May 1955.

Sir,

I have the honour to submit this study of Fibrocystic Disease of the Pancreas in competition for the Thomson Memorial Medal.

I am,

Yours faithfully,

5th Year Medicine.
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INTRODUCTION

In 1905 Landsteiner described the findings of "cystic pancreatitis" associated with meconium ileus and staphylococcal peritonitis in a female child of five days. This was the first authentic report of the lesions in fibrocystic disease of the pancreas. A few isolated cases appeared in the literature in the ensuing years, but it was not until 1933 when Blackfan and Wolbach published their autopsy findings in eleven cases, that the attention of paediatricians and pathologists became focussed on this hitherto unrecognised disease. Five years later, in 1938, Dorothy Andersen subscribed a brilliant paper in which she related the natural history, the clinical manifestations, and the histo-pathology of "cystic fibrosis" of the pancreas.

The material now presented is based on observations made during the three vacations I was privileged to spend in the Department of Clinical Pathology, The Hospital for Sick Children, Great Ormond Street. The study was initiated in 1952 when I assisted Dr. J. C. W. MacFarlane in the estimation of serum anti-thrombin levels. My interest in fibrocystic disease was further stimulated when it was my good fortune to follow up a case of meconium ileus from admission to discharge.

During a later visit to the hospital I resolved to
make a critical survey of the records of six cases and
to examine them personally. The chosen cases exhibit
various aspects of the condition, namely, meconium ileus
recovering after operation, fibrocystic disease in two
sisters, a case with severe respiratory symptoms,
another with predominant alimentary symptoms, and a
sixth who was apparently well-controlled. The detailed
histories are included as an appendix. My experience
of technical procedures forms the background of a
section concerned with laboratory diagnosis, and
discussions with Dr. A. P. Norman and Ward Sisters
provides the foundation for the description of the
management of the disease.
The clinical signs and symptoms of fibrocystic disease of the pancreas are conveniently grouped into three classes. The first of these, meconium ileus, is an acute surgical emergency in the newborn. This condition is caused by the paucity of pancreatic secretion before birth which results in a failure of liquefaction of meconium. Thus the intestine is obstructed by a solid or semi-solid core of alimentary tract secretions. In this series, Michael G. exemplifies that aspect of the disease. Surgical intervention a few hours after birth enabled this little boy to survive, although he later showed signs of pancreatic and pulmonary dysfunction.

The second stage is described as the infantile type in which the patient exhibits signs of chronic pulmonary fibrosis, with cough, anorexia, and failure to thrive. The clinic picture arising from the inability to produce the exocrine secretion of the pancreas is characteristic; this is illustrated by all six children whose cases are considered in this report. Should cases in the infantile group survive, they reach the third stage in late infancy and childhood. The associated signs and symptoms resemble those of coeliac disease although the respiratory manifestations may predominate. In the first year or so after birth,
confusion may arise between the two conditions but age of onset provides the clue, coeliac disease is seldom found within the first six months of extra-uterine life. Gloria B. was treated as a coeliac for four years before a true diagnosis of fibrocystic disease of the pancreas was established.

The pulmonary lesion accounts for the recurrent respiratory infections which constitute the main threat to life. The organism most frequently encountered is the coagulase positive Staph. aureus. There may, however, be a variety of infecting micro-organisms as in the case of Christine H., where Strept. viridans, Proteus, and N. catarrhalis were cultured. In the sisters, Gloria and Lesley B., infection was due to Pseudomonas pyocyaneus - a tiresome organism which is difficult to combat and almost impossible to eradicate. The chest infections are at first bronchopneumonic in nature and their resolution tends to be incomplete, so that one episode merges into the next. This gives rise to a combination of physical signs, including chronic bronchiolitis and emphysema, which present as constant clinical features. If the child should survive long enough, as in the case of fourteen-year-old Gloria B., bronchiectasis develops. In this particular instance the changes were minimal but sufficiently widespread to forbid surgical interference. Another late feature is the onset of cor pulmonale which may cause sudden
death. The little boy, Leslie M., was admitted to hospital because of incipient heart failure during his six years history; this cast gloom on an already poor prognosis.

Involvement of the Islets of Langerhans with consequent dysfunction of carbohydrate metabolism is not a feature. Nevertheless it is noteworthy that Christine H. of this series had a diabetic sugar curve on admission. This may be explained by the presence of infection and the increased metabolic rate making overwhelming demands on a severely damaged pancreas.
AETIOLOGY

Landsteiner attributed the pancreatic changes to an inflammatory process and his was the first of many theories to be advanced within the past fifty years. Blackfan and Wolbach (1933) were of the opinion that the cause lay in a primary vitamin A deficiency, but after a detailed study the American workers abandoned the idea in favour of an abnormal pancreatic secretion. Vitamin A deficiency was again postulated by Andersen (1938) along with two other possibilities, namely a congenital anomaly and a foetal inflammation. Her first suggestion has now been generally abandoned as a cause.

Wissler and Zollinger considered the disease to be due to transplacental infection, but this theory is incompatible with the occurrence of fibrocystic disease of the pancreas in only one of twins. Also, Werthemann and others have pointed out that both twins are always affected in congenital syphilis and toxoplasmosis, where the agent passes from mother to foetus. The presence of the pancreatic lesion in one twin is in harmony with the genetic character of the disease.

