Portal Diversion for the Treatment of Glycogen Storage Disease in Humans

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IT HAS BEEN almost a decade since the first attempt was made to treat a child with hepatic glycogen storage disease by portal diversion.[28] On the basis of animal experiments,[23,28] it was hoped to make dietary glucose more readily available to peripheral tissues, to coincidentally deglycogenate the liver, and to palliate other complications such as acidosis. This patient, as well as a second one described by Riddell, Davies, and Clark[21] had the operation of portacaval transposition, a procedure developed in dogs by Child and associates[5] whereby the diverted portal inflow is replaced with venous blood from the suprarenal inferior vena cava.

Although the transposition was used in order to avoid the potential hazards of Eck fistula, it was suggested in our original report and in subsequent ones by Hermann and Mercer[11] and ourselves[25] that an end-to-side portacaval anastomosis probably would be just as effective and that certainly it would be technically safer by virtue of omission of the second venous anastomosis. The simpler procedure of portcaval shunt has been used in all subsequent cases that have appeared in the literature[2,6,9] as well as for the last five cases in our series herein reported. Folkman and associates have recently shown that a further reduction of operative risks in patients with glycogen storage should be possible by parenteral hyperalimentation and consequent preoperative amelioration of hepatomegaly, acidosis, and other metabolic abnormalities.[9]

The present communication has two general purposes. The first is clinical. Our own as well as the collected world experience with portal diversion for hepatic glycogen storage disease will be recounted, adding now to a total of 13 cases and including follow-ups of 9½ and 8 years, respectively, for our oldest patient and for Riddell's patient[21] who immigrated from Bristol, England, to Canada in 1968. This latter boy was recently seen and studied in Denver along with our own six surviving patients. Emphasis will be placed on the long-term relief of the metabolic disturbances and growth retardation in patients with deficiency of three different kinds of enzymes: glucose-6-phosphatase (Type I), amylo-1-6-glucosidase (Type III), and phosphorylase (Type VI).

The second objective will be to consider the reasons why portal diversion has been so valuable. Partly on the basis of experiments recently carried out in dogs,[26] it will be suggested that the multiple and striking benefits of portal diversion in glycogen storage disease de-

The work was supported by research grants from the Veterans Administration; by grants AI-AM-08898 and AM-07772, and GM-04761 from the National Institutes of Health; and by grants RR-00051 and RR-00069 from the general clinical research centers program of the Division of Research Resources, National Institutes of Health.

Presented at the Annual Meeting of the American Surgical Association, Los Angeles, California, April 25–27, 1973.

rive more from the bypassing of pancreatic hormones (particularly insulin) around the liver than by the simple rerouting of alimentary glucose as was originally believed.

Methods

There were seven patients in the Colorado series with the ages and the enzyme defects shown in Table 1*. In addition, the patient reported from Bristol, England, by Riddell, Davies and Clark[21] was studied including biopsy 7⅔ years postoperatively. Determination of the enzyme defects in the Colorado cases was by biochemical analysis in the St. Louis Laboratories of liver wedge biopsies which were obtained before or at the time of portacaval diversion and frozen on dry ice. The methods of analysis as well as the disease classification according to numerical types have been well accepted in standard endocrinology and metabolism texts.[3,13,22]

The major complaints of the children or their parents were variable (Table 1). All of the patients were stunted in growth and in Case 5 this was the most important complaint. Episodic hypoglycemia was documented in all but Case 5. Patients 2, 3, and 4 (all Type I disease) had recurrent metabolic acidosis with lactic acidemia which had required numerous hospitalizations for therapy. The same three patients had repeated seizures. Other miscellaneous problems are mentioned in Table 1. Patients 6 and 7 were brother and sister; a sibling died at age 5, apparently of metabolic complications of glycogen storage disease. Two siblings of patient 2 died of hypoglycemia and acidosis.

The kind of portal diversion is indicated in Table 1. Our first two patients had portacaval transposition; end-to-side portacaval shunt was used for the last 5.

* Types I, III, and VI are the hepatic glycogenoses which might theoretically benefit from portal diversion. At our institution, a 23-month-old child from Christchurch, New Zealand, with Type IV glycogen storage disease (α-1,4-glucan: α-1,4-glucan 6 glycosyl transferase deficiency) received a side-to-side portacaval anastomosis but not with the metabolic objectives of the present report. With Type IV disease, an abnormal glycogen resembling amylopectin which apparently causes a foreign body tissue reaction is deposited in the liver and causes progressive cirrhosis that leads to death at the age of 2 years or younger. The portacaval shunt was performed in an attempt to control massive ascites but death followed 1 month later from hepatic insufficiency and a hemolytic crisis.

TABLE 1. *Patients with Glycogen Storage Disease Treated or Studied at the University of Colorado*

Case No.	Age at Operation	Glycogen Storage Disease		Type and Date of Portal Diversion	Major Symptoms
		Type	Enzyme Deficiency		
1	8½	III[B]	Amylo-1, 6-glucosidase	Portacaval Transposition 10/15/63	Hypoglycemia GI bleeding Nose bleeds Retardation of growth Abdominal distension
2	7	I	Glucose-6-phosphatase	Portacaval Transposition 6/26/68	Hypoglycemia Acidosis Convulsions Retardation of growth
3	7	I	Glucose-6-phosphatase	Portacaval shunt 5/2/72	Hypoglycemia Acidosis Convulsions Retardation of growth Nose bleeds Skeletal deformity
4	11	I	Glucose-6-phosphatase	Portacaval shunt 5/17/72	Hypoglycemia Acidosis Convulsions Retardation of growth Symptomatic hyperuriciemia
5	10	VI	Reduced liver phosphorylase	Portacaval shunt 8/2/72	Lethargy Retardation of growth
6	5	III	Amylo-1, 6-glucosidase	Portacaval shunt 11/7/72	Hypoglycemia Acidosis Retardation of growth
7	3	III	Amylo-1, 6-glucosidase	Portacaval Shunt 11/8/72	Hypoglycemia Acidosis Retardation of growth
Bristol	7	I	Glucose-6-phosphatase	Portacaval Transposition 5/5/65	Hypoglycemia Convulsions Retardation of growth Abdominal distension Respiratory infections Intellectual retardation

In Cases 3, 4, 6, and 7 parenteral hyperalimentation as described by Folkman *et al.*[9] was used for 29, 13, 6, and 7 days. When performing the end-to-side portacaval shunts, all tributaries of the portal vein were ligated and divided from just above the pancreas to the division into the right and left portal branches. An elipse was removed from the vena cava. The back wall of the portacaval anastomosis was sutured from the inside and the anterior wall was completed externally.[27] Postoperatively, hyperalimentation was continued until the patient resumed an oral diet and then tapered and discontinued from 6 to 8 days postoperatively.

Growth was assessed by measurements of height and weight and by serial radiographic studies. The latter usually included wrist and hand X-rays, which were graded for bone age by the standards of Greulich and Pyle[10] and for osteoporosis. Because of the variability of height measurements, lower extremity scanograms employing a calibrated steel rule were obtained. In Cases 3–7, serum alkaline phosphatase, calcium, phosphorus, and magnesium concentrations were obtained before and serially after operation and 24-hour urine calcium and phosphorus excretion was measured. These remained normal throughout except for a transient and minor hypocalcemia immediately postoperatively in four of the five patients in whom full data were obtained.

The effect of hyperalimentation and/or portal diversion upon liver size was determined quantitatively with colloidal gold (Case 1) or 99M technetium (Cases 3–7) sequential scans, using planimetry in some instances. Kidney size was followed by similar measurements of anteroposterior renal scans or by determining the supero-inferior length of the right or left kidney on intravenous urograms.

Standard liver function examinations were routinely obtained before and after operation, including serum bilirubin, alkaline phosphatase, SGOT, SGPT, lactic dehydrogenase (LDH), prothrombin time, total protein and electrophoresis, and plasma ammonia. Fasting venous plasma sugars, lactates, pyruvates, and pH's were measured. Five-hour glucose tolerance tests were performed with glucose sampling at 0, 30, 60, 90, 120, 180, 240, and 300 minutes. In many of these tests insulin concentration[18] and pH of the venous blood samples were also analyzed.

