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Cholangiodysplastic Pseudocirrhosis

Light and Electron Microscopic Examination

Márta Balázs, V. F. Lukács, J. Dénes, and Gy. Gorácz

Department of Pathology, János Hospital of Budapest,
Council, 3rd Department of Internal Medicine and 1st Department of Surgery,
Apáthy István Hospital for Children, Department of Pathology,
Heim Pál Hospital, Budapest, Hungary

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Summary. The familial type of cholangiodysplastic pseudocirrhosis is presented. This chronic liver disease is caused by malformation of the intrahepatic bile ducts. The female infant was 5 months old when the diagnosis was established. The liver biopsy was studied by light and electron microscopy. Electron microscopic examination revealed active proliferation of ductular cells and progression of fibrogenesis, findings consistent with the rapid and fatal course of the disease. In the case presented an acute cholangitis occurred, but after healing the progression of the original process led to hepatic insufficiency. It is suggested that cholangiodysplastic pseudocirrhosis is a chronic, progressive liver disease the course of which might be hastened by the complication of cholangitis; the process itself causes liver cirrhosis without inflammation.

Key words: Bile Canaliculus — Bile Ductule — Intercalary Cell — Collagen Fibril — Basal Membrane.

A special type of chronic liver disease, which is based on the abnormal development of intrahepatic bile ducts, has been designated (Essbach, 1961) "cholangiodysplastic pseudocirrhosis." The congenital liver lesion is essentially characterized by focal excessive formation and cystic dilatation of the intrahepatic bile ducts, accompanied by proliferation of connective tissue. In some reported cases the disease lasted for a longer period, without disorganization of liver tissue. This makes possible the naming of the disease "pseudocirrhosis." In other instances—following repeated cholangitic attacks—it may form the basis of a true cholangitic cirrhosis (Essbach, 1961; Strauch *et al.*, 1965).

The liver lesion may be complicated by malformation of other organs, especially polycystic degeneration of the kidneys, particularly sponge kidney, also known as the Cacchi-Ricci syndrome (Wohlgemuth and Mühl, 1963; Kovács *et al.*, 1969). Data concerning the familial occurrence of the disease are also available (Althoff, 1964; Kovács *et al.*, 1969).

Our purpose in describing this case is the rarity of the disease, its familial incidence, and its electron microscopic elaboration which permitted a detailed analysis of the intrahepatic bile duct system.

Case Report

Gy. V., 2 female,was born 4/3/71. Birthweight was 2400 g. *Her brother died in 1956, aged 5 months. Autopsy revealed congenital heart failure, sponge kidney, and cholangiodysplastic pseudocirrhosis.*

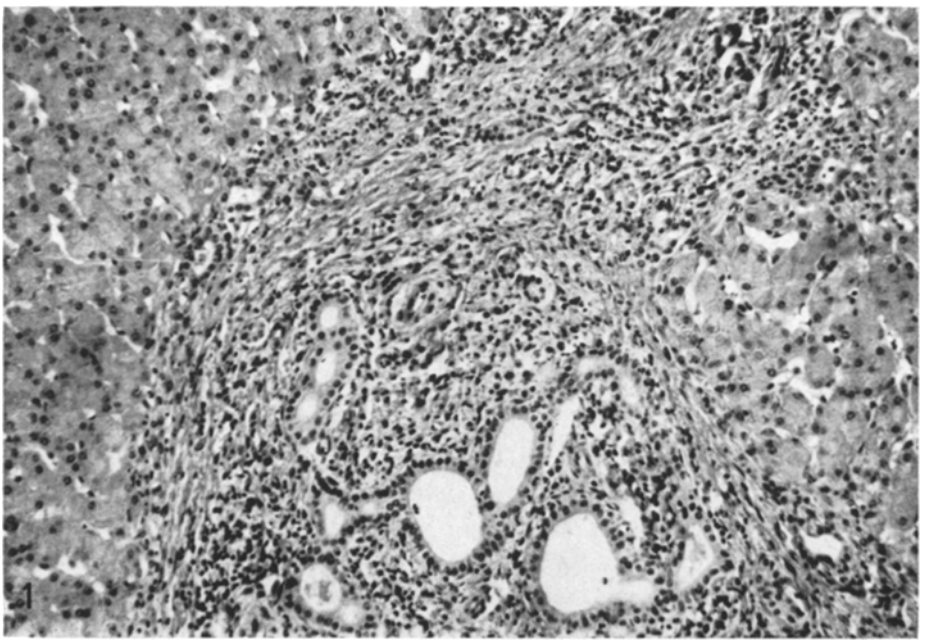


Fig. 1. Light microscopy of the liver shows groups of bile ducts with varying width in widened portal connective tissue. Around them inflammatory infiltrations are visible. ×120

