Progress in Pediatrics

CYSTIC FIBROSIS OF THE PANCREAS AND ITS RELATION TO CELIAC DISEASE

A CLINICAL AND PATHOLOGIC STUDY

DOROTHY H. ANDERSEN, M.D.
NEW YORK

The pathology and pathologic physiology of celiac disease remain obscure in spite of the many attempts that have been made to understand them. It has become clearer in recent years that celiac disease is a clinical picture "characterized by arrest of growth, a distended abdomen, and attacks of diarrhoea with large, pale, foul-smelling stools" [1] rather than a disease entity and that the underlying pathologic condition may differ in different cases.[2] A tradition exists that pancreatic steatorrhea can be readily differentiated from idiopathic steatorrhea by the low percentage of split fat in the stools associated with the former and the normal percentage characterizing the latter. A careful survey of the literature, however, reveals few cases of either disease in which careful clinical observations have been followed by adequate postmortem examination. The present study was initiated because of the findings in case 44 (XX), in which a patient with celiac disease who had a high percentage of split fat in the stools and who had responded favorably to treatment for celiac disease was found at autopsy to have cystic fibrosis of the pancreas. This demonstrated that the recognized criteria of differentiation between the steatorrhea due to pancreatic insufficiency and that due to other causes are unreliable.

To establish more reliable criteria it is necessary to study cases in which normal acinar tissue has been proved by postmortem examination to be absent or inadequate and to compare them with cases of celiac disease associated with a normal pancreas. The plan of the present investigation has been to collect the cases in which pancreatic insufficiency has been proved by microscopic examination of the pancreas, to

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From the Pathological Laboratory, Babies Hospital, and the Department of Pathology, College of Physicians and Surgeons, Columbia University.

1. Holt, L. E., and Howland, J.: Diseases of Infancy and Childhood, ed. 10, edited by L. E. Holt Jr., and R. McIntosh, New York, D. Appleton-Century Company, 1933, p. 210.

2. Göttche, O.: Intestinaler Infantilismus, Jahrb. f. Kinderh. **111**:81, 1926.

study the clinical histories and associated pathologic findings and to compare these histories and findings with those in cases of celiac disease in which the pancreas appeared essentially normal on microscopic examination.

The entire series of 49 cases of pancreatic fibrosis here presented are listed in table 1. They have been obtained from four sources: 1. Twenty cases were collected from the pathologic files of the Babies Hospital. 2. One case was contributed by Dr. Bruce Chown, of the Children's Hospital of Winnipeg, Manitoba, Canada, and another by Dr. Paul Klemperer, of Mount Sinai Hospital, New York. 3. Twenty cases were collected from the literature on celiac disease and pancreatic insufficiency.[3] 4. Seven cases were collected from the literature on vitamin A deficiency.[4] The 22 new cases are designated by Roman numerals also.

3. (*a*) Landsteiner, K.: Darmverschluss durch eingedicktes Meconium; Pankreatitis, Zentralbl. f. allg. Path. u. path. Anat. **16**:903, 1905. (*b*) Kornblith, B. A., and Otani, S.: Meconium Ileus with Congenital Stenosis of the Main Pancreatic Duct, Am. J. Path. **5**:249, 1929. (*c*) Passini, F.: Pankreaserkrankung als Ursache des Nichtgedeihens von Kindern, Deutsche med. Wchnschr. **45**:851, 1919. (*d*) Gross, F.: Pankreasatrophien im Säuglings- und Kindesalter, Jahrb. f. Kinderh. **112**:251, 1926. (*e*) Benoit, W.: Hyperinsulinismus bei eingeborener Atresie des Pankreasganges, Endokrinologie **16**:313, 1935. (*f*) Tiling, W.: Angeborene Pankreasgangsatresie und Inselhypertrophie: Ein Beitrag zur Diagnostik der Pankreaserkrankungen, Arch. f. Kinderh. **106**:9, 1935. (*g*) Burghard, E.: Pankreaserkrankungen im Säuglingsalter, Klin. Wchnschr. **4**:2305, 1925. (*h*) Harper, M. H.: Two Cases of Congenital Pancreatic Steatorrhoea with Infantilism, M. J. Australia **2**:663, 1930. (*i*) Hess, J. H., and Saphir, O.: Celiac Disease (Chronic Intestinal Indigestion): A Report of Three Cases with Autopsy Findings, J. Pediat. **6**:1, 1935. (*j*) Fanconi, G.; Uehlinger, E., and Knauer, C.: Das Coeliakie Syndrom bei angeborener zystischer Pankreasfibromatose und Bronchiektasien, Wien. med. Wchnschr. **86**:753, 1936. (*k*) Siwe, S. A.: Ueber die exocrine Funktion des Pankreas und die Folgen ihres Wegfalles: Ein Fall von fast totaler Agenesie des exocrinen Teiles des Pankreas, Deutsches Arch. f. klin. Med. **173**:339, 1932. (*l*) Parmelee, A. H.: The Pathology of Steatorrhea, Am. J. Dis. Child. **50**:1418 (Oct.) 1935. (*m*) Clarke, C. G., and Hadfield, G.: Congenital Pancreatic Disease with Infantilism, Quart. J. Med. **17**:358, 1924. (*n*) Garsche, R.: Zur Klinik und Pathogenese der Pankreasinsuffizienz im Kindesalter, Ztschr. f. Kinderh. **58**:434, 1936-1937. (*o*) Huet, G. J.: A Case of Intestinal Infantilism with Chronic Pulmonary Infection, Maandschr. v. kindergeneesk. **3**:343, 1934.

4. (*a*) Blackfan, K. D., and Wolbach, S. B.: Vitamin A Deficiency in Infants: A Clinical and Pathological Study, J. Pediat. **3**:679, 1933. (*b*) Wilson, J. R., and DuBois, R. O.: Report of a Fatal Case of Keratomalacia in an Infant, with Postmortem Examination, Am. J. Dis. Child. **26**:431 (Nov.) 1923. (*c*) Corneal Ulcers and Roughened Conjunctivae Associated with Fat Intolerance, Cabot Case 17242, presented by R. W. Daffinee, with discussion by H. L. Higgins and T. B. Mallory, New England J. Med. **204**:1264, 1931.

TABLE 1.—*Summary of Cases of Cystic Fibrosis of the Pancreas in Which Postmortem Examination Was Done*

Case No.	Author	Age at Onset: Difficulty in Feeding	Age at Onset: Cough	Age at Death	Sex	Predominant Clinical Symptoms	Postmortem Observations: Cause of Death	Postmortem Observations: Data on Pancreas	Postmortem Observations: Other Data
				Group I.—Infants Dying Before the Age of One Week					
1	Landsteiner, 1905....	Birth	—	5 days	F	Vomiting; failure to pass meconium	Meconium ileus; peritonitis (Staph. aureus)	Cystic fibrosis; duct of Wirsung patent	Uric acid infarcts of kidney
2	Kornblith and Otani, 1929	Birth	—	5 days	F	Vomiting; failure to pass meconium	Meconium ileus; ulcers of ileum and colon; peritonitis	Cystic fibrosis; stenosis of duct of Wirsung	Meckel's diverticulum; atelectasis of lungs; uric acid infarcts of kidney
3 (I)	Andersen, 1938.....	Birth	—	4 days	M	Vomiting; failure to pass meconium	Band across lumen of ileum with obstruction; peritonitis	Cystic fibrosis	Meckel's diverticulum, uric acid infarcts in kidneys
4 (II)	Andersen, 1938.....	Birth	—	6 days	F	Vomiting; prematurity	Multiple atresia of ileum; volvulus; peritonitis (Str. haemolyticus)	Cystic fibrosis	Aspiration of gastric contents
5 (III)	Andersen, 1938.....	Birth	—	6 days	F	Failure to pass meconium; distended abdomen	Atresia of jejunum; fetal peritonitis	Cystic fibrosis	Congenital malformations of heart; jaundice of liver; atresia of cystic duct; congenital atelectasis of lungs
				Group II.—Infants Dying Between the Ages of One Week and Six Months					
6	Blackfan and Wolbach, case 2, 1933	Birth	Birth	5 wk.	M	Infection of respiratory tract	Bronchopneumonia; bronchiectasis	Cystic fibrosis	Keratinizing metaplasia in trachea; hemosiderosis of liver and spleen
7 (IV)	Andersen, 1938.....	Neonatal	7 wk.	8 wk.	F	Feeding problem; failure to gain	Purulent bronchitis; bronchopneumonia with abscesses (Staph. aureus)	Cystic fibrosis	Otitis media (Staph. aureus)
8	Passini, 1919, case 2..	Neonatal	?	2 mo.	F	Poor development; large stools	Bronchopneumonia; empyema	Cystic fibrosis; loss of islands	
9 (V)	Andersen, 1938.....	?	6 wk.	2½ mo.	F	Failure to gain; cough	Bronchiectasis; purulent bronchitis; lobular pneumonia (Staph. aureus)	Cystic fibrosis; atresia of Wirsung's duct ?	Atresia of cystic duct; atrophy of gallbladder; cysts of cystic duct and gallbladder; congenital strictures of ureter; congenital malformation of aorta
10 (VI)	Andersen, 1938.....	Neonatal	5 wk.	2½ mo.	M	Failure to gain; cough	Purulent bronchitis (Staph. aureus); bronchopneumonia	Cystic fibrosis; atresia of Wirsung's duct (?)	Congenital strictures of ureter; fatty liver; hemosiderosis of liver and spleen

11 (VII)	Andersen, 1938.....	?	3 wk.	2¾ mo.	F	Poor development; cough	Purulent bronchitis (Staph. aureus); bronchopneumonia	Cystic fibrosis; atresia of Wirsung's duct (?)	Squamous metaplasia of trachea; atresia of cystic duct (?); atrophy of gallbladder; hemosiderosis of liver and spleen
12 (VIII)	Andersen, 1938.....	?	5 wk.	2¾ mo.	F	Feeding problem; cough	Bronchiectasis, lower lobe of right lung; bronchopneumonia	Cystic fibrosis	Hemosiderosis of liver and spleen
13 (IX)	Andersen, 1938.....	?	2½ mo.	3¼ mo.	M	Pneumonia	Purulent bronchitis; abscesses of lungs; bronchopneumonia; suppurative pleurisy (Staph. aureus and Str. haemolyticus)	Cystic fibrosis	Hemosiderosis of liver
14 (X)	Andersen, 1938.....	Neonatal	6 wk.	3½ mo.	M	Prematurity; underdevelopment; cough	Purulent bronchitis; bronchopneumonia; abscesses of lungs (Staph. aureus)	Cystic fibrosis	Otitis media, right; hemosiderosis of liver and spleen
15	Gross, 1926, case 10...	?	?	3¾ mo.	?	Cachexia; bronchitis	?	Cystic fibrosis	?
16 (XI)	Andersen, 1938.....	?	3½ mo.	4 mo.	M	Malnutrition; bronchopneumonia	Acute bronchitis; bronchiectasis; lobular pneumonia (Staph. aureus and albus, B. influenzae)	Cystic fibrosis	Atresia of cystic duct (?); atrophy of gallbladder; fatty liver; otitis media; hemosiderosis of liver
17 (XII)	Andersen, 1938.....	?	2 wk.	4 mo.	F	Underdevelopment; cough	Purulent laryngitis, tracheitis and bronchitis (Staph. albus); lobular pneumonia	Cystic fibrosis; subacute pancreatitis	Prolapse of rectum; hemosiderosis of spleen
18	Blackfan and Wolbach, 1933, case 13	?	?	4 mo.	F	Failure to gain; cough; asthmatic breathing	Bronchopneumonia; chronic bronchitis and peribronchitis; bronchiectatic abscesses	Cystic fibrosis	Keratinizing metaplasia of bronchi and uterus; hemosiderosis of spleen and liver
19	Blackfan and Wolbach, 1933, case 3	1 month	1 mo.	4½ mo.	M	Failure to gain; cough; vomiting and diarrhea, following infection at age of 1 month	Bronchitis; peribronchitis; bronchopneumonia; bronchiectasis with abscesses	Cystic fibrosis	Keratinizing metaplasia of trachea; hemosiderosis of spleen
20 (XIII)	Andersen, 1938.....	Neonatal	4 mo.	4¾ mo.	F	Failure to gain; cough and fever	Acute bronchitis; bronchiectasis; bronchopneumonia	Cystic fibrosis	Atresia of cystic duct (?); atrophy of gallbladder; hemosiderosis of liver and spleen
21 (XIV)	Andersen, 1938.....	None	4 mo.	5½ mo.	M	Pneumonia	Purulent tracheitis and bronchitis; bronchiectasis; abscesses of lung (Staph. aureus); acute fibrinous pleurisy	Cystic fibrosis	Otitis media; thrombophlebitis of left lateral sinus; acute leptomeningitis; fatty liver

TABLE 1.—*Summary of Cases of Cystic Fibrosis of the Pancreas in Which Postmortem Examination Was Done*—Continued

Case No.	Author	Age at Onset: Difficulty in Feeding	Age at Onset: Cough	Age at Death	Sex	Predominant Clinical Symptoms	Postmortem Observations: Cause of Death	Postmortem Observations: Data on Pancreas	Postmortem Observations: Other Data
22	Wilson and DuBois, 1933	?	Before 3 mo.	5¾ mo.	F	Xerophthalmia; failure to gain; frequent colds	Bronchiectasis with abscesses; fibrinous pleurisy	Cystic fibrosis; keratinizing metaplasia of occasional ducts	Keratomalacia with corneal ulcers; keratinizing metaplasia in trachea, bronchi, salivary glands, pancreas, pelvis of kidney, uterus; inclusion bodies in salivary glands; hemosiderosis of liver and spleen
23 (XV)	Andersen, 1938.....	Birth	3 mo.	6 mo.	M	Failure to gain; intolerance to fat; xerophthalmia; cough	Bronchiectasis with abscesses; lobular pneumonia (Staph. aureus)	Cystic fibrosis	Lipoid pneumonia; interstitial nephritis; hemosiderosis of liver and spleen
24 (XVI)	Andersen, 1938.....	None	4 mo.	6 mo.	F	Cough; pertussis (?)	Suppurative tracheitis and bronchitis (Staph. albus haemolyticus)	Cystic fibrosis; subacute interstitial pancreatitis	Atresia of cystic duct; atrophy of gallbladder; fatty liver; hemosiderosis of spleen
				Group III.—Children Dying After the Age of Six Months					
25	Cabot case 17242, 1931	? Neonatal	6¾ mo.	7 mo.	M	"Spots in the eyes" at 4½ mo.; failure to gain	Bronchopneumonia with abscesses (Str. haemolyticus)	Cystic fibrosis; chronic pancreatitis	Keratomalacia; nephrolithiasis; atresia of cystic duct; atrophy of gallbladder
26	Blackfan and Wolbach, 1933, case 10	Birth	Birth	7 mo.	F	Failure to gain; cough since birth; attacks of fever and pyuria	Bronchiectasis with abscesses; pleurisy	Cystic fibrosis; keratinizing metaplasia of occasional ducts	Keratinizing metaplasia of mucosa of nares, trachea, bronchi, renal pelvis, ureters, periurethral glands, uterus and ducts of pancreas and submaxillary glands; hemosiderosis of liver and spleen
27	Benoit, 1935.....	Birth	?	7 mo.	F	Failure to gain since birth; foul fatty stools	Purulent bronchitis	Cystic fibrosis; atresia of ducts of Wirsung and Santorini; proliferation of duct epithelium	Hemosiderosis of spleen
28 (XXII)	Andersen, 1938..... (from Klemperer)	Birth	4 mo.	8 mo.	F	Failure to gain; intolerance to fat; cough	Purulent bronchitis; bronchiectasis with abscesses	Cystic fibrosis; cystic fibrosis of accessory pancreas in jejunum	Hyperplasia of bronchial epithelium
29	Passini, 1919, case 1..	Neonatal	?	9 mo.	?	Poor development; large stools	Bronchopneumonia	Cystic fibrosis; loss of islands	

30	Blackfan and Wolbach, 1933, case 7	Birth	8 mo.	9 mo.	M	Feeding problem; projectile vomiting; cough	Bronchitis; bronchiectasis with abscesses; bronchopneumonia; fibrinous pleurisy	Cystic fibrosis	Keratinizing metaplasia of trachea, bronchi, ducts of glands of larynx, pharynx and tongue, and renal pelvis; fatty liver; hemosiderosis of spleen
31	Tiling, 1935.....	Before 5 mo.	5 mo.	9 mo.	F	Poor development; large foul stools	Purulent bronchitis; bronchopneumonia	Cystic fibrosis; atresia of ducts of Wirsung and Santorini	Hemosiderosis of spleen
32 (XVII)	Andersen, 1938.....	Neonatal	6 mo.	9 mo.	M	Failure to gain; cough	Purulent bronchitis; bronchopneumonia (Staph. aureus haemolyticus)	Cystic fibrosis; dilated pancreatic duct	Fatty liver; fatty myocardium
33	Burghard, 1925.....	Birth	About 7-8 mo.	10 mo.	F	Failure to gain; 4 to 6 foul fatty stools daily	Purulent bronchitis; lobular pneumonia	Cystic fibrosis	Fatty liver
34	Hess and Saphir, 1935, case 1	Birth	9 mo.	10 mo.	F	Poor development; frequent large foul stools from birth; large abdomen	Bronchopneumonia with abscesses	Cystic fibrosis; fat in island cells	Fatty liver; infiltration of intestinal mucosa with fibrosis of submucosa
35	Fanconi, Uelinger and Knauer, 1936, case 2	4 weeks	6½ mo.	10 mo.	?	Failure to grow; cough	Purulent bronchitis; bronchiectasis; chronic and acute bronchopneumonia	Cystic fibrosis	Fatty liver; fat in myocardium
36	Harper, 1930, case 2..	?	12 mo.	12-13 mo.	F	Failure to gain; fatty stools; diarrhea	Purulent bronchitis; bronchopneumonia	Cystic fibrosis; inclusion of embryonal tissue	Fatty liver
37 (XVIII)	Andersen, 1938.....	Birth	3 mo.	14 mo.	F	Failure to gain; large foul stools from birth	Purulent tracheitis and bronchitis; lobular pneumonia (staphylococcus and streptococcus)	Cystic fibrosis	Ethmoiditis and maxillary sinusitis; congenital anomaly of transverse mesocolon; hemosiderosis of liver and spleen
38 (XIX)	Andersen, 1938.....	3 months	14 mo.	17 mo.	F	Large foul stools; cough	Purulent bronchitis; bronchopneumonia (Staph. aureus)	Cystic fibrosis	Biliary cirrhosis; umbilical hernia; hypertrophy of colon
39	Hess and Saphir, 1935, case 2	Birth	18 mo.?	18 mo.	M	Frequent stools from birth; large foul stools after 6 mo.; vomiting; large abdomen	Bronchopneumonia with abscesses	Cystic fibrosis	Infiltration of intestinal mucosa with fibrosis of submucosa; fatty liver
40	Gross, 1926, case 18...	?	?	19 mo.	?	Heubner-Herter disease	Pneumonia	Atrophy of pancreas with replacement by fat; increase in number of islands	

TABLE 1.—*Summary of Cases of Cystic Fibrosis of the Pancreas in Which Postmortem Examination Was Done*—Continued

