# Chapter 7

# Hepatotrophic Substances

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BLOOD returning from the nonhepatic splanchnic organs via the portal venous system can specifically influence the morphologic features, regenerative capacity, and function of the liver. The portal blood constituents responsible for these effects have collectively been termed portal hepatotrophic factors. Much of the in vivo evidence about portal hepatotrophic factors has been obtained by seeing what happens to the liver when it is deprived of all or part of the portal venous return, by surgically removing nonhepatic splanchnic viscera, or by infusing hormones or other substances systemically or directly into the liver circulation.

In this review, the effects of hepatotrophic substances upon hepatocytic structure and function are treated separately from their influence upon the regeneration that follows partial hepatectomy. The failure to make this distinction has probably been responsible for many of the controversies about new developments in portal hepatotrophic physiology. This was clear in the discussions of a symposium on this subject held in May 1977.[1]

## HEPATOTROPHIC EFFECTS EXCLUDING REGENERATION

The most easily achieved portaprival state occurs when all the splanchnic venous return is diverted around the liver via an anastomosis to the vena cava, leaving the liver with only an arterial supply. This procedure of portacaval shunt is also called Eck's fistula, after the Russian military surgeon who described it in dogs more than 100 years ago.[2] Based on the short-term survival of one of his eight dogs, Eck thought that a completely diverting portacaval shunt in dogs was compatible with prolonged good health. In 1893, however, Hahn, Massen, Nencki, and Pavlov[3] showed that dogs with Eck's fistula developed anorexia, weight loss, hepatic atrophy, and encephalopathy.

The atrophy of hepatocytes caused by Eck's fistula, as well as other

structural changes, occurs with great rapidity, being 90% complete within 4 days.[1-6] Ultrastructurally, the most striking and specific changes are depletion and disruption of the rough endoplasmic reticulum and reduction in the membrane-bound ribosomes. The same general light- and electron-microscopic changes occur after portal diversion in the livers of rats, dogs, swine, baboons, and man, with some variations in degree.[7] Thus the hepatic injury of Eck's fistula is common to all species studied.

What is the explanation of the changes caused by portacaval shunt? When Bollman[8] summarized the situation of Eck's fistula in 1961, the flow hypothesis was widely accepted. It stated that Eck's fistula syndrome was caused by a suboptimal volume as opposed to quality of hepatic blood flow. This conclusion was apparently incontrovertibly supported by experiments in which the portal flow lost after portacaval shunt was replaced with vena caval and arterial blood, respectively.[9,10] With this portal blood replacement, most of the adverse effects of Eck's fistula in dogs were avoided. Thus, portal blood seemed to possess no physiologically important special qualities.

The fallacy of the flow hypothesis became evident during efforts to define the necessary conditions for successful auxiliary liver transplantation.[11] With two livers present, the organ given blood returning from the nonhepatic splanchnic organs remained healthy, whereas the liver deprived of such nourishment atrophied in spite of adequate portal flow from nonsplanchnic sources.[12] Apparently, the liver with first access to the splanchnic venous blood was extracting something efficiently enough so that the second organ suffered from its absence.

The transplant preparations that had made the foregoing physiologic effect apparent had a flaw that prevented complete acceptance of what had become known as the hepatotrophic concept. There was a potential inequality of the two organs in that the homograft was under immunologic attack despite host immunosuppression, whereas the animal's own liver was not. Consequently, other experiments were designed.

At first, a split or partial transposition was developed that, in effect, divided the dog's own liver into two fragments.[13,14] With this operation, splanchnic venous blood was provided for one portal branch of the liver, whereas the other portal branch was detached and supplied with blood from the inferior vena cava. The quantity of flow was measured in many of these experiments[13,14] and found to be generally greater on the side perfused by vena caval blood. The lobes supplied with systemic venous blood atrophied grossly and histopathologically, whereas the lobes given normal portal blood hypertrophied.

The two sides had other easily quantifiable differences. The splanchnic-fed lobes had more glycogen and glucokinase activity and lower concentrations of cyclic AMP and active phosphorylase. The biochemical dissociation was shown in many other ways[15] that are beyond the scope of this review, but the reasonable inference was that these two liver sides were living in different metabolic worlds in which hormone control played a dominant role. 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 greatly reduced. although not eliminated, by either total pancreatectomy or alloxan diabetes.[16,17] While emphasizing the role of insulin, these investigations 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.

