 3 years. This animal is alive and well.

An analysis of this phenomenon might help in the understanding of the mechanisms of immunological tolerance, since it would appear that liver grafts in the pig do produce specific immunological tolerance that is similar to that produced classically in embryos. These pigs are, however, immunologically mature when grafted. The advantage of this type of immuno-

suppression is that it is donor specific, non-toxic and it does not make the animal liable to infection. Although liver allografts do not have this effect in the dog or the rat, the phenomenon may occur in the rhesus monkey. Although the number of liver allografts has been small, many skin and kidney grafts have been performed in the rhesus monkey and it is extremely unusual for these animals to accept skin or a kidney for more than two weeks, without powerful immunosuppressive therapy (BALNER, personal communication).

A small series of pig-to-primate liver xenografts were performed. These grafts perfused poorly and suffered centrilobular ischaemic damage; in addition there was widespread intravascular coagulation. Immediate haemorrhagic rejection did not occur and one baboon lived for 3½ days with a pig's liver and eventually died of pneumonia. The pig-to-baboon experiments have been published (CALNE et al., 1968a). The experiments of pig-to-rhesus monkey, Java monkey and chimpanzee are to be published shortly.

On the basis of experimental liver grafting in a variety of species and the limited experience in man it would, nevertheless, seem to be essential at present to treat patients with liver transplants with the same immunosuppressive therapy that has been found to be effective in kidney transplantation, namely azathioprine, steroids and possibly antilymphocyte serum.

Clinical liver transplantation

Indications

The indications for clinical liver transplantation have not yet been fully established but any fatal disease of the liver that is still confined to the liver is potentially suitable. Thus there are two main categories, namely primary malignant disease of the liver and non-malignant cirrhotic processes, including biliary cirrhosis and biliary atresia in infants.

The relatively common types of primary malignant disease of the liver are liver cell cancer and cholangiocarcinoma. In the United Kingdom both these diseases tend to remain localised in the liver for long periods and metastasise locally within the liver before spreading to other situations, in particular the lungs. In many parts of Africa and Asia liver cell carcinoma metastasises rather early and is frequently associated with cirrhosis. Fatal liver disease is extremely common in Asia and Africa, but in the United Kingdom probably accounts for only 200 deaths a year in young people, or approximately 10% of deaths due to irreversible kidney disease in a similar age group (TERBLANCHE and RIDDELL, 1967). Thus it should be possible for three or four centres to cope with all those requiring liver transplantation in the United Kingdom.

Maintenance of the patient

Lack of satisfactory support of the patient, both before and after surgery, has been the main reason for the slowness of development of liver trans-

plantation compared with that of the kidney. Exchange transfusion, ex-vivo liver perfusion, either through an animal's liver or a human cadaver's liver, or cross circulation with man or an animal, may all temporarily improve the state of the patient in liver failure, but none of these procedures can be repeated indefinitely. Repeated exchange transfusion will utilise a vast amount of blood and the patient may develop antibodies against blood constituents. This may also occur in ex-vivo perfusion and cross circulation. There are also infective immunological and haemodynamic dangers to a human partner of cross circulation. At their best, none of these methods compare with recurrent dialysis for renal disease.

Technique

Most workers would agree that the orthotopic position is to be preferred in clinical liver transplantation. The operation is very similar to that performed in experimental animals. Our own technique based on that of STARZL et al. (1968) is described in detail elsewhere (CALNE, 1969). It can be conveniently divided into three phases – recipient hepatectomy, donor hepatectomy and insertion of the organ graft.

Recipient hepatectomy

Under light general anaesthesia with two intravenous infusions into the superior caval system, a laparotomy is performed by a wide bilateral subcostal incision. Hepatectomy may be straightforward if the liver is shrunken and cirrhotic, but an enlarged malignant liver with associated portal hypertension can make this stage of the operation difficult and tedious. Previous surgery, for example liver biopsy, bile duct cannulation, porto-caval anastomosis, together with the associated adhesions add to the operative problems. Every small blood vessel that is divided must be secured, and ligated or diathermied. Portal hypertension will result in considerable oedema of the peritoneal connections of the liver and all porto-systemic communications will be enlarged and under high pressure. The liver is skeletonised until it is attached only by its vascular connections and common bile duct. The inferior V. cava above and below the liver, portal vein, hepatic artery and common duct are all controlled with fine slings.

Donor hepatectomy

As soon as death of the donor has been confirmed by doctors not concerned with the transplantation operation the abdomen is opened by a bilateral subcostal incision. A cannula is inserted into the superior mesenteric vein and the liver is cooled with chilled Hartmann's solution containing heparin, 2000 U/l. The infusion is by gravity drainage of approximately 1 metre from a drip stand and the solution is at 4° C (Fig. 3). A second cannula is inserted into the inferior V. cava below the renal veins to allow egress of the perfusate and collection of blood which can be used for trans-

