Chapter 48
Portal-Systemic Shunting for Metabolic Disease

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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.[32, 36, 37, 38, 39, 41] 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.[25, 32, 37, 38, 39, 41] 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.[37] A similar diminution in cholesterol and/or lipoprotein synthesis has been con-

Fig. 48.1 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),[33] with kind permission of the authors and the publisher, C. V. Mosby.

Fig. 48.2 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),[40] with kind permission of the authors and the editor of *Annals of Surgery*.

firmed in rats, dogs, swine and baboons: this has been reviewed elsewhere.[32] Reductions in hepatic lipid synthesis also have been documented in patients treated by us with portacaval shunt for familial hypercholesterolaemia (FH),[1,9,23] and it has been shown that total body cholesterol is greatly reduced.[23] 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.[1,23,32] 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[26] and dogs;[27] 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 during the past 15 years, summarized elsewhere,[32] 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 functions 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 20 years ago.[33] 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 almost 20 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.*[3] (Figure 48.1). The transposition was used in order to avoid the potential hazards of Eck fistula. It was appreciated then, and amply confirmed since,[25,32] 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 ten 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 48.2). The degree of azygous bypassing was similar to that observed with a comparable angiographic study three months after the operation.

Two more portacaval transpositions were performed, one by Riddell *et al.*[28] In Riddell's patient, the cavoportal anastomosis clotted[40] (Figure 48.3). 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 seven-year-old child died two days later. We[34] and Hermann and Mercer[14] 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[40] 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 48.1). Type I disease (glucose-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 48.1).

Metabolic effects

After portal diversion, most of the children who had preexisting 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

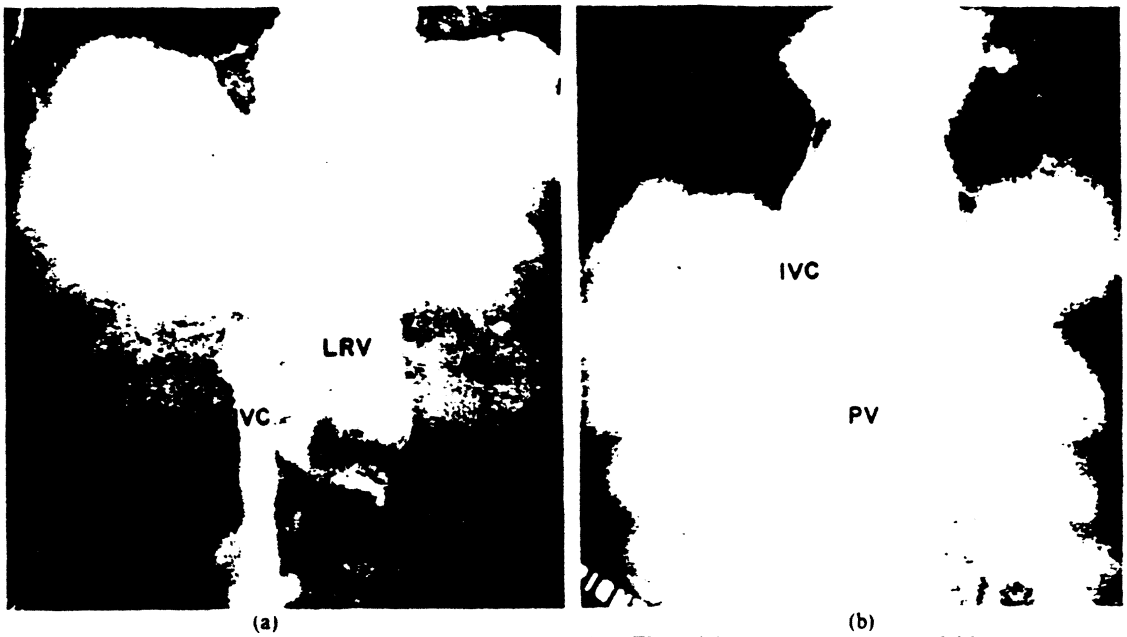

Fig. 48.3 Studies of the Bristol case of portacaval transposition. The original operation was on 5 May 1965, and the examination depicted was performed in December 1971 by Dr R. J. Sommerville at the Foothills Hospital, Calgary, Alberta. (a) Inferior vena cavagram showing obstruction at the anastomotic 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),[40] with kind permission of the authors and the editor of *Annals of Surgery*.

changes (Figure 48.4). The flat peripheral insulin curves typical of type I glycogen disease[20] 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 individula hepatocyte size similar to that produced in animals by portacaval shunt.[40]

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 I disease (Figure 48.5). Correction of other metabolic defects was observed, including abnormal bleed-

Table 48.1 Patients with glycogen storage disease (GSD) treated by portal diversion. Patients 1 and 2 had portacaval transposition; all others had portacaval shunt.

