

Metabolic considerations of the portal circulation

In the last 20 years, understanding has evolved about what has become known as the 'hepatotrophic' concept. The hepatotrophic hypothesis holds that there are specific substances in the portal venous blood, not found in equal concentration in other kinds of blood, which are important for the maintenance of normal hepatic morphology, function, and the capacity for regeneration (Starzl & Terblanche 1979).

Hypotheses are usually formulated to explain observations that are otherwise incomprehensible, and so it was with the suggestion that portal venous blood contains hepatotrophic substances. The phenomena that required explanation were those which followed completely diverting portacaval shunt (Eck's fistula).

THE ENIGMA OF ECK'S FISTULA

When the Russian surgeon, Nicholas Eck, described his technique and experience with end-to-side portacaval shunt in dogs, he was convinced that the procedure was harmless, and that it would find clinical application for the treatment of patients with intractable ascites (Eck 1877). These hopes were dampened by Pavlov, the great St. Petersburg physiologist, and his associates who demonstrated liver atrophy, fatty infiltration, and other striking abnormalities in livers deprived of portal blood flow by completely diverting portacaval shunt (Hahn et al 1893). Furthermore, they noted in their dogs the almost invariable development of weight loss, alopecia, and a progressive neurological disorder which premonitored death. The complex neurological manifestations were called 'meat intoxication' because they could be precipitated with a high protein diet. The later work of McDermott et al (1954), showed that the syndrome was associated with elevations in blood ammonia, and it is now established that the canine disease was the analogue of hepatic encephalopathy in humans.

It was obvious that something taken from the blood supply of the liver was the explanation for the devastating

anatomical and physiological changes which resulted from Eck fistula. Whether the loss of specific substance(s) contained in the portal blood (the qualitative theory) was responsible or if these consequences simply followed from a reduction of the total hepatic blood flow (the flow hypothesis) was disputed for decades. The dispute did not qualify as a great debate since there was so little movement on both sides over long periods of time as summarized in a recent monograph (Starzl et al 1983b) and because publications favouring the flow hypothesis by Mann (1944), Child et al (1953) and Fischer et al (1954) and their associates were not challenged. Yet, scepticism remained. As late as 1961, Bollman, one of the foremost students of experimental hepatic surgery, wrote, 'In the 83 years since it was first reported, the Eck fistula has been reasonably successful in hiding its secrets as well as giving rise to many additional questions fundamental to an understanding of the functions of the intestine, liver, and brain.'

THE MODERN EXPERIMENTS

The double liver models

Within two years after Bollman wrote those words, inquiries were begun which laid bare the secrets of the Eck fistula. The experiments were originally designed to determine the optimal techniques for revascularization of auxiliary liver homografts. It was hoped that such extra livers could be transplanted to a heterotopic location in humans without disturbing the diseased native liver. When auxiliary dog livers were placed in the paravertebral gutter, given an hepatic arterial supply, and provided with a portal venous inflow from the inferior vena cava (Fig. 115.1), the extra livers atrophied with astonishing speed (Starzl et al 1964). The atrophy could be reduced or prevented if the homografts were provided with portal inflow from the recipient splanchnic venous system (Marchioro et al 1965). In subsequent experiments (Marchioro et al 1967), the same interactions were demonstrated between two portions of the dog's own liver in which the only physiological vari-

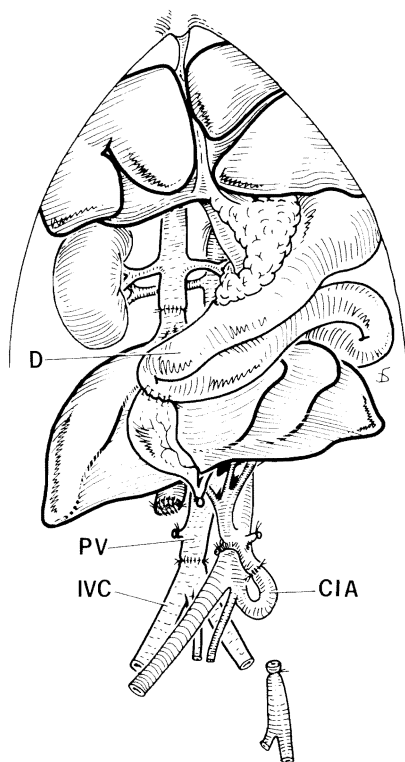


Fig. 115.1 Auxiliary liver transplantation in dogs. Note that the reconstituted portal blood supply is from the distal inferior vena cava. D = duodenum; CIA = common iliac artery; PV = portal vein; IVC = inferior vena cava. Note donor liver placed below the renal vessels. Reproduced with permission from Starzl et al 1964