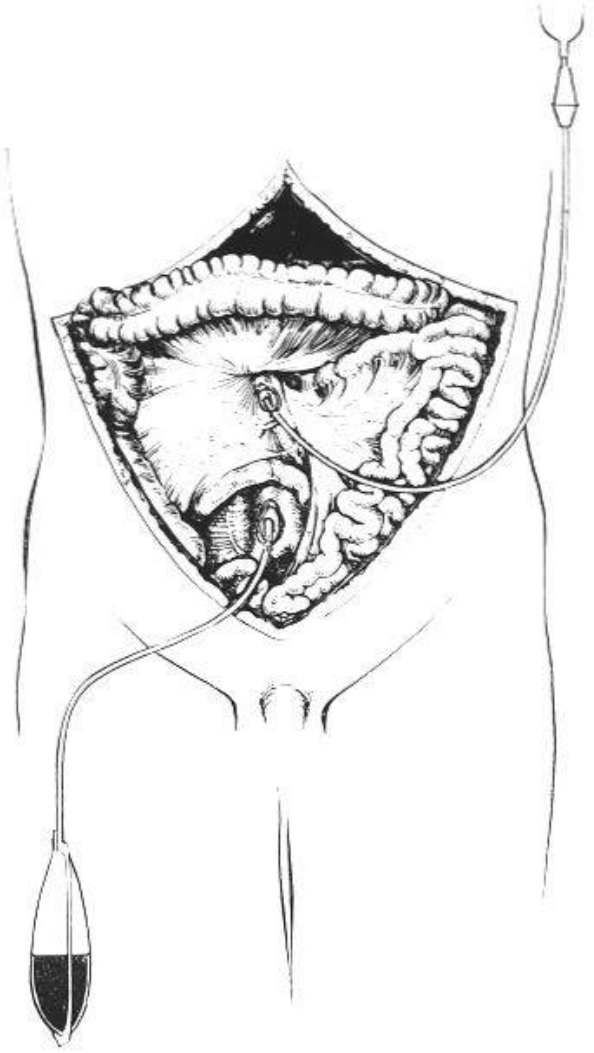

Fig. 3. Technique for cooling of the donor liver by infusion of cold heparinised Hartmann's solution into the superior mesenteric vein. Blood and perfusate are drained from the V. cava below the renal veins.

fusion into the recipient if it is compatible. The cooling of the liver must start within 15 min of death otherwise irreversible damage to the liver will occur. The most suitable donors for liver transplantation are patients for whom resuscitation has been attempted, but for reasons not connected with the transplantation operation, it has been decided to abandon the resuscitation. Under these circumstances it is possible for the transplantation team to be notified so that they can be prepared for the operation, which is complicated and requires a large number of personnel and instruments. Since the availability of suitable donors in any one institution is limited, it is felt that if clinical liver transplantation is to be developed in the United Kingdom it will be necessary for hospitals to collaborate. We do not feel justified in moving a potential donor from one hospital to another for the purposes of organ transplantation. Instead, we move the transplant team and the recipient to the same hospital as the donor. A close liaison has been established between Addenbrooke's Hospital, Cambridge, and King's Col-

lege Hospital, London, where there are complementary interests in liver transplantation and liver disease.

STARZL et al. have utilised whole body perfusion and cooling of the corpse immediately after death (MARCHIORO et al., 1963). After removal of the liver it is perfused continuously under hyperbaric oxygen with dilute blood according to the method of BRETTSCHNEIDER et al. (1968). This has allowed 8 hours of preservation. By simple cooling with Hartmann's solution, followed by infusion of an innocuous plasma solution containing dextrose and bicarbonate, it is possible to have good preservation of the liver for 3–4 hours, but after 4 hours slow deterioration of the liver occurs (SCHALM, 1968; CALNE, unpublished observation).

Once cooling of the donor liver has commenced, hepatectomy is undertaken. The liver is skeletonised as in the recipient operation, the inferior V. cava is divided in the chest, a small cuff of diaphragm around the cava is removed with the specimen and care is taken to ligate individually the two lateral and one posterior phrenic veins. The most difficult part of the donor hepatectomy is dissection of the hepatic and coeliac arteries. Since they are surrounded by a dense plexus of nerves and connective tissue and since the artery is not pulsating, it may be difficult to distinguish its wall from the nervous tissue. It has been found helpful to control the hepatic artery with a sling and then to follow the abdominal aorta up from the region of the renal arteries to the diaphragm in order to locate the origin of the superior mesenteric and coeliac arteries. The superior mesenteric artery is traced distally in order to determine whether an accessory hepatic artery arises from it, in which case the superior mesenteric artery is taken with a cuff of aorta for anastomosis. The coeliac artery is also taken with a cuff of aorta. The splenic, left gastric and gastroduodenal arteries are ligated and divided. Care is taken not to pull excessively on the artery as this may fracture the intima. The V. cava below the liver is divided at the level of the renal veins. The right adrenal vein is ligated and divided, the portal vein and common bile duct are divided at the level of the duodenum. The cannula is removed from the portal vein. In some cases the hepatic artery has been perfused in a similar manner to the portal vein, but this is not essential. After removal, the liver is inserted in a sterile plastic bag surrounded by chilled saline, the outside of the bag is packed with ice.