Patient number	Age (years)	GSD type	Date of operation	Preoperative symptoms: Hypoglycaemia	Acidosis	Growth retardation	Persistent hypoglycaemia postoperatively	Survival after shunt
1	8	III	15 October, 1963	Yes	Yes	Yes	No	Alive 19½ years
2	7	I	26 June, 1968	Yes	Yes	Yes	–	Died 2 days
3	7	I	2 May, 1972	Yes	Yes	Yes	Yes[a]	Alive 11 years
4	11	I	17 May, 1972	Yes	Yes	Yes	No	Died 4½ years
5	10	VI	2 August, 1972	–	–	Yes	–	Alive 10⅔ years
6	5	III	7 November, 1972	Yes	Yes	Yes	No	Alive 10½ years
7	3	III	8 November, 1972	Yes	Yes	Yes	Yes[a]	Alive 10½ years
8	8	I	13 August, 1973	Yes	Yes	Yes	Yes[b]	Alive 9⅔ years
9	12	I	14 December, 1973	Yes	Yes	Yes	Yes[a]	Alive 9½ years
10	1	I	2 October, 1976	Yes	Yes	Yes	Yes[a]	Alive 6½ years

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

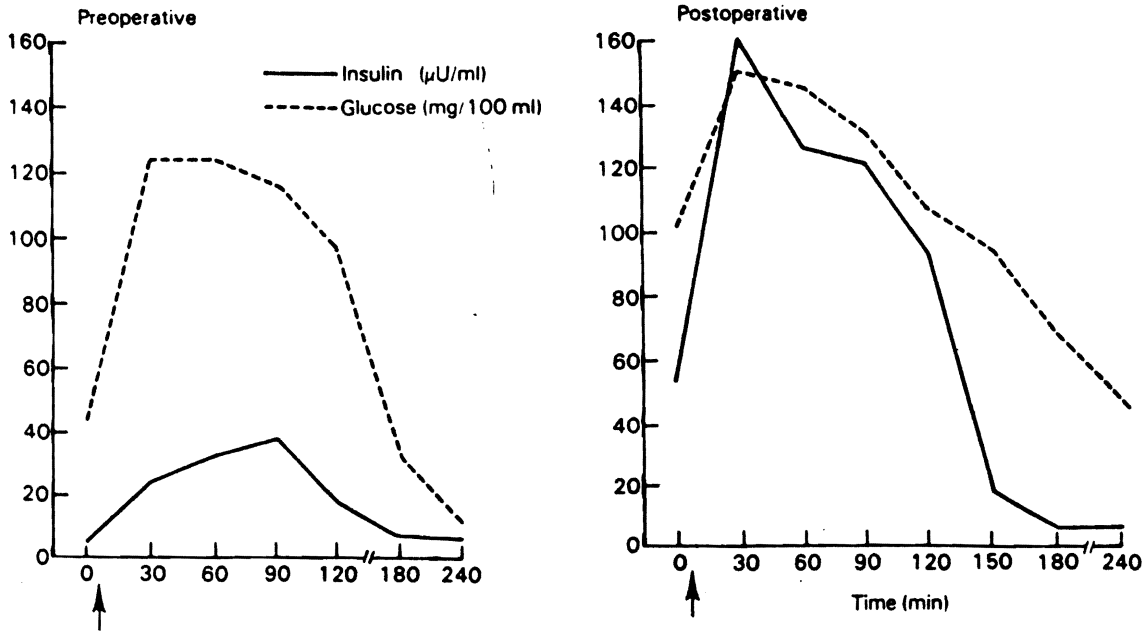

Fig. 48.4 Plasma insulin and glucose concentrations in response to an oral glucose tolerance test before and after portacaval shunt in a child (Patient 8, Table 48.1) with type I glycogen storage disease.

ing, uric acid elevations and abnormal calcium metabolism.[40] These observations have been confirmed by others.[4, 7, 19]

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 48.2, i.e. approximately 0.5 cm/month.

