

# HEPATIC CIRRHOSIS ASSOCIATED WITH FIBROCYSTIC DISEASE OF THE PANCREAS

## CLINICAL AND PATHOLOGICAL REPORTS OF FIVE PATIENTS

BY

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The purpose of this paper is to describe five patients who developed an unusual type of hepatic cirrhosis in the course of fibrocystic disease of the pancreas, and to comment on the aetiology of the cirrhosis. These five patients were among 116 children who were treated for fibrocystic disease at the Children's Hospital, Melbourne, during the period January, 1946, to January, 1953.

While hepatic cirrhosis has been noted in children dying from fibrocystic disease, references are uncommon and only one detailed record (Pugsley and Spence, 1949) of cirrhosis of the type observed in these patients has been found.

### Case Reports

**Case 1.** B.D., a girl aged 9 years, was admitted to the Children's Hospital in May, 1946, having been ill for six months with a cough, mucopurulent sputum, loose, semiformal, pale yellow stools, intermittent fever and wasting. She had been a normal full time baby and her progress in infancy was normal. Both parents and her only sister, aged 2 years, were in excellent health. At the age of 2 years she developed attacks of 'looseness of the bowels' during which her motions were pale, yellow and semiformal, and during such episodes she would be listless and flushed. No definite precipitating cause could be found for these attacks, which usually lasted one to two weeks and occurred three to four times a year. In the intervals her health and appetite were good and her diet well balanced. In December, 1945, she insidiously developed a cough which proved resistant to sulphona-mide treatment and shortly afterwards she started to expectorate blobs of yellow mucopus. Gradually she lost weight and became listless; her bowel motions became frequent, pale, semiformal and offensive. Six months after the cough developed she was admitted to hospital.

Examination revealed a pale, sick, wasted girl with flushed face, slightly cyanosed lips and clubbed fingers and toes. The chest was barrel shaped, the percussion note hyper-resonant, air entry poor, and fine râles were heard over the entire chest. The abdomen was protuberant, the superficial veins prominent, the liver

palpable three fingerbreadths below the right costal margin, its edge and surface feeling hard and nodular. The tip of the spleen was palpable. The patient's stools were large, pale, of the consistency of a thick porridge and malodorous. Analysis showed that there was 43% of fat by weight in the dried faeces and 67% of this quantity was split fat. The Mantoux test, performed with 0.1 ml. of 1 in 1,000 old tuberculin, and the Wassermann reaction were negative. The child coughed much yellow mucopus, from which *Staphylococcus aureus* was grown. Radiological examination revealed widespread and uniform mottling in the lung fields, diffuse emphysema, thick, heavy bronchovascular markings and enlarged, dense hilar shadows. The blood examination disclosed only a polymorphonuclear leucocytosis. Duodenal aspiration was not attempted as the child was too ill.

The clinical course during the next four months until death on September 27, 1946, was slowly and steadily downhill. A persistent, distressing cough attended by expectoration of large quantities of mucopurulent sputum, an irregular temperature, cyanosis and emaciation were the prominent features. During most of this time the stools were bulky, pale, and foul smelling, and contained an excessive amount of fat. On several occasions the girl developed bronchopneumonia but only temporary relief followed the administration of penicillin; for a period of one month she had ascites which spontaneously cleared. An attack of severe bronchopneumonia terminated this distressing illness.

**Necropsy.** The post-mortem examination revealed extensive suppurating bronchiectasis involving all lung lobes; there were many patches of bronchopneumonic consolidation, while the intervening pulmonary tissue was very emphysematous, engorged and oedematous. The liver was enlarged to half again the normal size, and the surface fissured and lobulated in a remarkable manner; the nodules were smooth and varied in size from 4 to 0.25 cm. in diameter. Microscopic sections showed multilobular cirrhosis with bands of fibrous tissue in which were inflammatory cells and bile ducts, separating masses of parenchyma, the cells of which were not arranged in a definite pattern; many of the liver cells were vacuolated and poorly stained. The extrahepatic bile ducts and gall bladder were normal. The spleen was

enlarged to twice the normal size and the splenic veins distended, but no abnormality was detected on microscopic examination. The pancreas was smaller than normal, soft and rather flabby on palpation; section showed white strands of fibrous tissue and an absence of the normal lobular pattern. Histological examination revealed a varying picture of gross fibrosis, atrophy of glandular tissue and dilatation of the ducts. The islet tissue was normal and in many places surrounded by masses of fat and fibrous tissue. The cardiovascular, alimentary, nervous, endocrine, and renal systems appeared normal on macroscopic examination.