Insertion of the organ graft

Once it is established that the donor liver is anatomically satisfactory, and is cold, the recipient hepatectomy is completed. In 2 of our cases the donor liver came from a child and was transplanted into an adult. The recipient's inferior V. cava was left intact, the liver being filleted off the cava, which was occluded above and below the liver. This enables the accessory hepatic veins to be individually oversewn or ligated and the main hepatic veins to be clamped (Fig. 4). In the 8 adult orthotopic cases we have excised the liver together with a small amount of V. cava above and below

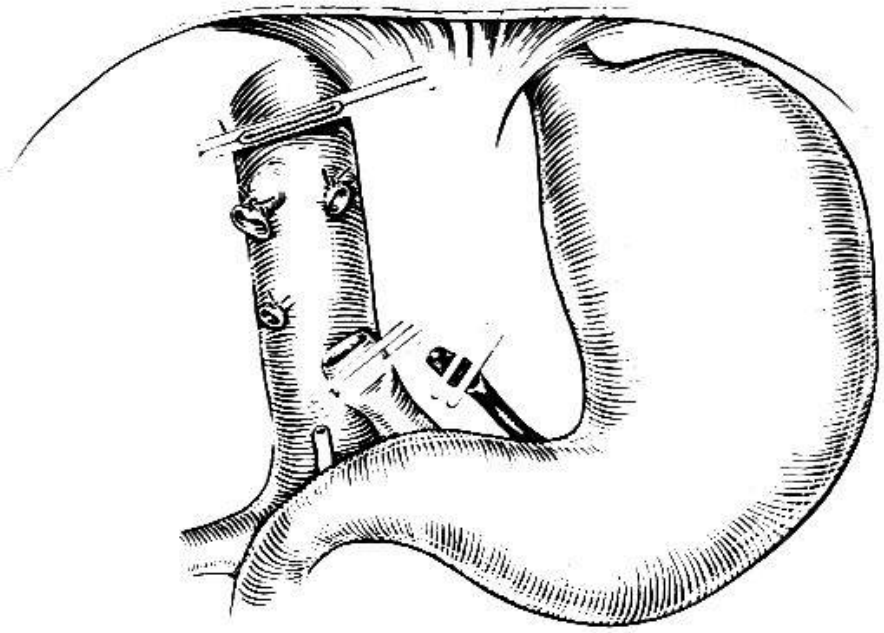

Fig. 4. Diagram of recipient hepatectomy preserving the inferior V. cava in preparation for implanting the liver from a small donor into a large recipient.

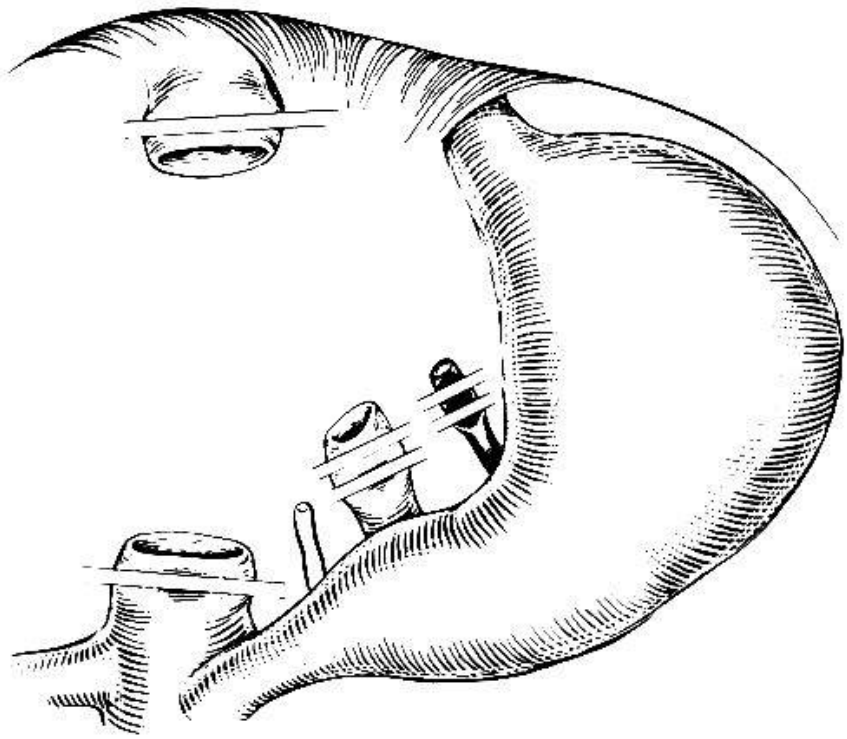

Fig. 5. Diagram showing liver and V. cava removed when the liver donor is of approximately the same size as the recipient.

the organ (Fig. 5). It is not necessary to shunt blood from the cava or portal vein to the superior caval system but there may be a transient fall in blood pressure when these vessels are clamped (STARZL et al., 1968). Rapid infusion of blood into the superior V. cava may be necessary for a short period. The suprahepatic IVC is anastomosed first, the posterior wall is sutured from within the vessel and the anterior wall outside. The portal anastomosis is