Eventually, another kind of double liver fragment model provided much more decisive information.[15,17,18] In these experiments, one portion of the liver was fed by the effluent of hormone-rich blood returning from the pancreas. duodenum, stomach, and spleen, while the opposite lobes were perfused via a venous graft with nutrition-rich blood returning from the intestine (Fig. 1A).

The histopathologic results in 60-day experiments or even as early as 4 days were dramatic. The lobules in liver lobes receiving pancreaticoduodenal venous effluent became bigger and crammed with glycogen in contrast to the shrunken deglycogenated lobules in lobes receiving intestinal venous return.
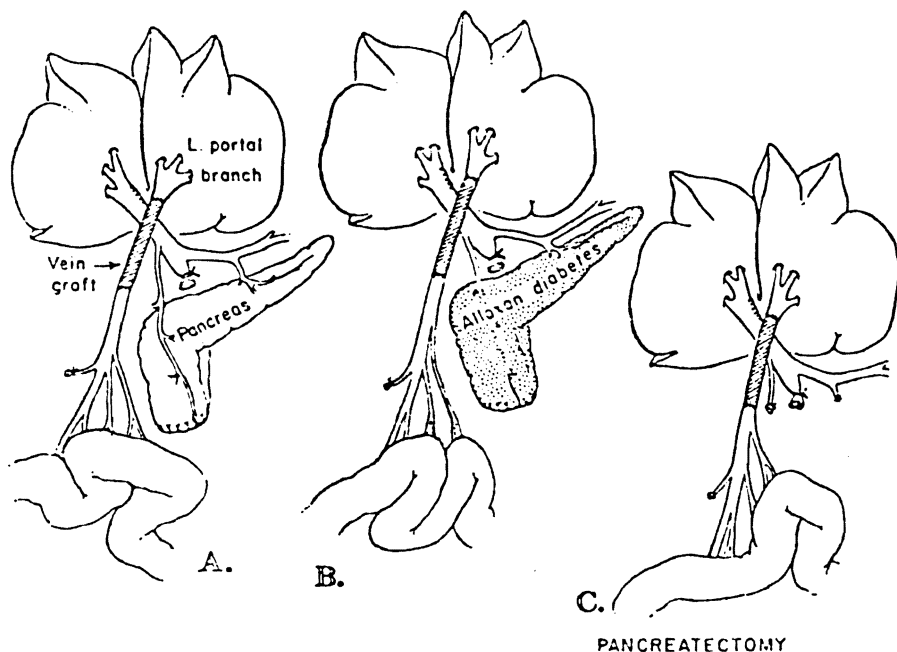


### Splanchnic division

FIG. 1—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. In other experiments. the intestinal blood was directed into the right lobes with pancreatic flow to the left side. (A) Nondiabetic dogs. (B) Alloxan-induced diabetic dogs. (C) Dogs with total pancreatectomy. (By permission of Surgery, Gynecology, and Obstetrics 140:549–562, 1975.)

An accurate way to quantitate hepatocytic size was developed for such experiments.[15] With light-microscopic tracing. hepatocytes were drawn on a standard thickness paper and weighed. The weights were called size units. In Figure 2, the right lobar hepatocytes, which had pancreatic input, had an obvious advantage as compared to those on the left, which were fed with intestinal venous return. The cell size data could then be summarized in graphs or tables.

In splanchnic division experiments (Fig. 1). the previously mentioned possibility that insulin was the major cause for the kind of cell size difference seen in Figure 2 was strengthened by additional 60-day experiments in which alloxan diabetes (Fig. 1B) and pancreatectomy (Fig. 1C) were superimposed.[16,17] The animals were treated daily with subcutaneous insulin, which presumably was delivered to both sides of the liver without preference. The size advantages for the right-sided hepatocytes were cancelled about equally in the animals subjected to alloxan diabetes or pancreatectomy. In all such experiments, the nearly equal effects of alloxan poisoning and pancreatectomy have tended to minimize any major role of glucagon as a hepatotrophic factor, at least as far as cell size was concerned.