**Case 2.** Acute and severe bronchopneumonia deriving from bilateral suppurating bronchiectasis was the cause of the urgent admission of C.S., a girl aged 10 years, to the Children's Hospital on September 3, 1946, where she died within two hours. Her clinical record has been compiled from the parents' history and the medical records of her family doctor and paediatrician. She was the only child of healthy parents and pregnancy and delivery had been normal. The rate of growth and physical and mental development in early childhood seemed fairly normal, but at intervals she passed large, foul-smelling stools, and the abdomen was a little distended. During August, 1942, when aged 6 years, she contracted morbilli and later developed bronchopneumonia, but resolution was slow and incomplete. However, she recovered sufficiently to resume school but had a persistent cough and was very thin. In May, 1943, another severe attack of pneumonia further impaired the child's general health and nutritional state. Examination in August, 1943, revealed a thin, listless child whose weight was 36 lb. and whose abdomen was distended. The fingers were clubbed and coarse râles were heard over the anterior part of the right upper lung field and in the right axilla. Radiological examination showed coarse nodular infiltration involving the upper half of the right lung field, and the axillary region of the left lung field, while the hilar shadows and bronchovascular pattern were very heavy. Assay of the duodenal contents showed a normal quantity of trypsin.

Treatment with a high-protein, reduced-fat diet was instituted. During the next three years until death, the girl's general health and physical growth were seriously impaired and she had a persistent and troublesome cough, productive of mucopurulent sputum. She was able to attend school at irregular intervals only, and two severe attacks of bronchopneumonia left her so weakened and dyspnoeic that she became an invalid. A sudden and severe exacerbation of bronchopneumonia rapidly terminated this steadily progressive and unrelenting disease.

**Necropsy.** Post-mortem examination revealed widespread gross suppurating bronchiectasis affecting all the pulmonary lobes, thick, creamy mucopus filling the bronchial tree. Subpleural abscesses,

suppurating bronchopneumonic areas, and extensive emphysema and oedema were observed throughout both lungs. The liver was similar to that found in the first patient in the group and exhibited extensive fissuring and lobulation (Fig. 1). The gall bladder was small, white, fibrosed and contracted, while the extrahepatic bile ducts were patent. Microscopic examination revealed a pattern identical with that described for the first patient. Some of the liver cells showed vacuolation but otherwise were normal. The pancreas was small, of soft, fleshy consistency, and section, especially of the tail, showed it to be smooth and traversed by strands of fibrous tissue. Microscopic examination revealed extreme fibrosis, atrophy of the glandular tissue and dilatation of the ducts and acini to form cystic spaces. There was much small round cell reaction throughout. The islet tissue was scattered throughout the generally disorganized pancreatic tissue. The spleen was enlarged to approximately twice normal size but no other abnormal features were noted. The cardiovascular, renal, alimentary and endocrine systems appeared normal on macroscopic examination.

**Case 3.** R.O'B., a boy aged 9 years was admitted to the Children's Hospital in July, 1949, with shortness of breath, cyanosis, distressing cough, and general ill-health of some years' duration. He was the only child of apparently healthy parents, and after a normal delivery he had failed to gain weight satisfactorily. When aged 2 months his stools were noted to be bulky, pale and malodorous. He was given a high-protein, high-carbohydrate diet and then gained weight satisfactorily, but his stools remained bulky and offensive. At the age of 3 years he developed pneumonia, was very ill for a period of four months, and thereafter had a persistent intractable cough. Subsequently he had frequent attacks of pneumonia from which he recovered slowly. Examination

