particularly indicated in this case owing to the history of sensitivity when penicillin was given one year previously.

SUMMARY

A child with apparently minor illness when examined on admittance to hospital was given 500 mg. of erythromycin intramuscularly because of laryngeal redness and enlargement of cervical nodes. Within a few minutes, generalized convulsion occurred, and 20 minutes after the antibiotic was given the patient was dead. At autopsy, conditions typical of anaphylactic shock were observed.

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Fibrocystic Disease of the Pancreas and Diabetes in an Adult with Unusual Pulmonary Manifestations

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CYSTIC FIBROSIS OF THE PANCREAS is predominantly a disease of infancy. Although the cause is still unknown, much progress has been made toward a better understanding of the disease since the first complete description in this country by Anderson[1] in 1938. Several years later, when the widespread involvement of all the mucus-producing exocrine glands in the disease was described, the term *mucoviscidosis* was suggested because of the thickening of the mucus which occurs. More recently di Sant 'Agnese[5] pointed out that both names are improper because the pancreas is usually but not always involved and the disease is not confined to the mucus-producing exocrine glands. In the light of present knowledge, he suggested the term generalized *exocrinopathy* as being more accurate from a descriptive point of view.

In the American and English literature there are few references to cystic fibrosis of the pancreas in adults. In 1955 di Sant 'Agnese[5] reported his findings in 325 patients he observed over a 15-year period in Babies Hospital, Columbia University. The oldest patient in the series was 19 years of age. In 1946, Hellerstein[8] reported a case in a 35-year-old Negro male who died 12 hours after admission to a hospital with Friedlander's pneumonia; there was no antecedent history and the diagnosis of cystic fibrosis of the pancreas was based upon the incidental observation at necropsy of numerous cysts and diffuse fibrosis in the pancreas. Hellerstein[9] recently called attention to the fact that many cases of cystic fibrosis of the pancreas in adults were reported in the German literature and cited a reference to the adult cases in *The System of Pathology* by Henke-Lubaesch. In 1954 Baxter[2] reported experience with the disease at Ohio State University and stated that before antibiotics the life span of patients was measured in months or a very few years, perhaps only one or two. He indicated that with proper management some patients may live until they are 18 to 22 years of age. This obvious disparity in survival ages reported by previous German and present-day observers leads one to wonder whether the German adult cases reported might not be attributable to cystic fibrosis following pancreatitis.

Di Sant 'Agnese[5] has proposed the following four criteria for present-day clinical diagnosis of cystic fibrosis of the pancreas:

1. Pancreatic deficiency.
2. Pulmonary pathologic changes
3. Excess chlorides in sweat.
4. Family history (assists only).

These criteria are based on his observations that there is complete absence of pancreatic exocrine function in 90 per cent of the patients; pulmonary pathologic change occurs in all patients at some time in the disease; and finally, abnormal sweat with increased chloride and/or sodium content occurs in 99 per cent of patients. Absence of the disease in siblings does not rule out the disease in the patient.

In reviewing the literature, we were unable to find a single reference to cystic fibrosis of the pancreas and associated or co-existing disease since 1938. In 1950 Molnar[11] reviewed the literature up to that time in a case report and made no reference to associated diabetes.

In 1955 di Sant 'Agnese[6] presented an excellent and comprehensive review of the pulmonary manifestations of fibrocystic disease of the pancreas, one of the unusual aspects of the case herein presented. He said that respiratory involvement has a variable onset from the age of a few weeks to several years, occurring between six months and two years of age in the great majority of cases. It must be recognized, he pointed out, that this is in reality a generalized disease of which the pancreatic and pulmonary lesions are only one expression. The 292 patients reported upon had, at some time during their illness, pulmonary disease of variable degree —severe in most instances and accounting for 90 per cent of the deaths. He made the observation that if patients reached late childhood without irreversible damage being done to their lungs, they seemed to improve and the degree of clearing in the roentgen picture was surprising. With regard to prognosis in this group, he suspected that at least many would go on to chronic pulmonary disease as adults. The oldest in the reported group was 18 years of age.

The following unusual case of cystic fibrosis of the pancreas is presented because the patient is an adult who has associated diabetes and the pulmon-

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ary disease has not followed the usual course described in the literature.

CASE REPORT

The patient, a 24-year-old white woman, was admitted to the hospital on October 13, 1947, because of persistent and severe chronic bilateral lung disease characterized by a chronic productive cough and roentgenographic evidence of extensive pathologic change in both lungs which was refractory to antibiotic therapy.