At age 4 months, the infant was hospitalized twice because of bronchopneumonia and anemia. At that time no liver enlargement was found. At age 5 months, the infant was readmitted and at this time hepatosplenomegaly was observed, together with marked venous dilatations in the abdominal wall. The following laboratory values were recorded: erythrocytes: 3800000; leukocytes: 16000; bq: 10.5 percent; ESR: 55 mm/h; SGOT: 120 E; SGPT: 11 E: LDH: 119 mE; thymol: 14 E; A. sol: ++++; BSP retention: 7.5 percent; serum bilirubin normal; alkaline phosphatase: 25 KAE. Intravenous cholangiography showed no secretion, either in the Intravenous urography and kidney scintigraphy revealed uniformally enlarged kidneys on both sides. Laparotomy revealed hepatomegaly, with a hard consistency, and several adhesions peripherally. The cholecyst seemed normal in size. A sample was dissected from the right lobe of the liver.

Light microscopic examination showed that the lobular architecture of the liver was still recognizable in some places, but in certain areas there were early signs of focal reorganization. The portal connective tissue showed an excessive growth nearly everywhere; it was widened and connected with massive septa. In the connective tissue, there were numerous bile ducts of varying widths, often with cystic dilatation, with signs of severe inflammation, consisting mainly of leukocytes. The inflammation penetrated into the epithelial lining of the ducts, and inflammatory elements could also be observed in the lumina of the ducts (Fig. 1). Signs of bile stasis were not visible in bile ducts or liver cells *Diagnosis: cholangiodysplastic pseudocirrhosis, acute cholangitis.*

The infant improved briefly following administration of steroid, Tribetacid, B_{12}, Cotazym, etc. Her body weight increased, and the hepatosplenomegaly decreased. At age 10 months, a *control needle biopsy* was performed. This showed *diminution of inflammation, but the cirrhotic reorganization has increased.*

At age 12 months, the patient died in hepatic failure. *Autopsy* was performed at the Institute of Pathology, Medical University of Szeged. Diagnosis: cirrhosis juvenilis cholangiodysplastica; sponge kidney associated with acute pyelonephritis; right lobe pneumonitis. (We are grateful to Prof. Ormos for the post-mortem and histologic examinations.)

For electron microscopic examination the following *methods* were used: the liver tissue was fixed in 2 percent osmium tetroxide buffered according to Palade, dehydrated in graded alcohols, embedded into Araldite. The sections were cut on an LKB ultratome. The electron micrographs were taken with a SEM 3-1 electron microscope. Tentatively, semithin (0.5 μ) sections stained with toluidine blue were examined.

Results

On *electron microscopic examination* the nuclei of the liver cells as well as the amount and distribution of cytoplasmic organelles did not show marked differences. In some liver cells, the mitochondria were of varying sizes, the cristae were disorganized, and at some places formed ringlike figures (Fig. 2, inset). In many liver cells, the bile canaliculi were markedly dilated, and the canalicular cell surface was smooth (Fig. 2). Throughout Disse's spaces, the collagen fibers were markedly increased. They formed a continuous wide layer in most places, but the formation of basal membrane was not demonstrable (Fig. 3). It was noted, as a particular phenomenon, that the disorganization of neighboring areas of the liver cells was caused by strands of collagen fibers that had been invaginated into the liver cells on their vascular poles. (Fig. 4).

The lumina of bile ductuli were usually wider than normal. The epithelial cells of the bile ducts varied in shape, size, and development (Fig. 5). Their nuclei were normal, their cytoplasm in some places rich in organelles (Fig. 6) at other sites, however, the cytoplasm contained only a few organelles and numerous delicate filaments. It was noted that a great number of intercalary cells were not connected with the lumen (Fig. 5).