The recessive nature of the condition has been proved by the work of Andersen and Hodges, Lowe et al, and Carter. From a genetic point of view the disease appears to be completely lethal since none of the
patients has survived long enough to reproduce. This failure of patients to survive and transmit the disease should result in the elimination of responsible genes. Instead the somewhat high frequency of the lesion in the population indicates that the losses are somehow recouped. Goodman and Reed\textsuperscript{12} assume that some of the genes which are lost to each generation are replaced by the mutations of normal genes (in persons without the disease) to abnormal, which express themselves in later generations. Negroes are affected less often than persons of European descent. Consanguinity among parents is not a factor. Baar\textsuperscript{13} suggests that owing to an increased mutation rate, the disease is now more common than it was thirty years ago.

Glanzmann’s\textsuperscript{14} claim that fibrocystic disease of the pancreas is not due to a genetic factor but to Rhesus isoimmunization, has not been confirmed.

In 1944 Farber\textsuperscript{15} published a theory that unaltered mucous secretion caused inspissation in the ducts of various organs with secondary obstruction, atrophy, and fibrosis. He gave two possible causes; firstly, deficiency of mucinase, and secondly, hyperfunction of the parasympathetic nervous system. Bergstrand\textsuperscript{16} observed that two of his cases strongly supported Farber’s theory of imbalance of the autonomic nervous system. In 1952 Bodian\textsuperscript{17} concluded that the basic pathology was a "mucosis". His was essentially an attempt to uphold Farber’s opinion.
More recently, in 1953, Baar surveyed the literature on fibrocystic disease and he suggested that "if the idea of malformation is taken in a wider sense, including an inherited functional abnormality of one or more derivatives of the mid-gut, we have an attractive hypothesis which would cover the known findings, but which is difficult to prove."

Darling et al. have tentatively advanced a new concept. They found that nine children with fibrocystic disease of the pancreas had a markedly higher concentration of chloride in the sweat from the skin of the abdomen than that of comparable controls. Most of the chloride seemed to be associated with sodium, and a much smaller percentage with potassium. Children with fibrocystic disease seem unusually sensitive to heat prostration in hot weather. This seems largely the result of the increased content of salts in their sweat, in association with a propensity to an excessive rate of perspiration. Metabolic data show that both serum chloride and serum sodium levels tend to fall secondarily to subnormal levels during hot weather. Further work is necessary before these findings can be evaluated and correlated with the histological findings.
PATHOLOGY

Histological findings indicate an abnormality of mucus-producing cells throughout the body. However, since our chief concern is with the alimentary and respiratory condition, pathological description will be limited to those systems.

ALIMENTARY SYSTEM

Distension of the acini and ducts with normal-staining mucus has been demonstrated in the mucus-producing salivary glands, the mucous glands of the mouth, and in those of the oesophagus, stomach, and intestines. The fundamental abnormality of mucous secretion is to be found in the epithelial cells lining the intralobular ductules and ducts of the pancreas, and to a variable extent in the acinar cells. It is difficult to distinguish between acini and ductules. The dilated structures usually contain eosinophilic-staining material which is either homogeneous, laminated, or granular. Distension of normal mucus-producing cells is also seen.

Lobular atrophy of the parenchyma is a feature. This appears to vary with the course of the disease, being gross in older children. It would seem that the
viscid mucus causes obstruction which predisposes to retention of pancreatic secretions, and progressive flattening and atrophy of the lining acinar cells. In association with these changes the intracellular enzymes are liberated and activated, and appear to destroy the exocrine tissue with consequent fibrosis. Bodian suggests that the lesion is progressive.

The Islets of Langerhans appear qualitatively normal on microscopy. They seem to be crowded together by reason of the atrophy and shrinkage of fibrous tissue, but it is not possible to assess their absolute numbers in the absence of total counts. In older children dying from the disease Bodian claims there is an apparent reduction in the total number of Islets, but this is in no way comparable with the amount of destruction of exocrine tissue. Some damage is to be expected as a result of chronic ischaemia caused by fibrosis.

Hypoplasia of the gall-bladder and atresia or stenosis of the cystic duct are common findings. Apart from these the liver shows no noteworthy features. Eosinophilic material blocks the intrahepatic bile ducts and in consequence some atrophy of liver cells is evident. Focal biliary fibrosis is seen more often than simple ductule hyperplasia in the older age groups, and this is presumably due to biliary obstruction.

Webster and Williams have presented clinical and
pathological studies of cases of hepatic cirrhosis associated with fibrocystic disease of the pancreas. An extreme degree of an unusual type of multilobular cirrhosis was determined at autopsy in three cases, and during life in two. The hepatic cirrhosis did not cause any clinical disability, with the exception of transient ascites in one patient. Liver function tests were normal. Emphasis is laid on the fact that such cirrhosis of the liver is a long term development in the condition, and it is considered to be the result of protracted nutritional deficiency.

Four cases of fibrocystic disease have recently been described with persistent jaundice as a predominant clinical sign. The authors suggest that the condition be considered in the differential diagnosis of icterus in the child.

**RESPIRATORY SYSTEM**

Distension of mucus-producing cells and glands with basophilic secretion occurs throughout the upper and lower respiratory tract. It may be that the increased viscosity of the mucus leads to its accumulation in the respiratory tract following interference with its normal disposal by swallowing and cough. This predisposes to infection probably because of the
slower removal by the ciliae of foreign matter and micro-organisms in the viscid mucus. It is known that in certain circumstances mucus may enhance bacterial virulence. This is likely to occur when the mucus is viscid and no longer able to fulfil its usual function of an easily removable and constantly moving surface to mucous membranes and ducts: instead it forms a protective coating to bacteria.

