THE ECK FISTULA IN
ANIMALS AND HUMANS

THOMAS E. STARZL, Ph.D., M.D.
KENDRICK A. PORTER, M.D.
ANTONIO FRANCAVILLA, M.D.

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FOREWORD

Dr. Starzl's monograph is so extraordinary we have asked two other eminent surgical students of the portal circulation to comment. Dr. Dean Warren's appreciation precedes the monograph and Dr. William V. McDermott's critique follows it.

MARK M. RAVITCH, M.D.
EDITOR-IN-CHIEF

COMMENT

This monograph of Eck's fistula by Starzl is the most authoritative publication since that by Pavlov and his associates in 1893. Pavlov pointed out the near-total lack of scientific data available from Eck's study, but commented that the operation would be important because it could open doors for the clarification of important problems in the pathology, physiology, and pharmacology of the liver.

No one has grasped this opportunity with the brilliance and dedication of Starzl, and in this arena he has no peers. I know of no other source from which this outstanding scientific and clinical correlation could have come.

W. DEAN WARREN, M.D.

SELF-ASSESSMENT QUESTIONS

1. The most important hepatotrophic hormone or substance is:
   a. Phenylalanine.
   b. Glucagon.
   c. Epinephrine.
   d. Insulin.
2. Side-to-side portacaval shunts reduce encephalopathy by maintaining partial portal perfusion of the liver. True or false?
3. Dean Warren is Dean of the following medical school:
   a. Washington University.
   b. Johns Hopkins.
   c. Emory.
   d. None of the above.
4. The unique feature of the Warren shunt is its:
   a. High flow.
   b. Unusual efficiency in decompressing esophageal varices.
   c. Partial maintenance of hepatopetal portal flow.
5. In animals or humans with normal livers, completely diverting portacaval shunt causes:
   a. Hepatocyte atrophy.
   b. Deglycogenation.
   c. Reduction and disruption of rough endoplasmic reticulum.
   d. Intracellular fat deposition.
6. The risks of encepalopathy after portacaval shunt are greater the more normal the preexisting hepatic function. True or false?
7. The metabolic effects of completely diverting portacaval shunt have been used to treat at least three inborn errors of metabolism. True or false?
8. Both completely diverting and selective portal-systemic shunts greatly improve the life survival curves of patients with esophageal varices. True or false?
9. Complete portal diversion causes subtle and clinically insignificant changes in a few kinds of hepatic function. True or false?
10. The liver has important and easily demonstrable immunologic functions. True or false?

Answers are found at the end of the article.

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is a Professor of Surgery at the University of Pittsburgh School of Medicine. His clinical practice is at the Presbyterian University Hospital, The Children's Hospital of Pittsburgh, and the Oakland Veterans Administration Hospital. His interest in the specific effects of portal venous blood dates back to 1956. The way in which research in this field has interrelated with liver transplantation, another of his interests, has been described in this monograph. Much of the progress that was made in understanding "hepatotrophic" physiology was made possible by Dr. Starzl's long-standing collaborations with the two European co-authors of this article.

is Chairman of the Department of Pathology, The St. Mary's Hospital and Medical School, London. In September, 1963, Ken Porter and Tom Starzl (then at The University of Colorado) met at a meeting about renal transplantation, held at the National Science Foundation in Washington, D.C. The results being obtained with this procedure in Colorado were so striking that Dr. Porter returned to Denver with Dr. Starzl to review what was going on there. From that visit came a collaboration that has lasted for more than two decades. Dr. Porter's chapters in Dr. Starzl's books on renal (1964) and hepatic (1969) transplantation were monographs in their own right. Dr. Porter's talents soon turned to an assessment in various experimental models of the effect upon liver morphology of portal venous as opposed to systemic blood. The histopathologic changes became the most important end points in many of the complex experiments that were used to examine the hepatotrophic hypothesis. As befits an Englishman, Dr. Porter's principal side interest is gardening.

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Francavilla

is Professor of Biological Chemistry and Chairman of the Department of Gastroenterology at the University of Bari, Italy. His principal work in the field of portal physiology began in 1971 during a fellowship at the University of Colorado. By using biochemical techniques which identified the metabolic footprints of hormone actions, he added a new dimension to research on the specificity of portal venous blood. The way in which Dr. Francavilla's biochemical studies supported and extended the histopathologic observations of Dr. Porter was a classic demonstration of the power of interdisciplinary research. Dr. Francavilla's work in this field has continued to the present time and is currently concerned with the biochemical events and control of hepatic regeneration. Dr. Francavilla's hobbies include soccer and the production of Puglia (regional Bari) wines.

THE DUAL BLOOD SUPPLY of the liver has been known for several centuries. However, the physiologic implications of this anatomical arrangement have become intelligible only in recent years. The fact that an artery passed to the liver was never confusing, since there was no reason to suspect that it carried blood different from that pumped through other organs.

In contrast, the portal vein was suspect. Because the blood in this vessel was returning from the intestine and other splanchnic organs, it could possess nutrients or other constituents from the nonhepatic splanchnic viscera to which the liver would be exposed in high concentration on first pass. The possibility that such portal substances could be important to liver health became known as the *hepatotrophic hypothesis;* confirmation of this hypothesis has been one of the most important recent developments in hepatic physiology.[1]

The hepatotrophic concept has direct relevance to many clinical problems, including those of liver transplantation and hepatic regeneration.[1, 2] However, our main concern in this monograph is to explore how knowledge of hepatotrophic physiology

should influence decisions about the appropriateness, timing, and type of portacaval shunt in patients with portal hypertension and esophageal varices, or in the small number of patients whose inborn errors of metabolism can be ameliorated by portal diversion.

THE PORTACAVAL SHUNT (ECK'S FISTULA): A CENTURY OF CONTROVERSY

The understanding of Eck's fistula has gone through several stages. In this discussion, the beginnings of each stage will be described in order of occurrence. Often, however, significant details continued to accrue for years or decades about each fundamental step. Consequently, the remarks in the following sections refer to studies widely separated in time, in some instances as much as 100 years apart.

ECK VERSUS PAVLOV

Two remarkable articles on portal physiology were published in the 19th century. Both authors were Russian. Their similarity ended there.

Nicholas Eck was a 29-year-old military surgeon without training in laboratory investigation whose unique contribution to the medical literature was an article scarcely more than 1 page long.[3] In it, he cited the widespread belief that a liver deprived of its portal blood flow could not sustain life. He stated that he had overturned this erroneous opinion by constructing completely diverting portacaval anastomoses (later known as Eck's fistula) in eight dogs. Seven animals died during or shortly after the operation. The eighth recovered fully and was observed for 2½ months before it escaped from the laboratory, never to be found.

Eck envisioned the clinical use of his operation and gave an explicit although brief account of this technique. His purpose he described as follows:
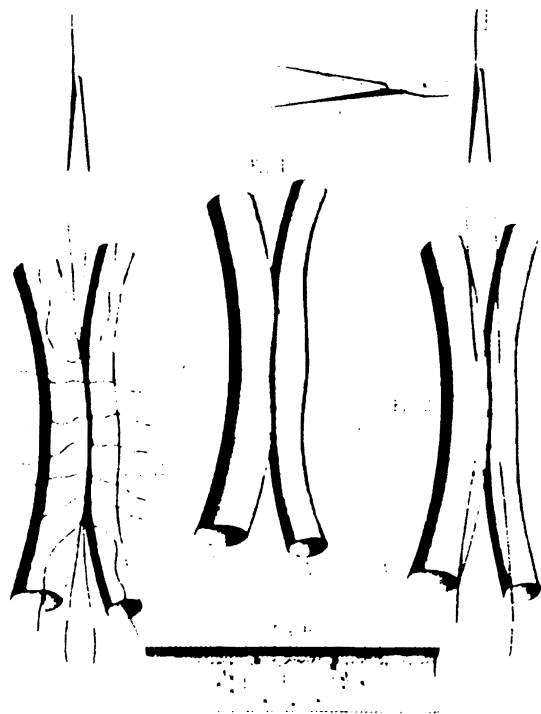
I am conducting these experiments with the purpose of clarifying some physiologic problems as well as to determine if it would be possible to treat some cases of mechanical ascites by means of forming such a fistula. I consider the main reason to doubt that such an operation can be carried out on human beings has been removed because it has been established that the blood of the portal vein, without any danger to the body, could be diverted directly into the general circulation and this by means of a perfectly safe operation.

His optimism may have been excessive in view of the perioperative mortality of 88%.

Eck concluded his article with the comment, "I had to postpone further experiments because I was called to join the active army." Although his work in surgical physiology had ended, immortality for Eck was assured. Warren[4] has brought together the discoverable fragments of information about the subsequent career of this enigmatic surgeon.

The second article, published in 1893 by Hahn, Massen, Nencki, and Pawlow,[5] was one of the most incisive and original contributions ever made in the field of hepatology. Pawlow (Pavlov), the senior author, was 44 years old and just becoming an international figure as the result of research on behavioral psychology and gastrointestinal physiology. His investigations were prototypic applications of the scientific method. He and his associates examined Eck's fistula in about 20 dogs. They described (complete with artist's illustrations) the primitive vascular anastomosis originally employed by Eck and in common use by the 1890s. The portal vein (or superior mesenteric vein) and the in-

ferior vena cava were approximated with an oval row of interrupted sutures, inside of which a suture loop was inserted to permit the adjacent vessel walls to be avulsed or cut with a specially designed scissors (Fig 1).

The size of the resulting aperture was unpredictable, and consistent results by other investigators were not achieved until many years later, when the fine anastomotic techniques introduced by Carrel and Guthrie[6] found their way into surgical laboratories (Fig 2). The side-to-side anastomosis of Eck's fistula was made completely diverting by tying off the portal vein superiorly (see Fig 2).

The benign nature of Eck's fistula was not confirmed by the Pavlov team. Animals with a good anastomosis had weight and hair loss. On a meat diet, they developed a neurologic disorder of ataxia and convulsions that presaged death. The syndrome was hepatic encephalopathy but was termed "meat intoxication," since it could be precipitated or aggravated by a meat diet. The main autopsy findings in Pavlov's animals after construction of Eck's fistula were atrophy and fatty infiltration of the liver.* Pavlov noted that these complex physiologic and morphological events did not occur or were minimized after shunt thrombosis or stenosis, or after revascularization by splanchnic collaterals of the tied-off portal vein above the site of the portacaval anastomosis. Such observations were still being made in more complicated and perhaps less convincing experiments more than 60 years later.[8,9]

Three quarters of a century passed before it was realized that the atrophy caused by Eck's fistula occurred with astonishing rapidity, being 90% complete within 3–4 days.[10,11] In addition, the use of electron microscopy in recent years has made it possible to develop a clear picture of the organelle changes caused by portacaval shunt in the hepatocytes of previously normal rats,[12–15] dogs,[10,11,16,17] subhuman primates,[17,18] and humans.[19,20]

In all of these species the most striking and specific ultrastructural changes were depletion and disruption of the rough endoplasmic reticulum (RER) and reduction in the membrane-bound polyribosomes (Fig 3).[10,11,16–18,20] Other features were fatty infiltration of the liver cells, a diminution in the number of glycogen granules, and deterioration of the appearance of the

Fig 1.—The primitive technique of side-to-side portacaval anastomosis used by Eck[3] and by Pavlov's group. Note that the connection between the two vessels was made by cutting or avulsing the adjacent walls inside a row of approximating simple sutures. The illustration is a photograph of the original drawing by Hahn et al.[5]
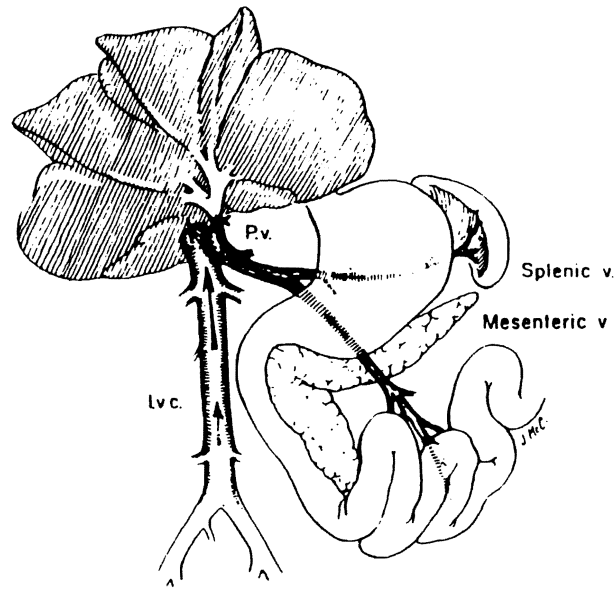
Fig 2.—Completely diverting portacaval shunt (Eck's fistula). A side-to-side anastomosis is constructed between the portal (or superior mesenteric) vein (P.v.) and the anterolateral surface of the inferior vena cava (I.v.c.). The shunt is made completely diverting by tying off the portal vein in the hilum of the liver. (From Starzl et al.[7] Reproduced by permission.)

mitochondria. In rats, Oudea and Bismuth[13] noted an increase in smooth endoplasmic reticulum (SER), but this was not prominent in dogs, baboons, or humans.

