CYSTIC FIBROSIS OF THE PANCREAS *

BY

C. E. SNELLING, M.B., AND I. H. ERB, M.B.

(From the Department of Paediatrics, University of Toronto, under the direction of Alan Brown, M.D., F.R.C.P., and from the Department of Pathology, Hospital for Sick Children, Toronto)

Cystic fibrosis of the pancreas has been found relatively frequently in post-mortem examinations of dystrophic infants at the Hospital for Sick Children, Toronto. Nineteen cases have been recognized during the past twenty years, and eleven of these during the past year and a half. Up to the present, in our experience, this condition is a pathological entity diagnosed for certain only after microscopic examination of the pancreas has been carried out. In addition pathological examination has revealed moderately constantly associated conditions in the patient, namely, bronchiectasis, lung abscess, metaplasia of epithelium and fatty liver.

An analysis of the clinical records of the nineteen cases has revealed an almost constant train of events but, as aptly stated by Blackfan and May (1938), 'the clinical manifestations were limited in variety but were so common to many disorders in infancy that it has not been possible to determine accurately the dependable diagnostic features.'

There were nineteen cases with the ages ranging from two to twenty-one months at the time of post mortem. Female sex predominance was observed, being found in eleven of the nineteen. Six of seven cases over six months of age were females. The social status of the whole group was poor. A marked irregularity of incidence has especially been noted, five cases being found in the years 1923 to 1925 and fourteen from 1937 to 1941, with none in the intervening period. The period of the year during which the mother was pregnant and the age of the parents showed no constant trend.

The symptoms are of two groups, nutritional and respiratory. The symptoms referable to nutrition were failure to gain or loss of weight, vomiting, loose and frequent stools, colic and abdominal distension. In most of the cases, particularly those under six months of age, these symptoms were present from birth, in spite of breast feeding being used for all or a large proportion of the time in fourteen cases. Low fat feedings were used in only two cases. Cod-liver oil or its equivalent in amounts considered adequate for vitamin A supplement were given in at least nine cases. Respiratory symptoms were cough, wheezing, rapid breathing and cyanosis. Fourteen patients showed

* Read at the Eighteenth Annual Meeting of the Canadian Society for the Study of Diseases of Children, Brockville, Ontario, June 14, 1941.

respiratory symptoms and in three these symptoms were observed from within a few days of birth.

Signs of malnutrition were observed in all. Many showed abdominal distension, hepatic enlargement, and presented the picture of moderate to severe chronic nutritional disturbance. One third were more than 40 per cent. below the average weight.

Physical signs of lung involvement such as bronchitis, collapse and consolidation of the lung, bronchopneumonia and bronchiectasis were present on admission or during the period of observation in all the cases.

X-ray examination of the lung showed changes, among which were increased linear markings, fibrosis, pulmonary collapse, shift of mediastinum and consolidation. In spite of chemotherapy and bronchoscopic suction the inflammatory process in the lung progressed to a more pronounced state, ending with the death of the patient.

Staphylococcus aureus was cultured from the lung in all but one case, in which no culture was made. Secondary anaemia was present in many but was not a constant feature. Pyuria was found twice.

Post-mortem examination revealed extensive changes in both pancreas and lung in eighteen of the nineteen cases. In one case the lung changes while of the same nature were only minimal in extent. Although in the cases encountered some years ago the gross examination of the pancreas did not suggest anything abnormal, more recently gross changes have been recognized, doubtless due to the fact that they are being looked for. These consisted chiefly of an increase in the firmness of the gland and a variation in the size and shape of the individual lobules, which tended to be spherical rather than of the normal diamond shape. Attempts to trace out the pancreatic ducts in the gross met with little success, but this need not necessarily be interpreted as due to malformation of the ducts.

Microscopically all degrees of fibrosis of the pancreas were found from delicate bands of interlobular connective tissue (fig. 1 A) to a dense, diffuse fibrosis (fig. 1 F). Likewise the changes in the acini varied from a mild dilatation to huge cysts lined by a cuboidal or flattened epithelium and containing varying amounts of pink-staining material which sometimes had a concentric arrangement (fig. 1 B to E) or may even have undergone calcareous degeneration. In one pancreas (fig. 1 F) there were numerous large irregular cystic spaces in the head of the gland suggestive of malformation of the duct with partial obstruction and dilatation. The islands did not appear to be affected by the process.