In the larynx, trachea and large bronchi the effect of mucosis is to permit of a low-grade infection, but this is of no import, although persistent infection sometimes leads to a metaplastic change in the lining epithelium. In the smaller bronchi the secondary factor of obstruction complicates the picture. This is due to viscid mucus and may be partial or complete, and can thus produce either emphysema or collapse. Obstruction is most frequent in the smaller bronchioles and therefore collapse and emphysema tend to be at first lobular and peripheral in distribution: later they become confluent and segmental. Infection causes the secretion to become muco-purulent, with the result that it damages and weakens the bronchial walls which thus become dilated. Peribronchiolar extension of the infection into the collapsed air vesicles follows with the production of scattered nodules of bronchopneumonia. Later, destruction of the bronchiolar walls leads to the production of bronchiolar abscesses.
Whether the abnormal mucus is sufficient to produce a cough is controversial. Bodian advances the opinion that the slight cough, which is often noted in early infancy, is probably associated with mild infection; whereas the severe cough of the child's later life is caused by established infection. The similarity of the paroxysmal cough in fibrocystic disease and in pertussis may be explained by the increased viscosity of the mucus which is conferred by the content of desoxyribose nucleoprotein.

The evolution of bronchiectatic change is accompanied by deterioration in the general condition and by clubbing of the fingers and toes. The diffuse sputum and bubbling râles of classical bronchiectasis are absent. Collapse is usually symptomless and clinical signs may be minimal. The characteristic deformity of the chest is produced by emphysema, and the resultant downwards displacement of the liver may be misinterpreted as hepatic enlargement. Pulmonary hypertension at length develops with the supervention of right ventricular hypertrophy and failure. In the older child this may be the immediate cause of death. At anytime the infection may cause a widespread pneumonia which is always accompanied by severe emphysema. It is the latter which produces much of the respiratory difficulty and distress. A case has been reported where an infant of six weeks presented with the clinical and radiographic
picture of an interstitial plasmocellular pneumonia. An apparently complete recovery was followed by a fatal relapse. Autopsy revealed a congenital pancreatic fibrosis.
THE LABORATORY DIAGNOSIS OF FIBROCYSTIC DISEASE OF THE PANCREAS

The results of laboratory investigations must be considered in conjunction with the history and with the clinical and radiological examinations. There is no specific diagnostic test for the condition. The majority of the tests, with the possible exception of the antithrombin test, are concerned with pancreatic function; the most direct and most reliable estimation of pancreatic function concerns the tryptic activity of the duodenal juice. According to Norman, "the results of other tests may be suggestive, but the finding of very marked deficiency of tryptic activity of the duodenal juice is crucial".

The technical procedures may be grouped as confirmatory or as screening tests.

Confirmatory:-
Marked reduction or absence of trypsin in the duodenal juice.

Screening:-
1) Low results in the antithrombin test.
2) Faeces microscopy for the presence of undigested muscle fibres.
3) Deficiency of proteolytic enzymes in the faeces.
4) Excess fat in the faeces.
5) Fat absorption tests.
Tryptic Activity of the Duodenal Juice

The method employed in the Hospital for Sick Children for the estimation of the tryptic activity of the duodenal juice is that described by Andersen and Early (1942).\textsuperscript{25} The great advantage of their method is the ease of performance and the crude nature of the test which makes it readily adaptable for routine laboratory use. The test involves the digestion of gelatin at various dilutions of the juice. The aspirate must be both yellow and alkaline and must not be diluted by gastric juice nor by the slightly alkaline saliva. The aspiration of duodenal juice is difficult, and may prove exhausting both for the patient and for the nursing staff, in view of the almost complete failure of the secretory elements of the pancreas. The most satisfactory method of duodenal intubation seems to consist of the passage of a modified Levin radio-opaque tube under fluoroscopic screen control.\textsuperscript{26} Should this procedure prove unsuccessful, or if nothing can be aspirated in spite of the tube being in position, then it is best to leave the tube in situ and to attempt aspiration at intervals during the next few hours.

In 95\% of cases this test gives reliable and accurate results. Provided the rigid criteria of the validity of the sample are fulfilled, doubtful results are minimal. Tryptic activity may be absent in other rare pancreatic dysplasias, and may be absent or
diminished in severe illness in older children, and
marasmus in infancy. In the third instance a later
repetition will give a normal result.

Digestion of gelatin at a titre of 1:400 or over
certainly excludes fibrocystic disease of the pancreas,
and digestion at over 1:50 probably excludes it.
False positives may be due to bacterial proteolytic
activity and any results at low dilution should perhaps
be repeated using the soya bean inhibitor technique.

Johnstone (1952)\textsuperscript{27} It has become apparent that a very
few cases of fibrocystic disease of the pancreas are
able to digest gelatin at titres between 1:25 and 1:400
in the early stages, and only later lose completely all
pancreatic secretory activity. A positive result at
low or moderate dilutions cannot therefore be held to
exclude fibrocystic disease in cases where the clinical
features are strongly suggestive.

Leubner et al. (1955) have described a modification
of the gelatin viscosity method for routine use in
determining the proteolytic activity of duodenal fluid,
and they have compared it with the Andersen-Early
method. Gibbs, Bostick, and Smith (1950) presented
two cases of "cystic fibrosis of the pancreas", proved
at post-mortem, which indicate that the diagnosis
cannot be eliminated by normal vitamin A absorption
curves nor by the finding of trypsin in the lower normal
range in the duodenal juice.
Antithrombin Test

Most adult patients with acute pancreatitis have a distinctly elevated plasma antithrombin titre throughout the course of the acute illness. Antithrombin titres thus seem to represent a highly sensitive plasma response to the formation of trypsin in the pancreas. This led Innerfield et al. (1951) to investigate the antithrombin level in cases characterised by decreased trypsin level. The plasma under examination was first defibrinated by a thrombin solution, and after incubation of this for varying lengths of time, fractions were pipetted into tubes containing normal plasma. The time taken for the fibrin to form in each was noted and then expressed as a percentage of the mean of the normals on the same day. They concluded from their observations that in the first few days or weeks of life, the fibrocystic passes through an initial stage of pancreatic atresia or obstruction, varying from complete to incomplete, with or without extensive parenchymal damage: hence the low antithrombin titre.

