F I B R O C Y S T I C D I S E A S E

of the

P A N C R E A S.

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C O N T E N T S.

C O N T E N T S (continued)

INTRODUCTION.

Despite Andersen's finding (1946) of fibrocystic disease of the pancreas in 3% of all infants who came to autopsy, there is still a widespread belief in this country that it is a rare disease and some even have doubted its existence as an entity. Even in America, whence has come most of the literature, Attwood and Sargent could write in 1942 that the diagnosis was rarely made during life.

Having started with the conception that this disease was a nebulous entity which did exist but was rare, experience has proved to me that it is in fact not uncommon and it is hoped that, at the least, this thesis will serve to re-emphasise this fact.

This study cannot claim to be complete nor in large part original: the original part has been limited to obtaining the case histories, first suggesting the diagnosis in Cases 1, 5 and 7 and passing the duodenal tubes.

All the cases have been seen during tenure of the appointment of Joint Paediatric Registrar to St. Mary's Hospital, Paddington (where all the cases have been admitted) and to the Princess Louise Kensington Hospital for Children where Case 3 and the case shown in Plate 14 have been seen: as Registrar these cases

have come under my immediate care under the direction of my chief, Dr Lightwood.

It is realised that this is a small number of cases and that the conclusions drawn would more properly be called impressions, but it is from impressions that the better understanding of disease has come.

P A R T I.

REVIEW OF THE LITERATURE.

HISTORICAL: This disease has had a remarkable history. The association of pancreatic disease and steatorrhoea has been known for more than a century (Garrod & Hurtley 1912), but it was not until 1905 that the pathological lesion of the pancreas, now associated with fibrocystic disease, was described by Landsteiner. Garrod & Hurtley (1912) described a boy of 6 years old who had had steatorrhoea from birth, but no impairment of physical development or general health. His parents were first cousins: one sib had died at 7 months of bronchitis, another at 11 months of broncho-pneumonia. The latter had also had steatorrhoea from birth. Because in their case they found Tryptic digestion unimpaired, Garrod & Hurtley concluded that there were no signs of pancreatic disease, although they did not entirely exclude the possibility of some function of the pancreas being in abeyance. Andersen (Brennemann's Practice of Paediatrics) considers that this was the first case of fibrocystic disease of the pan-

creas in which careful clinical observations had been made, but there is doubt about this being the correct diagnosis. Reference will be made to this point again later.

The association of the digestive disturbance and the pathological pancreatic lesion was first described by Passini (1919) in a child who died at the age of 5 months of broncho-pneumonia having had abnormal stools since birth. Miller & Perkins (1920) described a boy of 3 years who had had steatorrhoea from birth and had been subject to coughs. He weighed only 26lbs and died at home of septic pneumonia following the removal of carious teeth under anaesthesia. No autopsy was performed. They considered their case to be identical with that of Garrod and Hurtley and that there was no disease of the pancreas. This case however probably was, and that of Clarke and Hadfield (1923-4) certainly was one of fibrocystic disease of the pancreas. Their patient died at the age of 4 years of broncho-pneumonia; her stools had always been frequent, large, greasy and very offensive, and despite an enormous appetite she was well below average height and weight. 2 of her 7 siblings had died at the age of 2 months of respiratory infections. Autopsy in this case showed in the lungs purulent bronchitis and multiple

small abscesses, a very large fatty liver and a shrunken pancreas which microscopically showed much fibrosis and replacement of most of the secretory gland tissue by fat.

Siwe (1931) first confirmed the diagnosis by examination of the duodenal juice. Parmelee (1935) described 2 cases of congenital steatorrhoea with a history of frequent bulky stools from the neonatal period and failure to gain weight despite a sufficient intake of food. Both died of broncho-pneumonia and in both at autopsy fibrosis of the pancreas was found. He considered that these cases were distinguishable from coeliac disease by their early onset, the high proportion of neutral fat in the stools and the fact that the digestive abnormality was never overcome. He could find only 4 cases in the literature with a similar history and post-mortem findings. Blackfan & Wolbach had however described in 1933 13 cases of vitamin A deficiency in infants of whom 10 had died of broncho-pneumonia. The clinical histories of these 10 are very suggestive of fibrocystic disease, but in only 6 were found pathological pancreatic lesions consisting of fibrosis and cyst formation. They observed eosionophilic material in the ducts and acini, and deduced that it was inspissation of this material which caused the pancreatic lesions:

these lesions moreover they state had been observed "scores of times".

Pathologically then the disease was becoming increasingly recognised, but Cockayne (1933) reporting a case of congenital steatorrhoea referred to its great rarity, although he noted the high mortality from broncho-pneumonia.

In 1938 clinical recognition of the disease became more frequent. Harper described 8 cases of congenital steatorrhoea with post-mortem reports of 5 showing pancreatic lesions. Blackfan & May had recognised in 15 years 35 cases with a history of frequent episodes of diarrhoea, poor weight gain, death from pulmonary infections and pathological lesions of the pancreas: the latter they had found in lesser degree in a further 200 cases. This was the first indication that the disease was not at all uncommon, but they considered that it was not possible to determine accurately dependable diagnostic features in life, although they recognised that the history was usually of gastro-intestinal or respiratory upset.

It remained for Dorothy Andersen (1938) in describing 49 cases, 27 from the literature and 22 of her own, to show that fibrocystic disease of the pancreas was a definite and common clinical entity with a characteristic course and clinical history whose pre-

senting features divided cases into 3 main groups. Since this time she has written extensively about the disease and all the credit for placing it on a firm basis from the clinical and biochemical aspects must be attributed to her. On the pathological side however pride of place must be given to Farber whose work (1942 & 1944) has shown that the same fundamental defect, i.e. inspissation of viscid secretion, affects not only the pancreas but other mucus-secreting glands throughout the body, and that this is the cause of the pulmonary lesions and not deficiency of vitamin A which Andersen has postulated.

From the first description of the pathological lesion of the pancreas, therefore, 33 years elapsed before the clinical picture was fully pieced together and 37 years before our present knowledge of the pathogenis was fully evaluated, although pathologists had recognised the frequency of the pancreatic defect before clinicians.

AETIOLOGY: Andersen (1946) lists 4 theories which have been adduced to explain the occurrence of this disease:- 1. Lack of vitamin A in the Mother's diet during pregnancy (Snelling and Erb 1942).

2. An intrauterine infection.

3. Infection in early infancy.

4. That the disease is inherited as a Mendelian recessive character.

As she points out, there is no evidence in case histories to support the first 3 theories. A case in which one twin only was affected is a strong argument against the first and second theories, while the third does not explain cases of meconium ileus. Farber (1944 B) states that inclusion bodies in the pancreas, lungs and salivary glands are not found more often in children dying of fibrocystic disease of the pancreas than in children of the same age dying of other causes. On the other hand Andersen found that in affected families 25% of siblings were affected, i.e. the expected incidence for a Mendelian recessive character, which favours this theory: she does, however, point out that the majority of a large family may be affected, a fact which is difficult to explain on this theory. As signifying an inherited trait, she also found in affected families an incidence of miscarriages greater than in the general population

and a suggestive history, not infrequently, in relatives. But in no proved case had there been parental consanguinity. She (1946) retracted her earlier statement (1938) that there was a greater incidence among females since increased experience of the disease had shown no sex incidence.

PATHOGENESIS: Harper (1938) ascribed the pancreatic lesion to a failure of development. Andersen (1938) considered that the lesion could reasonably be interpreted as the result of obstruction of the small or large pancreatic ducts. She formed the impression of a general tendency to atresia of ducts throughout the body, although she concluded that, as far as the pancreatic lesions were concerned, it was the smaller ducts which were the primary site of obstruction at least in the majority of cases. Hurwitt & Arnheim (1942) found in a case of meconium ileus stenosis of the main pancreatic duct to which they attributed the pancreatic lesion. They pointed out, however, that, since the pancreatic ducts are always open in the foetus and are not recanalised as is the intestine, this explanation would not suffice for all cases. Farber (1944 B) found that in the majority of cases there was no congenital atresia or stenosis of the main pancreatic duct.

Andersen (1939) mentions that the pancreatic changes have been ascribed to dehydration, but

Farber (1942) by using controls in his experiments showed this theory to be untrue.

Blackfan & Wolbach (1933) put forward the theory that the pancreatic lesions are secondary to the "production of an abnormal secretion which inspissates and leads to distension and atrophy of ducts and acini". Andersen (Brennemann's Practice of Paediatrics) accepts this theory, but considers that the pulmonary lesions are secondary to it and due to lack of vitamin A. Parmelee (1935) had rejected this explanation on the ground that there was no xerophthalmia in his cases. Farber (1942 & 1944 B) had found dilated glandular structures filled with inspissated material in both upper respiratory and intestinal tracts and concluded that the disease affected all mucus-secreting glands throughout the body with production of very viscid mucus which became inspissated in the ducts and that the consequent loss of the normal protective action of mucus in the bronchial tree could explain the liability to pulmonary infections. Moreover, acting on the knowledge that vagal stimulation produces a viscid secretion, he (1942) reproduced in kittens the pathological pancreatic lesions of fibrocystic disease by injecting them for periods of 2 - 6 weeks with pilocarpine.

In meconium ileus there is found filling and blocking the terminal part of the ileum a mass of

meconium so pultaceous that intestinal peristalsis is powerless to move it forward and obstruction results. The theory that the reason for the meconium becoming such a solid mass is exclusion of pancreatic ferments from the gut has been upheld by Farber's finding (1944A) that meconium is liquefied in vitro by pancreatic extracts.

Andersen (1938) concluded that at least in the majority of cases the pancreatic lesions were present at birth but the period in foetal life at which they appear remains unsolved. Since the islets of Langerhans are present and since these bud from the acini in the latter part of the 3rd foetal mouth, Andersen (1946) considers that the pancreas is probably normal up to that time.

PATHOLOGY: Farber (1944B) has described fully the pathological picture. Much had already been described by Andersen (1938) but it is Farber who has correlated all the findings by showing that they are the result of a systemic disease.

Ext.Appearances: There is emaciation with loose skin, absence of subcutaneous fat, atrophy of the musculature especially that of the buttocks and delayed skeletal development. Varying degrees of rickets, scurvy and vitamin A deficiency may be found. Andersen (1948) obtained evidence of severe vitamin A deficiency in 23% of cases, especially among the younger, but rarely of rickets owing to

the slow growth.

The Pancreas is usually firmer, thinner and slightly smaller than normal. In some cases the gross appearance is normal: in others the external surface is irregular because of the great variation in size and shape of the lobules of pancreatic tissue and the shrinkage of the fibrosed portions. On cross section dilated ducts can sometimes be seen naked eye. Andersen (1938) described the loss of the normal diamond shaped pattern of the lobules and mentioned that with experience a gross diagnosis could be made more often.

The Lungs of those who survived for more than a few months after birth are almost invariably diseased. Hyperexpansion is the most common finding due to the thick tenacious mucoid or muco-purulent exudate in the trachea or bronchi. Bronchiectatic and bronchiolectatic abscesses, thickening of bronchiolar walls and varying amounts of broncho-pneumonia are usual findings with areas of obstructive emphysema or collapse depending on the degree of bronchial obstruction. If the process is of long standing considerable pulmonary fibrosis is found and a chronic interstitial form of broncho-pneumonia. Fibrinous or suppurative pleurisy may also be found (Andersen 1938).

The Gall Bladder is often small and contains bile which is thicker and more sticky than normal. Andersen

(Brennemann) has found atresia of the cystic duct or its occlusion by secretion with significant frequency as well as occlusion of the hepatic ducts.

The Liver, according to Farber, is usually increased in size and fatty and that the latter change is in direct relation to the amount of pancreatic fibrosis and atrophy. Andersen has found no fatty change in the livers of those who have received appropriate dietary therapy.

Local areas of hepatic cirrhosis were found occasionally by Andersen (1938) usually along the margin of the organ. Farber confirms this and ascribes it to intrahepatic biliary obstruction.

MICROSCOPICALLY in the pancreas the most common finding is atrophy of the exocrine portion with an increase of connective tissue. In some cases large mononuclear and lymphocytic infiltration is seen. Acini and ducts are filled with a homogeneous eosinophilic material and the ducts are usually dilated and lined by flattened cells. The islets are normal. Farber describes two extremes of this histological picture not necessarily related to the age of the patient:-

1. Almost complete disappearance of the acinous tissue with fibrosis and dilated ducts.

2. No increase of fibrous tissue and no dilatation of ducts, but eosinophilic material filling

the acini and small ducts.

Andersen however (1946) considers that the lesion varies with the age of the patient: in meconium ileus the only abnormality is the eosinophilic material in the acini and ducts, but by the age of 1 year many acini are atrophied and by 3 years they may be entirely replaced by fat.

In the Lungs the appearance is that to be expected from the gross appearance, but Farber has also shown that in the tracheal and bronchial walls distended mucous glands may be seen filled with inspissated material similar in appearance to that found in the pancreas. Similar changes are found in the salivary glands and in the mucous glands of the oesophagus, duodenum, jejunum and accessory pancreatic tissue.

In the Liver small areas are sometimes seen, in which the liver cells have been replaced by fibrous tissue: dilated small bile ducts are also seen filled with eosinophilic material identical with that seen in the pancreas and elsewhere.

Histological evidence of vitamin A deficiency is found very irregularily and is even then only a small part of the pathological picture

(Farber). Blackfan & May (1938) found it in only 7 of their 35 cases, but Andersen (1938) considered it to be a more commong finding.

Farber found one case with the typical changes in the lungs and the liver, but not in the pancreas.

BACTERIOLOGICALLY: Staphylococcus aureus is the commonest organism cultured from the lungs.

CLINICAL FEATURES: These have been described by Andersen (1938, 1945 & 1946, in Brennemann's Practice of Paediatrics) who divides cases into 3 groups.

1. Cases of meconium ileus which present within a few days of birth with intestinal obstruction. Andersen considers that complete obstruction rarely occurs unless volvulus or peritoneal bands are present in addition.

2. Cases which present in the first 6 months of life. Andersen (1938) divided them into (a) those which present on account of nutritional difficulty and (b) those which present with respiratory infection. More recently however she classifies all cases in group 2 as those with early onset of respiratory infection and subdivides them into (a) a small group with intermittent or continuous watery diarrhoea and (b) a larger group who fail to gain weight on an adequate diet and who have

large foul formed stools: these may have been present from birth or develop at any time up to 6 months. There is often no increase in the number of the stools and the gross appearance is often normal in the first few months of life, but the smell is usually offensive, and after solids have been added to the diet the stools are usually large. (1945 B). Andersen (1946) found that in 19 out of 42 cases abnormal stools were noticed during the first month of life, in 11 more before 6 months, in 8 they had been considered normal for 6 months or longer, and in 4 the stools were first considered to be abnormal in hospital before the age of 10 weeks. But mothers who had previously borne normal children noticed abnormal stools before the age of 6 months in 22 out of 23 cases, whereas mothers who had not had previously normal children noticed them by 6 months in only 7 out of 19 cases.

If the weight gain is poor in the first month of life, cough is most likely to supervene before the age of 6 months.

In this group, which is the commonest, Andersen found xerophthalmia occasionally.

3. Cases which present either on account of nutritional difficulty as cases of coeliac disease or with rectal prolapse or on account of respiratory

tract infections, as cases of recurrent bronchitis, bronchiectasis, chronic sinusitis or chronic otitis media.

These children are undersized, but not grossly so, and are well nourished. They have suffered from several attacks of bronchitis, perhaps of pneumonia also, but, after an attack of broncho-pneumonia at any time between the ages of 1 and 4 years, they develop a chronic cough, fail to gain and become thin and irritable.

They always pass 2 - 4 large stools daily. Andersen (1946) found that in 16 cases with onset of cough after the age of 6 months, abnormal stools were noticed in the first month of life in 7, between 1 and 6 months in 5 and after 6 months in 4. But 8 out of 9 mothers who first noticed abnormal stools after the 1st month had had no normal children previously.

For those who survived the first year of life, Andersen (1945 C) found that they had gained weight slowly during the first year and the majority were most below the average at the end of the 1st year, but that during the second year growth was often steady, so that by the end of it the weight was nearly normal. Over the age of 2 both treated and untreated cases have weights and heights in the lower normal range.

Rickets is rare on account of the slow growth, but before treatment signs of lack of vitamins A, D (not amounting to frank rickets) or K are not uncommon.

INVESTIGATIONS:

1. DUODENAL INTUBATION. Gimson (1947) recommends the employment of a radio-opaque rubber tube to follow its path by screening. A rough measurement of the length of tube needed to reach the duodenum is made against the child and the tube is passed through the nose first thing in the morning, after the child has fasted since the previous day. The stomach contents are aspirated and, keeping the stomach empty, attempts are made to pass the tube along the greater curvature to the pylorus. Changes of posture of the child may help, first upright, then leaning over to the right, inclining forward and backward, and finally leaning to the left. If these are unsuccessful after an hour or two, the child is left to play with the tube strapped to the cheek at the estimated distance from the duodenum in the hope that the gastric peristaltic waves will carry it into the duodenum. Suction is applied to the tube every 15 minutes and duodenal contents, when obtained, are bile stained and alkaline to litmus. Andersen (1942 A) gives a light breakfast followed by fluids ad. lib. up to the time when the tube is passed. She has found it

possible to massage the tube to the pylorus: if no duodenal juice has been obtained after 4 hours the tube is withdrawn for fear of producing dehydration. Screening is essential to ensure that the tube is actually in the duodenum and, if no enzymes are found in the juice obtained, intubation must be repeated to confirm this.

Hess (1912) showed that all 3 enzymes were present in the duodenal juice in early infancy and he found trypsin in the new born before they were put to the breast. Andersen (1942 A) found little amylase before the age of 3 months and a low content of all 3 enzymes in marasmic infants: the lowest levels were, hoever, four times higher than the highest found in cases of fibrocystic disease of the pancreas. Trypsin is estimated since its determination is easiest technically: amylase is unsatisfactory because the swallowing of saliva may give false results and the estimation of lipase is unsatisfactory technically.

EXAMINATION OF THE STOOLS (a) Microscopically.

Andersen (1945 A) found microscopic examination of the stools useful since, in all cases of fibrocystic disease of the pancreas, fat droplets or fatty acid crystals constituted about half the visible material. Moreover she found this a useful method for rapid "screening" of suspected cases, since absence of steatorrhoea excluded fibrocystic disease. Garrod &

Hurtley (1912) considered that the presence of undigested muscle fibres in the stools was a good indication of lack of pancreatic function.

(b) Estimation of faecal fat: Andersen (1945 A) found great variation in the amounts of fat excreted by normal children:

	2 - 6 months	6 - 12 months	1 - 2 years	2 - 6 years
Total fat:	5.2 - 43.1	11 - 25.5	6.1 - 25.8	9.4 - 18.9
Neutral fat:	7.8 - 51.9	13.1 - 50.1	22.9 - 63.9	19.3 - 45

Table 1: The total fat is expressed as a percentage of the dried weight of the stool and the neutral fat as a percentage of the total fat.

For cases of fibrocystic disease of the pancreas also she found considerable variations in the amounts of fat excreted.

	Birth - 6 months	6 - 12 months	1 - 2 years	2 - 6 years
Fat:	41 - 61%	32 -62	20-54	29-48

Table 2: The fat is expressed as a percentage of the dried weight of the faeces.

There has been a controversy over the significance of the amounts of neutral and split fat in the stools. Earlier observers, e.g. Katz (quoted by Garrod & Hurtley 1912) had reached the conclusion that it was justifiable to suspect an affection of the pancreas in cases in which less than 70% of the fat in the faeces was in the form of fatty acids and soaps, pro-

vided that the patient was not an infant nor suffering from profuse diarrhoea. Although Garrod & Hurtley and other observers had pointed out that this could not be taken as an absolute rule, Parmelee (1935) considered that the high percentage of neutral fat in the stools of cases of congenital steatorrhoea due to pancreatic disease was one point which distinguished them from cases of coeliac disease. Harper (1938) also used this point as a diagnostic aid, although in at least two of her cases the split fat amounted to between 80 and 90% of the total excreted and she quoted Thayssen's observation that the fat could be well split in pancreatic disease. Andersen (1945 A) considered that in fibrocystic disease of the pancreas most of the fat reaches the colon in the form of neutral fat which is then split by bacterial action: moreover she found that the proportion of split fat increased if constipation was present or if the stool was left for a few days before examination. May (1947) envisages splitting of the fat by a lipase in the succus entericus but too late for its absorption. He considers that the determination of the percentages of neutral fat, fatty acids and soaps is of no value.

