Portacaval Shunt in Patients with Familial Hypercholesterolemia

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Portacaval shunt was performed in ten patients with homozygous and two with heterozygous familial hypercholesterolemia (FH). Total serum cholesterol was lowered by 20% to 55.4% during follow-up periods of 14 months to almost 9 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 months, 18½ months, 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.

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IN MARCH 1973, a 12-year-old girl with homozygous familial hypercholesterolemia (FH) was treated with end-to-side portacaval shunt. Her serum cholesterol and low density lipoprotein concentrations were lowered significantly.[1] This same effect of portal diversion has been seen by us in other cases[2] and has been confirmed elsewhere.[3-12]

Portal diversion has not been widely applied in patients with FH, partly because the long-term influence of the operation on the disease has not been known. In

addition, there has been anxiety about the potential risks of portacaval shunt, including the possibilities of hepatic encephalopathy and/or intellectual deterioration. To answer these questions of effectiveness and morbidity, we report here on the fate of 12 patients with FH who were treated with portacaval shunt from 14 months to 10 years ago.

Methods

Information about the 12 patients is given in Table 1. Eight of the patients were children. All of the patients had FH and all but two were homozygous for the abnormality. Low density lipoprotein (LDL) receptors were determined by Goldstein and Brown[13,14] on cultured fibroblasts obtained from all patients (Table 1) and many of their close relatives. Nine of the ten patients with homozygous disease were LDL receptor-negative and the other was receptor-defective. One of the two patients (patient 11) with heterozygous disease was from a kindred in which FH homozygous relatives were receptor-negative. The other (patient 6) had no relatives.

Continuity of care before and after portacaval shunt was at the referring university centers (Table 1) where special metabolic, vascular, and other studies were and are being performed. The clinical observations and biochemical data were obtained at these centers.

Except for the 2-year-old child, all of the patients had been treated for long periods before a conclusion was reached that they were refractory to or noncompliant with medical management. Previous treatment had always included a diet low in saturated fat and cholesterol as well as the lipid lowering medications listed in Table 1. Plasmapheresis had been tried in five of the 12 patients and had been stopped because of inconvenience,

TABLE 1. Clinical Features of 12 Patients with Familial Hypercholesterolemia (FH)

	Principal Care Center	Age/Sex	LDL Receptor Status	Previous Treatment	Portacaval Shunt Date
1.	(JP) University of Colorado, Denver	12/F	Negative	Diet, cholestyramine, nicotinic acid, clofibrate, dextro-throxine	3-1-73
2.	(MC) Southwestern University, Dallas	7/F	Negative	Diet, cholestyramine, nicotinic acid, clofibrate	10-4-74
3.	(FV) Universite René Décarte, Paris	8/M	Negative	Diet, cholestyramine, nicotinic acid, clofibrate, plasmapheresis	8-5-75
4.	(AM) Rockefeller University, New York City	5/M	Negative	Diet, cholestyramine, nicotinic acid, clofibrate	12-14-78
5.	(CP) National Institutes of Health, Bethesda	14/M	Negative	Diet, cholestyramine, nicotinic acid, clofibrate, dextro-thyroxine, hydroxy-methyl glutaric acid, colestipol, plasmapheresis	6-19-79
6.	(PC) Rockefeller University, New York City	52/M	Heterozygote (50% of normal)	Diet, cholestyramine, nicotinic acid, clofibrate, colestipol, Beta-sitosterol	8-7-79
7.	(JC) University of Colorado, Denver	10/M	Negative	Diet, cholestyramine, nicotinic acid, colestipol, plasmapheresis	11-10-79
8.	(DP) University of Cincinnati, Cincinnati	31/F	20% of normal	Diet, cholestyramine, nicotinic acid, dextro-thyroxine, plasmapheresis	4-21-81
9.	(TH) National Institutes of Health, Bethesda	21/F	Negative	Diet, cholestyramine, or colestipol, nicotinic acid, clofibrate, plasmapheresis	11-11-81
10.	(DP) National Institutes of Health, Bethesda	7/M	Negative	Diet, cholestyramine, nicotinic acid, neomycin, colestipol, d-thyroxine	
11.*	(HP) National Institutes of Health, Bethesda	37/M	Heterozygote (50% of normal)	Diet, cholestyramine, or colestipol, nicotinic acid, neomycin	11-17-81
12.	(MW) University of California, Los Angeles	2/F	Negative	Diet, cholestyramine, nicotinic acid	3-11-82

* Father of patient 10, uncle of patient 5.

poor acceptance by the patients, ineffectiveness, or all three reasons. After portacaval shunt, the majority of the patients were treated again with one or more of these measures. The conditions that pertained at blood sampling times before and after operation are noted in Table 2.

All 12 patients had tendinous and cutaneous xanthomas. These were prominent in eight of the ten patients who had homozygous disease. In each patient, the presence of cardiovascular disease was looked for with catheterization and/or non-invasive techniques. The only patient who was free of cardiovascular disease was 2 years old (Table 3). The most common diagnoses were aortic stenosis, coronary artery disease, and atherosclerosis of the aorta or its large branches (Table 3). Five of the patients had sustained a previous myocardial infarction, and four had undergone a coronary artery bypass operation (Table 3). Four patients had angina pectoris and five more had a history of angina that had been relieved following a myocardial infarction or coronary artery bypass.