Another feature of the Eck fistula liver which escaped notice for a long time was a marked increase in hepatocyte renewal, which has been described in rats,[14] dogs,[10, 11] and baboons.[17, 18] After portacaval shunt, the mitotic index and/or the rate of thymidine incorporation as measured by autoradiography rose within a few days to a new and stable level three or four times higher than the preoperative resting level. The stimulus for the low-grade hyperplasia is unknown. It may represent a response to an increased hepatocyte death rate. Since hepatocyte hyperplasia and hypertrophy are parallel in most situations of liver regeneration, the combination of atrophy and hyperplasia after Eck's fistula is a special situation that has generated much discussion.[11, 14]

ROUS VERSUS MANN

Peyton Rous and L.D. Larimore[21] were intrigued by the possibilities that portal venous blood might contain hepatotrophic factors and that the extrahepatic diversion of these factors by
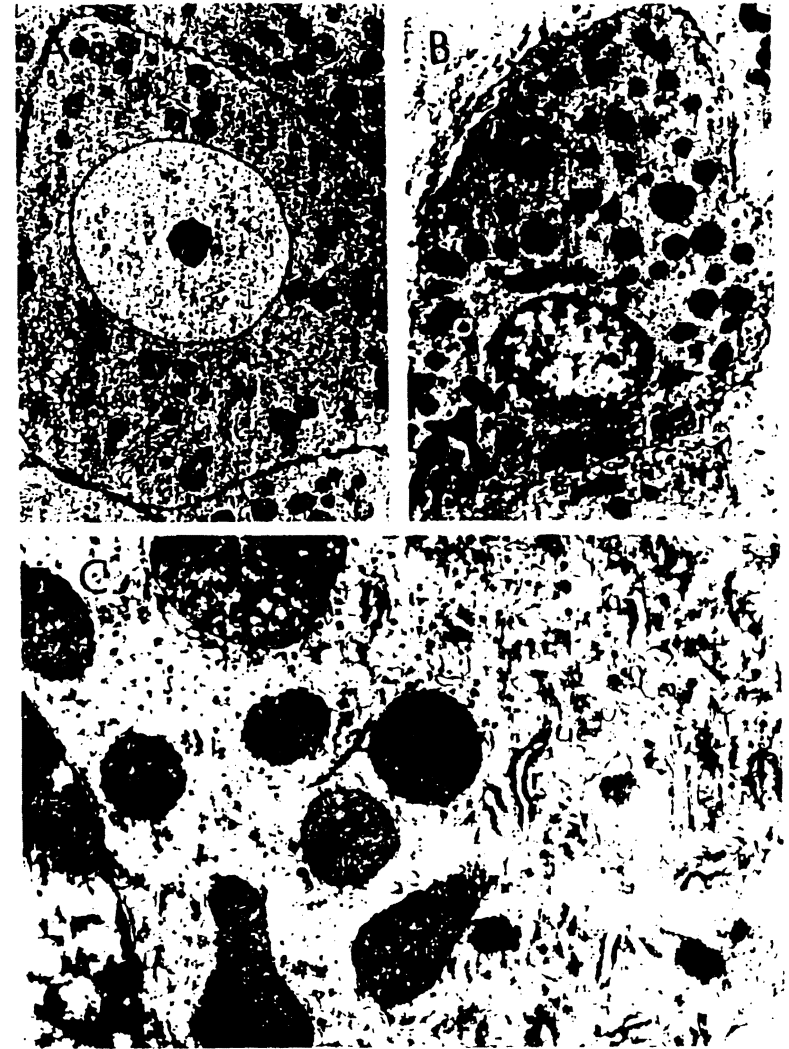
Fig 3.—Human liver biopsy appearances before (A) and after (B and C) portacaval shunt for familial hypercholesterolemia. Rough endoplasmic reticulum (r) and glycogen are abundant in the preoperative biopsy specimen. The hepatocyte is normal. Six months after portacaval anastomosis (B, C), there are major changes. Note that only isolated profiles of rough endoplasmic reticulum remain. Glycogen is absent, and there are numerous fat droplets (electron micrographs; A, ×3015; B, ×5575; C, ×25,100). (From Starzl et al.[20] Reproduced by permission.)

portacaval shunt could be responsible for the hepatic atrophy and the poor health of animals with Eck's fistula. In 1924 they wrote, "Is the liver atrophy functional? If so, its completeness would indicate that that liver has no essential activity . . . none on which its maintenance depends . . . that is not intimately

connected with substances derived from organs drained by the portal system." Unfortunately, their experimental models did not permit decisive experiments that might have supported these suspicions. Rous was lost to the field of hepatology when he turned his attention to oncology.

In contrast, F.C. Mann, of the Mayo Clinic, maintained an interest in hepatic and gastrointestinal physiology for his entire professional life. Mann did not believe that the portal blood had special qualities important for liver health, mainly because firm evidence to support the presence of such portal substances had never been unearthed by others or by him.[22, 23] Mann envisioned the liver mass as a byproduct of, or a kind of encrustation upon, its complex capillary bed, which in turn was controlled solely by the volume of blood presented to it. He wrote, "restoration of the liver depends . . . upon the flow of portal blood through the organ [liver] and . . . the primary stimulus is the [quantity of] the portal blood itself."[22] This was the flow hypothesis.

THE FLOW HYPOTHESIS

The experiments of Mann merely failed to support the possibility that the portal blood has special qualities; Mann was never able to produce evidence to contradict what later came to be known as the hepatotrophic concept. In contrast, the studies by Child et al.,[24] using portacaval transposition in dogs as the experimental model, were erroneously but generally interpreted as crucial evidence favoring the flow hypothesis and disproving the hepatotrophic concept. By replacing the diverted splanchnic venous blood with an inflow from the inferior vena cava to the hepatic end of the portal vein (Fig 4), Child et al. avoided most of the adverse effects of Eck's fistula. These studies[24] and those of Fisher and his associates[25, 26] gave firm support to the concept that the quality of portal venous inflow was not a prime determinant of hepatic structure, function, or the capacity for regeneration. In some of Fisher's experiments involving end points of regeneration, the diverted portal blood was replaced by arterializing the hilar portal stump.[25]

Subsequent workers accepted that the *quantity* of total hepatic blood flow was the main consideration in supporting liver health. This acceptance was maintained in spite of the demonstration that canine livers after venous transposition actually showed centrilobular atrophy,[24] and major deglycogenation,[27, 28] and thus were not in fact normal. The concensus favoring the flow hypothesis was an uneasy one, and in 1961 Bollman, one of Mann's younger associates, wrote, "In the 83 years since it was first reported the Eck fistula has been reasonably successful in hiding its secrets as well as giving rise to many additional ques-
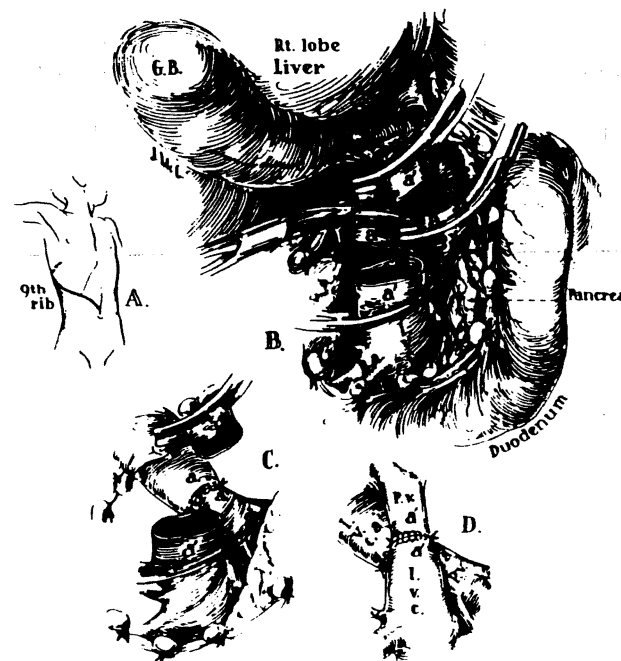
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Fig 4.—The operation of portacaval transposition. The procedure is a standard laboratory experiment but it has been used clinically to treat two patients with glycogen storage disease. Note that the central portal vein is revascularized with vena caval blood. (From Starzl et al.[28] Reproduced by permission.)

tions fundamental to an understanding of the functions of the intestine, liver and brain."

THE HEPATOTROPHIC HYPOTHESIS FROM STUDIES OF LIVER TRANSPLANTATION

The flow-oriented view held sway until it was definitively challenged by investigations that originated in studies of experimental liver transplantation. These studies were thoroughly reviewed almost 15 years ago.[29] The most illuminating observations were made when an extra liver was transplanted to an ectopic site without disturbing the animal's own liver. It was noted that auxiliary hepatic homografts underwent remarkable atrophy[30] if they were revascularized by a technique described by Welch.[31] With Welch's method, the auxiliary liver was provided with an arterial blood supply from the aorta or an iliac artery, and the portal vein was anastomosed to the inferior vena cava (Fig 5). The atrophy of the auxiliary organ was rapid and extreme (Fig 6), even though the blood supply was analogous to that in Child's portacaval transposition.[24] One possible expla-
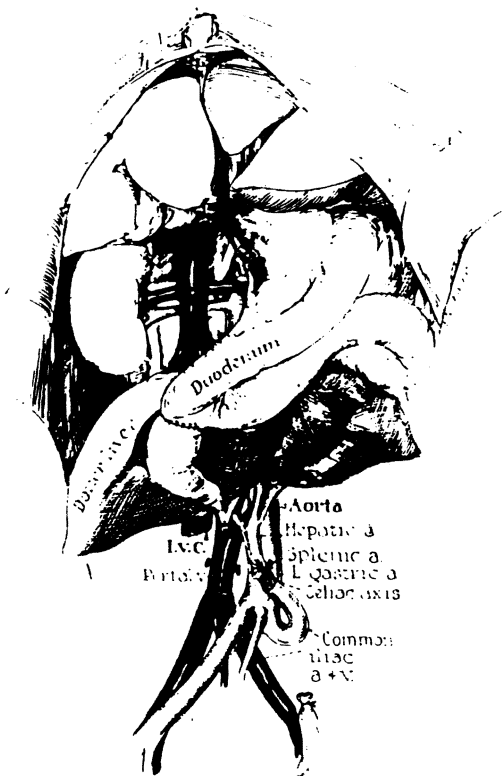
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Fig 5.—Auxiliary liver transplantation in dogs by a modification of Welch's original technique. Note that the reconstituted portal blood supply is from the distal inferior vena cava. (From Starzl et al.[30] Reproduced by permission.)

Fig 6.—An auxiliary homograft *(right)* and the recipient dog's own liver *(left)* 45 days after transplantation. Note the well-preserved but dimensionally reduced general structure of the homograft. At the time of transplantation, both the host organ and the transplant had been about the same size. (From Starzl et al.[30] Reproduced by permission.)

nation advanced was that the animal's own liver, in situ, which was perfused first by splanchnic venous blood, was extracting a disproportionate share of unspecified hepatotrophic substances and that the auxiliary organ atrophied because of its disadvantaged competitive situation.[30]

The hypothesis was supported by Marchioro and his associates,[32] who showed that transplant atrophy could be prevented by diverting the nonhepatic splanchnic venous blood away from the host liver and through the graft. The atrophy then affected the native liver. Confirmatory observations were reported by Thomford,[33] Halgrimson,[34] and Tretbar[35] and their associates. Thomford et al.[33] showed that atrophy in Welch's auxiliary homografts could be prevented in recipients that had undergone immunosuppression, if host livers were removed within a few days after transplantation, and Tretbar et al.[35] and Halgrimson et al.[34] demonstrated that the shrinkage could be reduced by diverting portal blood away from the host liver, even though the

portal blood was not directly channeled through the transplant. Observations by Sigel and his associates[36,37] with hepatic autografts implanted on intestinal vascular pedicles or directly revascularized in the neck could be interpreted in the same way.

The transplant preparations that made possible the foregoing observations had two serious flaws; these flaws prevented investigators from coming to definitive conclusions about the pathogenesis of the atrophy. First, the total flows delivered to the two coexisting livers were often different. Second, there was by definition another inherent inequality of the two organs: the homograft was usually under immunologic attack, despite host immunosuppression,[29,30] whereas the animal's own liver was not. Consequently, other experiments were undertaken that were designed to circumvent one or both of these deficiencies.

One preparation not involving transplantation was used by Marchioro and his associates[38,39] and termed a split (or partial) transposition. In essence, the procedure entailed the creation of two liver sections that differed only in the nature of their portal venous inflow. Splanchnic venous blood was provided for one portal branch to the liver, whereas the other portal branch was supplied with blood from the inferior vena cava (Fig 7); flow to the liver tissue given vena caval blood was at least as great as that on the opposite side.[39] Later, Price,[40] Lee,[41] and Chandler[42] and their associates performed analogous experiments, either with canine partial hepatic autografts or with isografts of inbred
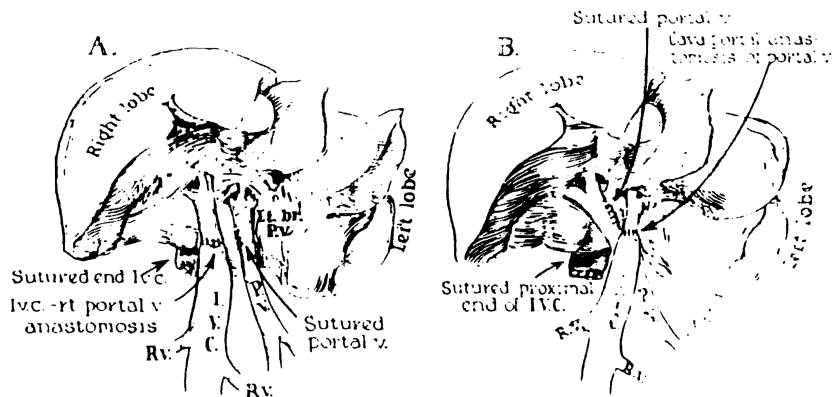
Fig 7.—The operation of partial (split) transposition in dogs. Note that one of the main portal veins (left in **A**, right in **B**) retains the natural splanchnic flow and that the other one receives the total input of the suprarenal inferior vena cava. (From Marchioro et al.[39] Reproduced by permission.)

rat livers. All of these experiments showed hypertrophy in the hepatic tissue that was perfused with splanchnic blood, and atrophy in the hepatic remainder, which was provided with systemic venous inflow.

The impressive evidence obtained from 1964 to 1972 that portal hepatotrophic factors were physiologically important was not taken seriously by skeptics because of the failure to identify the mysterious portal blood substance(s). One possibility sometimes cited as an explanation for a specific benefit of portal blood was a high portal vein oxygen concentration. This concept was incorrectly attributed to Blalock and Mason,[43] as we have pointed out elsewhere.[44] When the oxygen content of splanchnic venous blood actually was compared to the oxygen content of inferior vena caval blood in unanesthetized awake dogs long after portacaval transposition, such an "advantage" of higher portal oxygen content did not exist.[44]

THE HORMONAL NATURE OF THE HEPATOTROPHIC SUBSTANCES

FROM DOUBLE LIVER EXPERIMENTS

In 1973, the explanation was advanced that endogenous hormones returning from the splanchnic organs were the principal hepatotrophic agents.[45] This conclusion was based partly on the histopathologic results from another kind of "double liver" model which was used in an effort to pinpoint the splanchnic organs from which the so-called hepatotrophic factors came. Marchioro et al. used this approach in one of their auxiliary homograft experiments,[32] and Pouyet et al. modified the ap-

proach in a nontransplantation model.[46] The most useful preparation was one in which blood returning from the pancreas, duodenum, stomach, and spleen passed to one portion of the liver while the other liver portion was perfused with venous blood returning from the small intestine (Fig 8).[45]

The results were unequivocal. The liver portion perfused with blood returning from the upper abdominal viscera remained healthy. In contrast, the liver portion provided with intestinal blood became atrophic, deglycogenated, and infiltrated with fat. The organelle structure of the atrophic portion was like that after portacaval shunt, including disruption and depletion of the RER.