At the same time. these experiments emphasized that insulin was not the only factor. When endogenous insulin was removed from the splanchnic division experiments in which subcutaneous exogenous insulin was given, the dominant hepatic tissue became that supplied by intestinal venous return. Translating these findings into more practical terms, the most favorable condition for portal perfusion was with splanchnic venous blood that contained normal amounts of endogenous insulin. The least favorable condition was perfusion with systemic venous blood. Intermediate in quality was splanchnic
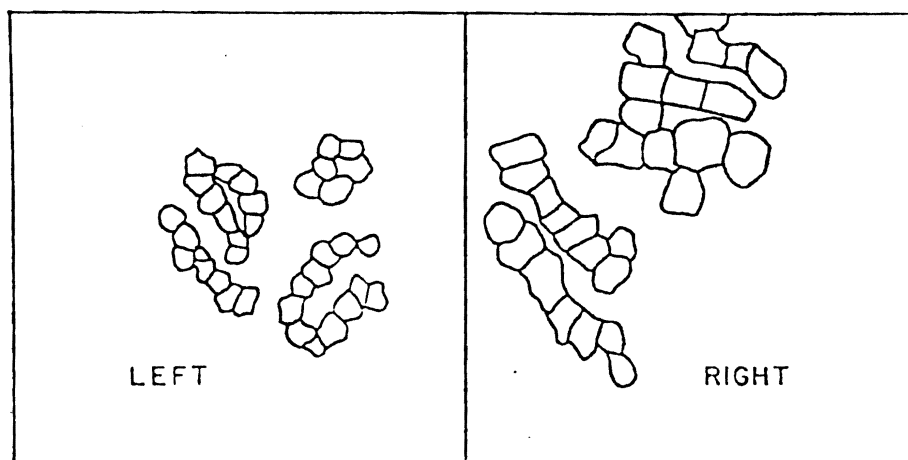


FIG. 2—Hepatocyte shadows traced during histopathologic examination. These were later cut out on standard paper and weighed as an index of hepatocyte size. The right lobes with the large hepatic cells received venous blood from the pancreas, stomach, duodenum, and spleen. The relatively shrunken left lobes with the small hepatocytes received intestinal blood. (By permission of Surgery, Gynecology, and Obstetrics 137:179-199, 1973.)

E 1.—*Number of Labeled Hepatocytes per 1,000 Hepatocytes in Livers of Normal Dogs and Dogs with Splanchnic Division*

| Type Dog | Number of Experiments | Right Lobes Mean SD | Left Lobes Mean SD |
|---|---|---|---|
| l | 11 | 1.6 ± 0.5 | 1.5 ± 0.4 |
| hnic division (nondiabetic) | 6 | 17.3 ± 3.8 | 4.0 ± 1.0 |
| hnic division (alloxan) | 4 | 4.9 ± 0.4 | 17.8 ± 3.6 |
| hnic division (pancreatectomy) | 5 | 5.1 ± 1.0 | 17.5 ± 3.9 |

s blood that was deficient in endogenous insulin but rich in other as yet
wn elements.
insulin effect on cell proliferation was also convincingly unmasked by
ided liver experiments[16,17] (Table 1). The liver lobes receiving pancreatic
(the right lobes in the experiments shown, Table 1) of nondiabetic dogs
tted to splanchnic division had autoradiographic evidence of hepatocyte
lasia relative to the lobes receiving intestinal blood, although both sides
eater cell renewal than normal after 60 days. This right lobar dominance
iminated, being transferred to the left side by either alloxan or pancrea-
iy diabetes in those animals being treated with subcutaneous regular
. The emergence of dominant left lobes (Table 1) after the elimination
ogenous insulin indicated, as previously emphasized from other lines of
ce, the presence of potent but unknown additional intestinal portal fac-

