

## SYMPOSIUM ON PORTAL HEPATOTROPHIC FACTORS

At the 24th annual meeting of the American Association for the Study of Liver Diseases on November 1, 1973, the Roche Symposium on Portal Hepatotrophic Factors was presented. The participants of this symposium and their presentations were as follows:

Development of the Hepatotrophic Concept: a Century of Controversy. Thomas E. Starzl (Denver, Colorado).

The Hepatotrophic Concept from a Biochemist's Point of View. Hans A. Krebs (Oxford, England).

The Identification of Hepatotrophic Substances by Tissue Culture Techniques. Rudi Schmid and D. Montgomery Bissell (San Francisco, California).

The Hepatotrophic Substance and Liver Regeneration. Nancy L. R. Bucher (Boston, Massachusetts).

Clinical Ramifications with Particular Reference to Portacaval Shunting, Glycogen Storage Disease, and Idiopathic Familial Hyperlipoproteinemia. Charles W. Putnam (Denver, Colorado).

Glucagon as a Modifier of Hepatic Regeneration in the Rat. J. B. Price, Jr., A. Whittemore, M. Kasuya, P. Fodor, and A. B. Voorhees, Jr. (New York, New York).

Induction of Premature Structural Differentiation of Fetal Hepatocytes by Glucagon. H. F. Chiu and M. J. Phillips (Toronto, Canada).

Implications in Hepatology. Hans Popper (New York, New York).

The symposium was concerned with an old controversy in light of new, recently accumulated information. The subjects discussed dealt with the effects of substances in portal venous blood on liver morphology, function, and regenerative activity.

Until the last few years, there was no agreement at all that venous blood returning from the various splanchnic organs contributed anything specific to the welfare of the liver. Convincing evidence that this was true was first provided by experiments with auxiliary hepatic transplantation in which one of two coexisting livers was given splanchnic venous blood, whereas the other organ was revascularized with an equal or greater volume of portal inflow from nonsplanchnic sources. The liver cells nourished by splanchnic blood underwent hypertrophy, glycogen accumulation, and hyperplasia relative to the liver cells which were denied this kind of portal perfusion. The same kinds of observations of the importance of splanchnic venous blood have been made in a variety of other experiments, including many not involving transplantation.

What is the nature of these so-called hepatotrophic effects? Tentative answers have come from experiments which divided the splanchnic blood into two components—one derived from the upper intestinal organs (pancreas, spleen, stomach, and duodenum) and the other derived from the rest of the small intestine and the colon. With this kind of splanchnic division, the liver fragment receiving the hormone-rich effluent from the upper abdominal organs flourished, whereas the liver fragment given the nutrient-rich intestinal blood underwent atrophy and deglycogenation. Studies of cyclic adenosine monophosphate, glucokinase, phosphorylase, and other enzymes in the hepatic tissues provided further circumstantial evidence that an *interaction* of pancreatic hormones (particularly insulin and glucagon) was a crucial aspect of the hepatotrophic effect. Indeed, the analysis of Krebs underscored the naivete of ascribing the hepatotrophic

effects to any single hormone as opposed to the *interrelationships* of hormones and probably other factors as well, including nutrients. It was pointed out by Krebs that some of the essential amino acids (lysine in particular) may have actions which simulate hormones.

One approach for working out the explanation for splanchnic hepatotrophic effects is selective ablation of different splanchnic organs or hormone-producing tissues. Some preliminary data were presented on the influence of total pancreatectomy and alloxan diabetes on the liver tissue of animals subjected to the splanchnic division described above, but the complicated nature of these experiments has been a serious disadvantage. Bissell's technique of monolayer culture of metabolically active liver cells could permit far more precise analysis of hepatotrophic factors by permitting the addition or subtraction of hormones or other substances from the medium. Preliminary efforts of this kind of systematic screening were described.

Since the emergence and increasing acceptance of the hepatotrophic hypothesis, secondary controversies have erupted about the importance of splanchnic venous blood in the control of regeneration. In partially hepatectomized animals deprived of portal blood, Bucher observed that hyperplasia is delayed and less vigorous than when portal blood is provided. Price showed, in a similar preparation, that the infusion of insulin and glucagon restored hyperplasia to normal levels. These observations support the general point of view that hepatotrophic substances are not central to the initiation of regeneration, but

that their absence may blunt the vigor of a regenerative response. To use Bucher's term, the hepatotrophic substances are "permissive and enhancing." Chiu reported the profound effect that at least one hormone (glucagon) could have on the differentiation of fetal hepatocytes.

Finally, some clinical notations were made in the context of the hepatotrophic hypothesis. First, successful techniques for auxiliary liver transplantation have been designed with the objective of routing splanchnic venous blood into the ectopic homograft. Second, the palliation by portacaval shunt of patients with the specific enzyme defects of hepatic glycogenoses was reinterpreted in light of recent advances in understanding of the hepatotrophic concept. Finally, in the same vein, a case of portal diversion for the treatment of homozygous type II hyperlipidemia was described with astonishing clinical palliation and with a serum cholesterol drop from about 1000 to 250 mg per 100 ml. The switch-off of cholesterol and lipoprotein metabolism in this important case illustrated again the profound physiological consequences of bypassing hepatotrophic substances around their usual first order hepatic capillary bed.

It was obvious from the Symposium discussions that the hepatotrophic hypothesis has opened an inviting new field for investigation in hepatology. The far-reaching implications of the concept were the subject of the exciting review by Dr. Hans Popper of New York, which concluded the Roche Symposium and which has been preserved in its entirety in the following pages.