To assure accuracy of preoperative and postoperative comparisons in individual cases, serum cholesterol levels were included for analysis only when these were measured at the same center. The analytic techniques were based on the Liebermann-Burchard color reaction[15] or on enzymatic assay.[16] In most cases, less frequent determinations were made of serum triglycerides, low density lipoprotein (LDL) cholesterols, and high density lipoprotein (HDL) cholesterols. Standard liver function tests were obtained.

The portacaval shunts were performed by anastomosing with fine continuous suture the cut end of the portal vein to an elliptical defect in the anterior or anterolateral wall of the suprarenal inferior vena cava. Tributaries to the portal vein above the site of its transection were looked for and ligated. The anastomoses were made slightly larger than the natural diameter of the portal vein. Although hypercoagulability has been described in FH,[17] no anticoagulants were given during or after operation. Thrombosis after portacaval shunt in children with portal hypertension has been so high that most pediatric surgeons prefer to use the operation only in patients older than 8 or 10 years and for those whose anastomosis can be made at least 1 cm in diameter.[18,19] Although these minimum conditions did not

TABLE 2. Serum Lipids in mg/dl* (Mean and 1 SD) before and after Portacaval Shunt

Case	Therapy at Sampling Preop	Therapy at Sampling Postop	Months of Sampling Preop	Months of Sampling Postop	Total Cholesterol (mg/dl) Preop	Total Cholesterol (mg/dl) Postop	LDL Cholesterol (mg/dl) Preop	LDL Cholesterol (mg/dl) Postop	HDL Cholesterol (mg/dl) Preop	HDL Cholesterol (mg/dl) Postop	Triglycerides (mg/dl) Preop	Triglycerides (mg/dl) Postop
1.	Diet	Same	3-0	1-18	769 ± 47 [9]	343 ± 71¶ [18]					94 ± 18 [9]	68 ± 33‖ [12]
2.	Diet, cholestyramine	Same (plus later nicotinic acid, probucol, clofibrate)	6-0	1-96	998 ± 44 [12]	532 ± 72¶ [14]	801 ± 28 [5]	473 ± 70¶ [11]	89 ± 7 [5]	30 ± 11¶ [11]	113 ± 14 [9]	90 ± 25‖ [14]
3.	Diet, cholestyramine	None	60-0	1-72	868 ± 78 [9]	535 ± 48¶ [15]					170, 193	65, 112
4.	Diet, (metabolic ward)	Same	4-0	16-21†	593 ± 42 [43]	455 ± 25¶ [35]	503 ± 50 [33]	395 ± 32¶ [35]	37 ± 12 [32]	25 ± 6‖ [35]	66 ± 9 [42]	119 ± 36‖ [35]
5.	Diet, nicotinic acid	Same	10-0	2-7‡	750 ± 17 [5]	495 ± 52‖ [6]	696 ± 9 [5]	457 ± 43‖ [6]	28 ± 9 [5]	23 ± 8.6 [6]	105 ± 12 [5]	86 ± 22 [6]
6.	Diet, (metabolic ward)	Same	7-0	17-21	543 ± 23 [56]	330 ± 21¶ [45]	439 ± 26 [54]	247 ± 44¶ [45]	33.8 ± 6.7 [54]	42.2 ± 5.4 [45]	229 ± 50 [56]	85 ± 12¶ [45]
7.	Diet, nicotinic acid, cholestyramine (noncompliant)	Colestipol (non-compliant)	36-0	1-36	1038 ± 98 [7]	693 ± 68¶ [9]						
8.	Diet	Same	3-0§	1-15	576 ± 15 [4]	461 ± 60‖ [7]	538 ± 14 [4]	419 ± 58‖ [7]	20 ± 2 [4]	29 ± 7 [7]	93 ± 6 [4]	67 ± 30 [7]
9.	Diet, nicotinic acid	Same	8-0	1-3	1034 ± 156 [7]	743 ± 37‖ [3]	957 ± 157 [5]	691 ± 43‖ [3]	27 ± 9 [5]	23 ± 3 [3]	200 ± 57 [7]	156 ± 43 [3]
10.	Diet, nicotinic acid	None	19-0	1-9	860 ± 46 [6]	525 ± 42‖ [4]	818 ± 60 [5]	470 ± 45‖ [4]	23 ± 5 [6]	29 ± 5 [4]	213 ± 55 [6]	120 ± 8¶ [4]
11.	Diet, nicotinic acid	Same	22-0	1-9	382 ± 39 [6]	304 ± 9.1¶ [5]	315 ± 32 [6]	246 ± 11.6¶ [5]	26 ± 3.6 [6]	44 ± 16 [5]	287 ± 74 [6]	137 ± 18.7‖ [5]
12.	Diet, cholestyramine, nicotinic acid, Vitamin E	Same	8-0	1-13	750 ± 137 [4]	480 ± 41¶ [5]	711 ± 71 [3]	427 ± 53‖ [2]	26 ± 21 [3]	19 ± 11 [2]	101 ± 42 [4]	65 ± 12 [5]

* Divide by 38.66 for cholesterol values in millimoles/L and by 136.8 for triglyceride values in millimoles/L.

† Outpatient data in text.

‡ The values were during the first seven postoperative months, after which monthly plasmapheresis was begun because the patient had a myocardial infarction.