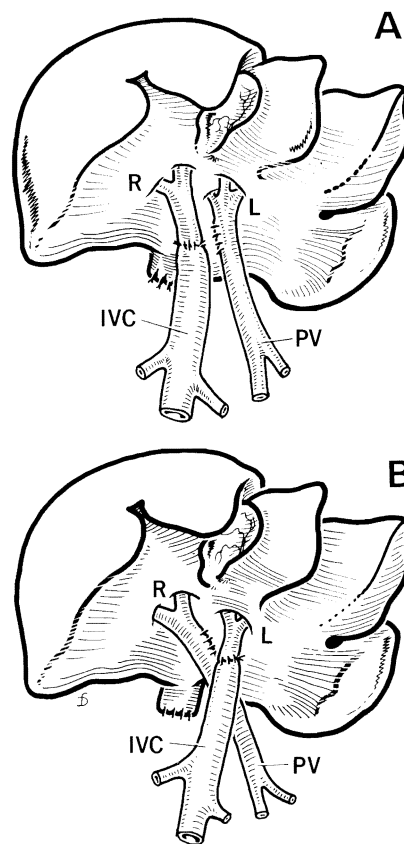


Fig. 115.2 The operation of partial (split) transposition in dogs. Note that one of the main portal veins (left in A, right in B) retains the natural splanchnic flow and that the other one receives the total input of the suprarenal inferior vena cava. PV = portal vein; L = left branch portal vein; R = right branch portal vein; IVC = inferior vena cava. Reproduced with permission from Marchioro et al 1967

able was the kind of venous inflow directed into the right and left portal vein branches (Fig. 115.2). The liver fragment given normal splanchnic flow hypertrophied and underwent hyperplasia compared to the atrophic portion nourished with high flow systemic venous or arterial blood (Marchioro et al 1967, Starzl et al 1973b). It was evident from such 'split liver' preparations that some substance(s) present in the portal venous blood which was vital for the health of the liver was being efficiently extracted by the liver tissue to which the splanchnic venous blood was first exposed, thus becoming unavailable for the other liver or liver fragment. When venous blood from the splanchnic system was subdivided in another kind of split liver experiment (Fig. 115.3), the venous effluent from the pancreas had better hepatotrophic qualities than that from the intestines (Starzl et al 1973 b), an advantage that was reduced or eliminated with pancreatectomy or the production of alloxan diabetes (Fig. 115.3) (Starzl et al 1975a, b, c). Thus, the circumstantial evidence had become strong that the elusive substance in portal venous blood was endogenous insulin.

Hormone infusion experiments

In 1975, the insulin theory was tested directly (Starzl et al 1976). Dogs with portacaval shunt had insulin infused directly into one of the tied-off main portal vein branches (Fig. 115.4). In the infused lobes, this simple expedient prevented the liver cell atrophy and multiple ultrastructural changes in the hepatocytes which follow Eck fistula and which were present in the contralateral uninfused liver lobes.

Evisceration experiments

The importance of insulin as a hepatotrophic substance was further emphasized with extirpation of various splanchnic viscera including the pancreas (Starzl et al 1978a, b). In all of the double liver, infusion and evisceration experiments, other minor but cumulatively important hepatotrophic effects were observed independent of insulin, but none had the potency and significance of insulin.