In the survivors a second stage develops within weeks or months; this is characterised by interstitial pancreatitis secondary to the extravasation of obstructed pancreatic enzymes. The enzymes enter the circulation and give rise to the elevated titres.

A third stage, featuring the late changes in the disease, is associated with normal antithrombin titres.
Apparently minute quantities of trypsin are generated from a few feebly functioning pancreatic acini.

In 1952, MacFarlane repeated his observations on the serum antithrombin level in 67 cases of fibrocystic disease of the pancreas. Of these, 60 showed a significant reduction in the antithrombin titre, while the remainder gave results similar to 353 controls, which included 73 members of families containing an affected child. During the investigation of the serum antithrombin level in pregnancy, MacFarlane and Norman (1954) showed that the sera of 30 babies (1 to 14 days old) revealed an antithrombin content much lower than that of normal serum; whereas in the routine examination to exclude fibrocystic disease of the pancreas, the antithrombin content had been within the normal range in the serum of all the 2-month-old normal babies tested. This observation appears to invalidate the antithrombin test in the first two months of extra-uterine life.

In this series Michael G. had an abnormally low result - 30% of normal - on the second day after birth. Almost two months later the antithrombin content of his serum had risen to 65% of normal.

The test is empirical. The underlying mechanism is as yet uncertain. It may well be that it does signify an absorption of trypsin into the blood. MacFarlane asserts that where the clinical picture is unequivocal the positive antithrombin titre may be held
to be sufficient laboratory proof, obviating the necessity for duodenal intubation in these circumstances alone. In all other cases estimation of the trypic activity of the duodenal juice is the only proof positive. MacFarlane has produced no evidence to correlate the antithrombin level with the activity of the pancreatic tissue, nor with its pathological state.

Investigation of the faeces

Microscopic examination of fresh stools is a guide to the state of pancreatic function. Excess of undigested and partly digested muscle fibres almost always indicates pancreatic failure. Payne\textsuperscript{33} states that "fat globules in excess of three or so per high power field are suggestive of pancreatic insufficiency except in the very young infant".

The estimation of the proteolytic activity of fresh faeces is of value. Absence of digestion of gelatin at a dilution of 1:100 is highly suggestive of fibrocystic disease in children under one year, but in later years the absence of adequate digestion no longer indicates fibrocystic disease, because more normal children fail to digest gelatin. O'Brien and Powell\textsuperscript{34} recommend the estimation of the trypic activity of the stools in the newborn, where examination of the duodenal juice is technically difficult and not justifiable. Studies on the gelatin liquifying properties
of certain bacteria by Johnstone (1950), with particular reference to the laboratory diagnosis of fibrocystic disease, suggested that the test may be invalidated by the presence of proteolytic bacteria. Cathie has shown that it is unlikely that contamination of the stool, by B. proteus or similar organisms, will interfere with the result.

**Fat absorption tests**

In children with fibrocystic disease there is a slight or absent post-prandial increase of the esterified fatty acids of the blood, indicating a marked failure of fat absorption from the bowel and reflecting a markedly impaired pancreatic function. In such cases a test meal of 36% cream of 4% fat/Kg. body weight given orally, followed by estimation of the esterified fatty acids of the blood at fasting and six hourly post-prandial levels, affords a convenient test for evaluating pancreatic function.

A fat absorption test using iodised oil has recently been advocated as a screening test in fibrocystic disease. The test depends on the fact that iodised fat (Lipiodol) is digested and absorbed by normal children, and that the iodine is subsequently excreted in the urine in high concentration. In children with disturbed fat absorption the digestion of iodised fat is impaired and the amount of iodine excreted in the urine is greatly diminished.
THE MANAGEMENT OF

FIBROCYSTIC DISEASE OF THE PANCREAS

There is no way of preventing the disease by reason of its genetic determination and its recessive inheritance. Norman states that it is legitimate to advise patients who want another child to accept the risk. When a baby is expected in an affected family the obstetrician should be warned of the possible occurrence of meconium ileus. A surgical opinion must be sought on the slightest evidence of abdominal distension, constipation or vomiting.

If the child appears normal but fails to gain in weight, or if the stools are loose and offensive, then investigation of the proteolytic enzymes in the stools and duodenal juice, and an estimation of the serum anti-thrombin level should be carried out.

Breast-fed babies generally thrive for a time on breast milk alone, but the administration of pancreatin between feeds is usually necessary. All bottle-fed infants require pancreatin in doses of 1-2 G. before feeds. This is given in the form of granules suspended in milk. Feeds consist of partly skimmed milk with added sugar. Affected babies require larger feeds and a much higher calorie intake than the normal; this may be obtained by adding casein, casein hydrolysate, or protein milk powder to the feeds.
Pre-digested cereals such as Benger's are of use. Consequent weight gain is normal if adequate feeds and sufficient pancreatin are given; however one must anticipate the greater requirements of such children.

Mixed feeding is carried out as in the normal child. The dose of pancreatin is increased until the motions are solid, inoffensive and not more than two in the day. They should sink in water. The usual dose of pancreatin is 2-4 G. per feed.

