CASE REPORTS

CONGENITAL FIBROCYSTIC DISEASE OF THE PANCREAS

A REPORT OF TWO PROVED CASES OF DISSIMILAR CLINICAL TYPES IN SIBLINGS

BY

AGNES R. MACGREGOR, M.D., F.R.C.P.Ed., and KENNETH RHANEY, M.B., Ch.B.

(From the Department of Child Life and Health, Edinburgh University)

In her important paper on cystic fibrosis of the pancreas, Andersen (1938) showed that this disease manifests itself as one of three clinical syndromes. This has been confirmed by many subsequent workers. The syndromes have the following salient features:

(1) Newly born infants who die within a week of birth from intestinal obstruction due to inspissation of meconium, sometimes associated with peritoneal bands, volvulus or atresia.

(2) Infants between one week and six months old, in whom the principal features are early failure to thrive, often despite a good appetite, large fatty stools, and intolerance to fat in the diet. These infants invariably present an intractable infection of the respiratory tract resembling whooping-cough, with paroxysms of coughing and cyanosis. This infection appears to be the immediate cause of death.

(3) Children over six months of age, who present the clinical features of the coeliac syndrome.

It is now recognized that congenital fibrocystic disease of the pancreas has a high familial incidence. In a recent paper on the genetics of the disease, Andersen and Hodges (1946) reviewed the literature and concluded that 'it occurs among siblings, twins and more distant relatives with a distribution which is compatible with the hypothesis that it is carried as a relatively infrequent hereditary trait.' They collected from the literature several instances in which one sibling suffered from congenital intestinal obstruction and another from proved pancreatic disease presenting one of the other clinical syndromes (Flax et al., 1942; Deem and McGeorge, 1941; Attwood and Sargent, 1942; Philipsborn et al., 1944). In none of these instances were both siblings examined at autopsy. The following case records illustrate the occurrence of dissimilar clinical types in siblings, one of whom suffered from congenital intestinal obstruction. Both were proved by post-mortem examination to have cystic fibrosis of the pancreas.

Case Reports

Case 1. The patient was a female infant aged four months at the time of admission to hospital. She was the second child of her parents, the first-born being a healthy girl of six years. She was admitted because of cough since birth, and stridor for two months. She was said to have been one month premature (birth weight $5\frac{1}{2}$ to 6 lb., spontaneous delivery). She was well at birth, but attempts to institute breast feeding failed after three days. She was given boiled cows' milk, and later National Dried Milk, in appropriate amounts with the addition of adequate vitamins. The appetite was good until one week before admission, when it became capricious, and at some feeds only one ounce was taken.

She was said to have had a cough since birth, but this did not cause distress. Two months before admission she began to vomit after feeds, and developed stridor, which was accompanied by cyanosis during the last month. At that time she developed acute catarrh with nasal discharge. The cough became worse, with paroxysms. This was associated with great distress and cyanosis, and aphonia developed. During the last week before admission, the symptoms became more severe. Diarrhoea developed, 'frequent loose, brown stools' being passed. The appetite became poor and she began to lose weight.

CLINICAL EXAMINATION. The infant was well proportioned but of poor nutrition, her length being 22 inches, and her weight 8 lb. 13½ oz. The abdomen was not distended, and no enlargement of the liver or spleen could be detected. Muscle tone was poor, and great weakness resulted from the paroxysms of coughing. There was slight cyanosis. The alae nasi were moving. There was no nasal discharge. The fauces were slightly congested. The chest was held in the position of inspiration. The lower ribs were indrawn on inspiration. A resonant percussion note was obtained, and on auscultation the expiratory phase was prolonged.

No abnormality of the alimentary system was found. The nervous system was normal. The white blood count was 12,000 per c.mm. of blood, haemoglobin 75 per cent. (Sahli). The

temperature was 98° F., the pulse 134 per minute, and respiration 36 per minute. X-ray examination on admission revealed 'no gross pulmonary lesion.' Three days before death a second examination showed 'exaggerated shadows at both bases, consistent with bronchiectasis.'

FURTHER PROGRESS. Death occurred after sixteen days in hospital. During this time she became progressively weaker and the respiratory difficulty more severe. Vomiting followed all feeds, and the stools became frequent, offensive, and watery. They were not noticeably fatty. During the whole period in hospital the temperature was normal or subnormal, except for two occasions when it rose to 99° F. Owing to the cyanosis, oxygen was administered continuously. Laryngoscopic examination revealed no obstruction in the larynx, which was inflamed. There was thick secretion in the pharynx. Six days before death she collapsed and was pale, cold, cyanosed, and gasping for breath. Penicillin was given by intramuscular injection until death, without obvious beneficial result.

