Medical treatment after Kasai procedure and prognosis of biliary atresia. D. Alagille. Service d'hépatologie pédiatrique. Département de pédiatrie. Hôpital de Bicêtre. 94275 Le KremlinBicêtre, France.

With respect to its frequency and severity, biliary atresia is the first cause of neonatal cholestasis. Its spontaneous prognosis, always lethal, has been improved by Kasai's procedure, allowing for bile flow restoration in two thirds of cases and disappearance of jaundice in one third of cases. However, even when evolution is initially favourable, complications occur often (bacterial cholangitis, portal hypertension, secondary reappearance of jaundice), probably because extrahepatic biliary atresia is a disease concerning also intrahepatic biliary ducts.

Treatment of postoperative cholangitic episodes.

In a series of 129 infants operated on for biliary atresia with postoperative bile flow restoration, cholangitis never occurred in 28 who underwent hepatoportocholecystostomy. Forty-six of the 101 infants who underwent hepatoporto-enterostomy had a total of 105 cholangitic episodes (range 1 to 8 episodes per child). Escherichia coli was found in 50% of the 1st and 2nd episodes from blood (51) or liver (32) cultures. Children were initially given IV antibiotics with specific biliary excretion (cefotaxime and aminoglycosides). This initial choice was replaced secondarily according to the bactericidic studies.

Long-term course was related to the progressive destruction of intrahepatic bile ducts (IHBD) secondary to the number and severity of cholangitic episodes. Five years after surgery, only 25% of children were alive, all of them presenting with biliary cirrhosis and portal hypertension. Ten years after surgery, this percentage was almost identical but only 21 children had normal blood bilirubin levels. This means that about 75% of children with biliary atresia are potential candidates for liver transplantation at different ages, the earliest being about 1 year.

Medical treatment for potential candidates for liver transplantation.

Four medical problems have to be resolved.

1. Fat-soluble vitamin supplementation, which has to be given parenterally.

2. Prevention and correction of the nutritional consequences of chronic cholestasis. Caloric supply is the main target. With biliary salts lacking in intestinal lumen, medium-chain triglycerides are the lipids best absorbed. Nocturnal enteral feeding is frequently necessary, especially during the few months before liver transplantation. Parenteral nutrition is sometimes the only way able to correct severe malnutrition.

3. Prevention of G-I bleeding related to portal hypertension: surgical portosystemic shunting is contra-indicated in all potential candidates for liver transplantation. Endoscopic sclerotherapy, propranolol treatment and avoiding all acetyl salicylic acid containing drugs are the essential combined preventive measures.

4. A large program of bacterial and viral immunizations has to be performed and regularly controlled by specific antibodies research.

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So, the best conditions for the success of liver transplantation are obtained. In all groups world-wide, biliary atresia represents now 60 % of the indications for liver transplantation in children.

THE REGULATION OF HUMAN ERYTHROPOIESIS BY GROWTH FACTORS.

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In vitro erythropoiesis is governed by the combined action of burst promoting activity (BPA) and erythropoietin (EPO). Of the five purified recombinant human HGFs, both IL-3 and GMCSF have BPA activity, but neither induce erythropoiesis in the absence of EPO. Studies of in vitro hematopoiesis in serum free conditions reveal that a subset of normal marrow erythroid progenitors respond to erythropoietin alone to form recognizeable erythroid colonies. The remaining fraction requires both BPA and EPO. The same is true of monocyto- and granulocyto-poiesis. Neither IL-3 nor GMCSF induce granulocyte or macrophage colony formation from progenitors when they are added to cultures in low concentrations. But, when either G- or MCSF are added, colony formation flourishes. G- or MCSF themselves have little effect on colony formation. The source of growth factor production has been explored using strains and lines of marrow stromal cells including fibroblasts and endothelial cells as well as lymphocytes. The cells and the HGF RNA's have been probed using northern blot and in situ hybridization techniques. The results show that GMCSF can be induced by IL-1 or TNF treatment of fibroblasts and endothelial cells, by LPS stimulation of monocytes, as well as by antigen stimulation of T cells. But IL-3 MRNA is produced only in T cells and perhaps in NK cells. Less than 5% of T cells are capable of production of either IL-3 or GMCSF expression even at maximum stimulation. These results demonstrate a complex system of HGF production as well as collaboration between HGFs at the level of the progenitor cells. Collaboration between growth factors has been demonstrated in preclinical trials by Donahue et al who has shown that pre-treatment of simians with IL-3 sensitizes the marrow to subsequent infusion of GMCSF. The result is a dramatic increase in platelet, reticulocyte and phagocyte production.