Case No.	Author	Age at Onset: Difficulty in Feeding	Age at Onset: Cough	Age at Death	Sex	Predominant Clinical Symptoms	Postmortem Observations: Cause of Death	Postmortem Observations: Data on Pancreas	Postmortem Observations: Other Data
41	Siwe, 1932.....	6 months	19 mo.	2 yr.	F	Prematurity; poor development; foul stools; large abdomen; cough	Varicella; pharyngitis; bronchitis	Replacement of acinar tissue by fat; atresia of Wirsung's duct with normal duct of Santorini	Rickets; mild cirrhosis of liver; fatty liver
42 (XXI)	Andersen, 1938..... (from Chown)	About 18 mo.	2¼ yr.	2½ yr.	M	Foul stools	Bronchopneumonia (staphylococcus)	Cystic fibrosis	Fatty liver
43	Fanconi, Uelinger and Knauer, 1936, case 1	Before 4 mo.	4 wk.	3 yr.	F	Failure to gain; large foul stools; cough	Bronchiectasis; purulent bronchitis	Cystic fibrosis	Osteoporosis; fatty liver; fat in myocardium; cystitis, pyelitis, interstitial nephritis
44 (XX)	Andersen, 1938.....	4 months	3 yr.	3 yr. 1 mo.	F	Poor development; intermittent diarrhea; fatty stools; hunger	Abscesses of lung; bronchopneumonia	Cystic fibrosis; atresia of Wirsung's duct (?)	Torticollis; infiltration of intestinal mucosa; fatty liver; otitis media
45	Parmelee, 1935, case 2	Neonatal	3 yr. 10 mo.	4 yr.	F	Failure to gain; large stools; intolerance to fat	Mucopurulent bronchitis and bronchiolitis; lobular pneumonia with abscesses	Cystic fibrosis; narrow pancreatic duct	Atresia of cystic duct (?); atrophy of gallbladder; fatty liver; narrow common and hepatic bile ducts
46	Clarke and Hadfield, 1924	Birth	?	4½ yr.	F	Poor development; fatty stools from birth; large abdomen; hunger	Purulent bronchitis; bronchopneumonia; abscesses of lung	Replacement of acinar tissue by fat	Large colon with infiltration and fibrosis of submucosa; ulcer of ileum; fatty liver; edema of extremities
47	Garsche, 1936-1937, case 3	6 months	4⅓ yr.?	4⅓ yr.	F	Failure to gain; large foul stools; protuberant abdomen; alternate hunger and anorexia	"Grip" pneumonia	Fibrosis; replacement of acinar tissue by fat; concrements	Fatty liver; mild biliary cirrhosis of liver
48	Huet, 1934.....	Nursing period	6 yr.	10 yr.	M	Poor development; fatty stools; chronic infection of lung	Purulent bronchitis with dilatation of bronchi; fibrosis of lung	Cystic fibrosis; hyperplasia of islands	Cirrhosis of liver (Laënnec's); fatty liver
49	Parmelee, 1935, case 1	Early infancy	11 yr.	14½ yr.	F	Feeding problem; rancid fatty stools; intolerance to fat; hunger; protuberant abdomen; maxillary sinusitis; chronic bronchitis; anemia	Purulent bronchitis; acute bronchopneumonia	Cystic fibrosis with normal ducts	Maxillary sinusitis; fibrinous pericarditis; ascites

CLINICAL PICTURE

A perusal of the clinical histories reveals the unexpected fact that the cases form three groups, which differ in their clinical features and in the age at which death occurred (table 1). The first group includes newborn infants; the second, infants from 1 week to 6 months of age, and the third, all those over 6 months of age. In all cases the pancreas at death showed such extensive lesions of the acinar tissue that it is inconceivable that the external secretion of the pancreas could have been produced in normal volume.

Group I.—This group consists of cases of 5 infants all of whom were born at term and died before the age of 1 week with symptoms of intestinal obstruction. In the 2 cases quoted from the literature [5] the

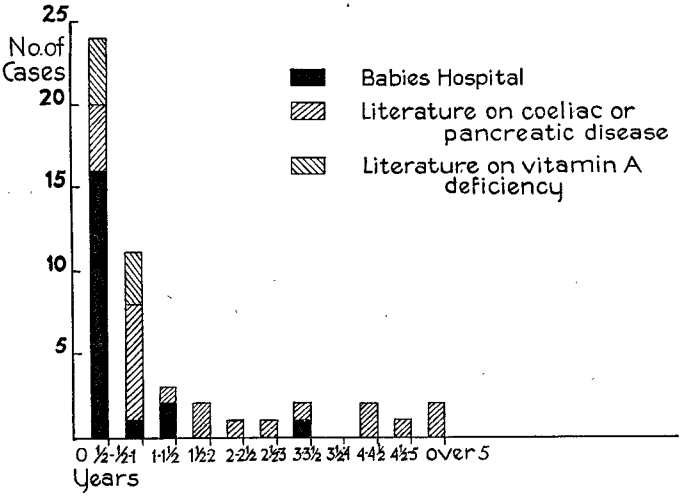

Fig. 1.—Chart showing the age at death in 49 cases of cystic fibrosis of the pancreas. The shading of the columns indicates the sources from which the cases were collected.

obstruction appeared to be due to inspissated meconium without any break in the continuity of the intestinal lumen. In 1 there was staphylococcic peritonitis and in the other meconium peritonitis resulting from perforation of the ileum. There was stenosis of the duct of Wirsung in 1 case [3b] but not in the other.[3a] Reports on the remaining 3 cases of this group were found in the pathologic files of the Babies Hospital. In case 3 (I) the obstruction was due to a band of fibrous tissue across the lumen of the terminal portion of the ileum near the ileocecal valve. In the other 2 cases (cases 4 [II] and 5 [III]) the obstruction was due to atresia of the jejunum and of the ileum, respectively. Fetal

5. Landsteiner.[3a] Kornblith and Otani.[3b]

peritonitis was present in the 3 latter cases. In all 5 of the cases the pancreas showed extensive fibrosis with the formation of cysts. The following associated congenital anomalies were found in 3 of the 5 cases: Meckel's diverticulum (2 cases), atresia of the cystic duct (1 case) and congenital malformation of the heart (patent interventricular septum), in case 5 (III). An extensive search through the literature has revealed no additional instance of atresia of the small intestine in which the pancreas showed cystic fibrosis, and the frequency of this association is unknown. The files of the Babies Hospital contain 1 case of intestinal atresia in which the pancreas was normal on microscopic examination. However, the literature contains several cases of atresia of the duodenum with hypoplasia of the pancreas.[6] Kornblith and Otani [3b] stated the opinion that in their case and in that of Landsteiner [3a] the absence of pancreatic juice caused inspissation of meconium with subsequent intestinal obstruction. The atresia of the intestine in 2 cases cannot be explained in this way. The possibility that the atresias of the intestine, of the cystic duct and of the large and small pancreatic ducts are due to a common cause will be discussed later in the present paper.

Group II.—The cases of 19 infants who died between the ages of 1 week and 6 months form this group. Two of these cases were found in the literature on celiac disease and 4 in that on vitamin A deficiency, and the remaining 13 are reported for the first time in this paper. In all of them the pancreas showed cystic fibrosis, and comparison of the microscopic slides and descriptions revealed a close similarity in the various cases. The characteristic features of the clinical picture may be summarized as follows: (1) failure to gain with an adequate diet, beginning in the neonatal period; (2) a large abdomen at birth; (3) hunger; (4) absence of vomiting or diarrhea; (5) large stools, sometimes recognized as fatty; (6) intolerance to fat in the diet, and (7) chronic infection of the respiratory tract.

Clinically there are two subgroups: (*a*) The larger number of cases are those of patients who were first seen because they presented a nutritional problem or because, having been admitted on account of infection of the respiratory tract, they were found on investigation to be retarded in growth and development. (*b*) Six cases, all of which are described here for the first time, are those of patients who were brought to the hospital because of infections of the respiratory tract, and gave no history of previous nutritional difficulty.

In subgroup *a*, comprising 13 cases in which the feeding problem was recognized, the presenting symptom was usually failure to gain,

6. Niosi, G. S.: Atresie multiple congenite del duodeno e del dijiuno accociate ad assenza della cistifellea e ad ipoplasia d'alto grado del pancreas, Pathologica **28**:414, 1936.

first noticed during the neonatal period; in some cases there were large foul stools from birth. Dr. Katharine Merritt made a study of the charts of the patients in the Babies Hospital, and I have her assurance that the feeding was adequate in quantity and quality, as nearly as could be ascertained. Repeatedly one met the comment that the infant seemed hungry and consumed with relish anything that was given. Vomiting was rare, except during the course of an infection. There was often a mild increase in the number and size of the stools, which occurred from two to six times daily, but they were not characteristically diarrheal and were only occasionally recognized as fatty stools during this age period. No analysis of fat in the stools was recorded before the age of 6 months. Occasionally it was noticed that the baby was intolerant of fat (case 23 [XV]) or of cereals (case 44 [XX]). Physical examination revealed underdevelopment and poor nutrition (fig. 2 *A, B*). Often, but not always, the abdomen was enlarged, and sometimes an umbilical hernia was present. Xerophthalmia was found in 2 infants.

In each of the 19 cases comprising group II there was ultimately an infection of the respiratory tract. This sometimes began with coryza, but more often the symptom first noticed was a spasmodic, nonproductive cough resembling that of pertussis and often so interpreted. The age at which this cough appeared ranged from 2 weeks upward; it is recorded for the individual cases in table 1. For weeks or months it remained as a chronic cough, gradually increasing in severity, with development of purulent bronchitis, bronchiectasis with abscesses, lobular pneumonia or any combination of these conditions. In 2 cases roentgenograms made soon after the onset of cough revealed no abnormality in the lungs (cases 14 [X] and 23 [XV]), but there were roentgen evidences of bronchopneumonia in all of the 12 cases in which the patients were examined late in the course of the disease. In several cases the transition from a condition marked only by chronic cough to purulent bronchitis was sudden.

The laboratory findings in the cases of group II did not contribute much to an understanding of the disease. There was no clinical or pathologic evidence of syphilis in any case. When serologic tests were done the reactions were negative (7 cases). The blood of the mother of 1 infant (case 10 [VI]) gave a positive Wassermann reaction; the infant's serum was not tested, but autopsy showed no morphologic evidence of syphilis. The hemoglobin content ranged from 8.5 to 23 Gm. per hundred cubic centimeters of blood, usually lying between 10 and 14 Gm. The red blood count ranged from 2,300,000 to 5,600,000 and was usually between 3,000,000 and 4,500,000. The observations were made after the infection of the respiratory tract

had appeared, and the anemia cannot with assurance be attributed to the pancreatic insufficiency. The urine was normal or showed a trace of albumin, except in case 23 (XV), in which there was pyuria. The blood sugar was determined in 1 case only; it was 75 and 87 mg. per hundred cubic centimeters on two occasions (case 23 [XV]). In the same case the stools were cultured for the typhoid and dysentery group of

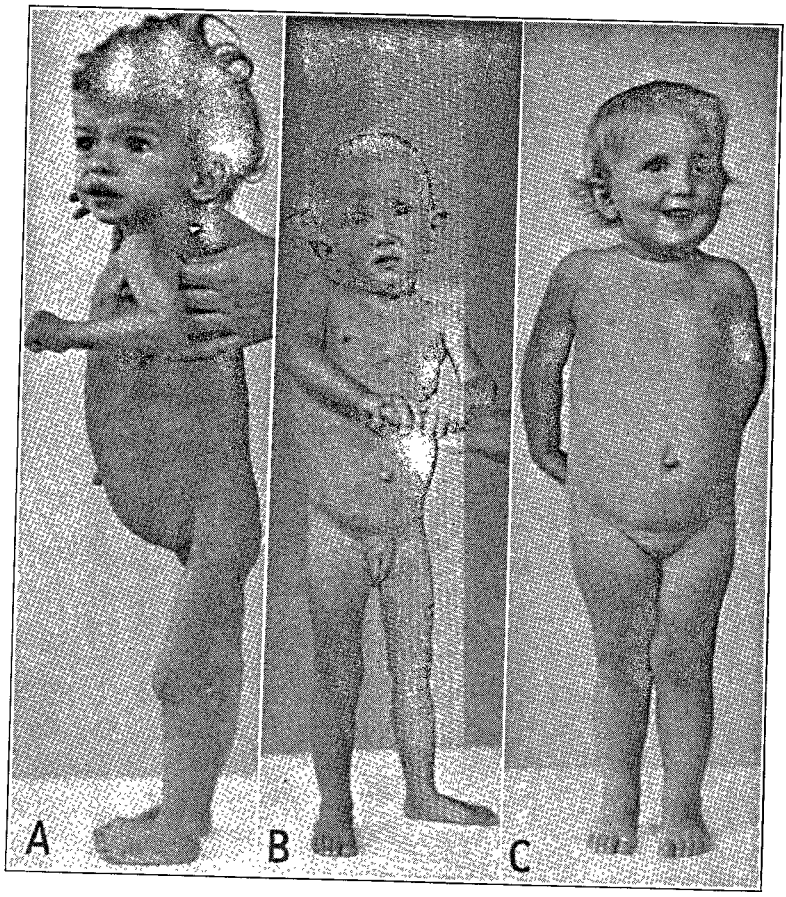

Fig. 2.—*A*, C. H. (case 37 [XVIII]) at the age of 1 year; *B*, M. D. (case 44 [XX]) at the time of admission to the hospital at the age of 22 months, and *C*, M. D. at the age of 3 years.

organisms, with negative results, and no agglutinins against these organisms were found in the blood. The stools were not examined for fat. Roentgen study demonstrated bronchopneumonia, osteoporosis of the shafts and epiphyses and absence of rickets.

I have found no obvious solution for the apparent clinical discrepancy between these two subdivisions of group II, one of which showed predominantly a nutritional disturbance and the other an infection of the respiratory tract; the two subgroups had in common the characteristic postmortem lesions of the pancreas and of the respiratory tract. One may attempt to explain the occurrence in the cases of subgroup II *b* of cystic fibrosis of the pancreas in the absence of serious and easily recognizable disturbances of digestion and nutrition during life by any one of four theories: 1. The lesion in the pancreas may be incidental and unrelated to the clinical picture caused by the lesions in the bronchi and lungs, as suggested by Blackfan and Wolbach.[4a] 2. The changes found in the pancreas may be responsible for the digestive and nutritional symptoms when these have occurred, but in some cases their appearance may have been delayed by some undetermined factor, such as breast feeding. 3. Symptoms which one would expect to result from the pancreatic lesion may have been present but unnoticed because the infant did not appear ill. 4. Symptoms specifically referable to deficiency of the external secretion of the pancreas may have been obscured by the early onset of the infection of the respiratory tract and attributed to the latter cause. The theory first suggested appears improbable, in view of the fact that every patient surviving the age of 6 months showed symptoms suggestive of celiac disease. The second theory is possibly true, but this also appears unlikely. Although 5 of the 6 infants in the cases of group II*b*, who did not present a feeding problem, were breast fed and might be thought to have been thus protected, there were 3 infants in the cases of group II*a* who were changed from breast feeding because of failure to thrive on it, which indicates clearly that nursing does not constitute a safe guaranty per se against the development of the nutritional disturbances. Moreover, there was no constant difference betwen the growth curves of the breast-fed and those of the artificially fed infants. The third possibility, that the failure to gain went unnoticed because the infants were active and ate well, is a likely one and is borne out by the fact that all children but 1 in the entire series were much below normal in weight and development when first seen. Finally, in favor of the fourth interpretation stands the fact that all 6 of the infants in group II*b* were admitted with acute pneumonia; attention was focused on this, and the subnormal weight was reasonably attributed to the infection.

Group III.—The group is composed of 25 cases of patients who ranged in age at death from 6 months to 14½ years. A nutritional disturbance was recognized clinically in all cases, and a diagnosis of celiac disease was made in most instances. The diagnosis of pancreatic insufficiency was made during life in 4 cases (case 27, 31, 41, 37

[XVIII]). The pathologic changes in the pancreas were similar to those in the previous cases with 4 exceptions: In the cases of Gross (his case 18),[3d] Clarke and Hadfield,[3m] Siwe [3k] and Garsche,[3n] the acinar tissue was entirely replaced by adipose tissue.

In group III the clinical course in the first months of life was similar to that in the cases of group II. The initial symptom was failure to gain, usually first noticed in the neonatal period and almost always present by the fifth month. Case 42 (XXI) is the single exception to this, for no abnormalities either in development or in digestive functions were noted until occurrence of the acute illness, at about the age of 16 months. In all the other cases there were large foul stools, sometimes recognized as fatty, beginning at birth or thereafter but always present by the sixth month. One gathers from reading the protocols that the abnormality in the stools became more obvious at about the sixth month and that it was then recalled that they had been somewhat abnormal previously. The change in type of stool at 6 months was sometimes specifically recorded.[7] The underdevelopment was also more striking than in the previously described cases of group II. Physical examination revealed the findings described for celiac disease: underdevelopment, a protuberant abdomen, often an umbilical hernia, weakness of the muscles and atrophy of the gluteal region. Osteoporosis was frequently described, but rickets was rarely found.[3k] Xerophthalmia was found once.[4c] The terminal event, in these as in the previous cases, was infection of the respiratory tract: bronchitis, bronchiectasis or bronchopneumonia, often with otitis media and sometimes with infection of the accessory nasal sinuses.

Laboratory findings were recorded in only a few of the reports. Anemia was sometimes mentioned, but in 3 of the 4 cases of the Babies Hospital it was not present prior to the infection of the respiratory tract. The examination of the blood and urine did not otherwise give significant results. The stools were usually described as pale or putty colored, extremely foul, rancid, soft and pasty. In 2 cases (cases 37 [XVIII] and 44 [XX]) cultures were negative for typhoid and dysentery bacilli on repeated occasions. In 1 case (35) 52 per cent of the protein and 50 per cent of the fat ingested were discharged in the stool. In most cases microscopic examination showed no droplets of neutral fat, but these were present in the cases of Burghard,[3g] Siwe [3k] and Clarke and Hadfield.[3m] The stool was analyzed for fat in 4 cases: In Harper's case [3h] the stool contained 60 per cent of fat in the dried weight, of which 76.6 per cent was fatty acid; in case 37 (XVIII) the stool contained 39.8 per cent of fat in the dried weight, of which 64 per cent was fatty acid; in case 44 (XX) the stool contained 53.5 per cent

7. Harper.[3h] Clarke and Hadfield.[3m] Garsche.[3n]

of fat in the dried weight, of which 69 per cent was fatty acid; Siwe [3k] found 82 per cent and 96 per cent of the total fat as neutral fat on two occasions. The proportion of fatty acid to total fat was therefore within normal range in 3 cases but extremely low in 1. It is of interest that in the first 3 cases the pancreas showed cystic fibrosis, while in Siwe's case [3k] there was complete replacement of the acini with adipose tissue.

The blood sugar value was low in several cases (3 from the literature [8] and cases 37 [XVIII] and 44 [XX] from the Babies Hospital), and spontaneous attacks of hypoglycemia have been described.[9] Dextrose tolerance tests were done in 4 cases. In 2 (Siwe,[3k] case 44 [XX]) there was a rise from a low fasting level to over 200 mg. per hundred cubic centimeters in an hour, with an abrupt drop at two hours. These curves are similar to those described by Harris [10] as characteristic of hyperinsulinism. In a third case (Huet [3o]) the fasting level was 140 mg., rising to 204 mg. in an hour and dropping to 138 mg. in two and one-half hours. In the fourth case (case 37 [XVIII]) the curve was flat, as with celiac disease. In case 37 (XVIII) the serum cholesterol value was low (total 107, free 36.6, combined 70.4 mg. per 100 cubic centimeters, ratio of combined to free, 1.92). The amount of serum lipase (tributyrinase) was normal in this case, and that of serum amylase was about four times normal. The duodenal contents were examined for the presence of pancreatic ferments (diastase, trypsin, and lipase) in 3 cases, and none was found.[8]

PATHOLOGIC ANATOMY

Gross Examination.—The postmortem findings in the 5 cases of group I have been described. The following comments apply to the remaining 44 cases unless otherwise stated.