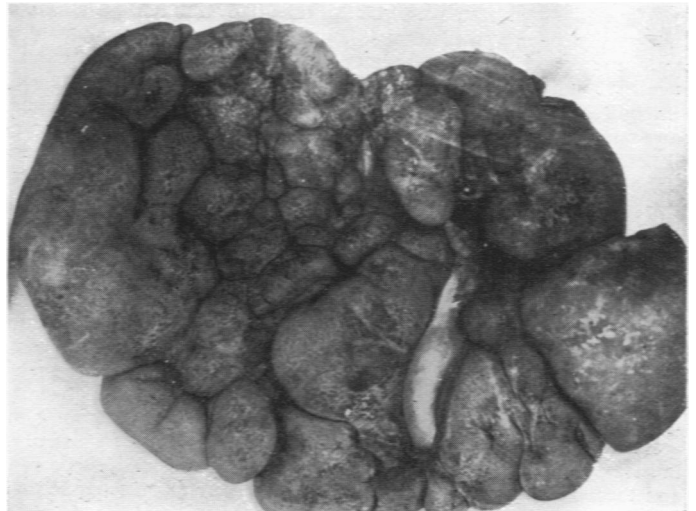


FIG. 1.—Photograph of the liver of C.S., aged 10 years (Case 2), to show the deep clefts and excessive lobulation distinctive of hepatic cirrhosis in advanced fibrocystic disease of the pancreas. Note the white, contracted, fibrosed gall bladder.

during this time showed that the abdomen was always distended, that his stools were pale, greasy and offensive, the fingers clubbed, and his general health poor. When he was 6 years old an assay of duodenal juice for trypsin resulted in a normal finding. The boy gained weight only slowly from a diet high in milk and meat protein but of reduced fat content; pancreatin therapy was maintained.

Examination in July, 1949, showed a pale, slightly cyanosed, undersized child weighing 44½ lb. The fingers and toes were clubbed, the respiratory rate was 40 per minute, and he had audible inspiratory and expiratory wheezes. The chest was barrel shaped, the percussion note hyper-resonant, and scattered rhonchi and râles were heard over the entire chest. The abdomen was difficult to palpate as the abdominal muscles were contracted during expiration to combat the gross pulmonary emphysema. The liver edge could just be felt but did not seem abnormal and the spleen was not palpable. His stools numbered two per day, were pale, semiformal, greasy and malodorous, and analyses of two specimens showed the proportion of fat in the dried stool as 40%, by weight. Large quantities of yellow mucopus were expectorated, and *Staphylococcus aureus*, which was resistant to penicillin *in vitro*, was recovered from the sputum. Radiological examination of the chest showed uniform patchy mottling throughout both lung fields, extensive emphysema and heavy hilar and bronchovascular shadows. The blood amino-acid curve following a gelatine meal showed a slowly rising curve; the fasting level was 5.8 mg. of amino nitrogen per 100 ml. of serum, and specimens of blood at half, one and a quarter, two and a half and five hours showed levels of 6.4, 7.2, 8.1 and 8.3 mg. per 100 ml. respectively. Duodenal intubation did not yield reliable specimens because of technical difficulties caused by severe coughing spasms. From July, 1949, until his death in November, 1949, the boy was constantly cyanosed, very short of breath, and had a very distressing cough which produced large quantities of thick mucopus. An attack of bronchopneumonia terminated this long illness.

**Necropsy.** The post-mortem examination revealed extensive bronchiectasis involving all the pulmonary lobes, the bronchial tree being filled with thick mucopus. The lung tissue was engorged, very emphysematous and displayed extensive patches of bronchopneumonia. The liver was enlarged to half again the normal size, and was similar to the livers in Case 1 and Case 2, the surface being deeply and irregularly fissured and lobulated. Section showed many strands of fibrous tissue with rounded areas of smooth liver substance, some of which were bile stained. Microscopically bands of fibrous and fibrocellular tissue separated masses of liver parenchyma, the cells of which were not arranged in a regular and uniform lobular architecture; many cells were vacuolated. The gall bladder and extrahepatic biliary ducts were normal. The pancreas was small and on palpation felt granular. Microscopically the normal gland structure was replaced by cellular fibrous tissue, the acini and ducts being either dilated, atrophied or fibrosed. Islets of Langerhans were scattered throughout this cellular fibrous tissue. The spleen was somewhat enlarged and the Malpighian

corpuscles prominent. The genito-urinary, alimentary, cardiovascular, nervous and endocrine systems were normal.