full implications of portal blood deprivation on liver function are not
i, since whatever changes occur in the portaprival state are undoubtedly
Liver function after Eck's fistula, or after the better tolerated portacaval
osition of Child, was long thought to be essentially normal, the main
ncy being inefficient clearance of ammonia.[19,20] With the striking orga-
hanges described earlier after portal blood deprivation, however, the
are apt to be wide ranging. An example is the striking antilipidemic
of portacaval shunt in dogs,[16,21-24] rats,[25,26] baboons,[7-15] pigs,[27,28] and
[30] The consequent falls in cholesterol phospholipids and possibly tri-
des may be due in part to reduced hepatic lipid synthesis.[16,25,27,28,31,32]
effect of portal factors upon hepatic lipid synthesis has been demon-
in the same splanchnic division models shown in Figure 1, after 60
Lipid synthesis in normal unaltered dogs measured either with in vitro
ivo techniques was the same on both sides of the liver (Fig. 3). After
nic division in nondiabetic animals, the liver perfused with blood from
creas and upper splanchnic organs synthesized more cholesterol than
er liver portion perfused with venous return from the intestine. This
ige in cholesterol synthesis was reversed with alloxan diabetes and total
tectomy. As before, these results (Fig. 3) indicated the dependence of
cholesterol synthesis upon the pancreas, but the reversal effect dem-
d a major contribution by nonpancreatic venous blood as well. The
nclusions were reached in other experiments in which hepatic choles-
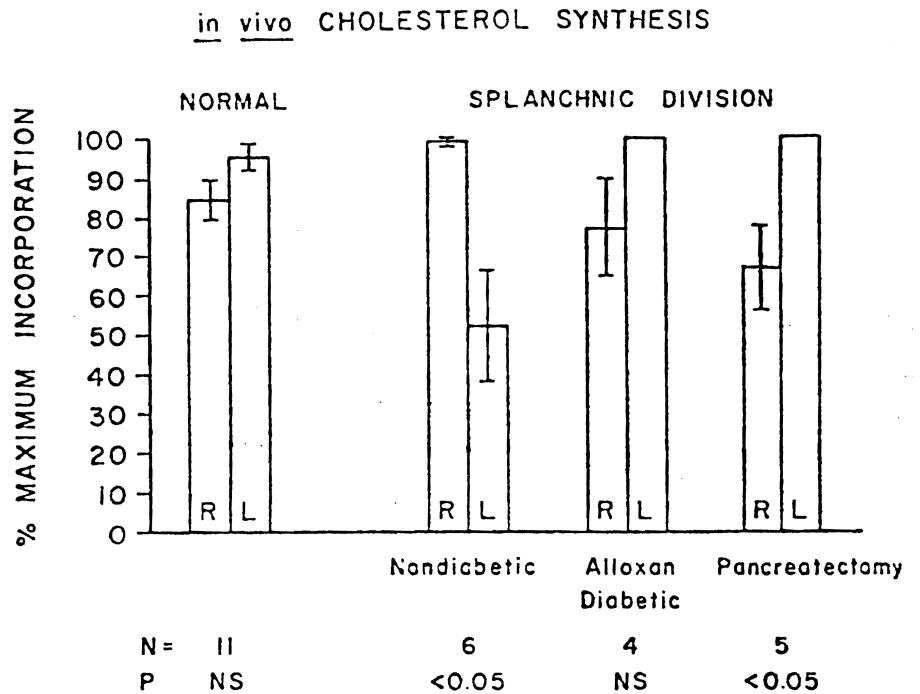
## in vivo CHOLESTEROL SYNTHESIS



FIG. 3—In vivo cholesterol synthesis in the right and left liver lobes in normal dogs and in dogs submitted to splanchnic division. In all the splanchnic division experiments, the right lobes received pancreaticogastroduodenosplenic blood, while the left lobes were nourished with intestinal venous blood. The animals with splanchnic division were nondiabetic, alloxan-diabetic, or diabetic as the result of total pancreatectomy. The $p$ values compare the synthesis rates for the two sides, the greater rate of synthesis being assigned a value of 100%. For the other side, a proportionately lower percentage was calculated. (By permission of Surgery, Gynecololgy, and Obstetrics 140:381–396. 1975.)

terol synthesis was measured after stepwise portacaval shunt in which intestinal flow was diverted at a first stage followed by secondary diversion of the pancreaticogastroduodenosplenic blood.[15]

We now return from the double liver fragment models full cycle to Eck's fistula. If insulin was a vital portal hepatotrophic factor, the reason for its unmasking by the double liver fragment experiments became understandable. The well-known efficiency of insulin's removal during a first pass through hepatic tissue[33] made the insulin relatively unavailable for a second liver or liver fragment. At the same time the protection afforded after portal diversion by flow augmentation procedures such as Child's portacaval transposition[9] or Fisher's portal arterialization[10] was explained. If insulin and other hepatotrophic substances were bypassed around a single liver, they would be returned to it in diluted form in direct relation to the total hepatic blood flow that these procedures increased.