The serum lipid components, cholesterol, triglycerides phospholipids (expressed as lecithin), and unesterified fatty acids were repeatedly examined before and after operation Lipoproteins were analyzed by cellulose acetate electrophoresis in Cases 3–7 at frequent intervals, particularly in the patients with Type I disease.

Renal function was followed with blood urea nitrogen (BUN), creatinine and creatinine clearance determinations and with examination of urine electrolytes, urea, proteins and sediment; deterioration of function never occurred. Plasma uric acid concentration and urine uric acid secretion were measured.

Complete blood counts including white cell differential and quantitative platelet counts were followed. Minor abnormalities of several clotting factors have previously been reported for Case 1.[28] Patients 3–7 were screened for platelet defects prior to hyperalimentation or operation. The tests performed included a platelet count, Ivy bleeding time, prothrombin consumption,[29] platelet aggregation,* and *in vitro* platelet adhesiveness.[31] Major abnormalities of platelet function were discovered only in Cases 3 and 4. These patients had Type I disease, and both had follow-up platelet studies.

Needle or open biopsies were performed from 4 to 113 months after portal diversion in all six of the surviving Colorado patients as well as in Riddell's patient. The tissues were examined by light microscopy for evidence of fibrosis, cirrhosis and hepatitis. The amount of fat in the cells was determined in frozen sections. When pre- and postoperative biopsies were available the size of the hepatocytes before and after portal diversion were determined by a method previously described.[26] Electron microscopy was also used on the biopsies from six of the eight patients. In addition to the histopathologic examinations, the postoperative tissues were measured for glycogen concentration and if there was sufficient tissue, analysis was carried out of the enzymes studied preoperatively.

In addition to studying the Colorado cases and Riddell's English patient, personal inquiries were made about the fate of the other five patients reported in the literature to have had portal diversion procedures. Since this information was obtained in April, 1973, follow-up data may be considered relatively complete for every patient known to have been submitted to this kind of surgical therapy.

Results

Mortality and Morbidity

Portacaval Transposition. Our first patient had a remarkably untroubled convalescence and was discharged from the hospital nine days postoperatively. Before and after operation, there were elevations in the transaminases (Table 2), which even 9½ years later are still slightly increased. She had a splenectomy 43 months after transposition for thrombocytopenia at which time the portacaval anastomosis draining the splanchnic bed was proved to be open. When this patient was seen 9½ years postoperatively in March, 1973, there was no

* Chronolog platelet aggregometer.

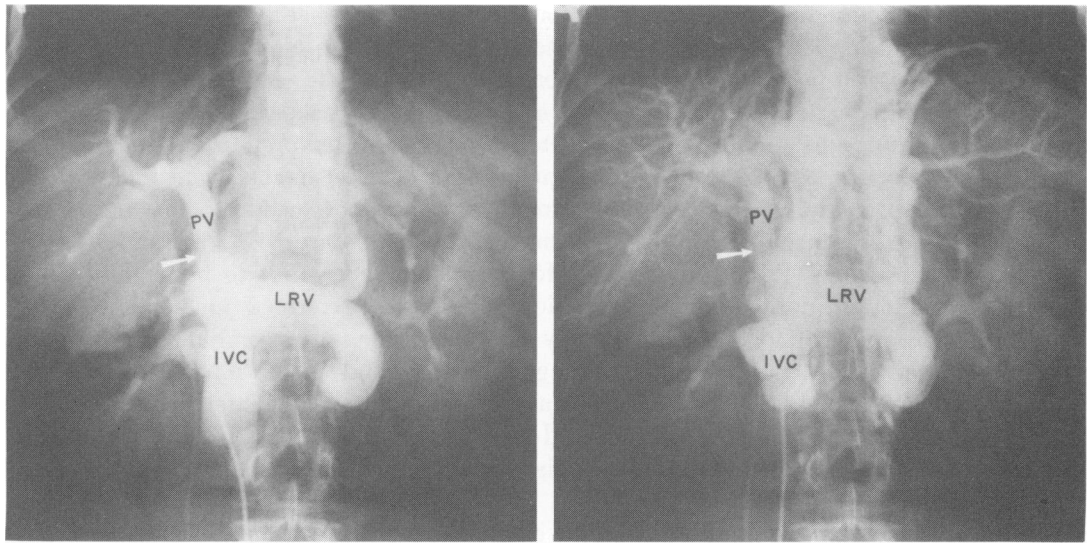

FIG. 1. Inferior vena cavagram in March, 1973, 9½ years postoperatively in Colorado Case 1 showing a patent caval-portal anastomosis (arrow) under two conditions of dye injection. Significant flow through the liver, as well as around it by the azygous and other collaterals were well seen at fluoroscopy. IVC—distal inferior vena cava; LRV—left renal vein; PV—portal vein.

evidence of portal hypertension indicating that the portacaval anastomosis draining the splanchnic bed was still open. An inferior vena cavagram revealed flow of systemic venous blood from the distal vena cava to the liver but with a major bypass around the liver from azygous and hemiazygous collaterals (Fig. 1). The degree of natural shunting was similar to that observed with a comparable angiographic study more than 9 years earlier when the patient was 3 months postoperative.[28]

The anastomosis through which the vena cava drains has failed in two other cases. The attempt at transposition cost the life of our second patient, when the liver was unable to transmit the rerouted vena caval flow, causing hepatic swelling and uncontrollable acidosis.[25] In Riddell's case, angiographic studies were carried out in Calgary, Alberta, in December, 1971, by Dr. Robert J. Sommerville and Dr. Noel Hershfeld, and confirmed by us in January, 1973. The vena cava was obstructed (Fig. 2, left), a complication which probably occurred a long time previously since collateral venous channels were highly developed and lower limb edema was minimal. The anastomosis draining the splanchnic venous bed was shown to be open (Fig. 2, right).

End-to-Side Portacaval Shunt. Patients 3–7 all had rapid recovery without any clinically evident morbidity ascribable to the procedure. Significant increases in SGOT and SGPT were usually present at some time preoperatively both before and at the time of paren-

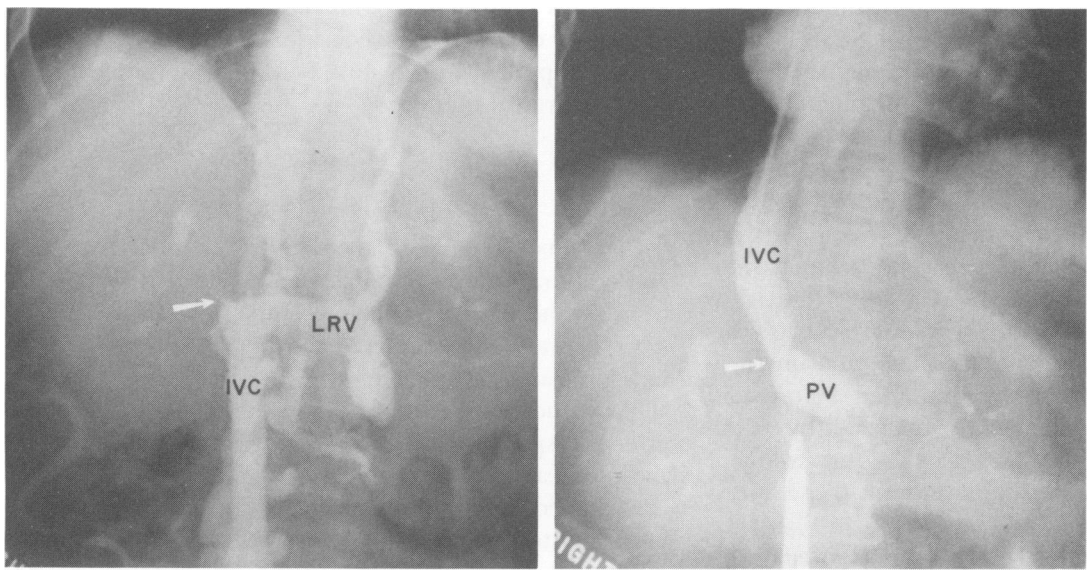

FIG. 2. Studies of the Bristol case of portacaval transposition. The original operation was on May 5, 1965, and the examination depicted which was in December, 1971, was performed by Dr. R. J. Sommerville at the Foothills Hospital, Calgary, Alberta. (*Left*) Inferior vena cavagram showing obstruction at the anastomotic site (arrow). IVC—distal inferior vena cava; LRV—left renal vein. Note the extensive collaterals via the azygous system. (*Right*) Demonstration of a patent portacaval anastomosis (arrow) by means of a retrograde catheterization. IVC—proximal inferior vena cava; PV—portal vein.

teral hyperalimentation. After operation the transaminasemia continued and the transaminase rises have been persistent in three of the five cases (Table 2). Minor and transient elevations of lactic dehydrogenase and alkaline phosphatase were also noted.