External Examination: The underdevelopment seen clinically was also obvious at autopsy, together with emaciation and muscular atrophy. The abdomen was usually prominent and there was often umbilical hernia. Rectal prolapse was observed twice. Congenital torticollis was noted once.

Body Cavities: The peritoneal cavity bore a smooth serosa. There was often moderate distention of the intestines, with some enlargement and hypertrophy of the colon. The liver was frequently enlarged to a moderate degree, extending below the costal margin. The pericardial cavity was normal except in 1 case, in which there was fibrinous peri-

8. Benoit.[3e] Tiling.[3f] Siwe.[3k]

9. Benoit.[3e] Tiling.[3f]

10. Harris, S.: Gastrointestinal Manifestations of Hyperinsulinism, Am. J. Digest. Dis. & Nutrition **2**:557, 1935.

carditis.[31] Fibrinous pleurisy was almost invariably observed. Suppurative pleurisy was described in 3 cases and fibrous thickening of the pleura in 1 case.

Heart: Fatty infiltration of the myocardium was noted in 3 cases. With the exception of a patent interventricular septum in 1 of the cases of group I and several instances of slight patency of the foramen ovale

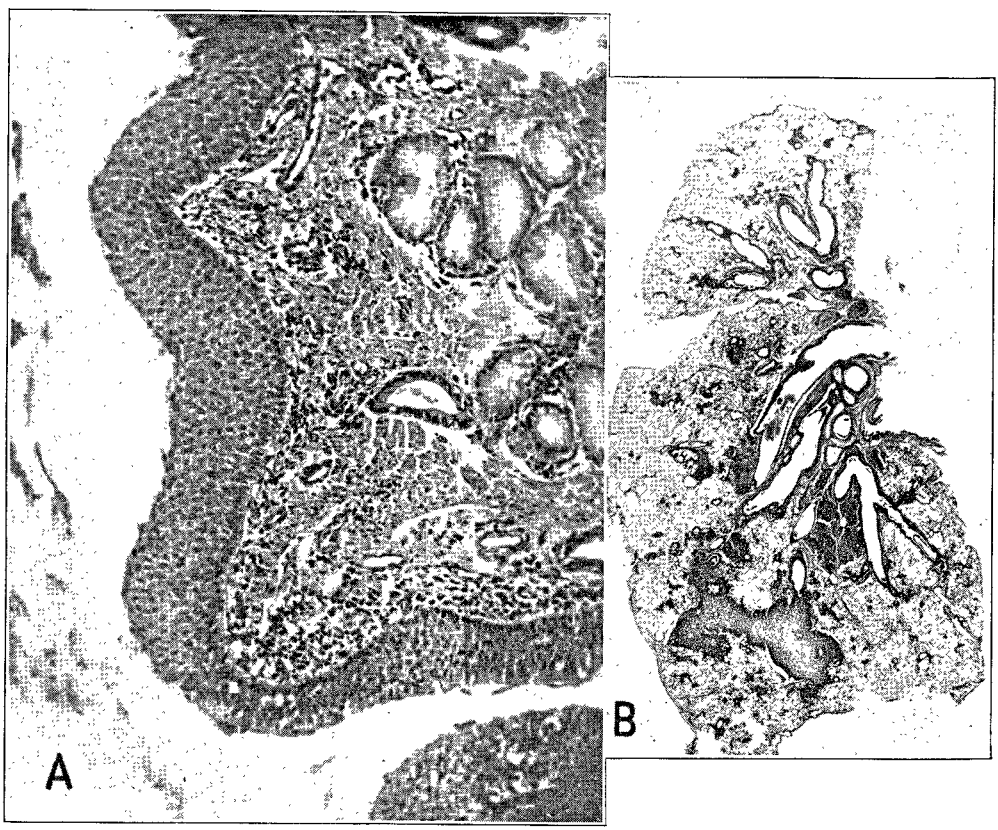

Fig. 3.—*A* (case 11 [VII]), photomicrograph showing squamous metaplasia of tracheal epithelium. *B* (case 20 [XIII]) shows tubular bronchiectasis, purulent bronchitis and bronchopneumonia.

or ductus arteriosus, there were no congenital malformations of the heart.

Aorta: A congenital abnormality of the origin and course of the right subclavian artery was seen in case 9 (V). No other abnormalities were noted.

Lungs: In every case of the series there was infection of the lungs; this was apparently primary in the bronchi. In the cases which I

have been able to study at first hand, these changes were remarkably uniform and consisted of (1) mild tubular dilatation of the small bronchi and bronchioles; (2) plugging of the lumens of most if not all of the bronchi with tenaceous, greenish gray mucopurulent material; (3) multiple small abscesses arising in the smaller bronchi and sometimes spreading to form multilocular abscesses; (4) fresh lobular pneumonia in the intervening parenchyma; (5) perforation of the abscesses through the pleura to produce fibrinous or suppurative pleurisy (fig. 3*B*). The larger bronchi and trachea also contained mucopurulent material, with some congestion of the underlying mucosa. In Huet's case,[3o] in which the pulmonary infection was especially prolonged, there was some fibrosis of the lung.

Spleen: This was normal or slightly enlarged, with small malpighian corpuscles and red pulp. In 1 case, in which there was cirrhosis of the liver,[3o] the spleen was large and somewhat fibrous.

Liver: A fatty liver, noted in 19 cases, was more frequently met with in the children over 6 months of age (21 per cent of group II, 60 per cent of group III). The liver was enlarged in these cases but not in the others. Usually it had a brownish tinge. In some of the smaller infants it was dark red. Biliary cirrhosis was present in 3 cases and Laënnec's cirrhosis in 1.

Gallbladder and Bile Ducts: In 8 cases, including 1 of group I, the gallbladder was small and contained only a small amount of translucent gray mucus. The cystic duct was atretic in 4 of these cases and was not examined in the other 4, but it is reasonable to assume that it was atretic in them also. Six or 30 per cent of the cases of the Babies Hospital presented this finding. No abnormalities of the common or hepatic ducts were noted.

Pancreas: In most instances no gross abnormalities were detected. Siwe [3k] and Clarke and Hadfield [3m] observed the fatty infiltration, which they confirmed microscopically. Sensitized by my previous experience with this disease, I have been able to make a gross diagnosis in recent cases. The pancreas was normal in size or somewhat small, and the shape and color were normal. On section it was firm, sometimes more so than normal, and occasionally there was a slight grating sound as the knife passed through calcified concretions. The lobules appeared rounded and uneven in size instead of having the normal diamond-shaped pattern. Many lobules were fused together by fibrous tissue. The pancreatic duct was examined in 12 of the 49 cases. It was described as atretic in 3 cases; [8] there was stenosis near the orifice in 2.[11] Attempts to dissect out the duct were unsuccessful in 4 of 5 of the cases of the Babies Hospital, in all of which the lumen appeared to end

11. Kornblith and Otani.[3b] Parmelee.[31]

in fibrous tissue at a distance of 5 to 15 mm. from the ampulla of Vater. In 1 of these cases the duct of Santorini was readily dissected, though narrow. Because of the difficulty of dissecting the pancreatic duct in small infants, the failure to do so is not considered as absolute proof that the duct was atretic. In 2 cases (Landsteiner,[3a] case 32 [XVII]) the duct was patent, and in case 32 it was dilated throughout. In 1 case it was described as normal.[31]

Adrenal Glands: No abnormalities were noted.

Kidneys and Ureters: There was congenital stricture of the ureters with mild hydronephrosis in cases 9 (V) and 10 (VI). Nephrolithiasis was reported once.[4c] In 2 cases the kidneys showed mild chronic interstitial nephritis (Fanconi and others,[3j] case 23 [XV]).

Pelvic and Reproductive Organs: No abnormalities were noted.

Alimentary Tract: Moderate distention of the small intestine and dilatation and hypertrophy of the colon were occasionally recorded. There were ulcers of the ileum in 1 case.[3m] Rectal prolapse was recorded twice.

Middle Ears and Accessory Nasal Sinuses: No notes were found in the pathologic reports in the literature. Parmelee [31] recorded chronic sinusitis in his first case and otitis media in the second case as clinical findings. Otitis media was observed in cases 14 (X), 16 (XI), 21 (XIV) and 44 (XX) and maxillary sinusitis in case 37 (XVIII) of the series of the Babies Hospital.

Additional Findings: In case 21 (XIV) there was thrombophlebitis of the left lateral sinus, with leptomeningitis.

Microscopic Examination.—Heart: No abnormalities were noted other than those described grossly.

Aorta: This was rarely mentioned and may be considered normal.

Lungs: The bronchi presented the changes of greatest interest. Bronchitis and peribronchitis were found in all cases, and the bronchial lumens were filled with purulent exudate. In addition, the epithelium of the bronchi was often composed of more cell layers than usual, and in the cases reported in the literature on vitamin A deficiency there was squamous metaplasia of the superficial layers with keratinization.[4] In 1 of the cases of the Babies Hospital (case 11 [VII]) and in the case contributed by Dr. Klemperer (case 28 [XXII]) there was likewise squamous metaplasia, but careful search did not reveal it in the other cases of the Babies Hospital. There was moderate to marked tubular dilatation of the bronchi in all of the cases of the Babies Hospital, and bronchiectasis was frequently reported in the literature (fig. 3 *B*). In most of the cases of the Babies Hospital there were abscesses arising in the smaller bronchi, as shown by fragments of bronchial walls present in or near them and by their location. Staphylococci were seen in the

necrotic centers. The alveoli showed patchy, usually very recent, lobular pneumonia, with normal or emphysematous areas between the consolidated ones. In 1 case [30] there were areas of fibrosis. The pleural surface bore a fibrinous or fibrinopurulent exudate.

Trachea: There was squamous metaplasia with keratinization in 5 of the cases reported as instances of vitamin A deficiency and in case 11 (VII) (fig. 4). Purulent tracheitis was frequently reported.

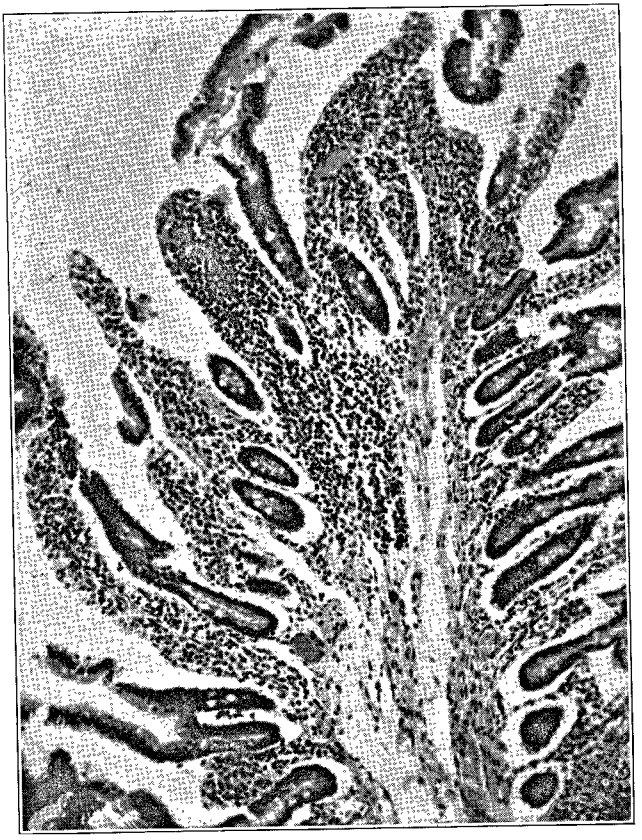

Fig. 4 (case 44 [XX]).—Photomicrograph of jejunal mucossa.

Spleen: The malpighian corpuscles were usually small; the pulp was congested and contained greater or lesser amounts of hemosiderin. Polymorphonuclear leukocytes were often present in small numbers.

Liver: Hemosiderin in the liver and in the Kupffer cells was almost invariably observed. Large amounts of fat were present in the cells in a large percentage of the cases. Biliary cirrhosis was noted 3 times, and in several of the cases of the Babies Hospital there was a slight

increase of fibrous tissue in the portal areas. Laënnec's cirrhosis was seen once.[30] In several of the cases of the Babies Hospital there was slight atrophy of the columns of cells, with congestion of the sinusoids. In 2 instances multinucleated hepatic cells were observed.

Gallbladder and Bile Passages: These were rarely examined histologically. There were small epithelial cysts containing mucus and

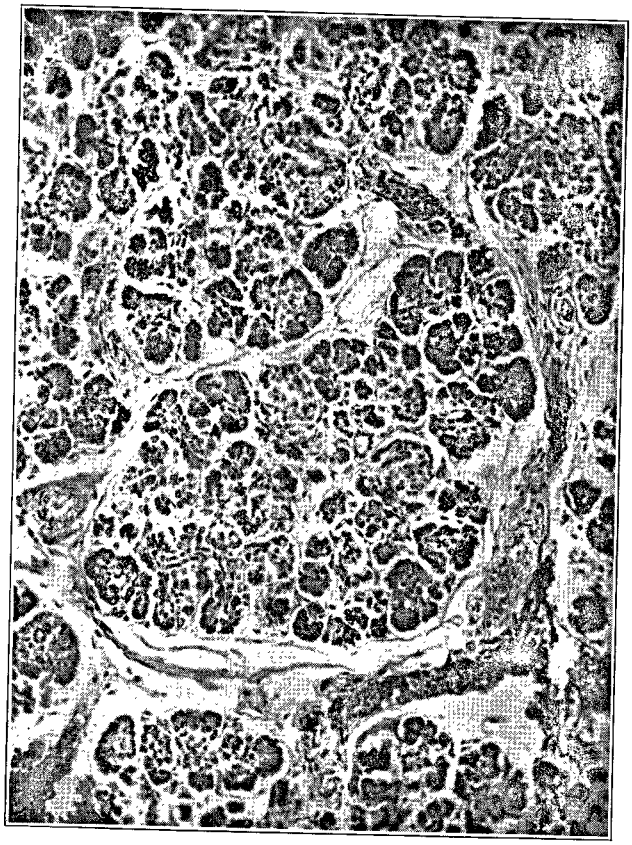

Fig. 5.—Photomicrograph of normal pancreas of a patient who died at the age of 3 days.

apparently arising from the mucous glands in the gallbladder and in the cystic duct in case 9 (V).

Adrenal Glands: No abnormalities were noted.

Pancreas: In 45 of the cases the pancreas presented a microscopic picture which is described by the term "cystic fibrosis" (figs. 5 to 11). The acini contained concretions of various sizes, and the acinar cells were flattened to form a thin epithelial wall around them. The smaller concretions were surrounded by relatively normal cells, which occa-

sionally contained eosinophilic granules. The flattening of the epithelium varied approximately with the size of the concretions. The small ducts contained similar material and were often difficult to distinguish from the acini. Metaplasia of the epithelium of occasional ducts was described.[12] The concretions themselves were more or less deeply eosinophilic. The smaller ones were homogeneous; the larger were often laminated and were sometimes composed of fragments of deeply

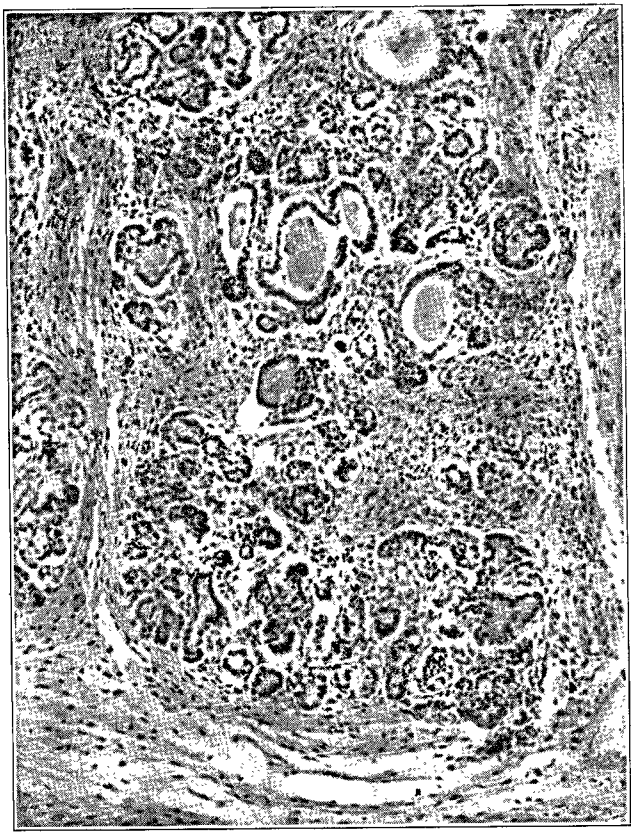

Fig. 6 (case 4 [II]).—Photomicrograph of pancreas of a patient who died at the age of 6 days.

eosinophilic material surrounded by a paler substance; occasionally they were calcified. Sometimes there were desquamated epithelial cells, one or two phagocytes or a rare polymorphonuclear leukocyte in the cysts which contained the paler material. The size of the cysts varied in each case, but large ones were not often noted in the youngest infants. Surrounding the acini and also the lobules there were moderate to large

12. Huet.[30] Blackfan and Wolbach.[4a]

amounts of fibrous tissue, the quantity varying roughly with the age of the child. This sometimes contained a few fibroblasts or young fibrocytes and was always infiltrated with lymphocytes, plasma cells and phagocytes. These varied in number from occasional scattered cells to a number sufficient to warrant the diagnosis of subacute or chronic pancreatitis. In the latter case occasional polymorphonuclear leukocytes

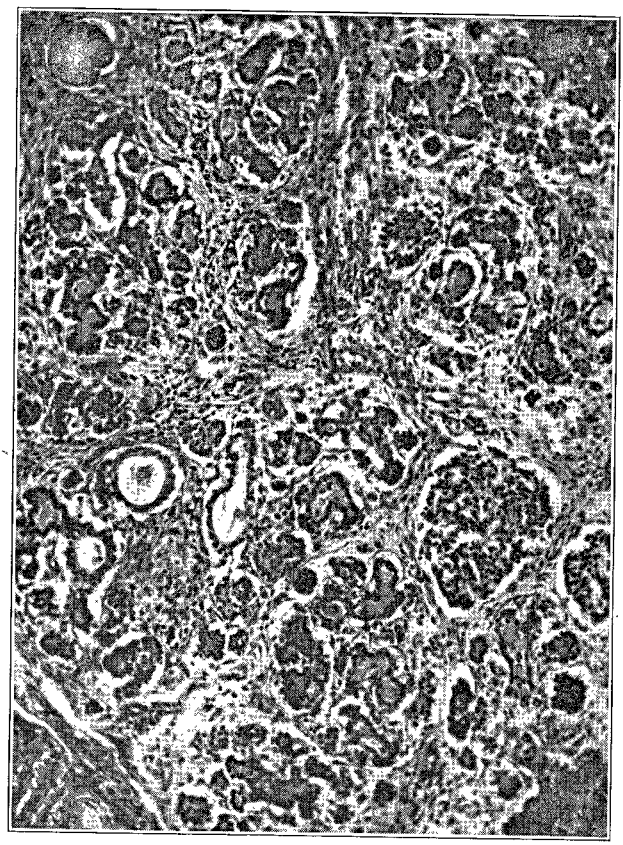

Fig. 7 (case 7 [IV]).—Photomicrograph of pancreas of a patient who died at the age of 8 weeks.

were observed. These infiltrations were diffuse and did not bear a consistent relation to the ducts. The islands of Langerhans were usually normal in number and appearance, although they were considered to be decreased in number in several cases.[13] Hess and Saphir [31] observed fat in the island cells in 1 case. In several cases the islands retained their connection with adjacent acini or ducts but appeared normal in other respects. In Harper's case [3h] a mass of embryonal tissue was seen.