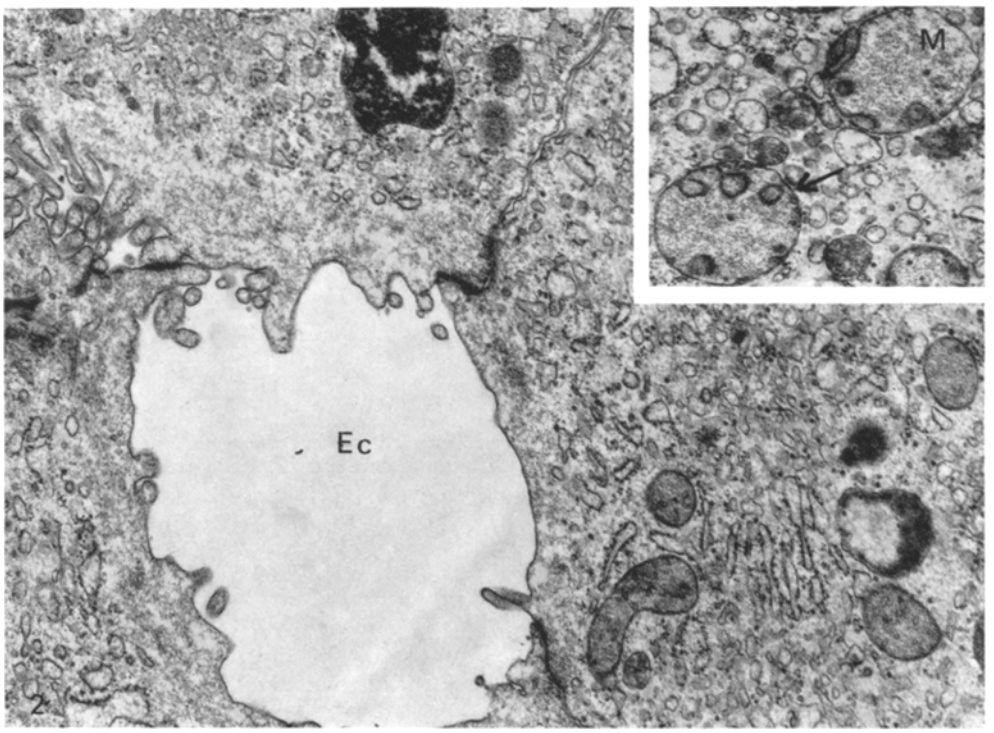
On the surfaces of the epithelial cells, facing the lumina, the microvilli were at many places disorganized, and occasionally edematous (Figs. 6 and 8). The cell boundaries were preserved. The lateral membranes of epithelial cells were tortuous, and formed in some places excessive interdigitations (Fig. 7). In many places around the ductuli, the basal membrane was easy to recognize (Fig. 6), but there

Fig. 2. Electron microscopy illustrates a bile canaliculus (*EC*) surrounded by three liver cells. The canalicular surfaces of the cells are smooth, and microvilli are missing in most parts. The pericanalicular ectoplasm is widened. Cell boundaries are preserved. Inset: Mitochondria (*M*) are of varying sizes, cristae are disorganized, forming at many sites (*arrow*) ringlike formation. $\times 25000$

Fig. 3. Portion of nucleus (*N*), cytoplasma, sinusoid (*S*) and Disse's space (*Di*) of the liver cell. In the Disse space, the proliferation of collagen fibrils (*C*) is visible. The fibrils form a continuous layer. $\times 25000$

Fig. 4. Portions of two liver cells and one nucleus (*N*). From the direction of Disse's space, bundles of fibers (*C*) invaginate into the cytoplasm of liver cells. $\times 15000$