None of the five patients was jaundiced immediately prior to operation, although patient 3 had had mild hyperbilirubinemia just before beginning hyper-alimentation. The bilirubin returned to and remained normal after operation. The other liver function tests, including serum protein electrophoresis, were always normal post-operatively.

The patients were placed on a normal diet after operation with no restrictions in protein intake. No clinical evidence of hepatic encephalopathy was observed and, in fact, the patients' parents without exception noted increased animation and mental acuity. Blood ammonia levels were always normal.

Effects on Growth

The remarkable increase in height in Case 1 was reported previously.[28] This child weighed 29 Kg. prior to operation and was 124.5 cm. tall. Eleven months later she had gained 4½Kg. weight and 11½ cm. in height. On the Harvard growth chart this jump in height represented a change from less than the 10th to the 50th percentile. By June, 1967, 44 months post-transplantation, her height had increased to 155 cm. At present, she is 172 cm. tall and weighs 82.7 Kg. Her weight and height positions on the growth chart are now over the 97th percentile levels.

Accelerated growth has now become evident in the three children with the longest follow-ups after end-to-side portacaval anastomosis (Cases 3–5), averaging 0.5 to 1.0 cm. per month of height increase, as well as commensurate increases in the more accurately quantifiable long bone length in the 8½ to 11½ months of follow-up (Table 3). The phenomenal effects of doubling the bone age in Case 3 (Table 3) can be visually appreciated by comparison of the wrist and hands with X-ray examination (Fig. 3). Patients 3, 4 and 5 also had calcification of previously osteoporotic bones. This was particularly striking in Case 5 (Fig. 4). The last two patients have not yet begun accelerated growth.

Effect on Organ Size

Liver. As described by Folkman,[9] both the patients with Type I disease (Cases 3 and 4) had declines in liver size following hyperalimentation and these decreases were maintained after end-to-side portacaval shunt. The child with Type VI disease (Case 5) was not prepared with hyperalimentation but he also had a postoperative decrease in hepatomegaly (Fig. 5). This effect of operation was not a striking feature of the recovery in Cases 1, 6, and 7. These children had Type III disease. The minimal or absent liver shrinkage was previously noted in Case 1.[25,28] In that patient, it was pointed out that with the increased body growth and fixed liver size, the child grew up around the enlarged organ to the extent that its relative although not its absolute size decreased.

Kidney. Kidneys in patients 4–7 appeared to have slight decreases (4 to 12 mm) in size during the 5 to 11 months of follow-up (Fig. 6). Quantitative data on kidney size was not available in Cases 1 and 3.

Metabolic Effects

Carbohydrates. With the exception of the child with Type VI disease (Case 5), all patients before operation had documented fasting hypoglycemia which caused

TABLE 2. *SGOT Values (Normal 3-27 International Units) before and after Portal Division. Note That All the Patients Had Significant Abnormalities Preceding Treatment*

Days before (−) and after operation (+)	Case Number					
	1	3	4	5	6	7
− 30	250	650				
− 15		75*	37			910
− 10	220	88*	11*		690	470
− 5		179*	66*	197	131*	392*
0		110*	188*		60*	185*
+ 1	220	182	218	387	216	343
+ 2			190	296	106	332
+ 3	255			321	84	
+ 4						
+ 5			36	699		271
+ 6	236	51		813	168	
+ 7			30	571		316
+ 8		40		510	198	
+ 9			16	473		305
+ 10		67		308	311	
+ 11						
+ 12				49		
+ 13		58				
+ 14				300		
+ 15		49				
+ 16						
+ 17		142				
+ 18						
+ 19						
+ 20		151				
+ 21	280					
+ 77			64			
+ 84	198					
+109				125		
+127					568	838
+159			40			
+208			41			
+253				174		
+258	294					
+264			69			
+295			35			
+315		36				
9 Yr 5 Mo	40					

* Receiving hyperalimentation

TABLE 3. *Age, Height, and Weight Data of Seven Patients Who Underwent Portal Division. Patients 1 and 2 Had Portacaval Transposition. The Other 5 Had End-to-side Portacaval Shunt*

Case No.	Chronologic Age at Operation (Years)	Date of Operation	Time of Follow-up (Months)	Bone Age (Years)		Postoperative Height Increase (CM)		Postoperative Leg Length (CM)		Weight Gain or Loss (KG)	
				At Operation	Now	At Operation	Now	At Operation	Now	At Operation	Now
1	8½	10/15/63	113	Not done	15 Yr	124.5 (<10%)	172.0 (>97%)	Not available		29.0	82.7
2	7	6/26/63	Died in 2 days	Not done		91.4 (<3%)				14.7	
3	7	5/2/72	11½	3 Yr 6 Mo	7 Yr 4 Mo	100.0 (<3%)	111.3 (<3%)	44.6	51.4	20.1	31.2
4	11	5/17/72	11	7 Yr 10 Mo	7 Yr 10 Mo	118.7* (<3%)	124.1 (<3%)	57.0	60.2	27.6	27.7
5	10	8/2/72	8½	8 Yr 6 Mo	9 Yr 0 Mo	122.3 (<3%)	127.5 (<3%)	59.8	64.0	26.0	29.3
6	5	11/7/72	5	2 Yr 0 Mo	2 Yr 0 Mo	93.6 (<3%)	94.5 (<3%)	38.2	39.4	15.8	15.1
7	3	11/8/72	5	1 Yr 6 Mo	1 Yr 6 Mo	85.5 (<3%)	85.5 (<3%)	34.3	34.5	13.1	12.8
Bristol	7	5/5/65	92		13 Yr 0 Mo		158.5 (25%)				43.6

* In the 3 years preceding operation, accurate hospital records showed a total height increase of only 3 cm. The percentages in parentheses indicate percentile position on height growth chart.

symptoms. This was particularly severe in Cases 3 and 7 in which the fasting glucoses were frequently below 15 mg./100 ml. (to as low as 7 mg./100 ml.). After portal diversion, symptomatic hypoglycemia was no longer a significant problem in patients 1, 6, and 7 (all Type III disease). The two children with Type I disease (Cases 3 and 4) were improved but they were still unable to go without food for more than 4 hours and 8 hours, respectively.

Pre- and postoperative 5-hour glucose tolerance tests were obtained in five of our six survivors. In the sixth (Case 4), preoperative tests could not be obtained because of the need for continuous parenteral hyperalimentation. In Cases 1 and 3 the glucose tolerance tests after 9½ postoperative years and 1 year, respectively, had a considerably increased hyperglycemic response to the ingested sugar (Fig. 7). The glucose tolerance tests in Cases 5, 6, and 7 were not much changed from 5 to 8 months after end-to-side portacaval shunt.

Insulin. Systemic insulin was measured during 5-hour glucose tolerance tests in our six survivors and in the Bristol case. The examinations were 5, 5, 8½, 11, 11½, 92 and 113 months after portal diversion. The results are summarized in Figure 8. Super normal insulin responses were observed in three cases, a normal response in a fourth, and subnormal responses in the other three. The two patients who exhibited the flattest insulin curves were the ones with flat glucose tolerance tests.