An accurate way to quantify hepatocyte size was developed for such experiments.[45] With light microscopic tracing, hepatocytes were drawn onto a standard thickness paper and weighed. The weights were called size units. The cell size data could then be summarized in graphs or tables. In Figure 9, the right lobar hepatocytes, which had pancreaticoduodenosplenic input and so had an obvious advantage, are compared with those on the left, which were fed with intestinal venous return. The foregoing histopathologic observations made the pancreas suspect as a major hepatotrophic source and insulin the most likely principal hepatotrophic substance.

The morphological observations were bolstered by the so-

Fig 8.—Splanchnic division experiments. In these dogs, the right liver lobes received venous return from the pancreaticogastroduodenosplenic region, and the left liver lobes received venous blood from the intestines. **A**, nondiabetic dogs; **B**, alloxan-induced diabetic dogs; **C**, dogs with total pancreatectomy. (From Starzl et al.[47] Reproduced by permission.)
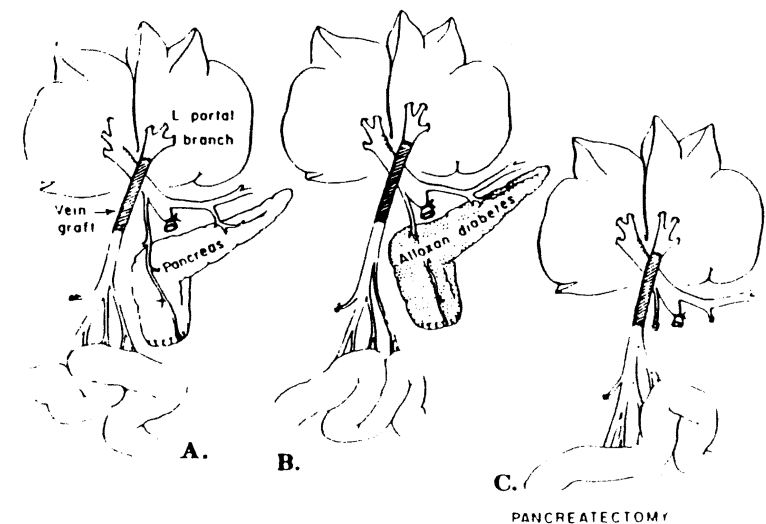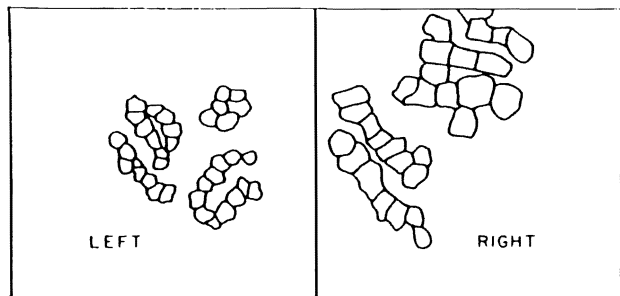
Fig 9.—Hepatocyte shadows traced during histopathologic examination. These were later cut out on standard paper and weighed as an index of hepatocyte size. The right lobes with the large hepatic cells received venous blood from the pancreas, stomach, duodenum, and spleen. The relatively shrunken left lobes with the small hepatocytes received intestinal blood. (From Starzl et al.[45] Reproduced by permission.)

called double liver preparations (see Figs 7 and 8) by numerous biochemical studies in the two liver sides which included glycogen, glucokinase, cyclic AMP, active phosphorylase, and lipids.[45] There were major differences in the liver segments according to the nature of the portal venous inflow. The details of the biochemical disassociation are beyond the scope of this review, but the reasonable inference was that the two liver sides were living in different metabolic worlds, in which hormone control was the dominant factor. Futhermore, the nature of the biochemical differences suggested that endogenous insulin, which was being efficiently extracted by the first liver tissue to which it was exposed, played an important role. The significance of endogenous insulin was further highlighted when the advantages enjoyed by the lobes perfused by splanchnic venous blood were found to be greatly reduced, although not eliminated,[17, 47, 48] by either total pancreatectomy or alloxan-induced diabetes (see Fig 8). These investigations, while emphasizing the role of insulin, showed equally clearly that nonpancreatic hormones or other substances also contributed to the total hepatotrophic effect of splanchnic venous blood. Although the influence of these extrapancreatic factors remains unchallenged, they have not been identified.

Complicated though they were, the double liver segment models were crucial to an understanding of the enigmatic Eck fistula. If insulin was a vital hepatotrophic factor, the reason for its unmasking by the double liver fragment experiments became understandable. The well-known efficiency of insulin removal during a first pass through hepatic tissue[49-51] made the insulin relatively unavailable for a second liver or a liver segment and thus exaggerated the effect of portal blood deprivation.

At the same time, the protection afforded after portal diversion by flow augmentation procedures such as Child's portacaval

transposition[24] or Fisher's portal arterialization[25] was explained. If insulin and other hepatotrophic substances were bypassed around a single liver they would be returned to it in a diluted form in direct relation to the total hepatic blood flow, which these procedures increased.

FROM HORMONE INFUSION EXPERIMENTS

Eventually it became necessary to return full cycle back to experiments utilizing Eck's fistula. If the secrets of Eck's fistula were explained mainly by the deprivation of the liver of direct access to endogenous insulin, the experiment shown in Figure 10 should have been a direct test of that hypothesis. Nonhypoglycemic infusions of insulin, glucagon, and other substances were made for 4 days into the ligated left portal vein after construction of Eck's fistula.[10, 11] The experiment was designed to evaluate any direct protective effect of hormones on the left lobar hepatic tissue as well as to assess a spillover effect on the right lobes after recirculation. The results were unequivocal. Insulin greatly reduced the atrophy that otherwise halved the size of the cells within 4 days, and it preserved the hepatocyte ultrastructure. In small doses glucagon did not potentiate the action of insulin and in large doses it may have reduced the insulin benefit. Glucagon alone, in large or small doses, had no effect.[10, 11]

Fig 10.—Experiments in which Eck's fistula is constructed and postoperative infusions of hormones are made into the left portal vein. (From Starzl et al.[11] Reproduced by permission.)
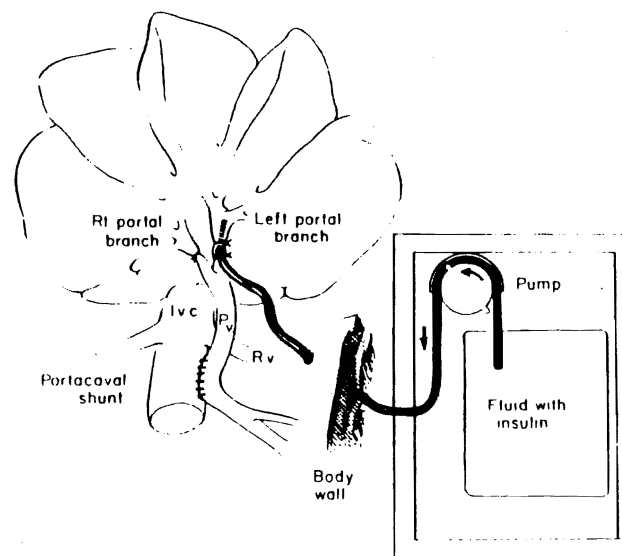
The effect of insulin on hepatocyte proliferation in these experiments was also striking. After construction of Eck's fistula, the mitotic rate was already increased to about three times normal (from 1.6 to 4.8/1,000 hepatocytes). Insulin more than tripled this cell renewal, with no spillover to the contralateral lobes. Glucagon alone had no effect, nor did it potentiate the action of insulin.[10, 11]

FROM EVISCERATION AND HEPATOCYTE CULTURE EXPERIMENTS

Thus, relative "hepatic insulinopenia" was established as the most important element in the liver injury of Eck's fistula. However, the clarity with which insulin has emerged as the principal portal hepatotrophic substance has not diminished interest in the search for contributory hepatotrophic factors. The incomplete insulin protection observed in our infusion experiments was interpreted as a reflection of the existence of ancillary substances.[10, 11] Evidence that there are multiple hepatotrophic factors has been uncovered with all of the experimental models used by us.[10, 11, 17, 45, 47, 48, 52, 53]

However, the probability that there is multifactorial control of hepatocyte integrity has not deemphasized the central role of insulin in maintaining liver cells. This was recently demonstrated once again in animal studies after all the nonhepatic splanchnic viscera had been removed, including the pancreas.[52, 53] The intraportal infusion of insulin alone prevented most of the atrophy and other structural deterioration of hepatocytes that otherwise occurred, and it preserved the rate of spontaneous liver cell renewal, which was otherwise depressed. The hepatic protection in eviscerated animals[52] was almost identical to that observed with intraportal insulin therapy after portacaval shunt[10, 11] and was indistinguishable from the hepatic protection provided by insulin in diabetic rats.[54]

In hepatocyte tissue culture systems, many investigators have described analogous insulin effects.[55-58] The role of insulin in maintaining hepatocyte mitochondrial metabolism has also been emphasized.[59, 60] No potentiating effect of glucagon has been demonstrated in any of these models.

FUNCTION OF THE ECK FISTULA LIVER

BIOCHEMICAL PARAMETERS

Liver function after construction of Eck's fistula, or after the better tolerated portacaval transposition of Child et al.,[24] was long thought to be essentially normal, the main defect being inefficient clearance of ammonia.[61, 62] Only in the last 10 or 15 years has it been realized that subtle but cumulatively massive

changes in hepatic function are caused by portal diversion and for the most part by the bypassing of endogenous insulin. These alterations are so sweeping that an all-inclusive description would require a discussion of virtually every facet of hepatic physiology and metabolism.

The morphological counterpart of (and explanation for) such major changes in hepatic metabolism was described in an earlier section, when we noted that a relatively specific effect of portacaval shunt is the qualitative and quantitative loss of RER and its lining polyribosomes (see Fig 3). Since RER is the "factory" of the cell,[63, 64] a consequent reduction in many biosynthetic processes would be expected. Numerous studies have verified this hypothesis. We will comment here on effects chosen because of their clarity or because of their probable or proved clinical significance.

The effect of portal diversion on hepatic lipid metabolism has been unusually well studied. Since portacaval shunt reduces the serum concentration of cholesterol in animals[17, 65] and in humans,[20, 66] it was natural to wonder if this peripheral antilipidemic effect could be explained by a reduction in hepatic lipid synthesis. In our initial investigations of this possibility, we demonstrated reductions of more than 80% in canine hepatic cholesterol and triglyceride synthesis.[17] Although a similar diminution in cholesterol and/or lipoprotein synthesis was confirmed in rats,[67-69] dogs,[70] swine,[71-73] and baboons,[70] not all workers could verify these findings. The rigorously controlled studies in rats by Proia et al.,[68] which are the only reported animal experiments concerning Eck's fistula and lipid synthesis in which body weights were maintained or increased postoperatively, have done much to explain the discordant reports. In addition to demonstrating a reduction in cholesterol synthesis, Proia et al.[68] made the crucial observation that the total body cholesterol was diminished after portal diversion. As will be discussed later, data on hepatic lipid synthesis also are available from patients treated by us with portacaval shunt for familial hypercholesterolemia. It may be considered proved that lipid homeostasis is altered to an extraordinary degree by portacaval shunt, the reduction in hepatic lipid synthesis being the greatest change.

It has been equally well established that bile acid synthesis is greatly reduced by portacaval shunt.[68, 74-76] Another synthetic pathway that has been well studied after portal diversion is the hepatic urea (Krebs-Henseleit) cycle, which has been shown by Reichle et al. to be depressed by Eck's fistula in rats[77] and dogs[78]; they demonstrated a reduction in several of the enzymes involved in this metabolic pathway.

As detailed studies are made of other hepatic synthetic or metabolic processes after portacaval shunt, it will not be surprising if all are found to follow the same pattern. This possibil-

ity is supported by many studies during the past 15 years that have shown that portacaval shunt lowers the activity of the hepatic microsomal mixed-function enzyme system.[79-86] Aside from illustrating the principle of a wide-ranging decline in hepatic synthesis functions after portacaval shunt, these observations are of potential specific importance because the microsomal mixed-function enzyme system, for which multiple cytochrome P-450 and P-448 species serve as terminal oxidases, metabolizes a variety of drugs and foreign chemicals as well as endogenous compounds such as steroids and fatty acids. The depression of this enzyme system with its broad-ranging functions would relate to enormous numbers of metabolic effects of portal diversion.

There is no reason to suspect that depression of the microsomal mixed-function oxidase system is caused by factors other than the loss of the hormone-rich splanchnic venous blood. Proia et al.[86] have shown that the poor diet and weight loss in animals with Eck's fistula are not responsible. Furthermore, Pector et al. have shown that the hepatic alterations in the mixed-function oxidase system are the same whether the tied-off central portal vein is arterialized[80] or revascularized with systemic venous blood using the transposition technique.[81] These latter experiments showed that the mere restoration of the "wrong" kind of hepatic blood flow could not prevent the changes which are specific to portal diversion. The results of Pector's experiments[80, 81] were predictable from the earlier work of Marchioro et al.,[39] in which flow augmentation with systemic venous or arterial blood did not prevent atrophy of liver tissue that had lost its portal venous inflow.

The most important single factor in the etiology of the complications of Eck's fistula is depriving the liver of direct access to endogenous insulin. In accordance with this concept, Kato[87] has shown that the activity of the mixed-function oxidase system is depressed in rats with alloxan-induced diabetes in the same way as it is depressed by portacaval shunt.

Questions of Immunology

It can be considered firmly established that portacaval shunt causes many alterations in hepatic metabolism. Far more speculative is the possibility that immunologic function may be changed.

