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NEW DEVELOPMENTS IN HEPATOLOGY

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During the last two decades, there has been a revolution in the understanding of hepatic pathophysiology and in the treatment of liver disease. There is not time to review all of the new developments. Instead, I will touch briefly on two areas which are still evolving and in which I have worked. The first topic will concern portal physiology.

HEPATOTROPIC FACTORS

The notion that portal venous blood possessed qualities not found in other kinds of blood repeatedly surfaced in and receded from the literature during the nearly 100 years before 1964. However, the hypothesis of portal blood specificity was not established until the early 1960's when it was found that auxiliary liver homografts placed in an ectopic location and doubly revascularized with arterial plus systemic venous blood underwent striking atrophy and other abnormalities within a few days. This small graft had been the same size as the native liver at the time of transplantation a few weeks earlier. Such acute atrophy also was found in non-transplant models such as this so-called split transposition. With this preparation, one liver fraction was nourished with splanchnic venous blood via a portal branch. It remained healthy. The other liver fraction supplied with equal volumes of or greater systemic venous inflow underwent atrophy and tissue damage.

The hypothetical ingredients in venous blood returning from the splanchnic organs were termed HEPATOTROPIC FACTORS. But what were they? The first solid clues were not unearthed until 1972 and 1973. Then, using different kinds of split liver techniques in dogs, circumstantial evidence was obtained that the hepatotropic factors were endogenous hormones. One particularly useful preparation was splanchnic division in which venous return from the pancreas and other upper abdominal organs was given to part of the liver whereas the other part was given intestinal venous return. The liver region nourished with venous blood from the pancreas and duodenum had large and ultrastructurally healthy hepatocytes. The hepatocyte size differences could be quantitated by cutting them out under the light microscope on standard size paper and then weighing the silhouettes. The weights were called size units. The pancreatic-fed hepatocytes were glycogen rich and were part of large lobules. Liver tissue denied this kind of blood had atrophic and ultrastructurally damaged hepatocytes. Pancreatectomy or the creation of alloxan diabetes eliminated or diminished the regional differences.

The unmasking of these effects in split liver models had a simple explanation. It appeared that the splanchnic hepatotropic substances were largely cleared by one passage through hepatic tissue. Therefore, hepatotropic factors passing through one liver fragment became unavailable for the other competing fragment which suffered accordingly. From the evidence just cited, endogenous insulin seemed to be the most important hepatotropic factor. However, all of our work indicated that other splanchnic factors were also important. The nature of these non-insulin contributory splanchnic factors which have been assumed to be multiple has not been accurately determined. Other hormones (such as glucagon) and nutrients absorbed from the intestinal tract have been suggested.

A crucial experiment to test the hepatotropic role of insulin was carried out in 1975, using the ECK fistula (complete portacaval shunt) model. In all species so far studied including man, complete portal diversion causes characteristic hepatic changes which in dogs are essentially complete within four days. The changes are identical to those in the portaprival liver fragments of split liver experiments just described. Hepatocytes shrink

to about half their original size and become infiltrated with fat. Various organelles become abnormal, the most specific change being disruption and quantitative loss of rough endoplasmic reticulum. There is an increase in thymidine incorporation and mitotic activity to about three times the previous level.

Insulin was tested in such dogs in the following way. At the time of ECK fistula, a continuous infusion of non-hypoglycemic doses of insulin (with or without glucagon) was given into the tied off left portal vein. The lobes could then be compared to the pre-shunt control tissues as well as to the non-treated right lobar tissues as well as to the findings in control untreated animals after ECK fistula.

The results were clear. Insulin prevented most of the acute damage caused by ECK fistula, but only in the directly infused left lobes. Atrophy was largely prevented and so were most of the expected light and electronmicroscopic changes. Glucagon with insulin or by itself had no demonstrable effect.

In addition to the foregoing effects, insulin treatment in ECK fistula dogs influenced the rate of hepatocyte cell renewal. Thymidine incorporation and actual mitoses were increased about four times in the infused lobes but not on the other side.

At long last, the explanation for the mysterious ECK fistula syndromes was at hand. In essence, these seemed to be caused largely by the loss of direct exposure to hormones (especially insulin) which were being diverted from their natural transhepatic route, even though they were returned in diluted form through the arterial circulation. The secondary complications of ECK fistula such as encephalopathy and weight loss were derivative from the liver changes. With the liver changes came other subtle but profound metabolic consequences. For example, there was a fall in serum lipids components such as cholesterol and phospholipids. Which was at least partly due to a reduction in hepatic cholesterol synthesis.