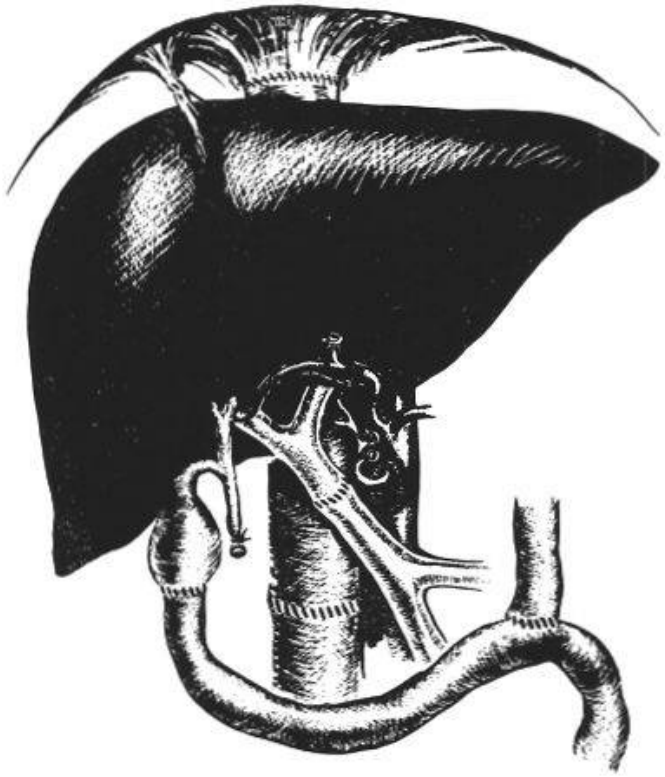

Fig. 6. The diagram of orthotopic liver transplantation in which a Carrel patch at the origin of the coeliac artery is anastomosed to the aorta. An accessory right hepatic artery arising from the superior mesenteric is anastomosed end-to-end to the hepatic artery of the recipient, the V. cava is anastomosed end-to-end above and below the liver and the portal vein end-to-end. The common bile duct is tied and the gall bladder anastomosed to a Roux loop of jejunum. The falciform ligament of the donor is anastomosed to that of the recipient.

then performed in a similar manner end-to-end. Clamps are taken off the portal vein and the first 30 ml of blood are discarded from the intrahepatic IVC, which is then clamped and the clamp on the suprahepatic IVC is removed. The liver is then perfused with portal blood and takes on a purple-pink colour. The coeliac artery of the donor is next anastomosed to the end or the side of the hepatic artery or alternatively the Carrel patch is anastomosed to the aorta just below the recipient coeliac artery. If there is an additional hepatic artery arising from the superior mesenteric, this is also anastomosed to the hepatic artery end-to-end or end-to-side (Fig. 6). When the clamp is removed from the hepatic artery the liver soon becomes a pink colour, pinker than normal probably due to reactive vasodilatation. The infrahepatic IVC is now anastomosed end-to-end to that of the recipient except, in the cases of children's liver transplanted into adults, when the infrahepatic IVC has been tied (Fig. 7). The falciform ligament of the graft is sutured to that of the recipient's to help support the organ and prevent rotation (Starzl et al., 1968).

Biliary drainage has been the most difficult operative procedure. The easiest technique is to anastomose the gall bladder to the duodenum or a Roux loop and tie the common duct below the entrance of the cystic duct

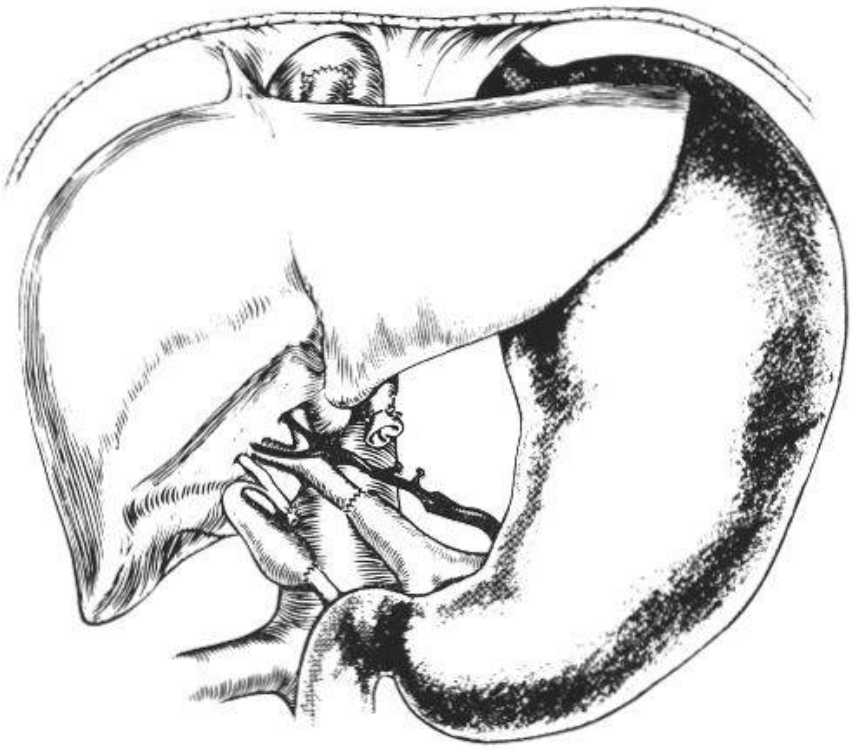

Fig. 7. Diagram of technique in which the liver from a small donor is transplanted into a larger recipient. The V. cava above the liver is anastomosed to the main hepatic vein of the recipient, the intrahepatic V. cava is tied, the coeliac artery is anastomosed to the hepatic, the portal vein end-to-end to the portal vein. The common bile duct of the donor is tied. The fundus of the gall bladder is anastomosed to the common bile duct of the recipient. (By courtesy of the British Medical Journal.)

