In: Liver and Biliary Disease 3rd Edition 1992
pgs-1335-1345

1435

CHAPTER 50

Portal–Systemic Shunting for Metabolic Disease

Thomas E. Starzl, Kendrick A. Porter & Shunzaburo Iwatsuki

For many years portal venous diversion has been used for the haemodynamic objectives of stopping or preventing haemorrhage from oesophageal varices or, less commonly, to treat intractable ascites. Since 1963, a new dimension has been added to the old operation of portacaval shunt by employing this procedure to alter favourably the course of three inborn errors of metabolism: glycogen storage disease, hyperlipoproteinaemia and alpha-1-antitrypsin deficiency. In this chapter we will discuss the results and the potential postoperative risks of portal diversion for these new indications, as well as the possible mechanisms of benefit.

MECHANISM OF PORTAL DIVERSION EFFECTS

It has been increasingly appreciated during the last two decades that venous blood from the splanchnic viscera has liver-supporting qualities not found to the same degree in other kinds of arterial or venous blood.[37,41–44,46] The main splanchnic venous 'hepatotrophic' factors are almost certainly endogenous hormones of which the single most important is insulin. Deprivation of the liver of the so-called hepatotrophic effects of portal blood has been noted under several experimental conditions (including portacaval shunt) to cause hepatocyte atrophy, deglycogenation and fatty infiltration. With electron-microscopic studies, relatively specific findings have been disruption and reduction of the rough endoplasmic reticulum (RER) and diminution of its lining polyribosomes.[30,37,42–44,46] Since RER is the 'factory' of the cell, a consequent reduction in many biosynthetic processes would be expected. Numerous studies have verified this hypothesis. We will comment here upon examples chosen because of their clarity or because of their probable or proven clinical significance.

The effect of portal diversion upon hepatic lipid metabolism has been unusually well studied. We demonstrated

reductions of more than 80% in canine hepatic cholesterol and triglyceride synthesis.[42] A similar diminution in cholesterol and or lipoprotein synthesis has been confirmed in rats, dogs, swine and baboons: this has been reviewed elsewhere.[37] Reductions in hepatic lipid synthesis also have been documented in patients treated by us with portacaval shunt for familial hypercholesterolaemia (FH),[2,11,27] and it has been shown that total body cholesterol is greatly reduced.[27] It may be considered proved that lipid homeostasis is altered to an extraordinary degree by portacaval shunt, with the reduction in hepatic lipid synthesis being the greatest change.

It has been equally well established that bile acid synthesis is greatly reduced by portacaval shunt.[2,27,37] Another synthetic pathway that has been well studied after portal diversion is the hepatic urea (Krebs–Henseleit) cycle. This has been shown by Reichle *et al.* to be depressed by Eck fistula in rats,[31] and dogs;[32] they also demonstrated a reduction in several of the enzymes involved in this metabolic pathway.

As detailed studies are made of other hepatic synthetic or metabolic processes after portacaval shunt, it will not be surprising if all follow the same pattern. This possibility is supported by many studies summarized elsewhere,[37] which have shown that portacaval shunt lowers the activity of the hepatic microsomal mixed-function enzyme system. Aside from illustrating the principle of a wide-ranging decline in hepatic synthesis after portacaval shunt, these observations are of potential specific importance because the microsomal mixed-function enzyme system, for which multiple cytochrome P450 and P448 species serve as terminal oxidases, metabolizes a variety of drugs and foreign chemicals as well as endogenous compounds such as steroids and fatty acids. The depression of this broad-ranging enzyme system would relate to many of the metabolic effects of portal diversion.

GLYCOGEN STORAGE DISEASE (GSD)

Portal diversion was first performed for glycogen storage disease almost 26 years ago.[38] The rationale for the procedure was then naive by present-day standards. It was hoped that by short-circuiting splanchnic venous blood around the liver, glucose would be made more readily available to peripheral tissues, with relief of the hypoglycaemia, and that the liver would be coincidentally deglycogenated. Subsequent animal experiments suggest that the consequences of portacaval shunt are far more subtle and wide-ranging than this simple view.

That first patient, who had type III glycogen storage disease, is still alive more than 26 years after portacaval transposition. The bypassed portal venous blood was replaced with blood returning from the inferior vena cava, an operation which was first described in animals by Child *et al.*[5] (Figure 50.1). The transposition was used in order to avoid the potential hazards of Eck fistula. It was appreciated then, and has been amply confirmed since,

Figure 50.1 The operation of portacaval transposition that was used for the first two patients with glycogen storage disease who were treated with portal diversion. Note that the central portal vein is revascularized with vena caval blood. From Starzl *et al.* (1965),[38] with kind permission of the authors and the publisher, C.V. Mosby.

[30,37] that most animals, including subhuman primates, develop wasting and encephalopathy after portal diversion, but it was not appreciated that humans would be an exception to this generalization.

Our first patient had a remarkably untroubled convalescence. An inferior vena cavagram almost 10 years postoperatively revealed flow of systemic venous blood from the distal vena cava to the liver but with a major bypass around the liver through azygous and hemiazygous collaterals (Figure 50.2). The degree of azygous bypassing was similar to that observed with a comparable angiographic study 3 months after the operation.

Two more portacaval transpositions were performed, one by Riddel *et al.*[33] In Riddell's patient, the cavoportal anastomosis clotted[45] (Figure 50.3). The other attempt cost the life of our second patient; the liver was unable to transmit the re-routed vena caval flow, causing hepatic swelling and uncontrollable acidosis. This 7-year-old child died 2 days later. We[39] and Hermann and Mercer[16] subsequently recommended that the simpler procedure of portacaval shunt be used. To our knowledge this approach has been followed in all later cases. By the spring of 1973[45] our own series of patients had reached seven, and six more had been formally reported in the literature from other centres. Since then our cases have increased in number to ten (Table 50.1). Type 1 disease (glucose