**Case 4.** K.R., a boy, was first seen in April, 1950, when 9 years old. He was the second child of healthy parents. The first child was 11 years old and well, the third child died of a respiratory tract infection at the age of 6 weeks, and the clinical features of the illness suggested fibrocystic disease; the fourth child died of fibrocystic disease (confirmed by necropsy) at the age of 2½ years, and the fifth child was aged 1 year and well. The mother, who was a reliable witness and was familiar with the clinical features of fibrocystic disease, stated that the boy had never been seriously ill: he had developed satisfactorily and his bowel motions were always normal. In February, 1950, he developed a cough which gradually became worse, was feverish, and later started to expectorate yellow sputum. Sulphadiazine therapy was not beneficial. The cough and fever persisted, the boy's appetite remained poor, he lost weight, and sweated profusely. A second course of sulphadiazine was without effect.

Examination in April, 1950, after an illness of eight weeks revealed a pale, sick, wasted boy with distended abdomen and clubbed fingers. The chest was barrel shaped and fine râles were heard over the whole of the chest but were more pronounced over the upper lobe of the right lung. Postural drainage produced thick yellow mucopus, culture of which yielded a profuse growth of *Staphylococcus aureus*. The liver was palpable two and a half fingerbreadths below the right costal margin, and the edge felt irregular and hard. The spleen was enlarged to a point one fingerbreadth below the left costal margin. On penicillin the boy rapidly improved: he ate well and gained weight: cough and sputum lessened and in one month he seemed well again. During the next three months the following observations were made. The stools were always formed, normal in appearance and not malodorous, but analysis on three occasions yielded between 40 and 46% of fat by weight of the dried specimen. Duodenal intubation yielded 10 ml. of a viscid, golden-yellow fluid, neutral in reaction and containing 25 units of trypsin (50-100 units normal). The blood amino-acid curve following a gelatine meal showed a fasting level of 5.4 mg. of amino nitrogen per 100 ml. of serum, and specimens at half, one and a quarter, two and a half and five hours showed levels of 4.5, 5.3, 4.7 and 4.4 mg. of amino nitrogen per 100 ml. respectively. Radiological examination of the chest showed mottling in the right upper lung field, heavy hilar shadows and accentuated bronchovascular markings. These changes gradually cleared during a period of three months. A bronchogram showed a little irregular bronchiectasis in the upper lobe of the right lung. Haematological findings were normal apart from a polymorphonuclear leucocytosis. Liver function tests revealed no reaction with the Van den Bergh test, or thymol flocculation test; the thymol turbidity was less than 1 unit; alkaline phosphatase was determined as 10 units (King and Armstrong) and serum protein as 6.7 g. %, with albumin 4.8 g. and globulin 1.9 g. %. Histological examination of the specimen

obtained by needle biopsy of the liver showed an excessive amount of dense cellular fibrous tissue while the liver cells revealed moderate vacuolation. No clear picture of a liver lobule was seen owing to the large amount of fibrous tissue.

By August, 1950, the boy was very well, having gained 28 lb. (12.7 kg.) in weight, and was entirely free of cough and sputum. No abnormal physical signs were detected in the chest but a radiograph showed a little streakiness and mottling in the upper part of the right lung field, and the hilar shadows and bronchovascular lung pattern were accentuated. He remained well until September, 1951, when he contracted a cold and started coughing and expectorating mucopus. He was feverish and developed many crepitations over the left lung anteriorly and posteriorly; a radiograph of the chest showed mottling in both upper lung fields. The sputum yielded on culture a strain of *Staphylococcus aureus* which was sensitive to penicillin. Following penicillin therapy he rapidly improved and though at the end of three weeks his cough and sputum cleared, the crepitations did not finally disappear from the left lung until another month had elapsed.

In February, 1952, he was very well and free of symptoms but a radiograph of the lungs showed increased hilar shadows and some streakiness in both upper lobes. The liver and spleen enlargement and finger clubbing were unchanged. Duodenal aspiration again yielded 10 ml. of golden-yellow viscid fluid with a pH of 7 and less than 25 units of trypsin per ml. The stool, though still formed, contained over 40% by weight of fat in the dried specimen. A fresh specimen of stool emulsified with water failed to digest the gelatine of an x-ray film. When seen last in November, 1952, his condition was unchanged.

This boy is one of a family with proven fibrocystic disease; he has cirrhosis of the liver, a recurrent staphylococcal lung infection, deficiency of trypsin in the duodenal juice and steatorrhoea.