13. Passini.[3c] Gross.[3d] Tiling.[3f] Huet.[3o]

The acinar tissue was absent and was replaced by adipose tissue in four cases,[14] as shown in the illustrations in Siwe's paper.

Kidney and Ureters: Keratinizing metaplasia in the renal pelvis was described in 3 cases[15] and in the ureter in 1 case. These are not the cases already mentioned as those in which there were ureteral strictures and in which the ureters were unfortunately not examined

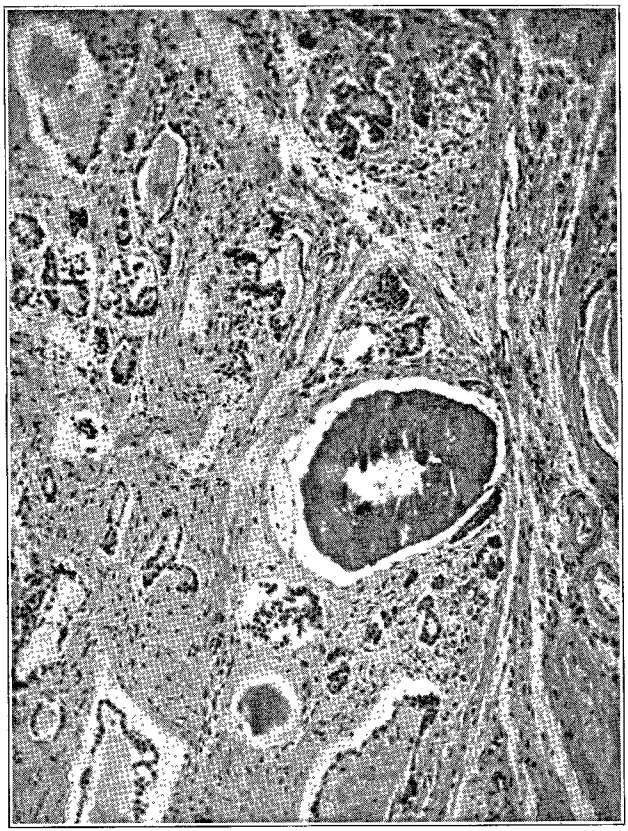

Fig. 8 (case 37 [XVIII]).—Calcified concretion in the pancreas of a patient who died at the age of 14 months.

microscopically. Mild chronic interstitial nephritis was observed in case 23 (XV).

Pelvic and Reproductive Organs: Keratinizing metaplasia of the uterine mucosa was described in 3 cases.[15] The periurethral glands showed similar changes in 1 case.

14. Gross.[3d] Siwe.[3k] Clarke and Hadfield.[3m] Garsche.[3n]

15. Blackfan and Wolbach.[4a] Wilson and Dubois.[4b]

Alimentary Tract: The esophagus and stomach were rarely mentioned, and no abnormalities were noted. A moderate infiltration of lymphocytes, plasma cells and occasional polymorphonuclear leukocytes was seen in the intestinal mucosa in 3 cases, and fibrosis of the submucosa was also present (Hess and Saphir,[3i] Clarke and Hadfield,[3m] case 44 [XX]). These children were aged 10 months, 18 months and 4½ years respectively. In most cases the intestine appeared normal.

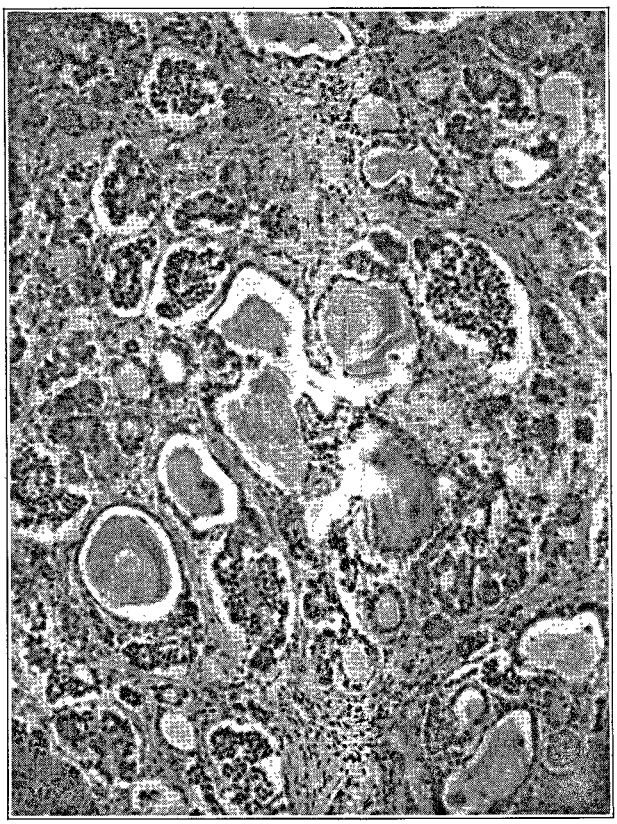

Fig. 9 (case 38 [XIX]).—Photomicrograph of pancreas of a patient who died at the age of 17 months.

Additional Findings: Keratinizing metaplasia was reported in the submaxillary gland and in the ducts of the glands of the tongue and larynx.[15] Inclusion bodies and some cellular infiltration were noted in the salivary glands.[4b]

Bacteriology.—Cultures were reported in 15 of the 49 cases. In 9 of them a pure culture of Staphylococcus aureus was obtained from the lung or pleura and in 1 from the peritoneum.[3a] Other cultures of

material from the lung showed Staphylococcus albus (2 cases), Streptococcus haemolyticus (1 case) or mixed infections in which Staph. aureus was present (3 cases).

ETIOLOGY

Frequency of Cystic Fibrosis of the Pancreas.—The performance in the laboratory of the Babies Hospital of 4 autopsies on patients with

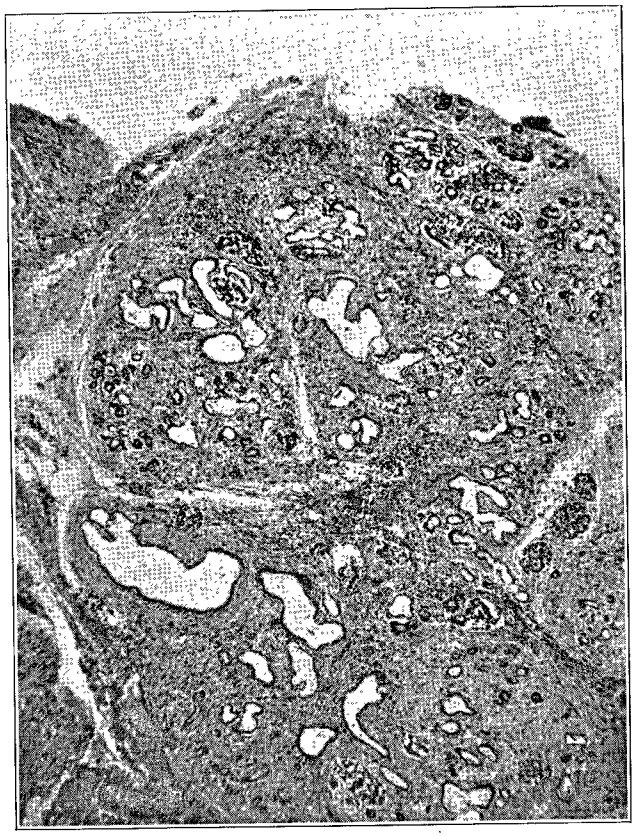

Fig. 10 (case 44 [XX]).—Photomicrograph of pancreas of a patient who died at the age of 3 years.

cystic fibrosis of the pancreas in a period of less than a year suggests that this lesion is not so rare as the scarcity of reports in the literature would lead one to believe. Microscopic sections of the pancreas were made in 605 of the last 1,000 autopsies in the Babies Hospital, and a survey of these sections was undertaken. The sections containing cysts were classified into three groups according to the estimated amount of acinar tissue involved. There were 20 cases or 3.3 per cent in which 90 per cent or more of the acinar tissue appeared to be nonfunctioning, and

these cases form the basis of this paper. In 21 or 3.5 per cent the lesion occupied approximately 20 to 90 per cent of the tissue. Three of the patients in these cases had histories similar to those of the first group, but the remainder died of a variety of causes. In 69 cases or 11.4 per cent there were smaller numbers of cysts, and these cases also form a miscellaneous group. In my experience the syndrome described in this paper is present only when the major portion of the acinar tissue

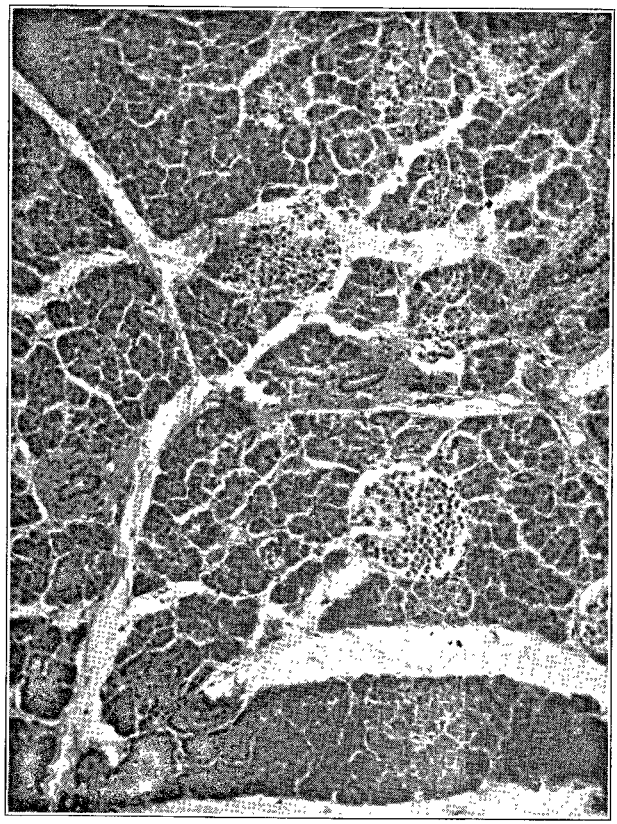

Fig. 11.—Photomicrograph of normal pancreas of a patient who died at the age of 3 years.

appears to be nonfunctioning. The incidence of 3.3 per cent seems unusually high for a disease so little known. The explanation probably lies in the fact that until recent years it has not been the custom to examine every pancreas microscopically. In cases of infants dying of bronchopneumonia in which neither the clinical history nor the gross examination had suggested a pancreatic lesion, sections of this organ were often not made. This explanation is supported by the fact that the

majority of the cases in which death occurred before the sixth month were culled from the autopsy records of the Babies Hospital, whereas most of the cases in which the patients survived longer were collected from the literature; in the latter the clinical history was suggestive of celiac disease. It is suggested that the disease occurs with approximately the frequency presented in my analysis but that the infants do not often survive to an age when the nature of the symptoms during life has instigated a postmortem study of the pancreas.

Sex.—The sex was recorded in 45 cases, in 30 (67 per cent) of which it was female and in 15 male.

Familial Occurrence.—The family history was given in 36 cases. In 3 instances 2 siblings of the family were found by postmortem examination to have cystic fibrosis of the pancreas (Passini,[3c] Blackfan,[4a] cases 23 [XV] and 28 [XXII]). In 5 other instances an older sibling was said to have died in early infancy of some congenital disease after a course similar to the patient's, but no postmortem examination was made (Tiling,[3f] Harper,[3h] Fanconi and others,[3j] (cases 7 [IV] and 12 [VIII]). In 2 of these cases the patients also had siblings who were living and well. In 15 cases there were normal siblings only, and in 10 cases the patient was the result of the first pregnancy. If only those families are considered in which there were siblings, the following figures appear: The disease is proved to have occurred more than once in 3 of 23 families and may have so occurred in 5 more. It is of interest that the mother in the 2 cases of Blackfan and Wolbach was intolerant to fat in the diet; the 2 infants were twins. Burghard's patient [3g] had a normal twin.

Race and Distribution.—The cases are reported from Germany, England, Holland, Australia and Canada and from the East, the Middle West and the West Coast of the United States. One of the patients of the Babies Hospital was a Negro, and the parents of the others came from Puerto Rico, Italy, Germany, Ireland and various parts of the United States. Patients were found to come from various economic strata.

Pathogenesis of the Pancreatic Lesions.—The changes in the pancreas may reasonably be interpreted as the result of the obstruction of the small or large pancreatic ducts. The ducts of Wirsung and Santorini were atretic in some cases but not in others, and sometimes one was atretic while the other was normal. In case 28 (XXII) an accessory pancreas in the jejunum showed changes similar to those in the pancreas itself. The stenosis or atresia, when present, may possibly have been the result rather than the cause of the pancreatic fibrosis. It was apparent that at least in the majority of cases the smaller ducts were the primary site of the obstruction.

The time at which the obstruction occurs is important in the consideration of pathogenesis. That the lesion may be congenital is proved by the presence of extensive fibrosis of the pancreas in the 5 infants who died in the first week of life. The neonatal onset of the nutritional disturbance in the majority of cases suggests that the pancreatic lesion is usually present at birth. In case 42 (XXI), however, no abnormalities were noticed in the child until an acute infection occurred at the age of 16 months. Since the details of the early development were wanting in this case, the evidence that it presented was not weighty; but the possibility of a postnatal origin in some cases cannot be excluded.

In a high percentage of these cases there were congenital abnormalities in addition to those in the pancreas; these abnormalities were nearly all atresias or stenoses of epithelium-lined passages such as the intestine, the cystic duct or the ureters. Biliary cirrhosis in the presence of normal common and main hepatic ducts may also be interpreted as the possible result of obstruction of the smaller biliary passages. One gains the impression that there was a general tendency to atresia of ducts. If these abnormalities were omitted, few malformations would remain, and those not the exterme variety that are so often observed in cases of multiple congenital anomalies.

One must therefore consider the possible causes of an obstruction of the smaller pancreatic ducts which occurs in fetal life in association with atresia or stenosis of other epithelium-lined passages and sometimes appears in several siblings of the same family. Three etiologic agents fulfil these requirements, namely (1) congenital malformation; (2) inflammation of the pancreas during fetal life, and (3) vitamin A deficiency during fetal life.

1. The evidence in favor of the view that cystic fibrosis of the pancreas is a congenital anomaly consists of three points: The lesion was present at birth in most if not all cases; it was familial, and it was associated with other congenital anomalies. Against this is the fact that the other anomalies were for the most part atresias or stenoses in other organs, which may well have been the result of some circumstance of gestation which affected various epithelium-lined passages.

2. The presence of slight degrees of inflammation in all the cases of group I and in some of the cases of groups II and III is the most important evidence that fetal inflammation was the cause of the lesion. The general tendency to atresia can be explained on the basis of inflammation, but the familial occurrence cannot. It is possible that in the cases of obstruction of the intestine in the newborn the pancreatic changes were secondary to ascending infection. Fibrosis of the pancreas is a common finding is cases of congenital syphilis, and the question of a syphilitic infection must be considered; a fetal infection

of unknown origin is also a possible explanation. Against these arguments there stands the fact that the microscopic appearance of the pancreas in the cases of intestinal obstruction was similar to that in the cases in which the patients died in early infancy but after the neonatal period, so that it is difficult to believe that the cause was different in the two groups. It is improbable that syphilis is the cause of cystic fibrosis of the pancreas because none of the infants showed other clinical or pathologic evidences of the disease. They were born at full term with few exceptions, and the serologic tests, when made, gave negative results. Moreover, the microscopic picture of the pancreas is different with the two diseases: Fibrosis, inflammation and abnormalities of fetal structure are the predominant changes observed in cases of syphilis, whereas in cases of cystic fibrosis of the pancreas the cysts predominate, the fibrosis is less extensive and the islands of Langerhans appear normal. The possibility of a fetal infection of unknown origin cannot be gainsaid, but the evidence for it is slight. In cases with a late onset one cannot entirely discard the idea of postnatal infection as the cause of the disease. In surprisingly few of the cases was there a history of diarrhea with loose or watery stools. The few bacteriologic studies that were made gave no evidence of dysentery. Moreover, in the process of examining the 605 pancreatic sections of the last 1,000 autopsies in the Babies Hospital, many cases of diarrhea and other diseases of the intestine were encountered, and in none of them was there any evidence of pancreatitis. All cases in which there was acute inflammation of the pancreas were investigated and observed to be examples of either acute peritonitis or septicemia with mesenteric adenitis. Garsche [3n] described 2 cases of pancreatic insufficiency; in 1 the condition began in the fifth year as infectious jaundice, and in the other there was a history of chronic diarrhea with onset at the about the age of 1 year. The fibrosis of the pancreas observed post mortem in these cases differed from cystic fibrosis of the pancreas in that cysts were absent and acinar tissue was present. The author stated the belief that this represented an earlier phase of the disease noted in his third case, which is included in the present series.

3. In spite of ignorance concerning vitamin A deficiency during fetal life, this lack has been considered as a possible cause of cystic fibrosis of the pancreas because the postnatal deficiency is known to produce proliferation and metaplasia of the epithelium in various places throughout the body.[16] This hypothesis would explain the presence of atresias of other ducts as well as the regular occurrence of fibrosis of the main pancreatic ducts. The familial incidence may be the result of insufficient

16. Wolbach, S. B., and Howe, P. R.: Tissue Changes Following Deprivation of Fat-Soluble A Vitamin, J. Exper. Med. **42**:753, 1925.

vitamin A in the maternal diet or of a disturbance in the mechanism of absorption of the vitamin in the mother. In the experimental and pathologic studies of postnatal vitamin A deficiency the pancreas is found affected slightly if at all. Vitamin A deficiency in the mother's diet is known to decrease the vitamin A reserves of the young [17] and to produce a high mortality during the fetal or neonatal life.[18] No adequate anatomic studies on congenital vitamin A deficiency have been reported. The question appears capable of an experimental solution, and an investigation of the problem is at present under way in this laboratory.

PATHOLOGIC PHYSIOLOGY

Relation of the Pancreatic Lesion to the Clinical Picture.—The literature relating to the exclusion of the pancreatic juice from the intestine has recently been summarized by Ivy [19] and by Greenberg,[20] and a review will not be attempted here. Such experiments in the dog result in a clinical picture closely resembling that of cystic fibrosis of the pancreas. The similarity is sufficiently marked to confirm the belief that the syndrome in the cases presented here was due to the pancreatic lesion. The symptoms produced by ligation of the pancreatic duct or by the creation of an external fistula are hunger, polyphagia, failure to gain weight or loss of weight and bulky foul stools. Unless special care is taken, early death ensues. The animal may survive and gain in weight in the presence of a small amount of functioning pancreas, the amount necessary being estimated at 10 per cent of normal. The same result may be obtained by feeding large amounts of a well balanced diet with high vitamin content or by feeding raw pancreas.[19] These symptoms are identical with those which accompany cystic fibrosis of the pancreas; they are not found unless approximately 90 per cent of the pancreas is involved. As in the dogs, gain in weight may occur with an adequate and appropriate diet (case 44 [XX]). In both instances a large portion of the ingested food is lost in the stools, and the loss of fat is especially striking. In both cases the percentage of split fat in the stools may be

17. Dann, W. J.: The Transmission of Vitamin A from Parents to Young in Mammals: IV. Effect of the Liver Reserves of the Mother on the Transmission of Vitamin A to the Foetal and Suckling Rat, Biochem. J. **28**:2141, 1934.

18. Hart, G. H.; Mead, S. W., and Guilbert, H. R.: Vitamin A Deficiency in Cattle Under Natural Conditions, Proc. Soc. Exper. Biol. & Med. **30**:1230, 1933. Mason, K. E.: Foetal Death, Prolonged Gestation, and Difficult Parturition in the Rat as a Result of Vitamin A Deficiency, Am. J. Anat. **57**:303, 1935.