The lung changes were striking and presented a great similarity from case to case. Perhaps the most outstanding feature was the plugging of numerous bronchi and bronchioles with thick, tenacious, greenish or yellowish, purulent exudate (fig. 2 A and B). Other lesions included widespread bronchiectasis of smaller bronchi and bronchioles (fig. 2 A, B, C) and multiple abscesses which in some instances perforated the pleura (fig. 2, D 3) giving rise to empyema. In most cases, also, there were areas of recent lobular pneumonia (fig. 2, D 1 and 2). In some cases the bronchiectatic cavities were partially lined by squamous

FIG. 1.—Photomicrographs of pancreas from six different patients with cystic fibrosis of pancreas. Ages at death ranged from 3 months to 21 months. All showed chronic lung changes. Ages in months: A. 21, B. $5\frac{1}{2}$, C. $9\frac{1}{2}$, D. 3, E. $5\frac{1}{2}$, F. 3. Hematoxylin and eosin, A to E $\times 110$ F $\times 25$.

FIG. 2.—Sections of lung from six different patients with cystic fibrosis of pancreas.
A. Infant of 10 months. B. Infant of 21 months. Pancreas shown fig. 1 A.
C. Infant of 5½ months. Pancreas shown fig. 1, B. D. 1. Infant of 3 months.
D. 2. Infant of 3 months. Pancreas shown fig. 1 D. D. 3. Infant of 7 months.
Hematoxylin and eosin $\times 1-8$.

epithelium (fig. 3 A). In others there was squamous metaplasia of the epithelium of the trachea (fig. 3 B). As pointed out above the predominating organism was staphylococcus aureus.

Although the outstanding changes were found in pancreas and lungs another almost constant finding was the presence of fat in varying amounts in the liver cells.

The sequence of events so far as the lung is concerned appears to be as follows: Whatever the cause of metaplasia of tracheal and bronchial epithelium the loss of ciliary activity results in a sort of physiological obstruction to the removal of secretion from the bronchi and bronchioles. As these secretions, infected usually by staphylococci, continue to accumulate in the bronchi the

FIG. 3 A.—Photomicrograph of wall of bronchiectatic cavity (fig. 2 C) showing epithelial metaplasia. For pancreas see fig. 1 B.

FIG. 3 B.—Photomicrograph of wall of trachea from 3 months old infant, showing epithelial metaplasia, and dilated glands in mucosa.

For pancreas see fig. 1 F.

Hematoxylin and eosin $\times 75$.

combination of pressure on the mucosal lining plus the toxic action of the bacteria frequently results in varying degrees of ulceration of epithelium with damage to the supporting structures, with varying degrees of dilatation of the bronchial tree. Strangely enough, these changes may be extensive in a given lobe of the lung and show evidence of much chronicity without any appreciable involvement of the surrounding lung parenchyma (fig. 2 D, 1 and 2). Usually, however, by the time the case comes to autopsy one or more lobes show quite extensive recent lobular pneumonia which may be interpreted as the last link in the long chain of events leading ultimately to the death of the patient.

Wolback and Howe (1925) demonstrated experimentally that vitamin A deficiency in the guinea pig and albino rat brought about a substitution of stratified keratinizing epithelium for normal epithelium. Similar metaplasia in infants was reported by Blackfan and Wolback (1933) describing the picture of vitamin A deficiency where they observed metaplasia of epithelium, particularly of the respiratory tract associated with pulmonary infections and of the pancreas where the picture was one of fibrocystic disease. They stated

that at first they regarded the pancreatic change as one of vitamin A deficiency, but since it was observed without other evidence of vitamin A deficiency and vitamin A deficiency might be present without pancreatic change the two were not necessarily connected. Blackfan and Wolback (1933) and later Blackfan and May (1938) expressed the view that the pancreatic change was due to the production of an abnormal secretion which inspissates in the ducts, leading to destruction and atrophy of ducts and acini. This may be responsible for the failure to utilize fats and vitamin A. Andersen (1938, 1939) observed the same pathological changes in a series of cases and stated that the changes in the lung and epithelium in other parts of the body may be secondary to a lack of vitamin A resulting from poor fat absorption as a consequence of primary change in the pancreas, because if no fat is absorbed vitamin A is not absorbed either. She felt that the pancreatic abnormality was probably a congenital defect because symptoms frequently commence at birth. Other possible explanations given by her were foetal inflammation of the pancreas or vitamin A lack in the mother. It is agreed by these authors that the lung changes are due to a metaplasia of bronchial epithelium with a lack of secretion and loss of ciliary action allowing infection and stagnation to take place in the bronchial tree and alveoli.