**Case 5.** P.A., a girl aged 11 years and 10 months, was admitted to the Children's Hospital in June, 1950, because of a chronic troublesome cough and abnormal bowel motions. She was the only living child of healthy parents, the first baby being stillborn after a difficult labour. From birth she failed to gain weight satisfactorily, and during the second year her stools became large, pale, loose and offensive, and the abdomen distended. At the age of 18 months a diagnosis of coeliac disease was made and she was given a diet containing liberal quantities of milk and meat, and a high carbohydrate content, but little fat. Progress was slow during the next four years but her general health was fair. In her sixth year she developed pneumonia, from which she recovered only slowly. After this she had a persistent, unrelenting cough. For the age period 6 to 11 years her general health was fair and attacks of measles and pertussis, when aged 8 and 10 years respectively, were not troublesome. As her bowel motions were less frequent and appeared normal, the mother introduced fat into her diet.

Examination in June, 1950, revealed a thin child with clubbed fingers who weighed 58 lb. and had a distended abdomen. The percussion note over the chest was hyper-resonant and there were scattered crepitations over the posterior and lower part of the right side of the chest. A hard liver edge was palpable one and one-half finger-breadths below the right costal margin and the splenic edge was felt three fingerbreadths below the left costal margin. A radiograph of the chest showed considerable and uniform emphysema with accentuation of the bronchovascular pattern. Yellow mucopurulent sputum yielded a profuse growth of *Staphylococcus aureus* on culture. The stools were bulky but formed and microscopically a number of specimens were found to contain many fat globules: several estimations of fat content gave values of between 46 and 56% by weight of the dried faeces. The fasting duodenal content was viscid, golden fluid, alkaline in reaction, and contained less than 25 units of trypsin per ml. The urine was free of albumin and microscopically normal. The findings by haematological examination were within normal limits, and the serum protein was determined as 7.6 g. per 100 ml. with an albumin-globulin ratio of 1:4. The liver function tests, including the Van den Bergh test, thymol flocculation, thymol turbidity and alkaline phosphatase all gave normal readings.

During the next year the girl remained in fair health, her appetite was good, and she passed one or two rather large formed stools daily. However, her cough persisted and she produced some blobs of yellow mucopus each day. On several occasions she became feverish and suffered an exacerbation of her cough. In May, 1951, her physical state was identical with that in June, 1950, with the exceptions that she had gained 7 lb. in weight and that crepitations were heard over both lungs posteriorly. A radiograph of the chest showed changes similar to those previously described, but the *Staphylococcus aureus* isolated from the sputum was now resistant to both penicillin and streptomycin. The blood examination and liver function tests again showed no departure from normal, and the duodenal assay showed less than 25 units of trypsin per ml. of duodenal juice. Liver biopsy was carried out through a small abdominal incision under local anaesthesia. The surface of the liver was pale and very irregular, exhibiting smooth nodules of varying sizes up to 1 cm. in diameter. Microscopic section showed a well-developed multilobular portal cirrhosis with considerable fibrosis and regeneration of liver cells to form nodules. The architectural arrangement of liver cells was variable, some being in lobules, others in masses, but the individual cells seemed normal. In July, 1952, her general condition was unchanged.

This child has chronic steatorrhoea, chronic generalized staphylococcal lung infection, very little trypsin in the duodenal juice and a cirrhotic liver.

### Discussion

In the three patients aged 9, 10 and 11 years respectively, in whom necropsy enabled the determination of its character, the cirrhosis of the liver

was distinguished by excessive lobulation (Fig. 1). Deep clefts divided the lobules which were the tangible expression of the regenerative capacity in which the liver is generally conceded to excel, and such configuration was most conspicuous on the inferior surface of the viscus. The nodulation attending the cirrhosis of the liver of the Banti complex, as exemplified by specimens in the Museum of Pathology of the Children's Hospital, Melbourne, does not compare with the lobular hyperplasia which characterized the livers of each of the children under discussion.