The patient's mother said that the patient had begun to have a nonproductive cough when about six months of age. The cough was worse at night and it often seemed as though her chest were filled with phlegm. She did not receive formal medical care in childhood and she was not examined by a physician until she was 17 years of age.

When she was approximately a year old, it was first noticed that her abdomen was distended, and this condition persisted from then on. Although her appetite was good in early childhood, she was decidedly underweight and seemed to have difficulty in assimilating food. It was also reported that her stools, which were frequently loose, had a bad odor. The patient had had measles, chicken pox, and mumps before she began going to school. These diseases were apparently uncomplicated and did not aggravate the cough.

She attended primary school without significant disability. In high school her weight increased to 117 pounds, she participated in sports (volley ball and basketball) and led a normal social life. Because of the abdominal distention the patient thought she was overweight and attempted to reduce by dieting. During this period, she recalled, she perspired excessively and was often "drenched with sweat" following mild physical activity such as dancing.

She consulted a physician for the first time in her life in October of 1949, at age 17, because of an upper respiratory tract infection, which responded to antibiotics. The result of a tuberculin test at this time was negative. An x-ray film of the chest showed a slight increase in the bronchovascular markings in the right second anterior interspace, which was regarded as of no clinical significance. A film taken three months later (Figure 1) was unchanged.

Following graduation from high school the patient was employed as a telephone operator. At age 20 she was married. Six months later she consulted a physician because of loss of weight, polydipsia and drowsiness. A diagnosis of diabetes mellitus was made, and an appropriate diet and the use of 55 units of insulin daily were prescribed. An x-ray film of the chest, taken on May 17, 1954, because the cough had become productive, showed scattered bilateral mottled infiltrates which resembled the lesions of tuberculosis. The results of a tuberculin test and of guinea pig inoculation of sputum were negative. Later a "fungus" was said to have been cultured from a specimen of sputum. Penicillin and terramycin (di-oxytetracycline) were given over a period of several weeks with no change in the symptoms referrable to the respiratory tract. An x-ray film of the chest taken April 13, 1955 (Figure 2) was unchanged when compared with the film taken in 1954, but showed extensive changes when compared with the film taken in 1950 (Figure 1).

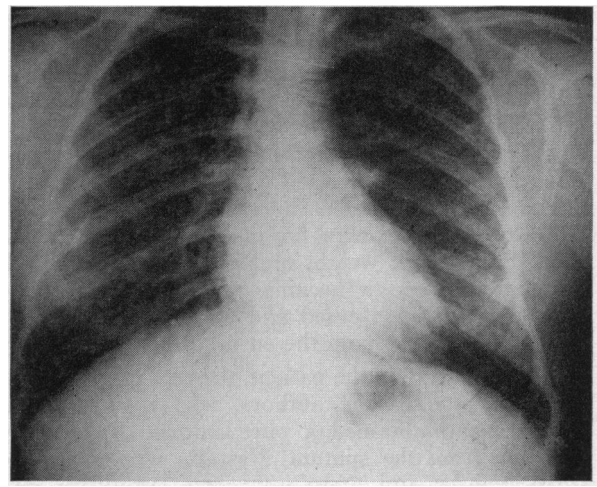

Figure 1.—X-ray film of chest taken January 10, 1950, when patient was 17 years of age. Interpreted as showing a slight increase in the bronchovascular markings, most prominent in the right second anterior interspace.

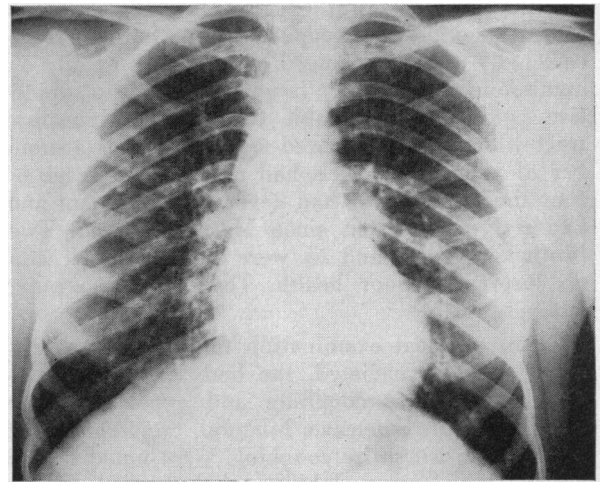

Figure 2.—X-ray film of chest taken April 13, 1955, showing the extensive roentgenographic changes since 1950. Patient 21 years of age at this time. This film is identical with one taken May 17, 1954. Note the prominent hilar shadows and the mottled "snowflake" infiltrates resembling tuberculosis. The result of a tuberculin test was negative.