POST-MORTEM REPORT. The body was that of a small, emaciated female infant. The chest was held in the position of inspiration, with the ribs elevated. There was no jaundice of the skin. The larynx, trachea, and main bronchi were filled with thick yellow pus, and the mucous membrane was slightly congested. There was no anatomical abnormality of the larynx.

The left pleural sac contained air under pressure, but the left lung was only partly collapsed. In both lobes there was interstitial emphysema, with large air bullae under the pleura and in the septa. The right pleural sac was healthy, and the right lung showed only vesicular emphysema. No consolidation could be detected in either lung. Throughout the whole bronchial system there was severe purulent bronchitis, all the bronchi down to the smallest visible twigs being filled with thick yellow pus. There was no obvious dilatation of the bronchi, and suppurative disorganization was not evident to the naked eye. The lymph nodes in the roots of the lungs were a little swollen and deep red.

The heart and pericardium were healthy. The alimentary tract showed nothing of note. The peritoneal sac was healthy. The liver was not enlarged but was bright yellowish brown, and showed a considerable amount of bile staining. The gall-bladder contained dark green bile, which was easily expressed into the duodenum. The spleen was of appropriate size and showed nothing of interest. The kidneys were rather paler than usual, but otherwise normal. The pancreas was rather below the expected size, of about normal consistence, but slightly nodular on the surface. It was not obviously fibrosed.

The head was not examined.

BACTERIOLOGICAL REPORT. The pus in the bronchi contained immense numbers of Gram-positive and Gram-negative bacilli, which, on

culture, proved to be a diphtheroid bacillus and *Bacillus lactis aerogenes*. *Staphylococcus aureus* was not found in the direct film or on culture.

MICROSCOPICAL REPORT. Pancreas (fig. 1, p. 59). The gland acini were formed of small, atrophied cells, and their slightly dilated lumina contained plugs of inspissated secretion. Similar material was present in the lumina of intralobular and interlobular ducts, which were slightly dilated. One of the larger ducts in the head of the pancreas was also dilated and its lumen obstructed by inspissated material. The islets of Langerhans were normal. In many parts there was a considerable increase of interlobular and interacinar fibrous tissue. The amount varied, and in those places where it was greatest there was a reduction in the number of acini.

Lung. The bronchi of all sizes were filled with mucus, among which were masses of bacteria and variable numbers of polymorph leucocytes and epithelial cells. The inflammatory cells were surprisingly scanty and much degenerated. Some bronchi showed a moderate amount of inflammatory cell infiltration of the wall, with both mononuclear cells and polymorph leucocytes. The epithelial lining was intact in the majority, but in some of the larger bronchi the ciliated epithelium had been replaced in parts of the wall by stratified squamous epithelium. Most of the mucous glands in the walls of the large bronchi were actively secreting, but others were lined with low cubical cells, and the lumina were dilated and contained inspissated secretion of a hyaline character, staining strongly with eosin (fig. 2, p. 59). There was no bronchiectasis and no disorganization of the bronchial walls. The inflammatory process had not extended to the alveoli. There was a moderate degree of vesicular emphysema.

Liver. There was severe fatty change, affecting principally the portal zones of the lobules. There was no increase in fibrous tissue and no abnormality of the bile ducts was noted.

SUMMARY. This was a case of purulent bronchitis with cystic fibrosis of the pancreas and fatty change in the liver.

Case 2. The patient was a male infant born sixteen and a half months after the birth of his sister (case 1). His birth weight was 5 lb. 14 oz. Delivery was spontaneous, but the baby was limp and cyanosed at birth. During the first two days respirations were shallow and murmury, and he had several attacks of respiratory failure with cyanosis. Chest expansion was poor, and a few crepitations were heard. Meconium was said to have been passed on two occasions: once on the second day and once on the third day. No abnormality of the meconium was noted. Death took place on the third day.

POST-MORTEM REPORT. The body was that of a male infant weighing 5 lb. 14 oz. The umbilical cord was partly dried. There was slight jaundice.