In their macroscopic features one liver was not to be distinguished from another, and uniformity was maintained in their morbid histology, which was that of multi-lobular portal cirrhosis. Irregular extensive fibrosis resulted in the assumption by the portal tracts of exaggerated space and prominence in the microscopic fields (Fig. 2) and swathes of fibrous tissue radiated from the portal areas to enclose lobules of liver cells, singly or in groups; in some instances (Fig. 3) infiltration of the portal regions by small round cells of lymphoid type was sufficiently heavy to obscure the underlying fibrotic process. Inspissation of bile in canaliculi formed by the hyperplasia of bile duct epithelium commonly observed in multi-lobular cirrhosis is illustrated in Fig. 2, and in this photomicrograph is also to be seen a measure of fatty infiltration. Total destruction of liver cells was the feature of the microscopic field photographed to provide Fig. 4, in which isolated groups of hepatic cells are discernible in a field of densely aggregated inflammatory cells.

Cirrhosis of the liver of the type described as occurring in each of these five children afflicted with fibrocystic disease of the pancreas is presented as the end-result of profound and prolonged deficiency. This view of the essential nature of the cirrhosis is founded on the clinical fact that all the patients considered suffered from mal-digestion of long duration; it is supported by the occurrence of a strictly comparable type of cirrhosis of the liver in renal amino-aciduria, in which nutritional deprivation is sustained for a very long period. A third point is that similar hepatic lesions have been produced in animals by experimental manipulations of diet.

Impaired nutrition is a clinical feature of most patients affected with fibrocystic disease, and is referable mainly to the mal-digestion which ensues on the loss of the major portion of the exocrine secretion of the pancreas. All of our five patients exhibited gross steatorrhea, four of the

five had abnormally bulky, pale, malodorous stools and abdominal distension from a very early age, and the two who were examined for inadequate protein digestion as indicated by amino-acid absorption after a gelatine meal were found lacking in this respect. The three patients who died had extensive atrophic and fibrotic pancreatic lesions, and minimal tryptic activity was established in the two as yet alive. It is interesting to note that in two patients, Cases 2 and 3, a normal trypsin level was demonstrable in duodenal content at the ages of 7 and 6 years respectively. Although the presence of trypsin in the duodenal aspirate is uncommon in fibrocystic disease, we have encountered this finding in an infant aged 14 months, who died one month after the appropriate test demonstrated adequate tryptic activity; none the less necropsy revealed advanced fibrosis and atrophy of the pancreas. It would seem that the presence of trypsin is by no means an infallible index of the amount of functioning pancreas.

In this connexion we have noted with interest the report of Gibbs, Bostick and Smith (1950) of two cases of cystic fibrosis of the pancreas, proved by necropsy, in which biochemical evidence was obtained during life that pancreatic achylia was not complete. In one of their patients two vitamin A absorption curves were within the normal range, and a definite trace of trypsin was present at the age of 10 months; in the other, a trypsin concentration within the normal range was found at the age of 8½ months, and this enzyme was still present in concentration unusually high for cystic fibrosis of the pancreas at the age of 14 months.

Renal amino-aciduria frequently results in serious nutritional deficiency from loss of amino acid, and multilobular portal cirrhosis of a type closely resembling that observed in the three of our patients who died of cystic fibrosis of the pancreas has been described in connexion with de Toni-Fanconi syndrome. Himsworth (1947) has described and illustrated two examples of the association of grossly nodular cirrhosis of the liver with renal amino-aciduria. The conspicuous impairment of nutrition which distinguishes both cystic fibrosis of the pancreas and renal amino-aciduria is attributable in both instances to protein wastage, and in both conditions distinctive and apparently identical types of hepatic cirrhosis develop as a long term manifestation of the disorder.

It has been abundantly demonstrated by animal experiment that protein dietary deficiency leads to accumulation of fat in the liver as the result of failure on the part of the cells of the hepatic parenchyma to discharge the function of phospholipid