If the secrets of Eck's fistula were explained mainly by depriving the liver of direct access to endogenous insulin, the experiment shown in Figure 4 should be a direct test of that hypothesis. Nonhypoglycemic infusions of insulin
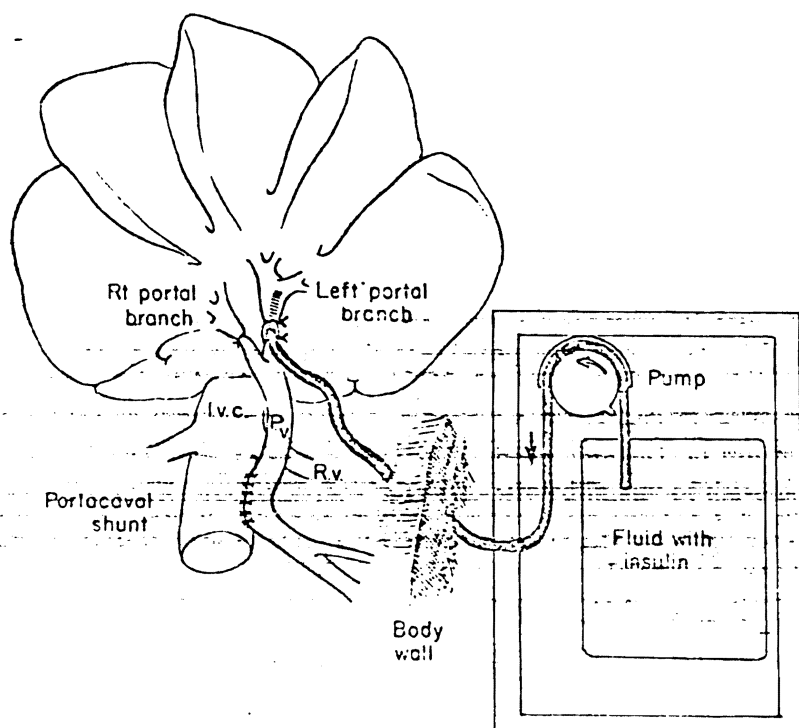
FIG. 4—Experiments in which Eck's fistula is performed and postoperative infusions are made into the left portal vein. (By permission of the Lancet 1:821-825, 1976.)

and other substances were made for 4 days into the ligated left portal vein after Eck's fistula.[5,6] The experiment was designed to evaluate any direct protective effect 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 acute atrophy that otherwise halved the size of the cells, and it preserved hepatocytic 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 either small or large doses had no effect.[5,6]

The effect of insulin on hepatocytic proliferation was also striking. After Eck's fistula, the mitotic rate was already increased to about three times normal (from 1.6 to 4.8 per 1000 cells). 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.[5,6]

Thus, relative "hepatic insulinopenia" was established as the most important element in the liver injury of Eck's fistula. It would be regrettable if the very clarity with which insulin has emerged as a principal portal hepatotrophic substance were to obscure the search for contributory factors. The observation that the insulin protection in our infusion experiments was not complete was interpreted as a reflection of missing ancillary substances. The same multifac-

torial theme has been consistent in all work from our laboratory on the hepatotrophic subject. However, the fact that the multifactorial control of hepatocytic integrity has not deemphasized the central role of insulin in maintaining liver cells was recently redemonstrated after removal of all the nonhepatic splanchnic viscera including the pancreas.[34] The intraportal infusion of insulin alone prevented most of the atrophy and other structural deterioration of hepatocytes. and it preserved the rate of spontaneous liver cell renewal which was otherwise depressed. The hepatic protection in eviscerated animals was almost identical to that observed with intraportal insulin therapy after portacaval shunt described above and was indistinguishable from the hepatotrophic effect of insulin in diabetic rats.[35] In hepatocyte tissue culture systems, many investigators have described analogous insulin effects.[36-39] The role of insulin in maintaining hepatocytic mitochondrial metabolism has also been emphasized.[40-41] No potentiating effect of glucagon has been demonstrated in any of these nonregeneration models.