19. Ivy, A. C.: Certain Aspects of the Applied Physiology of External Pancreatic Secretion, Am. J. Digest. Dis. & Nutrition **3**:677, 1936.

20. Greenberg, J.: An Attempt to Reproduce Coeliac Disease Experimentally in Young Animals by Excluding the External Pancreatic Secretion from the Intestine, Yale J. Biol. & Med. **6**:121, 1933.

normal.[20] A low or normal blood sugar value was found in the present cases, and a normal one has been described in experimental animals.[20] In infants the dextrose tolerance curve may be flat or high. The latter curve has been described in animals.[21] Observations on serum tributyrinase and amylase were recorded in only 1 case of cystic fibrosis of the pancreas, in which the tributyrinase content of the serum remained normal and the amylase content was high. These findings are present after experimental ligation of the pancreatic duct.[22] There is thus a close parallel between the picture presented by cystic fibrosis of the pancreas and that produced by experimental ligation of the pancreatic duct or by fistula.

The ability to split fat is found in varying degrees both in the patients observed clinically and in experimental animals, and this may be attributed to the lipase of the succus entericus. It is less easy to understand why the fatty acids are not absorbed. It most cases there are no microscopic changes in the intestine which would indicate failure to function normally, and when changes are present they are mild and may well be interpreted as the result rather than the cause of the abnormal stools. The normal mechanism of fat absorption is poorly understood, but recent work indiactes that fats are probably not absorbed as fatty acids but first undergo phosphorylation.[23] It is possible that some further step beyond the splitting of neutral fat into fatty acids is necessary in the preparation of fat for absorption and that some factor essential to this step is contributed by the pancreas.

The frequent occurrence of fatty liver in both the experimental animals and the cases collected here is another point of similarity which is not explained. The literature on the etiology of fatty liver is too vast to be reviewed here. The recent work of Dragstedt, Van Prohaska and Harms [24] may be mentioned: They have demonstrated a factor in the pancreas which is not found in pancreatic juice and which prevents fatty degeneration of the liver in pancreatectomized dogs. The application of these observations to the present problem awaits further study.

21. Galehr, O.; Ladurner, P., and Unterrichter, L.: Das Verhalten der Blutzuckerwerte nach Pankreasgangunterbindung, Arch. f. d. ges. Physiol. **218**: 477, 1928.

22. Crandall, L. A., Jr.: The Origin and Significance of the Blood Serum Enzymes, Am. J. Digest. Dis. & Nutrition **2**:230, 1935.

23. Sinclair, R. G., and Smith, C.: The Turnover of Phospholipoids in the Intestinal Mucosa, J. Biol. Chem. **121**:361, 1937.

24. Van Prohaska, J.; Dragstedt, L. R., and Harms, H. P.: The Relation of Pancreatic Juice to the Fatty Infiltration and Degeneration of the Liver in the Depancreatectomized Dog, Am. J. Physiol. **117**:166, 1936. Dragstedt, L. R.; Van Prohaska, J., and Harms, H. P.: Observations on a Substance in Pancreas (a Fat-Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatectomized Dogs, ibid. **117**:175, 1936.

Deficiency of Fat-Soluble Vitamins.—Vitamin A deficiency has been considered as a possible cause of cystic fibrosis of the pancreas; it will now be discussed as a probable result of the lesion. There was evidence of vitamin A deficiency in 10 of the 49 cases of the present series. Of the 12 reported cases of vitamin A deficiency in which postmortem examination was done, the pancreas was examined microscopically in 7, and in all 7 it was described as composed of epithelium-lined cysts and fibrous tissue. This association is too frequent to be accidental. Pancreatectomized dogs also fail to assimilate vitamin A normally.[25] Previous authors have suggested that there may be inadequate absorption of the vitamin from the alimentary tract if absorption of fat is inadequate.[26]. It is otherwise difficult to explain the fact that in several of the cases reported as instances of vitamin A deficiency the patient had received cod liver oil in amounts which were supposedly adequate (Blackfan and Wolbach's cases 3 and 7 [4a]). Two patients were given cod liver oil after admission to the hospital without beneficial effect,[27] while another recovered from xerophthalmia only after parenteral injection of carotene (case 23 [XV]). In the other cases of vitamin A deficiency the intake was probably inadequate.

The clinical tests for the determination of vitamin A deficiency have not as yet been applied in cases of cystic fibrosis of the pancreas. Studies on night blindness and on the vitamin A content of the serum have been made in cases of celiac disease.. Chesney and McCoord,[28] using the Price-Carr colorimetric method, found that the vitamin A content of the serum in 2 untreated patients with celiac disease was less than half the mean value of the vitamin in the serum of 12 controls; four hours after the administration of 2 cc. of halibut liver oil the serum of the controls showed a mean rise of approximately 900 per cent in vitamin A, whereas 1 of the patients with celiac disease showed a slight rise and the other no change. After treatment there was a rise in the basal level but not in the response to halibut liver oil. More recently Friderichsen and Edmund developed a modification of the method for determining dark adaptation which can be applied to small infants.[29] They demonstrated that a mild degree of failure in adaptation

25. Ralli, P. E.; Pariente, A.; Flaum, G., and Waterhouse, A.: A Study of Vitamin A Deficiency in Normal and Depancreatized Dogs, Am. J. Physiol. **103**:458, 1933.

26. Basu, N. K.: Vitamin A and Fat Metabolism, Ztschr. f. Vitaminforsch. **6**:106, 1937.

27. Blackfan and Wolbach.[4a] Cabot Case 17242.[4c]

28. Chesney, J., and McCoord, A. B.: Vitamin A of Serum Following Administration of Haliver Oil in Normal Children and in Chronic Steatorrhoea, Proc. Soc. Exper. Biol. & Med. **31**:887, 1934.

29. Friderichsen, C., and Edmund, C.: Studies of Hypovitaminosis A: II. A New Method for Testing the Resorption of Vitamin A from Medicaments, Am. J. Dis. Child. **53**:89 (Jan., pt. 1) 1937.

is not uncommon in infants under the age of 1 year and that it disappears one-half to one hour after feeding preparations high in vitamin A.[30] One child, aged 14 months, who presented symptoms of celiac disease, showed an especially severe degree of night blindness, which did not respond to therapy until mother's milk was given.[31] In this case and in those of Chesney and McCoord the state of the pancreas was not known. The earlier conviction that vitamin A deficiency is rare in celiac disease[32] must therefore be modified to the belief that subclinical degrees of the deficiency are not infrequent. The question deserves further investigation.

Severe vitamin A deficiency occurred in 10, or 23 per cent, of 44 cases of cystic fibrosis of the pancreas, as shown by the presence of keratinizing metaplasia of the epithelium of various organs and by xerophthalmia. Mild degrees of the deficiency may have been present in some or all of the remainder of the cases. It is not surprising that the deficiency was more marked in these cases than in those of celiac disease in patients over the age of 1 year, for the vitamin A reserves of the infant are low,[33] and there is correspondingly greater sensitivity to inadequate ingestion or absorption of the vitamin. The slow growth of these infants may be attributed in part to inadequate absorption of vitamin A.

The cause of death in all of the cases in which the patients survived the first week was bronchitis, bronchiectasis or bronchopneumonia, and this uniformity could not be accidental. The lungs of the 9 patients who showed keratinizing metaplasia of the bronchial epithelium were similar in other respects to those of the patients who did not. Mild tubular bronchiectasis with an increase in the number of cell layers in the bronchial epithelium was almost invariably observed in our series. The possibility that this was the result of a partial deficiency of vitamin A should be considered. Bronchiectasis is present in a high percentage of vitamin A-deficient rats,[16] but because of the frequency of this lesion in rats given adequate diets this species of animal is unsatisfactory for the

30. Friderichsen, C., and Edmund, C.: Studies of Hypovitaminosis A: III. Clinical Experiments in the Vitamin A Balance in Children After Various Diets, Am. J. Dis. Child. **53**:1179 (May) 1937.

31. Friderichsen, C.: Quantitative Investigations of the Resorption of A Vitamin in a Case of Coeliaki, Acta pædiat. **18**:377, 1936.

32. Parsons, L. G.: Celiac Disease; Rackford Memorial Lectures, Am. J. Dis. Child. **43**:1293 (May, pt. 2) 1932.

33. Debré, R., and Busson, A.: La vitamine A, son métabolisme, son rôle dans certains états pathologiques chez l'homme, Rev. franç. de pédiat. **10**:413, 1934. Wolff, L. K.: On the Quantity of Vitamin A Present in the Human Liver, Lancet **2**:617, 1932.

experiment.[34] Similar investigations on other species would be of greater interest.

The evidence for vitamin D deficiency is less clear. Severe rickets was described in only 1 case,[3k] but osteoporosis was often mentioned and was present in most of the cases of the Babies Hospital. This may be interpreted either as the result of failure of calcium absorption due to the fixation of the ingested calcium by the fatty acid in the intestine to form soaps, or as the result of vitamin D deficiency. The absence of rickets is not surprising in view of the slow growth of these children.

Deficiency of the Water-Soluble Vitamins.—No evidence of deficiency of water-soluble vitamins was recognized.

RELATION TO CELIAC DISEASE

In most of the cases of the present series in which the patients survived the first six months of life the clinical diagnosis was celiac disease; this diagnosis was based on the presence of most if not all of the characteristics of the celiac syndrome. The traditional points of differentiation between idiopathic and pancreatic steatorrhea, namely, the character of the stools and the failure of the latter condition to respond to a diet for patients with celiac disease, have been shown to be unreliable. At present the differential diagnosis can be made with certainty only by examination of the duodenal juice for pancreatic enzymes or by microscopic examination of the pancreas. In most of the reported cases of celiac disease neither of these tests was applied, and the reader is therefore uncertain as to whether the pancreas was normal or not. The literature has accordingly been searched for cases of celiac disease in which autopsy was done, and 32 of them have been found, exclusive of those in which cystic fibrosis of the pancreas or replacement of the acinar tissue with fat occurred. In the reports of 17 of them there was no definite statement that the pancreas was examined microscopically, namely, in the cases of Moorehead,[35] Pipping,[36] Bloch,[37] Schick and Wagner,[38] and Baginsky[39] and in 1 case of Passini,[3c] 1 of Miller,[40]

34. Passey, R. D.; Leese, A., and Knox, J. C.: Bronchiectasis and Metabolism in the Lung of the Laboratory Rat, J. Path. & Bact. **42**:425, 1936.

35. Moorehead, T. G.: Infantilism, Pancreatic and Intestinal, Dublin J. M. Sc. **149**:1, 1920.

36. Pipping, W.: Beitrag zur Kenntnis des intestinalen Infantilismus (Herter), Acta pædiat. **3**:342, 1924.

37. Bloch, C. E.: Clinical and Anatomical Investigations of Infantilismus, Acta pædiat. (supp. 2) **7**:207, 1928.

38. Schick, B., and Wagner, R.: Ueber eine Verdauungsstörung jenseits des Säuglingsalters (Atrophia pluriglandularis digestiva), Ztschr. f. Kinderh. **35**: 263, 1923.

(Footnotes continued on next page)

all but 2 of Fanconi's 6 cases [41] and 3 of the 6 cases of nontropical sprue collected by Thaysen.[42] In the remaining 15 cases the microscopic examination of the pancreas revealed no extreme changes. Four of these were cases of nontropical sprue or celiac disease beginning in adult life.[43] Since this disease is irrelevant to the present investigation, these cases will not be discussed. There remain 11 cases of celiac disease beginning in infancy or early childhood in which the pancreas was examined microscopically and was observed to show no extreme changes (Mautner,[44] Porter,[45] Hess and Saphir's case 3,[31] Fanconi's cases 34 and 40,[41] Poynton and Paterson,[46] Miller,[47] Kundratitz,[48] Still,[49] Poynton, Armstrong and Nabarro [50] and Fullerton and Innes [51]).

39. Baginsky, A.: Die wichtigsten Verdauungsstörungen des älteren Kindes und ihre Behandlung, Arch. f. Kinderh. **64**:161, 1915.

40. Miller, R.: The Pathogenesis of Celiac Disease, Arch. Pediat. **40**:88, 1923.

41. Fanconi, G.: Der intestinale Infantilismus und ähnliche Formen der chronischen Verdauungsstörung, Abhandl. a d. Kinderh. u. Grenzgebieten (supp. to Jahrb. f. Kinderh.) **21**:1, 1928.

42. Thaysen, T. E. H.: Non-Tropical Sprue: A Study in Idiopathic Steatorrhoea, Copenhagen, Levin & Munksgaard, 1932.

43. Thaysen.[42] Anderson, A. G., and Lyall, A.: Two Cases of "Fatty Diarrhoea" with Special Reference to Nitrogen Metabolism, Quart. J. Med. **2**:339, 1933. Holst, J. E.: Ein in Dänemark aufgetretener Fall von Sprue, Acta med. Scandinav. **66**: 74, 1927. Rosendahl, G., cited by Thaysen.[42] Gloor, H. U.: Klinische Erfahrungen über die Behandlung der perniziösen Anämie, Folia haemat. **39**:373, 1930.

44. There is some doubt as to whether the pancreas in Mautner's case (Mautner, H.: Die Herter-Heubnersche Verdauungsinsuffizienz [Coeliac Disease], Klin. Wchnschr. **4**:165, 1925. Lehndorff, H., and Mautner, H.: Die Coeliake, Herters intestinaler Infantilismus, Heubners schwere Verdauungsinsuffizienz jenseits des Säuglingsalter, Ergebn. d. inn. Med. u. Kinderh. **31**:456, 1927) showed cystic fibrosis. The pathologic description and the neonatal onset are in favor of this view. However, the illustration (1927) shows only fat droplets in the acinar cells, and as this evidence is objective the case has been placed in the group of those in which there was no cystic fibrosis.

45. Porter, L.: Pancreatic Insufficiency, Am. J. Dis. Child. **6**:65 (Aug.) 1913.

46. Poynton, F. J., and Paterson, H.: The Occurrence of Ascites of a Non-tuberculous Origin in Chronic Recurrent Diarrhoea in Childhood, Lancet **1**:1533, 1914.

47. Miller, R.: A Fatal Case of Coeliac Infantilism with Comments on the Morbid Anatomy of Coeliac Disease, Lancet **1**:743, 1921.

48. Kundratitz, K.: Zur Pathogenese des Herterschen intestinal Infantilismus (Heubners chronische Verdauungsinsuffizienz, Schick und Wagners Atrophia pluriglandularis digestiva, Lehndorf und Mautners Coeliakie, Coeliac Disease der english-amerikanischen Autoren), Jahrb. f. Kinderh. **116**:310, 1927.

49. Still, G. F.: The Lumleian Lectures on Coeliac Disease, Lancet **2**:193, 1918.

50. Poynton, F. J.; Armstrong, R. R., and Nabarro, D. N.: A Contribution to the Study of a Group of Cases of Chronic Recurrent Diarrhoea of Childhood, Brit. J. Child. Dis. **11**:145, 1914.

51. Fullerton, H. W., and Innes, J. A.: Case of Idiopathic Steatorrhoea with Multiple Nutritional Deficiencies, Lancet **2**:790, 1936.

TABLE 2.—*Summary of Cases of Celiac Disease With Autopsy in Which the Pancreas Showed no Marked Changes on Microscopic Examination*

Case	Author	Age at Onset of Digestive Disturbance	Age at Death	Sex	Predominant Clinical Symptoms	Cause of Death (Clinical)	Postmortem Observations	
							Data on Pancreas	Other Data
1	Mautner, 1925.....	Neonatal	2-3 yr.	M	Poor development; fatty stools; large abdomen; anemia	Acute lobar pneumonia empyema	Slight fibrosis with infiltration; fat in acinar cells	Fatty liver
2	Porter, 1913.....	4 months	3 yr.	M	Failure to gain; protuberant abdomen; vomiting; scurvy; large foul greasy stools with mucus; anorexia	Diarrhea; exhausiton	Slight fibrosis; acinar tissue normal; many islands	Emaciation; slight interstitial nephritis; intestines normal
3	Hess and Saphir, 1935, case 3	Before 4 mo.	3 yr.	F	Recurrent attacks of diarrhea; underdevelopment	Dehydration bronchopneumonia	Slight fibrosis and infiltration; acinar cells small, sometimes forming syncytium; islands normal	Emaciation; infiltration of intestinal mucosa; nephrolithiasis; fatty liver; multiple diverticula of stomach
4	Fanconi, 1928, case 40	1¾ years	3¼ yr.	?	Recurrent diarrhea; thin stools with mucus; multiple hemorrhages	Diarrhea	Acini normal; fat in island cells	Osteoporosis; multiple hemorrhages; fatty liver
5	Poynton and Paterson, 1914	1 year	3½ yr.	M	Infantile cholera; marasmus; polydipsia	Cachexia; anasarca and ascites	Small circumscribed areas of leukocytic infiltration between acini; no fibrosis	Fatty liver; edema and leukocytic infiltration of intestines
6	Miller, 1921.....	2 months	5½ yr.	M	Recurrent diarrhea; large abdomen	Acute intestinal disorder	Normal	Emaciation
7	Kundratitz, 1927.....	1½ years	6 yr. 2 mo.	F	Recurrent diarrhea; stools various, some with high fat content	Diarrhea; exhaustion	Normal	Fatty liver; stomach and intestines normal
8	Still, 1918.....	6¾ years	7 yr.	M	Loose bowels; wasting; large abdomen	Diarrhea; exhaustion	Some excess of fibrous tissue, especially around the ducts, the appearance being suggestive of some pancreatitis	Slight ascites; intestines thick, with swollen and congested mucosa; no ulcers
9	Fanconi, 1928, case 34	?	8½ yr.	F	Alternating constipation and diarrhea; stools thin, mucoid or fatty; bleeding; vomiting	Erysipelas	Fat in acinar cells, otherwise normal	Erysipelas; osteoporosis; fatty liver; fat in myocardium; anemia; hemosiderosis of spleen
10	Poynton, Armstrong and Nabarro, 1914	1 year	9 yr.	M	Recurrent diarrhea; large foul stools	Diarrhea; exhaustion	Marked fibrosis of interlobular tissue; gland tissue normal	Acute congestion and lymphoid infiltration of stomach and intestines (Bacillus of Flexner); fatty liver
11	Fullerton and Innes, 1936	Early infancy	33 yr.	F	Recurrent diarrhea; fatty stools; vitamin deficiencies (B_2, D, antianemic)	Septicemia (streptococcus)	Relative increase in islands, otherwise normal	Streptococcic septicemia; peritonitis; hydrothorax; fatty liver

A comparison of the records of this group with the cases collected for the present paper shows several points of difference in the clinical course (tables 1 and 2). In the former group the first gastrointestinal symptoms were noted between the ages of 2 months and 1 year in 5 cases and between the first and the seventh year in 4 cases; the age of the child at occurrence of these symptoms was not stated in the reports of the remaining 2, but it was before the eighth year. The first part of the illness consisted in recurrent attacks of diarrhea, the stools varying in different cases and at different times in the same case but in general changing gradually from a watery, greenish type in the early part of the course to a large, foul, pale type later. Underdevelopment and failure to gain weight were mentioned frequently. Death followed a recurrence of acute diarrhea in 6 cases; of the remaining cases the terminal event was erysipelas in 1, streptococcic septicemia in 1 and infection of the respiratory tract in 2; it was not stated in the report of 1 case. There was evidence of scurvy in 1 case [45] and possibly in another.[41]. In the case of Fullerton and Innes [51] the patient showed multiple vitamin deficiencies (B_2, D, antianemic factor). Death occurred in the majority of cases between the third and the ninth year, but 1 patient survived to the thirty-third year. In 2 cases the pancreas was entirely normal, and in the others, it showed mild changes, which consisted of mild fibrosis in 6 cases and slight cellular infiltration in 1 case. The acinar tissue was normal in 9 cases and contained fat in 1; in another the acinar cells were arranged as syncytium. The changes observed in the other cases were too various to be enumerated in detail. The liver was fatty in 8 cases; the intestines were normal in most instances but contained an excess of lymphocytes in the mucosa in 4. The striking points in the cases of this group which differentiated them from those in which there was cystic fibrosis of the pancreas are (1) the later age of onset; (2) a period of recurrent attacks of diarrhea preceding the appearance of fatty stools, in most of the cases without severe pancreatic change; (3) absence of hunger and polyphagia; (4) a longer survival; (5) absence of evidences of vitamin A deficiency, and (6) death as the result of an exacerbation of the diarrhea, though sometimes an intercurrent infection was responsible, whereas in the cases of pancreatic disease death was due to infection of the respiratory tract.