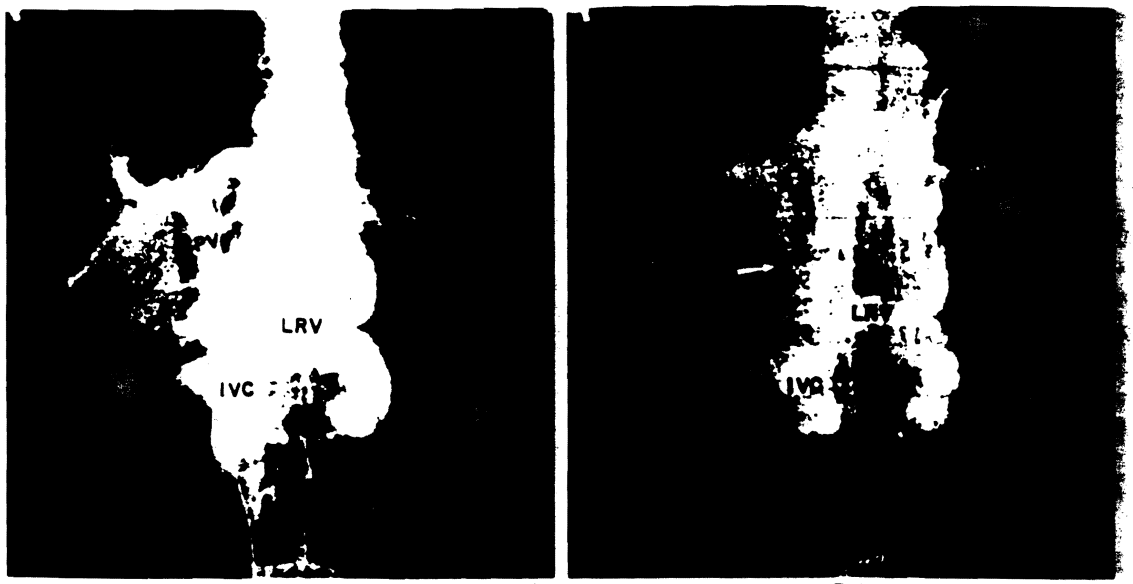


Figure 50.2 Inferior vena cavagram in March 1973 (9½ years postoperatively) in Colorado Patient 1, showing a patent caval–portal anastomosis (arrow) under two conditions of dye injection. Significant flow through the liver, as well as around it by the azygous and other collaterals, was well seen at fluoroscopy. IVC = distal inferior vena cava; LRV = left renal vein; PV = portal vein. From Starzl *et al.* (1973),[45] with kind permission of the authors and the editor of *Annals of Surgery*.

(a) (b)

Figure 50.3 Studies of the Bristol case of portacaval transposition. The original operation was on 5 May 1965, and the examination depicted was performed in December 1971 by Dr R.J. Sommerville at the Foothills Hospital, Calgary, Alberta. (a) Inferior vena cavagram showing obstruction at the anastomotic site (arrow). IVC = distal inferior vena cava; LRV = left renal vein. Note the extensive collaterals via the azygous system. (b) Demonstration of a patent portacaval anastomosis (arrow) by means of a retrograde catheterization. IVC = proximal inferior vena cava; PV = portal vein. From Starzl *et al.* (1973),[45] with kind permission of the authors and the editor of *Annals of Surgery*.

Table 50.1 Patients with glycogen storage disease (GSD) treated by portal diversion. Patients 1 and 2 had portacaval transpositions; all others had portacaval shunt.

Patient number	Age (years)	GSD type	Date of operation	Preoperative symptoms			Persistent hypoglycaemia postoperatively	Survival after shunt
				Hypoglycaemia	Acidosis	Growth retardation		
1	8	III	15 October, 1963	Yes	Yes	Yes	No	Alive
2	7	I	26 June, 1968	Yes	Yes	Yes	—	Died 2 days
3	7	I	2 May, 1972	Yes	Yes	Yes	Yes[a]	Alive
4	11	I	17 May, 1972	Yes	Yes	Yes	No	Died 4½ years
5	10	VI	2 August, 1972	—	—	Yes	—	Alive
6	5	III	7 November, 1972	Yes	Yes	Yes	No	Alive
7	3	III	8 November, 1972	Yes	Yes	Yes	Yes[a]	Alive
8	8	I	13 August, 1973	Yes	Yes	Yes	Yes[b]	Alive
9	12	I	14 December, 1973	Yes	Yes	Yes	Yes[a]	Alive
10	1	I	2 October, 1976	Yes	Yes	Yes	Yes[a]	Alive

[a]Overnight feeding via nasogastric tube starting 2½–4 years after portacaval shunt.
[b]Underwent orthotopic liver transplantation on 12 February 1982, and was well 14 months later (see text).

6-phosphatase deficiency) has been the most common indication for treatment, with type III disease (amylo-1,6-glucosidase deficiency) being a distant second (Table 50.1).

Metabolic effects

After portal diversion, most of the children who had pre-existing hypoglycaemia did not obtain relief from this problem or the relief was not complete. Thus, night feedings usually had to be continued. Studies of plasma insulin and glucagon in several of these patients have revealed changes (Figure 50.4). The flat peripheral insulin curves typical of type 1 glycogen disease[24] became significantly elevated after portacaval shunt, and there were smaller increases in glucagon. The glucose tolerance curves were very little different before and after operation.

Liver glycogen concentrations in all those patients who were later biopsied were not changed. In spite of this, in several of our patients and those reported by others, the liver underwent a very obvious reduction in size as measured with liver scan planimetry. Even if obvious shrinkage did not occur, postoperative biopsies always showed a diminution in individual hepatocyte size similar to that produced in animals by portacaval shunt.[45]

In contrast to the incomplete relief of hypoglycaemia, there was profound and permanent relief of all components of the hyperlipidaemia which is a characteristic of the type 1 disease (Figure 50.5). Correction of other metabolic defects was observed, including abnormal