§ These preoperative determinations followed a 2½-year period of biweekly plasmapheresis that was terminated 3 months before the portal diversion.

¶ Pre- and postoperative differences significant (p < 0.001).

‖ Pre- and postoperative differences significant (p < 0.05 > 0.001).

[ ] Number of samples.

TABLE 3. *Effect of Portacaval Shunt on Cardiovascular Disease and Visible Xanthomas*

Case	Previous Cardiovascular Status*	Postop Cardiovascular Examination	Tendinocutaneous Xanthomas	Other Clinical Observations (Postop)	Months Follow-up
1.	Aortic stenosis, and insufficiency, multiple lesions of coronary arteries, myocardial infarction one month previously, ventricular aneurysm, heart failure	Regression of aortic stenosis and coronary artery disease; marked improvement of heart failure; died of arrhythmia	Disappeared	Resumed normal activities except competitive sports	18½ (died)
2.	Aortic stenosis, bulky atheromas thoracic aorta, multiple lesions of coronary arteries	Double coronary artery bypass plus aortic and mitral valve replacement, November, 1976; Out-grown heart valves replaced, February 1981; now stable	Disappeared	Normal life, participates in sports such as soccer and basketball	103
3.	Aortic stenosis, large atheromas on angiogram in ascending thoracic and abdominal aorta, carotid and femoral bruits, coronary arteries patent	Restudied June 1982. Aortic valves atrophic and moderately insufficient, ascending aortic atheroma persistent with 36-mmHg gradient, Right coronary artery normal, Left coronary artery not cannulated. Dilatation and hypertrophy left ventricle	Almost gone, but tiny satellite lesions recently developed near old xanthoma sites.	Nearly normal activities, including soccer and jogging	93
4.	Mild aortic stenosis; normal coronary arteries, normal exercise stress test	No change clinically	Markedly diminished	Normal activities	53
5.	Aortic stenosis, atheroma mass ascending aorta, multiple lesions of coronary arteries, heart failure, peripheral bruits	Myocardial infarction 7 months postop, with ventricular aneurysm and heart failure; died of heart failure and arrhythmia	Only skin stains remained	Restricted activities, developed renal stones	30 (died)
6.	Multiple lesions of coronary arteries, previous myocardial infarction, previous coronary artery bypass, left ventricular dilatation	Same clinically	Not prominent before, diminishing	Minor activity restrictions, moderate improvement	45
7.	Aortic stenosis and insufficiency, atheromas on angiogram in aorta, coronary arteries patent	Aortic stenosis gradient reduced and aortic atheromas stable on restudy after one year. Coronary arteries normal	Disappeared	Normal activities	42
8.	Aortic stenosis, multiple lesions of coronary arteries, previous myocardial infarction, previous coronary artery bypass	No change clinically	Diminished	Has severe but quiescent multiple sclerosis, general condition and activity level improved	29
9.	Aortic stenosis, multiple lesions of coronary arteries previous myocardial infarction, previous coronary artery bypass, heart failure	Died 4 months heart failure, arrhythmia, diffuse coronary disease at autopsy	Not prominent before, diminished	Not rehabilitated because of pre-existing heart disease	4 (died)
10.	Aortic stenosis, coronary arteries open, ileofemoral bruits	No change clinically	Diminishing	Slightly restricted	18
11.	Multiple lesions of coronary arteries, previous myocardial infarction, previous coronary artery bypass	Improved clinically	Not prominent before, diminishing	Slightly restricted activities	18
12.	No abnormalities clinically	No change clinically	Diminishing	Normal activities	14

* Preoperative catheterization and angiography in all except patient 12; postoperative repeat studies in patients 1, 2, 3, 5, and 7. Patients 2, 3, 5, and 10 had angina pectoris immediately before operation, and angina already had been relieved in patients 1, 6, 8, 9, and 11 by a myocardial infarction or coronary artery bypass.

obtain in the majority of our patients, there were no technical difficulties.

Results

Convalescence following portacaval shunt was prompt and uncomplicated. Patients 1, 5, and 9 died of heart disease after 18½ months, 30 months, and 4 months, respectively. The other nine patients are alive after 14 to 103 months (Table 3).

Effect Upon Serum Lipids

Total serum cholesterol concentrations fell significantly in every patient after portacaval shunt (Table 2). When measured, LDL cholesterol levels were reduced commensurately (Table 2). The total cholesterol level declines were 20% to 55.4% (average 33.8%) and were maintained throughout the period of study. The decreases were evident in 1 to 4 weeks and had reached a relatively stable new level by 2 or 3 months.

In patient 4, two sets of results were available. As an outpatient on a low cholesterol diet, this child with homozygous disease had total serum cholesterol levels before operation of 745 ± 51(SD) mg/dl. Afterwards, these fell to 533 ± 24 mg/dl. With these conditions, the total serum cholesterol reduction was 28.5%. During metabolic studies in the hospital, he was given a liquid formula diet containing 150 mg/day cholesterol with a polyunsaturated/saturated fat ratio of 0.4. Both the baseline and post-shunt cholesterol levels were lower on this restrictive diet, with a reduction of 23.5% after operation. The in-hospital data is given in Table 2.