The parents of the older child must be instructed to ensure that he is given plenty of meat, cheese with a low fat content, and partly skimmed milk. It is better not to restrict the diet except to advise the exclusion of oily or fatty foods, if these substances make the motions pultaceous and offensive. Failure is due to an inadequate calorie intake. This may be caused by excessive loss in the faeces or by a poor diet; both are readily corrected. Anorexia is also a cause and this is generally the result of respiratory infection and may not necessarily be affected by increased pancreatin. Vitamins A and D, in concentrated form, are given to all children.

The use of detergents in the treatment of fibrocystic disease has been suggested. In the initial study evaporated or homogenised milk was added gradually to the diet in the place of skimmed milk, until the patient was taking 30 oz. milk daily.
The detergent used was sortate - a total of 6 g. of sortate in divided doses was given for each 30 oz. milk taken over a 24 hour period. In addition the patients were given a high protein and carbohydrate diet, 50,000 units daily of a water-soluble vitamin A preparation, and pancreatin. The management of the control patients was similar except that they received no milk containing fat and no sortate. On this schedule the controls gained less than 1 lb. in weight compared with significant weight gains in the others.

Infection is the greatest danger to life. The earliest sign of respiratory infection in a baby calls for immediate and rigorous antibiotic therapy. A severe infection requires large doses for long periods and for some weeks after the infection has apparently subsided. Babies with a severe infection may require oxygen for a time whilst under treatment, as they are liable to develop a staphylococcal pneumonia, and this condition rapidly deteriorates with the onset of spontaneous pneumothorax. This is liable to be masked by the emphysema. Surgical drainage is urgently required.

Early treatment with penicillin may be sufficient for very mild infections. Aureomycin or terramycin is much more effective and is easily given at home. It has been found in the Hospital for Sick Children that it is more practicable to give patients a small dose of 100-300 mg. daily. Nasal and throat swabs
are taken every three months and the organisms are tested for sensitivity. The doctor or parent is instructed to treble the dose at once should the child fall ill, and to ring up the hospital for further advice. In A.P. Norman's experience this small dose of antibiotic, which is insufficient to raise the blood level, appears sufficient to increase the child's well-being and to prevent mild symptoms. This may be a very definite clinical impression but there is no proof that this somewhat naive idea actually works. More severe respiratory infections are best treated in hospital. Postural coughing is invaluable.

McIntosh has shown that the general condition of the fibrocystic patient over 10 years of age is closely linked to the state of the pulmonary infection, and that this depends to some extent on the early diagnosis and thorough treatment of the initial infection. He concludes that adequate compensation for lost pancreatic function is readily attainable, but that the respiratory infection once established, is difficult to eradicate.

The patient should be permitted to lead a normal life and to attend an ordinary school. It is preferable that he should occupy a room of his own at home in order to minimise the risk of cross-infection if there are other siblings in the household. This may not be possible for economic reasons although local authorities may be approached by the physician in an effort to secure
a larger house. The two sisters in this series both suffer from pyocyaneus infection - the result of sharing the same room.
CASE HISTORIES
Michael G.  Sex: male  Date of birth: 29.8.52.

Admitted: 29.8.52.
Discharged: 4.11.52.

Family History: Fourth child. Parents well. First baby, a female, died of intestinal obstruction at three days. A diagnosis of rectal atresia was made and a colostomy was performed. No post-mortem was held. Two other siblings, aged 5 and 3, are well.

Clinical History: Normal pregnancy apart from being a breech for a time; delivery normal. Birth weight 9 lb. 1 oz. Vomited bile-stained material almost immediately after delivery. Abdomen appeared distended. No meconium was passed and a catheter was introduced into the rectum with no result. Child had not been fed.


X-ray examination: Distension of small gut with fluid levels. No air in the large intestine.

Operation. 29.8.52.

The abdomen was opened through a right paramedian
incision. The terminal ileum was collapsed and contained a grey putty-like material. There was a volvulus of the collapsed area and a partial atresia had been caused by twisting of this volvulus. This was removed and the loop of distended bowel excised.

Post-operative condition: There was some regurgitation and aspiration of gastric contents. A right and left upper lobe collapse resulted in spite of bronchial suction.

Progress

30.8.52. Sectopen 200,000 units daily and subsequently chloromycetin 125 mg. four times a day.

1.9.52. Antithrombin test - abnormally low result - 30% normal after 20 minutes incubation.

Examination of stool - 1) Excess fat globules.

2) Proteolytic activity - no digestion of gelatin at a dilution of 1 in 12.5 faeces.

Examination of meconium - No digestion of gelatin at a dilution of 1 in 6.25 of meconium.

Both faeces and meconium were tested at the lowest dilution possible and the results indicate a possible deficiency of trypsin.

9.9.52. Examination of duodenal juice - no digestion of gelatin at a dilution of 1 in 12.

10.9.52. X-ray examination revealed that the right chest was almost clear but that there was collapse of the left upper lobe which was still incompletely
re-expanded.

13.9.52. Pancreatin 3 G. before meals begun. Chloromycetin reduced and thereafter changed to aureomycin on September 23rd.

24.9.52. E.C.G. revealed some right ventricular hypertrophy.

30.9.52. Throat swab for culture and sensitivity revealed Staph. aureus sensitive to penicillin, streptomycin, chloromycetin, aureomycin, sulphadimidine and gantrisin.