(Fig. 6). Although this may function satisfactorily, there is danger of ascending infection, which is particularly liable in patients treated with immunosuppressive drugs. Two alternative techniques we have utilised have been to anastomose the common duct end-to-end to that of the recipient with a T-tube splinting the anastomosis, and the long limb being brought out through the recipient's own duct (Fig. 8; STARZL et al., 1966). 2 out of 5 of these anastomoses have leaked. In 3 cases the common duct was ligated below the cystic duct and the fundus of the gall bladder was anastomosed to the recipient common duct, thus preserving the patient's sphincter of Oddi (Fig. 7). In 1 case the gall bladder subsequently became infarcted. This was associated with the multiple septic infarcts of the liver and thrombosis of the recipient's hepatic artery. In the other cases the biliary drainage has been satisfactory. Ampicillin, 2 g, is instilled into the peritoneal cavity, which is closed with unabsorbable sutures. The abdomen is drained if this is felt to be necessary.

Heterotopic technique

A large variety of techniques have been described. We feel that heterotopic transplantation should only be performed when it is impossible to get an orthotopic liver of the correct size. There may be a place for using neonatal

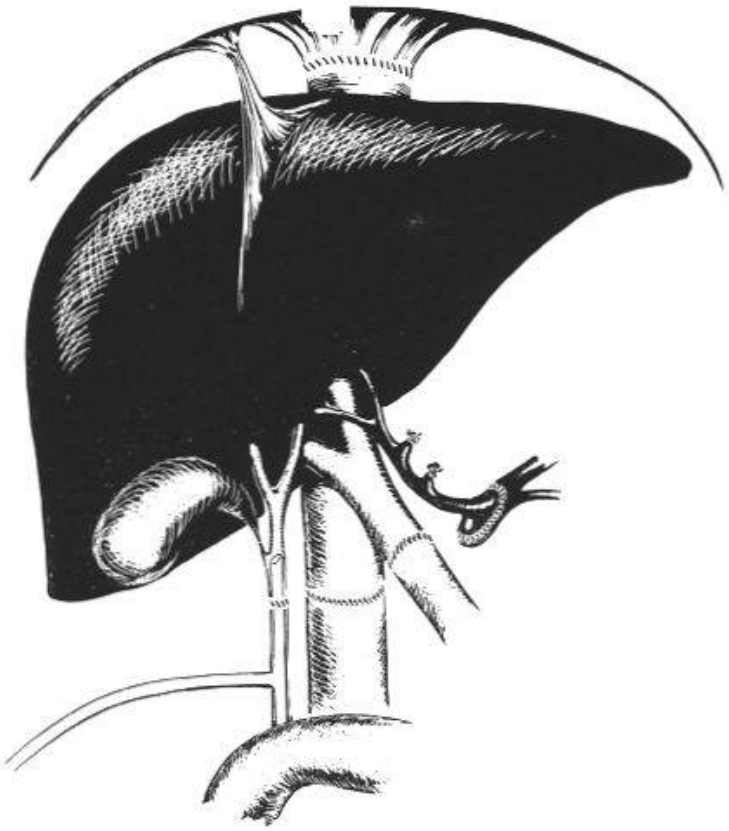

Fig. 8. Diagram of technique of orthotopic liver transplantation in which the common bile duct of the donor has been anastomosed end-to-end to that of the recipient and a T-tube brought out through the recipient common duct.

livers transplanted heterotopically in infants with biliary atresia since donors with livers of the correct size are very uncommon. We have used this technique once and it appeared satisfactory. The patient had severe portal hypertension, the spleen was removed and the small donor liver was placed in the splenic fossa. The splenic vein of the recipient was anastomosed to the portal of the donor, the thoracic aorta with the origin of the coeliac artery was anastomosed end-to-side to the common iliac artery, and the inferior V. cava below the liver anastomosed end-to-side of the common iliac vein (Fig. 9). The suprahepatic IVC was tied and the gall bladder was anastomosed to a Roux loop of jejunum, the common duct was ligated below the junction of the cystic duct. This liver appeared to be functioning satisfactorily with a good scan (Fig. 10), it was producing bile and lowering the serum bilirubin 3 weeks after operation, when the patient died of pneumonia. At autopsy, all the anastomoses appeared satisfactory, as did the liver parenchyma.