That lack of vitamin A ingestion is not the predisposing cause is shown by the finding that in at least nine of the present cases amounts of vitamin A considered adequate had been supplemented to the usual milk diet. No data are available on the vitamin A intake of the mother. However, figures from the Ontario Government on employment have been considered and this bears no constant relation to the incidence of this disease. Ebbs (1941), in a survey of the diets of pregnant women found that deficient diets were common during 1938-39 and up to the fall of 1940, when rather suddenly the deficient diet almost ceased to exist among the pregnant women in the clinic. It will be interesting to see if the incidence of this disease falls off.

Vitamin A deficiency as a result of poor absorption due to a primary pancreatic lesion will in due time lead to metaplasia of the bronchial epithelium and the respiratory symptoms. However, this sequence of events could hardly be present in three of our cases in which the respiratory symptoms were present within a few days of birth. A case of xerophthalmia in an infant seven-and-a-half months of age was observed by us. Sobee had been employed in feeding this patient from three weeks of age, with viosterol as a supplement. The earliest symptoms observed four months later were a head cold and stationary weight. Even at seven-and-a-half months there was no bronchopneumonia or bronchiectasis. Eight of the present patients came to post mortem at four months of age or under and all were fed on breast milk or whole-milk feedings. This is a short time for the changes to occur due to vitamin A lack after birth. It certainly would appear in these that the lung changes had begun prior to birth. This suggests that vitamin A lack in the mother is a probable cause of this trouble. In support of this, all of the patients had a poor social background.

The sequence of events in this syndrome can occur in at least two ways: (1) the condition is primarily in the pancreas as an inherited or congenital or acquired defect; or (2) the condition in the child is the result of some defect in the diet of the mother or her ability to pass vitamin A to the foetus.

(1) With a defect of the pancreas there is poor absorption of fat soluble vitamin A, followed by metaplasia of epithelium, particularly seen in the

bronchial tree. This change causes poor ciliary action of bronchial epithelium, stagnation of infection followed by bronchiectasis.

(2) If there is primarily a defect in the vitamin A supply from the mother, then at birth the pancreas and bronchial epithelium might both be affected. Due to poor pancreatic function vitamin A absorption is interfered with causing further changes in the lung with a result similar to that described above.

Staphylococcal infection of the lung occurs in practically all of these cases. In examining the pneumonia records for the hospital, of 184 cases of infants under two years of age, it is found that the staphylococcus is one of the causative organisms in forty-two, or twenty-five per cent. It is interesting to speculate about the factor which predisposes to staphylococcus infection in this condition.

Regarding diagnosis, from our experience to date this has been accurately established only at post mortem. The diagnosis has been made, with a query in a few ante mortem, but in one of these no changes were found in the pancreas and the lung showed the usual type of bronchopneumonia seen in infants.

May and McCreary (1940, 1941) using the barium sulphate meal, glucose tolerance test, stool fats estimation and vitamin A absorption test state that none of these tests were specific for the diagnosis of coeliac disease in differentiating it from other conditions (including cystic fibrosis of pancreas) which produce coeliac-like symptoms. Andersen states that this condition can be differentiated from coeliac disease by aspiration of duodenal contents and analysing for trypsin, lipase and amylase. These are absent in cystic fibrosis of the pancreas but not in coeliac disease.

It is possible that patients with milder forms of this condition recover but from our experience to date the prognosis is very unfavourable.

In treatment Andersen has advised that the patients be fed 20 to 40 per cent. more than the average required calories because she feels in that way with partial absorption the requirements will be met. In addition large amounts of vitamin A are given and pancreatin is mixed with the feeding. She feels that she has improved certain patients by this routine.

REFERENCES

- Andersen, D. H. (1938). *Amer. J. Dis. Child.*, **56**, 344.
 — (1939). *J. Pediat.*, **15**, 763.
 Blackfan, K. D., and Wolback, S. B. (1933). *Ibid.*, **3**, 679.
 —, and May, C. D. (1938). *Ibid.*, **13**, 627.
 Ebbs, J. H., Tisdall, F. F., and Scott, W. A. (1941). *J. Nutrit.*, **22**, 515.
 May, C. D., and McCreary, J. F. (1940). *J. Pediat.*, **17**, 143.
 —, — (1941). *Ibid.*, **18**, 200.
 Wolback, S. B., and Howe, P. R. (1925). *J. exp. Med.*, **42**, 753.