When the abdomen was opened a greatly distended loop of bowel presented. It was approximately six inches long, and its lower end was four inches proximal to the ileo-caecal valve. It contained meconium, which was of normal colour but more viscid and cohesive than usual. Proximal to this loop no abnormality was noted in the bowel and its contents. At the distal end of the loop the character of the contents underwent a sudden change, and the remainder of the ileum contained a small quantity of pale green, thick, paste-like material, which could be forced along the bowel only with great difficulty. The ileo-caecal valve was patent. The caecum contained a little of the same material. The colon contained white mucus and was contracted. Obstruction was apparently present at the distal end of the dilated loop, but had produced no hypertrophy of the wall. There was no stricture, peritoneal band, atresia, or volvulus.

The pancreas was macroscopically normal. The liver was intensely congested. The biliary passages were healthy. Both kidneys contained heavy deposits of uric acid crystals.

The larynx, trachea and main bronchi contained a small quantity of frothy, blood-stained fluid. The pleural and pericardial sacs were healthy.

Both lungs showed widespread pneumonia, only a small strip at the anterior border of the right lower lobe being healthy. The remainder of both lungs was intensely congested and of greatly increased bulk and consistence. The right lung was more affected than the left. The cut surfaces were very moist, and turbid fluid was expressed from the bronchi.

The heart showed no developmental abnormality. Both atria were distended. The ventricles were contracted. The oesophagus was congested throughout its length. The thymus gland was healthy.

The venous sinuses of the dura mater, and the veins in the lepto-meninges, were congested. The brain substance was healthy.

BACTERIOLOGICAL REPORT. A culture from the lung yielded a growth of *Bacillus coli* and *Staphylococcus albus*.

MICROSCOPICAL REPORT. Pancreas (fig. 3, p. 59). Atrophy of the acinar tissue was revealed. In most of the lobules the acini were reduced in number and in size, being composed of small cubical or flattened cells. In many acini the lumen was slightly larger than normal and was filled with inspissated secretion of hyaline appearance. Some of the acinar cells contained apparently normal secretory granules, but in others there were large, faintly acidophil, hyaline bodies, which occupied much of the cytoplasm, and appeared to be of the same nature as the inspissated material in the lumen (fig. 4, p. 59). In contrast, some acini, lined by atrophied cells, showed no visible lumen. The small interlobular, and many intralobular, ducts were slightly dilated and filled with inspissated secretion. Some of the intralobular ducts were empty and not dilated. The larger pancreatic ducts were not present in the

tissue available for examination. The islets of Langerhans were greatly reduced in number and size. There was a slight increase in interlobular and interacinar stroma, which was oedematous but showed no evidence of inflammation.

Lung. The lungs contained a large quantity of vernix, some of it in lumps, but most of it forming thick membranes lining the walls of terminal bronchioles and alveolar ducts. Proximal to it the respiratory passages were over-distended, but the distal parts were atelectatic and compressed. Widespread patchy exudate had developed in relation to the vernix and was composed mainly of polymorph leucocytes. Other areas were filled with blood and oedema fluid. There was no abnormality of the bronchial mucous glands.

The liver showed intense congestion, and in the portal zones some of the cells contained small globules of fat.

Oesophagus. There were no pathological features apart from intense congestion of the submucous coat.

The spleen showed nothing of interest.

Kidneys. The collecting tubules were dilated and contained the structureless debris found in association with deposits of uric acid crystals.

SUMMARY. This was a case of meconium ileus associated with cystic fibrosis of the pancreas. There was inhalation of the vernix, with pneumonia.

Comment

The occurrence of pancreatic lesions characteristic of congenital fibrocystic disease in these two siblings provides strong evidence in favour of the conclusion of Andersen and Hodges (1946) that meconium ileus in the newborn has the same etiology as the two clinical syndromes that reveal themselves in later infancy. It also confirms the conception that the clinical type of the disease is determined by the age at which the pathological process in the pancreas results in a severe deficiency of exocrine secretion. If this stage is reached at the time of birth, meconium ileus results; if in the early months of life, the respiratory type; if in later infancy, the coeliac type.

If the pathological changes are due, as is believed, to inspissation of secretion in the acini and ducts, and if the obstruction thus caused persists, the degree of atrophy, dilatation and fibrosis will depend, at least in part, upon the duration of life. Accordingly all these features were more fully developed in the pancreas of the older child, although at the time of her birth the pancreatic function was less impaired than in the case of the infant who developed meconium ileus.

Stenosis or atresia of the main pancreatic duct has been found in a proportion of cases of congenital fibrocystic disease (Kornblith and Otani, 1929; Hurwitt and Arnheim, 1942; Kauffmann and Chamberlain, 1943). Unfortunately the main pancreatic duct was not examined in either of the cases under discussion. In case 2 certain features were found that could not readily be explained by

FIG. 1.—Case 1. Pancreas shows dilated acini and ducts containing inspissated secretion. Other acini are atrophied. Inter- and intra-lobular stroma is increased. H. and E. $\times 115$.