## PORTAL BLOOD FACTORS AND REGENERATION

From the information in the foregoing section. portal blood factors are indisputably important in maintaining healthy liver cells. The assumption was a natural one that portal blood might have a specific effect on the hepatic regeneration that follows partial hepatectomy. This possibility was purely speculative, however, since hepatectomies were not performed in any of our early studies. However, a portal blood effect on regeneration after liver resection in rats was soon demonstrated.[42-44]

The nature of the regeneration-promoting substances and their origin remain in dispute. An additional question is whether they initiate regeneration or merely permit the process to proceed and, in either case, by what means. The conflicting conclusions reached in various laboratories on these issues result in part from the use of different experimental models and in part from the way in which data have been interpreted or the time after hepatectomy when the data have been acquired.

Much information about the origin of regeneration-promoting (or permitting) factors has come from evisceration procedures introduced in dogs[45] in conjunction with partial hepatectomy and adapted for rats.[46] An artifact existed in this early work in that exogenous insulin was incidentally administered as part of the postoperative parenteral fluid therapy. Later studies showed a striking depression and delay of regeneration after complete evisceration that could be restored toward or even to normal by treatment with a combination of insulin and glucagon in high doses.[47-49]

The crucial splanchnic factors did not seem to be from the intestine. Although an obtunded regeneration response was found after intestinal resection.[50] this could not be confirmed.[51,52] By contrast. an almost complete absence of liver regeneration after total pancreatectomy in rats and dogs was reported.[51,53,54] and this could be restored to normal by treatment with insulin and glucagon.[54] The crucial splanchnic organ for hepatic regeneration was con-

pancreas. and insulin and glucagon were the most critical
creatic role. while the other nonhepatic splanchnic organs
portance.[34]
this was an excessively simplified view was available from
ently confirmed.[?] that liver resection in diabetic rats is fol-
s regeneration. Our own investigations with split liver prep-
us hepatectomy in diabetic and nondiabetic dogs emphasized
pancreatic blood in supporting regeneration. but they also
t similar qualities in nonpancreatic splanchnic blood.[+] Al-
vere not so interpreted by them. Broelsch et al. demonstrated
nsplantation experiments that venous effluent from the je-
duodenum supported hepatic regeneration. albeit less well
he pancreas.[57]
recent study have again demonstrated the complexity of
ation by portal hepatotrophic factors and have strengthened
actorial hypothesis by clearly differentiating pancreatic in-
e originating in the rest of the intra-abdominal gastrointes-
se investigations. the removal of all the nonhepatic splanch-
ed in severe inhibition of DNA synthesis and essentially
on of the histopathologic expression of liver regeneration.
colon in place did not significantly improve the eviscerated
to hepatic resection. as measured with autoradiography.
at plasma pancreaticlike glucagon was thereby kept at a
centration. Nor did the infusion of exogenous glucagon.
n and insulin in combination into the portal vein have a
effect upon regeneration.

prior removal of the pancreas alone reduced but did not
se to 44% hepatectomy. The response to 72% hepatic re-
se dampened by pancreatectomy. Most importantly. extir-
of the nonhepatic splanchnic viscera. while preserving the
the response to hepatic resection even more than did pan-
. Thus, removal of the pancreas and other viscera had a
n regeneration.
t[59] and more recently Leffert and Koch[60] have similarly
ion as a complex series of events under multifactorial con-
ay an important regulatory role. precise delineation of their
e difficult with any of the presently available experimental
mone-free environment is hard to achieve in intact animals.
Small amounts of hormones could have major physiologic
egenerating hepatocytes may have changing sensitivity to
gon.[61-63] The same probably applies to other hormones.

## Portal Factors Initiate Regeneration?

tions conceivably could be responsible for growth initiation
' After partial hepatectomy in rats or dogs. well-ordered
cur in liver cyclic AMP and adenyl cyclase prior to and

during regeneration.[63,65-67] The various nonhepatic splanchnic evisceration (pancreatectomy, extirpation of all organs except the pancreas, total evisceration) which resulted in retarded regeneration caused severe pertubations i these hormonally controlled "messenger" components.[63] Whether these deviations have a cause-and-effect relation to the defective regeneration that wa observed or are merely coincidental remains speculative.