Fig. 5. Portion of ductule. In areas marked with arrows, the basement membrane may still be recognized, but in the upper part of the figure, the basal membrane is missing and two granulocytes (*Gr*) are visible in close connection with the ductular epithelial cells. $\times 7500$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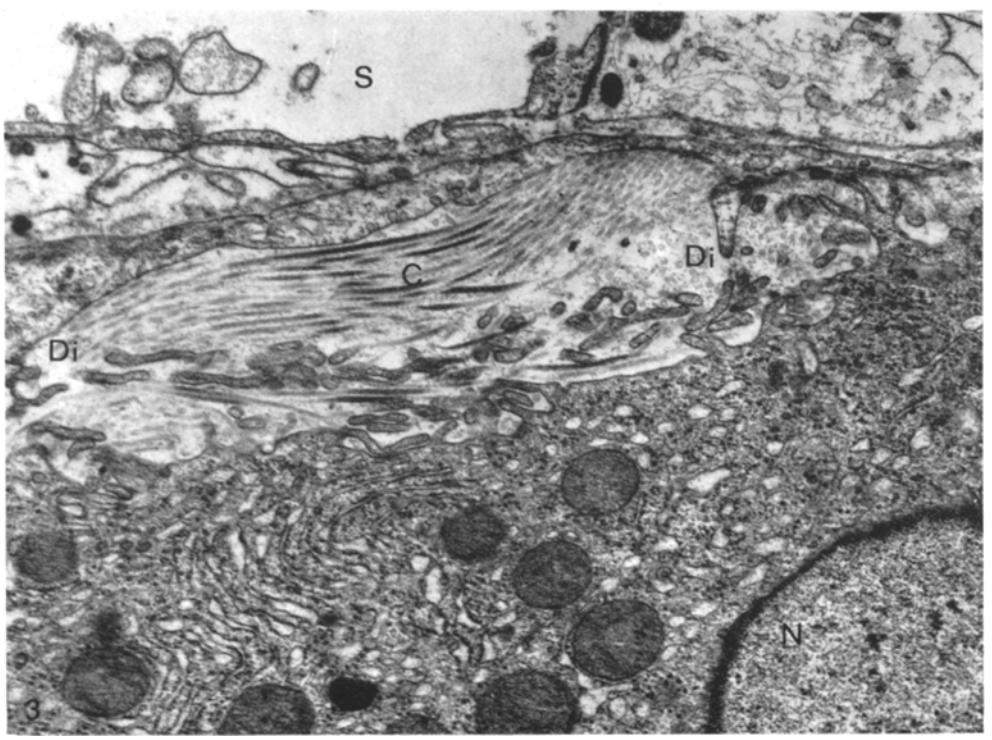
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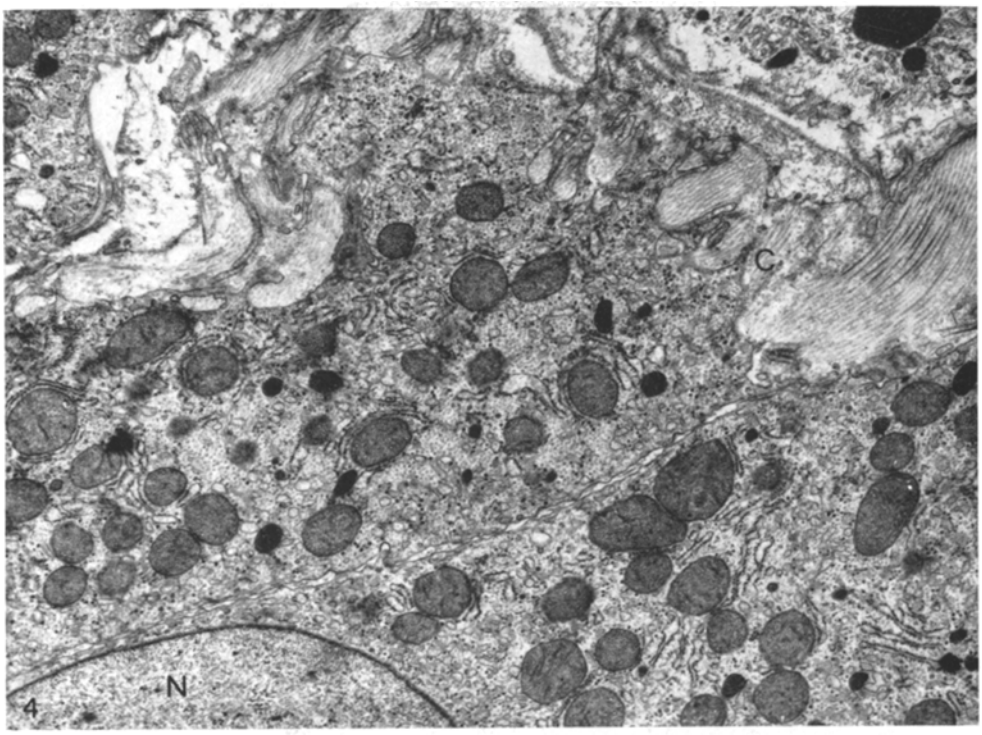
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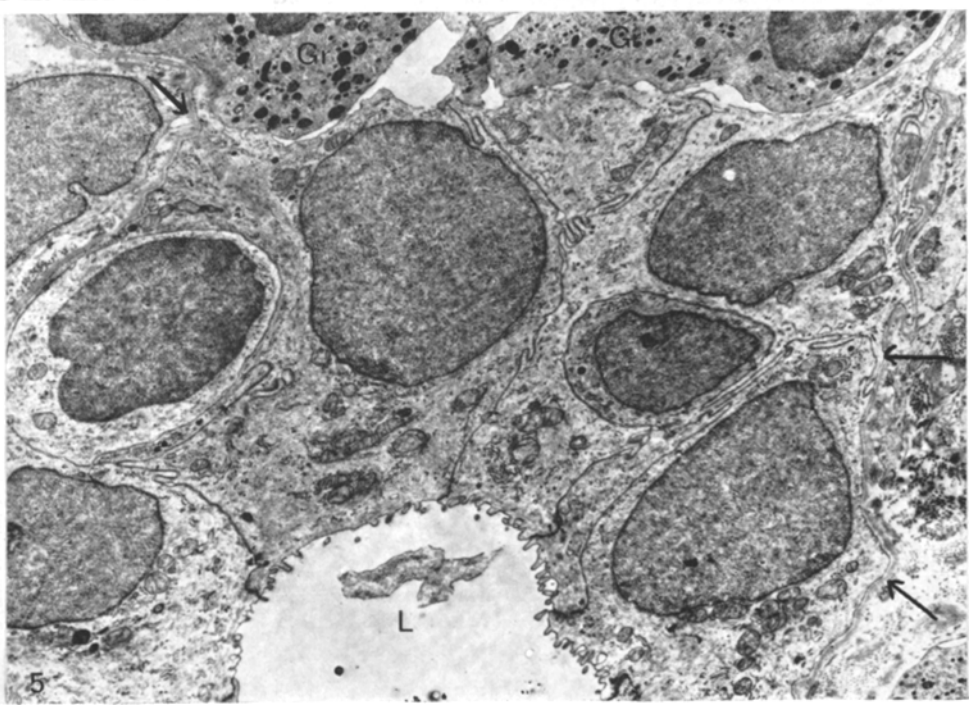
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were also areas where the membrane was periodically missing (Fig. 5). In the neighborhood of the ductuli, a small number of inflammatory cells—mainly leukocytes— were found. These were directly contiguous with the epithelial cells of the biliary ducts in areas devoid of basal membrane (Fig. 5). In other places they penetrated among the ductular cells (Fig. 8) and thus were also demonstrable in the lumen (Fig. 9).