Impaired coagulation

This is a danger in all liver transplants, particularly marked in patients with severe parenchymatous hepatic disease with jaundice. There is likely to be a defect of all clotting factors. Patients may be thrombocytopenic before operation but after replacement of blood, if there has been operative

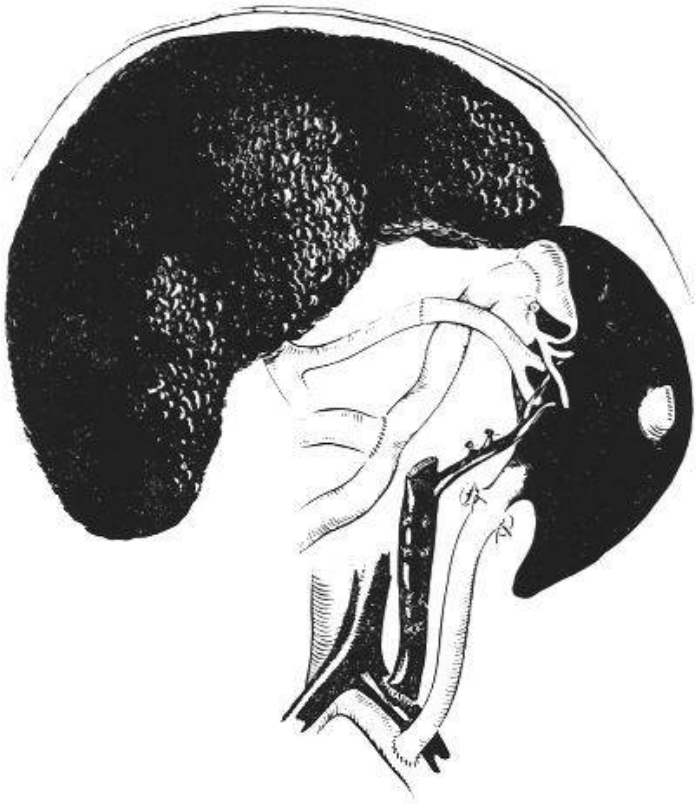

Fig. 9. Diagram of accessory liver transplant of a liver from a small donor to a larger recipient. The common bile duct is tied and the gall bladder anastomosed to a Roux loop of jejunum. The splenic vein of the recipient is anastomosed to the portal vein of the donor. The V. cava above the liver is closed and below the liver drains into a common iliac vein. A segment of abdominal thoracic aorta with the origin of the coeliac artery is anastomosed end-to-side to the recipient common iliac artery.

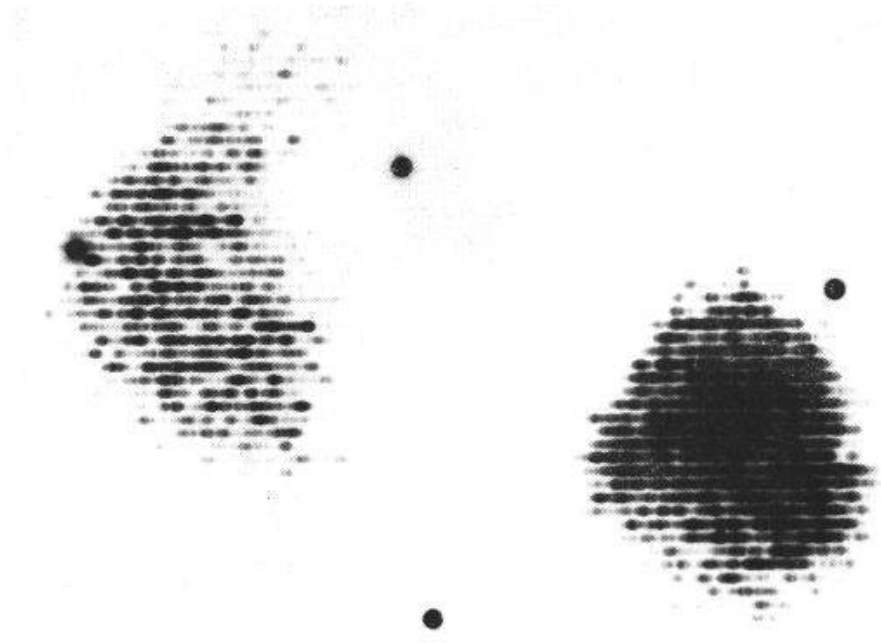

Fig. 10. Technetium scan of accessory liver transplant as shown in Fig. 9. The graft on the right shows a good uptake of radioactive colloid. The patient's own liver in the top left shows impaired uptake.

haemorrhage, thrombocytopenia may be very severe. It is essential to pay scrupulous attention to haemostasis throughout the operation. Prior to surgery, it may be advisable to give fresh frozen plasma and fresh blood. During surgery, if there is a shortage of fresh blood, we use banked blood and at the end of surgery try to give fresh blood together with human fibrinogen. In some cases ε-aminocaproic acid has also been given. If the transplant perfuses well on restoration of the blood supply and there is good initial hepatic function, the bleeding tendency stops very quickly. In one of our cases with an accessory graft, in which the liver had been an hour at 37° C without a blood supply before it was cooled, the ischaemic damage resulted in an uncontrollable haemorrhagic state and death of the patient the following day. A similar sequel occurred in a patient with an orthotopic liver transplant. This patient was hypotensive during surgery and the shocked state resulted in poor perfusion of the graft. Both of these patients suffered from severe cirrhosis.