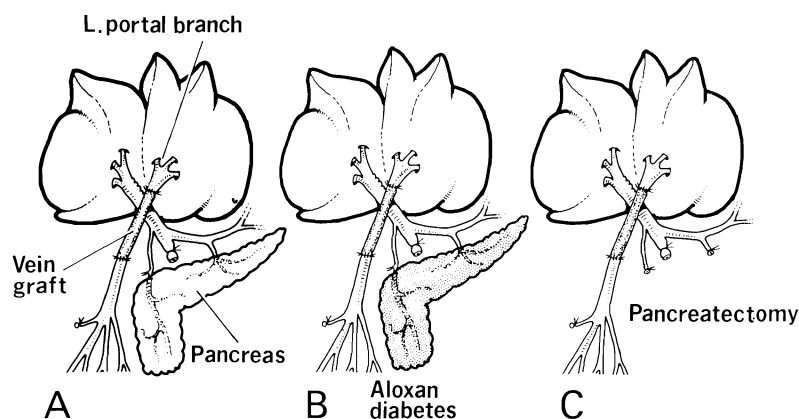


Fig. 115.3 Splanchnic division experiments. In these dogs, the right liver lobes received venous return from the pancreaticogastroduodenosplenic region, and the left liver lobes received venous blood from the intestines. A = non-diabetic dogs; B = alloxan-induced diabetic dogs; C = dogs with total pancreatectomy. Reproduced with permission from Starzl et al 1975b

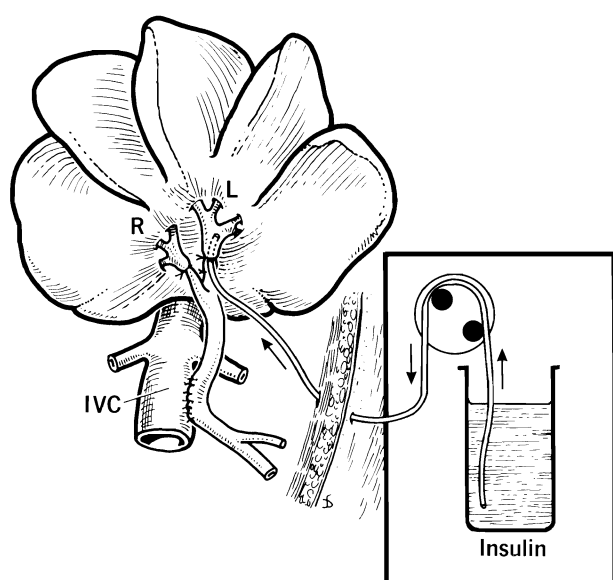


Fig. 115.4 Experiments in which Eck's fistula is constructed and postoperative infusions of hormones are made into the left portal vein. R = right portal branch; L = left portal branch; IVC = inferior vena cava

THE IMPLICATIONS OF ORGANELLE CHANGES

For a long time, it was assumed that the histopathological changes caused by portacaval shunt in dog livers were species specific. However, it has become obvious that the resulting changes in the liver are much the same in rodents, dogs, swine, sub-human primates and humans (Putnam et al 1976). Furthermore, the atrophy proceeds with surprising speed, being 90% complete in dogs within three or four days (Starzl et al 1976).

With the development of electron microscopic techniques, many observers, whose work is summarized else-

where (Starzl et al 1983b), described the sweeping changes in hepatocyte organelles which paralleled the atrophic changes in the rapidity of their development. The most specific alterations were depletion and disruption of the rough endoplasmic reticulum (RER) and reduction in the membrane-bound polyribosomes. Since RER is the 'factory' of the cell (Fawcett 1981, Jones et al 1966), a consequent reduction in many hepatic biosynthetic processes would be expected.

THE BIOCHEMICAL POINT-OF-VIEW

Numerous studies summarized elsewhere (Starzl et al 1983b) have verified the foregoing expectations and have illustrated the spectrum of changes in hepatic function that may be expected after portacaval shunt. The effort of portal diversion on hepatic lipid metabolism has been unusually well studied. Reductions occur in the synthesis of cholesterol, triglycerides, and other moieties including the low-density lipoproteins which are responsible for the transport of endogenous cholesterol. Other synthetic pathways that are depressed by Eck fistula in experimental animals include those of bile acid metabolism as well as the hepatic urea (Krebs-Henseleit) cycle.