The cases in which there were no striking pancreatic changes do not present as uniform a picture as those in which there were pancreatic changes and possibly do not represent a disease entity. Most if not all of them can be interpreted as cases of recurrent diarrhea of unknown cause with fatty diarrhea in the latter part of the course. Whether the diarrhea was due to a single cause is unknown, and bacteriologic studies have yielded no satisfactory conclusions. A probable

cause was demonstrated in only 1 of these cases as the Flexner bacillus, but this may have been a secondary invader. It appears probable that the cases of celiac disease in which the course terminated in recovery belong to the group in which the pancreas was essentially normal, since in the recorded cases of cystic fibrosis of the pancreas the oldest patient died before the fifteenth year.

The clinical picture of celiac disease, with retarded development, muscular weakness and atrophy, a large abdomen, large foul stools and a favorable response to the standard regimen for this condition, is found in cases of chronic recurrent diarrhea in which the pancreas is normal and also in cases of cystic fibrosis of the pancreas. Celiac disease may therefore be regarded as a clinical syndrome rather than a disease entity. Cystic fibrosis of the pancreas is a disease entity which produces the celiac syndrome when the children survive the first year of life. The remaining cases of celiac disease, including most if not all of those in which recovery occurs, form a group which is less uniform and which may represent one or more disease entities. At present the differential diagnosis can be made with certainty only by examination of the duodenal contents for pancreatic enzymes or by microscopic examination of the pancreas.

THERAPY

As yet too little is known of cystic fibrosis of the pancreas to warrant a detailed account of treatment. There are, however, several indications which should be recorded. 1. The children who survived the first few months of life are those who received mother's milk with the addition of cod liver oil or other preparations of the same order and who were later given a diet for celiac disease. 2. The frequency of vitamin A deficiency suggests that large doses of fat-soluble vitamins should be given. In some cases it may be advisable to give them parenterally. A diet low in fat appears to produce improvement in the stools, but the hazard of vitamin A deficiency and of pulmonary infection is so great that it seems unsafe to use it; fatty stools are preferable to fatal purulent bronchitis. 3. Experiments on ligation of the pancreatic duct in dogs have demonstrated that the animals require a greater quantity of food than normal to maintain health. The absolute amount of food which is absorbed increases with the amount ingested, although the proportion decreases.[19] It is suggested that this observation be applied in the cases of pancreatic insufficiency and that the caloric intake be in excess of the usual amount for the age.

SUMMARY AND CONCLUSIONS

Forty-nine cases of pancreatic fibrosis in infants or older children on whom postmortem examination was done have been collected and

analyzed. Forty-five of these were cases of cystic fibrosis of the pancreas and 4 were cases in which the acinar tissue of the pancreas was replaced by adipose tissue.

Clinically the cases fell into three groups, as follows:

1. In 5 cases death occurred in the first week of life, from some form of intestinal obstruction.

2. In 19 cases of infants the patients died between the ages of 1 week and 6 months, of purulent bronchitis, bronchiectasis or bronchopneumonia. In 13 of these cases the patients presented feeding problems, the essential features of which were hunger, failure to gain on an adequate diet in the absence of vomiting or diarrhea, and the presence of foul bulky stools.

3. In 25 cases the children died of pulmonary infections between the ages of 6 months and 14½ years. All these patients presented symptoms which were recognized as preceliac in type or which led to the diagnosis of celiac disease.

The chief pathologic changes were as follows:

1. The acinar tissue of the pancreas was replaced by epithelium-lined cysts containing concretions and surrounded by fibrous tissue. The islands of Langerhans were intact.

2. The lungs showed bronchitis, bronchiectasis, pulmonary abscesses arising in the bronchi, lobular pneumonia or any combination of these. Staph. aureus was the usual bacteriologic agent.

3. There was evidence of vitamin A deficiency in many of the patients who died before the age of 1 year.

4. Atresia of the small intestine, of the cystic duct or of the pancreatic duct was frequently noted.

The cause of the pancreatic lesion was unknown. In all probability it was usually if not always present at birth. Sixty-seven per cent of the patients were girls. There were 3 proved instances of familial occurrence. The racial and geographic distribution was wide. Cystic fibrosis involved 90 per cent (estimated) of the pancreatic tissue in 3.3 per cent of 605 unselected cases in which autopsy was done in the Babies Hospital.

The relation of the pancreatic lesion to the other clinical and pathologic observations has been discussed:

1. The clinical syndrome was comparable to that which follows ligation of the pancreatic duct in dogs; it can be attributed to the pancreatic lesion. Under favorable circumstances the symptoms of the condition sometimes disappeared temporarily (for a period of several months) under the influence of appropriate dietary treatment.

2. The frequent occurrence of vitamin A deficiency was probably due to failure of absorption of this vitamin. It is suggested that the pulmonary infection was possibly secondary to vitamin A deficiency.

3. Osteoporosis was frequent and can be interpreted as the result of inadequate absorption of either vitamin D or calcium or both.

4. The fatty degeneration of the liver and the occasional lymphocytic infiltration of the intestinal mucosa are considered secondary.

Thirty-two further cases of celiac disease in which postmortem examination was done have been collected from the literature. In 11 of these, the disease began in childhood and the pancreas was examined microscopically. No marked changes were observed in the pancreas. The clinical and pathologic observations in these cases have been compared with those in the cases of pancreatic insufficiency. The former group is less homogeneous, but the disease usually began as chronic recurrent diarrhea of unknown origin, with fatty stools in the latter part of the course. Onset and death were later than in cases of pancreatic insufficiency.

The clinical picture of celiac disease may be presented either by patients with pancreatic insufficiency who survive the first year of life or by patients with chronic recurrent diarrhea who have no essential abnormalities in the pancreas. The two groups of cases can be differentiated with certainty only by examination of the duodenal contents for enzymes or by microscopic examination of the pancreas. It is concluded that celiac disease is a clinical syndrome, not a disease entity, and that it may be produced by two or more disease entities, one of which is cystic fibrosis of the pancreas.

CASE 7 (IV).—A. L. was a girl. The parents were well. One sibling died at the age of 3 months, having had diarrhea and having failed to gain. The birth was normal and occurred at term. The weight at birth was 8½ pounds (3,856 Gm.). The child was nursed until the eighth day, when she was given similac "because the mother's milk had Staph. albus." The child had boils on the arms. At this time the weather was extremely hot and she failed to take her formula well. The stools were green and foul but numbered not more than 4 a day. The child had several cyanotic attacks. She was admitted to the Babies Hospital at the age of 6 weeks, the complaint being failure to gain weight.

Physical Examination.—The weight was 7½ pounds (3,402 Gm.), the length 55 cm. and the temperature 99.6 F. The patient was well developed and thin, with a vigorous cry. There was a small umbilical hernia. The ear drums were a little red, the right more so. Otherwise the examination gave negative results.

Laboratory Findings.—The hemoglobin content was 23 Gm. per hundred cubic centimeters. The red cell count was 5,600,000, and the white cell count 26,000. There were 63 per cent polymorphonuclears. The urine was normal except for a trace of albumin. The Kahn reaction was negative. There were 2 to 5 stools daily; these were large, foul, soft and yellow or green.

Course.—During the first part of her stay the infant took feedings well and appeared hungry. There was a small gain in weight. After a week the temperature rose to 101 or 102 F. and the respiratory rate to 60. The patient lost a little weight and began to cough. The subsequent course was that of pneumonia. The child died fifteen days after admission.

Autopsy.—The age at death was 8 weeks, the weight 7 pounds (3,175 Gm.) and the length 57 cm.

Gross Examination: The peritoneal cavity appeared normal except for distention of the small and especially of the large intestine.

The lungs bore a yellowish gray fibrinous exudate. The surfaces were studded with abscesses measuring 2 to 10 mm. in diameter. The intervening lung tissue was purplish red. The cut surface was honeycombed with small anastomosing cavities which appeared to be infected dilated bronchi. A probe was passed from the larger ones directly into the bronchi. The hilar lymph glands were large, gray and moist.

The liver weighed 240 Gm. It had a brownish tinge but otherwise appeared normal.

The pancreas was normal externally and on section.

The right middle ear was normal. The left middle ear and mastoid antrum contained a thick purulent exudate.

The remaining viscera showed no significant gross changes.

Bacteriologic Examination: This showed Staph. aureus haemolyticus in material from the left middle ear and in the pleural exudate.

Microscopic Examination: The bronchi and bronchioles were filled with purulent exudate. The walls of the bronchioles were infiltrated with lymphocytes, myeloid cells and an occasional polymorphonuclear leukocyte. Several large abscesses containing numerous bacteria were present. Many of the intervening alveoli contained coagulated fluid, but the walls were free from exudate. Gram's stain showed that many bacteria, morphologically classed as staphylococci, were present in the abscesses and in the exudate in the alveoli and bronchi and on the pleural surface.

Some of the cells of the liver contained fat vacuoles. Brown pigment was present in both hepatic and Kupffer cells. The iron stain showed that iron-containing pigment was abundant in the hepatic cells and in the Kupffer cells.

In nearly all the lobules of the pancreas, the ducts were mildly to widely dilated and the lumens contained pale vacuolated mononuclear cells or laminated hyaline concretions. The islands were intact. Fibrous tissue containing many fibroblasts separated the acini as well as the lobules. Small numbers of lymphocytes and mononuclear cells and a few eosinophils were seen in this fibrous tissue (fig. 7).

The other organs appeared normal.

Anatomic Diagnosis: The diagnosis was purulent bronchitis; lobular pneumonia with abscess formation (Staph. aureus haemolyticus); acute fibrinous pleurisy (Staph. aureus haemolyticus); purulent otitis media (Staph. aureus haemolyticus); cystic fibrosis of pancreas, and accidental involution of the thymus.

CASE 9 (V).—M. A. was a girl. The parents and one older sibling were living and well. The patient was the result of the second pregnancy. The birth was normal. The weight at birth was 5 pounds and 10 ounces (2,251 Gm.). The child never took the breast well and was given a supplementary formula containing cow's milk and dextrimaltose with ½ teaspoon of cod liver oil. The appetite was good for the bottle but not for the breast feeding. There were 2 or 3 regular

bowel movements a day. Two weeks before admission to the hospital the baby began to cough. Two days before admission the cough became more frequent and spasmodic, and the coughing spells were followed by dyspnea and on two occasions by vomiting. The appetite decreased. The temperature was normal.

Physical Examination at Two Months.—The temperature was 99.4 F., the weight 7 pounds and 2 ounces (3,232 Gm.) and the length 53 cm. The child appeared small but well. The skin was sallow, with marked hypertrichosis. The pharynx was mildly injected. There was a frequent spasmodic, high-pitched, choking cough. Respirations were rapid and shallow, with moderate retraction of the lower costal margins and of the suprasternal notch. There were a few moist rales at the bases of both lungs.

Laboratory Findings.—The hemoglobin content was 11 Gm. per hundred cubic centimeters. There were 4,340,000 red cells and 13,450 white cells per cubic millimeter, of which polymorphonuclears constituted 41 per cent, lymphocytes 56 per cent, mononuclears 2 per cent and eosinophils 1 per cent. The urine was normal. Culture of material from the throat showed Staph. albus nonhaemolyticus and Staph. aureus haemolyticus. Blood cultures were negative. Roentgenograms of the heart showed bilateral bronchopneumonia, more marked on the left.

Course.—The child was thought to have pertussis or capillary bronchitis. Her condition rapidly became worse, and she died at the age of 2½ months, twelve days after admission to the hospital.

Autopsy.—The age at death was 2½ months, the weight 3.3 Kg. and the length 54 cm.

Gross Examination: The child was small but fairly well nourished. There was a mucopurulent discharge in both nostrils. The abdomen was prominent, with slight protrusion of the umbilicus. The peritoneum contained 3 cc. of clear fluid. The arch of the aorta lay below and somewhat to the left of the normal position, so that the superior surface was at the level of the bifurcation of the trachea. The right subclavian artery arose below the left subclavian artery and followed an anomalous course; it passed behind the trachea and esophagus, going diagonally upward and laterally along the posterior wall of the right chest to pass over the first rib at the usual point.

The heart was normal except for some dilatation of the right ventricle.

The right lung weighed 65 Gm. The pleura was smooth. The posterior half of the lung was firm and nodular, with dilatation of the interlobular lymphatics. The anterior portion was emphysematous, with patches of atelectasis. The cut surface was firm, moist and salmon pink, with gray areas around the bronchi. All the bronchi and bronchioles appeared a little enlarged and thickened, with a thick white exudate in the lumens. The left lung weighed 60 Gm. It resembled the right.

The spleen weighed 10.5 Gm. It was pale red, with indistinct malpighian corpuscles. An accessory spleen 1 cm. in diameter lay near the hilus.

The liver weighed 135 Gm.; it appeared normal except for a yellowish tinge. The gallbladder was atrophic and contained 1 or 2 cc. of thick gray translucent mucoid material. The cystic duct was not patent, but the hepatic and the common duct were normal.

The pancreas was of almost normal size and had a pinkish tinge. On section the lobules were irregular in size, rounded and often fused together. Wirsung's duct could not be demonstrated. The duct of Santorini was present and patent, though small. The pancreatic tissue around it was similar to that seen elsewhere.

The left kidney weighed 15 Gm. There was mild hydronephrosis, but the cortex appeared normal otherwise. There were three areas of stricture, one at the ureteropelvic junction and the others just below. The circumference was 1 mm. at the narrowest point and 4 mm. below the strictures. The right kidney weighed 14 Gm. and appeared normal. There was a slight narrowing of the uteropelvic junction but no dilatation of the kidney pelvis.

The adrenals, alimentary tract and cervical organs were normal.

Microscopic Examination: The bronchi and bronchioles were dilated and filled with an exudate of polymorphonuclear leukocytes, cellular débris and bacteria. The bronchial epithelium was intact for the most part. There were occasional areas where the epithelium was pseudostratified, but no areas of squamous metaplasia were noted. Near the bronchioles the alveolar walls were thickened, and some of the alveoli were filled with polymorphonuclear leukocytes, red cells and lymphocytes. The less affected alveoli were emphysematous. The Gram stain showed many gram-positive cocci in the cellular débris in the bronchial lumens.

The malpighian corpuscles of the spleen were small and surrounded by red cells and polymorphonuclear leukocytes. The pulp contained eosinophils, normoblasts and phagocytes in which was brown pigment. The iron stain showed that a moderate amount of iron was present within phagocytes.

The hepatic cells contained fat vacuoles and granules of hemosiderin. A few lymphocytes and myelocytes were found in the portal areas.

In the mucosa of the gallbladder there were many epithelium-lined cysts containing mucus. Both the common and the cystic duct contained small epithelium-lined cysts full of mucus.

The acini of the pancreas varied in size, ranging from small and atrophic structures to large cysts. Many of them contained eosinophilic material and were lined by more or less flattened epithelium. There was a moderate increase in interstitial tissue, which was infiltrated with plasma cells and lymphocytes. An occasional polymorphonuclear leukocyte was present. The islands of Langerhans were normal.

There were occasional areas of pseudostratification in the mucosa of the fundus of the uterus.

The cortex of the thymus was depleted of small cells. Many eosinophils and myelocytes were present.

The adrenal glands, kidneys, intestines, thyroid and vagina appeared normal.

Bacteriologic Report: The lungs contained Staph. aureus haemolyticus. No growth occurred in material from the peritoneum.

Anatomic Diagnosis: The diagnosis was cystic fibrosis of the pancreas; bronchiectasis; acute bronchitis; lobular pneumonia; acute splenic tumor; atresia of the cystic duct; cysts of the cystic duct and of the gallbladder; congenital malformation of the ureters (strictures of ureters at and below the ureteropelvic junction); hydronephrosis on the right, and congenital malformation of the aorta (anomalous origin and course of the right subclavian artery).

CASE 23 (XV).—M. D. was a boy. The parents were well. One older sibling died of cystic fibrosis of the pancreas and bronchopneumonia at the age of 9 months at the Mount Sinai Hospital, and her case is included in this report (case 28 [XXII]). There were no other pregnancies.

The child was born in Sloane Hospital after a normal pregnancy. He appeared normal at birth. The weight at birth was 7 pounds and 11 ounces (3,487 Gm.). The infant received breast milk and a complementary formula of evaporated milk

and dextrimaltose. A little blood was found in the stools, but there was no known infection. After birth the child's weight fell to 6 pounds and 5 ounces (2,863 Gm.) but it had increased to 6 pounds and 12 ounces (3,062 Gm.) on discharge from the hospital on the nineteenth day. At that time the patient was having 6 or 7 loose stools a day, which contained blood, mucus and curds.

During the subsequent three and one-half months the infant did not do well, and a great many formulas were tried. Cod liver oil was first given at 8 weeks, but this "went right through the child," increasing the number of stools. The boy received outdoor sunshine. An "iron solution" and orange juice increased the number of stools. Transfusions produced some improvement. At 3 months the child weighed 10 pounds and 5 ounces (4,678 Gm.), but he then lost weight and was thought to have heat prostration. At 4 months roentgenograms of the chest and abdomen appeared normal. At this time the infant was put on a formula containing goat's milk and banana powder, which produced improvement in his general condition and reduced the stools to 2 a day. At 4½ months his temperature rose to 103 F., and leukocytes were found in the urine.

Beginning at the third month, there was a discharge in the right conjunctival sac, which improved on local treatment. A week later an ulcer appeared in the left cornea, and a diagnosis of xerophthalmia was made. The child was given carotene by mouth and also in the left eye, with healing of the ulcer but an increase in the number of stools. The child ate well and vomited only occasionally. The infant was admitted to the hospital at the age of 4½ months with a temperature of 104.8 F.

Physical Examination.—The infant was weak, dehydrated and poorly nourished, weighing 10 pounds (4,536 Gm.). Both scleras were hazy and slightly thickened. There was a small ulcer in the upper medial portion of the left cornea. There was no photophobia; the fundi appeared normal. The pupils reacted slightly to light. The ears, nose and mouth appeared normal. There was slight enlargement of the costochondral junctions. The heart and lungs were normal. The abdomen was scaphoid and soft, with prominent intestinal loops. The liver extended 3 cm. below the costal margin, and the spleen was palpable.

Laboratory Examination.—The hemoglobin content was 9.2 Gm. per hundred cubic centimeters; there were 2,300,000 red cells and 36,100 white cells per cubic millimeter, with polymorphonuclears 74 per cent, lymphocytes 22 per cent and eosinophils 3 per cent. After several transfusions the hemoglobin content was 18.4 Gm. and the red cell count 5,000,000. The urine was cloudy; the specific gravity was 1.012; analysis showed a heavy trace of albumin, no sugar, no acetone, benzidine (3 plus), many white cells and bacteria and a few red cells. Cultures of the urine produced an organism of the paratyphoid group which did not agglutinate with stock serums against Bacillus paratyphosus A, B or C, Bacillus enteritidis or Bacillus aertrycke. The blood showed no agglutinins for stock cultures of various members of the paratyphoid and dysentery groups. The chest and abdomen appeared normal on roentgen examination except for distention of the colon. Intravenous urography gave normal findings.