Quite understandably, the morphologic effects of ECK fistula in dogs can be duplicated by another straightforward procedure, namely, removal of all non-hepatic splanchnic organs. Here also, the structural and ultrastructural changes can be greatly reduced or even prevented by the continuous infusion of insulin into the now virtually nonexistent portal circulation. Note the atrophy that occurs, and its nearly complete prevention with intraportal insulin therapy.

There are broad implications to the realization that the liver is more than a way-station for splanchnic hormones and that a functional interplay exists between these hormone sources and the liver. Although the clearest example is with insulin, the same potential exists with polypeptides, nutrients, and other substances of splanchnic origin which are normally brought to the liver in high concentration on first pass. The role of this splanchnic organ-hepatic axis in understanding liver physiology and liver disease is a task to which we will be addressing ourselves for a long time to come. Before leaving this subject, I would be remiss not to mention Japanese surgeons such as WATANABE and USUI who have worked with us. Here in JAPAN, much of the brilliant work of OZAWA and his associates in KYOTO concerned with hepatic high energy phosphate metabolism is directly relevant to the hepatotrophic concept.

HEPATIC REGENERATION AND HEPATOTROPHIC FACTORS

The suspicion has been entertained by us and by these others that splanchnic factors influence the hepatic regeneration that follows liver injury or partial hepatectomy. That hormones such as insulin can effect the rate of hepatocyte proliferation has been clearly established in many experimental models including the insulin infusion experiments described earlier. Particular attention is drawn to the work of BUCHER (HARVARD) and the SAN DIEGO workers directed by ORLOFF.

Furthermore, evisceration changes the normal course of regeneration events. If total pancreatectomy is performed at the time of or before partial hepatectomy, regeneration is delayed and diminished but by no means eliminated. Retention of the pancreas but removal of all other non-hepatic splanchnic organs has a similar or even greater but still incomplete inhibiting effect on regeneration. However, when all the non-hepatic splanchnic organs are excised, regeneration is brought to a dead standstill, and it cannot be restored to normal with insulin or insulin/glucagon therapy. The total lack of mitoses two and three days after 72% hepatectomy is seen here.

What is the role of hepatotrophic factors in liver regeneration? The hypothesis that hormone interactions create an initiating climate for regeneration is compatible with this data on secondary messenger systems. After liver resection in rats and dogs, early rises and later declines in cyclic AMP, adenylyl cyclase, hormone binding and polyamine concentration precede regeneration by many hours. These orderly changes are perturbed by

all of the evisceration procedures that inhibit or abolish regeneration, but it is not known if such associations and iatrogenically caused disassociations represent cause or effect.

INTRAHEPATIC GROWTH CONTROL FACTORS

About a year ago, we concluded that our investigations of hepatic growth control needed a new direction. We began a search for factors within the liver itself that could influence liver growth. Although this concept had important historical roots going back 20 years, it has been controversial because of conflicting and inconsistent experimental results.

Our approach was simple. By ultracentrifugation at 140,000 g, we made canine hepatic cytosol extracts that were free of cell membranes, organelles and viruses. Such cytosol contains proteins and other constituents that are soluble but no insulin and very little glucagon. The cytosol was tested in the same ECK fistula model described earlier by injecting it as a 4-6 hour bolus into the tied off left portal vein, just after completion of the portacaval shunt.

The results which were published in LANCET in December, 1978, were remarkable. Cytosol from normal adult livers had no effect upon the events that follow ECK fistula, nor did the cytosol prepared from liver fragments remaining after 72% hepatectomy performed one day earlier. However, two-day regenerating liver changed the pattern of results and three-day regenerating liver was even more potent. In the directly infused left liver lobes these latter cytosol extracts initiated a burst of regeneration which had a delayed onset. The increased mitoses were not clearly seen until two days after the pulse of cytosol had been given, with a response that was doubled again at three days and almost completely confined to the directly treated lobes.