Studies during the last 20 years have suggested, or have claimed to demonstrate that there is a reduced response to antigens introduced into the portal as compared to the response to those introduced into the systemic venous system.[88-95] Partial removal of the antigens by the liver and thus a diminished host

reaction to their presence has been the most common explanation. Alternatively, some investigators have suggested that antigen delivery to the liver via the portal vein could contribute to the induction of tolerance.[88, 96-98] Many of these investigators have envisioned the normal liver as a barrier against, or as a modulator of, a host of environmental antigens, toxins, or carcinogens from the gastrointestinal tract which could injure the whole animal or the liver itself. Obviously, such a first-pass screening function would be mechanically disconnected by portacaval shunt. In addition, the depression of the hepatic mixed-function oxidase system after portacaval shunt, described in the preceding section, could further jeopardize such a guardian role.

The expectation that the liver could remove or inactivate antigens has led to efforts to create "privileged" situations with a variety of homografts. The organs used for such test systems have included kidneys[99-105] and hearts.[106] The venous return of the transplant in these preparations has been directed through the liver via an anastomosis to the portal vein (Fig 11). In addition, pancreatic islet cells[107, 108] and parathyroid cells[109] have been transplanted directly into the portal circulation or into the liver.

The results have been variable. In rats, all reports have described a protective effect of the portal site, but usually only

Fig 11.—Experimental models used in dogs and pigs to test the hypothesis that the liver can remove transplantation antigens. A, orthotopic renal transplantation in which the venous return was into the inferior vena cava. B, orthotopic transplantation, but venous return is into the portal vein. (From Mazzoni et al.[110] Reproduced by permission.)
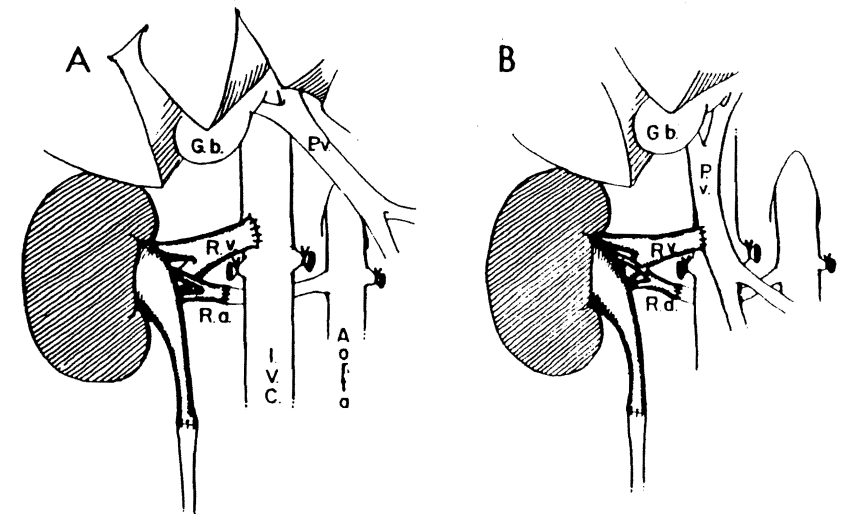
across easy histocompatibility barriers.[105, 106, 108, 109] Mazzoni et al.[103, 104] had similar positive results in pig kidneys, but their findings were not confirmed by Hickman and Terblanche[101] or by later studies by Mazzoni himself.[110] Barker and Corriere,[99] Fukuda et al.,[100] and May et al.[102] saw no amelioration of the rejection of primary canine kidney homografts drained through the portal vein.

The concept of hepatic clearance of antigens was thought by us to be so important that Mazzoni, one of the main proponents of this hypothesis,[103, 104] was invited to our laboratory in 1976 and 1977 to verify his own earlier observations. He was unable to do so. When he transplanted kidneys into mongrel dogs or into pigs so that the renal venous drainage was into the portal system of the hosts (see Fig 11), graft survival was not significantly increased compared to graft survival when renal venous drainage was into the vena cava.[110]

On the basis of Mazzoni's later investigations,[110] it seems unlikely that any specific benefit from organ transplantation to the portal vein can be expected in patients. The question that remains is whether the portal site allows amelioration of rejection in rats and mice. It is unlikely that the issue of "portal" implantation will ever be important in transplantation, but the intriguing possibility that the liver is a subtle modulator of immune events has not been disproved. For the moment, however, it must be concluded that there is no sound factual basis for this concept and that a change in immunologic reactivity is not, therefore, an expected consequence of portacaval shunt.

RELEVANCE OF ANIMAL STUDIES TO HUMAN PHYSIOLOGY

The histopathologic alterations in, and changes in function of, the liver caused by portacaval shunt are essentially the same in rats, swine, dogs, monkeys, baboons, and humans.[18] However, until about 30 years ago it was not known whether the lethal consequences of portacaval shunt represented more than a species peculiarity of the dog. Until then, Eck's fistula had not been evaluated in other animals. In humans, portacaval shunt had not been performed on anybody who had a previously normal liver, and consequently any opinions about the metabolic effects of Eck's fistula in man were purely speculative. The dearth of information began to end with the classic clinical articles of McDermott et al.,[111, 112] which seemed to be confirmed by Hubbard[113] a few years later. Unfortunately, misinterpretation of the observations in these reports actually delayed an understanding of the physiology of human portacaval shunt for almost two decades.

THE MCDERMOTT-HUBBARD ARTIFACT

McDermott et al.[111, 112] and Hubbard[113] each reported on two patients who had carcinomas of the head of the pancreas and grossly normal livers except for biliary obstruction. In order to perform pancreaticoduodenectomy, it was necessary to resect the portal vein, and in all four patients, the end of the transected superior mesenteric vein was anastomosed to the side of the inferior vena cava.

The results were devastating. Within a few weeks or months, all four patients developed episodic hepatic encephalopathy, malnutrition, fatty infiltration of the liver, and hypoalbuminemia. When the patients died, 4–20 months postoperatively, all were tumor free. It was concluded that these were examples of Eck's fistula in humans with normal livers, that humans were even more sensitive than dogs to the metabolic complications of Eck's fistula, and that the ability of patients to tolerate portal diversion was inversely related to the quality of preexisting hepatic function.

None of these conclusions was valid. The errors were caused by the investigators' failure to appreciate that the operations were not pure Eck's fistulas. In addition to the portal diversion, all four of the patients also had removal of variable amounts of the pancreas, which later investigations proved to be the single most important source of hepatotrophic substances. Eventually it was realized that man is less, not more, susceptible than experimental animals to the metabolic complications of Eck's fistula. Finally, it is not true that portacaval shunt is tolerated best in patients with the worst hepatic disease; the converse is true.

THE SPECIES FACTOR IN ENCEPHALOPATHY

The weight loss, alopecia, and encephalopathy first described in dogs after portacaval shunt construction have been less severe or inconstant in rats.[114–117] In swine, some investigators have been able to carry out studies for 2–4 months after portacaval shunt construction,[71–73] but others have found the operation to cause hepatic failure and encephalopathy within days.[118, 119] Subhuman primates including Rhesus[120] and Macaca mulatta[121] monkeys as well as baboons,[17, 18] may develop the Eck fistula syndrome in such a fulminant form as to make it difficult to perform metabolic studies. The brains of the baboons have shown the same glial proliferation and central pontine myelinolysis[18] seen in rats[117] and monkeys[122] after portal diversion.

Fortunately, the remarkable encephalopathic complications

produced after the subhuman primate operations have not been duplicated in humans with previously normal livers. The human experience with pure Eck's fistula in the presence of normal hepatic function has been in patients with types I, III, and VI glycogen storage disease (GSD) or familial hypercholesterolemia (FH).

The patients with GSD generally tolerated portacaval shunt well in spite of the fact that their well-functioning livers usually had significant preexisting structural abnormalities.[19, 66] Of nine GSD patients followed by us for 4¾ to 19½ years after portal diversion, only one developed hepatic insufficiency and encephalopathy—8 years after portacaval shunt. This girl was successfully treated with orthotopic liver transplantation[123]; it was possible to take down the portacaval anastomosis and use the portal vein to revascularize the new liver. None of the other patients with GSD treated with portal diversion are known to have developed encephalopathy.

The picture was even clearer in patients who had portacaval shunts constructed for FH. Characteristically, patients with this disease start with completely normal liver structure and normal hepatic function. Only one of our 13 patients, and none of the 26 others reported from other centers,[124] had overt manifestations of the Eck fistula syndrome on follow-up of 1 to nearly 10 years. The exception in our series was a 3-year-old girl who had a single episode of unconsciousness 9 months after portacaval shunt construction at a time when the blood ammonia was 85 μg/dl (normal in that laboratory, <55 μg/dl). Encephalopathy was accepted as the diagnosis because no other explanation was found. The child is well on a low-protein diet.

The histopathologic changes caused by portal diversion in the livers of these patients (see Fig 3) have been indistinguishable from those in animals.[20, 124] It is noteworthy that blood ammonia levels, when measured, have always increased to or beyond the upper limits of normal[124]; low-grade elevations of serum transaminase and alkaline phosphatase levels have been common. Although the patients have been clinically well and on a normal diet after portacaval shunt construction, there has been no reason to doubt that their hepatic function has been impaired. Nevertheless, their behavior and physical development have not been obviously altered.

The only other use of portal diversion in the presence of a normal or nearly normal liver has been in patients with esophageal varices from extrahepatic portal venous obstruction (presinusoidal block). The thrombosed portal vein in many such patients is replaced with a multitude of collaterals which are frequently so well developed that they have been referred to collectively as "cavernous transformation." It has been suspected

for a long time, and unequivocally demonstrated in a recent publication of Warren et al.,[125] that flow in the collaterals is hepatopetal and thus important in perfusion of the liver with hormone-rich splanchnic blood, albeit by circuitous routes. If a sound portal-systemic anastomosis can be constructed (usually with splenorenal, cavomesenteric, or makeshift shunts), control of variceal hemorrhage is almost always achieved. At the same time, the collateral splanchnic venous flow to the liver described above is "stolen" from the liver through the shunt.[125]

In spite of this physiologic penalty, clinical results after technically satisfactory shunt procedures usually have been good, as exemplified by a recent report of Grauer and Schwartz.[126] Of their 19 patients, none developed liver failure or encephalopathy on follow-up as long as two decades. The observations were consonant with those of previous workers.[127, 128]

Even more reassuring were the results obtained in the French hepatology unit of Alagille and summarized by Alvarez et al.[129] Seventy-six children with portal obstruction had portal-systemic shunts (32 central splenorenal, 32 Marion mesocaval, 6 interposition mesocaval, 3 makeshift, 2 distal splenorenal, 1 portacaval). Seventy of the shunts remained patent. Although blood ammonia levels were slightly elevated, none of the patients developed encephalopathy, as judged by neurologic examinations and electroencephalograms every 6–12 months, and by analysis of academic performance. Physical growth was not interrupted; in fact, it was accelerated.

Nevertheless, hepatic dysfunction and encephalopathy have been reported by Mikkelsen et al.[130] with or without portal diversion in patients with extrahepatic portal block; in two such patients Warren et al.[125] achieved reversal of encephalopathy after disconnecting the portal-systemic shunts and restoring the hepatopetal flow.

Voorhees et al.[131] have added the chilling note that patients treated with portal-systemic shunt for extrahepatic portal block at Columbia University, New York, have had a high incidence of psychological and psychiatric perturbations, which they suggested might be occult manifestations of encephalopathy. These latter conclusions have not been verified, and careful psychological and intelligence examinations in patients with familial hypercholesteremia[124] have not turned up anything resembling Voorhees' observation.

The resistance of man to encephalopathy after portacaval shunt has not been explained satisfactorily. One possibility is that the natural diet of humans is more compatible with the depressed hepatic function of Eck's fistula than the diet of some of the animal species. In various animals, the clinical manifestation of hepatic encephalopathy can be forestalled or amelio-

rated with special low-protein diets, and obviously the same kind of dietetic management is a standard reaction if hepatic encephalopathy occurs in patients.

THE HUMAN ECK FISTULA SYNDROME VERSUS PREEXISTING LIVER FUNCTION

The McDermott-Hubbard artifact led to speculation, if not to an absolute conviction, that the risks of the Eck fistula syndrome in humans were proportionate to the quality of preexisting function, being greatest with a completely normal liver. It was rationalized that severely diseased livers that had already lost hepatopetal portal flow to collaterals would not be much further affected by a portacaval shunt and that such livers would have had compensatory increases in hepatic artery flow. In contrast, the argument continued, normal or near-normal livers that still retained significant portal venous flow would sustain a major insult by abrupt diversion of this flow.

It would be a perversion of scholarship to cite statements by distinguished hepatic surgeons who have defended this kind of sophistry during the last 30 years. Suffice it to say, during much of this same period the inescapable conclusion from clinical experience with various shunting procedures has been the opposite of the foregoing hypothesis. For two decades, the risk in most patients being considered for portal diversion has been stratified, by the so-called Child classification, according to the quality of hepatic function.[132] Patients with the best hepatic function are placed into Child class A, those with the worst function are placed into class C, and the others are placed in class B. All major studies that have taken into account such disease staging have shown the best results after portal-systemic shunt operations to be in class A patients and the worst to be in class C patients. Parenthetically, the Child class A patients are the most apt to have residual hepatopetal flow, although the association is too imperfect to be useful in predicting the outcome.[133, 134]

ECK'S FISTULA FOR METABOLIC OBJECTIVES IN HUMANS

Benefits have been seen after end-to-side portacaval shunt in patients with three inborn errors of metabolism: glycogen storage disease (GSD), familial hypercholesterolemia (FH), and α_1-antitrypsin deficiency. In each instance, the amelioration of symptoms has been the tradeoff for the hepatic damage caused by putting the liver into the portoprival state.

GLYCOGEN STORAGE DISEASE

When portal diversion was first performed for GSD almost 20 years ago,[28] the rationale for the procedure was different from our understanding today. In 1963 it was hoped that by short-circuiting splanchnic venous blood around the liver, glucose would be made more readily available to peripheral tissues, with relief of hypoglycemia; it was further expected that the liver would be coincidentally deglycogenated, since this had been observed in animals.[27, 28] As this monograph has made clear, the consequences of portacaval shunt are more subtle and wide ranging than the simplistic view suggested.