Course.—The child was given several transfusions and large amounts of vitamins A, B_1 and D both by mouth and by injection. He was given a formula containing evaporated goat's milk and banana powder. There was a dry cough. The stools numbered 2 to 4 a day and varied in character. Many were soft, large and yellow. The patient was given mandelic acid, but this was discontinued as he became lethargic and acidotic. He was discharged after two weeks in the

hospital with improvement in the eyes and in the urine but without change in the general condition. After discharge the cough became worse, and the weight decreased to 9 pounds and 1 ounce (4,111 Gm.). There were two further admissions. The course was essentially one of progressive bronchopneumonia and bronchiectasis, terminating fatally at the age of 6 months.

Autopsy.—The age at death was 6 months and the weight 3.61 Kg.

Gross Examination: The body was that of an emaciated white infant. The head was somewhat square, with moderately prominent frontal bosses. There was extreme pallor of the conjunctivas and mucous membranes. The corneas were normal. The ears and mouth appeared normal. The nose exuded a thin fluid. In both cheeks there were prominences at the sites of the parotid glands, which were large, firm and freely movable and measured about 3 by 3 by 0.5 cm. The submaxillary glands were also large and firm. The salivary glands could not be removed because of restrictions on the incision. The thorax was symmetric, with a wide costal angle and slightly flaring ribs. There was slight prominence of the costochondral junctions. The abdomen was moderately rounded. The extremities were pale and thin, and there was marked muscular atrophy throughout the body. The peritoneal cavity appeared normal. The liver extended 5 cm. below the xiphoid, and the diaphragm lay at the level of the fourth rib on the right and the fifth on the left. The intestines, especially the ileum, were moderately distended. No abnormalities were found in the pleural and pericardial cavities.

The heart weighed 32 Gm. The pericardium and valves appeared normal. The myocardium was pale, soft and somewhat flabby. The foramen ovale was closed.

The right lung weighed 90 Gm. There were a few strands of fibrin over the posterior surface of the lower lobe. On palpation the lower lobe was coarsely nodular, the nodules measuring up to 2 cm. It was purplish red, with a pale network of dilated lymphatics. On section the lower lobe contained many small irregular cavities, measuring 1 to 5 mm. in diameter, which contained pus and communicated with the small bronchi. There were firm yellowish areas of consolidation around these centers. There were similar bronchiectatic cavities in the lower portion of the upper lobe. The left lung resembled the right.

The spleen weighed 17 Gm. The contours were normal. The cut surface was firm and bright red, with small malpighian corpuscles.

The liver weighed 185 Gm. It was normal in shape, with a smooth, pale red surface mottled with yellowish areas. The lobular markings were indistinct but normal in pattern.

The pancreas appeared normal in size and consistency. On section the lobules were rounded. An attempt was made to dissect out the pancreatic duct, but this was not identified.

The adrenals were small, with a thin cortex containing no lipoid.

Each kidney weighed 27 Gm. The capsules stripped with some difficulty, leaving a pale, slightly granular surface with dilated stellate venules. The cut surface was pale. The pelves and ureters appeared normal in contour but bore a reddish and granular mucosa.

The lower portion of the esophagus was somewhat dilated, and the mucosa was thickened and granular. The stomach, duodenum, jejunum and appendix were normal. There were some dilatation and hypertrophy of the terminal portion of the ilium and of the colon.

The organs of the neck, the brain and the spinal cord were not removed because of restrictions on the autopsy. The other organs appeared normal.

Microscopic Examination: The myocardium appeared normal. There was serous atrophy of the subepicardial fat.

The abscess cavities of the lung were observed to have originated as bronchiectatic cavities. In some areas their walls were formed of granulation tissue; in other places they were lined by a layer of epithelium 2 to 6 cells in thickness. There were a few areas of squamous metaplasia. The lumens of the cavities contained débris, purulent material, bacteria and, in a few places, phagocytes full of large fat vacuoles. There were also abscesses in the lung parenchyma and areas of fresh lobular pneumonia. The Gram stain showed that the bacteria in the abscesses were gram-positive cocci in clumps; morphologically they resembled staphylococci.

The epithelium of the trachea was about 4 to 6 cells in thickness. There were numerous bacteria on the surface. The ducts of some of the mucous glands showed a tendency to squamous metaplasia. The mucosa bore an ulcer beneath which there was an infiltration of polymorphonuclear leukocytes and lymphocytes.

The malpighian corpuscles of the spleen were small but normal in number. Around them were collars of red cells, among which were a few polymorphonuclear leukocytes and phagocytes. The pulp was congested; in it were a few nests of red cells and phagocytes containing hemosiderin.

The liver was normal except for small amounts of hemosiderin in the liver cells and large amounts in the Kupffer cells.

In one section of the pancreas only occasional acini appeared normal. The majority formed cysts lined with flat or cuboidal epithelium containing granular eosinophilic material and concretions. The latter were composed of concentric rings of deeply eosinophilic material and resembled corpora amylacea. Some of the cysts were irregular in shape. There was a definite increase in the connective tissue between the alveoli and also in that between the lobules. The lobules therefore varied greatly in size, and in many cases they were fused together. The islands of Langerhans appeared normal in number and in appearance. Another section was similar to the first. Small numbers of lymphocytes and plasma cells infiltrated the interstitial tissue.

Study of the kidney revealed small areas of interstitial infiltration with plasma cells and mononuclear phagocytes. There were a few gram-positive cocci and minute gram-negative cocci in the infiltrated areas.

The submucosa of the jejunum showed a slight increase in connective tissue, but otherwise the tissue was normal.

In the mucosa of the ileum there was some increase in the number of plasma cells and lymphocytes. Otherwise the tissue was similar to that of the jejunum.

Bacteriologic Examination: The material from the left lung showed Staph. aureus, slightly hemolytic.

Anatomic Diagnosis: The diagnosis was cystic fibrosis of the pancreas; avitaminosis A (clinical); bronchiectasis with abscess formation due to Staph. aureus; lobular pneumonia; lipoid pneumonia (mild); acute fibrinous pleurisy; interstitial nephritis; acute splenic tumor, and hemosiderosis of the liver and spleen.

CASE 37 (XVIII).—C. H., a girl, was admitted to the hospital at the age of 8 months with the diagnosis of early celiac disease. The parents and two older siblings were living and well. The mother had spent seven months in a tuberculosis sanatorium four years earlier but had been well afterward. The patient was the result of the third pregnancy. There was no familial history of intestinal disease such as the patient's, but the mother had a sister who died at the age of 9 months of "carcinoma of the liver." The birth was normal; the weight at birth was 7

pounds and 12 ounces (3,515 Gm.). The child was never fed from the breast because the mother had had abscesses of the breast with the first baby. For the first three months the infant received a formula which contained cow's milk and Karo. There were large foul stools before the age of 2 weeks, while the child was still in the hospital. They were grayish and yellow or green on different occasions. The child always gained weight slowly. Feedings were always taken well, with no vomiting. Administration of viosterol in halibut liver oil was begun at 14 days, and this was changed to cod liver oil at 7 months. Orange juice was given at 20 days. At the age of 3 to 5 months the formula was grade B milk and 6 tablespoons of calcium caseinate to 1 quart (946 cc.) of milk and 6 ounces (177 cc.) of water. At 3 months the child began to receive jello, junket, ripe banana, scraped apple and fruit juices. At 4 months cereal was begun, and at 5 months strained vegetable and egg yolk were added. Fish and chicken were given for a few days before the child's admission. The appetite was excellent, and everything was consumed with relish. The infant sat alone at 6½ months and stood with support at 7 months, and the first tooth appeared at 8 months. The skin was dry but without eczema. After the age of 3 months there was constant discharge from the nose, with a cough which became progressively worse. The gain in weight was slow, none occurring between the ages of 5 and 8 months.

Physical Examination.—On admission the infant was small and active and did not appear ill (fig. 2). The weight was 6.3 Kg. There was a deep, almost brassy cough, which occurred in short paroxysms without whoop or vomiting. The abdomen was prominent and somewhat distended, the rectus muscles were somewhat separated, and there was a small umbilical hernia. There were dry rales at the bases of the lungs.

Laboratory Examination.—The hemoglobin content was 15.7 Gm. per hundred cubic centimeters; the red cell count was 5,000,000 and the white cell count 11,300, with 33 per cent polymorphonuclears, 62 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. The urine was normal. The Kahn reaction was negative. The dextrose tolerance test gave the following values: control, 67 mg. per hundred cubic centimeters; 1 hour, 89 mg.; 2 hours, 86 mg. The urine contained no sugar. The values of the intravenous tolerance test with 5 Gm. of dextrose were as follows: fasting, 61 mg. per hundred cubic centimeters; 45 minutes, 92 mg.; 75 minutes, 55 mg.; 2 hours, 54 mg.; 3 hours, 53 mg. The calcium content of the serum was 9.4 mg. and the phosphorus content 4.7 mg. per hundred cubic centimeters. The carbon dioxide-combining power of the plasma was 37.6 volume per cent. Serum cholesterol values were as follows: total, 107 mg. per hundred cubic centimeters; free, 36.6 mg.; combined, 70.4 mg.; ratio of combined to free, 1.92. The total dry weight of a sample of the stool was 46.9 Gm.; the neutral fraction weighed 6.7 Gm.; the free fatty acid, 11.95 Gm., and the total ether-soluble material (lipoids), 18.65 Gm. (39.8 per cent); the ratio of free fatty acid in the total ether-soluble material was 64 per cent. The lipase content of the serum (tributyrinase) was normal. The amylase content of the blood (viscosimetric method) was approximately 0.56 units per cubic centimeter (normal, 0.08 to 0.25). The reaction to tuberculin was negative. The results of culture of material from various sources were as follows: stools, negative for typhoid and dysentery on repeated examination; nose, Str. haemolyticus, Staph. aureus and diphtheroids, later a pure culture of Pneumococcus type XIX; throat, Staph. aureus, Str. haemolyticus and a few pneumococci; left ear, Str. haemolyticus, later also Staph. aureus; right ear, Str. haemolyticus, later also Staph. albus and aureus. The serum did not agglutinate with Bacillus typhosus, B. paratyphosus A, B and C,

Bacilli dysenteriae Sonne, Shiga or Flexner, Bacillus abortus, or Bacillus melitensis. At the age of 8 months roentgen study of the chest and of the gastrointestinal tract gave negative findings. The forearms showed no rickets. There were transverse lines in both radiuses at 9 months. At this time the chest appeared normal, and the temporal bones showed a suggestion of exudate in the mastoid cells on the left.

Course.—Bilateral otitis media appeared and did not respond well to myringotomy. Both mastoids became infected. The stools were so foul as to require the isolation of the patient. She was given a high caloric diet for celiac disease, which did not alter the stools. The child was discharged after two and one half months in the hospital at the age of 10½ months; the weight was 6 Kg. She was readmitted at the age of 1 year because of fever and weakness. The weight was 5.3 Kg. Furuncles were present in the scalp. The abdominal distention had increased, and there was gluteal wasting. The appetite had decreased. At this time the hemoglobin content was 19.6 Gm. and the red cell count 4,750,000. Roentgen study of the chest showed bronchopneumonia, with heavy shadows in the lower part of the pulmonary field on the left, which were consistent with bronchiectasis or with multiple abscesses of the lung. The patient continued to lose weight and strength. Colonic irrigation produced great quantities of extremely foul grayish-green feces. The child was given iron, brewers' yeast, percomorph liver oil and, in the last three weeks, parenteral injections of liver extract. Nine days before death bronchopneumonia developed, and culture of material from the throat showed the type VI pneumococcus. The patient died three months after admission.

Autopsy.—The age at death was 14½ months, the weight 5.72 Kg. and the length 72 cm.

Gross Examination: The body was emaciated. The protuberant abdomen had a circumference of 48 cm. The anus was red, and the rectal mucosa protruded from its orifice and was inflamed. The arms and legs showed marked wasting. The peritoneal cavity contained 5 cc. of straw-colored fluid. There was a small amount of delicate fibrinous exudate over the serosal surfaces of the small intestine. The terminal portion of the duodenum joined the jejunum through an opening in the transverse mesocolon, which was 4 cm. in diameter. A finger passed through this opening came up between the two layers of mesocolon. The pleural and pericardial cavities appeared normal.

The ductus arteriosus admitted a fine probe.

The left lung bore a few fibrous tags on the posterior surface of the lower lobe. The anterior margin of the upper lobe, the lingula and the posterior surfaces of both lobes were purple, noncrepitant and depressed. The remainder of the lung was pink and aerated. The large bronchi were full of bright yellow, thick pus, which extended into the small bronchi. The walls of the small bronchi were somewhat thickened, and the lumens were slightly dilated. The hilar lymph nodes were enlarged and grayish red to deep red; they measured up to 1.5 cm. in length. The right lung bore subpleural punctate hemorrhages. The apex was purple, firm and sunken. The inferior portion of the lower lobe contained areas of consolidation, the largest measuring 2 cm. in diameter. The cut surface resembled that of the left lung. The larynx, trachea and main bronchi contained thick yellow mucoid pus. The mucosa was pink.

The spleen weighed 14 Gm. The cut surface was deep purplish red with indistinct malphighian corpuscles.

The liver weighed 380 Gm., was of normal consistency and was purplish red. The gallbladder and bile ducts were normal.

The pancreas was pinkish gray and of normal consistency. The main duct was patent throughout. There was some irregularity in the size of the lobules, and some of them were adherent to one another.

The intestines were thin walled. The upper portion of the small intestine contained fecal material, which was soft and bright yellow. The ileum and colon contained solid gray fecal material, which was so dry that the surfaces bore the imprint of the lymph follicles. The cecal mucosa appeared congested.

The heart, adrenals, kidneys, pelvic organs and ribs showed no abnormalities.

A thick green exudate was found in the ethmoid cells on the left and in the right maxillary antrum. The middle ears and mastoids appeared normal.

Microscopic Examination.—In one section of pulmonary tissue the bronchi were somewhat dilated and were filled with an exudate of polymorphonuclear leukocytes, phagocytes and débris. The bronchial epithelium was infiltrated with lymphocytes, plasma cells and a few polymorphonuclear leukocytes. Some of the alveoli contained a fresh purulent exudate. The remaining alveoli were emphysematous. The Gram stain showed that the bronchial and alveolar lumens were filled with clumps of gram-positive cocci resembling staphylococci. Another section was similar to the first except that the major portion of the alveoli contained an exudate.

In the trachea there was a slight inflammatory reaction of the mucosa. The epithelium was of normal height.

In the spleen the malpighian corpuscles were partly depleted of lymphocytes. In the centers of the corpuscles were large cells with deeply eosinophilic cytoplasm, some of which showed nuclear fragmentation. The pulp contained many red cells and some yellow pigment which stained for iron.

Most of the liver was normal. Beneath the capsule there was a zone where the fibrous tissue was increased around the portal areas. A few polymorphonuclear leukocytes were present, and there was some proliferation of the bile ducts. A number of multinucleated liver cells were seen near this. The stain for iron showed a small amount of hemosiderin in both liver and Kupffer cells. The trichrome stain showed an increase in connective tissue beneath the capsule and, to a lesser extent, around the portal areas throughout the section.

The acini of the pancreas varied greatly in size. Many resembled cysts and contained eosinophilic concretions, some of which were laminated. Some acini contained desquamated epithelial cells, lymphocytes and rare polymorphonuclear leukocytes. The epithelium was flattened. There was a marked increase in intralobular and interlobular connective tissue, in which occasional polymorphonuclear leukocytes and lymphocytes were noted. Some of the ducts were dilated and contained eosinophilic material. The islands were normal. Von Kossa's stain revealed that occasional concretions were calcified in the center (fig. 8).

The mucosa of the intestines was congested and contained lymphocytes, plasma cells and eosinophils. The lymph follicles were somewhat depleted of cells.

The other organs showed no abnormalities.

Bacteriologic Examination: Culture of material from the ethmoid sinus yielded Staph. aureus haemolyticus; of material from the peritoneum, no growth, and of the blood, no growth.

Anatomic Diagnosis: The diagnosis was celiac disease (clinical); cystic fibrosis of the pancreas; purulent laryngotracheobronchitis; lobular pneumonia due to Staphylococcus and Streptococcus; acute ethmoiditis on the left, due to Staph. aureus haemolyticus; acute maxillary sinusitis on the right; early biliary cirrhosis of the liver; congenital anomaly of the transverse mesocolon; patent ductus arteriosus, and hemosiderosis of the liver and of the spleen.

Case 44 (XX).—M. D., a girl, was the first child. She was first admitted to the hospital at the age of 23 months with the complaint of hunger and delayed development. She was born at term by breech delivery. The weight at birth was 6 pounds and 1½ ounces (2,764 Gm.). While in the hospital the infant lost 1 pound (454 Gm.) but otherwise appeared normal. Because of insufficient milk she was not nursed. The formulas were as follows: For the first three months, lactic acid, milk, Karo and water; for the next three months, malted milk; then, for a period not stated, soft-curd milk with chocolate; since the age of 13 months, evaporated milk and water. Administration of cereals was started at 4 months and stopped at 13 months, after which the child had very little starch. Vegetables were first given at 6 months; liver, lamb chops and bacon, at 7 to 9 months, and orange juice, at 2 months.

Cod liver oil and viosterol were given in winter but not in summer. At the time of admission the girl was being given all vegetables except potato. Her development had been delayed. The weight was as follows: at 6 months, 9 pounds (4,082 Gm.); at 12 months, 11 pounds (4,990 Gm.); at 23 months, 15 pounds and 6 ounces (6,974 Gm.) The first tooth appeared at 12 months; she sat at 12 months and walked with support at 10 months but had never walked alone. She was beginning to talk. She ate a great deal, yet never seemed satisfied and never gained well. At the age of 4 months, when first given cereal, she had large bowel movements. Before the age of 1 year she had persistent diarrhea, with about 8 stools a day; these were greenish and foul-smelling. During the twelve months before admission the stools were said to have numbered 1 or 2 a day; they were brown and soft but not frothy. Rectal prolapse occurred frequently. There was no nausea or vomiting. There had been no acute illnesses. The child was observed in the clinic for two weeks, being given a diet normal for an infant, and was then admitted for study.

Physical Examinaiton (fig. 2*B*).—The child appeared active but small. The head was large, with moderate frontal bosses. The buttocks were flat and the extremities thin and underdeveloped. The heart and lungs were normal. The edge of the liver was palpable, but the spleen and kidneys were not felt. The patient kept her head turned to the left.

Laboratory Examination.—The hemoglobin content was 13.6 Gm., the red cell count 4,600,000 and the white cell count 8,000, with 51 per cent polymorphonuclears, 46 per cent lymphocytes and 3 per cent eosinophils. The Kahn reaction was negative. The urine was normal. The stools numbered 1 to 3 daily; they were large, loose, gray and soapy, with foul odor. Repeated cultures were negative for typhoid and dysentery organisms. Analysis of stool showed that the moist weight was 57 Gm., with 67 per cent water; the ether-soluble material was 53.5 per cent of the dry weight and the material soluble in purified petroleum benzine 50.8 per cent, with free fatty acids in the sum of neutral and free fatty acid fractions, 69.1 per cent, and free fatty acids as soaps in the total free fatty acids, approximately 18.2 per cent. The calcium content of the blood serum was 10.2 mg. per hundred cubic centimeters; phosphorus, 4.3 mg.; albumin, 4.09 Gm., and globulin, 1.86 Gm. The dextrose tolerance test, after 1.75 Gm. of dextrose per kilogram of body weight had been given by mouth, gave these values: control, 52 mg. per hundred cubic centimeters; thirty minutes, 157 mg.; one hour, 204 mg.; two hours, 78 mg. There was no sugar in the urine. Roentgen study showed no evidence of rickets or syphilis. With a barium sulfate enema the colon and emptying time appeared normal. A series of roentgenograms showed that the gastrointestinal tract was normal except for some dilatation of the distal portion of the ileum.