Proliferation was not the only cytosol effect. The atrophy characteristic of ECK fistula proceeded for two days after the delivery of the active liver extracts, but between the second and third days, there was a dramatic reversal. Now the hepatocytes returned to normal size at the same time as other structural and ultrastructural features of these liver cells were restored to or toward normal. The result at three days was a liver in which healthy hepatocytes in the left but not the right liver lobes were undergoing changes indistinguishable from vigorous regeneration.

Such observations create a new dimension for research in regeneration. The findings will have to be reconciled with the earlier work on hepatotrophic factors. Is the appearance of the growth factor in regenerating livers dependent upon portal blood input? Or does the cytosol contain an independent self-start factor intrinsic to the liver which simply cannot find the environment to proceed without hepatotrophic input? There are other lines of inquiry. Isolation and identification of the growth factor should be possible by standard biochemical techniques, and it should be tested for species and organ specificity.

CLINICAL IMPLICATIONS

Implications of the hepatotrophic concept have already been mentioned or implied including: the planning of optimum vascularization of homografts; the possibility of the provision of an hepatic renewal stimulus in patients with acute hepatic disease who exhibit poor regeneration; the better understanding of a variety of liver diseases as these are influenced or even caused by perturbations of the hepatic-splanchnic axis; and a better understanding of non-hepatic diseases (diabetes mellitus, for example) the course of which is probably effected by interorgan relationships.

In addition, the hepatotrophic concept should be part of the consciousness in choosing portal-systemic shunt procedures for control of hemorrhage from esophageal varices. In principle the WARREN-type procedure should be the best since it can decompress the dangerous gastroesophageal venous collaterals with minimum acute loss of residual hepatopetal flow.

Historically, portacaval shunt has been used clinically for mechanical objectives-decompression of the portal venous system and relief of ascites. More recently, portal diversion has been performed for metabolic purposes. The first such application was for glycogen storage disease. We have treated ten such patients who now have potential follow-ups of 2-1/2 to 15 years. Their liver enzyme deficiencies were of glucose-6-phosphatase (Type 1, six examples), amylo-1-6-glucosidase (Type 3, three examples), and phosphorylase (Type 6, one example). All ten children had growth retardation, and nine had recurrent hypoglycemia and acidosis. Secondary hyperlipidemia, coagulation disorders, hyperuricemia and bone dysplasia were common.

After complete portacaval shunt, the insulin rise in systemic blood after a glucose meal was markedly

increased compared to preoperatively. All metabolic abnormalities were immediately ameliorated or fully corrected except for nocturnal hypoglycemia. All the children had striking growth spurts, at an average rate of more than 0.5 cm per month for the first year. Later biopsies of the livers showed no decrease in the glycogen concentration and no change in the enzymes. However, the hepatocytes had undergone the kind of atrophy described earlier in animals. This plus the increased total body growth resulted in a relative decrease in the hepatomegaly which was a common preoperative complaint. Bone growth and maturation were striking.

The subsequent important investigations of FOLKMAN et al. of HARVARD have shown that many of these benefits can be achieved by continuous alimentation with glucose or an elemental diet delivered through a gastrostomy or oral feeding tube. The relative roles of portal diversion versus continuous alimentation (singly or together) for the treatment of glycogen storage disease will undoubtedly be clarified in the next few years.

In a second metabolic disease, namely homozygous Type II hyperlipidemia, a reasonable non-surgical option is not available. Patients with this terrible disorder have serum cholesterol concentrations of 600-1200 mgm%. They progressively develop xanthomatous deposits in numerous external contact areas. Such deposits internally in the coronary arteries and heart valves inevitably lead to lethal cardiovascular complications, usually by the teenagers. Medical and dietary treatment are ineffective.

In 1973 we performed end-to-side portacaval shunt on this patient. Her serum cholesterol concentrations fell from about 800 mgm% preoperatively to about 350 mgm% at the same time as visible xanthomatous deposits disappeared and a moderate aortic stenosis regressed. Unfortunately, she had suffered a major myocardial infarction a few weeks before the portal diversion, leading to a myocardial aneurysm. Nineteen months after the portal diversion she died suddenly while walking from school. The cause of death probably was a cardiac arrhythmia.

We have treated three other patients with Type II hyperlipidemia. One subsequently had an aortic valve replacement and triple coronary artery bypass. The two oldest of these patients who have follow-ups now of 3-1/2 to 4-1/2 years had major cholesterol declines as well as resorption of xanthomas. Careful metabolic studies on one of these patients revealed a substantial decline in hepatic cholesterol synthesis analogous to that observed in normal dogs. It is likely that decreased hepatic lipid synthesis is only one of multiple factors accounting for the anti-lipidemic effect of portacaval shunt. In any event, the anti-lipidemic effect of portal diversion has been confirmed in many centers throughout the world.