The first patient who had total portal diversion is still alive almost 20 years after portacaval transposition. She had type III GSD. A patient similarly treated by Riddell et al.[135] also survived long term. Our second patient died 2 days after portacaval transposition, probably because the liver could not transmit the high-volume flow of the inferior vena cava.[19] Simple end-to-side portacaval shunts were used in all of the eight subsequent patients in our series,[19, 66] of whom seven are alive after 6½ to more than 10 years.

The amelioration of symptoms of GSD was confirmed by other observers, whose cases have been summarized by us[19, 66] and by other reviewers.[136, 137] In 1972, Folkman et al.[138] added an important therapeutic dimension by showing how preoperative parenteral hyperalimentation could reduce the operative risk by normalizing preexisting hepatomegaly, acidosis, and other abnormalities, including hyperlipidemia. In an extension of this concept, Greene et al.[139] and Crigler and Folkman[140] showed that continuous or frequent feeding (including overnight alimentation) is more than an alternative to portacaval shunt in the treatment of this disorder—it is, rather, the therapy of choice. Nevertheless, follow-up of the early patients with GSD treated with portal diversion is of considerable interest.

The ages of our ten patients, types of disease, and symptoms are summarized in Table 1. Type I disease (glucose-6-phosphatase deficiency) was the most common indication for treatment, with type III disease (amylo-1,6-glucosidase deficiency) being a distant second.

Metabolic Effects

After portal diversion, most of the children who had preexisting hypoglycemia did not have relief of this symptom or the relief was not complete. Thus, night feedings usually had to be continued. Studies of plasma insulin and glucagon in several of these patients revealed the pattern shown in Figure 12. The flat peripheral insulin curves typical of type I GSD[141] became elevated after portacaval shunt, and there were smaller increases

TABLE 1.—Patients With Glycogen Storage Disease (GSD) Treated by Portal Diversion*

PATIENT	AGE (Years)	GSD TYPE	DATE OF OPERATION	PREOPERATIVE SYMPTOMS			PERSISTENT HYPOGLYCEMIA POSTOPERATIVELY	SURVIVAL AFTER SHUNT
				Hypoglycemia	Acidosis	Growth Retardation		
1	8	III	10/15/1963	X	X	X	No	Alive 19½ years
2	7	I	6/26/1968	X	X	X	—	Died after 2 days
3	7	I	5/2/1972	X	X	X	Yes†	Alive 11 years
4	11	I	5/17/1972	X	X	X	No	Died after 4¼ years
5	10	VI	8/2/1972			X	—	Alive 10½ years
6	5	III	11/7/1972	X	X	X	No	Alive 10½ years
7	3	III	11/8/1972	X	X	X	Yes†	Alive 10½ years
8	8	I	8/13/1973	X	X	X	Yes‡	Alive 9¾ years
9	12	I	12/14/1973	X	X	X	Yes†	Alive 9½ years
10	1	I	10/2/1976	X	X	X	Yes†	Alive 6½ years

*Patients 1 and 2 had portacaval transposition; all others had portacaval shunt.
†Overnight feeding via nasogastric tube was begun 2½–4 years after portacaval shunt.
‡Orthotopic liver transplantation was done on Feb. 12, 1982. The patient is well 14 months later (see text).
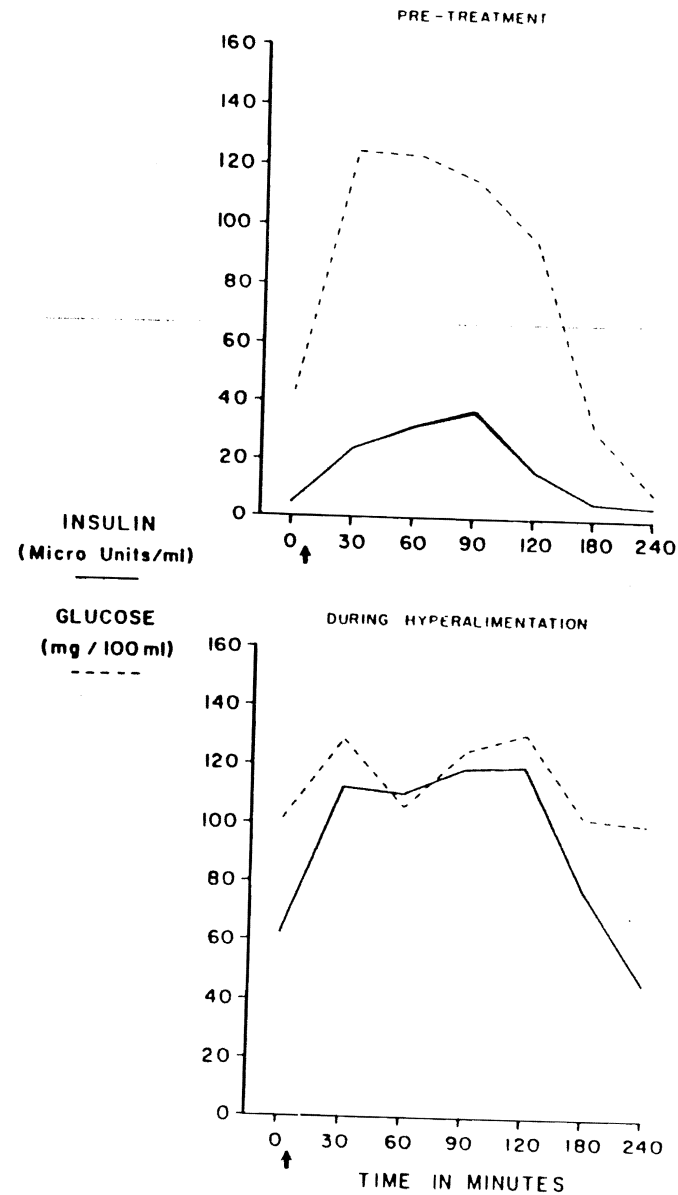

Fig 12.—Plasma insulin and glucose concentrations before and after portacaval shunt in a child with type I glycogen storage disease. (From Starzl et al.[66] Reproduced by permission.)
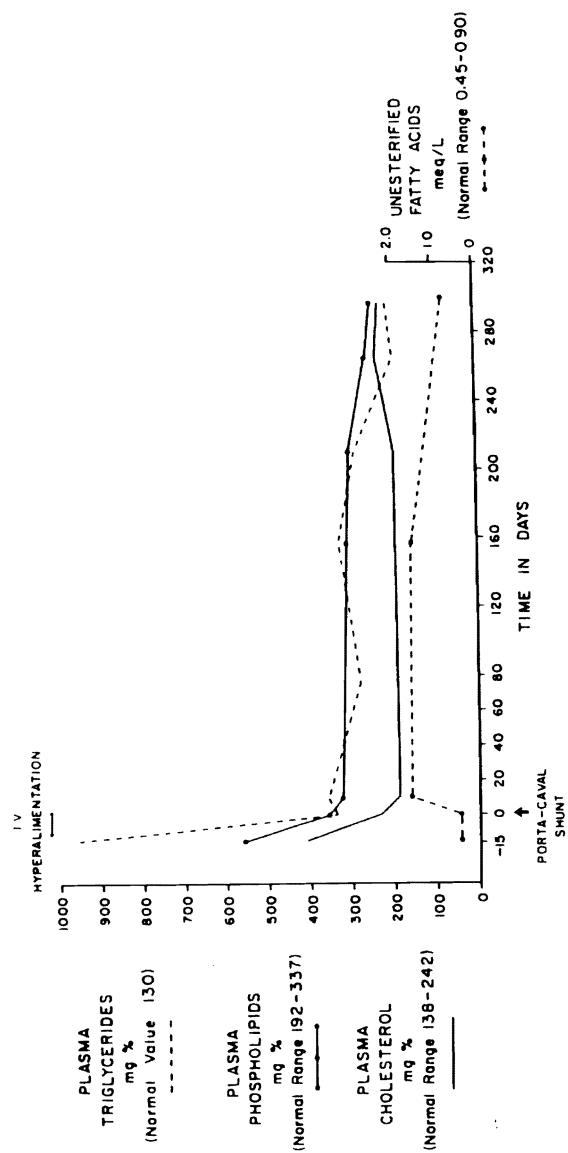
Fig 13.—Effect of parenteral hyperalimentation and end-to-side portacaval shunt on the plasma lipids of a patient with the diagnosis of type I glycogen storage disease. Note the rapid and relatively complete reversal of all abnormalities. (From Starzl et al.[19] Reproduced by permission.)

in glucagon. The glucose tolerance curves were much the same before and after operation.

Liver glycogen concentrations in those of our patients who later had liver biopsies were not changed, nor were the measures of enzyme activity. It is of interest that Corbeel et al.[137] of Belgium found a striking increase of *active* glucose-6-phosphatase after portacaval shunt in a child with type Ib GSD. It was speculated that the portal diversion had unmasked a nonfunctional glucose-6-phosphatase by improving the defective transport of this enzyme across microsomal membranes.

In spite of failure to alter the hepatic glycogen concentration,[19, 66] the liver size in several of our patients and those reported by others underwent a very obvious reduction, as measured by liver scan planimetry. Even if obvious gross shrinkage did not occur, postoperative biopsies always showed a diminution in individual hepatocyte size[19, 66] similar to that produced in animals by portacaval shunt.

In contrast to the incomplete relief of hypoglycemia, all components of the hyperlipidemia which is a characteristic of the type I disease were profoundly and permanently relieved (Fig 13). Correction of other metabolic defects was observed, including abnormal bleeding, uric acid elevations, and abnormal calcium metabolism.[19, 66, 135–138]

Growth

All ten of our patients had growth retardation before portacaval shunt. Afterward, height increases, which in most cases had virtually ceased, occurred during the first postoperative year at the rates listed in Table 2, approximately 0.5 cm/month.

TABLE 2.—Growth Rate and Complications After Portal Diversion for Glycogen Storage Disease

PATIENT	GROWTH RATE (cm/mo. over 40–120 mo.)	COMPLICATIONS
1	0.49	
2	Operative death	
3	0.50	Macroadenomatosis
4	0.28	Died 4¾ years after shunt; primary pulmonary hypertension, NH$_3$ = 85, macroadenomatosis
5	0.53	Renal artery stenosis surgically corrected 32 months after shunt
6	0.62	
7	0.50	
8	0.49	Macroadenomatosis; liver transplantation after 8½ years
9	0.88	Renal stone 2 months after shunt; mild arterial hypertension, macroadenomatosis
10	0.4	Growth cessation after 2 years
Mean	0.54	

The same phenomenon has been described in almost all of the other reported cases.

Quantitative measures of growth were obtained with radiographic techniques.[19] An example of the results is shown in Figure 14. Comparison of the wrists and hands in this 7-year-old, stunted child before and 11½ months after operation shows the phenomenal effect of bone age doubling. In addition to the changes in bone size, mineralization occurred, and new wrist bones appeared. Circulating somatotropin in these patients was normal.[19] The growth spurts may have been at least partially attributable to the increased insulin distribution to the periphery, mentioned earlier (see Fig 12), since insulin has been recognized as a major growth hormone, comparable in potency to somatotropin.

Morbidity from Portacaval Shunt

The patient who exhibited hepatic encephalopathy 8 years after end-to-side portacaval shunt for type I GSD also developed multiple filling defects in her enlarged liver. When the diseased liver was replaced at transplantation, all of the metabolic abnormalities of type I GSD were completely relieved.[123] It has been proved from the study of more than a half-dozen liver-based inborn errors of metabolism that the phenotype of the transplanted organ permanently retains its original donor specificity.[142]

One other child developed a blood ammonia concentration of 85 µg/dl (normal, < 60 µg/dl in that laboratory), but there were no symptoms of encephalopathy. This patient died almost 5 years after portacaval shunt construction during an attempt at transcaval radiographic visualization of the portacaval anastomosis. Except for the slightly elevated blood ammonia concen-

Fig 14.—The dramatic wrist and hand bone growth and mineralization in a patient with type I glycogen storage disease by 11½ months postoperatively. The bracket on the left index finger is 5 cm in length. (From Starzl et al.[19] Reproduced by permission.)

PRE-OP   II ½ MONTHS POST-OP
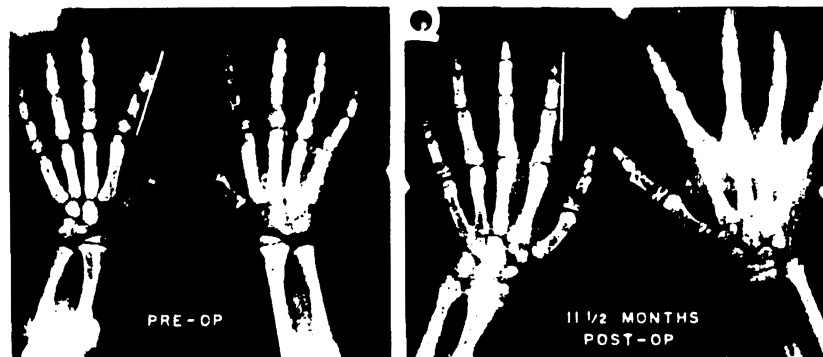
tration, standard liver functions were normal. At autopsy the liver showed macroadenomatosis, very similar to that in the child who underwent liver transplantation. An autopsy finding that had not been suspected in life was advanced right ventricular hypertrophy and dilatation. The smaller pulmonary arteries and arterioles showed medial muscle hypertrophy, medial and intimal fibrosis, scattered fibrinoid necrosis, and numerous plexiform lesions. Such cardiopulmonary complications have been documented in other patients with type I GSD and other liver diseases.[143] This complication did not have an obvious relationship to the portacaval shunt. The macroadenomatosis seen in these patients is very common in patients with type I GSD and was recently reported in seven of eight nonshunted patients, aged 3–28 years.[144]

The Present Status of Portal Diversion

Portacaval shunt in the treatment of GSD has been supplanted by the continuous night feeding schedule advocated by Greene et al.[139] Portacaval shunt, if it has any role at all, is reserved for failures of this more conservative and liver-sparing approach. We have not performed a portacaval shunt for GSD since October 1976.