Most of the patients were kept on the same medical management after operation as that used before. However, the cholesterol levels dropped by 38%, 20%, and 39% in patients 3, 8, and 10, respectively, despite discontinuance of all medications and relaxation of diet. In patient 2, a previously reported immediate decline of 41%[20] was increased to 46% (Table 2) after other drugs were added to diet and cholestyramine.

Because of a myocardial infarction 7 months after portacaval shunt, patient 5 was started on monthly plasmapheresis. Portal diversion had already caused a 34% reduction in serum cholesterol (Table 2). Before operation, plasmapheresis had been tried and eventually stopped because of the return of serum cholesterol to baseline levels within 10 days after each treatment. Now, plasmapheresis caused a greater reduction in serum cholesterol which required 20 days for recovery.

Serum triglyceride levels also usually fell, but this change was significant in only five of nine cases, in which sufficient data were available for assessment (Table 2). A significant rise was seen in patient 4. HDL cholesterol
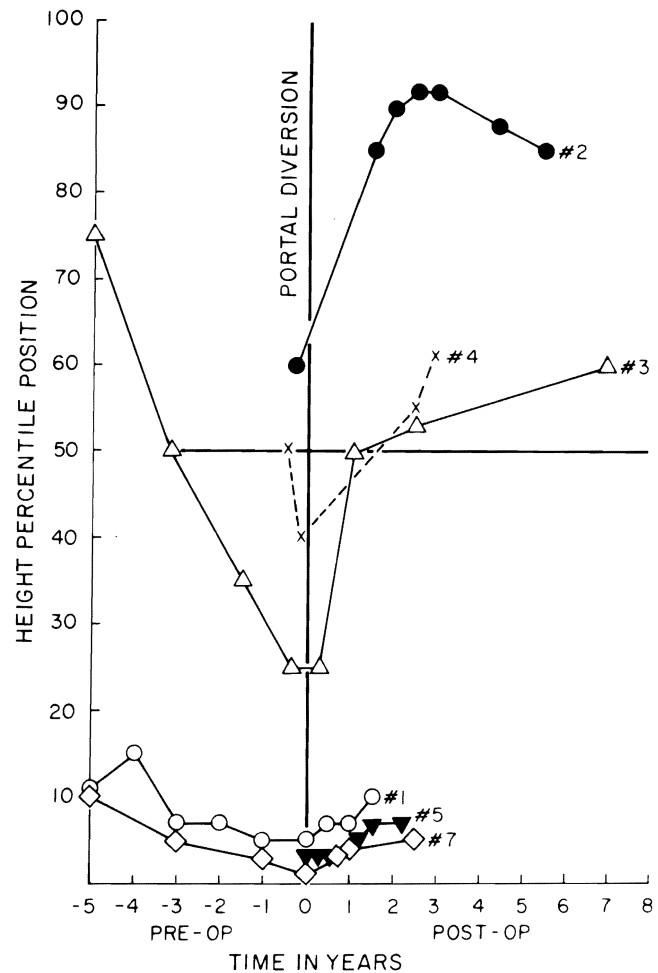

FIG. 1. Percentile height position, taken from standard growth charts, of the first six pediatric patients before and after portacaval shunt. All patients gained height after operation more rapidly than before, causing their percentile position to move up on the age-corrected growth charts.

values were available from eight patients; significant falls were seen in only two patients (Table 2). Significant increases in HDL cholesterol were not seen.

All 12 patients with tendinocutaneous xanthomas had regression or disappearance of the lesions (Table 3). If the xanthomas were prominent, complete disappearance, when this was achieved, required 1½ to 3 years.

Physical and Emotional Development

Four of the first six pediatric patients were below average in height development, and five patients had exhibited a recent failure to grow. All six patients had growth spurts after operation (Fig. 1). Similar weight trends were seen (Fig. 2).

None of the 12 patients had emotional or intellectual deterioration. Patients 4 and 6 had full verbal performance assessment of their intelligence quotient (I.Q.)
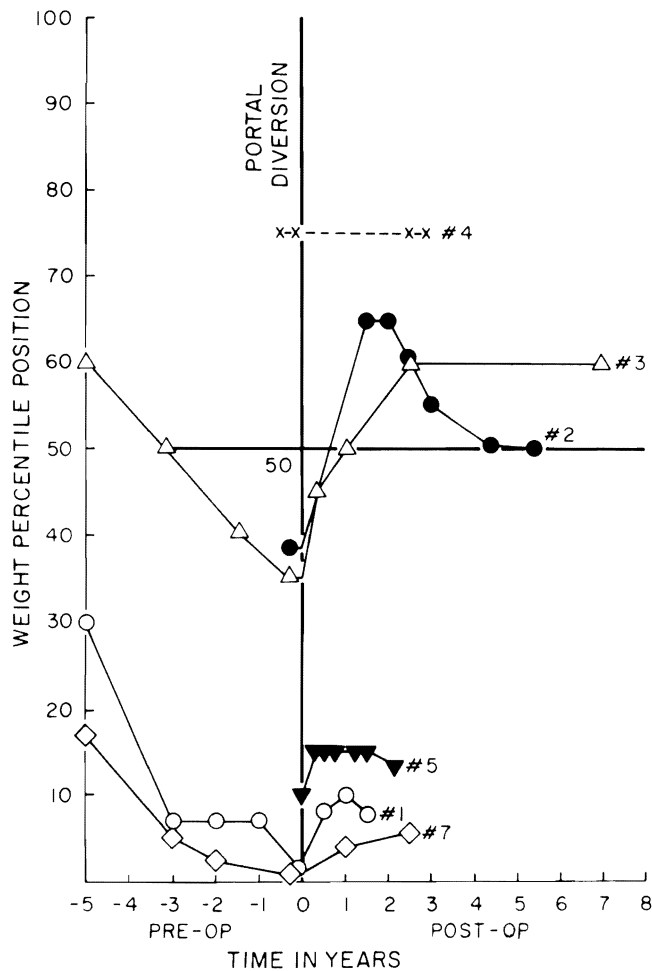
FIG. 2. Changes in percentile weight positions of the first six pediatric patients before and after portacaval shunt. The points were taken from age-corrected standard growth charts. All patients gained weight after, and all but patient 4 improved their percentile position.