Discussion

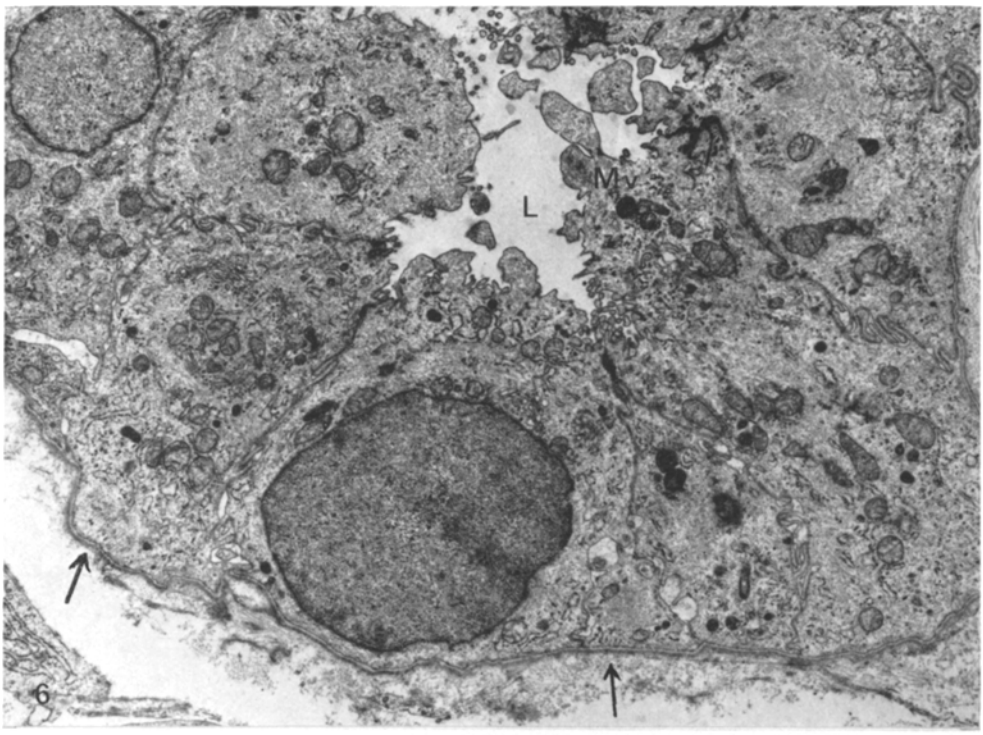
Under normal circumstances intrahepatic bile ducts develop in the fetus to a length of 23 mm, by simultaneous regression of the secondary bile sheet. In the case of the malformation discussed, this regression of the secondary bile sheet fails to come about, and as a result, supranumerary bile ducts persist within the portal tracts. We speak of dysplasia of bile ducts when plus-minus variants occur, *i.e.*, the histologic picture varies in different areas, in some places corresponding to hyperplasia, in others to hypoplasia (Essbach, 1961; Cain and Kraus, 1971).