Andersen (1945 A) used 3 day collections of stools to determine the faecal fats, but May (1947) considers that only a fat balance test is of value: in normals 95% of the fat intake should be absorbed.

(c) The nitrogen excretion in the faeces is increased (May 1947). Normally between 87% and 62% of ingested nitrogen is excreted in the urine, depending on whether a protein-rich diet is given or a protein-poor. (Wright 1945).

3. Haematology: There is no anaemia except in younger infants (Andersen in Brennemann's Practice of Paediatrics): it is then of the iron deficiency type.

4. Blood Chemistry: (a) The glucose tolerance curve is frequently normal (May 1947) in contrast to the flat curve found in coeliac disease. The type of curve obtained however varies with the diet given in the preceding week, a high carbohydrate diet giving a flat curve (Himsworth 1935) and Andersen considers the test to be of little value.

(b) Serum proteins: may be found diminished in younger infants, but the albumen globulin ratio is normal. (Andersen).

(c) Vitamin A absorption is poor.

(d) The serum carotene level is always low (it is usually normal in coeliac disease (Andersen).

(e) The blood cholesterol is usually below normal levels (100 - 200 mgms per 100 c.c.).

(f) The prothrombin time may be lowered (Andersen).

5. RADIOLOGY: Attwood & Sargent (1942) state that

the following changes are found:-

(a) Chest: The hilar shadows are increased in density and prolonged out into a surrounding mottling which gradually diminishes towards the periphery. Broncho-pneumonic changes are bilateral and, in contrast to the usual findings, affect the upper zones as much as the lower. The chronicity of these lesions and the addition of areas of collapse are noted.

(b) Intestinal tract: Dilated loops of small gut are seen with fluid levels in them. There is "clumping" of barium in the small gut.

They point out that none of these changes are specific, but that the combination of pulmonary and intestinal lesions is suggestive: the latter may be seen in infants in chest radiographs. Andersen (Brennemann) mentions also osteoporosis, and in the chest peribronchial thickening with or without plain film evidence of bronchiectasis.

DIAGNOSIS: This is suggested by the history and confirmed by examination of the duodenal juice (May 1947). Other causes for chronic disturbance of nutrition must be borne in mind (May).

1. Starvation.

2. Infections either of the alimentary tract or of any other part of the body. Congenital Syphilis is included in this group: it may also cause fibrosis of the pancreas.

3. Abnormalities of structure or motor function of the gastro-intestinal tract.

4. Coeliac disease.

Andersen (Brennemann) also includes specifically in the differential diagnosis epidemic diarrhoea, pertussis, asthma and lipoid pneumonia. She states that abdominal enlargement and steatorrhoea does not occur with bronchiectasis unless the pancreatic defect is present also.

PROGNOSIS: The oldest recorded case died at the age of 14½ years (Parmelee 1935), but the age at which patients die depends partly on the age at which they present, but chiefly on when they develop the respiratory infection.

Cases of meconium ileus die within a few days of birth, unless operation is performed, but even so the prognosis is bad. Farber (1944 A) mentions 4 cases which were relieved by operation and given specific treatment, but they died within a few months of inter-current infection.

In group 2 the prognosis is bad, although it is improved by treatment (Andersen 1945 C). She states that the prognosis depends on the age and onset of the cough and the time at which treatment is given. If cough develops in the first month the prognosis is hopeless, but if after one month and before 6 months old it is improved, especially if treatment

is given. In those who develop cough before the age of 6 months and who are untreated 90% die before they are 1 year old: but if dietary therapy is begun several weeks or months after the first onset of cough there is usually a gradual gain in height and weight, and ultimately disappearance of the cough (the latter occurs more often in cases of group 3 than of group 2).

In group 3 Andersen found that patients survived longer with late onset of cough and that 62.5% of untreated cases which developed cough after the age of 6 months survived the first year. The prognosis was improved by treatment and even where a chronic cough had developed before treatment was started it often finally disappeared though growth was delayed. If, however, purulent bronchitis was already present treatment did not avert the fatal outcome.

Andersen (Brennemann) considers that there is essentially normal growth and activity in cases diagnosed before the onset of respiratory infection and given treatment.

May (1947) states that in a few instances the nutrition has been greatly improved by dietary therapy only to have the child succumb to an advanced pulmonary lesion, the treatment of which has been unsuccessful to date, but penicillin may prove

more useful.

TREATMENT: Andersen calculates that between 25 and 40% of the dietary calories are lost in the faeces, and recommends giving 180 calories per kilo of body weight per day in the 2nd year.

The diet should be a low fat one with double the normal protein intake i.e. 10 - 12 Gms per kilo of body weight per day in young infants and 6 Gms in older children. The diet should contain 25% of protein for adequate protein utilisation (1945 B). Protein hydrolysates are recommended in doses of 2 - 3 Gm. per kilo. A high intake of carbohydrate is well tolerated. At the Hospital for Sick Children, Great Ormond Street, as much as ½lb. of extra glucose has been given per day to infants of 6 months (Tizard 1948). Between 20 and 40,000 units of vitamin A should be given daily by mouth since it is not well absorbed if given parenterally.

Pancreatin is recommended in doses of 1 Gram per 8 ounces of feed in infants and 1 - 2 Gm. per meal in older children.

Prophylactic sulphadiazine may be of value while for frank pulmonary infections penicillin is the treatment of choice, provided the organism, which is usually staphylococcus aureus, is sensitive.

Vitamin deficiencies are corrected as necessary.

(Except where otherwise specifically stated, all references to the above are to Andersen's work, and most of it is taken from her article in Brennemann's Practice of Paediatrics).

May (1947) advises some restriction of fatty and starchy foods, but not if this makes the diet unattractive. Casein Hydrolosates are recommended and pancreatin in doses of 6 Gms up to 4 months and 21 Gms per day at 5 years, using 5 grain enteric coated capsules. But he states that these cannot safely be given to infants in whom treatment is most urgent, although there is hope that individually enteric coated granules may be practical in them. The results, using pancreatin, he considers to be less impressive than those with a predigested food. He advises giving vitamins by mouth in doses 4 times the normal.

RESULTS OF TREATMENT: As stated above under Prognosis, Andersen considers they are in the main good. Farmelee (1935) treated his case which lived to 14½ on a low fat, high protein diet, and the boy grew normally until he was 11 years old, although his weight was always subnormal. Harper (1938) found that her patients gained weight on a diet of similar composition with extra calories.

Andersen (1945 B) found that increasing the dietary fat, increased not only the loss of fat in the

stools, but also the loss of protein and carbohydrate. She considered (1945 C) that diet and vitamin A were more effective than pancreatin, but that the latter was especially useful in marasmic infants and that in them it aided the utilisation of food and reduced the total amount of fat excreted without altering the ratio of neutral to total fat (1945 A). Although pancreatin did not appear to be of service in children who were doing well, she concluded that in the present state of our knowledge it should be given.

PART TWO.

PRESENT STUDY.

FREQUENCY OF THE DISEASE: 6 proved cases are described in the Appendix and one unproved, (Case 7). All have been seen during the past 16 months at St. Mary's Hospital. Excluding the unproved case, Case 3 which was only admitted for a few days for duodenal intubation from another hospital and Case 2 which was admitted because of the suspected diagnosis of fibrocystic disease of the pancreas, 4 unselected cases are left which have occurred among 240 routine admissions, giving an incidence of 1.7%.

AETIOLOGY: No evidence of insufficient maternal diet, intrauterine or neonatal infection has been obtained. There has been no parental consanguinity and no proved case in a sibling, but a suggestive family history has been obtained in 2 cases: in Case 4 the other 3 children in the family all died elsewhere before the age of 6 months of bronchopneumonia: all had offensive stools and two had never thrived. Also in Case 4 a history of high infantile mortality was obtained among both the mother's and father's relatives. In Case 2 a suggestive history was obtained about one of the mother's brothers.

In only one instance (Case 6) has a miscarriage

PATHOLOGY: Cases 1. 2. 3 and 4 have all come to post-mortem, and for all the immediate cause of death was broncho-pneumonia.

External Appearances: Wasting has been noted in all cases, and in Case 4 specific mention was made of the almost complete disappearance of sub-cutaneous fat. In this case also peripheral oedema and petechiae were noted. No macroscopic evidence of rickets, scurvy or vitamin A deficiency was found.

Respiratory System: For all cases purulent material was noted in the main bronchi and/ or trachea, and in 2 (Cases 2 and 3) this was noticeably thick. Hyperexpansion was found in 3 cases (2, 3 and 4), patchy collapse in 3 (2, 3 and 4). Multiple small abscesses were found in 2 (Cases 1 and 4) and pleural adhesions in 2 (Cases 2 and 4). Widespread bronchiectasis was present in Cases 2 and 4 and pulmonary fibrosis was apparent in Case 4.

The lungs of Case 3 have not yet been dissected.

Pancreas: Appeared normal in size in Case 3, but was smaller than normal in the other cases. In Case 3 the diamond shaped pattern of the lobules had been lost. The organ felt nodular in 3 cases (1, 2 and 3) and in all small cysts were seen on

cross section (Plate 1). In one case (2) an increased resistance to section was noted.

Liver: Was fatty in cases 2 and 4. In Case 1 small nodules up to 2 mm in diameter were seen, mainly on the surface.

Gall bladder: In only one case (3) was this organ noted to be small and to contain bile thicker than normal. No stenosis or atresia of ducts has been found, nor have any other abnormalities been seen.

MICROSCOPIC EXAMINATION: The pancreas has been abnormal in every case, the abnormality varying from eosinophilic material in the ducts only (foetus in Case 4) without dilatation of ducts or fibrosis (Plate 2: the photograph does not show the abnormality as well as the original section does) through moderate dilatation of ducts filled with eosinophilic material with increase of fibrous tissue and relative increase in number of islets (Plate 3) to gross dilatation of ducts surrounded by dense fibrous tissue (Plates 4 and 5).

The lungs have shown purulent bronchitis in all cases with eosinophilic material lining the bronchial lumen (Plate 6). In all cases bronchopneumonic changes have been apparent with areas of emphysema in other parts. In all cases destruction in places of bronchial and bronchiolar walls with

surrounding consolidation (Plate 7) has been noticeable. In one case only (Plate 8) has a dilated duct been seen in a bronchial wall filled with eosinophilic material and surrounded by fibrous tissue.

The Liver in one case showed extreme fatty degeneration (Plate 9). In another (Plate 10) the small nodules seen macroscopically were found to consist of areas in which the liver cells had been destroyed and replaced by fibrous tissue in which numerous dilated bile ducts filled with eosinophilic material could be seen.

The salivary glands in all cases showed changes similar to those seen in the pancreas (Plates 11 and 12).

The duodenum in one case showed similar changes (Plate 13).

BACTERIOLOGY: From laryngeal swabs streptococcus viridans has been recovered in 3 cases (1, 2 and 6), in 2 (1 and 2) insensitive to penicillin, in one (6) sensitive. Staphylococcus aureus was cultured in 2 cases (3 and 2), one penicillin sensitive and one not. In one case (1) haemophilus influenzae was grown.

CLINICAL FEATURES: The distribution of cases among Andersen's groups is shown in table 3.

	Group 1.	Group 2.	Group 3.
No. of cases	0	3	3

Table 3: Distribution of cases among groups.

In all cases, except Case 5, both nutritional and respiratory features have been present on admission to hospital. In Case 5 only the nutritional difficulty is present.

With the exception of Case 1 (in which the clinical picture became typical in time) a typical history has sooner or later been obtained of poor weight gain from an early age, despite good appetite and abnormal stools since at least before the age of 6 months with, in addition, (except in Case 5) respiratory symptoms. Abnormal stools were noticed from birth in 3 cases (2, 3 and 6) and from the age of 5 months in 2 (4 and 5): they had been noticed by the mothers to be offensive and pale in 4 cases, unformed in 3 cases, bulky in 2, frequent in 2 and formed in 2. In one case (5) the stools, previously formed, but bulky, pale and offensive, became unformed and frequent at the age of 6 months. In one case (1) the stools were considered normal by the mother except for a short period of 2 weeks, but they were always unformed and frequent in hospital and became eventually offensive. 2 of the 3 mothers who noticed abnormal stools from birth had had previously normal children. Of the mothers who first noticed the stools' abnormality later,

none had had previously normal children, but in one case (5) the stools had been considered normal by medical attendants.

All cases were below average weight when first seen (Fig.1.)

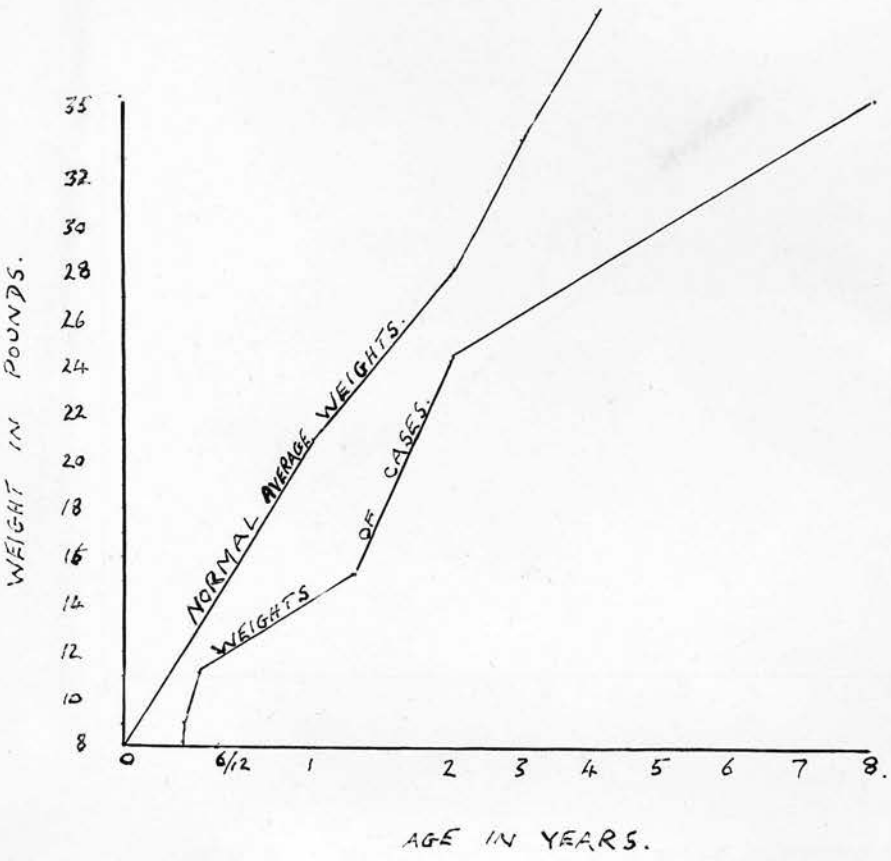


Fig. 1. Weights of cases compared with average for age.

In Case 3 the failure to gain was complicated by vomiting.

One mother (Case 4) had erroneously considered the weight gain to be normal, and Case 1 had gained well up to the onset of the respiratory infection. In all cases the latter led to actual loss of

weight and listlessness.

Retardation of growth in height was less apparent than growth in weight. (Fig.2.).

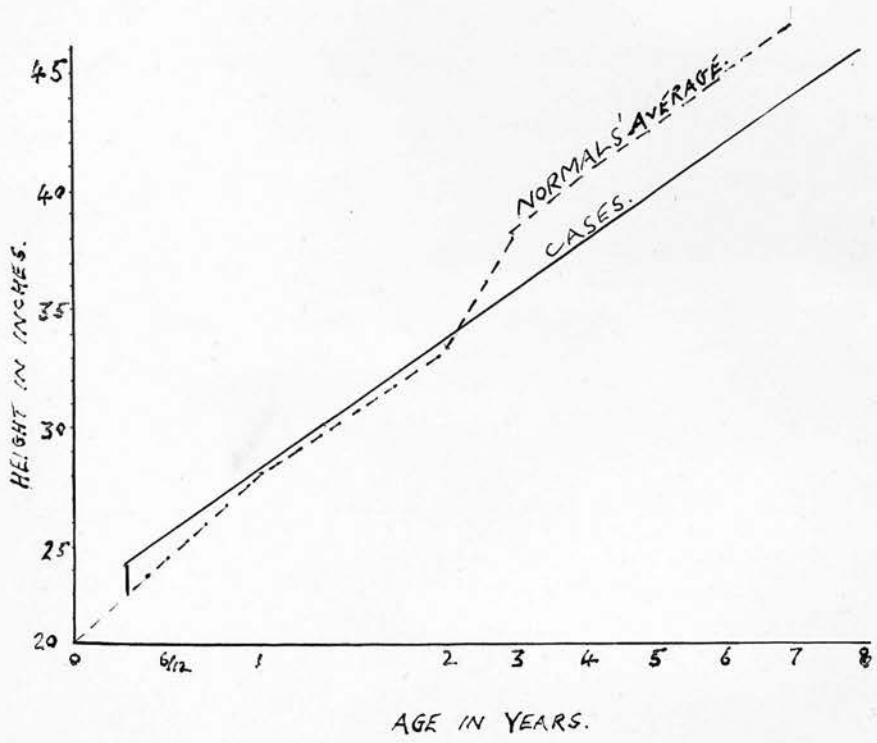


Fig.2. Heights compared with average for age.

4 cases presented in this study with respiratory symptoms and 2 with nutritional: but one of the 4 had previously presented elsewhere with nutritional symptoms. All the cases in group 2 presented with respiratory symptoms, 2 with a history of cough from birth (Cases 1 and 3) and in them respiratory infection developed at the ages of 5 and 4 months respectively (a distinc-

tion is drawn between cough and respiratory infection since the former, in the absence of signs of infection, is considered to be due to attempts to get rid of tenacious mucus from the bronchial tree). In the 3rd case respiratory infection developed at the age of 3 months (Case 2).

Of the cases in group 3 all first sought advice on account of nutritional difficulty, but one (Case 6) presented in this study with respiratory infection. Case 5 presented with severe nutritional deficiency and Case 4 with rectal prolapse: the latter had also been noticed in infancy in Case 6. In 2 cases (5 and 6) a history of respiratory infection was obtained in infancy, but in neither case did it last long or lead to a persistent cough. Respiratory infection supervened in Case 4 at the age of 22 months and in Case 6 at 8 years certainly if not before.

All cases in group 2 had received adequate vitamin supplements while all in group 3 had had inadequate supplements. But in both groups the muscles were noticeably flabby at the first examination and in 2 a small umbilical hernia was present (Cases 4 and 5). No signs of frank rickets, scurvy or vitamin A deficiency was seen in any case, but in 2 (Cases 4 and 5) a haemorrhagic tendency was seen and in the same two cases peripheral

oedema occurred.

Marked enlargement of the liver was found in Case 4 and finger clubbing in Case 6.

INVESTIGATIONS: 1. Duodenal Intubation. Gimson's method (1947) was origiønally followed, except that infants were allowed a last feed at 3 a.m. The Ryle's tube is passed at 9 a.m. through the nose. Experience has shown that this is the part of the procedure to which children very strongly object and furthermore that the hope of co-operation from older children at this stage is a vain one. A brief statement to the child, when the trolley has been brought to the bedside, that the tube is going up its nose and may tickle, followed by its rapid passage, aided by temporary restraint of the child if necessary, and encouragement during the act of swallowing is far kinder and less upsetting to the child. Children respond to sympathy and will leave the tube alone if asked to do so (this is a wise precaution). They do not appear to resent its presence in the stomach and will go to sleep or play. When the tube is in the stomach, it is screened for position to make sure it is not coiled up and left with the opaque end pointing towards the pylorus. The aim has been to leave it as near the pylorus as possible, but in general attempts to influence its position manually through the abdominal

wall have not been successful.