Quantitative measures of growth were obtained with radiographic techniques.[40] An example of the results is shown in Figure 48.6. Comparison of the wrist and hands in this seven-year-old stunted child before and 11½ 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 48.4) 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.

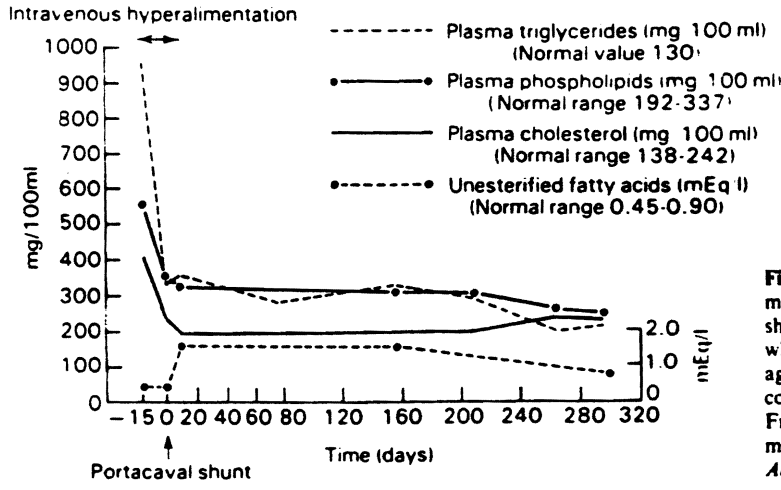

Fig. 48.5 Effect of parenteral hyperalimentation and end-to-side portacaval shunt on the plasma lipids of Patient 4, whose diagnosis was type I glycogen storage disease. Note the rapid and relatively complete reversal of all abnormalities. From Starzl *et al.* (1973),[40] with kind permission of the authors and the editor of *Annals of Surgery*.

Table 48.2 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 4¼ years after shunt. Primary pulmonary hypertension: $NH_3 = 85\mu g$/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 two months after shunt. Mild arterial hypertension; macroadenomatosis
10	0.4	Growth cessation after two years
Mean	0.54	

Encephalopathy and other risks

A patient who exhibited hepatic encephalopathy eight 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.[22] 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.[42]

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 five 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 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.[18] This complication did not have an obvious relationship to the por-

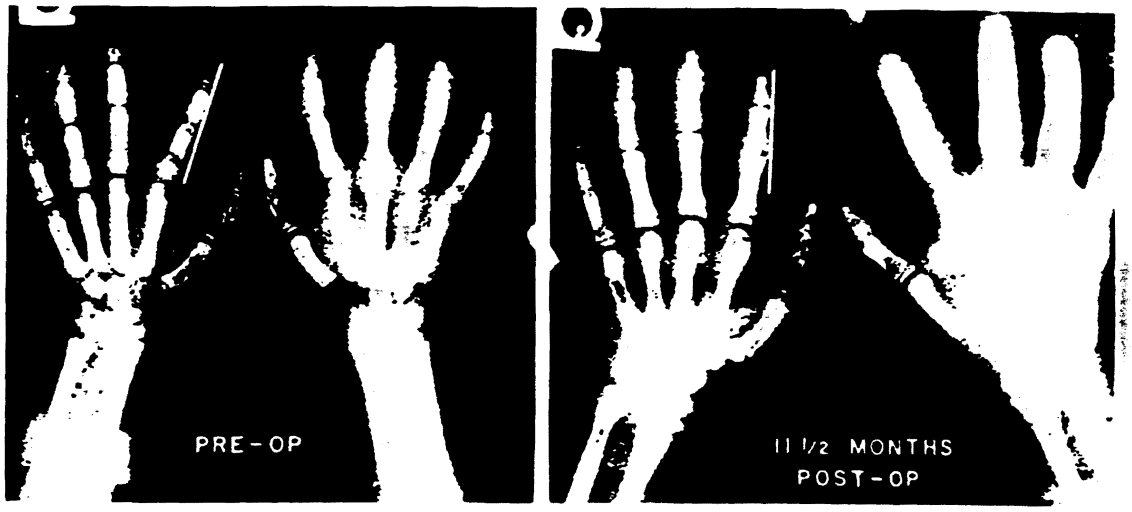

Fig. 48.6 The dramatic wrist and hand bone growth and mineralization in Patient 3 with type I GSD in the first 11¼ postoperative months. The bracket on the left index finger is 5 cm in length. From Starzl *et al.* (1973),[40] with kind permission of the authors and the editor of *Annals of Surgery*.