As detailed studies are made of other hepatic synthetic or metabolic processes after portacaval shunt, it will not be surprising if all are found to follow the same pattern. This possibility has been supported by many studies during the last 15 years, (Starzl et al 1983 b), that have shown how portacaval shunt lowers the activity of the hepatic microsomal mixed-function enzyme system. This enzyme system, for which multiple cytochrome P-450 and P-448 species serve as terminal oxidases, is central to the metabolism of a variety of drugs and chemicals as well as of endogenous compounds such as steroids and fatty acids. Thus, depression of this enzyme system predictably will

cause enormous numbers of subtle and profound metabolic effects after portal diversion.

It is rare in biological systems to have concepts as simple as the role of insulin as the principal hepatotrophic factor in portal venous blood. Substances other than insulin are also hepatotrophic and have a significant cumulative affect. However, no single factor rivals insulin in importance. Thus, it is not surprising that ultra-structural changes identical to those caused by Eck fistula can be induced in the livers of rats by the simple expedient of producing alloxan diabetes (Reaven et al 1973). Similarly, Kato (1977) has shown that the activity of the mixed-function oxidase system is depressed in rats after alloxan-induced diabetes in exactly the same way as it is depressed by portacaval shunt.

THE USE OF PORTACAVAL SHUNT FOR METABOLIC OBJECTIVES IN HUMANS

The changes in metabolism caused by portacaval shunt have been exploited to treat three inborn errors of metabolism. In essence, the hepatic injury caused by portacaval shunt and the consequent metabolic perturbations have been used to offset the even greater morbidity caused by the inborn error.

Glycogen storage diseases

Type 1 glycogen storage disease (GSD) was the first inborn error of metabolism to be defined in terms of a specific enzyme defect (glucose-6-phosphatase). In Type 3 GSD, hepatic amylo-1,6-glucosidase is deficient and in Type 6 disease, phosphorylase is deficient. When portacaval shunt was used to treat the glycogen storage diseases more than 20 years ago (Starzl et al 1965), the rationale was that if splanchnic venous blood was short-circuited around the liver, alimentary glucose would be made more readily available to peripheral tissues. It was envisioned that hypoglycaemia would be relieved thereby and that glycogen deposition would be slowed in the liver, which would no longer be presented with such a heavy glucose load at each meal. As already described, the consequences of portacaval shunt were more subtle and wide-ranging than that simplistic view suggested (Starzl et al 1973c, 1983b).

After portal diversion, most of the children who had pre-existing hypoglycaemia did not have relief of this symptom or else the relief was not complete (Starzl et al 1973c, 1983b). However, all of the patients underwent major growth spurts, the hepatomegaly was usually relieved, the hyperlipidaemia which is characteristic of Type 1 disease was profoundly and permanently reduced, and correction of other metabolic problems including abnormal bleeding, uric acid elevations and abnormal

calcium metabolism was observed (Starzl et al 1973c, Starzl et al 1983b). These palliative effects were obtained with an acceptable morbidity although at least one of the 10 children treated developed evidence of hepatic encephalopathy (Starzl et al 1983b).

Portacaval shunt for the treatment of GSD was virtually abandoned after it was found that continuous night-feeding, as advocated by Greene et al (1976), could achieve the same beneficial effects without the threat of encephalopathy. In intractable cases, it may be that liver transplantation should be offered as the first operation, since complete correction of Type 1 glycogen storage disease has been achieved with liver replacement by Malatack et al (1983). The recipient, who had been treated with an end-to-side portacaval shunt eight years previously, has had essentially normal carbohydrate metabolism from within a few minutes after revascularization of her new liver until the present time, almost three years later.

Familial hypercholesterolaemia (FH)

Patients with the disease of FH have an absence or deficiency of cell membrane low density lipoprotein (LDL) receptors. Because of this, they cannot catabolize endogenous cholesterol normally and they lack a 'switch-off' mechanism to control lipid (especially cholesterol) synthesis (Goldstein et al 1983). Patients who have the homozygous genetic trait are notoriously resistant to all forms of conventional therapy and, until recently, end-to-side portacaval shunt has been the most effective method of reducing serum cholesterol levels (Starzl et al 1973a, 1983a). In a series of the author's own patients, as well as in patients treated elsewhere with portal diversion, total serum cholesterol concentrations have almost always declined from 20 to 60% (average about 35%) after portacaval shunt (Starzl et al 1983a). This decline usually is maintained permanently.