FAMILIAL HYPERCHOLESTEROLEMIA

In March 1973, a 12-year-old girl with homozygous FH was treated with an end-to-side portacaval shunt; her serum cholesterol concentration fell markedly.[20] In patients with this disease, there is an absence or deficiency of cell membrane lipoprotein receptors[145,146] and thus no "switch-off" mechanism to control lipid (especially cholesterol) synthesis.

By the summer of 1982, 12 patients with FH had been treated by us in this way. Eight of the patients were children, aged 2–14 years. The four adults were aged 21, 31, 37, and 52 years. All but two were homozygous for the FH abnormality. Low-density lipoprotein (LDL) receptors were determined by Goldstein and Brown[145] on cultured fibroblasts obtained from all patients and many of their close relatives. Nine of the ten patients with homozygous disease were LDL-receptor negative and the other was LDL-receptor defective. Two of the patients had heterozygous disease.

The portacaval shunts were constructed 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,[147] no anticoagulants were given during or after opera-
tion. Thrombosis after portacaval shunt in children with portal
hypertension has been so high that most pediatric surgeons pre-
fer to use the operation only in patients older than 8 or 10 years
and in those whose anastomoses can be made at least 1 cm in
diameter.[127, 148] Although these minimum conditions did not ob-
tain in the majority of our patients, there were no thromboses
and no deaths.

Effect on Serum Lipids

Total serum cholesterol concentrations fell significantly in
every patient after portacaval shunt.[124] When measured, LDL
cholesterol levels were reduced commensurately. The total cho-
lesterol values declined 20%–55.4% (average, 33.8%), and this
decline was maintained throughout the period of study. HDL
cholesterol and triglyceride levels were variably effected. Ten-
dinocutaneous xanthomas regressed or disappeared in every pa-
tient (Fig 15).

Experience of Others in Treating FH

The consistency of the anticholesterolemic response was
greater in our patients than in patients treated by others. There
are reports on a total of 26 additional patients, 13 of whom were
treated in Johannesburg.[149]

In the 13 patients treated elsewhere than in Johannes-
burg,[150–157] serum cholesterol reductions of at least 30% were ob-

Fig 15.—The hands of a patient with hyperlipidemia 2 weeks before *(left)* and 16
months after *(right)* portacaval shunt. (From Starzl et al.[158] Reproduced by permis-
sion.)

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tained in ten, as well as regression of tendinocutaneous xantho-
mas to the same extent as originally reported by us.[20, 158] In two
of the three exceptional patients, shunt thrombosis was
proved,[151, 152] and in one of these the cholesterol level fell by
40% after a later mesocaval shunt.[152] In the third patient, de-
scribed by Soutar, Myant, and Thompson,[154] there was presump-
tive but not definitive evidence of shunt occlusion. The choles-
terol level, after an early fall of 40%, returned several months
later to near preoperative values. At the same time, initially
elevated serum glucagon levels, which are typically found with
a patent shunt,[74, 159] fell to baseline.

The early[160] and subsequent[149] reports from Johannesburg
have confirmed the value of portacaval shunt in FH but have
provided minimal incentive for expanded trials. Of 13 homozy-
gous patients with unstipulated membrane receptor status, one
died 2 days postoperatively of a myocardial infarction. The re-
maining 12 had significant but often modest falls in serum total
and LDL cholesterol levels, and the values later returned to or
toward preoperative levels in three. Xanthomas regressed in
eight patients, were stable in two, and increased in two. Almost
all patients developed postoperative splenomegaly, a finding
compatible with sluggish or obstructed splanchnic venous drain-
age or, alternatively, with a manifestation of FH that previously
had not been appreciated.[149]

A full explanation for the indifferent results in the Johannes-
burg series has not been forthcoming, but possibilities discussed
elsewhere[121] include a high incidence of shunt thrombosis or in-
effective portal diversion, peculiarities of the FH endemic to that
region of South Africa, or other less obvious factors.

The invariable and long-lasting lipid lowering in our 12 pa-
tients was achieved without surgical morbidity. The physical de-
velopment of children who were normal before operation has
proceeded, and the growth of those who were stunted before op-
eration has moved toward normal. As described in an earlier
section, emotional or intellectual deterioration secondary to the
portal diversion has not occurred, although one child had an
acute episode of encephalopathy which was managed with diet.

Mechanisms of Lipid Lowering

The mechanisms causing lipid lowering in patients with FH
probably are qualitatively similar to those in experimental ani-
mals, discussed earlier in this monograph.

Data relevant to mechanisms in humans with FH are also
available. Soutar et al.[154] found no change in LDL synthesis and
an actual rise in very-low-density lipoprotein (VLDL) synthesis
in the patient discussed earlier whose shunt may have closed.
Strikingly different conclusions were reached after metabolic
studies in three of the 12 patients of our own series. In our pa-
tient 2, Bilheimer et al.[74] showed that cholesterol and LDL syn-

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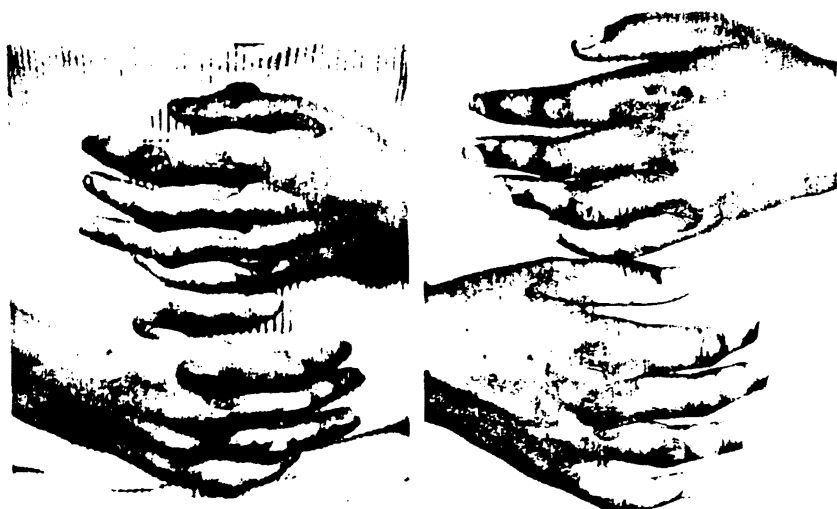
thesis, which were inappropriately high before portacaval shunt, were reduced afterward by 62% and 48%, respectively. The fractional catabolic rate, which was only a third of normal at the outset, as is typical for FH, fell further after operation. Ginsberg et al.[161] studied the heterozygous patient 6 in our series; that patient 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 in our own series and the heterozygous patient 6 has been described by McNamara et al.[75] 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 was reduced by 59% in patient 4 and by 43% in patient 6. These data are compatible with the extraordinary diminution or disappearance of tendino-cutaneous xanthomas (Fig 15) and with the hope that the lethal cardiovascular complications of FH can be slowed or forestalled by portacaval shunt.

Effect on Cardiovascular Disease

The degree to which the cardiovascular complications of FH can be relieved or prevented by portal diversion has not been established. Reversal of aortic stenosis was seen in two of our patients, but regression of atheromas in the coronary arteries and aorta was not regularly achieved.[124] Small and Shipley[162] have examined 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.[163] have suggested that anatomical stabilization of the vascular disease may be the best that can be achieved with a portacaval shunt, even in patients whose angina pectoris is relieved. Experience in several patients at our center and elsewhere[124, 153, 157] has shown the value of aggressive surgical correction of technically remedial cardiovascular lesions in combination with portal diversion. Of greater importance will be the implementation of aggressive therapy at a young age, before irreversible cardiovascular complications develop. In patients with FH who are refractory to therapy with diet and medications, portacaval shunt may be the treatment of choice. Postoperatively, medications and diet should be tried again, since further declines in postshunt cholesterol levels have been seen using diet and medications which had previously been ineffective.

The staged combination of portacaval shunt and the ileal by-

pass procedure of Buchwald et al.[164] has been tested in three patients. The combination had an apparently additive effect,[149, 156] even though ileal bypass alone has little or no effect on homozygous FH.[164] In dogs, Guzman et al.[165] have noted an additive effect of portal diversion (by portacaval transposition) plus ileal resection. Efforts by us[166] to document a complementary effect of ileal resection and portacaval shunt in dogs failed to confirm the claims of Guzman et al.,[165] and a subsequent report by Rucker et al.[167] from the Minnesota study has shown that the additive effect originally reported by Guzman was not sustained.

Limitations of Portacaval Shunt

Portacaval shunt, with or without supplementary treatment, is only palliative in patients with FH. The amelioration of the abnormal metabolic patterns of FH has derived from the countervailing and potentially dangerous hepatic abnormalities caused by portacaval shunt (see Fig 3). 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,[168-171] it is possible that the metabolic abnormalities of FH could be rectified by the ultimate step of liver transplantation.

PORTAL DIVERSION FOR α₁-ANTITRYPSIN DEFICIENCY

In both GSD and FH, the generally adverse effects of portal diversion have been accepted as the price for improvement of even more serious metabolic perturbations. There is a possibility that a third inborn error, α_1-antitrypsin deficiency, may be added to this list.[172]

Patients with this disorder have a low level of plasma α_1-antitrypsin (an α-globulin) and a high incidence of pulmonary complications.[173] In 1969, Sharp et al.[174] demonstrated a variable association of the α_1-antitrypsin deficiency with liver disease, an observation that has had overwhelming confirmation.[175, 176] It is now accepted that α_1-antitrypsin deficiency is a common cause of chronic liver disease both in the pediatric and in the adult populations.

The probable pathogenesis of the liver disease has been recently reviewed.[177] In essence, the basis for the liver injury may be the hepatic production of an abnormal α_1-antitrypsin which cannot be effectively transported out of the liver cells and which consequently becomes sequestered within the hepatocytes near the RER. Irritation by the entrapped glycoprotein has been postulated as the cause of the hepatic cirrhosis, portal hypertension, and hepatic failure that follow. The progressive and inexorable

course that this pathogenesis implies may have discouraged attempts to treat complications of the portal hypertension (such as variceal hemorrhage) with portal-systemic shunts. In addition, the results with portal diversion have been poor.[178-180] Only Sotos et al.[181] have reported encouraging results, and their observations were limited to two children.

We have performed end-to-side portacaval shunt in three children with the cirrhotic liver disease of α_1-antitrypsin deficiency.[182] The first two patients had major hemorrhages from esophageal varices. The third had ascites, but the principal reason for operation was the hope of influencing the metabolism of the α_1-antitrypsin.

Follow-up data of 3½, 5, and nearly 7 years are available.[182] Standard liver function tests have not changed greatly since the portacaval shunt, although the plasma ammonia levels have been elevated in both patients in whom measurement was systematically made. None of the three patients have had symptoms of encephalopathy, although patient 2 had mental slowness for the first 2 years after operation.

The possibility that the liver damage of α_1-antitrypsin deficiency can be slowed by portacaval shunt has been emphasized by the stabilization in all three patients of a previously deteriorating clinical state. However, the most objective evidence that the natural history of the disease was favorably altered by portacaval shunt came from the histopathologic studies of biopsy specimens obtained operatively and postoperatively in patients 2 and 3.[182] In patient 2, a biopsy specimen obtained 9 months after the portal diversion showed a reduced number of hepatocytes containing α_1-antitrypsin globules—28.5%, compared to 38.2% at the time the portacaval shunt was constructed. The hepatocytes were 22% smaller, and the amount of RER in their cytoplasm was greatly reduced.

In patient 3 the percentage of hepatocytes containing α_1-antitrypsin globules was 44.5% at the time of operation and 48.2% and 38.7% at 7 and 13 months, respectively, after portacaval shunt. The hepatocytes were 15% and 20% smaller at these postoperative follow-up times. The percentage of hepatocytes containing α_1-antitrypsin globules was reduced to 20.4% in the biopsy specimen obtained 35 months postoperatively. The hepatocytes remained 20% smaller than in the preoperative biopsy specimen, and the amount of both RER and SER in their cytoplasm was reduced. The severity of the macronodular cirrhosis was unaltered.

We assume that the portacaval shunt diminished the synthesis of the abnormal α_1-antitrypsin, presumably by altering the function of the RER and its ribosomes (see earlier section on hepatic function after construction of Eck's fistula) without commensurately reducing the transport of this glycoprotein.[172, 182]

With a better equilibrium between the production and transport of the α-globulin, it is possible that its intracellular accumulation has been slowed or probably even reversed.

PORTAL-SYSTEMIC SHUNT FOR COMPLICATIONS OF PORTAL HYPERTENSION

We have emphasized the morphological and metabolic changes caused by portal diversion and the explanations for these wide-ranging effects. The inescapable conclusion from all of the work on this subject in the last decade is that portal-systemic diversion is so inherently harmful to the liver that it should be considered only for life-threatening disease conditions or complications. Exploitation of portal diversion for its increasingly well-understood metabolic effects, as described in the preceding section, has been a recent development and one that is still in evolution. In contrast, there is little new of a conceptual nature that can be written about the use of portal-systemic shunting for mechanical and hemodynamic objectives, except for the contributions of W. Dean Warren and his associates.

As mentioned at the outset, Eck envisioned the use of portacaval shunt for the treatment of hepatogenic ascites.[3] In their historical treatise, Donovan and Covey[183] described how other surgeons interested in the procedure realized that it also might be a way to control hemorrhage from esophageal varices. Vidal[184] was probably the first (June 1903) to construct a portacaval shunt successfully. His patient, a 34-year-old alcoholic man, had ascites and a 7-week history of recurrent variceal hemorrhages. He survived more than 3 months after operation.