25.10.52. Antithrombin content of serum 65% normal after 20 minutes incubation.

4.11.52. Discharged. Pancreatin 3 G. before meals. Aureomycin 125 mg. twice daily for one week and daily thereafter.

The child was seen at the age of 4 months when he weighed 15 lb. He was very well, the stools were formed and he was starting mixed feeds. Aureomycin was increased to 100 mg. twice daily and his diet was augmented by pancreatin 4 G. five times daily, and by "abidec" minims 10.

At the age of 9 months weight was 20 lb. 10 oz., and he received mixed feeds with no special restrictions. There was no cough, chest was clear, and he had 3 bowel movements daily. Pancreatin was increased to 5 G. five times a day.

The child was well aged 1 3/12 years and he
weighed 23½ lb. There was no cough. Stools were sometimes loose and offensive.

When seen 1 year afterwards he had lost weight and his condition was very poor. Weight 28 lb. Motions bulky and loose, sometimes 4 daily. No abnormality found on physical examination.
Gloria B.  
Sex: female  
Date of birth: 18.1.40.

**Family History:** First child. Parents well, no consanguinity.

**Clinical History:** Normal pregnancy and delivery.  
Birth weight 7 lb. 10 oz. Breast fed for ten months.  
Normal progress until about 9 months but liable to coughs. At 9 months stools became offensive and cough more severe. Stools were frequent, pale and bulky following an episode of diarrhoea at the age of 1 year. There was much sputum and a tendency to lose weight despite a healthy appetite.

Rectal prolapse treated by injection at the age of 2 years, when early finger-clubbing, prominent abdomen, and wasting were noted. Total faecal fat 42.5%. Faeces contained undigested muscle fibres. Tonsillectomy and antral washouts in the same year. Otitis media diagnosed and cured.

Aged 4 years the child had frequent respiratory infections and passed large, pale stools. Body weight 30 lb. Treated as a coeliac. Diagnosis of fibro-cystic disease of the pancreas established by estimation of the tryptic activity of the duodenal juice. Treated with diet and pancreatin. Pulmonary symptoms and finger-clubbing gradually became more marked.

Adenoids removed at the age of 7. Low glucose
tolerance test - peak 125 mg. at 2 hours. Aged 9 years
the child weighed 56\frac{1}{2} lb. and stood 50\frac{1}{2}" tall. Thin
but fairly well. Appetite good. Cough persistent,
at times severe. Troubled with persistent nasal
discharge. Gross finger-clubbing. No abdominal
distension. Pancreatin continued at 10 G. daily.
High protein diet begun with limitation of fat at
times only.

Admitted for bronchography aged 10. Bronchogram
showed widespread minimal bronchiectatic changes.
Surgical treatment contra-indicated.

Readmitted 1 month after 11th birthday because of
loss of 5 lb. in weight in 2 months, associated with
persistent nasal catarrh, chronic cough and sputum.
Clinically, a thin child with gross finger-clubbing.
Mantoux, 1:1,000, normal. Chest x-ray showed catarrhal
lung fields with some consolidation in the left upper
zone and lipiodol residues present on both sides.
Pancreatin discontinued, cholera mucinase substituted.
Stools became more frequent and offensive. Mucinase
stopped, pancreatin 3 G. four times a day recommenced.

Thereafter stools usually formed but loose on
occasion. Maintained on aureomycin and terramycin for
18 months when at the age of 12\frac{1}{2} years a throat swab
showed pseudomonas pyocyaneus. Antibiotic changed to
chloramphenicol 250 mg. daily. Admitted to hospital 6
months later on account of severity of cough and
deterioration of general health.

Chest x-ray on admission confirmed the presence of considerable emphysematous change. Sputum for culture and sensitivity showed strept. viridans and pseudomonas pyocyaneus, the latter sensitive to streptomycin, chloromycetin and sulphathiazole. Discharged on pancreatin 4 G, three times a day, chloromycetin 125 mg, three times daily, and one capsule of compound vitamin B. The child gained weight on this régime and appeared fairly well on discharge. No evidence of active chest infection. Organisms in sputum tested for terramycin sensitivity because of danger of aplastic anaemia while on maintenance dose of chloromycetin.

Readmitted at the age of 14 because of increasing dyspnoea and severe cough with little sputum. Clinically, very wasted and faintly cyanosed. Pronounced finger-clubbing, very poor chest excursion, râles at both bases and frequent scattered rhonchi. She initially ran a fever of 101-102°F. and was treated with aureomycin 250 mg. three times a day, in addition to pancreatin and "abidec". Sputum contained pseudomonas pyocyaneus, antibiotic changed to streptomycin 750 mg. twice daily. Fever gradually subsided. Little change in her general condition.
Lesley B.  Sex: female  Date of birth: 30.3.47.

**Family History:** Second child. Parents well. Elder sister, Gloria, is a known fibrocystic.

**Clinical History:** Normal pregnancy and delivery. Birth weight 7 lb. 8 oz. Breast fed for 5 months then weaned on to cow's milk and solids. The child was seen at the age of 1 year at the Hospital for Sick Children on account of a slight persistent cough. Stools were inoffensive but loose on occasion. Progress was uneventful apart from rubella at the age of 2 years.

At 2 years 9 months the child weighed 36 lb. 6 oz. and she suffered from a persistent cough and frequent colds. The stools were normal. On physical examination there was moderate enlargement of the tonsils and cervical glands, but there were no signs in the chest. X-ray of the maxillary air-sinuses showed bilateral opacity.

The patient was seen at the age of 4 years because of a recurrent cough which was very severe in winter. Appetite was healthy but there had been no gain in weight. The stools were often pale but not offensive and there had been no diarrhoea.

For two weeks prior to examination the child had complained of pains in the tummy which usually began in the afternoon and lasted all evening. She vomited
anything she ate and the mother said the child had lived for two weeks on "lucozade".