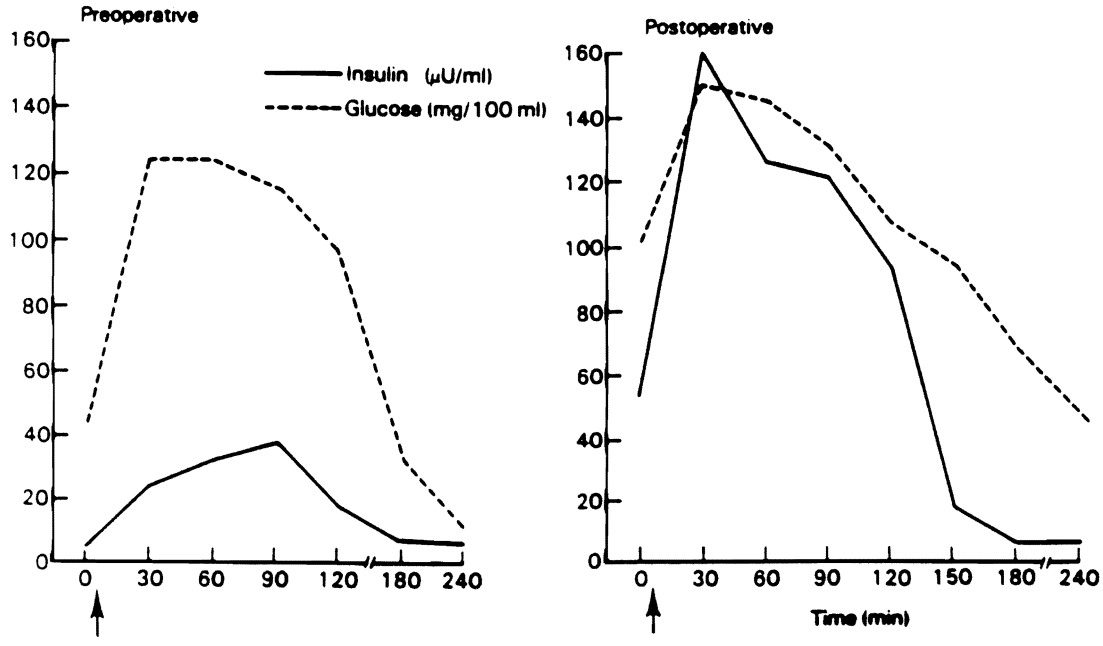


Figure 50.4 Plasma insulin and glucose concentrations in response to an oral glucose tolerance test before and after portacaval shunt in a child (patient 8, Table 50.1) with type I glycogen storage disease

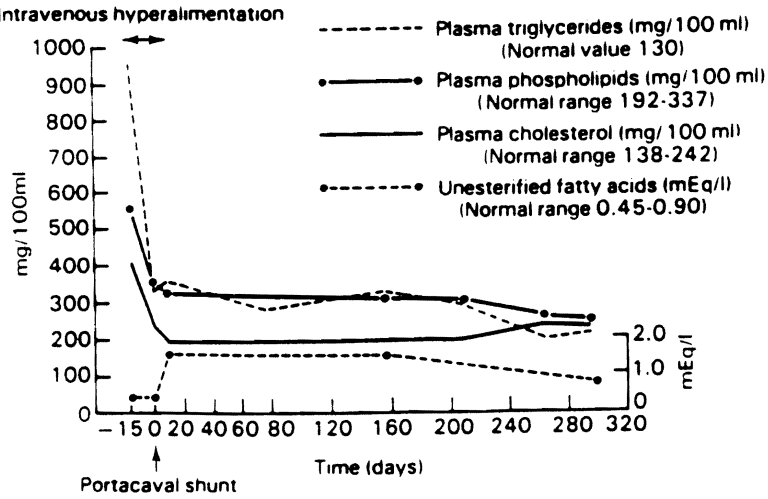


Figure 50.5 Effect of parenteral hyperalimentation and end-to-side portacaval shunt on the plasma lipids of patient 4, whose diagnosis was type I glycogen storage disease. Note the rapid and relatively complete reversal of all abnormalities. From Starzl *et al.* (1973).[45] with kind permission of the authors and the editor of *Annals of Surgery*.

bleeding, uric acid elevations and abnormal calcium metabolism.[45] These observations have been confirmed by others.[6,9,23]

Growth

All ten of our patients had growth retardation before portacaval shunt. Increases in height, which in most cases had virtually ceased, have occurred postoperatively at the rates listed in Table 50.2, i.e. approximately 0.5 cm/month.

Table 50.2 Growth rate and complications after portal diversion for glycogen storage disease.

Patient number	Growth rate (cm/month over 40–120 months)	Complications
1	0.49	
2	Operative death	
3	0.50	Macroadenomatosis
4	0.28	Died 4¾ years after shunt. Primary pulmonary hypertension; NH_3 = 85 μg/100 ml; macroadenomatosis
5	0.53	Renal artery stenosis surgically corrected 32 months after shunt
6	0.62	
7	0.50	
8	0.49	Macroadenomatosis. Liver transplantation after 8¼ years
9	0.88	Renal stone 2 months after shunt. Mild arterial hypertension; macroadenomatosis
10	0.4	Growth cessation after 2 years
Mean	**0.54**	

Quantitative measures of growth were obtained with radiographic techniques.[45] An example of the results is shown in Figure 50.6. Comparison of the wrist and hands in this 7-year-old stunted child before and 11¼ months after operation showed the phenomenal effects of bone-age doubling. In addition to the size change, mineralization occurred, as did the appearance of new wrist bones. Circulating somatotrophin in these patients was normal. The growth spurts may have been at least partially attributable to the increased insulin distribution to the periphery mentioned earlier (see Figure 50.4) since, in recent years, insulin has been recognized to be a major growth hormone, comparable in potency to somatotrophin. The simpler possibility that better nutrition was responsible must also be considered.

Encephalopathy and other risks

A patient who exhibited hepatic encephalopathy 8 years after end-to-side portacaval shunt for type I glycogen storage disease also developed multiple filling defects in her enlarged liver. The diseased liver was replaced at transplantation, and all of the metabolic abnormalities of type I GSD were completely relieved.[26] From the study of more than half-a-dozen liver-based inborn errors of metabolism it has been shown that the phenotype of the transplanted organ permanently retains its original donor specificity.[47]

One other child developed a blood ammonia concentration of 85 μg/100 ml (normal <60 μg/100 ml for that laboratory), but there were no symptoms of encephalopathy. This patient died almost 5 years after portacaval shunt during an attempt at transcaval radiographic visualization of the portacaval anastomosis. Except for the slightly elevated blood ammonia concentration, her standard liver functions were normal. At autopsy the liver had macroadenomatosis very similar to that in the child who underwent liver transplantation. An autopsy finding that had not been suspected in life was advanced right ventricular hypertrophy and dilatation. The smaller