Postoperative care and immunosuppression

If function of the graft is poor initially, then the patient will probably not survive. If the liver functions satisfactorily, the patient recovers very quickly from the anaesthetic and is usually awake at the end of the operation. This was particularly dramatic in a liver transplant performed on a 20-year-old man who was in deep coma prior to surgery and woke up after the operation and wanted to know what had happened to him. It is advisable to infuse glucose continuously in the immediate postoperative period as the serum glucose can fall rapidly. The patient is encouraged to do deep-breathing and leg exercises. The nasogastric tube is removed when bowel sounds return and the patient is put onto oral fluids.

The best method of immunosuppression has yet to be defined in liver transplantation. Certain principles are established. First it is essential not to give the patient large doses of azathioprine as this may have hepatotoxic effects: 1 mg/kg/day is the most commonly used dose. Steroids are given as for renal transplantation, beginning with 100 mg prednisolone a day and tailing down as quickly as possible. Antilymphocyte globulin has been given to some of our patients, kindly provided by Prof. BRENDEL and Prof. Sir MICHAEL WOODRUFF. The product supplied by Prof. BRENDEL was given in large doses up to 20 ml per day intravenously. After two weeks the patients developed rigors, pyrexial reactions and pain in the back. Unless the tissue match is particularly good, it is likely that steroids and azathioprine will need to be continued indefinitely. Antibiotics were administered when it was felt that there was clinical evidence of infection and particularly when this was supported by culture studies of the blood, bile, wound or sputum.

Pathological changes

These have been described elsewhere (CALNE et al., 1968b). Bile stasis and progressive centrilobular necrosis have been the most prominent morphological changes. Biopsies have shown centrilobular bile stasis eventually leading to a variable degree of centrilobular liver-cell necrosis in the absence of extrahepatic biliary obstruction. These changes may be a manifestation of rejection, drug toxicity or a mixture of the two. In addition we have observed mild to moderate cellular infiltration and fibrosis in the portal tracts in several patients. Cellular infiltration has in some cases extended into the liver parenchyma. This is similar to the pattern of rejection observed in liver allografts in other species. Severe ischaemic damage was noted in the accessory liver allograft referred to above. Some ischaemic damage was noted in all livers but this was often surprisingly mild. One patient who had septicaemia prior to surgery as a result of chlorambucil treatment for her primary cholangiocarcinoma developed multiple septic infarcts in the graft (CALNE et al., 1968b). At autopsy, there was clot in the recipient hepatic artery where the clamp had been applied. This was the only vascular anastomotic complication that occurred in our series of 12 cases. There were, however, 4 biliary leaks and 3 fatal lung infections.

Results

There have been a number of clinical liver transplants performed in a variety of institutions but the only long-term survivors have been at Denver and in our series. STARZL et al. (1968) published their experience of 10 patients transplanted between July 1967 and July 1968. At that time, six patients were alive at 1 year, 5 months, 4 months, 3 months, 6 weeks and 3½ weeks. Of the total 30 liver transplants in Denver, of which 4 were heterotopic, three patients lived more than 1 year, seven more than 6 months and eleven more than 6 weeks. Seven patients are alive at the present time (STARZL, personal communication). Our own results are shown in Table 1.

Conclusion

The experimental background of liver transplantation is now well established. The immunosuppressive effect of porcine liver allografts is of interest, even if confined to the pig, since it is not unlikely that the biological principles involved may be of a more general nature. The application of donor-specific immunosuppression is the chief objective of clinical organ transplantation, but until this is achieved it is necessary to give traditional immunosuppressive drugs at the maximum tolerated dose, and it is desirable to have a good tissue match between donor and recipient. The shortage of available donors and our inability to transport preserved liver long distances makes selective tissue typing difficult in practice. Cooperation between clinicians in different hospitals and improved methods of liver preservation

Table 1

Recipient (sex, age, diagnosis)	Donor (sex, age, diagnosis)	Technique*	Immuno-suppression	Survival	Comment
♂, 10 months Biliary atresia	♂, 2 years Tracheitis	O Accessory hepatic artery Cholecystojejunostomy	Nil	30 min	Cardiac arrest, cause undetermined
♂, 43 years Liver cell carcinoma and cirrhosis	♀, 35 years Subarachnoid haemorrhage	O Choledochodochostomy	Nil	1 day	Uncontrollable haemorrhagic state
♂, 17 years Hepatic necrosis	♀, 41 years Subarachnoid haemorrhage	O Choledochodochostomy	Steroids	1 week	Liver necrosis (? cause)
♂, 46 years Cholangiocarcinoma	♂, 64 years Head injury	O Cholecystojejunostomy	Azathioprine, steroids, ALG	3 weeks	Bile stasis, biliary fistula, septicaemia
♀, 58 years Biliary cirrhosis	♀, 43 years Barbiturate overdose	O Choledochodochostomy	Azathioprine, steroids, ALG	7 weeks	Bile stasis, pneumonia, biliary fistula
♂, 57 years Cholangiocarcinoma	♂, 52 years Subarachnoid haemorrhage	O Choledochodochostomy	Azathioprine, steroids	3 months	Biliary fistula, pneumonia
♀, 46 years Cholangiocarcinoma	♂, 5 years Mumps encephalitis	O Recipient IVC left intact Cholecystocholedochost.	Azathioprine, steroids	4 months	Biliary fistula, septic infarction of liver, clot in hepatic artery
♂, 41 years Liver cell carcinoma	♂, 13 years Head injury	O Accessory hepatic artery Choledochodochostomy	Azathioprine, steroids, ALG	4 ½ months	Rejection, bile stasis, centrilobular necrosis
♀, 44 years Liver cell carcinoma	♂, 4 years Head injury	O IVC left intact Cholecystojejunostomy	Azathioprine, steroids	Alive 20 months	Out of hospital Normal liver function
♂, 53 years Cirrhosis, liver cell carcinoma	♂, 37 years Head injury	O Previous portocaval shunt and colonic exclusion Cholecystocholedochost.	Azathioprine, steroids	11 months	Sepsis, internal biliary fistula
♂, 47 years Cirrhosis	♀, 50 years Head injury	A To splenic fossa Cholecystojejunostomy	Nil	1 day	Uncontrollable haemorrhagic state
♂, 2 years Biliary atresia	♂, 6 weeks Microcephaly	A To splenic fossa Cholecystojejunostomy	Azathioprine, steroids	3 weeks	Pneumonia