The mechanisms which cause lipid lowering in such patients are qualitatively similar to those in experimental animals discussed above, namely a reduction in the hepatic synthesis of cholesterol and other lipids. In a number of patients whose lipid metabolism was studied before and after portacaval shunt, cholesterol and LDL synthesis was greatly reduced along with that of bile acids. The most significant finding was the reduction of total body cholesterol mass by one half or more over a period of 12–18 months (McNamara et al 1982). With such data, it has not been hard to explain the extraordinary shrinkage or disappearance of tendinocutaneous xanthomas which are characteristically found in such patients (Starzl et al 1973a, 1974, 1983a) (Fig. 115.5).

In spite of its striking benefits to patients with homozygous FH, portacaval shunt has been only palliative. The palliation has been incomplete, since normal serum cholesterol values have not been achieved in any patient with



A



B

Fig. 115.5 The hands of a patient with hyperlipidaemia two weeks before (A) and 16 months after (B) portacaval shunt. Reproduced with permission from Starzl et al 1974

homozygous disease. The usual finding has been for serum cholesterol concentrations to drop from the range of 1000 to 600 mg% or from the 800 range to 500 mg%, etc. The new levels have been too high to allow the routine control or reversal of the cardiovascular complications of the disease.

The observations and experience with portacaval shunt for FH have subtly influenced the perception of the pathogenesis of this disorder. Previously, it was suspected that FH was a pancellular disease in which the deficiency of LDL receptors throughout the body was responsible for the runaway cholesterol synthesis. When it was realized that portacaval shunt had such a drastic affect on serum cholesterol metabolism, it became almost certain that the liver played a far more central role in cholesterol metabolism than had been appreciated, and it was suggested that liver transplantation might be curative (Starzl et al 1983a). A number of other studies have supported the hypothesis of hepatic control of cholesterol metabolism (Goldstein et al 1983). In early 1984, a child with homozygous FH whose heart had been destroyed by cholesterol deposits was treated by liver transplantation at the same time as the heart was replaced. The serum cholesterol levels were reduced about 70% from 1000 mg% to below 300 mg%, at the same time as rapid reabsorption of her tendinous cutaneous xanthomas occurred (Starzl et al 1984). Thus, as with glycogen storage disease, the most effective form of metabolic engineering in FH has been with the provision of a new liver.

Alpha-1-antitrypsin deficiency

In this disease, the liver produces an abnormal alpha-1-antitrypsin which cannot be effectively transported out of the hepatocytes. The entrapped alpha globulin apparently causes irritation that leads to hepatic cirrhosis, portal hypertension and hepatic failure (Hood et al 1980).

We have performed end-to-side portacaval shunt in three children with the cirrhotic liver disease of alpha-1-antitrypsin deficiency (Starzl et al 1983c). After follow-ups of six to nine years, the children are still alive. The possibility that the liver damage of alpha-1-antitrypsin deficiency had been slowed was supported by the histopathological studies of biopsy specimens obtained operatively and postoperatively in two of these patients. Many months after operation re-biopsy showed that the percentage of hepatocytes containing the alpha-1-antitrypsin globules was substantially reduced (Starzl et al 1983c).

Our speculation has been that portacaval shunt diminished the synthesis of the alpha-1-antitrypsin, presumably by altering the function of the RER and its ribosomes (see earlier) without commensurately reducing the transport of this alpha protein. With a better equilibrium between the production and excretion of the alpha-1-antitrypsin, it is