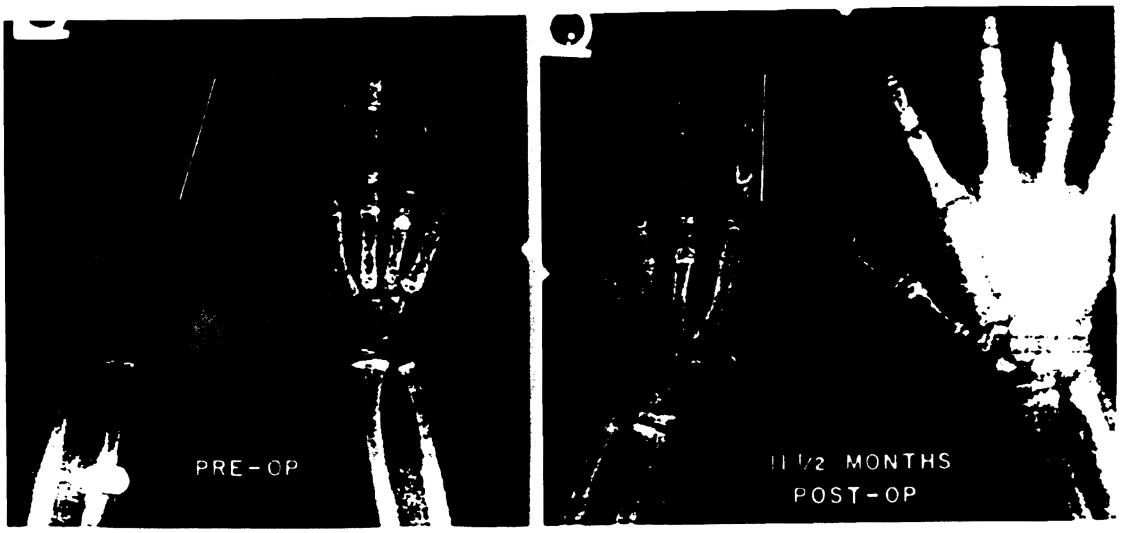


Figure 50.6 The dramatic wrist and hand bone growth and mineralization in patient 3 with type I GSD in the first 11½ postoperative months. The bracket on the left index finger is 5 cm in length. From Starzl *et al.* (1973),[45] with kind permission of the authors and the editor of *Annals of Surgery*.

pulmonary arteries and arterioles had medial muscle hypertrophy, medial and intimal fibrosis, scattered fibrinoid necrosis, and numerous plexiform lesions. Such cardiopulmonary complications have been documented in other patients with type I GSD and other liver diseases.[22] This complication did not have an obvious relationship to the portacaval shunt. The macroadenomatosis seen in these patients is very common in patients with type I GSD, and was recently reported in seven out of eight non-shunted patients aged 3 to 28 years.[19]

The present status of portal diversion

Portacaval shunt in the treatment of glycogen storage disease has been supplanted by the continuous night feeding schedule advocated by Green *et al.*[4] and Crigler and Folkman.[7] We have not performed a portacaval shunt since October 1976. Our present view is that patients who are unmanageable with conservative means should be considered candidates for the curative procedure of liver transplantation rather than for portal diversion.

FAMILIAL HYPERCHOLESTEROLAEMIA (FH)

In March 1973, a 12-year-old girl with homozygous familial hypercholesterolaemia (FH) was treated with an end-to-side portacaval shunt; her serum cholesterol concentration fell markedly[40] (Figure 50.7). In patients with this disease there is an absence or deficiency of cell membrane lipoprotein receptors[12,13] and thus a 'switch-off' mechanism to control lipid (especially cholesterol) synthesis is not present.

By March 1982, we had treated 12 patients with FH in this way.[48] Eight of the patients were children, aged between 2 and 14 years. The four adults were aged 21, 31, 37 and 52 years. All but two were homozygous for the FH abnormality. Low-density lipoprotein (LDL) receptors were looked for by Goldstein and Brown[12,13] on cultured fibroblasts obtained from all patients and many of their close relatives. Nine out of the ten patients with homozygous disease were LDL-receptor negative and the other was receptor defective. Two of the patients had heterozygous disease.

Effect upon serum lipids

Total serum cholesterol concentrations fell significantly in every patient (Figure 50.7) after portacaval shunt.[48] The total cholesterol declines ranged from 20 to 55.4% (average 33.8%) and were maintained throughout the period of study. When measured, LDL cholesterols were reduced commensurately. HDL cholesterol and triglyceride levels were variably effected. Tendinocutaneous xanthomas regressed or disappeared in every patient (Figure 50.8) simultaneously with the fall in cholesterol concentration.

Experience of others in treating FH

The consistency of the anticholesterolaemic response was greater than that noted by other authors, who have

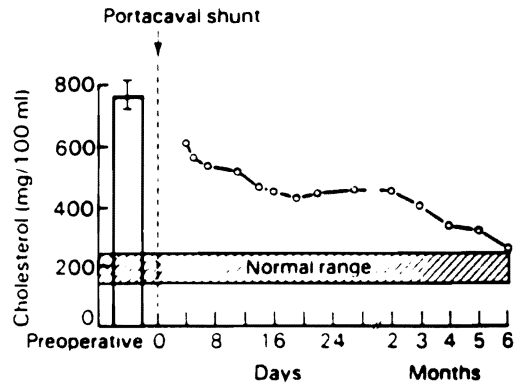
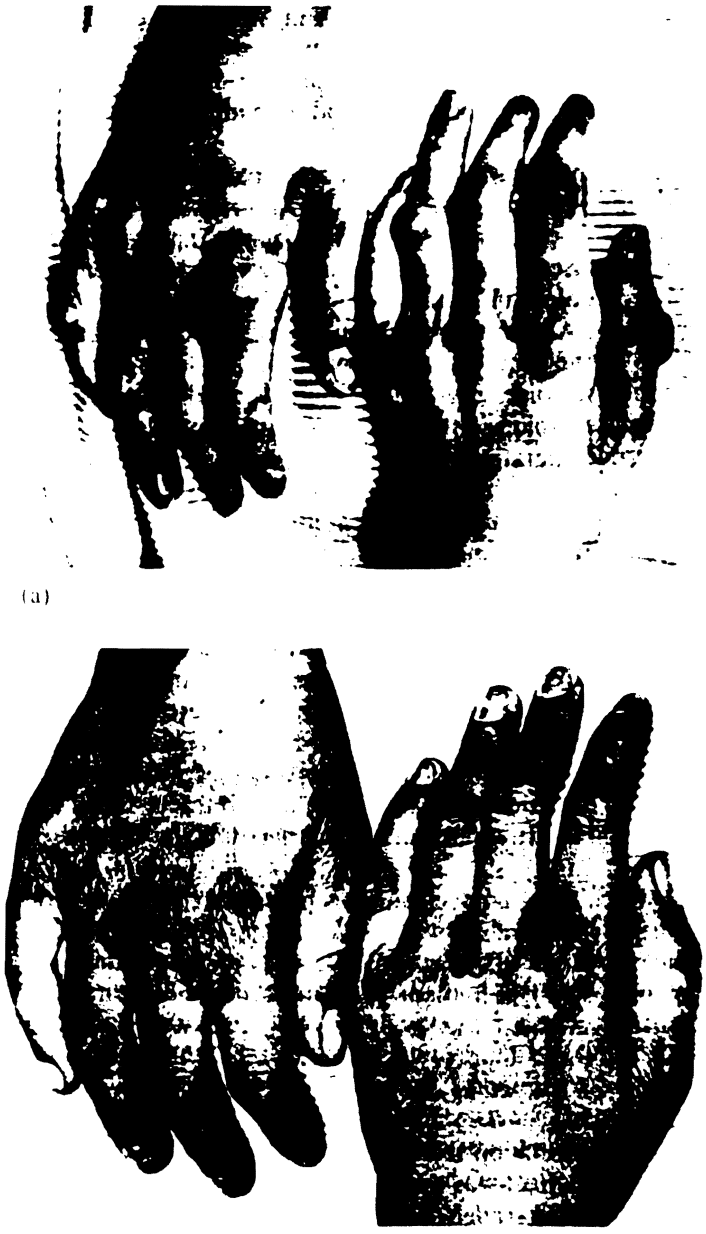