The potential link between multiple hormone changes and regeneration i strengthened by the intriguing studies of MacManus et al.,[63] who had prev ously shown with cultured thymus cells that increases in cyclic AMP level induced with epinephrine, parathormone, prostaglandins, and calcium imme diately preceded the initiation of DNA synthesis and active cell proliferation. The same early biphasic rises in cyclic AMP occur in rat livers 2½ and 12 h after partial hepatectomy with a return toward normal as DNA synthesis be gan.[65] These findings have been confirmed in rats,[65,67] and similar but less wel defined changes have been noted in regenerating dog livers.[63] In addition. increased cyclic-AMP-dependent protein kinases correlated perfectly in regen erating rat livers with the induction of ornithine decarboxylase.[67]

Ornithine decarboxylase has been implicated[68-70] as the rate-limiting enzyme in the polyamine biosynthetic pathways active in regeneration. Intravenou solutions containing triiodothyronine, amino acids, glucagon, and heparin in duced nuclear DNA formation and mitosis in the whole livers of unoperated nondiabetic rats,[71] and enhanced ornithine decarboxylase activity followed treatment with this solution.[72] Glucagon in this stimulatory solution could be completely replaced with a butyryl derivative of cyclic AMP, leading to the conclusion that cyclic nucleotide plays a critical role in the induction of hepatic DNA synthesis and cell mitosis.[73]

## Do Nonportal Factors Initiate Regeneration?

While portal blood factors clearly influence regeneration, they may not initiate this process but merely play a permissive role. The actual genesis of regeneration may have a quite different explanation and could even start in the liver itself. This possibility has not been fully explored, even though the literature is replete with reports compatible with such a hypothesis.

Publications between 1931 and 1953 suggested that liver mitosis could be stimulated in intact experimental animals by homologous liver mash injected intraperitoneally[74-76] or by intravenous injections of liver fractions.[77] McJunkin and Breuhaus were the first to demonstrate increased mitosis in a model using the already regenerating partially hepatectomized liver of the rat.[74] However, the first truly convincing evidence of a liver-specific mitotic stimulator was that a single administration of liver mash prepared from weanling rat livers and given intraperitoneally to adult rats caused hepatocyte proliferation that was maximum at 48 hr.[78,79] Although adult liver mash was not stimulatory, striking stimulatory activity was found when the regenerating remnant of an adult rat liver, 48 hr after partial hepatectomy, was used to prepare the liver mash.[79] Even after a year of twice-weekly injections, regenerating adult liver mash still had a hepatic mitotic stimulatory effect. Furthermore, in these chronically

treated rats, intra-abdominal tumors developed at a 67% rate, presumably because of the specific stimulus to proliferation. Only one of these tumors was a liver tumor, however, while the majority were intraperitoneal reticular sarcomas. Rats chronically treated with nonregenerating adult liver mash did not develop intra-abdominal tumors.[79]

The concept of a stimulatory substance originating in the regenerating liver itself lay dormant until 1971.[80,81] Then in 1975, a regenerative stimulator substance was demonstrated in the supernatant after high-speed centrifugation of an extract of rat liver mash. This regenerative stimulator substance was present in very young rat livers but only appeared after partial hepatectomy in adult livers. The extract from intact adult rat livers actually inhibited regeneration in the assay system used (34% hepatectomized rats).[82]

Meanwhile, evidence was accumulating that there was a circulating plasma or serum stimulatory factor in animals with regenerating livers. The relevant experiments were diverse and ingenious. Regenerative activity was increased in the intact liver of the unresected partner of a pair of parabiotic rats after partial hepatectomy in the parabiotic twin.[83] Although confirmed by some,[84,85] the concept remained in dispute until clarified by the more efficient cross-circulation experiments.[86-88] As total hepatectomy in one rat stimulated significant DNA synthesis in the cross-circulated partner with an intact liver, the source of the humoral factor was postulated not to be in the resected liver remnant,[88] but the rationale of this contention has subsequently been challenged.[80]

Although suggested earlier,[89] the stimulatory effect of serum from animals with a regenerating liver was first convincingly demonstrated in a cell culture system in 1952.[90] This finding has been confirmed and extended.[91-93] Serum or plasma also increased mitotic activity in vivo,[94-98] while hepatocytes proliferated in normal rats subjected to multiple exchange transfusions with blood from partially hepatectomized rats.[99] Finally, mitotic activity was increased in small liver autografts in partially hepatectomized animals.[100-103] The stimulating substance in the serum of rats with regenerating livers was characterized as a heat-stable protein of low molecular weight (approximating 26,000).[104]