Course.—The stools were typical of celiac disease. Proctoscopic examination showed nothing abnormal except prolapse of the rectal mucosa. The child was hungry but failed to gain with a diet standard for an infant. She was at first given a diet high in calories and soon after was transferred to a diet for celiac disorder, after which she did somewhat better. A tentative diagnosis of celiac disease was made.

For the year after her discharge at the age of 25 months she was followed in the clinic; she showed marked improvement with the regimen for celiac disease (fig. 2 *C*). The diet on her discharge consisted of 1¼ cups of banana powder (Merck), ½ cup of protein milk, 3½ cups of water, 3 eggs, 4 tablespoons of scraped beef, 2 tablespoons of vegetables, 6 tablespoons of cheese and 6 bananas. The girl gained weight and strength and ate ravenously. The stools remained fairly large, soft, yellow and foul. In other respects the child appeared normal, healthy and active.

At the age of 3 years the girl was readmitted to the hospital for operation for congenital torticollis. Her weight on admission was 27 pounds and 3 ounces (12.3 Kg.). On the second day after operation a temperature of 103.5 F. developed, and with it there appeared signs of pneumonia. Bilateral otitis media became evident during the following week. The patient died three weeks after the operation.

Autopsy.—This was done two hours post mortem. The age at death was 3 years and 2 months, the weight 9,750 Gm. and the length 92 cm.

Gross Examination: The skin was pale, and the body well nourished and fairly well developed. Over the right occiput there a small decubitus ulcer. A transverse scar 5 cm. in length extended from the suprasternal notch over the right clavicle. The chest was normal in contour. There was moderate abdominal distention. The subcutaneous fat was moderate in amount, and the muscles were well developed. The peritoneal cavity appeared normal. The liver extended 4.5 cm. below the xiphoid. The diaphragm was high and lay at the level of the third interspace on the right and the fourth rib on the left. The pleural cavities contained no free fluid, but the pleural surfaces bore a delicate fibrinous exudate.

The heart weighed 58 Gm. It appeared normal except for a patent foramen ovale with an opening 8 mm. in each diameter. The aorta was normal.

The right lung weighed 176 Gm. There were several small abscesses in the middle and in the lower lobe. The largest lay in the middle lobe, was multilocular and measured 1 cm. in diameter. The bronchial mucosa was thickened and congested. The tissue between the abscesses was mottled and uneven in consistency. The left lung weighed 158 Gm. It resembled the right. Small abscesses were scattered in both lobes.

The spleen weighed 26 Gm. It was bright red and soft, and the malpighian corpuscles were pale.

The liver weighed 738 Gm. It was large and pale yellow, and the margins were rounded. The lobulation was normal. The bile passages were normal.

The pancreas appeared to be about half the normal size, but it was not weighed. It was flabby and rather soft, but on section it was somewhat gritty. The lobules were irregular and appeared rounded. A prolonged search for the pancreatic duct revealed only a small duct which extended 8 mm. from the ampulla and was then lost in fibrous tissue.

The esophagus was moderately dilated in the lower half, and the epithelium was slightly thickened and congested. The stomach was small and normal. The

small and large intestines appeared normal except for moderate dilatation, especially of the colon. The colon contained a large amount of soft, putty-like, pale yellow fecal material throughout its length. There was no foul odor.

The other organs appeared normal.

Microscopic Examination: A section of the middle lobe of the right lung was taken through the multilocular abscess, which appeared as many small abscesses. Each abscess contained necrotic material surrounded by a wall of granulation tissue. In the remaining lung tissue the alveolar and bronchiolar walls were thickened and infiltrated with plasma cells and mononuclear phagocytes, and there was pus in the lumens of the bronchioles. The Gram stain revealed many pairs and short chains of gram-positive cocci in the abscesses. In another section the bronchi contained purulent material, and their walls were edematous and infiltrated with polymorphonuclear leukocytes and lymphocytes. There were irregular patches of recent bronchopneumonia.

There was congestion of the spleen. Small zones of red cells and a few polymorphonucler leukocytes were observed around the malpighian corpuscles. A little hemosiderin was present within phagocytes.

Nearly every liver cell was distended with a single large fat droplet. Otherwise the liver was normal.

A section from the body of the pancreas showed that the tissue (fig. 10) was composed of primary lobules about the size of a low power field, each of which was surrounded by and infiltrated with dense fibrous tissue. Within each lobule there were irregular clumps of tubules or cysts. Most of the tubules were composed of columnar epithelial cells without granules around a larger or smaller lumen, in which was a mass of homogeneous eosinophilic material resembling hyaline casts or corpora amylacea. The larger cysts were lined by flattened or cuboidal epithelium and contained granular protein precipitate or a large mass of hyaline material. These cysts and tubules were separated from one another by dense fibrous tissue in which there were occasional lymphocytes. None of the acini appeared capable of normal function. The islands appeared normal in number. Many were surrounded by a widened peripheral sinus, but they were not otherwise abnormal. There was no evidence of acute inflammation. A section from the head of the pancreas was similar to the section from the body. Many of the lobules were replaced by fat. The islets were small and less numerous than in the first section.

The cortical lipoid of the adrenal was scanty. There were hemorrhages in the capsule and in the fat near the gland.

A section of kidney was normal.

In the esophagus there was extensive ulceration of the epithelium, leaving a surface of submucosa densely infiltrated with lymphocytes and large phagocytes. Beneath the surface the submucosa was greatly thickened by edematous and recently formed fibrous tissue in which many fibroblasts and congested vessels were noted.

The stomach was normal except for several small collections of lymphocytes in the deeper layers of the mucosa.

The mucosa of the jejunum was infiltrated with lymphocytes, and large phagocytes and fibroblasts were present. The infiltration was most marked in the villi, which were thereby much thickened. The infiltration was about equal in degree throughout the mucosa (fig. 4).

The colon was similar to the jejunum except that the infiltration of the mucosa was less marked.

The rib was normal. There was no evidence of old or recent rickets.

Bacteriologic Report: Cultures of the lung showed Str. haemolyticus and Staph. aureus haemolyticus. Cultures of the blood, material from the pleural cavity and the spinal fluid were negative.

Anatomic Diagnosis: The diagnosis was celiac disease (clinical); cystic fibrosis of the pancreas; congenital atresia of the pancreatic duct (?); chronic enterocolitis; hypertrophy of the colon; torticollis (clinical); operative division of both heads of the right sternocleidomastoid muscle; otitis media (clinical); abscess of the middle lobe of the right lung; purulent bronchitis; lobular pneumonia (Str. haemolyticus and Staph. aureus haemolyticus); acute fibrinous pleurisy; acute splenic tumor; fatty liver; ulcers of the esophagus and congenital malformation of the heart (patent foramen ovale).

Summary.—This patient was considered to have fairly characteristic celiac disease, which began at the age of 4 months, with underdevelopment, malnutrition and typical stools. Chemical examination of the stools showed an approximately normal percentage of digested fat, a finding usually thought to eliminate the possibility of pancreatic steatorrhea. The impression that the child had celiac disease was strengthened by her extraordinary improvement on a diet for this condition (fig. 2 *B* and *C*). At autopsy no normal acini were found in the pancreas (fig. 10). The pancreas appeared to consist entirely of fibrous tissue, cysts and round islands of Langerhans. The pancreatic duct could not be followed more than 8 mm. from the ampulla of Vater. Death resulted from postoperative bronchopneumonia.

CASE 28 (XXII).—This was contributed by Dr. Paul Klemperer of Mount Sinai Hospital. J. D., a sister of M. D. (case 23 [XV]), was a first child and was born approximately eighteen months before her brother. She was under the private care of a series of physicians, and consequently the details of her clinical course were difficult to ascertain. Her mother stated that she presented a feeding problem and had loose stools from birth. Her diet was changed many times. Because of intolerance of fats the fat of the diet was limited, and it is probable that she did not receive adequate amounts of the fat-soluble vitamins A and D. She did not have symptoms of ocular disease. Her development was subnormal. At 4 months she began to have a discharge from the nose and at 7 months a chest cold and cough developed. The infant died at the age of 8 months.

Autopsy was performed at the Mount Sinai Hospital. The infant was poorly developed and nourished. The following note occurs on the protocol: "An unusual picture was presented by the pancreas. There was diffuse pancreatitis and marked dilatation of the ducts. The picture was one of chronic pancreatitis of unexplained etiology." The accessory pancreas in the jejunum presented a similar picture.

The anatomic diagnosis was acute and chronic mucopurulent tracheitis; bronchitis and bronchiolitis with bronchial dilatation; chronic peribronchitis; suppurative pneumonia (middle and lower lobes, right lung); chronic pneumonitis (lower lobe, right lung); bronchopneumonia (upper lobe, right lung; lower lobe, left lung); fibrinous pleuritis (middle and lower lobes, right lung); parenchymatous degeneration of the liver; acute congestion of the viscera, and aberrant pancreas in the jejunum.

Dr. Klemperer has permitted me to study the sections of the pancreas and of the lung. The pancreas was closely similar in appearance to that of M. D., the brother (case 23 [XV]), and the lung was also similar to the brother's except that there was more marked hyperplasia of the bronchial epithelium in the present case.

NOTE.—Reports of additional cases are included in the author's reprints.

DISCUSSION

DR. FREDERIC H. BARTLETT, New York: I should like to cite the instance of an infant who was admitted to the hospital at the age of 6 weeks and died at 3 months. Her weight at birth was 7 pounds and 5 ounces (3,317 Gm.), and she was well up to the eighth day of life. She was weaned because of the mother's infected breast. Many changes were made in her food: She was given breast milk, three trials at similac, breast milk again and protein milk; before she died she was taking protein milk and breast milk. Her appetite, as a rule, was fairly good during all this period. That is curious because her stools were at times loose and at times good. She did not gain weight, and her failure to gain was so persistent that my associates and I were puzzled. At the age of 7 weeks the child had pulmonary symptoms, which went on until she died, at the age of 3 months. This pulmonary condition was clinically diagnosed as pneumonia. The pathologic changes in this child were bronchopneumonia, cystic fibrosis of the pancreas, patent ductus arteriosus and patent foramen ovale.

The mother had another child, who died at the age of 8 weeks; she made this extraordinary statement: "Whatever my first baby had, this baby has too." It is interesting that this condition has been found in members of the same family. In such cases there is this fairly clear clinical entity: The infant is born looking well, has the proper weight and is fed with care; however, the child does not gain weight in spite of proper food; the bowels may or may not be loose; pulmonary infection supervenes. There is no vomiting, but the infant simply refuses to survive. As physicians look back over their records, they are often puzzled as to why a child who looked all right and who seemed to be in good condition died within the first four or five months of life with nothing to account for it.

In summary: Cystic fibrosis of the pancreas is a nucleus about which is being crystalized a symptomatology. The condition should be considered a new clinical entity, and I feel that Dr. Andersen has contributed a great piece of work in that connection.

DR. BENJAMIN KRAMER, Brooklyn: I wish to record 2 cases which I believe belong to this group; the patients were members of the same family. The little girl died at the age of 7½ months and the boy at the age of 2½ years. The clinical symptomatology will be presented in a detailed report by my associates. I want merely to present a few sections illustrating the pathology of this disease.

The first is a section from a normal pancreas, showing the meager amount of connective tissue between the acinar tissue and some of the islands of Langerhans. The second section, from the pancreas of the 7½ month old patient, shows the extensive fibrosis of the gland, with a few isolated acini and an apparent increase in the amount of island tissue. There are no cysts of the acinar tissue, but there is dilatation of the ducts. Other sections from the same pancreas show dilatations of the acini, which were filled with pink-staining material. The sections from the lung show a purulent exudate in the bronchioles, with infiltration of the bronchial walls and involvement of the peribronchial tissue. Emphysema of the lung is also present. A section of the liver shows almost complete filling of liver cells with fat. The nuclei are compressed to the cell periphery. Permission for an autopsy on the older child was not obtained, but the clinical course was so similar to that of his sister that there is little doubt that both suffered from the same disease.

Another interesting point in this connection was the early appearance of pulmonary symptoms. Both children had respiratory symptoms, including wheez-

ing and cough, during the first few months of life. These recurred from time to time. The terminal pulmonary condition began with asthmatic bronchitis, which developed into purulent bronchitis, bronchiolitis and finally bronchopneumonia. No histologic evidence of vitamin A deficiency was observed.

My associates and I favor the view that this is a distinct clinical entity which may be both congenital and familial. Although the symptoms may superficially resemble those of celiac disease and the patient may temporarily respond favorably to a regimen for the latter condition, the early onset of symptoms, which often begin at birth, the high mortality of this disease, the marked tendency of these patients to contract fatal diffuse bronchopneumonia and the peculiar pancreatic lesion separate this condition definitely from true celiac disease, which has been described by Gee and others.

DR. WILBURT C. DAVISON, Durham, N. C.: Could celiac disease in children, which apparently is the same syndrome as sprue in adults, be due to temporary damage or impairment of the pancreas? The activity of the duodenal enzymes and the ability to digest and absorb carbohydrates are reduced in celiac disease.

DR. LOUIS K. DIAMOND, Boston: During the past few years Dr. Blackfan, Dr. Wolbach, Dr. Farber and Dr. May have been engaged in correlating the clinical and pathologic manifestations of infants and children who presented these important changes in the pancreas.

In addition to 28 examples of this condition in its most severe forms, noted prior to 1935, they have observed minor degrees of changes of this nature in well over 100 patients of ages ranging from birth through early childhood.

The histologic picture in the 28 severely affected children has been strikingly uniform and apparently similar to that described by Dr. Andersen. The sequence of events, as outlined by Blackfan and Wolbach in 1933, appears to be as follows: An abnormal secretion is produced. This becomes inspissated, which leads to distention of the ducts and atrophy of the acini. Subsequently fibrosis occurs. The cause of this pancreatic lesion has not been determined. There are insufficient data concerning the role which the lesion plays in producing the clinical entity known as celiac disease.

It is to be expected that any interference with the absorption of fat might interfere with the absorption of vitamin A, but direct chemical studies of the blood and of the liver of 1 patient who at necropsy had these severe lesions in the pancreas showed that this child was able to absorb vitamin A if an adequate quantity was present in the food. Consequently, although absorption of vitamin A might be diminished, it would not be entirely absent if the patient's diet were adequate and especially if infection were not a complicating factor.

In this series of 28 cases, most of the patients were suffering from severe nutritional disturbance, complicated in many instances by chronic bronchopneumonia. Pathologically, 2 patients also showed the changes of vitamin A deficiency, 3 had meconium ileus, and 1 had hepatic cirrhosis. The symptoms of disease appeared early in life: at birth in 2 infants, before the age of 2 months in 2 others and before 9 months in the remaining 22 patients.

That this lesion is the underlying cause of celiac disease seems questionable. In only 3 of the 28 children with the severe fibrosis in the pancreas did the symptoms suggest a possible celiac state, and in only 1 instance were there confirmatory laboratory findings such as a flat dextrose tolerance curve, the clumping of the barium sulfate in the small intestines seen in roentgen study of the gastrointestinal tract, osteoporosis observed by roentgen examination and deficiency of minerals.

Also against the suggestion that the celiac syndrome is always the result of this particular pancreatic lesion, or even that it usually may play a part in its production, is the authoritative opinion of Parsons, who recently reviewed the necropsy observations in 12 cases of celiac disease and was unable to detect any pathologic changes in the pancreas.

DR. L. EMMETT HOLT JR., Baltimore: I hope Dr. Andersen will tell us how she feels about the relation of vitamin A deficiency to this picture. Some of the patients described in the literature were classified as having vitamin A deficiency; so I suppose there was definite evidence of this in some cases and not in others.

DR. FREDERIC W. SCHLUTZ, Chicago: I should like to know whether in the cases reported in the literature the pulmonary symptoms preceded the pancreatic symptoms. About a year ago my associates and I had under our care a boy 6 years of age who had had pulmonary symptoms and bronchiectasis since infancy and what appeared to be symptoms of celiac disease since the age of 4 years. On admission to the hospital the boy seemed to have pronounced evidence of the latter condition along with advanced bronchiectasis. Further study of the case, however, convinced us that he did not have celiac disease but was suffering from chronic fibrotic disease of the pancreas. The boy died of terminal pneumonia. At autopsy complete chronic cystic fibrosis of the pancreas and extensive bronchiectasis with a superimposed recent pneumonic process were noted. There was no gross or microscopic evidence of vitamin A deficiency. The possible association of vitamin A deficiency with this condition is interesting and should be carefully checked.

DR. DOROTHY H. ANDERSEN, New York: I have had no experience with sprue. It seems to me that the mechanism in pancreatic disease is complicated; I think the condition must be related in some way to sprue, but as yet this relation is unknown.

In regard to the cases presented, I should have said that in one third of the cases of the entire series there was fatty liver.

My statement about celiac disease did not imply that the pancreatic lesion is the cause of celiac disease in all cases but indicated that all of our patients with cystic fibrosis of the pancreas who survived the first year of life were clinically indistinguishable from those with the classic picture of celiac disease and that therefore it seems reasonable to refer to a celiac syndrome which may be produced by this disease entity or by one or more others.

In my search through the literature for cases of celiac disease in which there was autopsy with examination of the pancreas, I have found only 11. There were many more cases of celiac disease in which autopsy was done without examination of the pancreas. Clinical celiac disease is not as rare as the scarcity of reports would indicate, but I feel that in many instances other conditions observed post mortem, such as bacillary dysentery or the pancreatic lesion, may have altered the diagnosis. It would seem that the patients with celiac disease who survive to adult life have not had a severe pancreatic lesion. At present I do not know how to distinguish cystic fibrosis of the pancreas from early celiac disease except by examination of the duodenal juice for enzymes or by postmortem study of the pancreas.

The question as to whether vitamin A deficiency and the pulmonary lesion precede the pancreatic symptoms is an involved one. There is good evidence that the pancreatic lesion is present at birth or early in life, and in only 2 of the 44 patients who survived the neonatal period was there any evidence of infection during that period. In some cases the digestive symptoms were not noticed until after the

neonatal period. If the lesion is present at birth—and it is known that it can be present because it has been observed in 5 patients who died before the age of 1 week—one cannot imagine that it is due to dietary vitamin A deficiency. There remains the possibility that the pancreatic lesion results from vitamin A deficiency during the time of gestation; congenital vitamin A deficiency is a question about which little is known.

I do not know the cause of this disease. There is a good deal of evidence to show that at least in the majority of cases the pancreatic lesion comes first. In only 12 of the 44 cases was there histologic proof of vitamin A deficiency; in 2 there was xerophthalmia and in all 12 cases there were metaplastic changes in the epithelium. All the 44 patients had pulmonary lesions which were primary in the bronchi, and many had bronchiectasis. Of 12 previously reported cases of vitamin A deficiency in infants on whom postmortem examination was done, the pancreas was described in 7, and in all 7 cystic fibrosis of the pancreas was noted. This is too high a percentage to be accidental. The evidence at hand suggests that the pancreatic lesion prevents the normal digestion and absorption of fats, the poor absorption of fats results in poor absorption of the fat-soluble vitamin A and the epithelial metaplasia, bronchiectasis and bronchopneumonia are consequences of vitamin A deficiency. I do not understand why metaplasia of the epithelium is present in some cases and not in others.