Lipids. Portal diversion caused a dramatic improvement of the hyperlipidemia of Type I disease (Cases

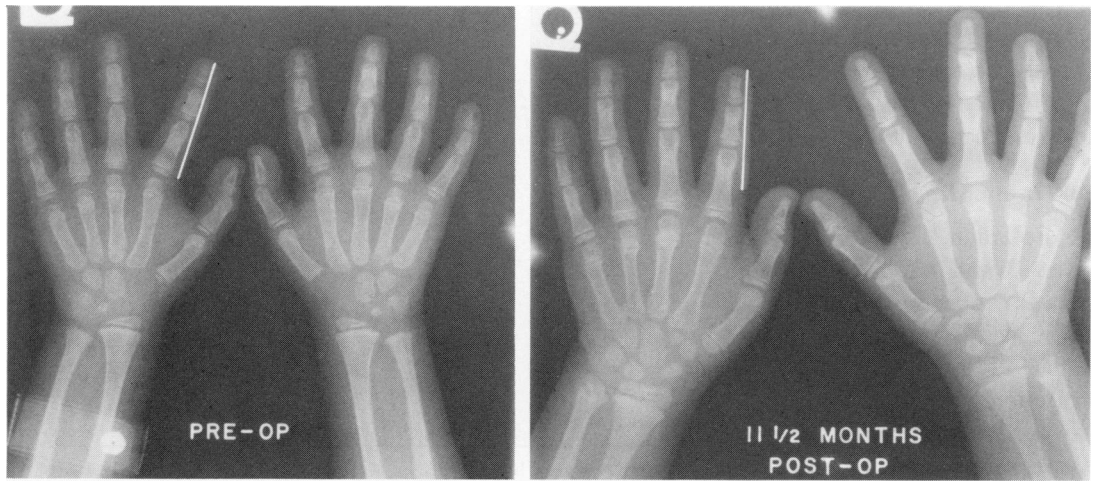

FIG. 3. The dramatic wrist and hand bone growth in Case 3 in the first 11½ postoperative months. The bracket on the left index finger is 5 cm. in length. In addition to the size change, note the mineralization that has occurred, as well as the appearance of new bones, particularly of the wrist.

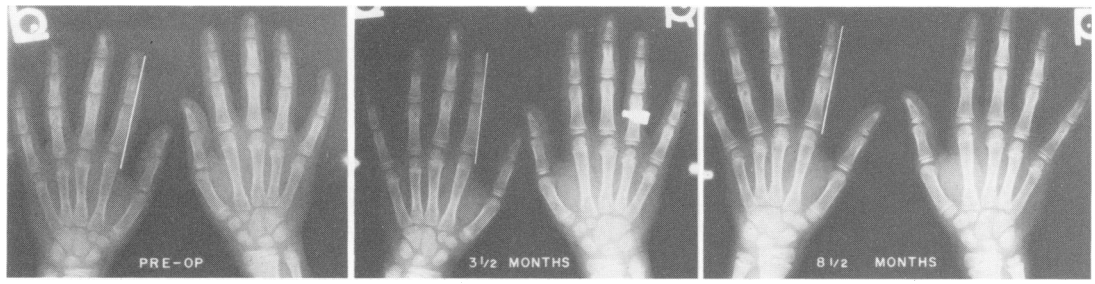

FIG. 4. Changes in the hand and wrist bones of Case 5 during 8½ postoperative months. There was a gain in hand size, but the main change was rapid mineralization of the previously osteoporotic bones. The brackets on the left index finger are 7 cm.

3 and 4, Table 4). All of the lipid components were brought toward normal ranges by preoperative hyperalimentation and the improvement was sustained after portacaval shunt. The evolution of recovery of lipid constituents in Case 4 is shown in Figure 9, and in Figure 10 the lipid clearing is documented in terms of lipoprotein analysis.

The portal diversion also had an acutely ameliorating effect upon the much less severe hyperlipidemia affecting the two most recently treated patients with Type III disease (Cases 6 and 7, Table 4). However, patient 4 had recurrence of elevated lipids in one sample at 5 months. At the same time, the boy's sister did not have worsening of lipid values. The lipids were essentially normal before and after operation in the patient with phosphorylase deficiency (Case 5).

Uric Acid. Four of the last five patients in the Colorado series had elevated serum uric acid concentrations. After portal diversion, these concentrations fell either slightly or significantly in all four patients (Fig. 11). However, in Case 7, the uric acid was normal preoperatively and rose afterward just beyond normal range.

Platelets. Major functional abnormalities of platelets were present in patients 3 and 4. They had abnormally prolonged bleeding times, decreased platelet adhesiveness, abnormal platelet aggregation reactions, and decreased prothrombin consumption. The abnormal platelet functions were rapidly corrected during intravenous hyperalimentation and remained normal after portal diversion, as reported in detail elsewhere.[7]

Growth Hormone. Patients 3, 4, and 5 had plasma somatotropin determinations after portal diversion. The same investigations were performed for an unoperated sibling of patient 4 for whom portacaval shunt is planned. In all four patients, the levels and circadian patterns of somatotropin were normal as were the responses to arginine stimulation.

Histopathologic Studies

Preoperative liver biopsies were available from six of the eight patients. In all the cases the liver cells were large and pale-staining and had centrally placed nuclei (Fig. 12, top). The clear cytoplasm contained fat globules and much glycogen. The amount of reticulin in the portal tracts was increased and slender septa linked portal tracts and extended from the enlarged portal triads into the surrounding parenchyma (Fig. 13). In two of the patients (Colorado Cases 6 and 7) this fibrosis was more extensive and the reitculin bands extended deeply into the lobules distorting the architecture and leading to the formation of small regeneration nodules and micronodular cirrhosis (Fig. 14). Proliferation of the bile ductules and cellular infiltration of the septa were not features of these cirrhotic livers.

After portal diversion the size of the hepatocytes di-

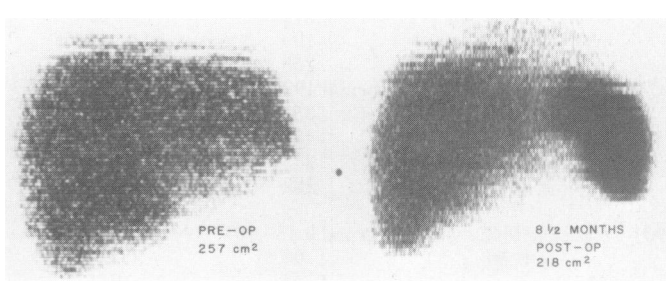

FIG. 5. AP 99M technetium liver scans in a child with Type VI (phosphorylase deficiency) disease (Case 5). The cm² areas were obtained from the anteroposterior projections by planimetry.

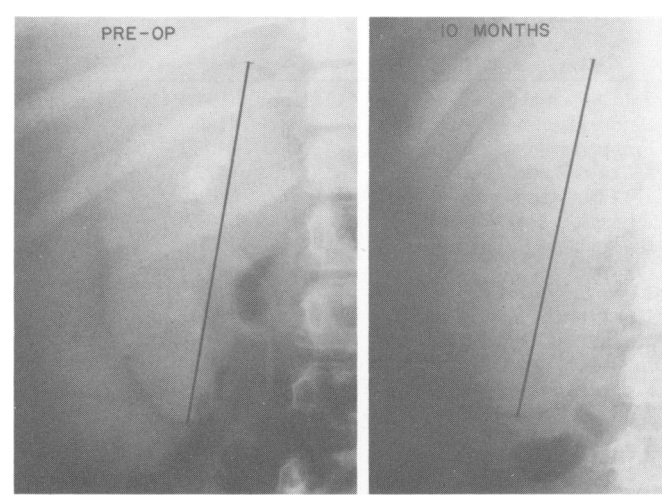

FIG. 6. Anteroposterior intravenous urography in Case 4 before and 10 months after end-to-side portacaval shunt. Although the X-ray projections have slight differences, the length of the right kidneys appears to be decreased slightly. The bracket encompasses 12 cm.

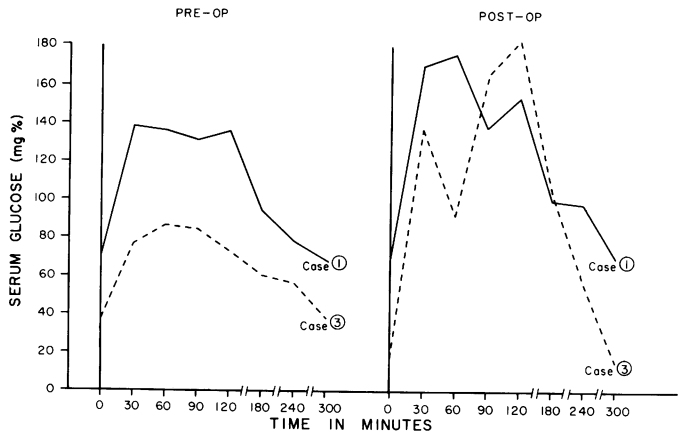

FIG. 7. Five-hour glucose tolerance tests after the ingestion of 1.75 Gm./Kg. of sugar in Cases 1 and 3. In both patients, the serum glucose after portal diversion showed higher and more persistent peaks.