using the Stanford Binet or Wechsler tests before operation and 1½ years later. Their scores did not change.

Hepatic and Renal Function

There were no major changes in bilirubin, prothrombin time, and serum protein concentration. Several of the patients had minor fluctuations in serum transaminase levels. Elevations in alkaline phosphatase were common but not progressive.

Sporadic increases of blood ammonia levels were seen after operation in patients who had multiple tests. Usually, the elevations were at or just above the upper reference range for the laboratory being used. Four patients had studies before and after portacaval shunt at the National Institutes of Health laboratories, where the normal blood ammonia range is 19 to 60 μg/dl. Before operation, blood ammonia concentrations in the four patients were 46.4 ± 7.6 (SD) μg/dl, and after operation,

these were 79.0 ± 22.9 μg/dl (p < 0.05). In the other cases in which the first determinations were postoperative, the highest postoperative values observed were in patient 6, a 52-year-old man with heterozygous disease who had ammonia concentrations as high as 200 μg/dl. As a result, he was placed for 14 months on a low-protein diet. Then, he was returned uneventfully to a diet containing 12% to 15% of calories as protein, with no increase in blood ammonia levels. He never developed encephalopathy and he was one of the patients whose I.Q. did not change.

Only one of the 12 patients has had clinical manifestations of hepatic encephalopathy. The exception was 2-year-old patient 12, who had a single episode of unconsciousness nine months after portacaval shunt at a time when the blood ammonia concentration was 85 μg/dl (normal in that laboratory was less than 55 μg/dl). Encephalopathy was accepted as the diagnosis because no other explanation was found. The child was placed temporarily on a low-protein diet and has now resumed a normal diet.

Renal function was not changed. Patient 5 developed renal stones one year after portacaval shunt. The stone formation was ascribed to hypercalcuria associated with the use of diuretics. However, the composition of the stones was not determined. Urologic care was not required.

Cardiovascular Disease

Patients 4, 10, and 12, who had no preoperative cardiac complaints, have remained asymptomatic for 44 months, 9 months, and 5 months after portacaval shunt, respectively, (Table 3). Eight of the other nine patients claimed improvement in physical activity and a reduction in symptoms which included angina pectoris in four of them. However, three of the nine patients died of cardiac complications at 4 months (patient 9), 18½ months (patient 1), and 30 months (patient 5); all of the portacaval shunts were widely patent at autopsy. All three patients had proven coronary artery disease before operation, and two had previously survived myocardial infarctions that had left them with chronic heart failure. The death of patient 1 was ascribed to an arryhthmia,[21] since reversal of coronary artery atherosclerosis was thought to be occurring on the basis of repeat coronary angiograms.[22] The heart failure of patient 9 became intractable after an attempt at post-shunt plasmapheresis, and she died of an arrhythmia several weeks later. Patient 5 had his first myocardial infarction 7 months after operation at a time when tendinocutaneous xanthomas were shrinking; despite efforts to expedite removal of lipid deposits by the addition of monthly plasmapheresis, he died of heart failure and an arrhythmia 2 years

later. At autopsy, the distal coronary arteries were in good condition. The proximal right coronary ostium was occluded partially, but the left coronary ostium was open. There was a partially occlusive atheromatous mass in the proximal ascending aorta. A similar mass with a present pressure gradient of 36 mmHg has been present in patient 3 for 7 years. During this time, aortic stenosis may have regressed but with residual aortic insufficiency.

Two definite examples of reversal of aortic stenosis were documented by cardiac catheterization. A gradient reduction from 56 to 10 mmHg occurred in patient 1 in 16 months.[22] A decline from 40 to 24–30 mmHg was seen in patient 7 over 13 months, during which time large atheromas of the thoracic aorta were unchanged.

Coronary angiography before and from 7 months to 7 years after portacaval shunt was performed in five cases (patients 1, 2, 3, 5, and 7) but was technically difficult because of the atheromatous disease of the aortic valves and ascending aorta. The appearance of the coronary arteries was thought to be better in patient 1, uninterpretable in patient 3, unchanged in patients 2 and 7, and possibly worse in patient 5. In patient 5, coronary angiography 9 months after portacaval shunt and 2 months after myocardial infarction did not show worsening of a 50% narrowing of the ostium of the right main coronary artery. It was suspected that spasm or an embolus to the left coronary artery may have been responsible for his large anterior wall myocardial infarction and ventricular aneurysm since the left main and left anterior descending coronary arteries were patent.