Disorders based on dysplasia of intrahepatic bile ducts could appear under different clinical and pathologic pictures, and there is some confusion in regard to classification. The isolated forms are called microhamartomas (bile duct adenoma) (Huchzermeyer and Gerhard, 1972); the diffuse form may be localized in the large intrahepatic bile ducts (Caroli's disease), or it may affect the small bile ducts, in which macro- and microcystic forms could be distinguished (Longmire *et al.*, 1971; Jorgensen, 1972; Heymsfield, 1973). Classification is further complicated by the congenital liver fibrosis first described by Kerr *et al.* (1961). This is also accompanied by dysplasia of intrahepatic bile ducts, and is often associated with cystic renal abnormalities (Foulk, 1970; Korányi and Mészáros, 1971; Murray-Lyon *et al.*, 1973; Sommerschild *et al.*, 1973; Thaler *et al.*, 1973). Sherlock (1968) has set up a common group for discussing congenital cystic and fibrotic liver disorders, and only combinations of the single components permit differentiation. According to recent data, "congenital cystic disease" of the liver is both pathologically and clinically independent of congenital liver fibrosis (Longmire *et al.*, 1971; Jorgensen, 1972; Murray-Lyon *et al.*, 1973). In our opinion, cholangiodysplastic pseudocirrhosis is a microcystic variant of congenital cystic disease of the liver, and its clinical process is characterized by repeated cholangitis and a rapid cirrhotic progression, whereas congenital liver fibrosis is characterized by a much slower progression and results primarily in portal hypertension.

According to Essbach (1961) cholangiodysplastic pseudocirrhosis occurs with $1^0/_{00}$ frequency. It was observed by Wohlgemut and Mühl (1963) in 1 percent of cases of juvenile cirrhoses. Diagnosis is possible only by histologic examination. In the differential diagnosis, other juvenile cirrhoses may come into question.

Fig. 6. Portion of a ductule. Edematous microvilli rise into the lumen (*L*). Cytoplasm of epithelial cells of bile ducts is rich in organelles and fine filaments. (Basement membrane marked with arrows. ×8000

Fig. 7. Ductular epithelial cell in centre of figure is irregular. Nucleus (*N*) is relatively small; cytoplasm is poor in organelles, and contains numerous delicate filaments (*F*). ×15000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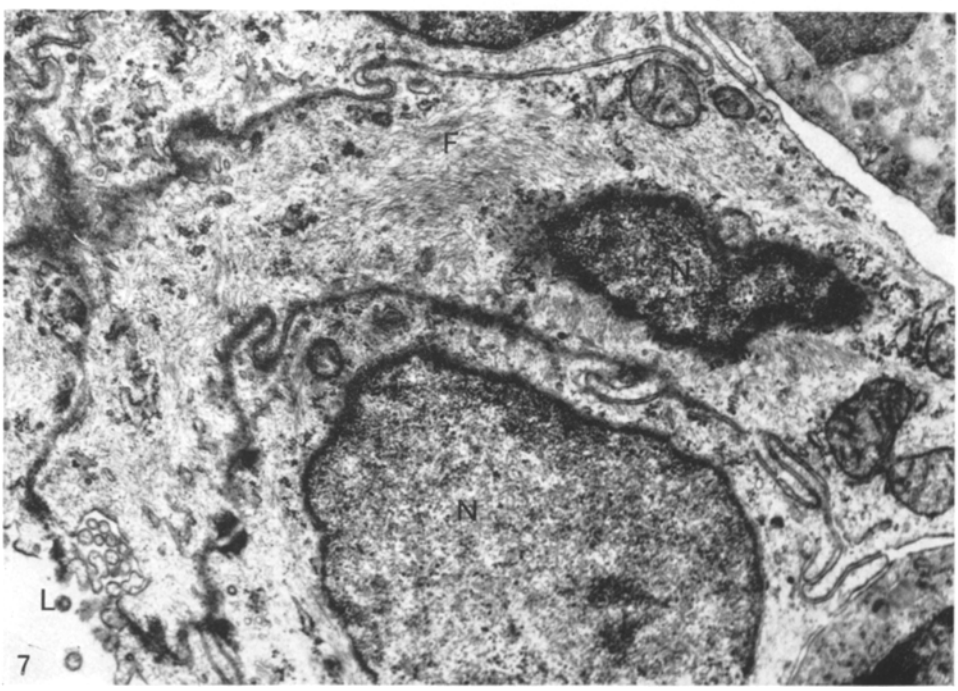
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In some cases the proliferating bile ducts are irregular, the epithelial lining is variously differentiated, they occur mostly at the interface between connective tissue and liver parenchyma, and are not connected within the bile duct system (Althoff, 1964).

In some rare cases, the disease is compatible with life. Adult cases are often associated with intrahepatic bile stone formation (Turnberg *et al.*, 1968; Longmire *et al.*, 1971; Heymsfield, 1973). Cholangitis is the most frequent complication. According to Essbach (1961), the cause of the great frequency of recurrent cholangitis is the succeptibility to infection of the twisted dilated bile ducts. A further complication is portal hypertension arising from progressive fibrosis (Goldschmidt *et al.*, 1969). In such cases, shunt operation is justified (Sommerschild *et al.*, 1973). In five cases of long-term survival, Cain and Kraus (1971) observed the development of multicentric hepatocellular carcinoma.