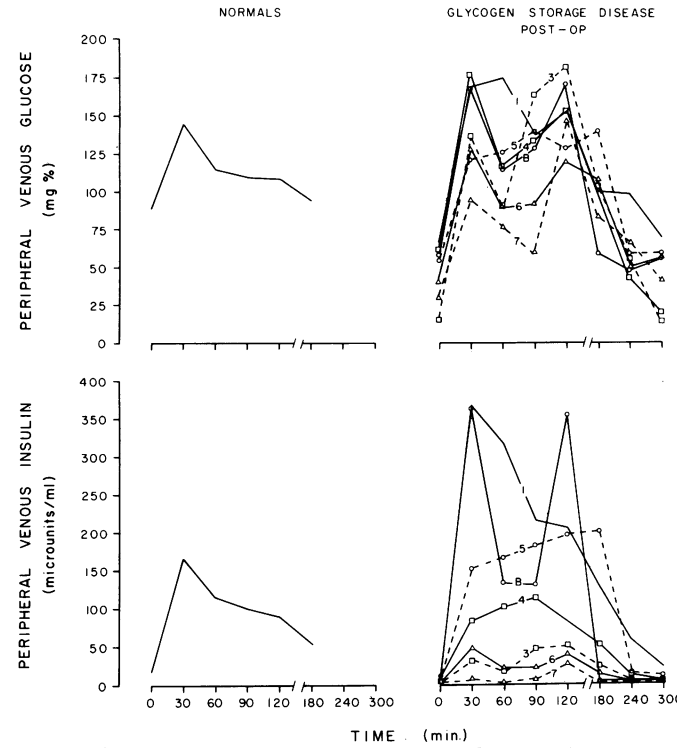

FIG. 8. Insulin concentrations with 5-hour glucose tolerance tests in 6 Denver survivors and the Bristol case. (*Left*) Normal glucose and insulin responses (4): (*right*) glucose and insulin responses in glycogen storage disease cases.

minished (Fig. 12, bottom) and the amount of fat in the cytoplasm of the liver cells increased. Both conditions persisted and were present as long as 1 year after operation (patient 3).

In two of the patients (Colorado Case 1 and the Bristol patient), only postoperative biopsies were available for study. In the Colorado case, cirrhosis had been a very prominent feature of the preoperative biopsy 9½ years previously as was recorded in the original case report,[28] but the tissue block could not be found for re-study. There was no description of the hepatic morphology in the Bristol case report. By 1973, both these livers showed a micronodular cirrhosis similar to that present in Cases 6 and 7 but with the additional feature of some bile ductule proliferation in the enlarged portal tracts and in the fibrous septa. The hepatocytes in these two cases contained much fat and glycogen and appeared smaller than normal but the lack of a preoperative biopsy for comparative study

TABLE 4. *Effect of End-to-side Portacaval Anastomosis on Plasma Lipids*

	Case Numbers*				
	3	4	5	6	7
Total Cholesterol (mg./100 ml.)	(Normal 138–242)	(Normal 138–242)	(Normal 138–242)	(Normal 138–242)	(Normal 138–242)
Before Hyperalimentation	460	408	224	324	389
Preoperative	155	236	—	262	250
2 Weeks Postoperative	125	190	306	161	171
4–11 Months Postoperative	126	225	197	200	400
Triglycerides (mg./100 ml.)	(Normal 70–80)	(Normal 110–120)	(Normal 100–110)	(Normal 50–60)	(Normal 30–40)
Before Hyperalimentation	2800	899	167	383	487
Preoperative	298	337	—	511	420
2 Weeks Postoperative	198	359	274	109	221
4-11 Months Postoperative	224	208	135	258	325
Phospholipids (mg./100 ml.)	(Normal 192–337)	(Normal 192–337)	(Normal 192–337)	(Normal 192–337)	(Normal 192–337)
Before Hyperalimentation	750	558	346	357	652
Preoperative	168	357	—	420	487
2 Weeks Postoperative	212	257	320	237	207
4–11 Months Postoperative	109	243	254	282	640
Nonesterified Fatty Acids (mEq./L.)	(Normal 0.45–.90)	(Normal 0.45–.90)	(Normal 0.45–.90)	(Normal 0.45–.90)	(Normal 0.45–.90)
Before Hyperalimentation	—	—	1.50	1.90	2.60
Preoperative	—	0.45	—	0.44	0.43
2 Weeks Postoperative	1.80	1.60	—	1.00	1.00
4–11 Months Postoperative	0.43	0.75	1.72	1.44	1.54

*Cases 3 and 4 were Type I; Case 5 was Type VI; and Cases 6 and 7 were Type III glycogen storage disease.

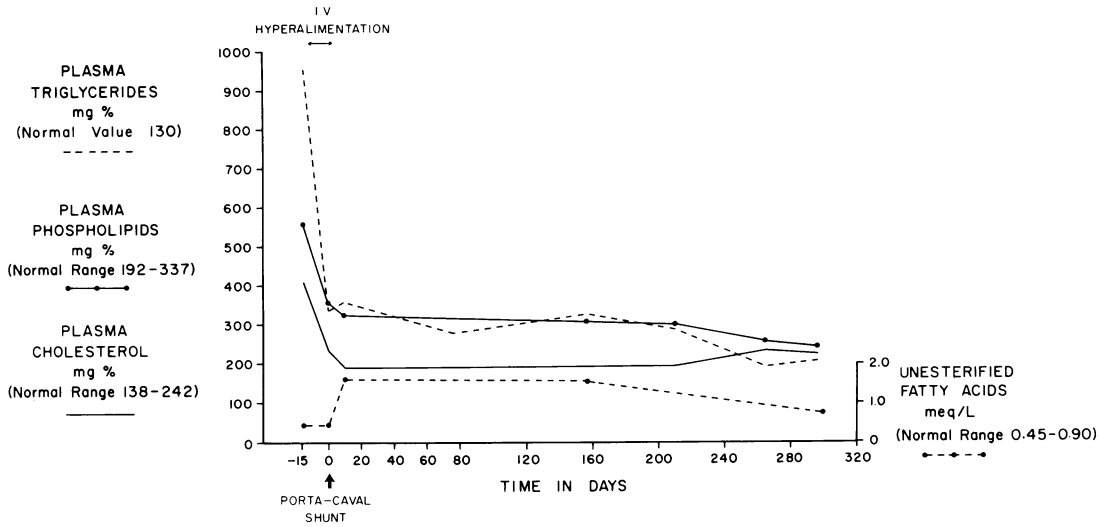

FIG. 9. Effect of parenteral hyperalimentation and end-to-side portacaval shunt on the plasma lipids of patient 4 whose diagnosis was Type I glycogen storage disease. Note the amazingly rapid and relatively complete reversal of all abnormalities.

prevented any statement about the occurrence of atrophy after portal diversion.

Tissue Chemistries

Tissues were examined from biopsies before portal diversion in all Colorado cases. After portal diversion, wedge biopsies were obtained in Case 1. Cases 3–7 had needle biopsies. The glycogen concentration was not altered from 5 to 113 months after portal diversion (Table 5). Enzyme concentrations in Case 1 were reported to be unaltered in Case 1 after 9 and 43 months. There was not enough tissue in the needle biopsies of Cases 3–7 to permit repeating the enzyme analyses.

Follow-ups Of Other Reported Cases

The fate as of April, 1973, of all previously reported patients known to have been submitted to portal diversion is summarized in Table 6, including the Bristol patient who was actually brought to Denver and studied. The patient operated upon in Cleveland in 1967 died 1½ years post-diversion of causes apparently unrelated to either the portal diversion or the enzymatic defect for which it was performed. The other four children in whom portacaval shunts were performed have all benefited, in one instance despite thrombosis of the anastomosis.