It is interesting that pathologic changes caused by portal diversion in the seemingly normal human liver are indistinguishable from those in animals. Shown here is a preoperative EM section, and at a higher power. Six months after shunt there was atrophy, organelle disruption, fatty infiltration and especially loss of rough endoplasmic reticulum. Despite this, the human (like the rat) has been resistant to encephalopathy and other devastating complications of ECK fistula which regularly kill dogs, swine and baboons within a few months.

We have also performed portacaval shunt in two children with alpha-1-antitrypsin hepatic disease. The procedures were done to control variceal hemorrhage. It has been interesting and surprising that the hepatic disease has not progressed in the 1 to 1-1/2 subsequent years of follow-up. It is conceivable that the benefits were more than simple portal venous decompression, and the deposition of the abnormal polysaccharide in the liver has been slowed.

LIVER TRANSPLANTATION

Liver transplantation is the other developmental area in hepatology which I will discuss. There are two kinds of liver transplantation. One is the placement of an extra (auxiliary) liver at some heterotopic site such as the right paravertebral gutter, leaving the diseased native liver in situ. As was described in the first section of this lecture, optimum revascularization of auxiliary livers includes portal inflow from the splanchnic venous system as was done here. There has been only one example of long survival after clinical auxiliary transplantation, that being of a patient treated for biliary atresia more than five years ago by FORTNER of NEW YORK. Forty-two other attempts throughout the world including four from our center failed within a short time.

The second and far more widely accepted kind of liver transplantation is liver replacement (orthotopic liver transplantation) after removal of the diseased native organ. The following remarks will pertain solely to orthotopic liver transplantation, and with particular emphasis on long-term follow-ups and recent developments.

DENVER CASE MATERIAL AND INDICATIONS

The first human orthotopic liver transplantation was performed in March 1963. Between then and

December 1977, a total of 141 consecutive patients were treated with this operation with potential follow-ups now for all survivors of more than a year.

The indications for operation were wide ranging. Patients below 18 years old accounted for more than half of our recipients (74 in all) and within this pediatric group there were 48 examples of biliary atresia. The other indications for liver replacement listed here in our pediatric series accurately reflects our present day attitude about appropriate case selection, with one exception. The exception is primary hepatic malignancy. I will return to this subject in a moment.

It has become clear that manifestations of liver based inborn errors of metabolism can be cured with liver replacement. We have had experience with WILSON's disease, alpha-1-antitrypsin deficiency, tyrosinemia, and Type IV glycogen disease (alpha glycosidase deficiency). This is the course of a boy with WILSON's disease treated eight years ago. Note the increase of serum ceruloplasmin from zero to normal. The deposits of copper were excreted, with remission of all symptoms. The child is still alive.

Nineteen of our liver transplantations in children and adults were carried out to treat nonresectable hepatomas, duct cell carcinomas, angiosarcoma, and cholangiocarcinoma. Ten of these patients lived beyond three months and nine of them later developed metastases such as shown here which usually contributed to or were primarily responsible for their deaths after a few months to several years. Similarly, the recurrence rate in the CAMBRIDGE-KINGS COLLEGE series in ENGLAND has been 70%. As more and more such cases have been documented, we have had less and less enthusiasm for and indeed we usually avoid transplantation for malignancy.

In spite of this pessimistic attitude, there is no denying that some patients with malignancy have benefitted from liver replacement. Our longest survivor who is now nine years and one month has been cured of an incidental hepatoma in her excised biliary atretic liver. This is the patient years later. Three of our patients lived for more than two years in spite of recurrences, and two of the three are still alive after 2-1/4 and 4-1/2 years.

Shown here are other indications for transplantation in adults. In the future, the leading indications for transplantation in adults undoubtedly will be chronic aggressive hepatitis and LAENNEC's cirrhosis. The presence of HBs Ag viremia is not a contraindication since effective postoperative treatment can be given with hyper-immune serum. Cases of cirrhosis pose a supreme technical challenge. If results are to be improved, candidates will need to be selected at an earlier time. Too often in the past, the recipients have been moribund by the time of operation.