The child is then returned to the ward and placed lying on the R. side. The stomach is kept empty by suction at 30 minute intervals and changes of posture of the child tried if necessary, but it is left to gastric peristalsis to carry the tube on. Owing to structural difficulties and pressure of work in the X-ray department it has not been possible to re-screen when the tube is considered to be in the duodenum: its presence there has been assumed from obtaining large quantities of bile stained fluid alkaline to litmus. Frequently a small amount of acid bile stained material has been obtained before this, but the difference between obtaining large amounts of alkaline fluid and obtaining small amounts of acid fluid is dramatic. Tubes are left in in all up to 6 hours in infants and 9 hours in older children (surprisingly the latter complain very little of hunger): on an average five hours have elapsed before the duodenum was reached with extremes of 2 and 9 hours.

Older children do not suffer from this procedure but infants lose weight, on one occasion (Case 5) as much as 1¼lbs. between one mornings weighing and the next. Because of this Andersen's method (1942 A) has more recently been adopted, allowing a feed or light breakfast at 6 a.m.

It must be admitted that both procedures have produced disappointing results and failures are frequent. Abdominal massage, the giving of drinks and introduction of a 25% solution of mag. sulph. into the stomach have not appeared to be of any value. Possibly leaving the stomach unemptied would produce better results, but I have not yet tried this: it would at least make this a less time-consuming procedure.

Nevertheless, even if duodenal juice is not obtained, the aspiration of very viscid mucus from the stomach in all cases has supplied useful confirmatory evidence of the diagnosis.

Trypsin alone has been estimated in the juice obtained by testing the ability of a drop of juice to digest gelatin spread over a photographic plate. Duodenal juice has been obtained in three cases in this study. In 2 cases (2 and 6) trypsin has been completely absent: in one (case 5) gelatin was digested by undiluted juice but not by a 1 in 10 dilution. Tryptic activity up to a 1 in 20 dilution has been found to be consistent with the diagnosis of this disease (Payne 1948). In normal children tryptic activity has been found up to a 1 in 400 dilution (Anderson & Matheson 1948).

2. Examination of the stools:

(a) Microscopically. This has been carried out in

2 cases (5 and 6). In both very many fat globules were seen. In one (6) repeated examination has shown the presence of undigested muscle fibres with very clear striations.

(b) Estimation of faecal fats: This has been carried out on 72 hour collections of stools, since this method was considered sufficiently accurate for clinical purposes. A fat balance test was attempted in Case 1 and a most anomalous result obtained which was attributed to loss of a considerable amount of stool in the napkin.

Results of fat analyses are shown in table 4.

	2 - 6 months	6 - 12 months	1 - 2 years	2 years onwards
Total fat	40 - 72%	none	60%	49 - 50%
Neutral fat	25 - 48%	none	25%	14 - 20%

Table 4. Fat excretion in cases of fibrocystic disease on normal diet. Total fat expressed as percentage of dried weight, neutral as of total.

(c). Only in case 6 has the nitrogen excretion in the faeces been estimated. It was found to be greatly increased, amounting to 4.47 Gms. per day compared with a urinary excretion of 7.8 Gms per day.

3. HAEMATOLOGY: In 2 of the 3 infants in this series an iron deficiency anaemia developed as the respiratory infection progressed, as it did in

Case 4 aged 2 years. Case 5 had a slight anaemia on admission, probably of nutritional origin, which was corrected by treatment. Case 6 the oldest in the series has no anaemia despite probable bronchiectasis.

4. Blood Chemistry:

(a) Glucose Tolerance Tests have been performed in 3 cases. In Case 6 it was normal, in Case 4 showed a delayed fall, while in Case 5 a flat curve was obtained, but this was after a high carbohydrate diet had been given for some weeks.

(b) Serum Proteins have been estimated in one case (4): the total was normal, but albumen: globulin ratio only 1:1.5. It is unfortunate that they were not also estimated in Case 5 when she was first seen elsewhere.

(c) Vitamin A absorption and (d) serum carotene have not been estimated.

(e) Blood cholesterol was estimated in Case 4 and a low reading obtained.

(f) Prothrombin times have not been estimated, but it seems highly probable that low levels would have been found in Cases 4 and 5.

5. RADIOLOGY: (A) CHEST: Emphysema has been noted in 3 cases (2, 3 and 6), parenchymal inflammatory changes in 4 (Cases 2, 3, 4 and 6), thickening of the bronchial walls in 2 (Cases 1 and 6) and collapse in one

(Case 2). No abnormality was noted in Case 5.

(B) INTESTINE: A Barium Meal was given in one case only (Case 3) and "clumping" of the meal in the small gut noted.

DIAGNOSIS: The following criteria have been considered essential for a firm diagnosis:-

1. Typical history.

2. Physical findings of nutritional and/or respiratory fault.

3. Steatorrhoea.

4. Absence of trypsin from the duodenal juice in 1 in 20 dilution or less.

In all cases the diagnosis was strongly suggested by the history and physical findings. Experience has shown that the importance of the history cannot be over-emphasised, since, in no case in which a typical history was obtained and a presumptive diagnosis made on this, has the diagnosis been disproved by examination post-mortem, or of the duodenal juice. If the history is typical, so are the physical findings, but it must be emphasised that an accurate history is essential and close questioning is necessary. Whenever it has been suspected that this disease was the basis of symptoms in a child, specific questions have been asked on the following points:-

(a) Appetite

(b) Amounts of food given.

(c) Progress as regards weight. All mothers remember birth weights and mothers who have had their children in hospital usually know the weight on discharge. Specific questions have been asked about the weight at different ages and mothers who have taken their children to Welfare Clinics can refer to their cards if they do not carry the details in their heads.

(d) Character of the stools in regard to gross appearance, number per day, size, colour and smell. If noted to be abnormal, the date at which such abnormality was first noticed has always been sought. It has been found useless to accept a mother's statement that the stools are normal, without ascertaining her criteria of normality.

(e) Cough (if any) with date of its onset and relation to weight gain and activity.

(f) Family history with reference to siblings and relatives with causes if possible of infantile deaths: frequently mothers have had to consult their mothers or mothers-in-law on the latter point. In cases in which siblings have died in circumstances which suggested their death from this disease, the points noted above were asked in regard to them also.

As regards the physical examination weight and height, state of nutrition, muscle tone, size of abdomen and in the chest emphysema and signs of

pulmonary infection, especially persistent infection, have been especially noted. In Case 1 it was the presence of persistent pulmonary infection which first suggested the diagnosis. In all cases the stools have been inspected personally for evidence of their gross appearance and smell. The very offensive smell has been found so distinctive that the diagnosis was strongly suggested by it on walking into the room where the child was.

The value of the history was impressed on me by the case of a boy aged 3 years (Plate 14) whom I admitted to hospital with the provisional diagnosis of fibrocystic disease of the pancreas. This boy presented with paroxysmal cough of sudden onset and was treated by me for 3 weeks for pertussis. However continued fever, loss of weight, persistent crepitations at both bases and the development of a "coeliac" appearance lead to a revision of this diagnosis. Up to the onset of this illness he had developed normally and the typical history of fibrocystic disease of the pancreas was not obtained. In hospital he was found to have steatorrhoea and saccular bronchiectasis in the posterior basic segment of the right lower lobe was demonstrated. Duodenal juice showed trypsin present in a dilution of 1 in 400. As the pulmonary infection was controlled by chemotherapy, the steatorrhoea disappeared and a final diagnosis of bronchiectasis, probably secondary

to a foreign body, was made.

Examination of the duodenal juice confirmed the diagnosis in 3 cases (2, 5 and 6). In cases where duodenal intubation was unsuccessful, the aspiration of extremely viscid mucus from the stomach was considered to be a point in favour of the diagnosis.

Microscopic examination of the stools has only been used in cases of group 3 where the presence of completely undigested muscle fibres has been considered highly suspicious. The presence of steatorrhoea was considered to be essential for the diagnosis.

The X-ray changes are non-specific and since a diagnosis can be made in their absence their importance has not been considered great: the presence of peribronchial thickening in an infant has however been considered suspicious.

Blood counts and estimations of blood chemistry have not been found of direct value for diagnosis.

Previous diagnoses considered in these cases included pertussis in 3, coeliac disease in 2, parenteral diarrhoea with broncho-pneumonia in 2, bronchiectasis in 1, lipoid pneumonia in 1, starvation in 1, vitamin D deficiency in 1 and Von Gierke's disease in 1.

PROGNOSIS: The oldest case in this series in 9 years old.

All the cases in group 2 have died despite treatment. Cases 1 and 2 received treatment too late while Case 3, in which specific treatment was started within 3 weeks of the onset of his respiratory infection, also died: but he had had a cough since birth.

All cases in which purulent bronchitis developed died (its presence has been assumed from aspiration of lumps of pus from the stomach during duodenal intubation). The onset of cyanosis has been found to indicate the inevitability of a fatal outcome.

Case 6 in which cough did not develop until the age of 2 years is still alive at 9. Case 5 is the only case diagnosed before the onset of respiratory infection and given treatment, but after 2 months of this she still has a long way to go before attaining normal growth and activity.

Of the two children still alive, the prognosis in Case 6, who has a chronic pulmonary infection, is considered to be bad, while the prognosis has been guarded in Case 5. It has been my practice to tell parents that children suffering from this disease are very liable to pulmonary infections and that it is upon this that the outlook depends.

TREATMENT: 1. Dietary. A low fat diet has been used with at least twice the normal requirements of protein. Hydrolysates have been given in addition

in a dosage of 2 Gm. per kilo of body weight daily. A high carbohydrate diet has been used and has been found to be well tolerated by infants.

Vitamins A and D have been prescribed orally, in concentrated form, in 3 times the normal dosage as well as extra vitamins B. and C. In one case only has vitamin K. been given (Case 3).

In all cases pancreatin has been given, in infants in the form of enteric-coated granules in doses of 5 -6 Gms. daily, and in the older boy in the form of 5 grain enteric-coated capsules in a dose of 16 Gms. daily.

2. CHEMOTHERAPY: Sulphonamides and penicillin have been used as necessary.

RESULTS OF TREATMENT: These have not been impressive, but treatment was started too late in five of the six cases to expect any benefit.

The obvious result of decreasing the dietary fat, namely the decrease of fat in the stools, was found in cases 5 and 6. The addition of pancreatin produced a striking decrease in Case 2 where faecal fats on a skimmed milk were 40% but only 21% on a half cream milk and pancreatin and a decrease in Case 5 from 22% on a low fat diet to 15.9% on a low fat diet and pancreatin. On the other hand in the boy of 9 pancreatin has had no effect on the

excretion of fat nor on the digestion of protein.

Pancreatin had a marked effect on acceleration of weight gain in Case 5 and in Case 3 with pancreatin the weight reached its highest ever, despite a marked worsening of the general condition. It remains to be seen whether Case 5 continues to make progress. Case 6 has not gained much weight on pancreatin which does, however, appear to have accelerated slightly his increase in height.

Penicillin has helped Case 6, but chemotherapy has been disappointing in the other cases in which it has been used for the pulmonary infection. Organisms insensitive to penicillin and sulphonamides have however been encountered frequently.

P A R T T H R E E.

D I S C U S S I O N.

NOMENCLATURE: The name of this disease is a complete misnomer for, as Farber (1944 B) has shown neither fibrosis nor cyst formation is essential nor is the pancreas invariably affected.

FREQUENCY: Andersen found the disease present in 3% of all autopsies in infants and in this study an incidence of 1.7% among routine admissions to hospital has been found.

AETIOLOGY: The evidence points to this disease being inherited, but the manner of its inheritance is not clear. Two facts (1) that the majority of a large family may be affected and (2) that parental consanguinity has never been established in a proved case are strong arguments against inheritance through a Mendelian recessive character, even although incidence of 25% among siblings expected for such a character has actually been found. It would appear that the inheritance can be explained by incomplete dominance. Dominance in human pedigrees is rarely complete and Fisher (quoted by Cockayne, 1947) has shown that many dominant defects in man are gradually becoming recessive and that a defect may behave in one family as a dominant and in another be completely recessive.

A dominant character is strongly suggested in this study in the family of Case 4, but not in the others.

PATHOGENESIS: The conception of Farber (1944 B) that this disease is systemic in distribution, affecting mucus-secreting glands in many parts of the body has been substantiated in this study. The theory that it is the production of viscid mucus which causes the lesions most easily explains the pathological picture and Farber's experiments (1942) demonstrated that parasympathetic stimulation leading to viscid secretion could cause the pancreatic lesions in animals.

Andersen's theory (1938) that vitamin A deficiency is responsible for the pulmonary lesions must be discarded for the latter do not occur in adult pancreatic lesions nor were they the cause of death in dogs in whom the pancreatic duct had been tied (Ivy 1936).

The reason for the production of viscid mucus is not clear, but two explanations suggest themselves:-

1. A relative or absolute increase in vagal tone.

2. An increased susceptibility of mucus-secreting cells to the action of acetyl-choline.

As there is no other evidence of increased vagal tone, the second explanation appears more likely and

would be consistent with a hereditary defect. It would be of interest to repeat Farber's experiments (1942) using 2 sets of animals and to give the second set secretin after both had been subjected to parasympathetic stimulation and proved lesions produced in the first set. (It still remains to be proved also that such stimulation produces lesions outside the pancreas). If secretion could produce an amelioration in the condition in animals, the work could be applied in humans also, but such treatment would appear to require to be life-long, even though Farber believes that the pancreas can regenerate in the young (1944 B), since it would not permanently undo the basic defect.

PATHOLOGY: The pathological features as described by Farber have been substantiated in this study. That fatty livers are found in untreated cases but not in treated cases, as described by Andersen, appears to be true.

Despite a careful search a dilated duct in a bronchial wall has been found in only one section (Plate 8), but I ascribe this to the fact that sections of trachea and large bronchi were not taken. Dilated ducts in the uterine mucosa have not been found despite prolonged search.

CLINICAL FEATURES: In my opinion Andersen's 1938 classification of cases in group 2 in to those who

present with nutritional and those who present with respiratory symptoms was better than her more recent classification in which all are grouped together as early onset of respiratory infection. It is true that the latter soon supervenes in all but the maintenance of a subgroup, in which nutritional symptoms are predominant and for some time isolated would serve to focus attention on them. In the respiratory group a distinction is drawn in this study between cough and infection: consequently those cases who have a cough from birth form a separate subgroup: this again would serve to focus attention on the symptom whose significance, in the absence of signs of infection, is easily overlooked. The suggested classification of cases in group 2 is therefore based on the presenting symptom as follows:-

A. Nutritional difficulty.

B. Respiratory 1. Cough

2. Infection.

This subdivision of cases would bring group 2 into line with group 3 where a similar division is already made.

DIAGNOSIS: Miller and Perkins (1920) found it necessary to question the mother closely to ascertain the exact date of the onset of symptoms and the importance of an accurate history has already been stressed in this study. It cannot be over-emphasised since without it

the diagnosis was missed for some time in no fewer than five out of the six cases in this study. That this disease is still frequently mis-diagnosed is well shown also. Garrod (I920) wrote that the more often the pancreas was borne in mind as the possible seat of obscure intestinal disorders the more often disease in it would be diagnosed. If one extends this statement in regard to this disease to suspecting its presence in every case of chronic nutritional and respiratory disturbance in children and more especially in infants, the fact that this disease does occur not infrequently would be more generally recognised. The reason for the long delay in the recognition of this disease is due to the fact that most of the cases die in infancy of broncho-pneumonia, which is an adequate cause of death and even in cases where the pancreas was sectioned many pathologists were prepared to ascribe the changes to dehydration. In older children the diagnosis made was coeliac disease with secondary infection but Andersen (I942A) considers that this is a rare disease , since she had only seen three cases in three years.

The diagnosis of this disease is satisfying from the clinician's point of view, since a firm diagnosis can be made on the clinical picture,

duodenal intubation and microscopic examination of the faeces: the latter two investigations do not require elaborate equipment or special experience in laboratory methods, and could be carried out in the ward.

In this series there is no sure proof that duodenal juice was actually obtained, but I am convinced that the material examined was in fact from the duodenum. For the sake of complete accuracy it is intended to screen the tubes in situ in the duodenum in future. While lack of trypsin in duodenal juice has been generally accepted as proof of the presence of this disease, a warning note should be sounded. Through the courtesy of Dr. G.M. Bull I am permitted to mention two cases which have come under his care; these are sister and brother aged 24 and I8 years respectively who have suffered from steatorrhoea since birth. Apart from this and subnormal developement they are well and there is no res--piratory infection in either. Recent examin--ation under screen control has shown complete abscence of trypsin from the duodenal juice in both. These cases are not cases of fibro-cystic disease of the pancreas as regarded generally since all of the latter (except for those in Group I) have developed chronic respiratory

infections in childhood and none has lived for more than I4 years. I believe that Dr. Bull's cases are similar to that described by Garrod and Hurtley (I9I2), namely a boy of six years who, despite steatorrhoea since birth, was in good health. Garrod (I920) reported that at I4 years the boy was of normal developement and activity.

Two possibilities in regard to the pathology of these cases are;-

1. A congenital stenosis of the main pancreatic duct.

2. That they are actually cases of fibro--cystic disease in which the pancreas, but not the lungs, are affected, analogous to the case mentioned by Farber (I944 B) in which at autopsy typical changes were found in the lungs and liver, but not in the pancreas. The fact that in Garrod and Hurtley's case three other children in the family died in infancy, two of respiratory infections, would suggest this.

Whatever the explanation of these cases, it is apparent that absence of trypsin in the duodenal juice in a child with steatorrhoea who has no respiratory infection does not warrant invariably a prognosis as grave as that usually considered in fibro-cystic disease of the pancreas.

The belief that in pancreatic disease a high proportion of neutral fat is found in the stools must now be discarded and agreement made with May's statement (I947) that estimations of the total fat in the stools are alone of value. In this study the faecal fat was found to be well split.

PROGNOSIS: With the proviso mentioned above, the prognosis is bad and if one accepts Farber's view of the pathogenesis it is unlikely to be influenced by treatment. Apart from cases in Group 2 in whom the prognosis is generally considered to be bad, the age at which older children die appears to depend on factors other than treatment. For example in this study there seems to be no reason for case 6 being still alive, while case 4 is dead, unless variations in the severity of the disease are postulated. That the latter exist from the pathological point of view is agreed both by Andersen (I946) and by Farber (I944 B), but they do not agree on whether the lesion varies with the age of the patient. Andersen considers that the least pathological changes are found in the youngest patients (who die of meconium ileus), but Farber did not find that this was necessarily so. In this series the least abnormal pancreas was in the 18 week foetus, but this is only to be expected since the pathological process must have a start and Andersen (I946) considers that the pancreas is

probably normal up to the third foetal month. There is not enough evidence to justify the theory that the severity of the lesion determines the age at death. That those children who were given by their mothers as much food as would satisfy their hunger had a greater resistance to infection and survived longer was, however, an impression gained in Cases 4 and 6.

Treatment: The results of treatment in my small experience have not been impressive, although it must be admitted that many of the cases were first treated specifically so late in the course of the disease that treatment could not reasonably be expected to be effective. However, it is hard to believe that the present scheme of treatment could produce any lasting benefit, if one accepts Farber's conception of the disease, which is at least reasonable. Andersen's evidence (1945 C) in support of the efficacy of dietary therapy in promoting growth and preventing the spread of respiratory infection is not wholly convincing: for out of 11 cases treated from infancy, 9 are below average weight and six have chronic coughs. The histories of cases 5 and 6 in this study show that respiratory infections in infancy do not necessarily become chronic, even without treatment. It appears to be true that pancreatin is of value in promoting weight gain in marasmic infants and that penicillin is of value in controlling

the pulmonary infection provided the organism is sensitive. But, these would appear to be no more than temporary measures which only at best avert the fatal outcome for a time. It is not without significance that the oldest recorded case to date, that of Parmelee (1935) was treated with a low fat diet only for it indicates, in my opinion, that the present treatment of this disease plays little part in controlling its course.

The rational treatment would be to give secretin or a similar substance, provided that animal experiments showed it to be of value. In that event the diagnosis would become more than of prognostic significance in a particular case alone, for subsequent members of the same family could be investigated shortly after birth and treated if found to be affected. The inference is however that such treatment would require to be life-long. It would appear that, short of preventing it, the only way to treat this disease is to start treatment within a short time of birth, but that effective treatment is not yet available.

A P P E N D I X

C A S E H I S T O R I E S.

CASE: I: Female aged 5 months. Admitted to hospital on 1.11.47. with a history of cough.

She was the first child of healthy unrelated parents. Birth weight was 5lbs.13ozs. She was breast fed for one month and then put on to Cow & Gate milk in adequate amounts. Adequate vitamin supplements were given from 1 month.