Both of the principal complications of portal hypertension, ascites and hemorrhage, have been extensively treated by a variety of portal-systemic shunts since Whipple[185] and Blakemore and Lord[186] ushered in the modern era of this field not quite 40 years ago. Although portal diversion often dries up ascites, its use for this purpose has been all but abandoned because of the mortality and morbidity (especially encephalopathy) of the procedures, because better diuretics have made ascites easier to control, and because the safer peritoneal-venous (LeVeen-type) shunts can be used if nonoperative care is unsuccessful.[187]

The boom in portal-systemic shunts to control variceal bleeding has lasted longer, but such procedures are being recommended far less frequently today than they were a few years ago. The downward trend undoubtedly will continue, for several reasons. The developments in hepatotrophic physiology summarized in this monograph have shown how destructive to the normal liver portal diversion can be. The incongruity of deliberately imposing such an insult on an organ already abnormal and laboring under the handicap of intrinsic parenchymal disease has

not escaped the attention of thoughtful clinicians. Furthermore, the results of randomized clinical trials during the last 20 years, in patients with or without previous variceal hemorrhage, have not demonstrated a statistically significant increase in survival after any kind of portal-systemic shunt compared to that achievable without operation.[188-194] The decrease in mortality from gastrointestinal hemorrhage after shunting has been canceled by perioperative deaths and or by a higher subsequent death rate from hepatic failure. Consequently, alternative methods to control variceal bleeding without changing the preexisting hepatic blood flow patterns have been viewed with increasing interest. The most promising techniques are sclerotherapy of the varices[195-197] and transhepatic embolism of the left gastric (coronary) vein.[198, 199]

The growing nihilism about portal diversion in patients with advanced hepatic disease will be justified to the extent that liver transplantation becomes an option in future years. An existing shunt, or for that matter, any kind of previous upper abdominal operation, is an extremely negative factor in a patient being considered for hepatic transplantation,[142] and may preclude such transplantation.

In the meantime, a limited number of patients will be bonafide candidates for portal-systemic shunts. Available shunting techniques are illustrated in Figures 16 and 17. The literature on the various shunt operations is so voluminous and so frequently contradictory that no effort is made to review it here. The interested reader can quickly obtain a relatively complete idea of what has been written by perusing any one of three recent reviews.[200-202]

PORTAL FLOW STUDIES IN SHUNT PLANNING

A logical decision about the type of shunt to be used cannot be made without ascertaining whether there is still perfusion of the liver by portal blood (hepatopetal flow). Although there is no completely accurate technique to obtain this information, rough estimates of residual portal flow can be made with late phase venograms after selective celiac or superior mesenteric arteriography,[203, 204] or by direct dye injection into the splanchnic venous system using splenoportography,[205] transhepatic portography,[206] or umbilical venography.[207] A more quantitative estimate may become a practical objective in the future. Rikkers, Miller, and Christian[208] have described a radiocolloid technique for quantifying the fraction of superior mesenteric venous blood that perfuses the hepatic sinusoids.

The concept of using this kind of hemodynamic information for preoperative assessment can be traced back through the literature for several decades, particularly in the publications of
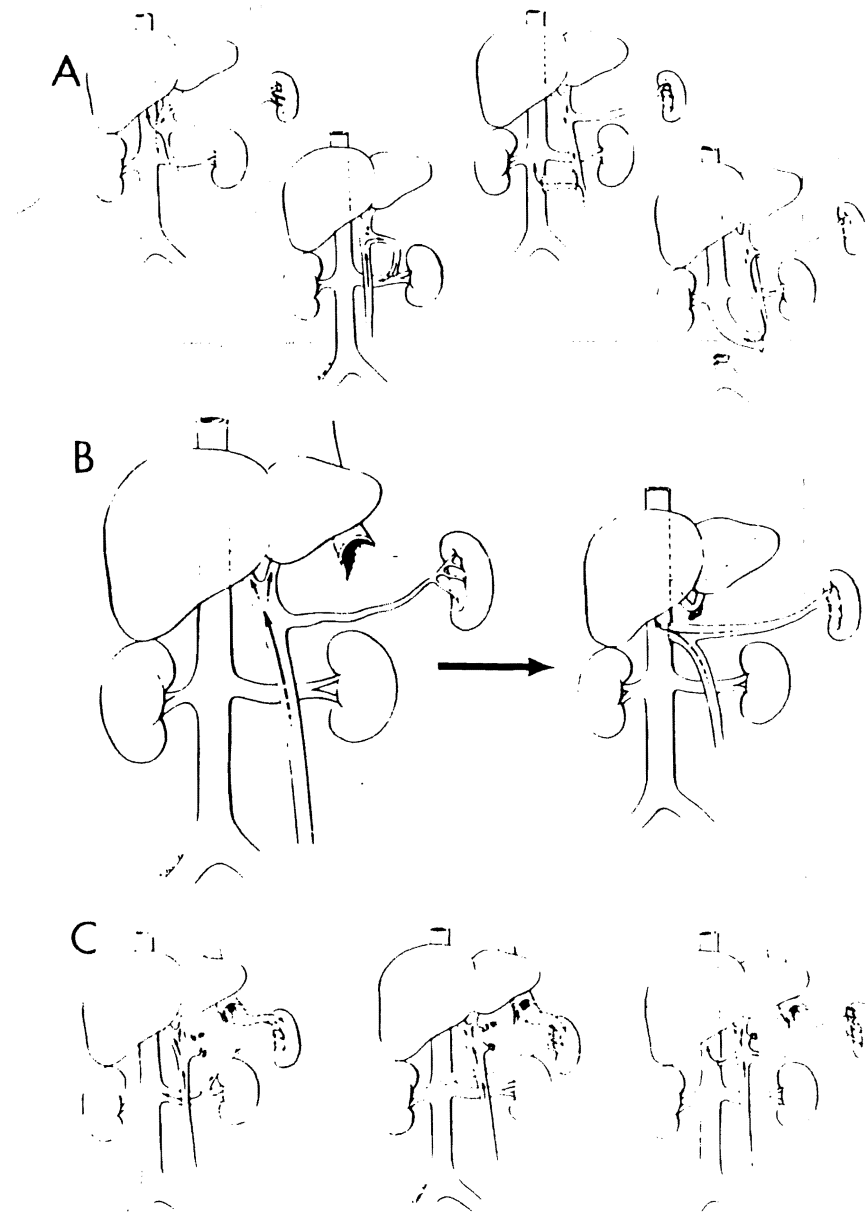

Fig 16.—Kinds of portal-systemic shunts. **A**, end-to-side portacaval shunt. **B**, variety of side-to-side shunts. **C**, selective portal-systemic shunts.
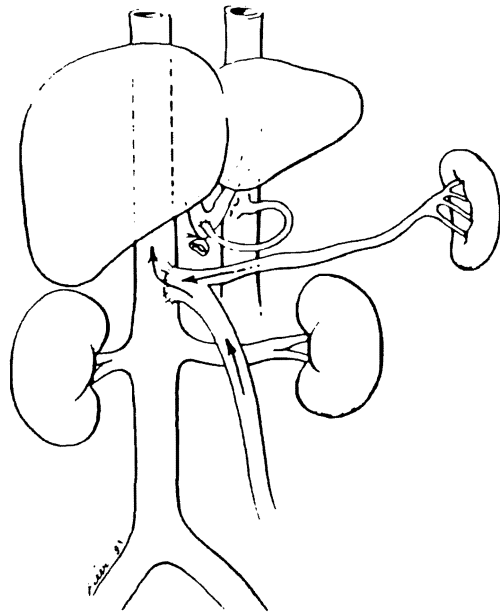
Fig 17.—End-to-side portacaval shunt, combined with arterialization of the tied-off central portal vein.

Womack and his associates,[209, 210] but its general acceptance came from the brilliant studies of Warren, Zeppa, and Fomon,[211] published in 1967. The Warren-Zeppa-Fomon article was the first step toward the increasingly accepted objective[212] of decompressing esophagogastric varices without paying the penalty of hepatic portal flow deprivation.

COMPLETELY DIVERTING SHUNTS

End-to-Side Portacaval Shunt

The standard shunt against which all other shunts must be compared is the end-to-side portacaval shunt (see Fig 16,A). With this operation, complete portal diversion is achieved quickly, easily, and with very little blood loss; the portal diversion is the same as that achieved with a well-constructed Eck's fistula in animals. Because pressure in the splanchnic venous system is reduced, hemorrhage from esophageal varices is practically eliminated. This is the sole benefit from the operation, with the possible exception of relief of ascites.

The other effects of the operation are predictably adverse. The loss of liver perfusion with hepatopetal portal venous blood, in those patients still possessing such a flow, immediately puts the patient at potential risk of the portoprival (Eck fistula) syndrome. Undoubtedly, the resulting encephalopathy is mainly a

reflection of diminished hepatic function. In addition, Price,[213] Harrison,[214] and Rikkers[215] and their associates have reported that the low venous pressure in the splanchnic bed after portacaval shunt can contribute to increased absorption of metabolites, intestinal toxins, and probably ammonia. This "low-pressure" absorption factor was recognized by Warren et al. more than 15 years ago,[211] as well as recently,[212] as a possible ancillary mechanism for the high incidence of encephalopathy seen after construction of completely diverting end-to-side or side-to-side portacaval shunts.

Side-to-Side Portal-Systemic Shunts

The side-to-side shunts are constructed with portacaval, cavomesenteric (Marion-Clatworthy), mesocaval, or conventional splenorenal anastomoses (see Fig 16,B). These shunts were once thought to yield different results than the end-to-side shunts; it was assumed they did not completely eliminate portal perfusion. However, all effective side-to-side shunts are merely variants of a common theme, as shown in Figure 16,B: all of the blood returning from the distal splanchnic bed, as well as a variable amount from the sinusoids of the liver itself, can pass into the systemic venous circulation. The claim that hepatopetal portal blood flow is partly retained after such side-to-side procedures has been shown to be untrue if the shunts are of adequate size.[201, 208, 216–224] Thus, the complications of hepatic failure, including encephalopathy, after the various side-to-side shunts in controlled series have been as common as after end-to-side portacaval shunts.[191, 221, 225] The mesocaval H-graft operation of Drapanas[226] is no exception, and in addition, the prosthesis used in this procedure has had an exorbitant rate of late thrombosis.[227]

SELECTIVE PORTAL-SYSTEMIC SHUNTS

The direct and indirect messages of this monograph have concerned the special qualities of portal venous blood in the maintenance of liver health. Extrahepatic diversion of this blood with a portal-systemic anastomosis imposes such a drastic handicap on the liver that this kind of procedure should be used rarely and only for overwhelming reasons. Furthermore, total portal diversion is a desirable feature of a shunting procedure only if the objective is the "metabolic engineering" described in an earlier section.

If the objective is to prevent recurrent hemorrhage from esophageal varices in a patient who still has significant hepatopetal portal venous flow, the decision to construct a selective portal-systemic shunt should be beyond rational criticism. The selective diversion procedures that have been used clinically include the original Warren-Zeppa-Fomon distal splenorenal

shunt (see Fig 16,C, left side); an uncommonly performed modification also described by Warren et al.,[212] whereby the distal splenic vein is anastomosed to the inferior vena cava (see Fig 16,C, middle); and the direct anastomosis of the coronary vein (left gastric) to the inferior vena cava, described by Inokuchi et al.[228] (see Fig 16,C, right side).

The problems with using selective shunts in patients with residual hepatopetal flow have been practical rather than conceptual. Experience with the Warren shunt has shown this shunt to be technically more sophisticated and difficult to construct than the conventional portacaval shunt. It cannot be easily constructed under the urgent circumstances of acute variceal hemorrhage, it is probably contraindicated in the presence of severe ascites, and it requires anatomically specific conditions that should be defined with preoperative angiography.[212] Yet if it can be accomplished, the Warren procedure effectively decompresses esophageal varices while maintaining portal venous flow. As would be predicted, it is associated with a demonstrably better preservation of hepatic biosynthetic processes, such as urea production,[229] than is portacaval shunt and it carries a far lower incidence of hepatic encephalopathy.[200, 215, 222–224, 230, 231] The stakes are so high for patients who meet the candidacy criteria for a distal splenorenal shunt that it is difficult to justify consigning them by random lot to a conventional totally diverting shunt group for the purposes of a clinical study. The probability that the selective shunts are superior is *not* a null hypothesis.

Nevertheless, randomized trials comparing distal splenorenal versus totally diverting shunts have not revealed a striking divergence in the life survival curves.[200, 222–224, 230, 231] If this trend continues, a better quality of life (as opposed to mere survival) may prove to be the only justification for the selective shunts.

If selective shunt procedures fail to provide a better life survival than totally diverting portacaval shunts, the most fundamental reason undoubtedly will be that the patients under treatment have progressive hepatic diseases of such an immutable course that the effect of therapeutic intervention cannot be measured accurately against the background "noise" (roar might be a better word) of the disease itself. However, other factors might play a minor role in masking the superiority of selective shunts, including a higher perioperative mortality while surgeons learn how to carry out the Warren procedure.

Finally, in most patients, the preserved residual hepatopetal portal flow is gradually "stolen" from the liver as blood from the high-pressure mesenteric bed is recruited into the low-pressure area drained by the distal splenorenal shunt.[222, 232–234] As demonstrated by Maillard et al.,[232] the distal splenorenal shunt carries a high flow that is driven by the splenic arterial input. Undoubtedly this protects the splenorenal anastomosis from thrombosis, but it also gives the selective shunt circuit some of the features of a thirsty and larcenous arteriovenous fistula. However, the consequent loss of portal hepatic perfusion is so gradual after distal splenorenal shunt[222, 235] that there is time (months or years) for compensatory physiologic adjustments, including augmentation of the hepatic arterial input. If a high intestinal venous pressure is maintained throughout this time, the absorption of ammonia and other so-called cerebral toxins should be lower than after completely diverting portacaval shunt (see earlier discussion).[215, 235]

THE CONCEPT OF PORTAL ARTERIALIZATION

The possibility of replacing the lost portal flow with arterial blood, after a completely diverting portacaval anastomosis, has been examined in many experimental laboratories. Clinical trials with such procedures have been under way in one American center[236] and one European center.[237] Theoretically, such operations could have a minor beneficial effect. The hepatotrophic constituents that are diverted around the liver become available in diluted form via the arterial system and would be brought to the liver in direct relation to the quantity of hepatic flow. As discussed earlier, this is the explanation for the benefits of both the Child portacaval transposition and the portal arterialization procedures.

Nevertheless, it is important to emphasize the limitations of any benefit from such flow augmentation procedures. Marchioro et al.[39] showed that the atrophic changes in liver segments deprived of splanchnic venous inflow could not be prevented by arterializing the liver tissue, even though the arterialization procedures increased the flow to several times normal. Consistent with these observations were those of Pector et al.,[80, 81] who showed that the depressed activity of the mixed-function oxidase system could not be restored after portacaval shunt by portacaval transposition or by rearterialization of the portal vein stump.

Portal vein arterialization in experimental animals has had a specific risk. Cohn and Herrod[238] reported venous sclerosis as a consequence of the high pressure and flow. Efforts to prevent overperfusion by using very small inflow vessels or by damping flow with deliberate stenosis predictably increase the risk of thrombosis.