There is little point in exhaustively discussing different liver diseases in connection with transplantation since anyone with end stage liver disease theoretically might be a candidate as is evident from this list. Relative contraindications include advanced age (beyond 50 years) and infection. Judgment must be exercised not to proceed too soon in the natural history of the patient's disease, and not to make the equally or more serious error of waiting too long.

Immunologic analysis has not greatly effected case selection. Almost all of our patients have been given livers with three or four HL-A mismatches. Indeed, the resistance of the liver to hyperacute rejection has prompted transplantations in the face of cytotoxic antibodies (11 examples) and the isoagglutinins of blood group mismatch (11 examples). Only two possible hyperacute rejections were seen, both with the blood group mismatch cases.

OPERATIVE PROCEDURE

In concept, the procedure is disarmingly simple, but blood loss may total thousands of milliliters. In cirrhotics, the combination of venous hypertension and deficient clotting factors can be corrected only with the arrival of a new liver.

The homograft is always preserved by infusing it with a cold electrolyte solution just as it is removed from the donor. If the infusion is with intracellular electrolyte constituents (COLLINS solution), preservation of cooled livers has been possible in dogs for as long as a day. These developments in preservation have permitted the successful shipment of livers from city to city in THE UNITED STATES, and also in the English program of CALNE and WILLIAMS.

As the vena caval anastomoses are constructed, slow infusion of electrolyte solution is continued via the portal vein. Air bubbles can be seen floating out of the graft in the hepatic veins effluent. If infusion is not continued during this time, the air bubbles in the homograft are released after revascularization and they may pass through abnormal right to left heart venous communications (secondary to liver disease) and on to the brain.

A high incidence of cerebral air embolus was eliminated with the infusion technique.

Increasingly in infants and young recipients, we have used microvascular techniques, particularly for hepatic artery and portal vein reconstruction. In our early experience, using standard vascular techniques, pediatric recipients had a high incidence of thrombosis in these vessels.

Biliary tract reconstruction has caused more complications than any other part of the operation. In our early experience, one of every three patients subsequently had biliary duct obstruction or biliary fistula. Even without obstruction or fistula, there was a high incidence of bacteremia, probably because of constant contamination of the biliary ducts through the cholecystoduodenostomies that were being used in those early days.

Since 1974 we have not used cholecystoduodenostomy. We think that duct to duct reconstruction (choledochocholedochostomy) is the best method. If this is not feasible (as for example in patients with biliary atresia), we use cholecystojejunostomy (to a ROUX-Y limb) or choledochojejunostomy.

CALNE et al. of ENGLAND have also changed their practices of biliary reconstruction. Their present preferred method is the creation of a cloaca between the homograft gallbladder and common duct, with anastomosis of the common chamber to the recipient common duct. The complexity of this procedure compared to more standard biliary reconstructions militates against its widespread acceptance.

Splenectomy is usually performed at the time of transplantation. The majority of recipients have greatly enlarged spleens and such serious hypersplenism that treatment with azathioprine and prednisone would be jeopardized without elimination of this factor.

NON-IMMUNOLOGIC COMPLICATIONS

In view of the enormous difficulty of performing liver transplantation, it is not surprising that the procedure has been followed by a long list of complications. Such complications have been responsible for more than half of all deaths within the first year. Included have been vascular thromboses, hemorrhage, the unknowing use of ischemically damaged grafts, and biliary tract obstruction and/or fistulization to provide a very incomplete accounting. These complications have influenced postoperative immunosuppressive management.

MANAGEMENT

The unique requirement after any transplantation is immunosuppression. We have treated our liver patients with double drug (azathioprine and prednisone) and triple drug (azathioprine, prednisone and antilymphoid globulin) regimens. Cyclophosphamide can be used interchangeably with azathioprine. Irreversible hepatic rejection can be prevented with these techniques in something like 80-85% of cases. However, the cost of such immunologic control may be fatal infection, particularly if there is any kind of other complication of a non-immunologic variety.

In our early experience, the assumption was almost automatic that postoperative dysfunction of the homograft was due to rejection. The logical response was increased steroid therapy. In 1975 and 1976 the validity of such assumptions was retrospectively assessed and found frequently to have been incorrect as already described. Instead of suffering rejection, many of these homografts were obstructed and others were being damaged by bacteria, virus or the very immunosuppressive drugs counted upon to protect the liver. A much more aggressive diagnostic approach was obligatory and from this time onward, no workup in the posttransplantation period was considered complete without one or more needle biopsies, and without percutaneous endoscopic or T-tube cholangiography.