The cough had been present since birth, at first only at feed times, irritative in type, but not severe. Two weeks before admission the cough had become worse with the onset of fever. These symptoms had persisted. Her appetite had been good up to the onset of the fever, when her weight was 12lbs 5ozs. Her stools had numbered 2 - 3 per day, being yellow in colour and not offensive, except for a period of 2 weeks from the age of 6 weeks, when she had passed 4 loose offensive stools per day.

On examination: T.101. P.148. R.48. Nutrition fair. Weight 11 lbs 1 oz. Frequent dry irritative cough. Musculature flabby. Marked inspiratory retraction of the lower intercostal spaces was present

and numerous fine crepitations were heard at the right base.

A blood count on 3.11.47. showed Hb.95%. R.B.C. 6,800,000, W.B.C.19,000, 49% lymphocytes. Hb. on 7.12.47. was 90%.

A cough plate grew no H. pertussis and a laryngeal swab grew strep. viridans sensitive to penicillin and H. influenzae insensitive to pen., but sensitive to streptomycin.

X-ray of chest on 4.11.47. showed frank thickening of the bronchial walls in the right lower zone, consistent with established bronchitis and mural changes. On 8.12.47. the picture was largely unchanged, but there was a suspicion of similar changes in the L. lower zone.(Plate 15.)

Dried stool on a ½ cream milk on 13.12.47. contained 40% of fat. Duodenal intubation was attempted at the beginning of December, but produced so much respiratory distress that it was abandoned. Extremely viscid mucus was however aspirated from the stomach.

For the first 2 weeks in hospital a full cream milk was given and on this regime 3 - 4 stools were passed per day. For the next week a skimmed milk was given and stools decreased to 2 per day. Thereafter a ½ cream milk was given and stools

numbered 2 - 6 per day.

Penicillin, streptomycin and sulphamezathine all failed to control either the fever or the respiratory infection. The respiratory rate remained between 50 and 60 per minute throughout. The cough, which had at first appeared to have a definite relation to observation noticed by the child (this led to a suspicion of its being a habitual cough), gradually became worse and in the last 10 days was most severe, paroxysmal and exhausting. Cyanosis was first noticed after 2 weeks in hospital and though it was dissipated temporarily by the use of an oxygen tent became permanent at the beginning of December.

Crepitations spread first to the left base from the R, then throughout both lung fields.

The weight steadily fell for the most part being 9lbs at death and this despite an appetite which was excellent except in the last week. The addition of 4 Gms. of Pronutrin and one drachm of glucose to each feed in December did not prevent the weight loss. As the child wasted the abdominal distension stood out in marked contract.

Stools were unformed and bulky throughout, and towards the end of November became offensive.

P.M. 17.12.47. The salient points were:-

External Appearance: Wasted female infant,

weighing 4.2 Kgm.

Respiratory: Both main bronchi contained much purulent material. There were widespread areas of confluent broncho-pneumonia in both lungs with abscess formation in places. There was no free fluid in the pleural cavity.

Digestive System: The pancreas was smaller than normal and more nodular. The cut surface showed small macroscopic cysts and these were also visible in the adjoining duodenal wall. (Plate I).

In the liver there were numerous small nodules up to 2 mm in diameter: these were chiefly seen on the surface, just under the capsule, but a few were visible also in the substance of the organ. The bile ducts were patent.

MICROSCOPIC EXAMINATION:

Pancreas: Grossly dilated ducts (Plate 1) with flattened lining cells were seen filled with eosinophilic material. Surrounding them was much fibrous tissue in which were mononuclear cells. There was almost complete disappearance of acinous tissue with an apparent increase in the number of islets.

Lungs: There was purulent bronchitis with eosinophilic material closely applied to the luminar aspect of the bronchial walls. (Plate 6).

Areas of broncho-pneumonic consolidation were seen with, in other areas, emphysema. In places (Plate 7) the bronchial walls could be seen to be completely destroyed with surrounding consolidation.

Liver: Small areas were seen on the surface in which the liver cells had been completely destroyed and replaced by fibrous tissue in which were numerous dilated bile ducts filled with eosinophilic material. Immediately surrounding these areas the remains of liver cells could be seen and farther out swollen liver cells before normal tissue was reached. (Plate 10).

The salivary glands (Plate 12) showed changes similar to those in the pancreas and similar changes were also seen in the duodenal wall. (Plate 13).

Summary: This Case presented at the age of 5 months with a respiratory infection of two weeks' duration, but cough had been present from birth. Stools and weight gain had been normal up to the time of the onset of infection.

Pathological Examination showed the immediate cause of death to be broncho-pneumonia and changes similar to those in the pancreas were found in the salivary glands, liver and duodenum.

Case 2: Female aged 4 months.

This child was transferred on 16.7.48. from another hospital where she had been under treatment for 6 weeks for a respiratory infection for investigation as a suspected case of fibrocystic disease of the pancreas.

She was the fourth child of healthy unrelated parents. Her three siblings were stated to be alive and well, but the eldest is said to be intolerant of fatty food (unfortunately it has not yet been possible to examine her).

One of the mother's brothers who had never thrived died at 10 years of "consumption of the bowels".

Her birth weight was 7½lbs. She was breast fed for 2 weeks and then given half cream Cow & Gate milk in adequate amounts and with full vitamin supplements. Despite a good appetite she never thrived and had always passed 5 - 6 pale offensive stools per day: these were hard and she strained passing them with rectal prolapse on one occasion.

At the beginning of June at the age of 3 months she developed a cough with fever, and was admitted to another hospital where broncho-pneumonia was diagnosed. Treatment with sulphadiazine and penicillin produced no improvement. The cough increased

in intensity and X-ray early in July showed left apical collapse with pleural reaction at the left base. Stools numbered 4 - 6 per day, and on a skimmed milk contained 40% fat, of which 75% was split fat.

She was admitted to St. Mary's Hospital on 16.7.48. Examination then showed a wasted dyspnoeic infant weighing 8lbs 15ozs. T.99. P.160. R.48. The abdomen was distended and the wasting of the buttocks was in marked contrast. There was a frequent paroxysmal cough. Height 24".

In the chest indrawing of the lower intercostal spaces was noted on inspiration, the percussion note was impaired at the L. base and fine crepitations were audible all over the L. hemithorax. The liver was just palpable.

Duodenal juice showed a total absence of trypsin. Faecal fat estimation on a diet of $\frac{1}{2}$ cream milk and after 2 days on pancreatin showed 21% fat with 96% split. A laryngeal swab grew a penicillin sensitive staph. aureus, but gave a heavier growth of strep. viridans insensitive to penicillin.

Blood count - Hb. 65%. R.B.C. 3,900,000. W.B.C. 15,000. 42% polymorphs.

X-ray chest on 17.7.48. showed L. basal parenchymal inflammatory changes. (Plate 16.)

Despite treatment with penicillin an irregular pyrexia developed and became swinging, reaching 104°, and crepitations spread over the R. chest also 2 days before death. The respiratory rate varied between 48 and 92. Cyanosis first appeared intermittently a week after admission and, though it was temporarily abolished by the use of an oxygen tent, it soon became permanent. The stools numbered 2 - 3 per day and were unformed, bulky, pale and very offensive. The appetite was never good and despite giving pancreatin enteric-coated granules Gm $\frac{1}{4}$ before each feed and the addition of pronutrin 3 Gms and glucose 1 teaspoonful to each feed after the diagnosis had been confirmed, there was progressive loss of weight to 8$\frac{1}{2}$lbs 2 days before death.

Post-mortem Report 4.8.48.

Wasted female infant. Abdomen protuberant.

Respiratory System: Trachea filled with thick purulent fluid. Extensive areas of broncho-pneumonia were present throughout both lungs with scattered areas of collapse. There was well marked bronchiectasis and bronchiolectasis in all areas. Throughout the L. pleural cavity there were fine adhesions and on the phrenic aspect of the L. lung there was a small multilocular cyst.

Digestive System: The liver was slightly enlarged and fatty. The intestines were distended

with gas. The pancreas was smaller than normal, nodular and gave increased resistance to sectioning.

Microscopic examination:

Pancreas: showed moderately dilated ducts (Plate 3) filled with eosinophilic material and surrounded by bands of fibrous tissue. The acinous portion had almost entirely disappeared and the islets appeared increased in number.

The lungs showed purulent bronchitis with destruction of bronchial walls in places and areas of broncho-pneumonia and emphysema.

The salivary glands (Plate 11) showed changes similar to those in the pancreas.

Summary: This case presented with a respiratory infection at the age of 3 months. Weight gain had never been satisfactory and stools had always been abnormal. A suspicious family history was obtained.

The diagnosis was proved in life and confirmed by post-mortem.

CASE 3: Male, aged 4 months. (Plate 17).

This child was admitted to hospital on 3.8.48. with a history of cough since birth and poor weight gain. His birth weight was 7¼lbs. and he was breast fed up to the time of admission to hospital. Mother and Father were alive and well and not related. A sister aged 3 was alive and healthy.

Since birth he had had a frequent irritative cough. Despite a good appetite he had never gained weight well, and his best weight was 8lbs.1oz. at the age of 3 weeks: he had, however, always vomited frequently, as often as three times a day, but rarely a whole feed: the vomiting had occurred as frequently without previous coughing as with. His stools had always numbered 4 - 6 per day and were green and not noticeably offensive. At 2 months the mother had taken him to another hospital where she was told the cough would clear up, and was given advice about feeding him.

On examination (5.8.48.) Temp. was 98°, P.128, R.28. Weight 7lbs 11ozs. Height 23 inches.

He appeared pale and thin with a distended abdomen and marked wasting of the buttocks. His muscles were flabby.

In the chest there was a marked mediastinal shift to the R. and the percussion note was hyper-

resonant all over the L. chest and at the R. base. No adventitia were heard and no other abnormality noted.

After a few days the mediastinal shift disappeared, although the basal emphysema persisted. On 12.8.48. he began to run an irregular pyrexia which persisted, the respiratory rate rose to 50 and latterly to 70, and crepitations were heard at the L. base. Staphylococcus aureus was cultured from a laryngeal swab and penicillin was given without effect. A few days before death a penicillin resistant Staph. aureus was grown from a laryngeal swab. The cough became more severe and paroxysmal, and by the end of August slight impairment of percussion note was elicited at the L. base and crepitations were audible all over the L. chest and at the R. base. Terminally these were present in all areas. In the last $2\frac{1}{2}$ weeks of life he became wheezy and cyanosed and the latter was only slightly improved by the use of an oxygen tent.

X-rays taken on admission confirmed the mediastinal shift and emphysema, and a Barium Meal done to exclude a diaphragmatic hernia showed clumping of the meal in the small gut. (Plates 19 and 20...) X-ray of chest taken on 26.8.48. showed a diffuse haze at the L. base, considered to be probably due to L. basal consolidation.(Plate 18.)

His appetite was very good throughout and between feeds he rarely had his fingers out of his mouth while awake. He continued to vomit, sometimes a whole feed, and as much as 3 - 4 times a day, but sometimes a few days passed with no vomiting. He was fed first with Full cream Cow & Gate milk and on this faecal fats were 72%, of which 48% was unsplit fats. A half-cream milk was given from the third week in August, and during the last week extra glucose to make up the calorie intake to the same as before, i.e. 70 calories per lb. From the end of August 3 drams of Hepovite (4 Gms of predigested protein per dram plus all vitamins) was given daily as well as adexolin min. 30, ascorbic acid 100 mgm. and B. plex 1 dram daily. At the same time 1 Gm pancreatin was given 20 mins. before each feed, i.e. 5 Gms daily in the form of enteric coated granules. None of these dietary changes had any effect on the stools which numbered, on an average, 4 per day and were bulky and unformed: they were soon noticed to be extremely offensive (it is interesting that during a short period when oral penicillin was given the offensive smell greatly diminished). Up to the end of August he had gained 2ozs. over his admission weight, and although the weight had risen slightly on each of the 3 previous days it rose more when pancreatin was given and reached

8lbs. 10ozs. on September 16th despite a marked worsening of his general condition. It fell again to 8lbs.5ozs. on the day before death.

Other investigations carried out were:-

1. W. R. & Kahn. Negative.

2. Blood Counts: 4.8.48. Hb.90%. C.I. 0.9.
W.B.C. 13,700. Polymorphs. 62%.

15.9.48. Hb.60%. C.I. 0.8.
W.B.C. 13,000. 40% polymorphs.

3. 4 attempts at duodenal intubation failed.

He died on September 20th 1948.

Post-mortem: on September 21st showed:-

1. In the respiratory system. A large amount of thick sticky pus was present in the trachea. The lungs were reserved for later dissection, but showed on the outside marked hyperexpansion along the anterior margins with scattered areas of collapse, largest at the L. base. Areas of consolidation could be felt inside, and the hilar glands were enlarged.

2. Digestive system: The liver was grossly normal.

The gall bladder was small and contained bile thicker than normal.

The stomach was not dilated, but the pyloric wall was definitely thickened.

The small intestine was considerably distended by gas.

The pancreas was of normal size, but felt nodular and the lobules had lost their diamond-shaped pattern. The cut surface showed a few small cystic spaces and a frozen section showed dilated ducts with increased fibrous tissue round.

The immediate cause of death was broncho-pneumonia.

Summary: This case presented with a history of cough since birth, failure to gain and abnormal stools. The respiratory infection started at the age of 4 months. There is a strong suspicion that the vomiting and failure of duodenal intubation were due to mild congenital pyloric stenosis. Despite lack of confirmation of the diagnosis by examination of the duodenal juice, the diagnosis was very strongly suggestive clinically, and specific therapy was given. On this, despite deterioration in his general condition, he gained weight until a few days before death better than he had ever done before.

Case 4: Female, aged 2 years.

The history is given chronologically, as it was obtained during her life and after.

She was first seen in January 1947 at the age of 1 year and 9 months, complaining of rectal prolapse which had recurred frequently in the past 6 months.

She was the fourth and only surviving child of healthy unrelated parents. Three brothers had all died in infancy of broncho-pneumonia, 2 at the age of 5 months and one at 2 months.

Her birth weight was 8lbs 6ozs., and she had been bottle fed: vitamin supplements were given in inadequate amounts between the ages of 2 and 10 months, but not after this. Her milestones were normal and she was stated to be active and cheerful and to have had no illnesses, although a slight irritative cough had been present for the past month. Stools numbered 1 - 2 per day.

On examination (21.1.47.) she was noticed to be thin. Weight was 24lbs. (average for age about 28lbs.). A mild coryza was present, her muscles were flabby and a small umbilical hernia was present. No other abnormality was detected and her symptoms were attributed to lack of vitamin D. Advice was given about diet and she

was put on the waiting list to have the prolapse attended to.

She was next seen 2 weeks later when she had lost 2lbs. in weight, despite a good appetite. A paroxysmal cough was heard at this time, but in March the cough was better although the rectal prolapse was unimproved. She was admitted to hospital at the beginning of May for treatment of the prolapse, but discharged home after 5 days, as she was thought to have pertussis. She was re-admitted 2 weeks later: the cough had become worse and loss of flesh was apparent to the Mother who had made similar observations during her sons' final illnesses. She had also lost her appetite and stools were 2 - 3 per day and offensive.

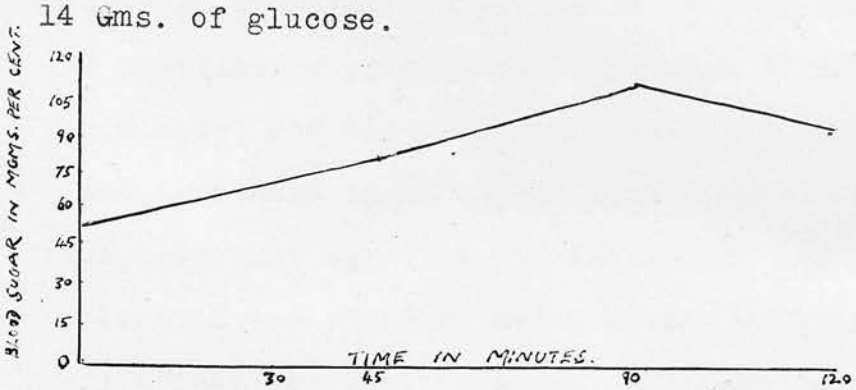
On examination (22.5.47.) T.101.6°. P.128. R.64. Wasted (weight 18lbs.4ozs.) dyspnoeic child, slightly cyanosed. In the chest the percussion note was hyperresonant and fine rales were heard in all areas. The abdomen was distended and the liver was palpable down to the level of the umbilicus and was smooth and firm. The spleen was not palpable.

Unfortunately Dr Lightwood was away at this time. A diagnosis of fibro-cystic disease of the pancreas was considered, but discarded as the stools were not pale. In view of the gross hepatomegaly without splenomegaly, and of the family history, she was in-

vestigated as a possible case of Von Gierke's disease.

1. Adrenaline response. Fasting blood sugar 60 mgm %, 30 mins. after 5 min. 1/1,000 adrenaline 70 mgm %.

2. Blood sugar curve following ingestion of 14 Gms. of glucose.



3. Blood cholesterol 80 mgms %.

These findings were considered to be consistent with the diagnosis of Von Gierke's disease with complicating broncho-pneumonia. Dr Lightwood, however, on his return in mid-June drew attention to the "coeliac" appearance, and stool examination at this time showed faecal fat to be 49% of which 86% was split. 3 attempts at duodenal intubation failed on account of the severe cough. X-ray of chest on admission had shown widespread broncho-pneumonic changes: this appearance was unchanged 3 weeks later. Mantoux 1/1,000 was negative. Blood counts showed on 24.5.47. Hb.80%, R.B.C. 3,700,000, W.B.C. 8,000 with 68% polymorphs of which about half were young forms, on 10.6.47. Hb.65% and

W.B.C.10,000 with 52% polymorphs, many of them young, and on 9/7 Hb.60%.

Despite the use of sulphamezathine which was given for 3 separate periods each lasting a week and of penicillin given for 3 periods, each of 2 weeks, irregular pyrexia persisted up to 103°, the cough became worse and the paroxysms very exhausting: crepitations persisted in all areas. The respiratory rate remained between 50 and 60 per minute, and the persistent cyanosis necessitated treatment in an oxygen tent practically continuously. Her appetite was never good and stools numbered 1 - 5 per day, being always unformed and very offensive: they remained unchanged on a low fat diet given from mid-June, and the decrease in their number during the last 3 weeks of life, when pancreatin 3 Gms. daily was given, was probably due to diminished food intake. The weight fluctuated much and was 18lbs 6ozs. at death. Hepaglandol 2 c.c. daily failed to improve the anaemia and 100,000 units Vit.A given twice weekly for 3 weeks before death had no appreciable effect. The hepatomegaly persisted unchanged. At the end of June oedema of the hands and feet appeared: plasma proteins at this time were 7 Gms % of which albumen was 2.8 and globulin 4.2 Gms. This oedema persisted despite a transfusion of ½ pint of blood and one pint of casydrol given a week before death. Petechiae appeared round the knees in the last few

Additions to the history were subsequently obtained. The child was bottle fed and was always hungry. Because of this the mother fed her 3 hourly with amounts which the Welfare Clinic had advised to be given 4 hourly. On this she had gained between 5 and 7 ozs. per week. Her stools were never formed, at first 2 per day, but between the ages of 4 and 6 months they increased to 4 daily and became noticeably pale, bulky and very offensive. Her abdomen was always large, but the Mother did not consider it abnormally so. With the onset of the cough she gradually became listless, began to lose weight, and her appetite failed while at home before her second admission to hospital.

Family History: The first child, a boy, died at the age of 2 months. His birth weight was 6½lbs. At the end of a month he weighed 6lbs.7ozs. He began to cough at 5 weeks old. His appetite was never remarkably good, but the stools were always putty coloured, bulky and offensive.

The second, a boy, weighed 6¾lbs. He took feeds well and gained well, weighing 11 lbs between 2 and 3 months old. His stools were always offensive. He began to cough at 4 months and died at 5 months old.

The third, also a boy, weighed 7½lbs. at birth. Infantile eczema appeared at 3 weeks old and although this gradually cleared up he never gained weight satisfactorily. At 2 months old he developed a dry paroxysmal cough which gradually became worse and he went off his food and lost weight. From the end of the 1st month his motions were very offensive, bulky, unformed and pale, numbering 3 per day. 2 weeks before death he weighed 9lbs: a week later the hands and feet "swelled up". He died at the age of 5 months.