Figure 50.7 Serum cholesterol concentrations after portacaval shunt in patient 1 of our FH series.



(a)

(b)

Figure 50.8 The hands of patient 1 of the hyperlipidaemia series: (a) two weeks before; and (b) 16 months after portacaval shunt.

reported a total of 26 additional patients,[48] of whom 13 were treated in Johannesburg.[10,51]

In the 13 patients treated elsewhere than Johannesburg (summarized in Starzl *et al.*[48]), serum cholesterol reductions of at least 30% were obtained in ten at the same time as tendinocutaneous xanthomas regressed. In two of the three exceptional patients, shunt thrombosis was proved and in one of these the cholesterol fell by 40% after a later mesocaval shunt.[8] In the third patient, reported by Soutar *et al.*,[36] there was presumptive but not definitive evidence of shunt occlusion. An early cholesterol fall of 40% returned several months later to nearly preoperative values. At the same time, initially elevated serum glucagon levels, which are typically found with a patent shunt, fell to base line.

Morbidity

The invariable and long-lasting lipid lowering in our 12 patients was achieved without surgical morbidity. The physical development of those children who were normal before operation has proceeded, and the growth of those who were stunted before has moved towards normal. Emotional or intellectual deterioration secondary to the portal diversion has not occurred, although one child had an acute episode of encephalopathy, which was managed with diet.[48]

Effect upon cardiovascular disease

Patients with homozygous FH usually die of heart disease before the age of 20 years. The degree to which the cardiovascular complications of FH can be relieved or prevented by portal diversion has not been established. Reversal of aortic stenosis was seen in two of our patients, but regression of atheroma in the coronary arteries and aorta was not regularly accomplished.[48] Small and Shipley[35] have examined the factors which could preclude the reversal of atherosclerosis; some of these, including secondary fibrosis, would not be corrected completely by the resorption of intravascular xanthomas. Farriaux *et al.*[8] have suggested that anatomical stabilization of the vascular disease may be the best that can be hoped for with portacaval shunt, even in patients whose angina pectoris is relieved. Experience in several patients from our centre and elsewhere[25,48,53] has shown the value of aggressive surgical correction of technically remedial cardiovascular lesions in combination with portal diversion. Of greater importance will be the implementation of aggressive therapy at a young age, before the development of irreversible cardiovascular complications. In patients with FH who are refractory to therapy with diet and medications, portacaval shunt may be the treatment of choice. Postoperatively, conservative treatment should be tried again because further drops in post-shunt cholesterol levels have been seen using diet and medications which were previously ineffective.

The staged combination of portacaval shunt and the ileal bypass procedure of Buchwald *et al.*[4] has been tested in three patients, with an apparently additive effect[10,28] in spite of the fact that ileal bypass alone has little or no effect in homozygous FH.[4] In dogs, Guzman *et al.*[15] have noted an additive effect of portal diversion by portacaval transposition plus ileal resection. Efforts by us[52] to document a complementary effect of ileal resection and portacaval shunt in dogs failed to confirm the claims of Guzman *et al.*,[15] and a subsequent report by Rucker *et al.*[34] from the Minnesota study has shown that the additive effect originally reported by Guzman *et al.*[15] was not sustained.

Limitations of portacaval shunt

Portacaval shunt, with or without supplementary treatment, provides only palliation for patients with FH. The amelioration of the abnormal metabolic patterns of FH has derived from the countervailing and potentially dangerous hepatic abnormalities caused by portacaval shunt.[48] The palliation is incomplete, since restoration of normal serum cholesterol values has not been achieved in any patient with homozygous disease. In contrast, the metabolic abnormalities of FH can be rectified nearly completely by the ultimate step of liver transplantation.[50] It has been demonstrated that the transplanted liver can provide the low-density-lipoprotein binding sites which are absent, or underrepresented in the native liver.[3] The striking benefit of liver transplantation has been confirmed by several authors.[17,29]

ALPHA-1-ANTITRYPSIN DEFICIENCY (see Chapter 43)

Patients with this disorder have a low level of plasma alpha-1-antitrypsin (an α-globulin), and a high incidence of pulmonary complications.[21] In 1969, a variable association of the alpha-1-antitrypsin deficiency with liver disease was reported, an observation that has had overwhelming confirmation.

The basis for the liver injury may be the hepatic production of an abnormal alpha-1-antitrypsin which cannot be effectively transported out of the liver cells and which consequently becomes sequestered within the hepatocytes near the rough endoplasmic reticulum.[18] Irritation by the entrapped glycoprotein has been the postulated cause of the hepatic cirrhosis, portal hypertension and hepatic failure that follow. The progressive and inexorable course that this pathogenesis implies may have discouraged attempts to treat complications of the portal hypertension (such as variceal haemorrhage) with portal–systemic shunts.

Between 1976 and 1979, we performed end-to-side portacaval shunt in three children with the cirrhotic liver disease of alpha-1-antitrypsin deficiency.[49] The first two patients had had major haemorrhages from oesophageal varices. The third had ascites, but the principal reason for operation was the hope of influencing the metabolism of the alpha-1-antitrypsin.