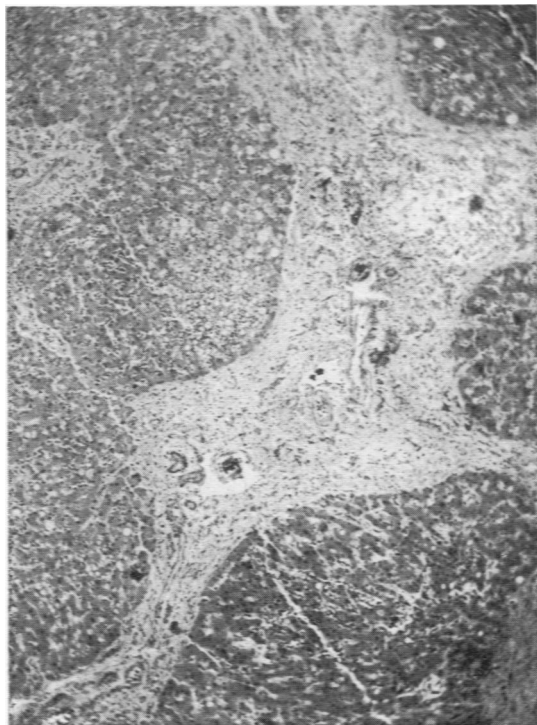


FIG. 2.—Broad band of fibrosis in portal zone; inspissation of bile in newly formed canaliculi; some fatty infiltration.

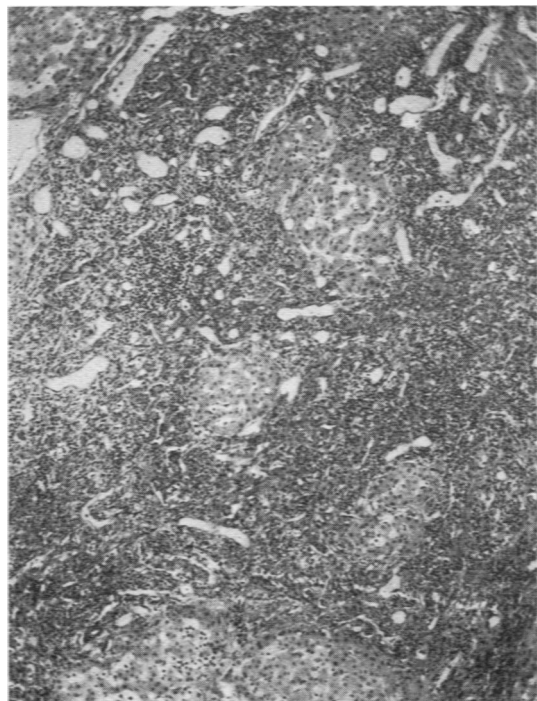


FIG. 4.—Groups of liver cells isolated by inflammatory cell aggregation ensuing on liver cell destruction.

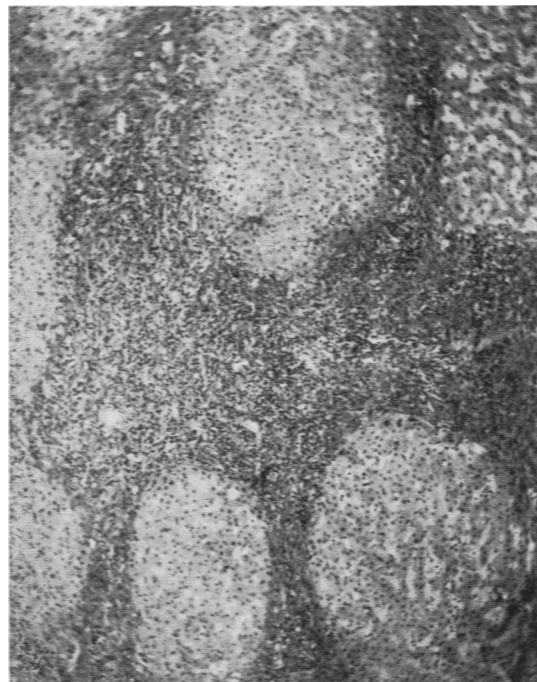


FIG. 3.—Portal fibrosis obscured by infiltration of small round cells of lymphoid type.



FIG. 5.—Liver of child aged 4½ years: fatty infiltration; fibrosis of portal tract; no radial interlobular extension of fibrotic process.

synthesis normally vested in them, a function to which certain amino-acids of protein derivation, notably choline and methionine, are essential. The prolonged retention of an excessive quantity of fat in liver cells leads eventually to their necrosis, with inevitable replacement fibrosis. Notable communications dealing with the supervention of diffuse fibrosis on prolonged and heavy fatty infiltration of the liver, and the scarring and nodulation which follow in the wake of necrosis, are those of Sellers, Lucas and Best (1948), of Himsworth and Glynn (1944) and of Himsworth (1947).