The mother's grandmother lost 5 of her 8 children in infancy of causes unknown. The mother's mother lost 1 child 20 days old of "convulsions", but reared 8 who are all alive and well. All have children who are healthy. The father's mother had 12 children, of whom 6 are now alive and well. 4 died at birth of causes unknown, one never thrived and died at the age of 8 months and one died at 11 months of pneumonia.

The final episode to date in this family's history was that the mother became pregnant again in December 1947 and a therapeutic abortion was performed in April in view of the family history. The section of the pancreas of this 18 weeks foetus is shown in Plate 2. It shows eosinophilic material in some of the ducts.
~~formation~~. In places in the section acinar budding could be seen.

External Appearances: A wasted child with oedema of the wrists and hands and of the legs below the knee. Conspicuous wasting of the muscles of the shoulder girdle. Groups of petechiae on both knees. Almost complete absence of subcutaneous fat.

Respiratory System: Both lungs widely adherent to the chest wall. The adhesions on the right side were more recent than those on the left. The trachea and main bronchi contained muco-pus. Both lungs were bulky and heavy, with marginal emphysema and peripheral hypostatic collapse, and many palpably solid areas. On section both lungs showed diffuse broncho-pneumonia throughout, with the deeper parts of the lung forming a firm pneumonic mass in which there was prominent interlobular fibrosis. There were numerous abscess cavities from which green pus exuded; none of these exceeded 5 mm in diameter. In nearly every area true bronchiectasis could be seen. The hilar glands were enlarged and firm, one being 3.5 x 2.8 cms.

Alimentary System: The liver was large, rather pale and oedematous. There was patchy fatty change, the fat deposition being in the periphery of the affected lobules.

The pancreas appeared normal in size and external features. On section there were a small number of minute mucus-filled cysts (not more than 1 mm diameter) in the head and neck. A rapid frozen section showed peri-acinar fibrosis and many dilated spaces.

The remaining organs showed no significant abnormalities.

MICROSCOPIC EXAMINATION:

The Pancreas (Plates 3 and 4) showed grossly dilated ducts filled with eosinophilic material and lined by flattened cells. They were surrounded by broad bands of fibrous tissue.

Lungs showed purulent bronchitis, bronchopneumonia, emphysema and areas in which the bronchial walls had been destroyed in places. In one area (Plate 8) a dilated duct filled with eosinophilic material was seen in a bronchial wall.

Liver (Plate 9) showed gross fatty degeneration.

Summary: This Case presented first with nutritional symptoms at the age of 21 months, but respiratory infection soon followed and lead to a fatal result. There is a very suspicious family history not only in siblings but also in relatives on both sides of the family.

The stools had been abnormal since before the age of 6 months and weight gain was never satisfactory. The diagnosis was not proved in life, but post-mortem confirmed the diagnosis which had been suggested clinically. The immediate cause of death was broncho-

pneumonia. Similar changes to those in the pancreas were found in the salivary glands and in the bronchial walls.

CASE 5: Female aged 16 months.

This child was transferred from another hospital as a case of coeliac disease. She was admitted to St Mary's Hospital on 30.7.48.

She was an only child of unrelated parents. The Father is alive and well. The Mother has suffered from asthma, and was in hospital with pericarditis for the first 4 months of the child's life. No significant history in relatives was obtained.

Her birthweight was 7lbs. 5ozs., her milestones were normal and, apart from an attack of bronchitis at the age of 8 months, which lasted for a week, she had been well apart from her present illness.

The Mother knew little about the baby's progress in the first 4 months (information from hospital in which baby was accomodated while mother was ill states that child was admitted at 3 days old weighing 6¼lbs. On discharge at 15 weeks weight was 10lbs. 12ozs. No abnormality was noted in the stools.)

About 1 month after she returned home with baby the stools were noticed to be pale, bulky and offensive, but were formed and hard, and numbered only 1 per day. At 6 months weight is stated to have been 23½lbs and the same at 9 months. No vit. supplements were given between 4 and 6 months, but C.L.O. and malt drs 1 daily and oranges, when

available, were given after this. At 6/12 stools increased to 2 per day and at 1 year to 6 - 8 per day and were now unformed and sometimes fluid. Up to now appetite had been good, but she now started to vomit after every meal, went completely off her food and would only take dry, unbuttered toast, cheese, tea and a little milk. She was kept on this diet for 2 months until admitted to another hospital. Vomiting last for 1 month only, but stools continued as frequent as before. At 14 months "bruises" appeared on the trunk and limbs, and after a week she was taken to another hospital and immediately admitted. Condition at this time (4.6.48.), very emaciated and miserable. Weight 14lbs 12½ozs. Petechial haemorrhages on arms and trunk with a larger haemorrhage round umbilicus. Oedema of hands and feet. Abdomen protuberant. Stools bulky and highly offensive. Only 4 teeth were present.

During her first fortnight in hospital her appetite was very poor and she would take only milk. Stools continued about 6 a day. She lost 1 lb in weight and though the petechial haemorrhages increased the peripheral oedema gradually cleared. Radio-stoleum m 15 b.d., Vit. C. 500 mgms daily; marmite and casydrol ozs 1 b.d. had been given since admission and on 16.6.48. a fat-free diet was started and plexan 2 c.c. I.M. on alternate days.

In the next 9 days she put on 1 lb in weight and the petechiae disappeared, but she then developed an ulcerative stomatitis with high fever. Staph. aureus was cultured from the ulcers and the condition cleared in a week with Penicillin. After this she made slow but steady progress and became slightly less miserable. Stools 1 per day. Weight on transfer 16lbs.

Investigations:

7.6.48. Hb.80%. R.B.C. 4.5m. W.B.C. and platelets normal. Bleeding and clotting times within normal limits.

21.6.48. Hb.94%. R.B.C. 4m. Slight macrocytosis.

8.6.48. Faecal fats 60% - 75% split. Micro. stool. Fat globules + + + +.

12.7.48. Faecal fats 22%.

On Examination at St. Mary's Hospital, 31.7.48:-

T.P.R. normal. Weight 15lbs 5ozs. Emaciated and miserable, whining continually during examination. 8 teeth present. Abdomen distended and buttocks markedly wasted. Liver not palpable. Muscles hypotonic and small umbilical hernia present.

Investigations:

4.8.48. Duodenal juice. Trypsin present in undiluted juice, but not in 1 - 10 dilution.

8.9.48. Micro. stools. No undigested muscle fibres. Faecal fats 15.6%. 80% split.

31.8.48. Glucose tolerance curve: After 13 gms

glucose. Fasting 80 mgms %, after 50 mins. 90, after 120, 95.

Blood Counts:

4.8.48. Hb.95%. M.C.D. 7.0 μ. W.B.C.10,000. 71% lymphocytes.

1.9.48. Hb.95%. M.C.D. 7.1 μ. W.B.C.12,000. 73% lymphocytes.

X-ray chest: (12.8.48.) N.A.D.

Treatment: Diet: low fat, high protein and carbohydrate with 30 gms Casydrol added daily and ½ oz. glucose b.d. Adexolin m 15 t.d.s. Vit. C. 100 mgms daily. Pancreatin granules started on 5.8.48. gms 2 t.d.s.increased to gms 3 t.d.s. on 17.8.48. when glucose was increased to ½oz. t.d.s.

Progress: Weight fell to 15 lbs following passage of duodenal tube, but rapidly rose hereafter reaching 17 lbs on 10.8.48. 17lbs.12ozs. on 19.8.48. and 18lbs 7ozs. on 26.8.48. i.e. an increase of 31bs 2ozs. in 3½ weeks. It fell again to 17lbs 7ozs. following unsuccessful duodenal intubation (performed to make diagnosis doubly sure) on 2.9.48., but rose again to 17lbs 14ozs on discharge.

She rapidly became much more cheerful, though still resentful of examination. She was very finicky about her diet, but on the whole ate well and very well of things she liked. Stools averaged 1 - 2 per day and were always pale, bulky, unformed and very offensive.

Summary: This case belong to Andersen's group 3 and presented with symptoms of severe nutritional deficiency. During the first 4 months of life she had not gained weight satisfactorily and the statement that she weighed 23½lbs at 6 months should be accepted with reserve since this would represent a gain of 13lbs in 2 months. Moreover, when she was 9 months old the grandmother diagnosed consumption of the bowels, and it seems most unlikely that such a lay diagnosis would be made in a healthy child.

Abnormal stools were noted at about 5 months, but the history of this early onset was not obtained at another hospital where coeliac disease was diagnosed, although duodenal intubation had not been performed.

The suspected diagnosis of fibrocystic disease of the pancreas was confirmed by duodenal intubation, and she gained 3lbs in 3½ weeks when pancreatin was given. Previously on a "coeliac" diet only she had gained 1 lb in 2 months.

No respiratory infection has yet occurred in this child.

Case 6: Male, aged 9 years. (Plates 21 & 22.)
This history is also given in chronological order as it was obtained.

He was first seen at St. Mary's in March 1947, on account of cough. The history obtained at this time was that apart from broncho-pneumonia at 2 weeks old and rectal prolapse at 6 months he had been well until the age of 2 years when he began to pass frequent bulky pale loose stools. He was taken to another hospital, diagnosed as a case of coeliac disease and treated for 2 years with diet without improvement. At the age of 4 laparotomy was performed for suspected chronic intussusception. None was found, but the mediastinal glands were enlarged and his Mantoux having been found to be positive and X-rays showing calcified abdominal glands, the diagnosis was changed to tabes mesenterica, and he was sent to a sanatorium for the next 2½ years. He had only been at home for a few weeks when at Christmas 1946 he became ill with paroxysmal cough and fever and he was suspected of having pertussis complicated by broncho-pneumonia. Since then the cough had continued, he had lost weight and become very apathetic and miserable. He was the only child of healthy parents.

On examination (March 1947 aged 8 years) weight

35lbs. (average 55lbs.) Height 45" (average 48"). Thin with distended abdomen. Slight finger clubbing. In chest, air entry was diminished at the right base and coarse crepitations were audible there. The liver was palpable one finger's breadth in the mid-clavicular line.

Mantoux 1/1,000 was strongly positive and X-ray of chest (10.3.47.) showed slight general emphysema with signs of generalised bronchitis and frank thickening of the bronchial walls in both lower zones (Plate 23). A Bronchography was unsatisfactory, but a suggestion of bronchial dilatation was reported in the R. middle lobe. From the sputum a penicillin sensitive growth of strep. viridans was obtained. Faecal fats were 50% with 80% split fat. W.B.C. 11,800 - 60% polymorphs.

He was given a course of sulphadiazine (21 Gms) and for 2 weeks penicillin inhalations. Breathing exercises and postural drainage were carried out throughout his stay in hospital, but the cough persisted with a fair amount of purulent sputum and there were persistent crepitations over the R. middle and lower zones. His stools numbered 1 - 2 per day, and were brown, formed and not remarkably offensive. On a normal diet he had gained no weight when, after 6 weeks in hospital, he was discharged to convalescence.

On his return in September 1947 he had gained 5lbs in weight (40lbs) and ½" in height (45½"). Finger clubbing was more pronounced, the percussion note over the chest was hyperresonant and crepitations were still audible in the R. lower and mid zones. The diagnosis of fibrocystic disease of the pancreas was now considered, the Mother was requestioned and the following facts elicited:-

1. Ever since birth the stools had been bulky, loose, pale and offensive, but this became more pronounced at the age of 2 years.

2. In infancy, despite a good appetite, he had never gained weight satisfactorily and his feeds had been changed frequently in an attempt to find one which suited him.

3. From the age of 2 years he had had an irritative cough at night. This had been worse and accompanied by purulent sputum since the previous Christmas.

Examination of the duodenal juice showed complete absence of trypsin. Microscopic examination of the stools showed numerous fat globules and completely undigested muscle fibres. Urinary nitrogen amounted to 7.8 Gms per day, faecal to 4.47. A glucose tolerance curve was normal, Hb. was 100% and W.B.C. 1,6,000 with 56% polymorphs. The predominant growth from the sputum was a

penicillin sensitive pneumococcus.

Postural drainage was continued with penicillin inhalations during his last 5 days in hospital. He was on a normal diet with the addition of Pancreatin (5 gr. enteric coated capsules) Gm. 2 4 times daily before meals, pronutrin 12 Gms per day, B. plex 3ī b.d., calcydic granules 3ī b.d., vitamin C. 100 mg. daily and adexolin M XV t.d.s. He was discharged home in the middle of November, weighing 41 lbs., to continue this treatment. His physical condition was unchanged.

Since this time no remarkable improvement has taken place except that the Mother states that he is a different boy, being now energetic and eager for play where before he was listless. About once a month the cough becomes worse with severe paroxysms sputum increases in amount and he has a fever up to 103° for a few days: he has been helped during these episodes by five day courses of penicillin inhalations.

Slight alterations have been made in his treatment. In January he was put on a "coeliac" diet, i.e. extra protein rations and bananas since his Mother was finding difficulty in giving him enough to eat: in actual fact he has fats since his Mother can obtain these privately. In April 1948 pancreatin was increased to 16 Gms daily.

In May the following investigations were repeated:-

	Without pancreatin.	With pancreatin.
Micro. faeces	Undigested muscle fibres	Undigested muscle fibres
Faecal fat	35.2%	42.3%
,, nitrogen	3.66 Gms per day	2.9 Gms per day
Urinary nitrogen	6.15 ditto	6.15 ditto

He was last seen on 3.9.48. Weight was 42lbs (average 71 lbs) and height 47½" (average 50"). X-ray chest is shown in Plate 21. Physical signs are unchanged and his stools continue to be formed and number 1 - 2 per day; his Mother, who has now given birth to an apparently normal infant, considers they are abnormally offensive.

Summary: This case falls into Andersen's group 3. He presented first as a case of coeliac disease at the age of 2 years when he began to cough. He is presumed now to have bronchiectasis on account of purulent sputum and persistent crepitations in the R. lower zone. Specific treatment with pancreatin has produced no dramatic improvement, although he is more active and has gained 2" in height in the past year.

CASE 7: Male, aged 2 years and 2 months.

Admitted to hospital on 13.9.48. with a diagnosis of asthma.

He is the third child of unrelated parents. The mother is healthy: the father suffers from hay fever. The eldest child is alive and well. The second died of bronchitis at the age of 11 weeks: he had never thrived. A sister of the father had never thrived and died within a few weeks of birth.

This child was born after a normal pregnancy and delivery, and weighed 7½lbs. at birth. Despite a good appetite he only gained about 4 ozs a week as an infant and at one year old weighed about 19lbs. The mother had noticed that his progress had not been as good as that of his elder sister. He had received adequate vitamin supplements and his milestones were normal.

His stools have never been formed. From the age of 6 months certainly and possibly earlier they have numbered 4 per day and have been bulky and offensive.

At the age of 2 months he began to wheeze and a month later was seen by a physician who diagnosed asthma. The wheezing has continued without intermission since and in the past 2 months he

has begun to breathe rapidly. A dry paroxysmal cough has been present during the past month and since its onset he has lost weight and energy, although his appetite has remained good. During the past 2 months recurrent rectal prolapse has occurred.

On Examination: Weight 21 lbs. 3 ozs. Height 30". Temp. normal. P.120. R.32. Dyspnoeic: alae nasi working. Frequent cough. He is generally thin with a prominent abdomen, but the buttocks are not markedly wasted.

In the chest a Harrison's sulcus is present, the percussion note is hyperresonant and fine crepitations are to be heard in all areas.

The liver is palpable 2 fingers breadths below the costal margin in the mid-clavicular line.

Investigations to date:-

1. Stool (a) microscopic examination. Fat globules+++ and completely undigested muscle fibres. (b) faecal fats 30%.

2. Blood Count: Hb.85%. W.B.C.11,000 with 53% polymorphs.

3. X-ray chest shows diffuse bronchitic changes.

SUMMARY: This case is yet unproved, since an attempt at duodenal intubation was unsuccessful, but the history of failure to gain, despite a good appetite, abnormal stools from an early age, wheezing

and recent onset of cough, plus the suggestive family history, the physical findings and the finding of steatorrhoea and undigested muscle fibres in the stools make a highly suggestive picture.

SUMMARY & CONCLUSIONS.

1. The literature of fibrocystic disease of the pancreas is reviewed.

2. Six proved cases and one unproved case are described in regard to the clinical picture, treatment, pathology, bacteriology, biochemistry and radiology.

3. The unselected cases represent an incidence of 1.7% of all hospital admissions among children and it is emphasised that the disease is therefore not uncommon.

4. The evidence points to the disease being inherited and inheritance by an incomplete dominant character is tentatively suggested.

5. The results of pathological examination in the three post-mortems fully studied are in agreement with previous work that this disease affects mucus-secreting glands generally in the body.

6. The view that inspissation of viscid mucus in these glands causes the pathological lesions throughout the body is considered to be consistent with the findings.

7. The importance of an accurate history is stressed.

8. It is suggested that cases in group 2 be divided into nutritional and respiratory sub-groups, depending on the presenting symptom and that cough

does not necessarily indicate infection.

9. The chances of successful duodenal intubation at any one attempt are considered to be about one in three.

10. Fibrocystic disease of the pancreas as generally regarded may not be the only condition (excluding congenital syphilis) in which trypsin is absent from the duodenal juice in children.

11. Reference is made to two cases in adults who have suffered from steatorrhoea since birth, but who have no signs of pulmonary or other infection, and in whom trypsin is absent from the duodenal juice.

12. It is suggested that these cases may be cases of fibrocystic disease of the pancreas in which the lungs are not affected. If this is so, they should be separated from those cases in which the disease is systemic in distribution.

13. Nevertheless absence or virtual absence of trypsin has been considered essential for diagnosis in the cases in this study as well as the presence of the typical clinical picture and steatorrhoea.

14. Fat in the faeces is well split in this disease and it is agreed that estimationsof the total fat only are of value.

15. Unless this disease is borne in mind as the possible cause of any chronic nutritional and/or respiratory disturbance in children it will be frequently misdiagnosed.

16. The prognosis is considered to be bad.

17. There is insufficient evidence to show that variations in the severity of the lesion determine the prognosis.

18. Present treatment is considered to be unlikely to produce more than temporary improvement and to exert little control over the course of the disease.

19. It is suggested that animals, in whom the lesions of this disease have been produced, be treated with secretin and the results observed.

20. If the results are satisfactory, the treatment should be extended to children, but it is considered that only treatment from an early age and throughout life would be efficacious.

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I wish to express my thanks to Dr.R.C.Lightwood for his interest,guidance and permission to record these cases;to Dr.U.James for permission to record case 3 and to Dr.U.Shelley for permission to record the case shown in Plate I4; to Prof.W.D.Newcombe for his help with and permission to use the pathological data and to Dr.J.Bate,who has performed two of the post--mortems,carried out the investigations in case 3 and given valuable advice about the histology; to Dr.A.B.Anderson for carrying out the biochemical investigations,to Dr.Rohan Williams for his help with and permission to reproduce the X-rays and to the Wright-Flemming Institute of Microbiology for the bacteriological results;to Dr.G.M.Bull of the British Postgraduate Medical School,Hammersmith for permission to record the cases mentioned in Part 3;to Mr.E.V.Willmott of the same hospital for the photomicrographs,to Mr.A.Evason for the clinical photographs and finally to Miss D.V.Sturgess for typewriting the manuscript.