Discussion

Recent animal work has indicated that the metabolic consequences of portal diversion are more complex as well as more profound than has been realized. The most important observations were with the kind of canine experiment that has been summarized schematically in terms of human anatomy in Figure 15. In these investigations, the splanchnic venous return was

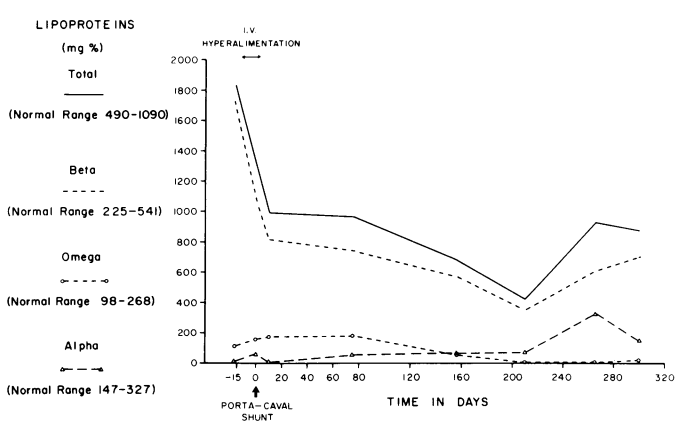

FIG. 10. Relief of hyperlipidemia in the same case as in Figure 9, but with the results expressed in lipoproteins as determined by cellulose acetate electrophoresis. The lipoproteins are expressed in three classes: alpha, beta (including the pre-beta component) and the omega (chylomicron) fractions.

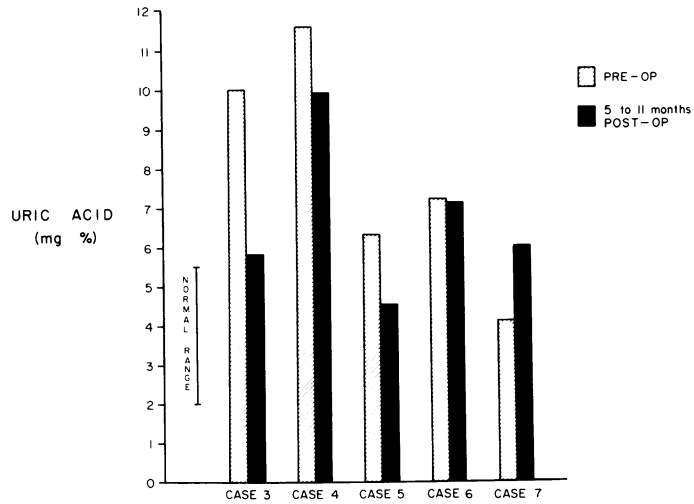

FIG. 11. Plasma uric acid values preoperatively and 5 to 11 months postoperatively in five patients treated with end-to-side portacaval shunt.

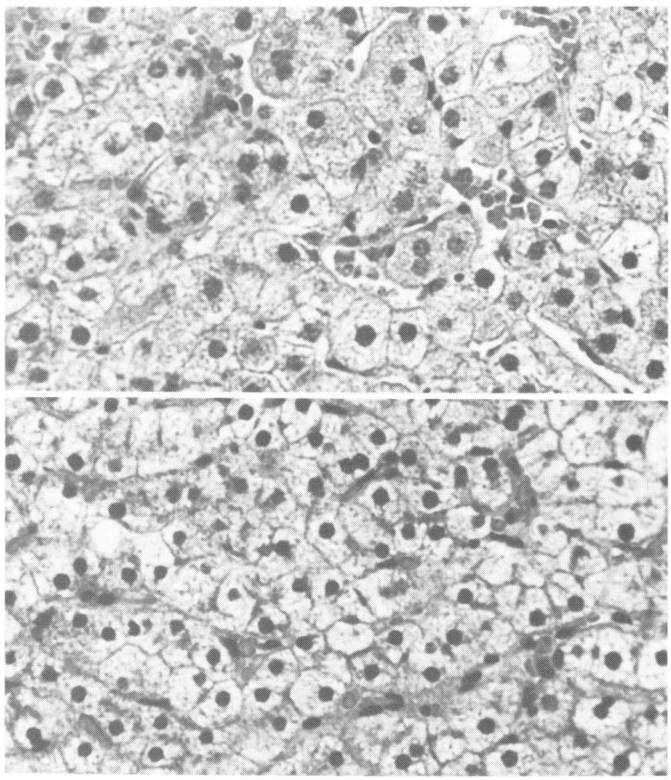

FIG. 12. Biopsies from liver of patient 3. (Top) Immediately before operation; (Bottom) 10 months after portal diversion. The hepatocytes are smaller in the second biopsy than in the first (H & E × 280).

divided so that one portion of the dog liver received the venous effluent from the intestine and was thus nutritionally enriched but hormonally deprived. This hepatic tissue underwent deglycogenation and gross shrinkage as well as atrophy of the individual hepatocytes. The other liver fragment was nourished by pancreatico-gastroduodeno-splenic venous blood and was shown by a series of biochemical examinations to be hormone-directed, particularly by pancreatic insulin and glucagon. Despite being deprived of intestinal nutrients, the latter hepatic tissue underwent glycogen storage, hypertrophy, and hyperplasia.[26]

Thus, under the special conditions of this kind of "double liver fragment" experiment, rerouting of pancreatic hormones around the normal dog liver had a far greater effect upon hepatic structure and function than the bypassing of venous blood rich in nutrients coming from the intestine. In trying to explain the benefits of portal diversion for glycogen storage disease, it is important to appreciate that with the procedures used for all our patients, *both* nutritional and hormonal substances were diverted extrahepatically and may have contributed to the postoperative benefits.

Of the metabolic corrections produced by portal diversion, the most dramatic were in the patients with Type I disease (Cases 3 and 4). These involved lipids to an even greater extent than carbohydrates. The profound changes in lipid metabolism after portal diversion in patients with Type I disease was first noted by Hermann and Mercer[11] and confirmed by Folkman *et al.*[9] and in our own patients. The virtual normalization of all lipid constituents required only a few weeks for completion.

The effect upon lipids did not seem to be secondary to a more fundamental change in carbohydrate metabolism. Repeat liver biopsies did not show a changed concentration of glycogen. Furthermore, episodic hypoglycemia was not completely relieved by the portal diversion, although the seriousness of the problem was considerably reduced, as was the degree of accompanying acidosis. Both of these children with Type I disease continued to require supplemental night or early morning feedings. It was interesting that this requirement had long since disappeared for the Bristol patient who also had the glucose-6-phosphatase deficiency.

Similarly, the portal diversion did not change the glycogen concentration in the livers of the three children with Type III disease or the boy with the Type VI defect. The episodic hypoglycemia in two of the three patients with Type III disease could still be documented biochemically after long fasting or several hours after the ingestion of a glucose load, although again with less severity than preoperatively. In these cases, as well as in those with the Type I defect, some of the expected glycemic effects of diverting glucose around the liver were probably cancelled by increasing the amount of insulin in the periphery. It is known that the liver extracts up to 50% of the endogenous insulin presented to it by the first pass of portal blood.[1,16,19] With avoidance of this primary exposure to the liver, Waddell and Sussman[30] demonstrated increased systemic venous insulin in dogs with Eck fistula and others have shown the same thing in humans after portacaval shunt.[12,20] A further hyperinsulinemic effect could then be caused after eating by stimulation of the pancrease by the arrival of a glucose load in the arterial circulation. Thus, failure to completely relieve hypoglycemic symptoms by diverting alimentary glucose to the peripheral tissues may have been due to one or the other or both the foregoing mechanisms.