The first convincing suggestion that such humoral factors came from the liver itself was made by Blomqvist.[79] Fisher, however, based on the experiments already discussed, did not favor this concept.[88] Then Levi and Zeppa[80,81] appeared to establish the link between the serum-stimulating factors and the liver by direct investigation with an isolated perfused rat liver system. They demonstrated increased DNA synthesis in normal livers perfused for 1 hr (after a 20-min stabilization period), using the effluent of a regenerating rat liver that had been subjected to a 70% partial hepatectomy 18 or 24 hr previously and testing this by either direct cross-circulation or perfusion of the normal liver with reconstituted effluent. Nonregenerating intact rat livers caused no increase in DNA synthesis in this system.[80] They subsequently showed that the cells synthesizing new DNA were mostly hepatic parenchymal cells situated predominantly in the peripheral region.[81] Unfortunately, this work could not be confirmed in carefully conducted studies.[105-106] The major objection was the

short time (1 hr) of exposure of the normal liver to the partially hepatectomized liver effluent. Attention has once again been directed to a liver source for the humoral factors, however,[2] and, if confirmed, would strongly support a liver-plasma physiologic axis that is important in liver regeneration.

By contrast, an inhibitor of liver regeneration remains an intriguing and controversial question despite investigation over the past half century. The controversy is highlighted in a number of excellent reviews.[107-110] Both serum and liver extract from intact adult rats have been shown to inhibit regeneration in the already regenerating liver,[2,95,110] while this inhibitor disappears within 2 hr of partial hepatectomy and is, in fact, replaced by a stimulatory substance.[82]

At this time, the true role of portal blood or liver factors in initiating or potentiating or in stimulating or inhibiting liver regeneration remains to be fully elucidated.

## CLINICAL IMPLICATIONS

Decisions in patients for or against portacaval shunt, as well as the type of shunt, should take into consideration the hepatotrophic concept. If hepatopetal flow is still present in the portal vein, the Warren-Zeppa shunt[111] preserves this flow while at the same time decompressing esophageal varices. The long-term results of controlled trials of this ingenious procedure are awaited with interest. If portacaval shunting does not prove to be of benefit in cirrhotic patients with bleeding esophageal varices,[112] the evaluation of nonshunt procedures will assume increasing importance.[113]

We believe that preservation of portal flow is a vital concern in patients with liver disease. However, the fact that man is resistant to the more serious metabolic consequences of Eck's fistula[*] has made it feasible to perform the procedure with benefit in patients suffering from glycogen storage disease. These patients have had correction of a number of preexisting metabolic abnormalities, as well as amazing growth spurts.[29,114,115] Continuous feeding may be an even better way of treating these children or at least is an ancillary measure that can be used with shunting.[116]

Lately, our greatest interest in portal diversion has been in homozygous type II hyperlipidemia,[29,30] a disorder that leads to lethal cardiovascular complications by adolescence. More than 20 patients throughout the world (3 in our personal experience) have had their serum lipids lowered by portacaval shunt. Only two outright failures of response have been recorded, and in both (one from Europe and one from South Africa) the shunts had clotted. The serum cholesterol concentration in our original case fell from 800 mg/dl to nearly normal, probably as a result, at least in part, of reduced hepatic cholesterol synthesis, as mentioned earlier. The falls in serum cholesterol in our patients 2 and 3 were also dramatic, the range of reduction being 40% to 60%. The unsightly xanthomas in the skin and tendons melted away with time. Relief of angina in some of these patients and diminution of aortic stenosis in others have suggested that resorption of the same material is occurring from the damaged vascular system.

hic concept has suggested new lines of inquiry in a more
the pathogenesis and/or treatment of several human disease
ng a variety of liver disorders and even diabetes mellitus. for
us insulin therapy may be the right drug by an inappropriate

o-workers,[117] in Volume IV of this series. pointed out that
iver to regenerate in the setting of fulminant hepatic failure
hasized in the past. In their view the available methods of
ot influence mortality unless sufficient regeneration occurred
could be stimulated therapeutically. As no major break-
made in the management of fulminant hepatic failure, the
with a better understanding of the controlling mechanisms
itiators and potentiators), methods of stimulating regenera-
nts will become available. Possible therapeutic modalities
herapy, as suggested in the past.[17] Whether the answer will
mixtures[71,73] or in pharmacologic doses of insulin and glu-
d by the study in mice with murine hepatitis,[118] still remains
natively. future therapy may well be with as yet unidentified
eration, which might even originate from the damaged or
itself.

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