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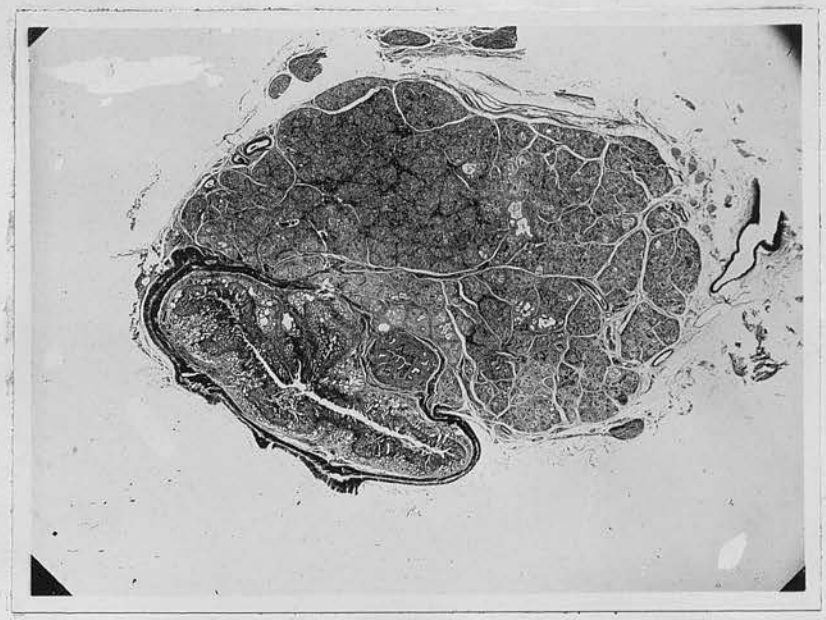

Plate I (Case I).Pancreas and duodenum showing dilated ducts in pancreas and duodenal wall.

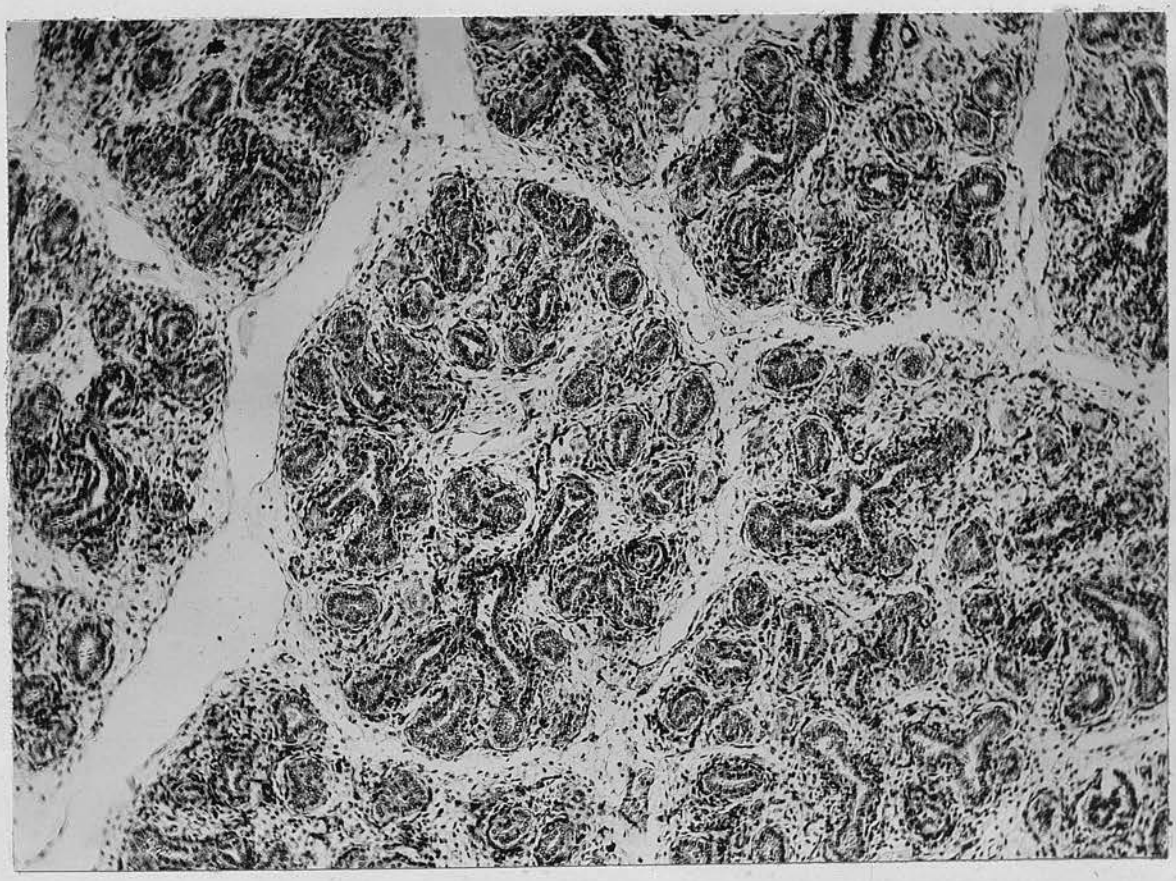

Plate 2(Case 4).Pancreas (H.E.x 95) of I8 week foetus showing eosinophilic material in some of the ducts without dilation or fibrosis.

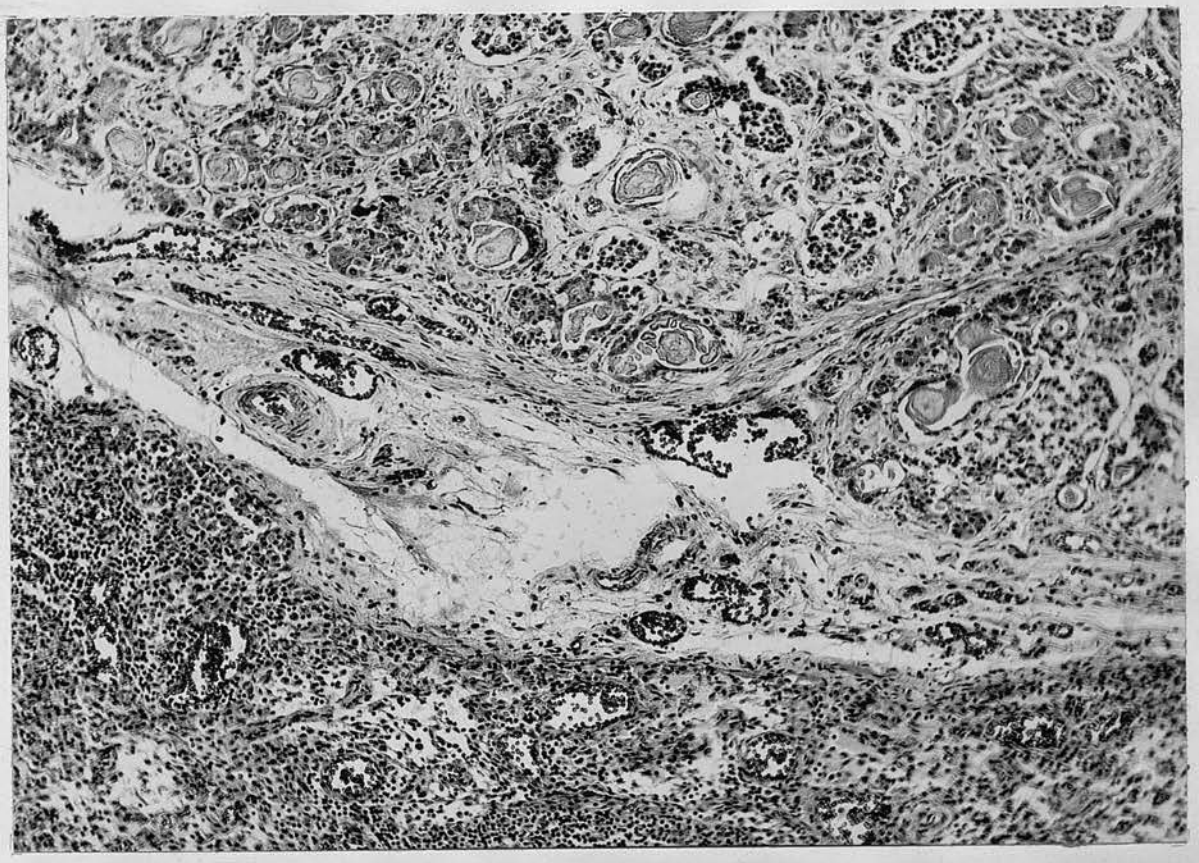

Plate 3 (Case 2).Pancreas (H.E.x 105) showing moderately dilated ducts lined by flattened cells and filled with eosinophilic material.A great increase in fibrous tissue is seen with almost complete disappearence of acini.

Plate 4 (Case 4).Pancreas (Van. G.x I20) showing grossly dilated duct lined by flattened cells and filled with secretion which is also seen in the surrounding smaller ducts.There is much fibrous tissue.

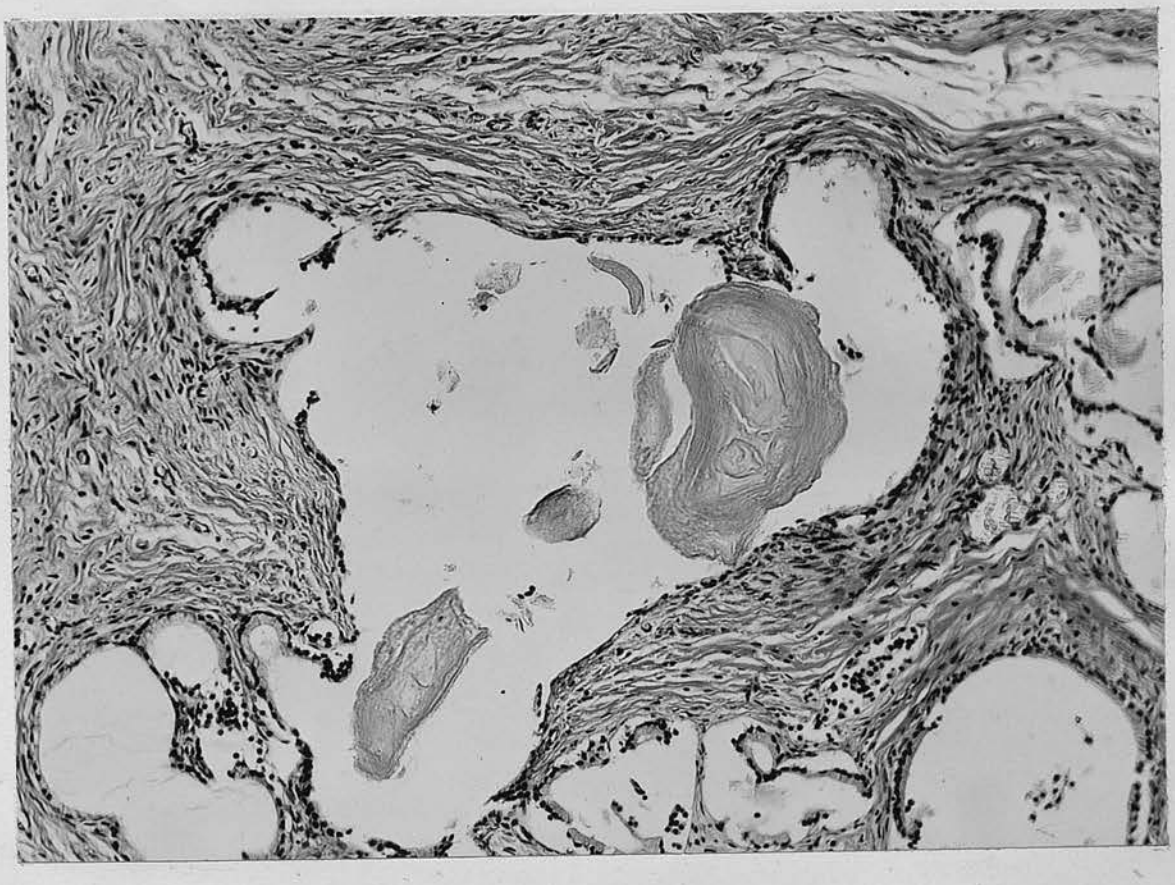

Plate 5 (Case 4).Pancreas (Van G.x I45) showing grossly dilated duct with eosinophilic material in the lumen which is lined by flattened cells and surrounded by much fibrous tissue.

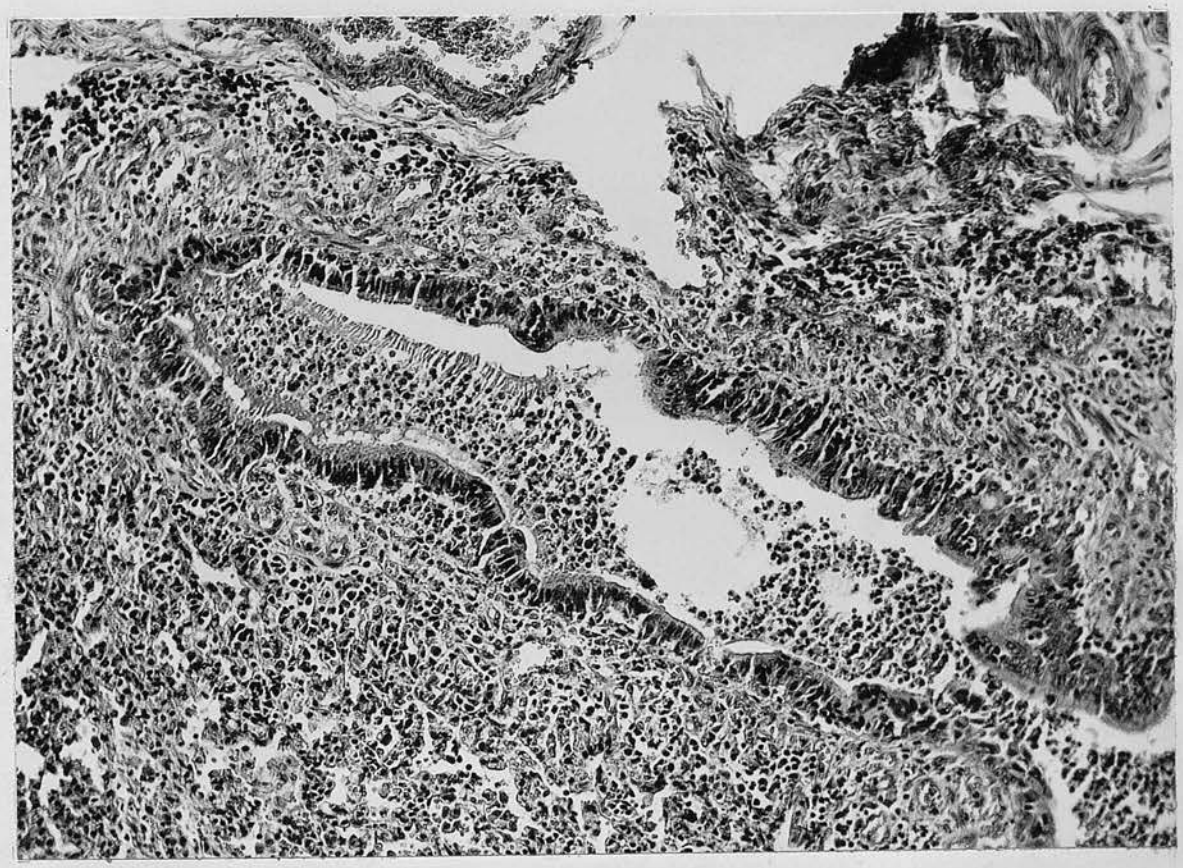

Plate 6 (Case I). Lung (H.E.xI05) showing purulent bronchitis with eosinophilic material lining the lumen and consolidation of the surrounding parenchyma.

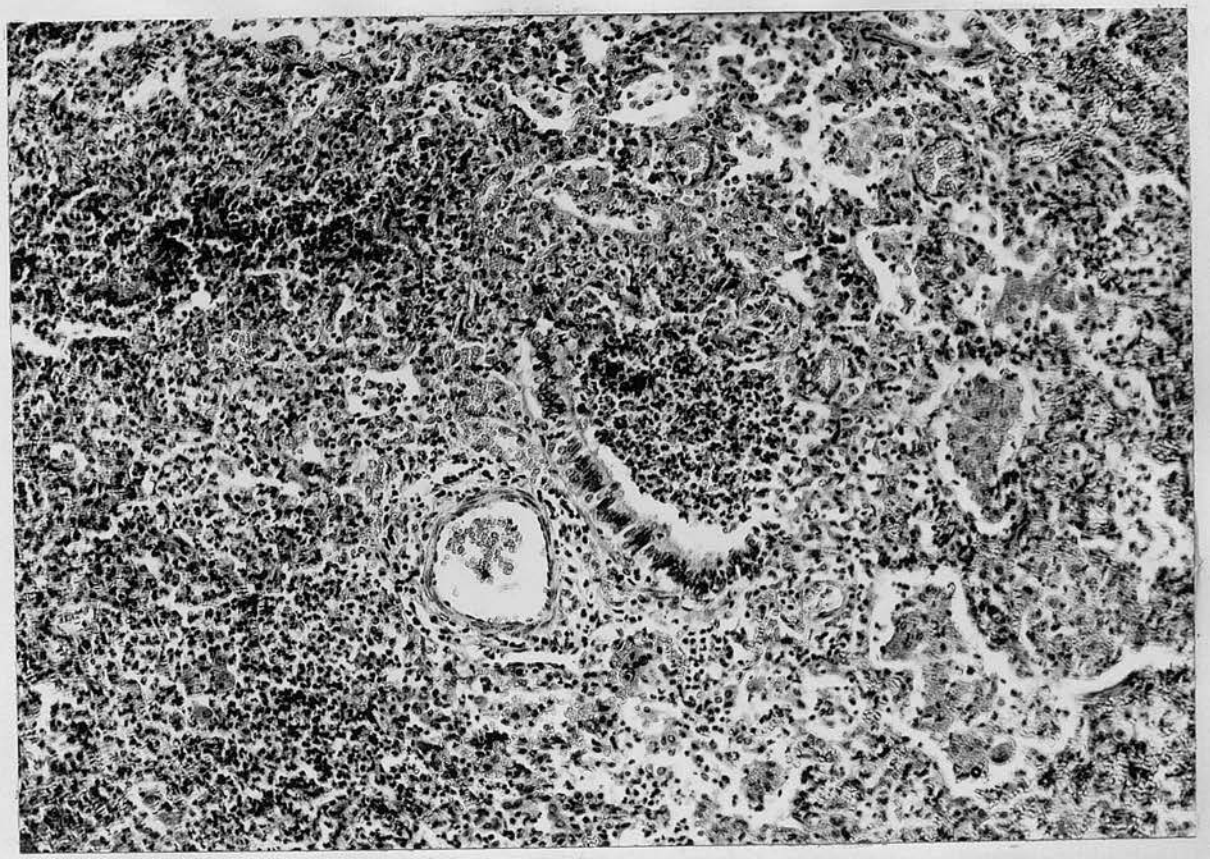

Plate 7 (Case I).Lung (H.E.x I45) showing destruction of bronchiolar wall with surrounding consolidation.

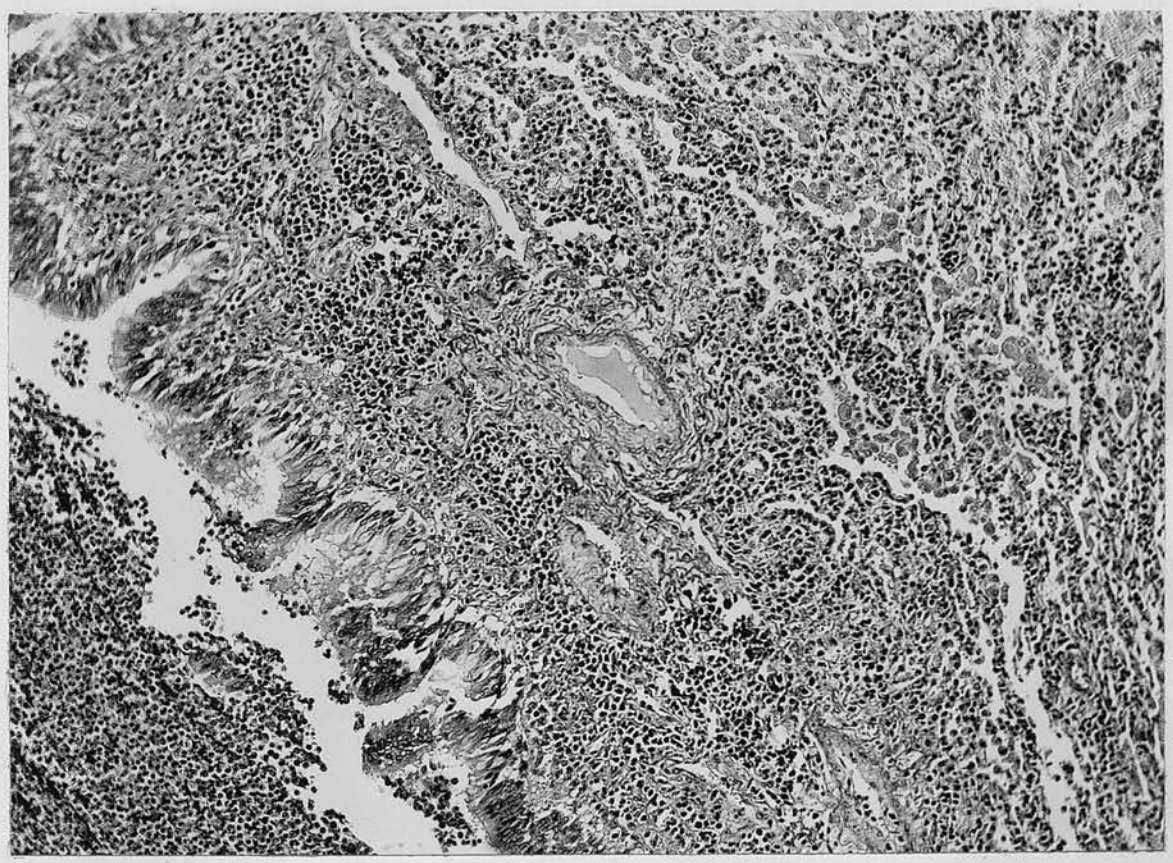

Plate 8 (Case 4).Lung (Van G.x I05) showing in centre of field a dilated duct filled with secretion and surrounded by fibrous tissue in the bronchial wall.