The post-necrotic scarring and nodulation described by experimental physiologists as having been induced in the livers of animals by dietetic methods closely resemble the lesions in our patients. Allan, Bowie, Macleod and Robinson (1924) and Chaikoff, Connor and Biskind (1938) demonstrated that dogs subjected to pancreatectomy and sustained by adequate diet and injections of insulin developed fatty infiltration of the liver. If the fatty infiltration persisted, it was followed by diffuse fibrosis or cirrhosis, the march of which, however, could be arrested by the inclusion of lecithin or choline in the diet.

In the clinical sphere similar observations have been made in African kwashiorkor, a disease caused largely by deficiency in dietary protein, in which fatty infiltration of the liver is a consistent and characteristic lesion; the manner in which cirrhosis of the liver, in appearance resembling that of a 'mild Laennec cirrhosis', may ensue in older children who have been denied the benefit of adequate treatment, has been described by Trowell, Davies and Dean (1952). Cirrhosis of the liver as the climax of prolonged fatty infiltration was also depicted by Waterlow (1948) in his monograph on fatty liver disease as he studied it in infants in the British West Indies.

In cystic fibrosis of the pancreas it seems highly probable that protein deficiency, due mainly to pancreatic dysfunction results in liver damage. The induction of persistent fatty infiltration of the liver and its culmination in cirrhosis is a slow process, scarcely to be consummated in the period of infancy; we have frequently observed fatty infiltration of the liver in babies, but it has not led to any appreciable degree of cirrhosis. In a child who died at the age of 4½ years, although the histology of the liver was that of fatty infiltration attended by increase and condensation of fibrous tissue in the portal tracts (Fig. 5), no penetration of newly formed connective tissue between the lobules was apparent. It would seem that survival for about 10 years is required for the full expression

of the hepatic deterioration which stems from protracted malnutrition.

Of particular interest in this regard is the report by Pugsley and Spence (1949) of a case of cystic fibrosis of the pancreas, remarkable in the fact that the patient lived until he was 17½ years of age. Such tenacity of existence in the presence of an extreme degree of pancreatic atrophy, extensive pulmonary suppuration, and advanced cirrhosis of the liver, had not before fallen within the scope of our reading or experience. The liver of which Pugsley and Spence reproduce a photograph is a facsimile in gross appearance of the livers of the children who provided the subject matter of this discussion.

It is to be remembered that almost all children affected with fibrocystic pancreatic disease die from gross respiratory tract suppuration and concomitant anoxia; both these factors are known to promote fatty accumulation in the liver, as in other organs, and may therefore contribute indirectly to the cirrhotic process. While lung infection has been a feature of the illness of each of the five patients, in the first and fourth pulmonary infection was not apparent until the children were each aged 9 years; when examined, one six months, and the other six weeks after the onset of respiratory infection, a well developed cirrhosis was present. It is therefore improbable that respiratory infection was a material factor in the production of cirrhosis in these two children, but it may have exerted an influence in this direction in the other three patients, in whom the pulmonary complication had been present for years.

The child who provided Case Record No. 1 developed transient ascites and was the only patient of the group to show clinical signs referable to the hepatic cirrhosis; in the two patients in whom liver function tests were carried out the findings showed no departure from the normal. The liver lesion therefore does not seem to cause any disability and its main interest and significance seem to lie in its mode of development. Whether it is possible to prevent the hepatic changes by giving the subjects of cystic fibrosis of the pancreas choline or methionine is a matter for conjecture.

### Summary

Clinical and pathological details of five subjects of cystic fibrosis of the pancreas, aged 9, 9, 10, 9 and 11 years respectively are presented. An extreme degree of an unusual type of multilobular portal cirrhosis was determined by necropsy in three of the children; in the other two, aged 9 and 11 years, the

diagnosis of cirrhosis of the liver was proved during life.

With the exception of transient ascites in one patient, the hepatic cirrhosis did not cause clinical disability, and liver function tests carried out on two patients resulted in normal findings.

Emphasis is laid on the fact that such cirrhosis of the liver is a long term development in cystic fibrosis of the pancreas, and it is considered as deriving from protracted nutritional deficiency.

We wish to thank Dr. A. P. Derham and Dr. J. H. Colebatch for permission to report Cases 1 and 5 respectively.

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#### Addendum

Since this paper was sent for publication we have seen another patient aged 10 years with fibrocystic disease of the pancreas who has an enlarged hard liver and spleen.