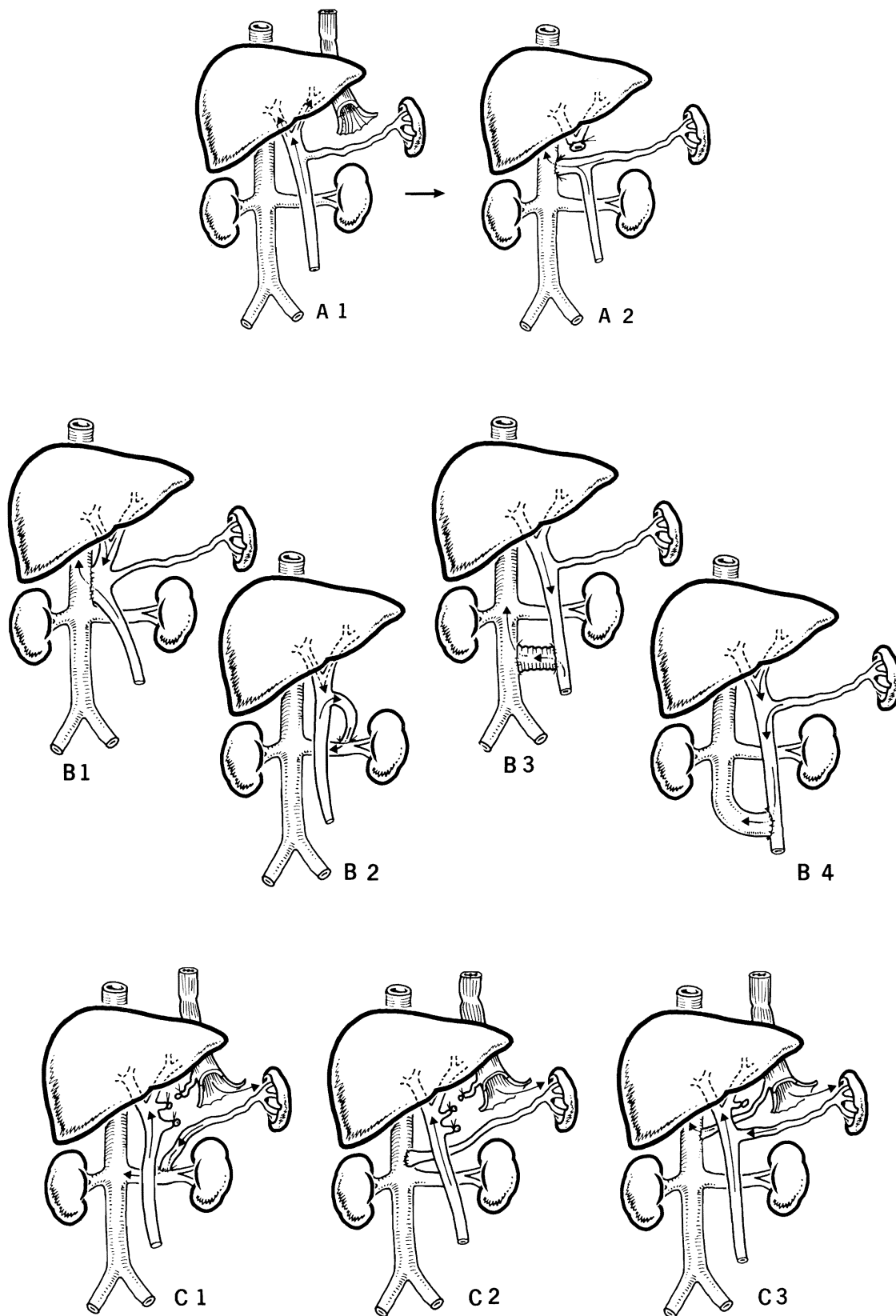


Fig. 115.6 Kinds of portal-systemic shunts: A. End-to-side shunt. B. Variety of side-to-side shunts: B1 = portal-caval; B2 = spleno-renal; B3 = interposition H. graft—mesenterico-caval; B4 = mesenterico-caval (Clatworthy). C. Selective portal-systemic shunts: C1 = distal spleno-renal; C2 = spleno-caval; C3 = coronary-caval

possible that its intracellular accumulation has been slowed or possibly even reversed.