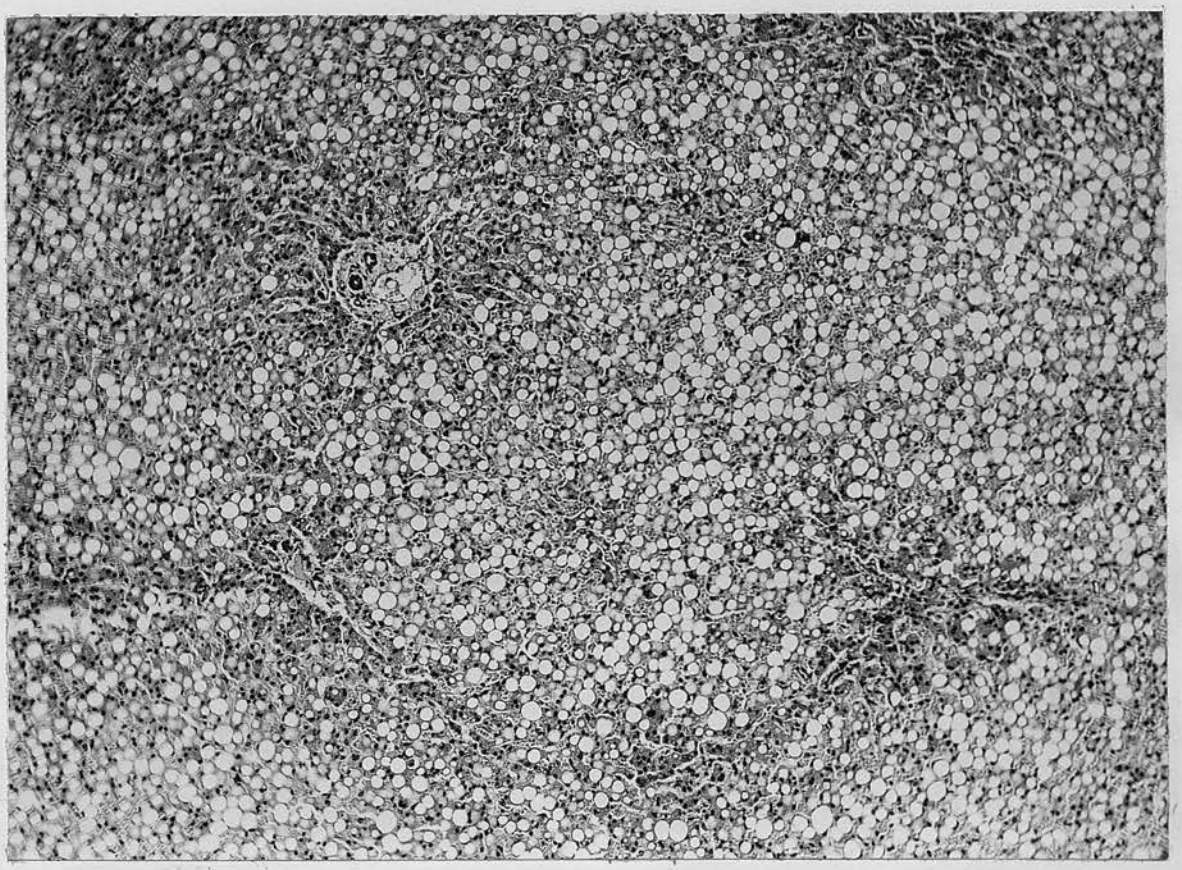

Plate 9 (Case 4).Liver (H.E. x 90) showing gross fatty degeneration.

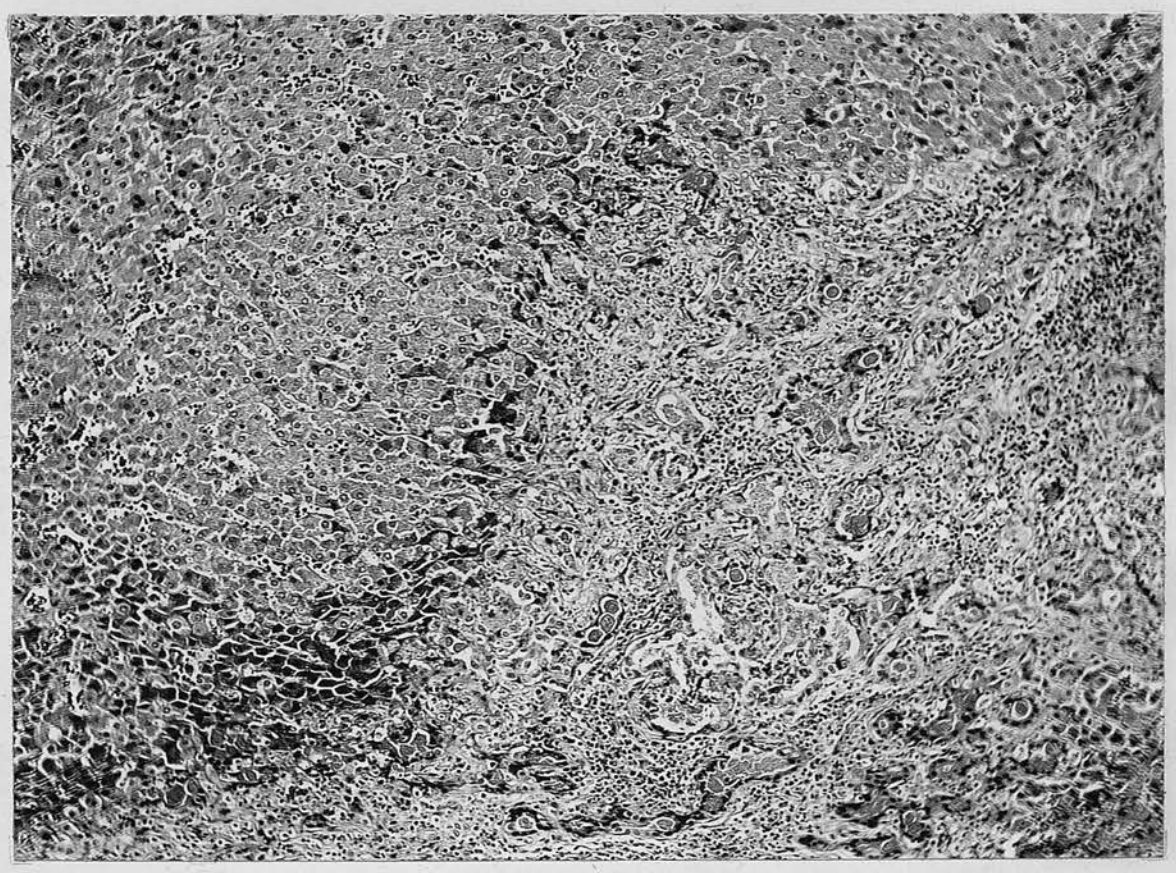

Plate IO(CaseI).Liver (H.E.x I40) showing on left swollen liver cells with dying cells between them and an area in which the liver cells have been replaced by fibrous tissue in which are numerous dilated bile ducts filled with eosinophilic material.

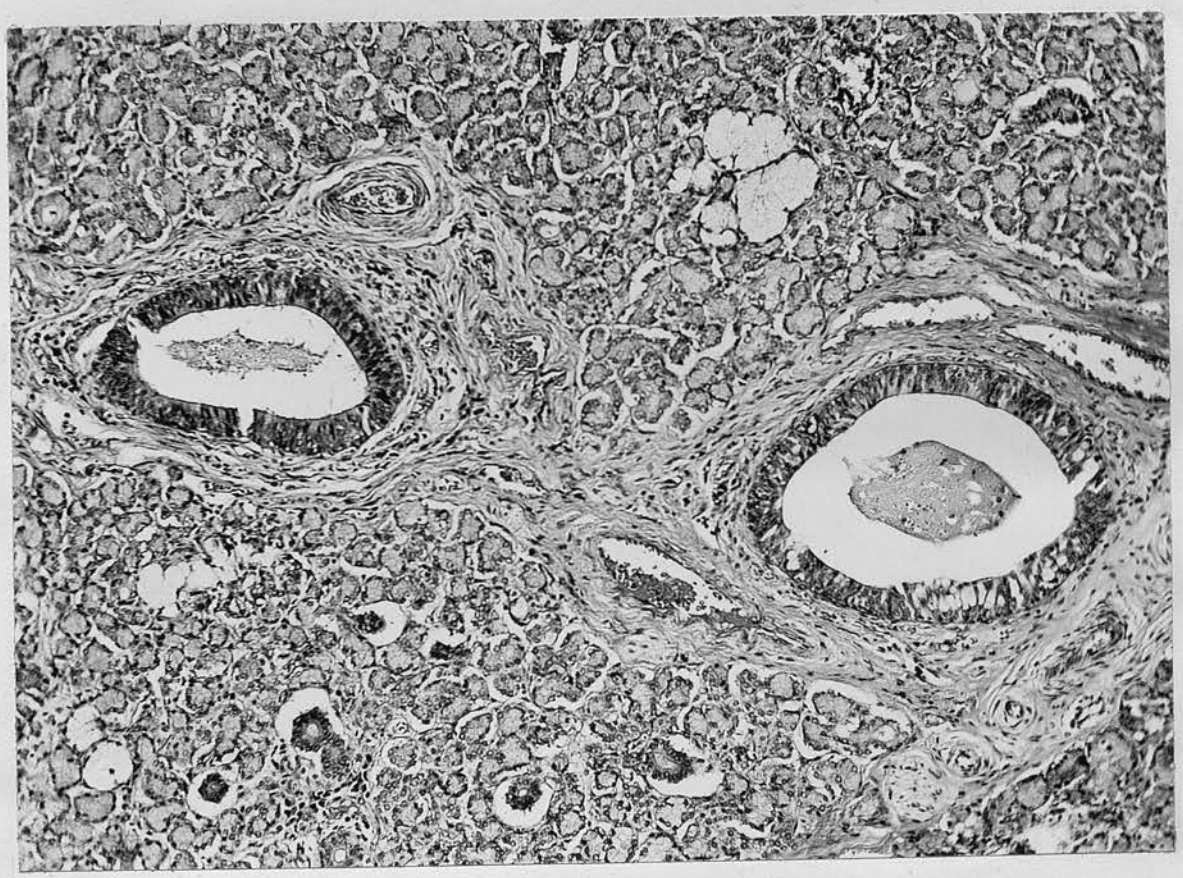

Plate II (Case 2).Salivary gland (H.E.x 95) showing 2 moderately dilated ducts with eosinophilic material in the lumen and surrounded by fibrous tissue.

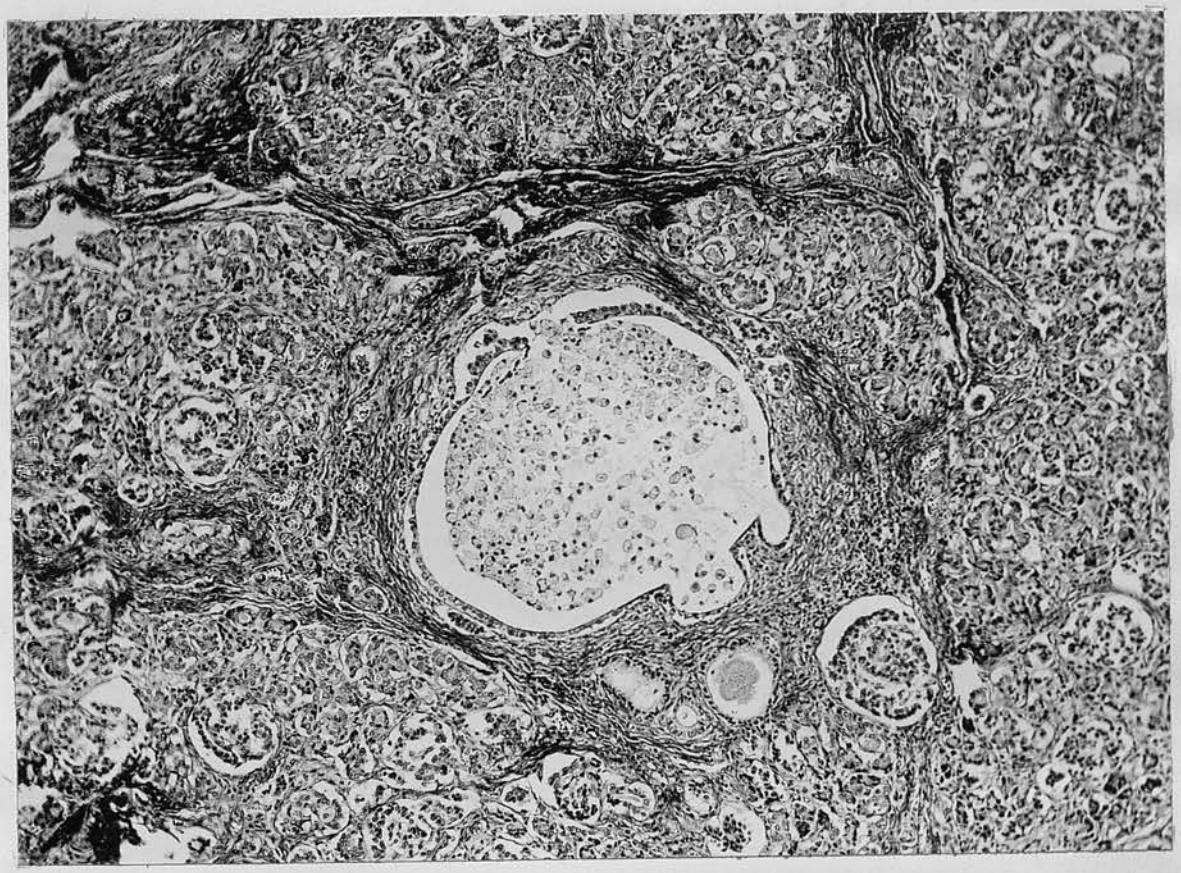

Plate I2 (Case I).Salivary gland (H.E.x 90) showing grossly dilated duct lined by flattened cells with bands of fibrous tissue round.

Plate I3 (Case I).Duodenum (Van G.x 90) showing dilated ducts in wall,the largest of which is filled with secretion. There is a great increase of fibrous tissue.

Plate I4. Child suffering from bronchiectasis showing "coeliac" appearence.

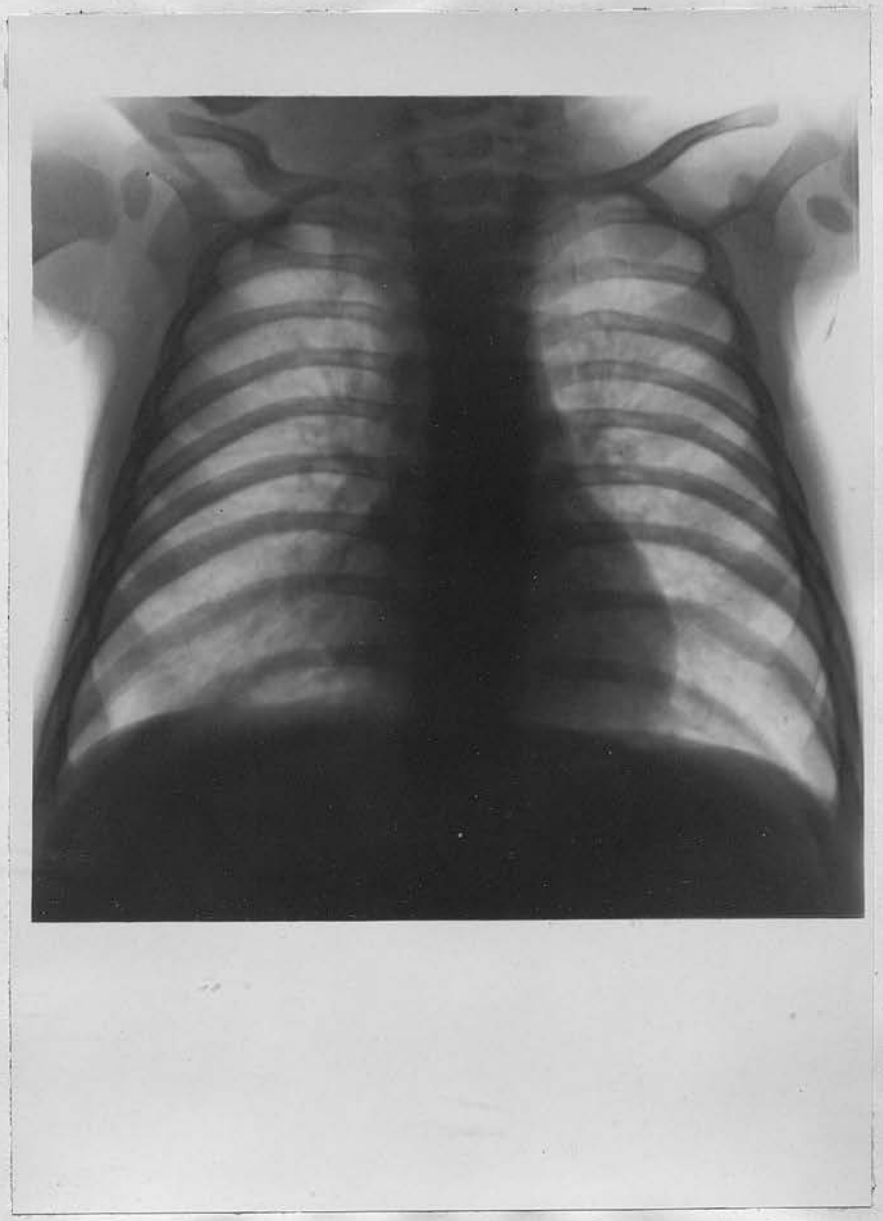

Plate I5.X-ray of chest (Case I) 3.II.47.showing diffuse bronchitic changes and consolidation at the R. base.