Patient 2 had a double coronary artery bypass and replacement of the aortic and mitral valves 25 months after portacaval shunt. Her rapid growth rate (Fig. 1) necessitated replacement of both valves 4½ years later. At reoperation, the coronary artery reconstructions were open, and the prosthetic valves were in good condition. Her rehabilitation has been complete.

Discussion

The effects of completely diverting portacaval shunt on liver structure are common to all species studied so far,[23] including humans with FH.[1] These include hepatocyte atrophy, glycogen depletion, fatty infiltration, and drastic alteration of the organelles.[1,23–27] The reduction of hepatocyte rough endoplasmic reticulum with depletion of its polyribosomes is unusually prominent[23–25] and is the probable explanation for reductions in many biosynthetic processes. These alterations are explained by the fact that the liver is deprived of first-pass exposure to hormones (especially insulin) and other putative hepatotrophic factors from splanchnic viscera.[24–27]

The hepatic changes caused by portacaval shunt are thought to be responsible for the hepatic encephalopathy, inanition and hair loss that occur regularly in dogs, inconstantly in other species, and to an apparently insignificant degree in humans with a previously undamaged liver. It has been known since the last century[28] that the complex physiologic and morphologic events following portacaval shunt do not occur or are minimized by shunt thrombosis and stenosis or by revascularization by splanchnic collaterals of the tied off portal vein above the site of anastomosis. In normal dogs,[24,29] and baboons,[24] partial diversion of the portal venous blood does not cause the lowering of serum cholesterol levels that is seen after total portacaval shunt.

After portacaval shunt, patients with Type I glycogen storage disease have striking reductions of serum cholesterol, triglyceride, and phospholipid levels.[30] This observation was an important factor in the decision to perform portal diversion in the first patients with FH.[1] The same cholesterol lowering effect was observed in all of our patients with homozygous or heterozygous FH. The LDL membrane receptor status was not predictive of the extent of the decline. Total serum cholesterol concentrations (and LDL cholesterol levels when measured) fell 20% to 55.4% while the patients were on comparable, or frequently less rigid, programs of medical management than those used after surgery. HDL cholesterol and triglyceride levels were variably effected. Tendinocutaneous xanthomas regressed or disappeared in every patient.

The consistency of the anticholesterolemic response was greater than that noted by other authors who have reported on a total of 26 additional patients, 13 of whom were treated in Johannesburg.[12] In the 13 treated elsewhere than Johannesburg,[3,5–11] serum cholesterol reductions of at least 30% were obtained in ten patients at the same time as tendinocutaneous xanthomas regressed. In two of the three exceptional patients, shunt thrombosis was proved,[5,6] and in one of these, the cholesterol level fell by 40% after a later mesocaval shunt.[31] In the third patient, reported by Soutar, Myant, and Thompson,[8] there was presumptive 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,[20,32] fell to baseline.

The early[4] and subsequent[12] reports from Johannesburg have confirmed the value of portacaval shunt in FH, but have provided minimal incentive for expanded trials. Of 13 homozygous patients with unstipulated membrane receptor status, one died 2 days after operation of a myocardial infarction. The remaining 12 patients had significant but often modest falls in serum total and LDL cholesterol levels, which later returned

to or toward preoperative levels in three patients. Xanthomas regressed in eight patients, were stable in two patients, and increased in two patients. Almost all of the patients developed postoperative splenomegaly, a finding compatible with sluggish or obstructed splanchnic venous drainage or alternatively with a manifestation of FH that previously had not been appreciated.[12]

One of the Johannesburg patients was proved to have an occluded portacaval shunt (splenorenal shunt was performed later with a good result), another was demonstrated to have revascularization of the portal vein stump with a large splanchnic collateral, and the rest were not studied with angiographic techniques, since they had not developed esophageal varices. However, sudden occlusion of the portal vein in subhuman primates and in humans often does not cause portal hypertension and varices.[33] Physiologic evidence of shunt patency, such as that obtainable by demonstrating postprandial hyperglucagonemia[20,32] or hyper-bile acidemia[20,34] was not given. Forman et al.[12] speculated that the unevenness of the results could have been due to ineffective portal diversion in some cases, to peculiarities of the FH which is endemic in that region, or to other less obvious factors.

The invariable and long-lasting lipid lowering in our 12 patients was achieved with little surgical morbidity. There has been no suspicion that any of the shunts has closed. The physical development of those children who were normal before has proceeded and the growth of those who were stunted before operation has moved toward normal. Emotional or intellectual deterioration secondary to the portal diversion has not occurred, as was once feared following the report of Voorhees et al.[35] Detailed I.Q. and psychologic examinations in two patients were unchanged before and after operation. There were no major perturbations of standard liver function tests, although increases of alkaline phosphatase were common. When measured, blood ammonia levels were always elevated, the most extreme example being in an asymptomatic adult who was treated for the first 14 postoperative months with a low-protein diet. Such temporary protein restriction also was prescribed for patient 12. One year after operation, one of the patients developed renal stones of unknown composition. Uric acid stones can be caused in rats by portacaval shunt.[36]

The mechanisms by which portal diversion reduces serum lipids probably are qualitatively similar in normal experimental animals and in patients with FH. After portacaval shunt, reductions of more than 80% in hepatic cholesterol and triglyceride synthesis were demonstrated in dogs.[24] Although a similar diminution in cholesterol and/or lipoprotein synthesis was confirmed in rats,[37–39] dogs,[40] swine,[41–43] and baboons,[40] not all

workers could verify these findings.[44–47] The rigorously controlled studies in rats by Proia et al.,[38] which are the only reported animal experiments in which body weights were maintained or increased after operation, have done much to explain the latter discordant reports. In addition to a reduction in cholesterol synthesis, Proia et al.[38] made the crucial observation that the total body cholesterol pool was diminished after portal diversion.