On examination she was $40\frac{3}{4}$" in height and she weighed 32 lb. 8 oz. There was no physical abnormality apart from a poor chest expansion and a few scattered areas of crepitations. A small amount of duodenal juice was aspirated after many failures. This showed complete digestion of gelatin at a dilution of 1:50. No abnormality was found on stool microscopy. The possibility of fibrocystic disease of the pancreas was considered but no mention was made to the mother or to the family doctor.

There was a slight improvement in the patient's condition in the ensuing six months, during which time she gained 2 inches in height and 2 lb. in weight. At the age of 5 years she was 42$\frac{3}{4}$" tall and she weighed 37 lb. 12 oz. The child's appetite was good but she complained of a persistent cough. On examination her chest had a tendency to bulge, and there were rhonchi and râles at both lung bases. The serum antithrombin titre was very low.

She was seen one month later because her cough had not responded to treatment. There was a considerable degree of emphysema and the liver was palpable 1 fingersbreadth below the costal margin. A daily dose of 50 mg. terramycin was instituted for three weeks.

At the age of 5 years 3 months the child was
readmitted for tonsillectomy. In addition to enlarged tonsils, air-entry was poor and the cough was persistent and severe. Three weeks after discharge she was brought back to hospital on account of a paroxysmal cough like that of pertussis. She had also lost weight. Examination showed poor air-entry throughout the lung fields.

Her condition improved with terramycin and progress was satisfactory until the age of 6 years, when she weighed 40 lb. 8 oz. and stood 45½" tall. The paroxysmal cough recurred and appetite was poor. Culture of organisms from a throat swab yielded a heavy growth of Pseudomonas pyocyaneus. Postural coughing brought about a dramatic improvement in the chest condition. In the ensuing two months chloramphenicol (250 mg. twice daily) was substituted for terramycin with little beneficial effect. Aged 7, the child weighed 46 lb. 1 oz. and was 48" in height. She had been on terramycin for 2 months when the report of a culture from a throat swab showed Pseudomonas pyocyaneus, which was insensitive to all but streptomycin. Further progress was painfully slow and when seen at the age of 7 years 9 months, in December 1954, she weighed 51 lb. 4 oz. The child was generally well but physical examination revealed a chest excursion of 3/4". Percussion rate was hyper-resonant. The breath sounds were rather distant with a few scattered rhonchi at the right base. No abnormality
was detected in the other systems.
Leslie M.  
Sex: male  
Date of birth: 9.1.49.

**Family History:** Third child. Parents well. First baby survived intestinal obstruction at 6 days, but died of gastro-enteritis at 1 year. Second child is well.

**Clinical History:** Normal pregnancy and delivery. Birth weight not recorded. Progress was good until the age of 2 months when the child developed a cough and nasal catarrh which persisted on and off until the age of 16 months. There was occasional vomiting and the stools were pale, bulky, and foul-smelling. Appetite was good but he failed to thrive. On admission at 16 months investigations revealed complete digestion of gelatin at a dilution of 1:25 of the duodenal juice, and x-ray examination showed the presence of catarrhal changes in the lungs. A diagnosis of fibrocystic disease of the pancreas was established.

Culture of the sputum yielded a heavy growth of coagulase-positive staphylococci insensitive to penicillin. The child continued to run an intermittent pyrexia with persistent cough and loss of weight. Diarrhoea developed after 2 weeks in hospital, this responded to oral Hartmann's Schedule. A recurrence of pyrexia, with signs of right lower lobe consolidation, was aborted by intensive penicillin and sulphisoxazole
therapy. The child was discharged on a high protein diet, supplemented with pancreatin and vitamins A, B, C, and D.

He continued to make progress until the age of 3 years when he was readmitted because of bulky, offensive stools and a recent failure to gain weight. There was no digestion of gelatin at a dilution of 1:6 of the duodenal juice, the antithrombin titre was within normal limits, and x-ray revealed emphysema, and opacity of both maxillary sinuses. The daily dose of pancreatin was increased, and terramycin, 150 mg. daily, was substituted for aureomycin, which had been given for 2 months prior to admission.

The child was readmitted at the age of 3 years 7 months, on account of severe cough and thick yellow sputum. His general condition was fair. Examination showed a moderate degree of finger-clubbing and a hyper-resonant chest. Five months later he became increasingly tired and air-entry was poor, with crepitations at both lung bases.

There was little improvement in his health throughout the next four months and the child was readmitted because of severe cough and pale, bulky, offensive stools. Weight gain in the preceding year had amounted to 3 lb. only. The patient was maintained on pancreatin, grains 120 three times a day, and he had recently had a course of aureomycin, 200 mg. four times a day. On
examination there was finger-clubbing and the chest was hyperresonant. There were a few scattered rales over the left axilla and right lung base. Radiological examination of the chest revealed scattered areas of collapse and consolidation in both lungs. Culture of organisms from a throat swab yielded Strept. viridans and coagulase positive staphylococci. The serum antithrombin content was very low.

The child improved considerably in himself and the stools became more normal, although there was no immediate weight gain. Following this, his course was very variable with frequent exacerbations of chest infection and looseness of the stools. His vital capacity was gauged to be 180 cc. and this was unaffected by aminophylline. A therapeutic test was done with 100 mg. of procaine amide intravenously, but this also failed to affect the vital capacity. After 6 weeks in hospital aureomycin 100 mg. 6 hourly was recommenced, and cortisone, in an eight hourly dose of 15 mg., was administered. In less than one week the vital capacity had increased to 470 cc.