It is our opinion that portal arterialization procedures will have no effect whatever on either the morbidity or mortality after a completely diverting portal-systemic diversion in patients with portal hypertension.

SUMMARY

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

These structural and metabolic changes in the liver after portal diversion are caused by the diversion around the liver of the hepatotrophic substances in portal venous blood, of which endogenous insulin is the most important. In experimental animals, the injury of Eck's fistula can be prevented by infusing insulin into the tied-off hilar portal vein.

The subtle but far-reaching changes in hepatic function after portal diversion have made it possible to use this procedure in palliating three inborn errors of metabolism: glycogen storage disease, familial hypercholesterolemia, and α_1-antitrypsin deficiency. In these three diseases, the abnormalities caused by portal diversion have counteracted abnormalities in the patients that were caused by the inborn errors. In these diseases, amelioration of the inborn errors depends on the completeness of the portal diversion.

In contrast, total portal diversion to treat complications of portal hypertension is undesirable and always will degrade hepatic function if a significant amount of hepatopetal portal venous blood is taken from the liver. When total portal diversion is achieved (and this is to be expected after all conventional shunts), the incidence of hepatic failure and hepatic encephalopathy is increased. If portal diversion must be done for the control of variceal hemorrhage, a selective procedure such as the Warren procedure is theoretically superior to the completely diverting shunt. In practice, better patient survival has not been achieved after selective shunts than after conventional shunts, but the incidence of hepatic encephalopathy has been less.

ACKNOWLEDGMENTS

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COMMENT

"Impressive" is probably the word that most effectively describes this monograph by Dr. Starzl. The extensive bibliography weaves together a series of clinical observations and animal studies into a fabric whose design reflects the role of insulin as *the* hepatotrophic factor in maintaining normal liver function. When diverted by portal systemic shunting, insulin fails to reach the liver in sufficient quantity to prevent deterioration.

For years Dr. Starzl has been one of the most imaginative, innovative, and energetic investigators in academic surgery. In this monograph, he and his co-authors describe some of their ingenious and difficult experiments, experiments designed to clarify the role of pancreatic internal secretion in the portal vein and the support of hepatocellular growth and function. Studies by Marchioro when he was working in Dr. Starzl's laboratory[1] were carried out on an animal preparation that has been described as a split (or partial) transposition. The procedure created two liver segments, one of which was perfused with portal blood while the other was supplied with blood from the inferior vena cava; these and confirmatory studies by Price et al.,[2] Lee et al.,[3] and Chandler et al.[4] indicated that hypertrophy occurred in the liver tissue perfused with portal blood but atrophy occurred in the liver segment provided with systemic venous inflow. These studies unequivocally supported the induction that portal blood was an important factor in the maintenance of hepatic function. No one who accepted the basic concept of the "wisdom of the body" could doubt this or fail to welcome the scientific confirmation of intuition. Later studies by Starzl and co-workers[5, 6] on the effect of insulin versus glucagon and other substances on hepatocyte proliferation emphasized the important role of insulin in general hepatic function as well as in carbohydrate metabolism, although the two are so intertwined that distinction is difficult. Thus, one cannot escape the conclusion that insulin is an important factor, although Starzl does suggest that there is probably multifactorial control of hepatocyte integrity. If one considers the rich substrate of "building blocks" in portal venous blood for carbohydrate, protein, and fat metabolism, and the many endocrine factors involved, it is obviously difficult to accept the existence of a single "hepatotrophic factor."

The search for a hepatotrophic factor has been a symbolic Grail to any number of investigators in the area of regeneration of the liver following major resection. This remarkable phenomenon begins immediately after removal of 50%–60% of the liver with explosive DNA activity and proliferation of mitotic cell division, and full restoration of hepatic mass occurs before the process ceases as abruptly as it began. The single hepatotrophic factor after hepatic resection has been as elusive as a simplistic solution to the extensive and varied metabolic abnormalities which may occur, unpredictably, after portal-systemic shunting in man.

A major section of Starzl's monograph is tenuously but importantly related to his thesis on the hepatotrophic factor in portal blood. He describes in detail the effects of portal diversion on a series of inborn errors of metabolism, an area in which he has been a pioneer. This section of the monograph is concerned with the apparent benefits observed after end-to-side portacaval shunt in children with glycogen storage disease (GSD), familial hypercholesterolemia (FH), and α_1-antitrypsin deficiency. The effects of the operation were undeniable. Nevertheless, there remains an unanswered question about these patients, in whom portal diversion was carried out for rare metabolic disorders. Why was there little evidence of portal-systemic encephalopathy (one suggestive case) in these patients, and only equivocal evidence of hepatic deterioration?

At this point, we might review some of the more significant observations on liver and general metabolic function concerned with diversion of portal blood around the liver. Starzl has emphasized that the single observation to be garnered from Eck's[7] limited experiments is that in one animal, the operation was compatible with life. Like many other important studies, the first significant observations were made in the laboratory of Pavlov, where he and his associates first described the phenomenon of "meat intoxication" in laboratory animals in whom Eck's fistula had been constructed.[8] In the following decades a number of studies carried out in Europe and the United States suggested that many factors could be causative, without, however, substantiating any of them. Van Caulaert and colleagues[9] and Gabuzda and colleagues[10] suggested that hyperammonemia might be related to the disorders in cerebral metabolism but thought that hyperammonemia was more likely due to hepatocellular dysfunction in the cirrhotic patient than to the portaprival syndrome associated with diversion of portal blood.

During the decade following World War II, the era of portal-systemic shunting in man for protection against hemorrhage from esophagogastric varices began and developed rapidly, spurred on by the clinical work of Whipple,[11] Blakemore,[12] Linton,[13] Rousselot,[14] McDermott,[15] and many others. Although well over 100 shunting procedures were carried out over a 10-year period, there was no report or even a suggestion that the shunts were related in any way to hepatic dysfunction, encephalopathy, coma, or death; in general, these adverse effects were thought to be due to a progression of the basic hepatocellular disease. The concept of the portaprival syndrome had not yet been articulated.

In 1953, at a time when it was hoped that the extension of radical surgery might improve the cure rate of cancer, we carried out pancreaticoduodenectomies with resection of the portal vein and establishment of an anastomosis between the superior mesenteric vein and the inferior vena cava.[15] It was not long before the peculiar constellation of intermittent neurologic disorders that appeared after the initial operation was recognized and thought to be related to the shunt, and probably similar to those found by Pavlov many years before. Clinical and metabolic studies demonstrated that in fact the neurologic disorder was related to the ingestion of nitrogenous material (urea and ammonium salts), could be prevented by the use of some of the early intestinal antibiotics, and was associated temporally with rapidly changing ammonia levels in the peripheral blood.[16] Shortly after this, Hubbard, replicating this operation for cancer of the head of the pancreas, recognized the same phenomenon (referred to by Starzl as the McDermott-Hubbard artifact). This resulted in a confirmatory publication from Hubbard.[17] Thus, the stage was set for extensive laboratory and clinical investigations on the effects of portal-systemic shunting. In the laboratory, a series of investigations on dogs with Eck's fistula confirmed the existence of the "meat intoxication" syndrome.[18] Following these initial clinical and laboratory observations, a review of portal-systemic shunts[19] confirmed the existence of the syndrome of portal-systemic encephalopathy, as it was later named by Sherlock.[20]

A simplistic explanation would be that the ingestion of nitrogenous material with subsequent digestion and eventual formation of ammonia, amines, and amides by the action of colonic bacteria would result in toxic encephalopathy if these substances bypassed the interposed detoxification mechanisms in the liver. The complexities and interreactions of human metabolism, however, rarely permit simplistic explanations, and it soon became clear that if the normal liver was deprived of portal blood, a series of adverse effects on hepatocellular function took place, (such as has been so beautifully outlined by Dr. Starzl in his review), in addition to the reversible syndrome of portal-systemic encephalopathy related to introduction of nitrogenous materials into the intestines. At this point, no hepatotrophic factors had been identified, although it was clear that the portal blood, compared to systemic, arterial, or venous blood, was rich in substrate, and that deprivation of these substances might adversely affect the liver.

As one moves from the clinic to the laboratory and back again, it becomes apparent that it is difficult to replicate in the laboratory some of the problems and diseases one finds in man, and, conversely, that one cannot morally and ethically carry out effective and controlled studies in man when adverse effects can be anticipated.

Thus, recognition of the adverse effects of constructing a portal-systemic shunt in an organism with a normal liver prevented any further studies in man, and in the laboratory it was impossible to induce changes identical to those seen in cirrhosis in man.

Chance observations in man do appear, and even an anecdotal reference may be relevant. For example, Starzl suggested that, in the course of pancreaticoduodenectomy with resection of the portal vein, the reports of ourselves[16] and Hubbard[17] were invalidated because resection of a major portion of the pancreas would itself deprive the organism of insulin, a purported major hepatotrophic factor. This may be a valid comment, but it would have been impossible to repeat such an experiment in man were it not for a chance observation that is worth reporting in some detail. Linton, one of the pioneers in shunt surgery, carried out an exploratory laparotomy on a woman in her mid-30s who had recently developed esophagogastric varices with repeated massive hemorrhages; at operation and after dissection of the portal vein, he found that the lumen was completely occluded by a rather loosely attached clot, which he was able to remove completely. Having embarked on the procedure with the intention of carrying out a protective shunt, it was not surprising at that time, and with the limitations of knowledge regarding the portaprival syndrome, that he carried on with the planned procedure of an end-to-side portacaval shunt. After operation the young woman had a course identical to that described for pancreaticoduodenectomy patients, developed a progressive deterioration in hepatic function (although the liver was entirely normal at the time of operation), was completely intolerant of protein, and eventually died of a complex series of events which do not require detailed reporting for the purposes of this discussion. Thus, chance confirmed that the changes originally reported by us[16] would occur in a human being with a normal liver in whom a portal-systemic shunt with complete diversion was constructed, even when the pancreas was left intact.

Continued observation and studies from many sources seemed to present more paradoxes than solutions. Why did this syndrome, related to protein intolerance in the presence of diversion of portal flow, occur universally in normal laboratory animals but in only roughly 30% of patients in whom the shunt was constructed for portal hypertension secondary to cirrhosis? Why did patients with periportal fibrosis from schistosomiasis and in whom diverting shunts were constructed have almost uniformly disastrous results, compared with cirrhotics, even when their liver function was completely normal? On the other hand, why

did children with an extrahepatic block and in whom spleno-renal or mesocaval shunts were constructed appear to do well without these particular metabolic problems (although Voorhees[21] has raised the question that untoward results may occur later in life)? Out of these paradoxes, and with the results of further experimental studies, the concept began to evolve that deprivation of flow to the liver was as important in the disordered metabolic state as the effects secondary to the shunting of toxic metabolites around the protective mechanisms in the liver.

The simplest paradox relating to the extrahepatic portal bed blocks seemed to be answered by neither the flow theory nor the newly developing hepatotrophic concept, since in these patients sinusoidal pressure was normal, collateralization had developed in the gastrohepatic ligaments, and flow was maintained through the hepatic parenchyma, despite the protective decompression provided by shunt. This clearly differed from the effects of an intrahepatic presinusoidal block, as in schistosomiasis, where the obstruction exists in the terminal branches of the portal circulation and collateralization around the block cannot occur.

Why, then, did so many patients with cirrhosis of the liver and other disorders associated with a portal bed block or an outflow block from the liver do remarkably well despite the construction of an end-to-side portacaval shunt? Without minimizing the serious problems of hepatocellular dysfunction and recurrent encephalopathy that occur unpredictably in these patients, between 50% and 70% will have a stable and satisfactory course for extended periods of time; absolute purity in clinical studies is almost impossible, particularly in this patient group, which includes alcoholics, so prone to recidivism. Any tentative answers are further clouded by the known inexorable progression of posthepatitic cirrhosis and the innumerable other problems related to the disease but not necessarily to the shunt.

Although Starzl emphasizes the role of hepatotrophic factors and deemphasizes the importance of flow, the observations of Child et al.[22] in 1953 are inescapable in that portacaval transposition *did* protect against the atrophy associated with shunting. Regeneration following resection proceeded well in these animals, in contrast to the Eck fistula dogs. Studies have been carried out on similar transposition preparations in our own laboratory.[23] In brief summary, one might say that the animals with portacaval transposition were strikingly different from the animals with Eck's fistula and remarkably like normal animals under the same laboratory conditions, although there were relatively minor disorders in a number of biochemical, metabolic, and microscopic parameters. Certainly the animals with portacaval transposition did not show the progressive liver atrophy, malnutrition, deterioration of liver function, recurrent encepha-

lopathy, protein intolerance, and death which made up the characteristic course of dogs with Eck's fistula. Thus, while portal flow may be and probably is ideal for the maximum maintenance of the mammalian liver, it is quite clear that in the laboratory at least, maintenance of systemic venous flow does protect against most of the adverse effects of portal-systemic shunting in the normal mammal. Ultimately we may be able to identify the group of patients who will show the portaprival state and recurrent encephalopathy after portal diversion and thus exclude from consideration for portal-system shunting those individuals who would predictably do poorly. There are other patients, however, who, for whatever hemodynamic or metabolic reasons, continue to do well after portal diversion and could be offered the protection of portal decompression. The selective shunt described by Warren and his colleagues[24-26] may well be an improvement on previous types of total shunts but also has some recognized and some potential problems.

This is not the place for an extended clinical discussion or analysis of pharmacologic, radiologic, or endoscopic methods of control of bleeding varices, but at the moment, none of these seems to provide the ideal solution we have all been seeking. To date, neither complex experimental preparations, nor sophisticated biochemical and metabolic techniques, nor the introduction or reintroduction of a variety of clinical therapeutic approaches have yet led to a solution which is simple, obvious, and correct.

WILLIAM V. McDERMOTT, JR., M.D.
DAVID W. & DAVID CHEEVER PROFESSOR OF SURGERY
HARVARD MEDICAL SCHOOL
BOSTON, MASSACHUSETTS

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SELF-ASSESSMENT ANSWERS

1. *d*	6. *False*
2. *False*	7. *True*
3. *d*	8. *False*
4. *c*	9. *False*
5. *a, b, c & d*	10. *False*