The results of light microscopic analysis agreed with previous findings (Wohlgemut and Mühl, 1963; Althoff, 1964; Kraus, 1964; Strauch *et al.*, 1965).

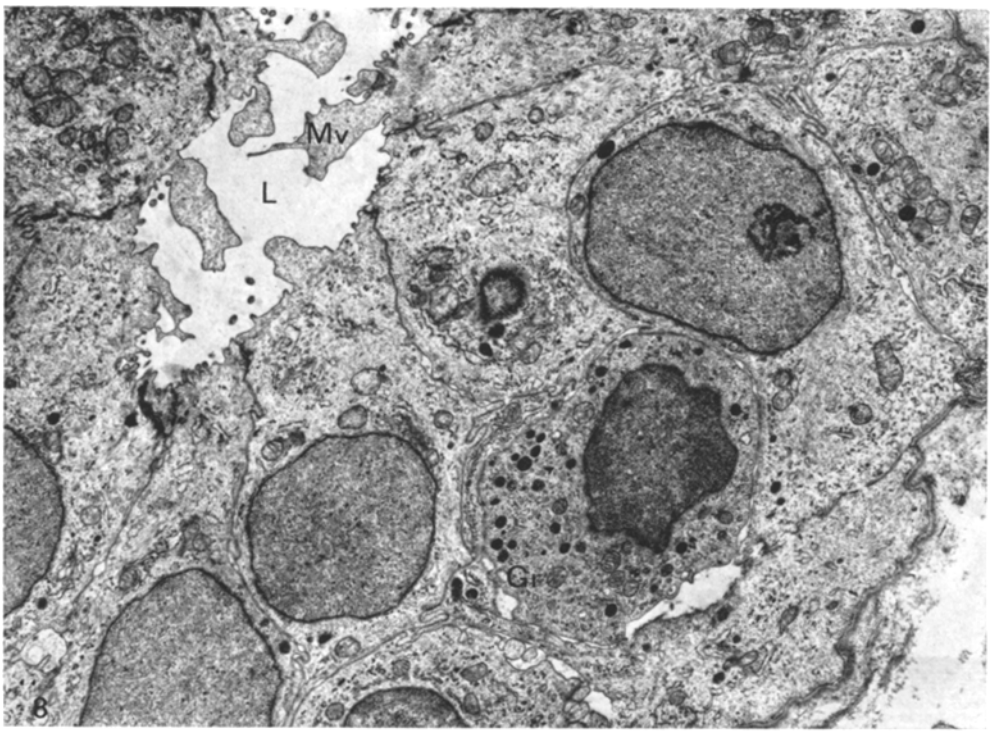
In the literature we did not find data on electron microscopic investigation of cholangiodysplastic pseudocirrhosis. Therefore we will discuss the ultrastructural features in greater detail and compare them with sporadic data based on electron microscopic examination of congenital liver fibrosis (Albukerk and Duffy, 1971; Thaler *et al.*, 1973).

The ultrastructural appearance of liver cells was mostly normal; only mitochondria showed nonspecific alterations in some liver cells. In Disse's spaces, great masses of collagen fibers were visible, which caused at many sites destruction of the vascular poles of the liver cells, and penetration into the cytoplasm; this was also observed in cases of aggressive chronic hepatitis (Balázs and Várkonyi, 1973).

The electron microscopic features of ductular epithelial cells are well known (Sasaki *et al.*, 1967; Balázs, 1971; Sternlieb, 1972), but their function has not been clarified (Erlinger and Dhumeaux, 1974). It is believed—and it also follows morphologically—that they are capable of performing active secretion and resorption, similar to the epithelial cells of the efferent pancreatic ducts and salivary glands (Fisher *et al.*, 1974). They secrete bicarbonate and chloride and absorb water, and are in this way responsible for the final composition of bile. Their secretory activity can be stimulated by secretion (Erlinger and Dhumeaux, 1974). Their absorptive capacity is evidenced by the fact that in cases of cholestasis, the elements of the cholestatic bile were also found in the cytoplasm of the ductular epithelial cells (Sasaki *et al.*, 1967). The secretion and composition of bile was studied by Turnberg *et al.* (1968) in an adult patient who suffered from polycystic liver disease. The amount of secreted bile was 2–3 times more than normal, while the concentrations of bilirubin and bile acids were one-fifth and one-tenth, respectively, of those observed under normal conditions. It is possible