Because insulins were not measured preoperatively in any of our longest surviving patients, the extent is not known to which portal diversion actually changed the concentration of this hormone in their systemic blood. However, Lockwood *et al.*[15] and Drash and Field[8] have shown that victims of glycogen storage disease have abnormally low peripheral insulin concentrations under conditions of fasting or glucose ingestion. After portal diversion, all six of our survivors as

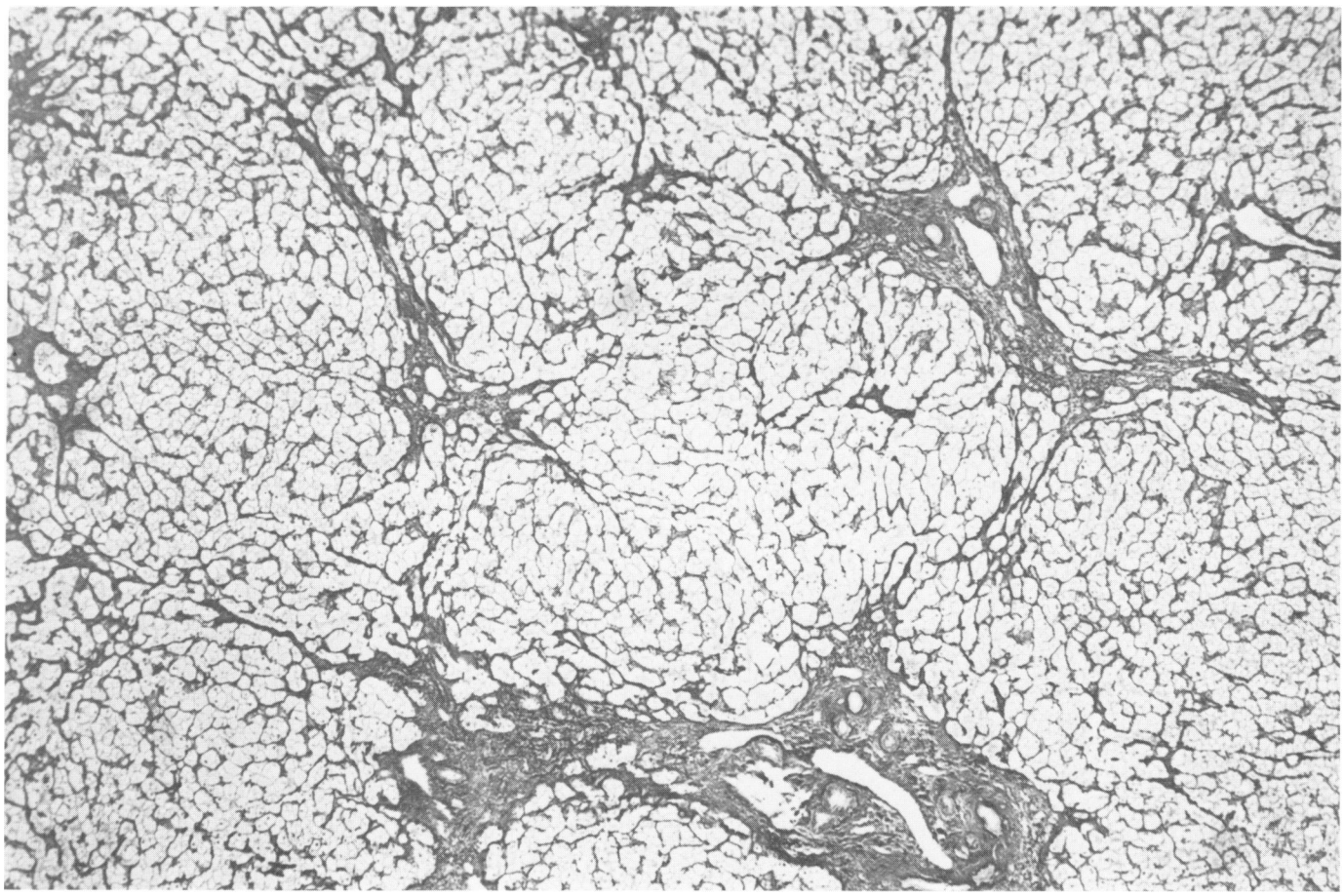

FIG. 13. Biopsy from liver of patient 5 immediately before portal diversion. The amount of reticulin in the portal tracts is increased and septa link portal tracts and extend into the surrounding parenchyma. Silver stain for reticulin (× 70).

well as the Bristol patient had insulin concentrations measured after stimulation with a glucose meal. The responses were supernormal in three of the seven cases and normal in a fourth. Consequently, a reasonable although circumstantial case can be made that the insulin supply to the peripheral tissues had been increased by the portal diversion.

In recent years, insulin has been recognized to be a major growth hormone,[24] comparable in potency to somatotropin. It may be that the phenomenal growth spurts of all of our long-surviving patients could be at least partly attributable to an increased insulin distribution to the periphery. The accelerated growth could not be explained by other factors such as relief of chronic acidosis or persistent hypoglycemia since these were sometimes not present preoperatively or else they were not completely corrected after the performance of the portacaval shunt. An effect on somatotropin would seem equally unlikely. In glycogen storage patients studied by Drash and Field,[8] plasma growth hormone has been normal and in the people studied by us with or without portal diversion, the same was true.

It is not presently possible to precisely explain all the metabolic benefits of portal diversion by a single hormonal or nutritional mechanism. Why the platelet dysfunction should have been corrected or why the manifestations or abnormal calcium or uric acid metabolism should have been ameliorated are examples. The exact reason for the liver shrinkage observed in several patients by liver scans also is not apparent. The glycogen concentrations were not altered after portal diversion. However, the biopsies obtained several months or longer after portal diversion revealed pronounced hepatocyte atrophy. With this finding which, in turn is most likely the consequences of hormone deprivation (particularly insulin) as discussed earlier, liver shrinkage could reasonably occur without an accompanying change in glycogen concentration.

With the new cases included in the present report, the position has been reinforced that simple end-to-side portacaval shunt is an effective and relatively safe method of palliating well selected patients with severe manifestations of hepatic glycogenosis. When portal diversion was first considered for these diseases, anxiety about the complications of simple Eck fistula prompted attempts at the metabolically less damaging

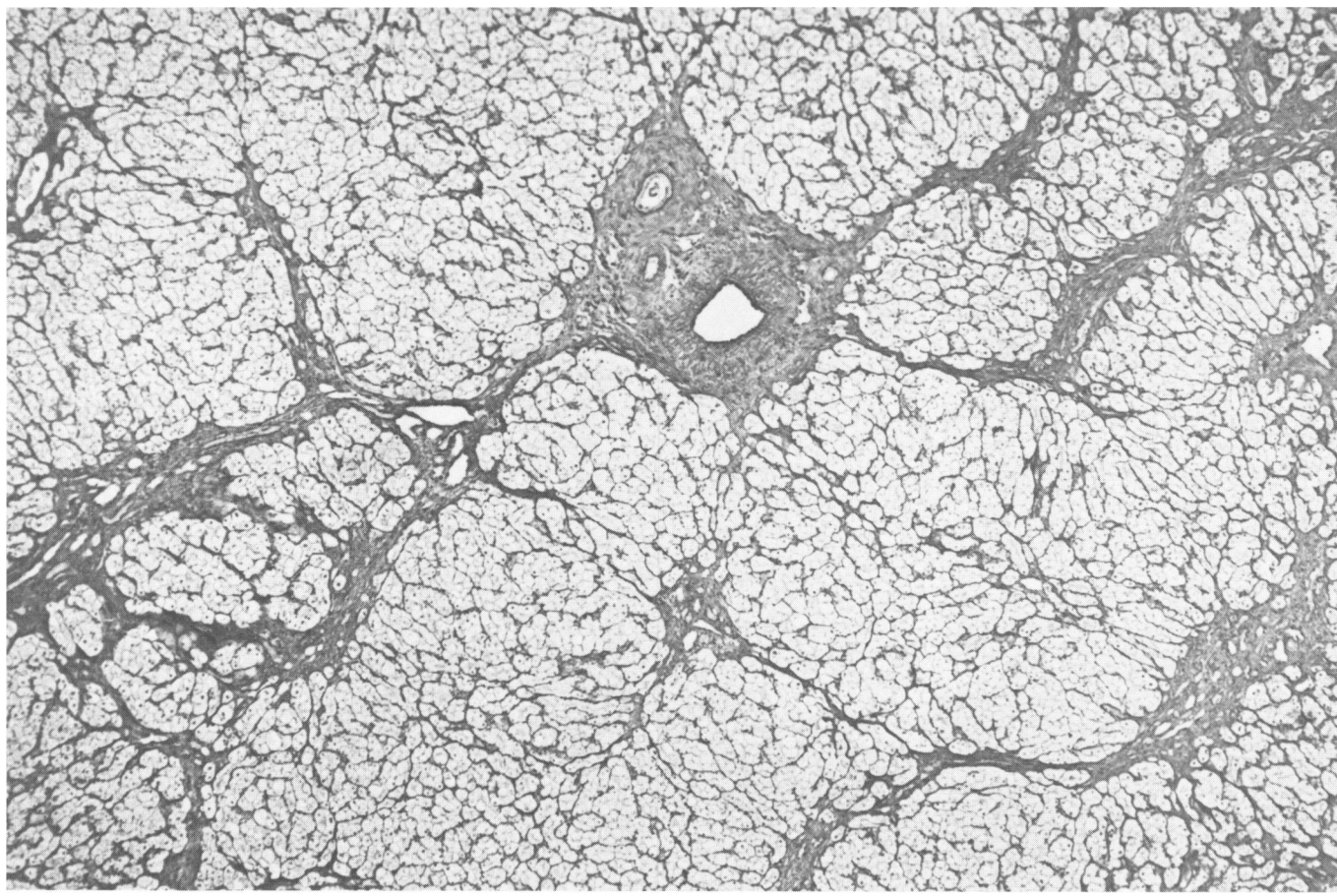

FIG. 14. Biopsy of liver of Patient 7 immediately before portal diversion. The normal lobular reticulin pattern has been destroyed and there is a micronodular cirrhosis. Silver stain for reticulin (× 70).