At the end of his eighth week in hospital a course of erythromycin was begun. This was followed by administration of all the other antibiotics in turn as the sputum sensitivities varied. The child continued to follow a variable course with unsatisfactory weight gain and recurrent bouts of pyrexia.
At the age of 5, after four months as an in-patient, his tonsils and adenoids were removed. Further progress was impeded by frequent colds and a severe cough. Mother said that the child had been breathless even at rest, and as soon as any of his antibiotics was stopped the cough became worse, with increased breathlessness and cyanosis. His appetite was poor and there was a recent history of diarrhoea and bulky, foul-smelling stools.

In October 1954, the patient was admitted because of incipient cor pulmonale and bronchial spasm. This responded to intravenous aminophylline. In the ensuing two months there was marked improvement and when examined by me in December 1954 he looked well with slight cyanosis of the facies. Marked finger-clubbing was present and there was some distension of neck veins.

The salient features of the examination were a pulse of 110 which was almost water-hammer in type, clinical absence of cardiac enlargement and the presence of a split pulmonary second sound. The chest was barrel-shaped and scattered rhonchi, with crepitations at both lung bases, were heard on auscultation. The liver was palpable 2 fingersbreadth below the costal margin, the surface was smooth and it was not tender. Continued treatment with aminophylline was most successful; the child was out of bed and running about after seven weeks in hospital.
Christine H.  Sex: female  Date of birth: 17.11.46.

Family History: Only child. Parents well.

Clinical History: Normal pregnancy and delivery. Birth weight not recorded. Progress was satisfactory until the age of 2 years 9 months when the child was admitted to hospital on account of a seven days history of diarrhoea and vomiting. The stools were greenish-yellow in colour and offensive. There were 8-10 motions each day with abdominal pain on defaecation. Mother said that the child had recently become irritable and apathetic, and that she had been off her food for two weeks.

On examination the patient was found to have a loose cough; occasional rales were heard on auscultating the chest. The limbs were hypotonic. Examination of the ears revealed a bulging left drum and injection of the right drum. A bilateral myringotomy was performed but no organisms were isolated from the pus. Estimations of the blood sugar revealed a diabetic curve, which on subsequent investigation returned to normal. There was no digestion of gelatin at a dilution of 1:6 of the duodenal juice. Stool microscopy revealed the presence of starch, undigested meat fibres, and excess fat globules. Of the total faecal fat 60.2% was unsplit. Chest x-ray suggested the presence of multiple small abscesses in the right middle lobe.
The child gained weight while in hospital. Her general condition was good, but the stools were offensive though well-formed. During the following two years she continued to thrive on a normal diet. At the age of 7 years 2 months the antithrombin content of the serum was 44% of normal. Throat swabs taken at three-monthly intervals yielded moderate growths of Strept. viridans, Proteus, and N. catarrhalis, on culture.

She regularly attended the Fibrocystic Out-patient Clinic and remained well. However the child was readmitted when she was 7 years 5 months old because the stools had been loose and offensive. This was corrected by increasing the daily dose of pancreatin. There were no remissions until one week before her eighth birthday, when she complained of a severe paroxysmal cough. Radiological examination of the chest showed changes compatible with the pulmonary manifestations of fibrocystic disease of the pancreas. She responded to antibiotic therapy and when seen as an out-patient in December 1954, at the age of 8 years 1 month, the child was generally well apart from a slight cough.
Lesley C.  
Sex: female.  
Date of birth:  
29.4.45.


Clinical History: Normal pregnancy and delivery. 
Birth weight 7 lb. 10 oz. The patient was breast fed for five months and from the introduction of mixed feeds she had a voracious appetite, offensive stools, and a tendency to lose weight. When first seen at the age of 10 months the child weighed 14 lb. 10 oz. but her appearance was normal. Chest x-ray was negative. The total faecal fat measured 42.7%. A low fat diet with pancreatin supplement brought about a rapid improvement in her general condition. At 18 months she weighed 21 lb. and in the following year she gained 6 lb. Extra protein was added to the diet. The child continued to thrive and she weighed 33 lb. 8 oz. when she was four years old. The stools were solid but became pale and foul-smelling if pancreatin was omitted.

At the age of 6 the child weighed 35 lb. and her general condition was poor. Appetite was moderate and she passed two large offensive motions daily. She also had a severe cough and there were scattered rhonchi throughout the chest. The liver was palpable 1\(\frac{1}{2}\) fingersbreadth below the costal margin.

Three months later she was 44" in height and she
weighed 38 lb. 10 oz. Appetite was good and the stools were formed. Following a month's course of aureomycin the patient's condition improved markedly.

From that time on the child kept remarkably well except for occasional colds and a slight cough. Terramycin and aureomycin were used alternately in a maintenance dose. Aged 7 years 9 months she weighed 45 lb. 6 oz. and was 35 inches tall. There was a continuous sero-purulent nasal discharge and chest movements were poor. The patient's condition returned to normal with the administration of terramycin, 250 mg. for 7 days. Thereafter progress was excellent and when seen in December 1954, at the age of 9 years 8 months, the child was very well. Her height was 52 inches and she weighed 53 lb. 11 oz.
CONCLUSIONS

In any case where the signs and symptoms remotely suggest a diagnosis of Fibrocystic Disease of the Pancreas, the need for thorough investigation is paramount. Though the present diagnosis and treatment appear satisfactory, the demand is for some other diagnostic criterion, based on a mucolytic enzyme system and not dependent on pancreatic secretion. The observation that an increasing number of diseases are being found to be essentially biochemical lesions, underlines this necessity.

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