Follow-up at 3½, 5 and nearly 7 years was reported.[49] Standard liver function tests have not changed greatly since the portacaval shunt (Table 50.3). The serum ammonia rose after portacaval shunt in all three patients, and the aminotransferase and alkaline phosphatase levels fell. The same pattern has persisted for a decade or longer in the first and third patients, neither of whom has practised any dietary restriction. All liver functions of patient 2 were abnormal at the time of portacaval shunt in March 1978. These tests worsened immediately afterwards, but then became stable for more than 9½ years. Subsequent hepatic deterioration which necessitated a liver transplantation was sudden, developing over 3–4 weeks. The low serum alpha-1-antitrypsin levels were not appreciably different before and long after the portacaval shunts (Table 50.3).

After portacaval shunt, all three patients had stabilization of a previously deteriorating clinical state. However, the most objective evidence that the natural history of the disease was favourably altered came from the histopathological studies of operative and postoperative biopsies. All 3 patients had macronodular cirrhosis at the time of the portacaval shunt with biopsy findings typical of the liver disease of alpha-1-antitrypsin deficiency. Two livers were biopsied at the time of portacaval shunt and later postoperatively. Both livers remained cirrhotic and the cytoplasm of some of the hepatocytes contained granules of alpha-1-antitrypsin. Most of the granules were small and the number per cell varied greatly; they were commoner at the periphery of the pseudolobules.

Serial biopsies were obtained in patients 2 and 3. When compared with the liver biopsies that had been obtained at the time of portacaval shunt, the severity of the cirrhosis appeared unaltered, but in patient 2 there was severe intrahepatic cholestasis which had not been present before. In both patients, the hepatocytes were approximately 20% smaller than when the portacaval shunt was performed. The percentage of hepatocytes containing alpha-1-antitrypsin also was lower. In the liver of patient 2, which was removed at transplantation 9½ years after portacaval shunt, it was 19.3% (compared to 38.2% in the pre-shunt biopsy and 28.5% in a biopsy taken 9 months later). In patient 3, the percentage 8¾ years after portacaval shunt was 19.05% (compared with 44.5% in the pre-shunt biopsy, 48.2% 7 months after portacaval shunt, 38.7% at 13 months and 20.4% at 2 years 11 months).

The explanation that has been advanced to explain the beneficial effect was that the portacaval shunt selectively damaged the rough endoplasmic reticulum where the synthetic processes of the liver are concentrated, without a commensurate reduction in excretory functions of the hepatocytes.[49] The hypothesis of a more favorable equilibrium between deposition of the alpha-globulin and its elimination has been strengthened by the further passage of time. Histopathologically, the reduction in the size of the hepatocytes and in the percentage of hepatocytes containing alpha-1-antitrypsin granules noted in the earlier biopsies has been maintained throughout a decade.

PORTAL DIVERSION VERSUS TRANSPLANTATION

In some infants or children, portacaval shunt could be envisaged as a temporizing step whereby definitive treatment with transplantation could be put off for many years and perhaps permanently. Appropriate case selection will be a problem. Candidates should be those like the three patients in our series who have developed serious

Table 50.3 Chemistries before end-to-side portacaval shunt and 8¾ to 12 years later.

	Normal	Patient 1		Patient 2		Patient 3	
		Age in years at testing					
		4⅔	16¾	6½	16[a]	11 1/12	9¾
Serum bilirubin (μmol/l)	<20	26	17	31	40	<20	25
Serum ammonia (μmol/l)	<40	59	116	29–53	95	<40	75
Serum aspartate aminotransferase (IU/l)[b]	<50	150	32	200	101	200	102
Serum alanine aminotransferase (IU/l)	<50	260	51	300	61	150	52
Alkaline phosphatase (IU/l)	<200	1800	595	1000	117	550	351
Prothrombin time (seconds)	11 to 11.5	12	12.8	13	15	11.5	12
Serum alpha-1-antitrypsin (g/l)	>2.0	0.3	0.5	0.16	<0.20	0.30	0.22
Serum protein (g/l)	>65	63	56	52	52	60	55
Serum albumin (g/l)	>30	33	35	35	28	30	28

[a]These tests were in early October 1987, 1 month before liver transplantation on 3 November. Liver functions deteriorated rapidly during the next few weeks, necessitating transplantation.
[b]IU = International Units

complications of liver disease but in whom reasonable liver function and hepatic mass remain. Many such patients are now being followed in hepatology and liver transplant clinics as candidates for elective liver transplantation.

The advantage of achieving palliation without transplantation, thereby avoiding the need for chronic immunosuppression, is obvious. It is by no means clear that portacaval shunting will be the best option in the long term, even if it is successful. The shunt operation has no effect on the protein inhibitor deficiency, whereas liver transplantation restores serum alpha-1-antitrypsin to normal.[18] The principal physiological function of alpha-1-antitrypsin is to inhibit neutrophil elastase.[1] The destruction of alveolar walls with consequent emphysema in patients with alpha-1-antitrypsin deficiency[20] presumably results from the unchecked activity of neutrophil elastase. A favourable effect on the lung disease is expected from liver transplantation, although with a maximum follow-up of only 14 years post-transplantation, it is too soon to be sure.

SUMMARY

Complete portacaval shunt was used to treat ten patients with glycogen storage disease (GSD). A favourable effect was noted on body growth and a number of metabolic abnormalities. More recently, continuous night feedings with an intermittently-placed gastric tube or through a gastrostomy have been shown to be helpful either before or after portacaval shunts. Such alimentation techniques have eliminated the need for shunts in almost all patients with GSD. Patients who are refractory to such management are candidates for liver transplantation.

Portacaval shunt was performed in ten patients with homozygous and two with heterozygous familial hypercholesterolaemia (FH). Total serum cholesterol was lowered by between 20 and 55.4% during follow-up periods of 7 to almost 15 years, with commensurate decreases in LDL cholesterol. The effect on HDL cholesterol and triglyceride levels was variable. Tendinocutaneous xanthomas diminished or disappeared. Growth and development in children proceeded or accelerated. There was no detectable emotional or intellectual deterioration. Hepatic failure did not occur, although blood ammonia concentrations and serum alkaline phosphatase levels increased relative to preoperative values. Cardiac symptoms were often improved, but evidence of reversal of cardiovascular lesions was inconclusive. Three patients with pre-existing heart disease died of cardiac complications after 4, 18½ and 30 months. Although portacaval shunt has been effective therapy for patients with FH who were intolerant of medical treatment, liver transplantation is a better treatment for refractory patients.