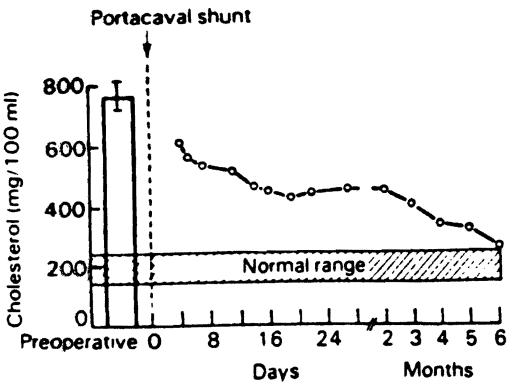

Fig. 48.7 Serum cholesterol concentrations after portacaval shunt in Patient 1 of our FH series.

tacaval 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.[16]

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 Greene *et al.*[12] and Crigler and Folkman.[5] Portacaval shunt, if it has any role at all, is reserved for failures of this more conservative and liver-sparing approach. We have not performed a portacaval shunt since October 1976.

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[35] (Figure 48.7). In patients with this disease, there is an absence or deficiency of cell membrane lipoprotein receptors,[10,11] 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.[43] 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 lipoproteins (LDL) receptors were looked for by Goldstein and Brown[10,11] 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 cholestrol concentrations fell significantly in every patient (Figure 48.7) after portacaval shunt.[43] 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 48.8) 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 reported a total of 26 additional patients,[43] of whom 13 were treated in Johannesburg.[8,45]

In the 13 patients treated elsewhere than Johannesburg (summarized in Starzl *et al.*[43]), 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.[6] In the third patient, reported by Soutar *et al.*,[31] 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.[43]