As with the two other inborn errors, the most effective way of treating alpha-1-antitrypsin deficiency has been with provision of a phenotypically normal liver (Hood et al 1980, Starzl et al 1982). This has been accomplished in several dozen patients, with the longest postoperative survival now being more than eight years. After the operation, the Pi (protease inhibitor) type of the recipient permanently becomes that of the phenotypically normal donor, and the depressed alpha-1-antitrypsin levels are promptly restored to normal. In future years, portacaval shunt to palliate alpha-1-antitrypsin deficiency will be rarely used if ever, whereas the direct and logical step of performing liver replacement will become common.

PORTAL SYSTEMIC SHUNT FOR COMPLICATIONS OF PORTAL HYPERTENSION

The inescapable conclusion from all of the work on the hepatotrophic concept in the last two decades, is that portal-systemic diversion is inherently harmful to the liver. Exploitation of portal diversion for its increasingly well understood metabolic effects has only contributed to suspicion about the use of portacaval shunt for mechanical and haemodynamic objectives.

The kinds of portacaval shunts that have been used for haemodynamic objectives are shown graphically in Figure 115.6. As summarized elsewhere, there is good reason to believe that all of the side-to-side shunts (Fig. 115.6B) result in complete diversion of the portal blood if they are made of adequate size, just as occurs with a straight-forward end-to-side shunt (Fig. 115.6A). In contrast, the selective shunts devised and popularized by Dean Warren and his associates in Atlanta, Georgia do compress oesophageal varices while at the same time maintaining a substantial portion of residual hepatopetal flow. For this reason, the selective shunts in Figure 115.6C are the most desirable physiologically.

It has been disappointing that randomized trials comparing selective distal splenorenal versus totally diverting shunts have not revealed a striking divergence in the patient life survival curves. Nevertheless, the incidence of hepatic encephalopathy has been less in practically all of these trials (Starzl et al 1983b). If this trend continues, a better quality of life as opposed to mere survival may prove to be the only justification for the selective shunts. It will then have to be concluded that the survival curves are similar with the various kinds of surgical treatment, because patients with progressive hepatic diseases severe enough to warrant such decompressing procedures have a course so immutable that the relative merits of different kinds of palliative treatment cannot be accurately measured.

HEPATOTROPHIC FACTORS IN REGENERATION

It is almost certain that the same portal substances which regulate the size of hepatocytes and the function of these liver cells play an important role in at least permitting, or possibly even initiating, the cell renewal (regeneration) by which the liver restores itself to its original size after part of it has been removed. This subject has been reviewed elsewhere (Starzl and Terblanche 1979) and is discussed in Chapter 5. Suffice it to say that the events of regeneration are enormously complex and although insulin is undoubtedly of great importance in the process, its role may not be so overriding as it has been shown to be in the regulation of hepatocyte size, organelle preservation and function.

SUMMARY

In all species so far studied, including man, portacaval shunt causes the same changes in liver morphology, including hepatocyte atrophy, fatty infiltration, deglycogenation, depletion and disorganization of the rough endoplasmic reticulum (RER) and its lining polyribosomes, and variable but less specific damage to other organelles. Many and perhaps all hepatic biosynthetic processes are quickly depressed, largely secondary to the selective damage to the RER which is the 'factory' of the cell.

These structural and metabolic changes in the liver after portacaval shunt are caused mainly by the diversion around the liver of multiple hepatotrophic substances in portal venous blood, of which endogenous insulin is the most important. The subtle but far reaching changes in hepatic function after portal diversion have made it possible to use portacaval shunt to palliate three inborn errors of metabolism (glycogen storage disease, familial hypercholesterolaemia, and alpha-1-antitrypsin deficiency). However, a far more specific method of treating these three diseases has been by liver transplantation (Chs. 118, 119, 121) whereby the defective liver is replaced by a homograft of normal metabolic phenotype.

Because of the harm caused to the liver by portal diversion, the use of completely diverting portacaval shunts to treat complications of portal hypertension has been viewed with increasing disapproval in recent years. If portal diversion must be done for the control of variceal haemorrhage, a selective procedure such as the Warren shunt (Ch. 113) is theoretically superior to the completely diverting shunts since some of the hepatopetal flow is thereby retained, assuring exposure of the liver to portal hepatotrophic substances.

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