Three paediatric patients with the liver disease of alpha-1-antitrypsin deficiency and with complications of portal hypertension had end-to-side portacaval shunts. Their clinical courses were stabilized for up to 12 years. Postoperative liver biopsies of two of the patients showed the typical histopathological changes caused by portal diversion, as well as an apparent reduction in the quantity of alpha-1-antitrypsin particles in the hepatocytes. The metabolic changes caused by portal diversion have apparently created a more favourable equilibrium between the synthesis and excretion of the abnormal alpha-1-antitrypsin.

Most patients with serious liver disease caused by alpha-1-antitrypsin deficiency are best treated by liver transplantation. However, a selected few may have good palliation from portacaval shunt.

REFERENCES

1. Bieth, J. (1978) Elastases: structure, function and pathological role. *Frontiers in Matrix Biology*, **6**, 1–82.
2. Bilheimer, D.W., Goldstein, J.L., Grundy, S.M. & Brown, M.S. (1975) Reduction in cholesterol and low density lipoprotein synthesis after portacaval shunt surgery in a patient with homozygous familial hypercholesterolemia. *Journal of Clinical Investigation*, **56**, 1420–1430.
3. Bilheimer, D.W., Goldstein, J.L., Grundy, S.C. *et al.* (1984) Liver transplantation provides low-density-lipoprotein receptors and lowers plasma cholesterol in a child with homozygous familial hypercholesterolemia. *New England Journal of Medicine*, **311**, 1658–1664.
4. Buchwald, H., Moore, R.B. & Varco, R.L. (1974) Ten years' clinical experience with partial ileal by-pass in management of the hyperlipidemias. *Annals of Surgery*, **180**, 384–392.
5. Child, C.G., Barr, D., Holswade, G.R. & Harrison, C.S. (1953) Liver regeneration following portacaval transposition in dogs. *Annals of Surgery*, **138**, 600–608.
6. Corbeel, L., Hue, L., Lederer, B. *et al.* (1981) Clinical and biochemical findings before and after portacaval shunt in a girl with Type Ib glycogen storage disease. *Pediatric Research*, **15**, 58–61.
7. Crigler, J.F., Jr & Folkman, J. (1978) Glycogen storage disease: New approaches to therapy. In Porter, R. & Whelan, J. (eds) *Hepatotrophic Factors*, pp. 331–356. *Ciba Foundation Symposium No. 55*. Amsterdam: Elsevier/Excerpta Medica.
8. Farnaux, J.P. & Bertrand, M. (1979) Hypercholesterolemia, portacaval shunt and coronary disease (letter). *New England Journal of Medicine*, **301**, 108.
9. Folkman, J., Philippart, A., Tze, W.-J. & Crigler, J. Jr (1972) Portacaval shunt for glycogen storage disease: value of prolonged intravenous hyperalimentation before surgery. *Surgery*, **72**, 306–314.
10. Forman, M.B., Baker, S.G., Mieny, C.J. *et al.* (1982) Treatment of homozygous familial hypercholesterolemia with portacaval shunt. *Atherosclerosis*, **41**, 349–361.
11. Ginsberg, H., Davidson, N., Le, N.-A *et al.* (1983) Marked overproduction of low density lipoprotein apoprotein-B in a subject with heterozygous familial hypercholesterolemia: effect of portacaval shunting. *Biochimica et Biophysica Acta*, **712**, 250–259.
12. Goldstein, J. & Brown, M.S. (1974) Binding and degradation of low density lipoproteins in cultured human fibroblasts: comparison of cells from a normal subject and from a patient with homozygous familial hypercholesterolemia. *Journal of Biological Chemistry*, **249**, 5153–5162.
13. Goldstein, J.L., Dana, S.E., Brunschede, G.Y. & Brown, M.S. (1975) Genetic heterogeneity in familial hypercholesterolemia: evidence for two different mutations affecting functions of low density lipoprotein receptor. *Proceedings of the National Academy of Sciences of the USA*, **72**, 1092–1096.
14. Greene, H.L., Slonim, A.E., O'Neill, J.A. & Burr, I.M. (1976) Continuous nocturnal intragastric feedings for management of Type I glycogen storage disease. *New England Journal of Medicine*, **294**, 1125–1129.
15. Guzman, I.J., Schneider, P.D., Coyle, J.J. *et al.* (1980) Combined hypolipidemia of portacaval transposition and ileal resection in the dog. *Surgery, Gynecology and Obstetrics*, **150**, 475–480.
16. Hermann, R.E. & Mercer, R.D. (1969) Portacaval shunt in the treatment of glycogen storage disease: report of a case. *Surgery*, **65**, 499–503.
17. Hoeg, J.M., Starzl, T.E., Brewer, J.B. Jr (1987) Liver transplantation for the treatment of cardiovascular disease: Comparison with medication and plasma exchange in homozygous familial hypercholesterolemia. *American Journal of Cardiology*, **59**, 705–707.
18. Hood, J.M., Koep, L.J., Peters, R.L. *et al.* (1980) Liver transplantation for advanced liver disease with alpha-1-antitrypsin deficiency. *New England Journal of Medicine*, **302**, 272–275.
19. Howell, R.R., Stevenson, R.E., Ben-Menachem, Y. *et al.* (1976). Hepatic adenomata with Type I glycogen storage disease. *Journal of the American Medical Association*, **236**, 1481–1484.
20. Larson, C. (1978) Natural history and life expectancy in severe alpha-1-antitrypsin deficiency, PiZ. *Acta Medica Scandinavica*, **204**, 345–351.
21. Laurell, C.-B. & Eriksson, S. (1963) The electrophoretic alpha-1-globulin pattern of serum in patients with alpha-1-antitrypsin deficiency. *Scandinavian Journal of Clinical and Laboratory Investigation*, **15**, 132–140.
22. Levine, O.R., Harris, R.C., Blanc, W.A. & Wellins, R.B. (1973) Progressive pulmonary hypertension in children with portal hypertension. *Journal of Pediatrics*, **83**, 964–972.
23. Liebschutz, D. & Soper, R.T. (1976) Portacaval shunt in siblings for Type I glycogenosis. *Journal of Pediatric Surgery*, **11**, 557–561.
24. Lockwood, D.H., Merimee, T.J., Edgar, P.J. *et al.* (1969) Insulin secretion in Type I glycogen storage disease. *Diabetes*, **18**, 755–758.
25. Madras, P.N. (1981) Portacaval shunt for familial heterozygous hypercholesterolemia. *Surgery, Gynecology and Obstetrics*, **152**, 187–190.
26. Malatack, J.J., Finegold, D.N., Iwatsuki, S. *et al.* (1983) Liver transplantation for Type I glycogen storage disease. *Lancet*, **1**, 1073–1076.
27. McNamara, D.J., Ahrens, E.H., Jr, Kolb, R. *et al.* (1982) Cholesterol homeostasis in two familial hypercholesterolemic patients with a portacaval anastomosis. *Circulation*, **66** (supplement II), 159.
28. Miettinen, T.A. (1980) Comparison of cholestyramine, ileal bypass, and portacaval shunt in the treatment of familial hypercholesterolemia. In *Atherosclerosis V: Proceedings of the Fifth International Symposium of Atherosclerosis*, pp. 470–473. New York: Springer-Verlag.
29. Mora, N.P., Cienfuegos, J.A., Ardaiz, J. *et al.* (1988) Operative events in the first case of liver grafting after heart transplantation. *Surgery*, **103**, 264–267.
30. Putnam, C.W., Porter, K.A. & Starzl, T.E. (1976) Hepatic encephalopathy and light and electron micrographic changes of the baboon liver after portal diversion. *Annals of Surgery*, **184**, 155–161.
31. Reichle, F.A., Bernstein, M.R., Hower, R.D. *et al.* (1973) Urea cycle enzyme activity in human hepatic cirrhosis and after experimental portacaval shunt. *Surgical Forum*, **24**, 246–248.
32. Reichle, F.A., Rao, N.S., Reichle, R.M. & Chang, K.H.Y. (1977) The mechanism of postshunt liver failure. *Surgery*, **82**, 738–749.
33. Riddell, A.G., Davies, R.P. & Clark, A.D. (1966) Portacaval transposition in the treatment of glycogen storage disease. *Lancet*, **2**, 1146–1148.
34. Rucker, R.D., Jr, Guzman, I.J., Snover, D. *et al.* (1982) Long-term hypolipidemic effect of portacaval transposition and distal intestinal resection without change in liver function tests. *Journal of Surgical Research* **32**, 423–428.
35. Small, D.M. & Shipley, G.G. (1974) Physical-chemical basis of lipid deposition in atherosclerosis: the physical state of the lipids helps to explain lipid deposition and lesion reversal in atherosclerosis. *Science*, **185**, 222–229.
36. Soutar, A.K., Myant, N.B. & Thompson, G.R. (1977) Measurement of apolipoprotein B turnover in very low and low density lipoproteins in familial hypercholesterolemia. *Atherosclerosis*, **28**, 247–256.
37. Starzl, T.E., Porter K.A. & Francavilla, A. (1983) The Eck fistula in animals and humans. *Current Problems in Surgery*, **20** (11), 688–752.
38. Starzl, T.E., Marchioro, T.L., Sexton, A.W. *et al.* (1965) The effect of portacaval transposition upon carbohydrate metabolism: experimental and clinical observations. *Surgery*, **57**, 687–697.
39. Starzl, T.E., Brown, B.I., Blanchard, H. & Brettschneider, L. (1969) Portal diversion in glycogen storage disease. *Surgery*, **65**, 504–506.
40. Starzl, T.E., Chase, H.P., Putnam, C.W. & Porter, K.A. (1973) Portacaval shunt in hyperlipoproteinaemia. *Lancet*, **2**, 940–944.
41. Starzl, T.E., Francavilla, A., Halgrimson, C.G. *et al.* (1973) The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood. *Surgery, Gynecology and Obstetrics*, **137**, 179–199.
42. Starzl, T.E., Lee, I.-Y., Porter, K.A. & Putnam, C.W. (1975) The influence of portal blood upon lipid metabolism in nor[illegible]