Reoperation of biliary tract complications has been possible in many cases of which this is an example. If other causes of postoperative liver dysfunction than rejection seem ruled out, increases in prednisone are necessary. Subsequently, an effort is made to wean the steroid quantities as rapidly as possible with retention of graft function.

RESULTS

1963-1976. During the 13 years from May 1963 to July 1976, 111 consecutive patients had attempts at liver replacement, 50 adults and 61 pediatric recipients: Of the 111 patients, only 31 (28%) lived for as long as one year. Ten of the one-year survivals were in the 50 adult cases, and 21 survivals were among the 61 pediatric cases.

After one year, 17 of the 31 patients who were alive at the one year mark later died after total survival periods of one to six years. The commonest reasons for late death were chronic rejection, uncorrected biliary obstruction, systemic infection, and recurrent malignancy in that order.

Fourteen of the original 1963-1976 series are still alive with follow-ups that now range from three to nine years. These patients have had a very high order of rehabilitation. The adults and adolescents have all returned to school or work, and the infants have entered and done well in school.

1976-1977. Another 30 patients (series II in this slide) were treated from July 1976 to December 1977 using the technical, diagnostic and management improvements mentioned earlier. There were 17 adults and 13 infants or children. The one year survival in this latest group was 15 of 30 (50%), including seven of the 17 adults and eight of the 13 pediatric recipients. Two late deaths occurred, one at 16-1/2 months because of portal vein thrombosis, and the other at 23 months because of systemic chicken pox.

Throughout our entire experience, the results with children have been better than with the adults. Overall one year survival with children was 40%, compared to 25% with adults.

The 40% overall pediatric figure was weighted by the large number of biliary atresias who suffered an unusual number of technical accidents. One year survival in the 48 atresia patients was 33%. In the 26 non-atresia patients, one year survival in our total experience was 50%.

THE QUALITY OF LIFE

The quality of life must be assessed after any heroic surgical procedure. As just described, the substantial total of 46 patients have lived for at least a year in the COLORADO experience. Of these 46 recipients, 27 are still alive. If the patients were in good condition with adequate liver function at one year, their prognosis for long subsequent survival was good. A bad prognosis was usually equally evident by one year.

FUTURE PROSPECTS

The next major improvement in liver transplantation will depend on better immunosuppression. Conceivably, an advance will be possible with better drugs, or with lymphoid irradiation techniques. One immediate possibility is the use of thoracic duct drainage (TDD) for its well known effect on lymphocyte depletion and reduction of cell mediated immunity. A less recognized but invariable consequence of chronic TDD is a striking reduction of all immunoglobulin classes and a concomitant drop in humoral antibody reactions.

Since February 1978, we have attempted TDD in all new liver recipients, placing the catheter just after completion of the transplantation or in two cases after a delay of several weeks. The amount of lymph removed per day has been 3-10 liters. Other immunosuppression has been with the double or triple agent programs described earlier.

Many patients with the new treatment protocol have had untroubled courses. This one had definite but easily controlled rejection. But as in the past the appearance of significant surgical complications (enteric fistulas for example) has been a lethal event. The survival of patients with thoracic duct fistula treated in the last year is five of nine (56%). None of the deaths were due to rejection. The follow-ups are 8 to 12 months.

The next step which we contemplate will be the use of TDD preoperatively. With advance lymphoid depletion, our plan will be to use far less steroids than has been our past practice.

SUMMARY

I have reviewed for you two developmental topics in hepatology. The first concerned those specific substances (termed HEPATOTROPIC FACTORS) in the portal venous blood that can influence liver structure function and the ability to regenerate. The clinical implications of the hepatotropic concept were summarized.

The second topic was the use of liver transplantation in modern day hepatology. In the last 15 years, enough progress has been made with liver replacement to give it a legitimate although still evolving place in our therapeutic armamentarium. Since 1976, half or more of all our patients with liver transplantation have survived for at least a year and it looks as if this record can be further improved. The longest survivor in the world after liver replacement is more than nine years, and in our series alone, there have been 17 three year survivors. This progress, painfully low though it has been, has encouraged us to continue in this difficult field.