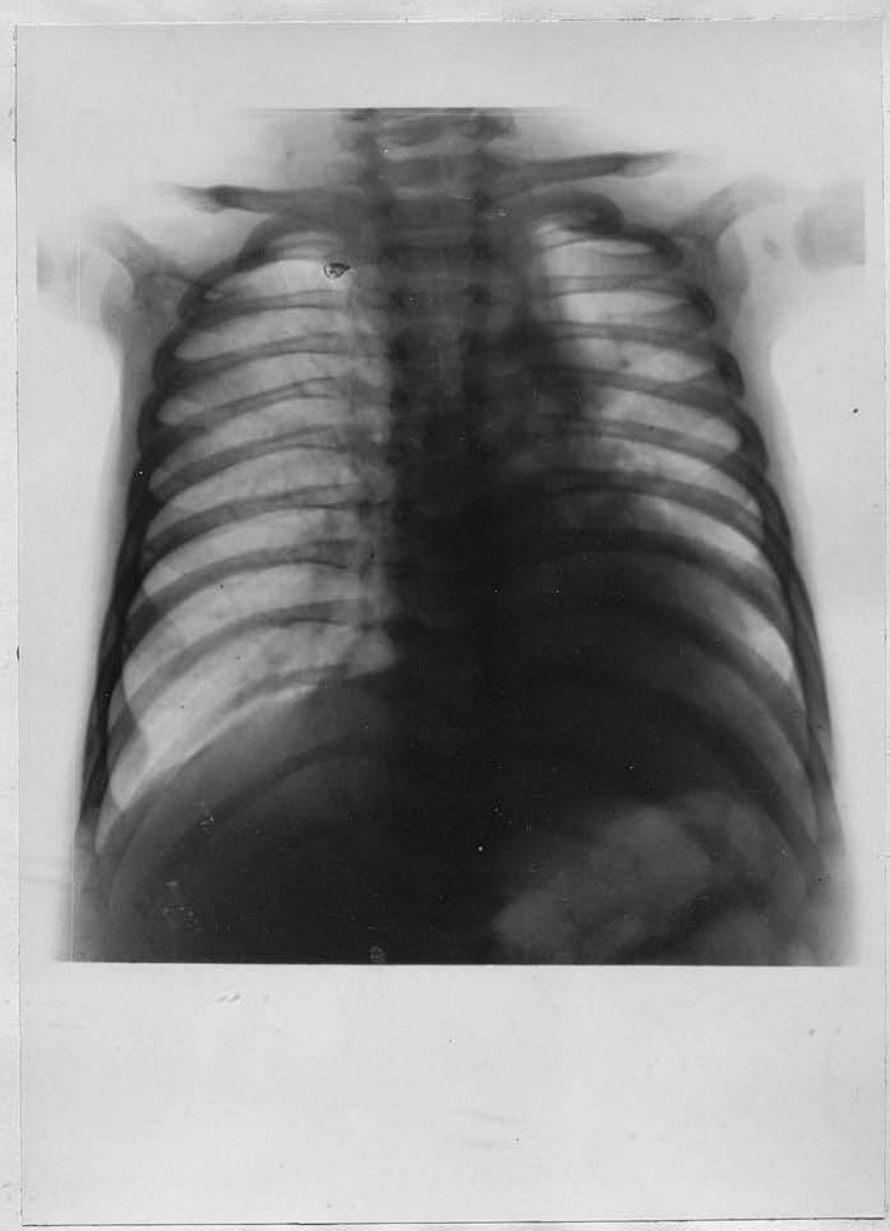

Plate I6.X-ray of chest (Case 2) I6.7.48. showing collapse-consolidation at the L. base with emphysema of the R. hemi-thorax.

Plate I7.(Case 3).Abdominal distension in contrast with the general wasting.

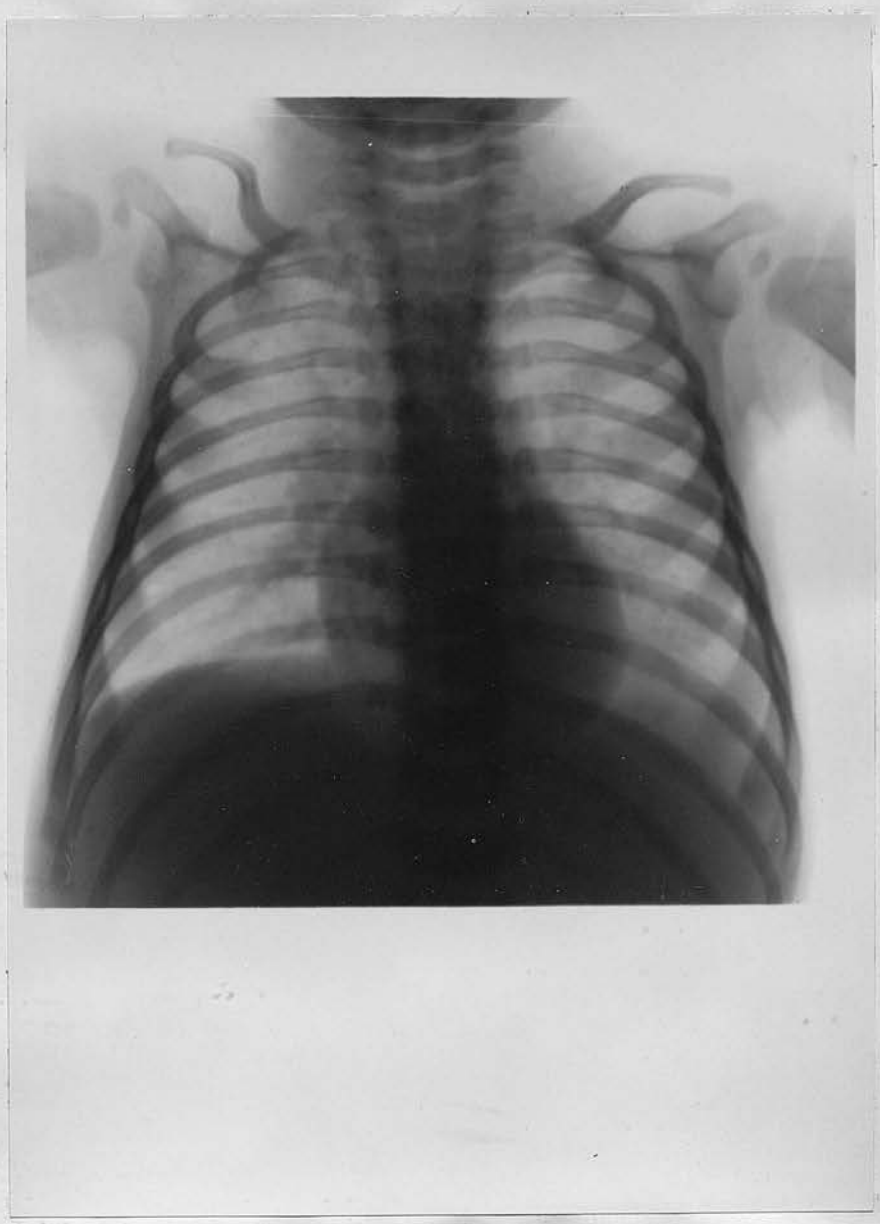

Plate I8.X-ray of chest (Case 3) 26.8.48. showing consolidation at the L. base.

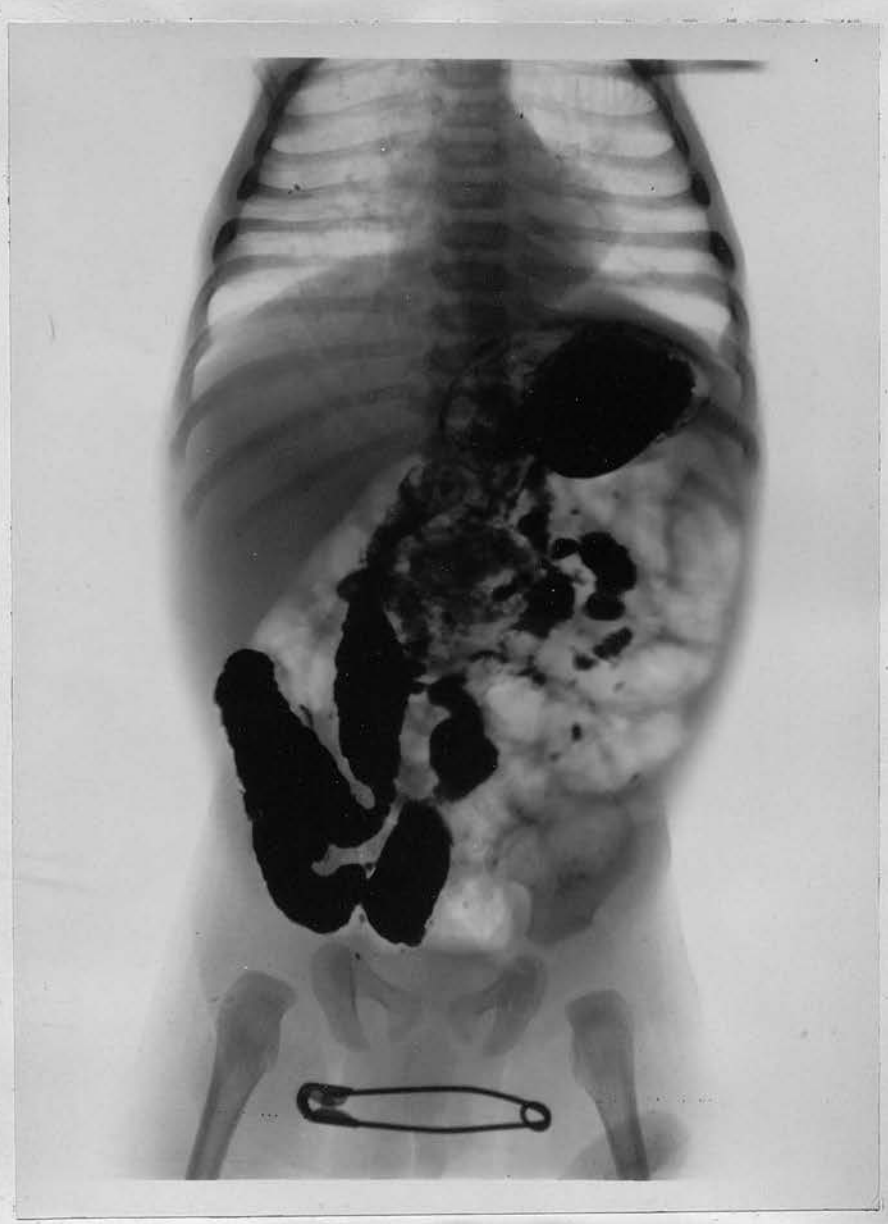

Plate I9.Barium meal of case 3(I0.8.48.) showing clumping of the meal in the small gut.

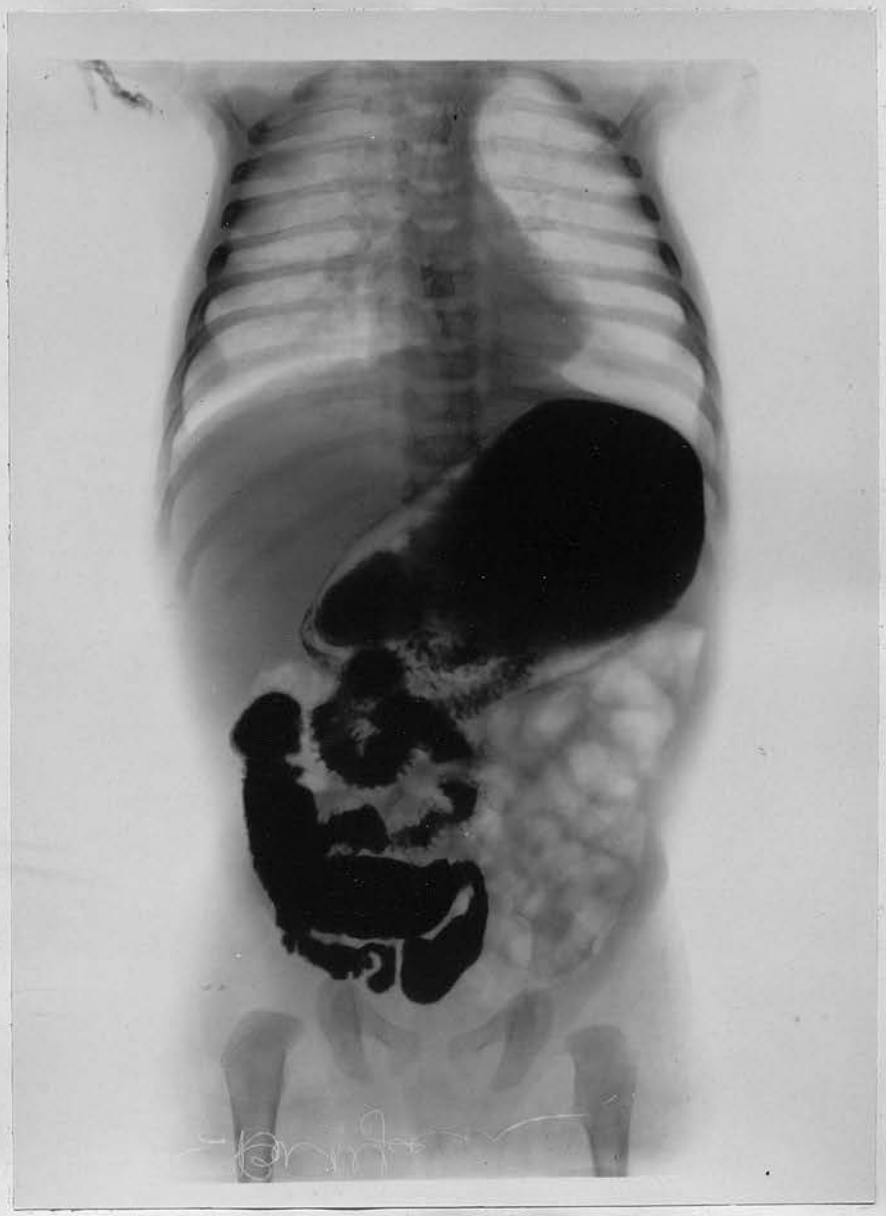

Plate 20.Barium meal (Case3) I0.8.48. showing sharp serrations of the margins of the jejunal pattern.

Plate 2I. Case 6 showing diminution of size compared with normal boy of the same age

Plate 22.Case 6.Side view showing prominent abdomen and clubbing of the fingers.

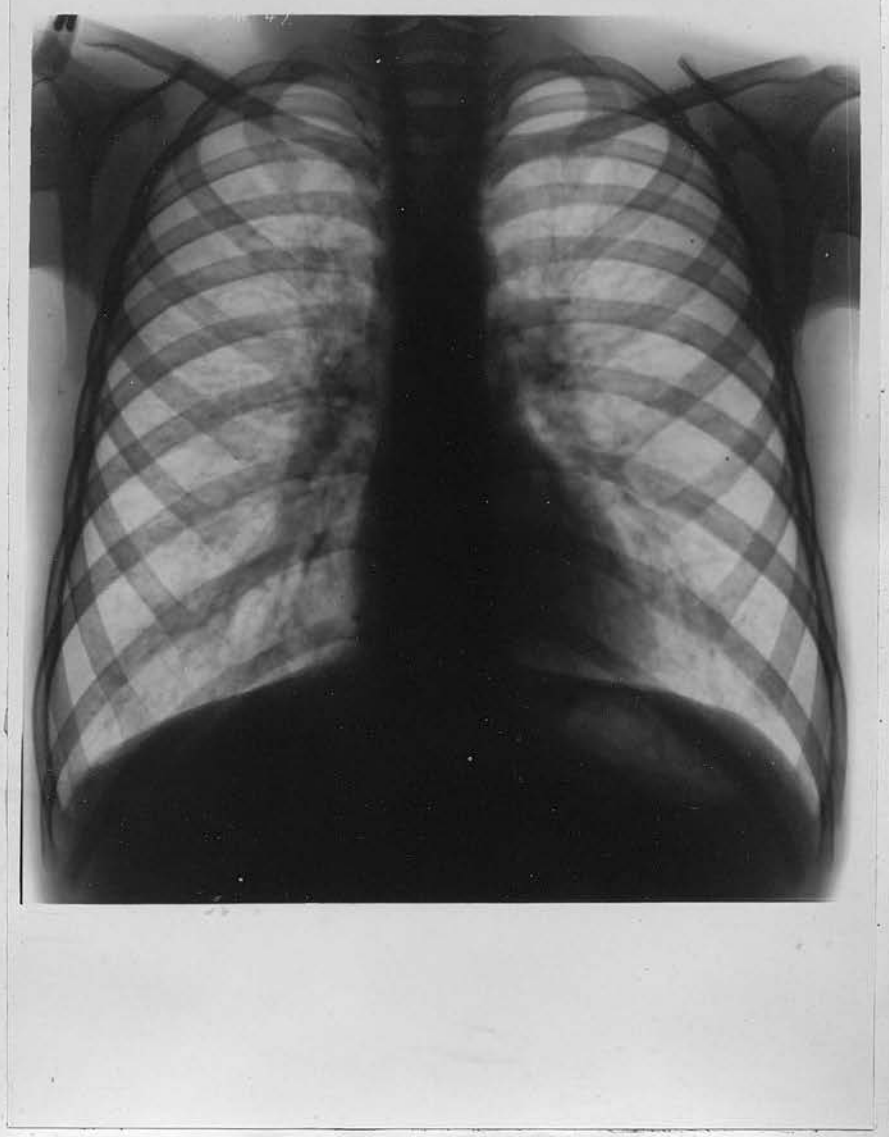

Plate 23.X-ray of chest (Case 6) IO.3.47. showing slight general emphysema with signs of generalised bronchitis and thickening of the bronchial walls in the lower zones.

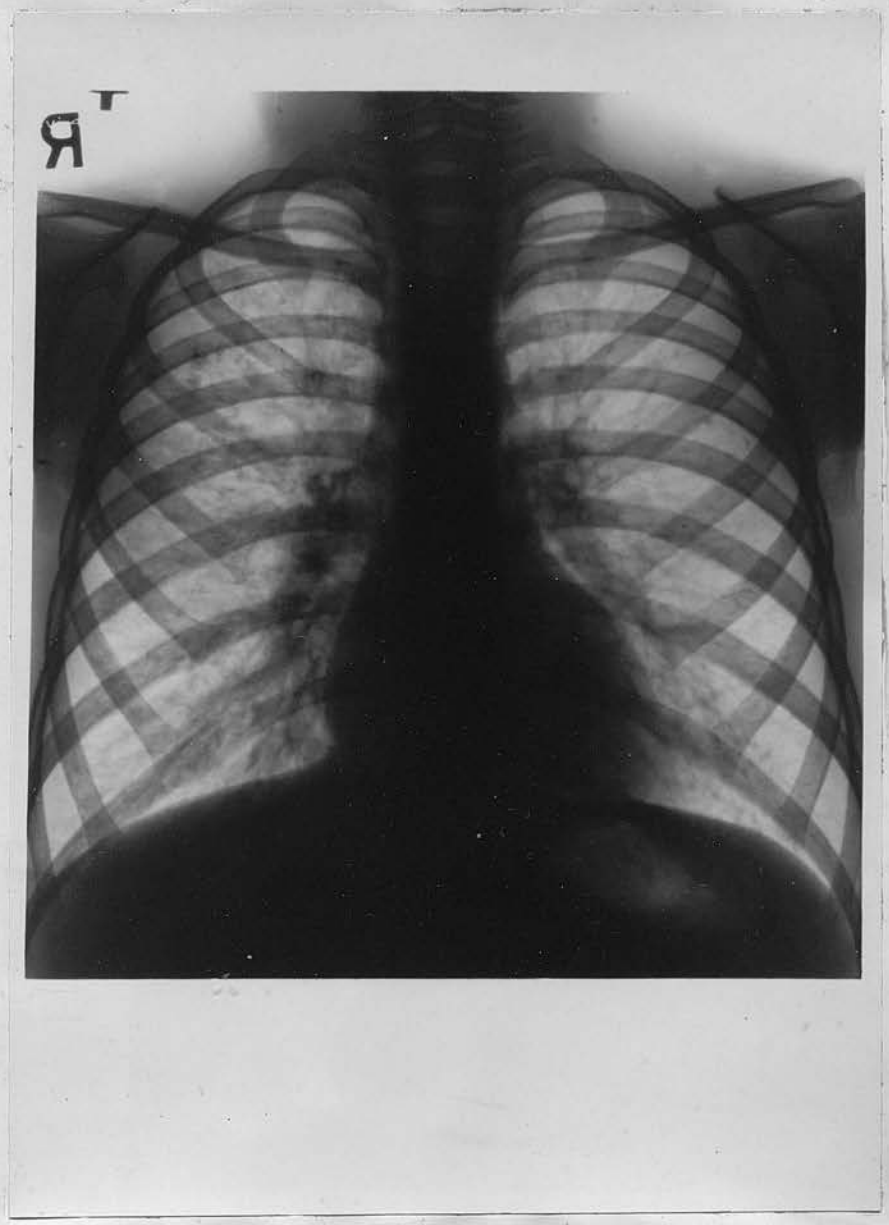

Plate 24 (Case 6). X-ray of chest (19.6.48.), showing alveolar retention of lipiodol in the right upper lobe. There are associated parenchymal changes at both bases, right more than left.