but technically more complicated operation of portacaval transposition. The fear that Eck fistula would have devastating effects on humans was based, at least in part, upon observations on two patients each by McDermott, Adams and Riddell[17] and Hubbard.[14] These four patients had carcinomas of the head of the pancreas which involved the portal vein. To permit partial pancreatectomy, the portal vein was resected and an end-to-side anastomosis was made between the superior mesenteric vein and the inferior vena cava. Three of the four patients died of inanition and at autopsy there was massive fatty infiltration of the liver. The syndrome was ascribed to the bypass of ammonia of intestinal origin around the liver and it was generally accepted that Eck fistula in humans with normal livers would be exceptionally dangerous. The fact that partial pancreatectomy was also performed was lost sight of. The recent research already alluded to about the hepatotrophic effects of pancreatic hormones has raised the question of whether or not the calamities of McDermott and Hubbard were not due at least as much to the pancreatic resection as to the portal-systemic venous diversion.

Be that as it may, the observations by us and by others authors have now established that simple end-to-side portacaval anastomosis is well tolerated in children with Types I, III or VI glycogen storage disease. Ammonia levels in our five patients with Eck fistula

TABLE 5. *Glycogen Contents of Liver Biopsies in the Colorado Cases*
Glycogen Content (% Wet Weight of Liver)

Case	Before any Treatment	Time of Pre-operative Hyperalimentation	At Diversion	Postoperative
1	—	None	10.1	9.7 (9 months)
				9.5 (43 months)
2	—	None	9.4	—
3	8.0 (Aug. 71)	29 days	11.0	8.9 (11½ months)
4	10.0 (1961)	13 days	5.2	7.7 (11 months)
5	—	None	12.6	11.8 (8½ months)
6	—	6 days	10.6	12.2 (5 months)
7	—	7 days	8.1	12.8 (5 months)

TABLE 6. *Previously Reported Cases of Glycogen Storage Disease Treated with Portal Diversion*

Center	G.S.D. Type	Age at Operation (Years)	Date of Operation	Procedure	Outcome
Colorado[25,28]	III[B]	8	10/63	Transposition	Alive
Bristol[21] (Riddell)	I	7	5/65	Transposition	Alive—Caval-portal anastomosis clotted
Cleveland[11] (Hermann)	I	1	4/67	Porta-caval shunt	Died 1½ years
Colorado[25]	I	7	6/68	Transposition	Died 2 days
New York[2] (Boley)	I	5	5/69	Porta-caval shunt	Alive
Columbus[6] (Clatworthy)	I	¾	6/70	Porta-caval shunt	Alive—Shunt clotted
Boston[9] (Folkman)	I	3	7/71	Porta-caval shunt	Alive
Boston[9] (Folkman)	I	2	11/71	Porta-caval shunt	Alive

have always been normal and at no time has there been evidence of hepatic encephalopathy. Although enzyme increases were observed for several days after the performance of end-to-side portacaval shunt, these unquestionably reflected pre-existing liver disease in most if not all of the cases. After operation, deterioration of liver function did not occur. Biopsies of the livers after portal diversion generally showed an increase in the amount of fat in the cytoplasm of the hepatocytes but did not show any progression in the amount of fibrosis or in the severity of the micronodular cirrhosis when this was present before operation. The frequency of scarring ranging from mild fibrosis to frank microndular cirrhosis in our cases before any operative intervention was surprising when the literature leads one to believe that fibrosis and cirrhosis are not complications of these types of glycogen storage disease. It is probable that closer attention to the pathologic findings will demonstrate a much higher incidence of fibrosis and cirrhosis than has been appreciated.

Summary

Seven patients with Types I, III, or VI glycogen storage disease were treated with portal diversion from 5½ months to 9½ years ago. The first two patients had portacaval transposition with one early death. The last five patients had the technically safer procedure of end-to-side portacaval shunt without any deaths and with no late findings of hepatic encephalopathy. The convalescence of the patients with either kind of portal diversion has been characterized by accelerated body growth and bone mineralization, incomplete relief of hypoglycemia and metabolic acidosis, striking amelioration of the hyperlipidemia of Type I disease, liver shrinkage in Types I and VI disease, and variable relief of such diverse other derangements as abnormal bleeding and elevated serum uric acid concentrations. The liver concentrations of glycogen were not affected by portal diversion. However, the hepatocytes were decreased in size in subsequent biopsies, thereby accounting for the reduction of liver size in most of the cases without a major alteration in glycogen. Contrary to the impression conveyed by the literature, there was a high incidence of pre-existing coincidental liver disease in our patients, including transaminase elevations and hepatic fibrosis or even cirrhosis. These abnormalities were particularly striking in Type III patients but did not appear in any of the cases to be made worse by portal diversion. The observations in these seven patients and in six more reported from other centers and followed up with personal examination by us in Denver or by personal communication with the responsible physicians elsewhere indicate that portal diversion should

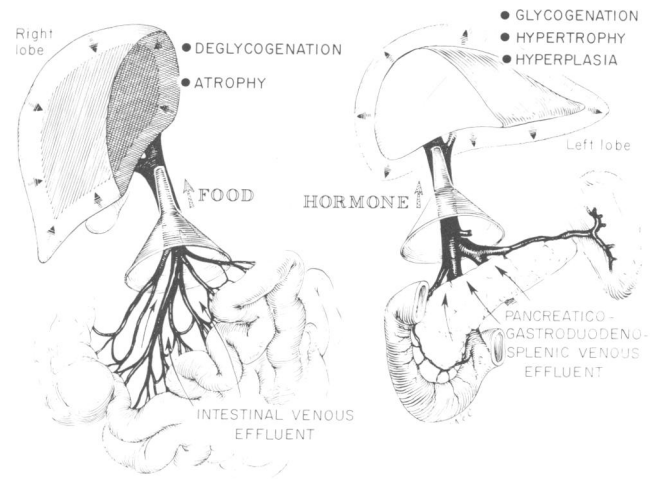

FIG. 15. Summary of experimental results in recently repeated canine experiments (26) in which one portion of the liver received portal venous inflow from the pancreas and the other portion received inflow from the intestine. The "food dominated" hepatic fragment underwent atrophy and deglycogenation whereas the "hormone dominated" fragment had hypertrophy, hyperplasia, and glycogen storage. These experiments which permitted dissociation of nutritional and hormonal influences indicated that the latter were more influential than the former in affecting liver structure and function.

have an important role in carefully selected cases of glycogen storage disease. Recent work in our laboratories has been reviewed which suggests that the effects of portacaval shunt are due more to the rerouting of pancreatic hormones around the liver than to the bypassing of alimentary glucose.

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Discussion

Dr. W. Kirt Nichols (Columbia): Let me share with you a similar instance of glycogen storage disease, Type III with portal hypertension treated at the University of Missouri Medical Center by Dr. Hugh Stephenson and myself.

(Slide) The patient is a 31-year-old caucasian male whose history dates back to childhood when he was evaluated during his first year of life, because of listlessness, irritability and a history of bleeding. Because of hepatosplenomegaly, a liver biopsy was performed with a subsequent diagnosis of Von Gierke's disease.

He was reevaluated in another hospital in 1956 and 1960 for retarded physical and sexual growth. Again, hepatosplenomegaly was noted. Liver biopsy (slide) showed irregular fibrosis and evidence of increased glycogen deposition. Fasting serum glucose levels were low.

In 1965 he was evaluated at another university hospital. Liver biopsy was again performed. The tissue was biochemically analyzed and the amylo-1, 6 glucosidase enzyme, or debrancher enzyme, was found to be defective.