FIG. 2.—Case 1. The wall of the bronchus shows dilatation of mucous glands, with inspissation of secretion. H. and E. $\times 160$.

FIG. 3.—Case 2. The pancreas shows atrophy of acini. The ducts and some acini are dilated and contain inspissated secretion. The stroma is increased. H. and E. $\times 160$.

FIG. 4.—Case 2. Pancreas. Acinus showing hyaline bodies in the cells and inspissated secretion in the lumen. H. and E. $\times 650$.

PLATE I

obstruction in the main duct, and suggested an abnormality of the acinar cells. Some of the intralobular ducts that showed no evidence of obstruction, being undilated and empty, were related to acini that contained inspissated secretion and were slightly dilated. Some acinar cells contained hyaline bodies similar to inspissated secretion in the lumen. This strongly suggests that they were producing an abnormal secretion.

In case 1, changes suggesting an abnormality of secretion were found in the mucous glands of the bronchi. Farber (1944b) has emphasized that the pancreas is not the only gland in which changes in the physical character of the secretion occur. To the involvement of the tracheal and bronchial mucous glands he attributes the accumulation of thick mucus in the respiratory passages, which causes the paroxysmal cough and respiratory obstruction.

It thus appears that the characteristic pathological changes of this disease are the result of an error of secretory function, and that other glands in addition to the pancreas may be affected. The names by which the condition has become commonly known, fibrocystic disease, or cystic fibrosis of the pancreas, are, therefore, unfortunate, for as May (1947) has observed, 'The pathology includes much more than fibrosis, but the name "cystic fibrosis" which has been proposed is definitely misleading. The dilated ducts and acini are not true cysts, and there actually is another rare condition in which there is an involvement of the pancreas with numerous true cysts.'

In most of the reported cases the organism responsible for the respiratory infection was *Staphylococcus aureus*. The character of the purulent bronchitis in case 1 was similar to that found in other cases of fibrocystic disease of the pancreas in which *Staphylococcus aureus* was the causative organism. This organism was not present in films and cultures made at autopsy: these yielded diphtheroid bacilli and *Bacillus lactic aerogenes*. The character of the pus and the microscopical appearance of the bronchi were in keeping with an infection of low virulence. It is possible that *Staphylococcus aureus* had been present, and had been eliminated by penicillin therapy, but no

bacteriological investigations of the bronchial secretions were made during life.

Summary

The occurrence of fibrocystic disease of the pancreas in siblings is reported. One died of respiratory infection at the age of four months, and the other with meconium ileus at the age of two days. In both cases the diagnosis was proved by autopsy.

The pathological changes in the pancreas appeared to result from an abnormal secretion of the acinar cells. A similar abnormality was present in the bronchial mucous glands of the infant that died of respiratory infection.

We wish to express our thanks to Prof. Charles McNeil, and Dr. W. F. T. Haultain for permission to publish the cases and for the use of the clinical records. We are also indebted to Dr. J. L. Henderson for clinical particulars of both cases and for helpful criticism. We are grateful to Prof. R. W. B. Ellis for his help and encouragement.

REFERENCES

- Andersen, D. H. (1938). *Amer. J. Dis. Child.*, **56**, 344.
 — and Hodges, R. G. (1946). *Ibid.*, **72**, 62.
 Attwood, C. J. and Sargent, W. H. (1942). *Radiology*, **39**, 417.
 Deem, H. and McGeorge, M. (1941). *New Zealand med. J.*, **40**, 155.
 Farber, S. (1944a). *J. Pediat.*, **24**, 387.
 — (1944b). *Arch. Path.*, **37**, 238.
 Flax, L. J., Barnes, M. and Reichert, J. L. (1942). *J. Pediat.*, **21**, 475.
 Hurwitt, E. S. and Arnheim, E. E. (1942). *Amer. J. Dis. Child.*, **64**, 443.
 Kauffmann, W. and Chamberlin, D. B. (1943). *Ibid.*, **66**, 55.
 Kornblith, B. A. and Otani, S. (1929). *Amer. J. Path.*, **5**, 249.
 May, C. D. (1947). *Chronic Disturbances of Nutrition in Diseases of Children*, ed. Paterson, D. and Moncrieff, A., **1**, 337. London.
 Philipsborn, H. F. Jr., Lawrence, G. and Lewis, K. C. (1944). *J. Pediat.*, **25**, 284.