and diabetic dogs and baboons. *Surgery, Gynecology and Obstetrics*, **140**, 381–396.

43. Starzl, T.E., Porter, K.A., Kashiwagi, N. *et al.* (1975) The effect of diabetes mellitus on portal blood hepatotrophic factors in dogs. *Surgery, Gynecology and Obstetrics*, **140**, 549–562.
44. Starzl, T.E., Porter, K.A., Kashiwagi, N. & Putnam, C.W. (1975) Portal hepatotrophic factors, diabetes mellitus and acute liver atrophy, hypertrophy and regeneration. *Surgery, Gynecology and Obstetrics*, **141**, 843–858.
45. Starzl, T.E., Putnam, C.W., Porter, K.A. *et al.* (1973) Portal diversion for the treatment of glycogen storage disease in humans. *Annals of Surgery*, **178**, 525–539.
46. Starzl, T.E., Porter, K.A., Watanabe, K. & Putnam, C.W. (1976) The effects of insulin, glucagon and insulin/glucagon infusions upon liver morphology and cell division after complete portacaval shunt in dogs. *Lancet*, **1**, 821–825.
47. Starzl, T.E., Iwatsuki, S., Van Thiel, D.H. *et al.* (1982) Evolution of liver transplantation. *Hepatology*, **2**, 614–636.
48. Starzl, T.E., Chase, H.P., Ahrens, E.H., Jr *et al.* (1983) Portacaval shunt in patients with familial hypercholesterolemia. *Annals of Surgery*, **198**, 273–283.
49. Starzl, T.E., Porter, K.A., Francavilla, A. & Iwatsuki, S. (1983) Reversal of hepatic alpha-1-antitrypsin deposition after portacaval shunt. *Lancet*, **2**, 724–726.
50. Starzl, T.E., Bilheimer, D.W., Bahnson, N.T. *et al.* (1984) Heart-liver transplantation in a patient with familial hypercholesterolemia. *Lancet*, **1**, 1382–1383.
51. Stein, E.A., Mieny, C., Spitz, L. *et al.* (1975) Portacaval shunt in four patients with homozygous hypercholesterolemia. *Lancet*, **1**, 832–835.
52. Thompson, J.S., Porter K.A., Hayashida, N. *et al.* (1983) Morphologic and biochemical changes in dogs after portacaval shunt plus bile fistula or ileal by-pass: failure of bile fistula or ileal by-pass to prevent hepatocyte atrophy. *Hepatology*, **3**, 581–587.
53. Weglicki, W.B., Ganda, O.P., Soeldner, J.S. *et al.* (1977) Portacaval diversion for severe hypercholesterolemia. *Archives of Surgery*, **112**, 634–640.