* O = Orthopic, A = Accessory

and transport are urgently required. Despite our present difficulties there can be no doubt that liver transplantation in man will eventually provide valuable therapy, comparable to that already resulting from kidney grafting.

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Zusammenfassung

Die experimentellen Grundlagen zur Lebertransplantation sind heute klar umschrieben. Die immunosuppressive Wirkung von Schweineleber-Allotransplantaten ist von Interesse, da es nicht unwahrscheinlich ist, dass – obwohl dieses Phänomen nur bei Schweinen beobachtet werden kann – die dabei beteiligten Mechanismen allgemeiner Natur sind. Die Anwendung der spenderspezifischen Immunosuppression ist das Hauptanliegen der klinischen Organtransplantation. Bis dies jedoch erreicht ist, muss man immunosuppressive Medikamente bis zur höchsten ertragbaren Dosis verabreichen. Es ist auch wünschbar, zwischen Spender und Empfänger eine möglichst gute Gewebeverträglichkeit zu haben. Die Seltenheit, geeignete Spender zu finden, und die Unmöglichkeit, eine konservierte Leber über grössere Distanzen zu transportieren, erhöhen die Schwierigkeit, eine Auswahl des Spenderorgans auf Grund einer Histokompatibilitätstestung zu treffen. Es ist unbedingt notwendig, die Zusammenarbeit zwischen den Ärzten verschiedener Spitäler und die Methoden der Konservierung und des Transportes der Leber zu verbessern. Trotz der gegenwärtigen Schwierigkeiten wird die Lebertransplantation beim Menschen ohne Zweifel eine anerkannte Behandlungsart werden, wie dies bereits für die Nierentransplantation der Fall ist.

Résumé

Les bases expérimentales de la transplantation du foie ne sont pas encore très bien définies. L'action immunosuppressive des greffes de foie de porc est d'un grand intérêt, même s'il ne s'applique pour le moment qu'au porc, car il n'est pas concevable que les réactions biologiques en jeu ne s'appliquent d'une manière plus générale. C'est l'utilisation de cette immunosuppression spécifique au donneur qui est l'objectif principal de la transplantation clinique d'organe; à défaut de cela, il est nécessaire de donner des médicaments traditionnels immunosuppresseurs aux doses maximales tolérables, et il faut rechercher une concordance aussi parfaite que possible entre les tissus du donneur et du récipiendaire. Le manque de donneurs adéquats et notre impossibilité de transporter sur de longues distances du tissu hépatique intact, rend la typologie tissulaire sélective pratiquement irréalisable en pratique. Il est absolument indispensable de réaliser une meilleure coopération entre les cliniciens des différents hôpitaux, et d'améliorer nos méthodes de conservation et de transport de tissu du foie. Malgré les difficultés pré-

sentes, il ne fait aucun doute que la transplantation de foie chez l'homme deviendra une méthode thérapeutique valable, comparable aux résultats obtenus avec la transplantation rénale.

Riassunto

Le basi sperimentali per il trapianto del fegato sono ora chiaramente definite. L'azione immunosoppressiva degli allotrapianti di fegato di maiale è interessante, in quanto non è da escludersi che i meccanismi responsabili – quantunque questo fenomeno si osservi solo nel maiale – siano di natura generale. L'applicazione di un'immunosoppressione specifica sul donatore rappresenta il problema maggiore del trapianto di organi in clinica. Fino al momento in cui questi risultati saranno ottenuti, è necessario somministrare i farmaci immunosoppressivi alle dosi massime tollerate. Bisogna pure sforzarsi di ottenere la migliore compatibilità tessutale possibile fra donatore ed ospite. Il fatto che raramente si trovano dei donatori adatti, e l'impossibilità di trasportare un fegato conservato su grandi distanze, aumentano la difficoltà della scelta di un organo prelevato dal donatore sulla base delle prove di istocompatibilità. È assolutamente necessario di migliorare sia la collaborazione fra i medici dei diversi ospedali che i metodi di conservazione e di trasporto del fegato. Malgrado le difficoltà attuali, il trapianto di fegato sull'uomo diventerà senza dubbio una terapia universalmente riconosciuta, come è già il caso attualmente per il trapianto renale.

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