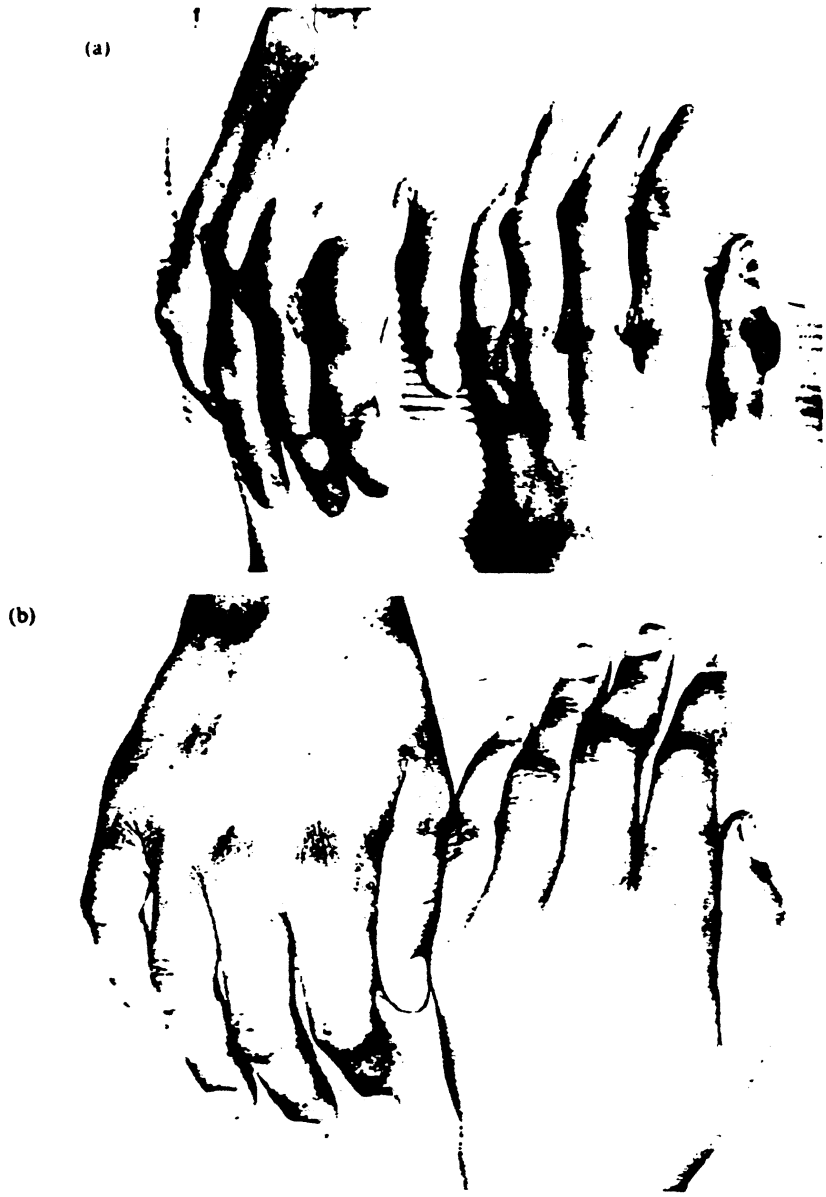

Fig. 48.8 The hands of Patient 1 of the hyperlipidaemia series (a) two weeks before; and (b) 16 months after portacaval shunt.

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.[43] Small and Shipley[30] 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.*[6] 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[21,43,47] 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 since 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.*[2] has been tested in three patients, with an apparently additive effect[8, 24] in spite of the fact that ileal bypass alone has little or no effect in homozygous FH.[2] In dogs, Guzman *et al.*[13] have noted an additive effect of portal diversion by portacaval transposition plus ileal resection. Efforts by us[46] to document a complementary effect of ileal resection and portacaval shunt in dogs failed to confirm the claims of Guzman *et al.*,[13] and a subsequent report by Rucker *et al.*[29] from the Minnesota study has shown that the additive effect originally reported by Guzman *et al.*[13] 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.[43] The palliation is incomplete, since restoration of normal serum cholesterol values has not been achieved in any patient with homozygous disease. It is possible that the metabolic abnormalities of FH could be rectified by the ultimate step of liver transplantation.

ALPHA-1-ANTITRYPSIN DEFICIENCY

Patients with this disorder have a low level of plasma alpha-1-antitrypsin (an α-globulin), and a high incidence of pulmonary complications.[15] 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.[15] 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.

We have performed end-to-side portacaval shunt in three children with the cirrhotic liver disease of alpha-1-antitrypsin deficiency.[44] 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 were performed.[44] Standard liver function tests have not changed greatly since the portacaval shunt, although the plasma ammonia levels have been elevated in both patients in whom this measure was systematically obtained. None of the three patients have had symptoms of encephalopathy, although Patient 2 had mental slowness for the first two postoperative years.

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 in Patients 2 and 3.[44] In Patient 2, a biopsy nine months after the portal diversion showed that the number of hepatocytes that contained alpha-1-antitrypsin globules was diminished to 28.5%, compared with 38.2% at the time of the original operation. The hepatocytes were 22% smaller and the amount of rough endoplasmic reticulum in their cytoplasm was greatly reduced.

In Patient 3, the percentage of hepatocytes containing alpha-1-antitrypsin globules was 44.5% at the time of operation, and 48.2 and 38.7% at 7 and 13 months, respectively, after portacaval shunt. The hepatocytes were 15 and 20% smaller at these postoperative periods. The percentage of hepatocytes containing alpha-1-antitrypsin globules was reduced to 20.4% in the biopsy taken at 2 years 11 months. The hepatocytes remained 20% smaller than in the preoperative biopsy, and the amount of both rough and smooth endoplasmic reticulum in their cytoplasm was reduced. The severity of the macronodular cirrhosis was unaltered.

Our assumption[44] is that the portacaval shunt has diminished the synthesis of the abnormal alpha-1-antitrypsin, presumably by altering the function of the rough endoplasmic reticulum and its ribosomes (see earlier) without commensurately reducing the transport of this glycoprotein. With a better equilibrium between the production and transport of the α-globulin,

it is possible that its intracellular accumulation has been slowed or probably even reversed.

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.

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 14 months to almost nine 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. Portacaval shunt has been effective therapy for patients with FH who were refractory or intolerant to medical treatment; it should be performed before the development of irreversible cardiovascular damage.

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 have been stabilized for between 3½ and almost seven 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 apparently have created a more favourable equilibrium between the synthesis and excretion of the abnormal alpha-1-antitrypsin.

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