SELECTED REFERENCES

Perusal of the references below will provide a nearly complete picture of the history and present state of the portal hepatotrophic field and of liver transplantation. Scholars interested in original publications will be able to track these easily, especially in references 1 and 6.

PORTAL HEPATOTROPHIC CONCEPT

1. Starzl, T.E. and Terblanche, J.: Hepatotrophic Substances. In *Progress in Liver Diseases*, Volume 6 (Popper, H. and Schaffner, F. eds.). New York, Grune and Stratton, in press.

This new field of hepatic physiology is summarized, describing the specific effects of venous blood from non-hepatic splanchnic organs in regulating liver structure, function and the capacity for regeneration.

2. Porter, R. and Whelan, J.: Hepatotrophic Factors. Elsevier, Excerpta Medica, North Holland, 1978, pp. 111-129.

This book records a Ciba foundation symposium held in London on May 9-11, 1977. Authorities from many countries discussed their work in hepatotrophic physiology, as well as the clinical and experimental implications of this work. Clinicians, physiologists, pathologists and biochemists were represented.

3. *Lancet*, 1: 127-130, 1979.

A growth control factor in regenerating dog liver was described. This growth factor which appeared in the hepatic remnant two days after subtotal hepatectomy stimulated mitoses and prevented atrophy in test dogs subjected to cec fistula. The paper has focused on mechanisms of growth control that are intrinsic to the liver itself.

LIVER TRANSPLANTATION

4. Calne, R.Y. and Williams, R.: Liver Transplantation. In *Current Problems in Surgery* (Ravitch, M.M., ed.). Chicago, Year Book Medical Publishers, Inc., in press.

The important clinical series of 74 cases from the Cambridgekings College London group are described, as well as laboratory research in these institutions. Although almost all of the recipients were adults, the opinions expressed have applicability to pediatric cases. Opinions about patient selection, biliary tract reconstruction and immunosuppression are somewhat different than those expressed in this.

5. Fortner, J.G., Yeh, S.D.J., Kim, D.K., Shui, M.H. and Kinne, D.W.: The case for technique of heterotopic liver grafting. *Transplant. Proc.*, in press.

This collection of 43 clinical auxiliary liver transplantations from many different centers was presented to the International Transplantation Society in Rome, September, 1978. The case for auxiliary transplantation is presented optimistically, perhaps excessively so in view of the poor results.

6. Starzl, T.E. (With the Assistance of Putnam, C.W.): *Experience in Hepatic Transplantation*. Philadelphia, W.B. Saunders, 1969, pp. 1-553.

The text contains the total world literature (299 references) on experimental and clinical liver transplantation to the spring of 1969, an account of all 42 human liver homotransplantations attempted to that time including 29 (25 orthotopic, 4 auxiliary) at the University of Colorado and detailed descriptions of surgical and anesthetic techniques, metabolic and immunoglobulin changes following liver transplantation are described. The laboratory development and clinical practice of immunosuppression for all transplanted organs is reviewed. Two chapters by Professor K.A. Porter of St. Mary's Hospital and Medical School, London, constitute a complete monograph of the pathology of animal and human auxiliary and orthotopic liver homografts as well as two chimpanzee to human heterografts.

7. Starzl, T.E., Koep, L.J., Halgrimson, C.G., Hook, J., Schroter, G.P.J., Porter, K.A. and Weil, R., III: Fifteen years of clinical liver transplantation. *Gastroenterology*, in press.

The first 141 orthotopic liver homotransplantations at the University of Colorado are described. These include the 74 pediatric cases of this chapter plus 67 adult cases. There is detailed documentation of causes of early and especially late deaths. The recent literature of clinical liver transplantation is brought up-to-date. This is the most recently written review of liver transplantation.

特別発言

本庄 一夫名誉教授

I should like to express our deep gratitude for your splendid lecture.

Three years ago when I visited your hospital at Denver, you kindly showed me to see a special ward, liver transplantation clinic. Even now, I never forget the deep impression I got when I met with a little pretty girl whose liver had been transplanted successfully by you.

Now, you gave us a very fine lecture principally on portal physiology and transplantation of the liver. So, I try to introduce briefly to you some works done in Japan relating to these subjects.