Data relevant to mechanisms in humans with FH are also available. Soutar et al.[8] found no change in LDL synthesis and an actual rise in VLDL synthesis in the patient discussed earlier whose shunt may have been closed. Strikingly different conclusions have been reached from metabolic studies in three of the 12 patients of our series. In patient 2, Bilheimer et al.[20] showed that cholesterol and LDL syntheses, which were inappropriately high before portacaval shunt, were reduced afterwards by 62% and 48%, respectively. The fractional catabolic rate that was only a third of normal at the outset, as is typical for FH, fell further after operation. Ginsberg et al.[48] studied the heterozygous patient 6, who responded to portal diversion with major reductions in LDL as well as VLDL apoprotein-B synthesis, in VLDL triglyceride synthesis, and in the already subnormal fractional catabolic rate.

The extraordinary degree to which cholesterol homeostasis was altered by portacaval shunt in the homozygous patient 4 and the heterozygous patient 6 has been shown by McNamara et al.[49] Exogenous cholesterol absorption was unchanged in both patients and bile acid synthesis was halved. Whole body cholesterol synthesis was decreased by 68% in patient 4 and by 41% in patient 6. The total body cholesterol mass 1½ years after portacaval shunt had been reduced by 59% in patient 4 and by 43% in patient 6. These data are compatible with the extraordinary diminution or disappearance of tendinocutaneous xanthomas and with the hope that the lethal cardiovascular complications of FH can be slowed or forestalled by portacaval shunt.

However, the degree to which cardiovascular complications can be relieved or prevented by portal diversion has not been established. Reversal of aortic stenosis was seen, but regression of atheromas in the coronary arteries and aorta was not regularly accomplished. Small and Shipley[50] have examined the factors that could preclude the reversal of atherosclerosis, and some of these, including secondary fibrosis, would not be corrected completely by the resorption of intravascular xanthomas. Farriaux et al.[31] have suggested that anatomic 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. The experience with patient 2 has shown the value of aggressive surgical cor-

rection of technically remedial lesions. Others have recommended the combination of portal diversion with corrective cardiovascular surgery.[7,11]

Of far 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. After operation, medications and diet should be tried again, since further drops in post-shunt cholesterol levels have been seen using diet and medications that were previously ineffective. Baker et al.[51] have reported an encouraging experience with probucol in five patients who had had variable responses to previous portacaval shunts. The experience with patient 5 suggested that plasmapheresis may become a procedure more acceptable to patients because of slower rebounds of plasma cholesterol levels between treatments.

The staged combination of portacaval shunt and the ileal bypass procedure of Buchwald et al.[52] has been tested in three patients with an apparently additive effect,[10,12] in spite of the fact that ileal bypass alone has little or no effect in homozygous FH.[52] In dogs, Guzman et al.[53] have noted an additive effect of portal diversion by portacaval transposition plus ileal resection. If the depression of bile acid synthesis, noted by Bilheimer et al.[20] and McNamara et al.,[49] after portacaval shunt for FH can inhibit the increased bile acid synthesis that is normally caused by ileal bypass in response to increased bile acid excretion,[52] an accelerated secondary depletion of the cholesterol pool might be expected.

Portacaval shunt, with or without supplementary treatment, provides palliation only for patients with FH. The amelioration of the abnormal metabolic patterns of FH has derived from the countervailing and potentially dangerous abnormalities caused by portacaval shunt. The palliation has been incomplete, since restoration of normal serum cholesterol values has not been achieved in any patient with homozygous disease. Because of the evidence of a central hepatic role in the regulation of lipid metabolism,[54–57] it is possible that the metabolic abnormalities of FH could be rectified by the ultimate step of liver transplantation. The list of inborn errors of metabolism already corrected by liver transplantation has become a long one.[58]

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DISCUSSION

DR. SEYMOUR I. SCHWARTZ (Rochester, New York): Within this paper are important messages that transcend the field of portal decompressive surgery. First, the work reinforces a lack of correlation between post-shunt hyperammonemia and the clinical manifestations of encephalopathy. But, more important, it also provides evidence that sudden and total diversion of portal flow into the systemic circulation, in the absence of hepatocellular dysfunction, and even in the absence of pre-existing naturally developed shunts and portal hypertension, is not associated with post-shunt encephalopathy; this is a finding which we have previously reported.

These results should liberalize the indications for portal decompressive procedures in patients with bleeding esophagogastric varices as a consequence of extrahepatic portal hypertension resulting from either portal vein thrombosis or from cavernomatous transformation of the portal vein.

PRESIDENT WARREN: This is a beautiful presentation by Dr. Tom Starzl, who is a fantastic student of human biology. This presentation is a major contribution to the study of lipid metabolism, as well as to that of the Eck fistula in man. When you look at his data, it will become clear that these are some of the most important findings to become available to us in this field.