Fig. 8. Lumen (*L*) of ductule is of medium width. On the surfaces of the epithelial cells, facing the lumen, a few edematous microville (*MV*) occur. Among the epithelial cells a granulocyte (*Gr*) is observed. ×8000

Fig. 9. Note granulocyte (*Gr*) in dilated lumen (*L*) of ductule. ×7500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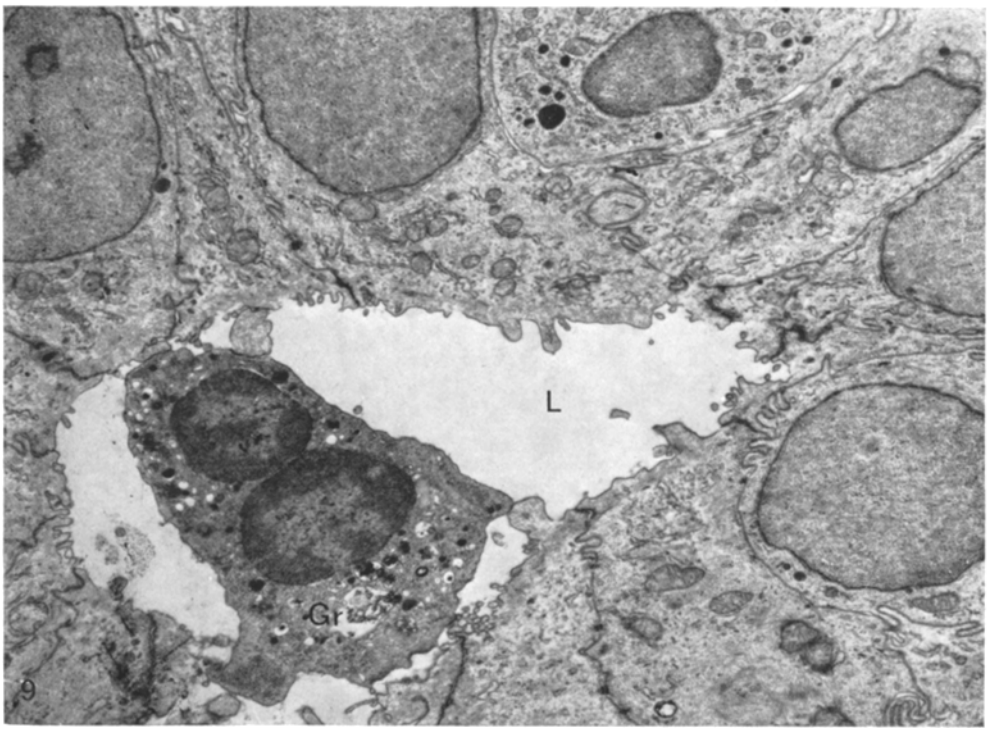
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that in cholangiodysplastic pseudocirrhosis, a considerable quantity of fluid may be present in the tortous, dysplastic bile ducts, but the concentration of fluid is lower, the bile ducts become dilated, and as a result, the microvilli of cells lining the lumen are also damaged.

We found a similar dilatation and destruction of microvilli in the bile canaliculi, which indicated and increased pressure in the bile duct system, as was also observed in experimental as well as in human cholestasis (Balázs, 1970, 1971; Lukács *et al.*, 1972). In our case, cholestasis was not demonstrable clinically, nor by light and electron microscopy. It may be possible, however, that the low bilirubin concentration of the congested fluid in the bile ducts is responsible for the fact that the fluid could not be seen.

Our examinations showed that the epithelial cells of the bile ducts varied in shape and development. There were among them numerous cells with processes containing only a few organelles and many intercalary cells. These phenomena indicate an active proliferation (Balázs, 1971; Sternlieb, 1972). In addition to the cellular cohésions, marked interdigitations secured cohesion of the loosely connected, young epithelial cells. Around the ductuli, the basal membrane was not continuous. It is probable that the penetration of inflammatory elements is related to the inadequate development, and thus to the increased permeability of the epithelial cells and basal membrane of the ductuli.

On the basis of our studies, we believe that in the case of cholangiodysplastic pseudocirrhosis, both fibrogenesis and proliferation of ductular cells are active, progressive processes, in contrast to congenital liver fibrosis, where, according to Albukerk and Duffy (1971), fibrogenesis has a primary role. In our case the liver disease led to cirrhosis within a few months, and ended in hepatic insufficiency, despite healing of the cholangitic complication. This we regard as evidence that the process is a chronic progressive liver disease, and is accelerated by cholangitic attacks.

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Dr. Márta Balázs
Department of Pathology
János Hospital of Budapest Council
1125. Budapest
Diósárok ut 1
Hungary