As stated in your speech, you paid your attention to hepatotrophic factor first in the course of your hard study on liver transplantation and finely discovered the role of insulin playing on the mechanism of liver regeneration.

In Kyoto university in Japan, as you mentioned in your speech, many young surgeons guided by Dr. Ozawa have started to investigate the restorative mechanism of the liver at the time of hepatic damage.

To preserve the function of the liver demanded by whole body, in other words, to bring the compensatory function into play, it is easily assumed that production of energy, ATP-synthesis is absolutely needed.

From this view point, we have been studying the mitochondrial energy metabolism of the liver under the various conditions.

Briefly explained, the clinical cases of liver carcinoma, liver cirrhosis and obstructive jaundice together with various kinds of experimental mammals had been investigated under the conditions of partial hepatectomy, portal vein branch ligation, bile duct ligation and others. As the results of these studies, we have confirmed the following facts.

An enhancement in mitochondrial phosphorylative activity plays an important role in maintaining the delicate energy balance of damaged liver. We have found that two mechanisms are basically important in increasing the mitochondrial ATP-synthesizing ability: One regulating the ATP-synthesizing ability per unit of respiratory enzymes and another controlling the contents of respiratory enzymes.

The former type, regulation of the ATP-synthesizing ability per unit of respiratory enzymes is of great importance in maintaining hepatic functional reserve and initiating liver regeneration.

The latter type, the control of the contents of respiratory enzyme is mainly observed in clinical cases affected with chronic disease.

Prof. Starzl had beautifully provided the evidences for the hepatotrophic effect of insulin on portal blood deprived dogs. Our studies also, with the experiments of portacaval shunts or splenocaval anastomosis, have shown the beneficial effect of insulin on hepatic energy charge and mitochondrial phosphorylative activity. Moreover, it was demonstrated that the mitochondrial activity per unit of respiratory enzymes increases with raised amount of portal insulin available to hepatocytes as a rapidly adaptive mechanism. However, if the contents of respiratory enzymes show a decrease transcending a certain limits due to severe damage to liver cells, an enhancement of mitochondrial activity can not be expected any more.

We also confirmed the fact that enhancement of mitochondrial activity precedes the DNA synthesis in remnant liver after partial hepatectomy.

One word must be added in closing this theme.

We found that a measurement of blood glucose curve after an oral glucose load is useful for understanding mitochondrial phosphorylative activity per unit of respiratory enzymes. We have two distinct patterns in the form of curve, parabolic and linear. This measurement is useful in assessment of critically decreased hepatic functional reserve in patients.

These studies above said have mainly executed and guided by Dr. Ozawa. As I had worked with him in the same surgical department until two years ago, I dared to speak on these subjects in place of him without losing the objective standpoint of view.

It must be noted that another group of investigators directed by Dr. Sugawara in Tokyo University have also been studying the portal physiology in the same direction along with our work.

Next topic I want to tell is the theme on portal vein branch ligation for the treatment of liver cancer.

About more than twenty years ago, based upon animal experiments, I tried to ligate the branch of portal vein supplying the affected lobe. Summarily expressed, this procedure was performed in more than twenty

patients with unresectable carcinoma. All the patients tolerated the procedure well and morbidity and mortality were mainimal even in patients with poor general condition. The responses to ligation differed considerably, but significant palliation was attained in some patients and one patient has lived for more than ten years after surgery. The effect of portal branch ligation on tumor is largely affected by the degree of tumor vascularity, tumor malignancy, and portal circulatory disturbances such as cirrhosis, portal hypertension or portal thrombosis. I believe that this procedure can well be recommended for clinical application in some selected cases with unresectable carcinoma of the liver, particularly for metastatic liver cancer.

Now, in our country, we have not yet experienced liver transplantation although we have a lot of data on animal experimentation. Surely, we have been deeply impressed with your informations on this subject. You have succesfully been performing this kind of operation as a very pioneer in the world. Availing of those most valuable suggestions of yours, we are now going to reflect on the present status in Japan confronting hepatic transplantation from various point of view.

With this last remark, my little comment shall be ended.

Again I should like to express my deep appreciation for your achievements and insatiable devotion in regard to the liver transplantation and hepatotrophic factor, and also express my gratitude to the president of this congress, Prof. Yokoyama for his kindness to let me have an opportunity to make a comment for Prof. Starzl, our guest of honour from Colorado.

Thank you!