I think it is much too early to draw the conclusion that an Eck fistula, in the presence of a normal liver mass, is nonencephalophaly producing. In fact, I will predict, as I have so often with things that Sy Schwartz has said in the past, that Dr. Starzl is wrong again. (Laughter)

Some of you will recall that we presented before this Association a

group of patients with portal vein thrombosis who had total shunts with complete decompression of the portal system. In this group it took about 20 years—that is, 20 years in the human—to produce encephalopathy. With that time span, that is a perfectly good risk in the patients in Tom Starzl's series, because their inherent risk from their hyperlipidemic is so enormous, and lowering of the lipids is the key to the success of the procedure. In portal vein thrombosis, however, there is an operation in which you do not lose portal flow, and such patients need not become an Eck-fistula human preparation.

If I would remember simply this, that with a normal liver cell mass, in contrast to the baboon, as Starzl has pointed out specifically, the delay before encephalopathy is very, very long. Its importance, however, has recently been emphasized by the study of an anomaly in the Krebs-Henseleit cycle in the ornithine transcarbamoylase deficiency in which very minimal elevations of ammonia ultimately lead to encephalopathy, although this may take 30 years or so.

The good news is that even after 20 years our patient with profound encephalopathy from a total shunt with a normal liver had virtually complete reversal of encephalopathy with closure of the shunt, and a return to an essentially normal functional status. Could you tell me how long post-shunt your oldest patient is?

DR. GEORGE H. A. CLOWES, JR. (Boston, Massachusetts): In the first part of his paper, Dr. Starzl listed a number of metabolic effects that are created by injury to the liver following portacaval shunt. Now, I would like to draw to your attention another one that's proving to be of great use at the present time; namely, the study of amino acid clearance by the liver in portacaval shunt, prior to portacaval shunt.

Two things have come out of this. It turns out that the total amino acid clearance of the liver can be measured in terms of amino acids cleared from plasma, and a normal clearance in response to injury or sepsis would be in the vicinity of 300 cc of plasma/sq m/m. In people who survive portacaval shunt, the average value has turned out to be something like 260 cc/m. And in those who died of metabolic deaths after surgery, it was only 180 cc.

This is a very significant difference, with a P value of something less than 0.001, and I believe that it explains in part the hyperlipidemia problem that Dr. Starzl told us about; namely that the protein synthesis is very closely related to VL/DL, and all the other aspects of cholesterol chemistry. I would urge you to use this method of amino acid clearance as a means for studying your patients preoperatively, and also for finding out what happens to them in the post-shunt period. I believe that in the near future amino acid metabolism and protein synthesis will fall together in relation to energy production, fat metabolism, and gluconeogenesis.

DR. HARRY H. LEVEEN (Charleston, South Carolina): Some years ago, in studying insulin-deficiency diabetes, we were able to show that the animals who had their insulin from the splenic vein diverted to the systemic circulation, rather than going through the liver, lessened their diabetes.

We also noticed that the cholesterol levels in humans injected with insulin into the portal vein dropped quite precipitously, and we wondered whether this might not account for the rapid atherosclerosis that is seen (1) after pancreatectomy with diabetes, and (2) in diabetics taking insulin systemically. Diabetics who are on insulin always inject their insulin systemically.

We took a series of 15 diabetics, and converted their insulin administration from systemic, in their arm, or wherever they injected it—we injected it intraperitoneally, and we were able to demonstrate that there was a good fall in circulating cholesterol values in those diabetics receiving their insulin intraportally.

I wonder whether or not some of the derangements that are seen in the liver that are adverse might not possibly be averted by (1) diverting the blood flow from the spleen, rather than the entire portal system, or (2) injecting some insulin intraportally; even though these patients are not diabetic, the delivery of insulin into the portal system might alleviate some of their normal ammonia.

DR. THOMAS E. STARZL (Closing discussion): I would like to thank the discussants, Drs. Schwartz, Warren, Clowes, and Leveen. The subjects that Dr. Leveen has raised are important, but they are so complex that it would require a good deal of time to give them adequate discussion. Dr. Leveen has raised the issue of whether in diabetes mellitus the proper drug (insulin) is being given by an improper route. This possibility is something that has fascinated many workers going back for at least 2 decades. I would be remiss in not mentioning the very fine work that Dr. Bill Waddell did on this question between 15 and 20 years ago.

Concerning the other discussants, I am in the unusual position, which I have been seeking lately, of agreeing with everybody. And to agree with Sy Schwartz and Dean Warren at the same time is quite a trick. (Laughter)

What we are looking at here is a balancing of benefits and penalties for this operation. I do believe that the portacaval shunt is a very damaging operation which in the circumstance of familial hypercholesterolemia is worth doing, since the benefits exceed the penalties.

But, we are looking at a procedure which requires, for its ultimate metabolic objectives, complete portal blood diversion; and that is something which in clinical practice I personally hate to do. Complete portal diversion puts the patient at potential jeopardy. I agree with Sy Schwartz about the relative safety of portal diversion in patients with normal and familial hypercholesterolemia or with extrahepatic block. But, in principle, I believe that the Warren procedure is the best kind of operation to be carried out for patients for whom you have the strictly mechanical objective of decompressing esophageal varices, because the same benefits can be realized, as with complete diversion but without paying a potentially terrible physiologic penalty. Our longest follow-up is over 9 years. Thank you very much.