On July 6, 1956, symptoms and signs of an intestinal obstruction developed. The abdomen was decidedly distended and felt doughy to palpation. A plain film of the abdomen was interpreted as showing possible obstruction in the mid small bowel and exploratory laparotomy was done. The surgeon stated that the proximal three feet of jejunum was reddened, dilated and filled with a gummy, putty-

like material which was also present in the large bowel. He found no band, tumor or other mechanical cause for the obstruction other than the existence of the above described material. The pancreas felt firm and contained no masses. Pancreatic biopsy was not attempted because of the patient's condition, although a diagnosis of suspected pancreatic insufficiency was made. Entozyme® was prescribed for the patient following her discharge from the hospital. She gained weight and got along fairly well although the cough became more severe, production of sputum increased and diabetes became difficult to control during the ensuing months.

In April of 1957 the patient, then 24 years of age, consulted one of the authors, who regulated the diabetes and obtained a pure culture of *Candida albicans* from the sputum. Nystatin was given for three months and there was some subjective improvement. Because roentgenographic conditions in the chest were unchanged after this interval, the patient was admitted to the Santa Barbara General Hospital on October 13, 1957, for further study. On admission she was expectorating daily several ounces of odorless mucopurulent sputum which occasionally was blood tinged. The chief complaint on admission was excessive fatigue. She had no subjective complaints referrable to the gastrointestinal tract which she considered significant. For a number of years her bowels had moved an average of four times daily. She had never been pregnant and had not menstruated since March of 1956. Two brothers, aged 27 and 25, were living and well with no history of poor health. There were no other siblings.

Upon physical examination the patient was observed to be emaciated, the body weight was 84 pounds. She was coughing and appeared to be chronically ill. Extensive, bilateral, crepitant, moist rales, made worse by coughing, were noted. There was no cyanosis or clubbing of the extremities. A soft mitral systolic murmur was heard. The blood pressure was 100/80 mm. of mercury. The abdomen was tympanitic but was not tender and no masses or organs were palpable.

Results of first and second strength purified protein derivative tests were negative for tuberculosis. Leukocytes numbered 13,700 per cu. mm. of blood. A culture of sputum produced *Pseudomonas aeruginosa* and a coagulase-positive *Micrococcus pyrogenes*. Subsequent cultures grew both *Candida albicans* and pseudomonas, which persisted. Staphylococci did not reappear. An x-ray film of the chest taken September 25, 1957 (Figure 3) showed an increase in the extensive "snowflake" infiltrative shadows in both lung fields since 1955. The sedimentation rate (Wintrobe) was 46 mm. in one hour. The urine showed a 4-plus reaction for glycosuria. Fasting blood sugar content was 123 mg. per 100 cc., and two hours postprandial was 228 mg. per 100 cc. Pulmonary ventilatory function determinations were as follows:

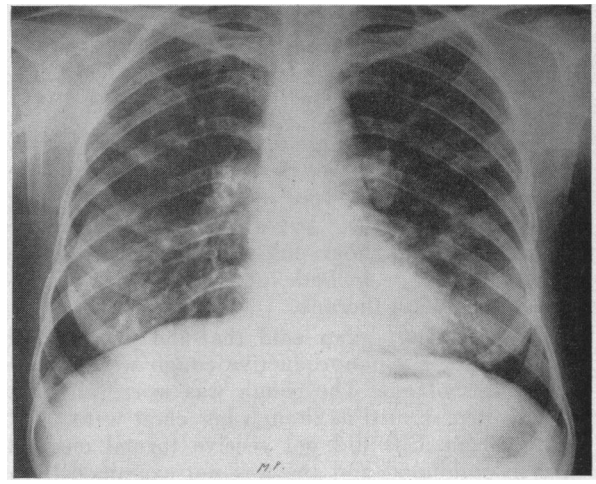

Figure 3.—X-ray film of chest taken September 25, 1957, showing extension and accentuation of the infiltrative shadows in both lung fields as compared with April 13, 1955.

Maximum breathing capacity—39.67 liters (48 per cent of predicted normal).

Vital capacity (3 seconds)—1,345 cc. (45 per cent of predicted normal).

Following sputum bacterial sensitivity studies the patient was placed on a regimen of nystatin, 4,000,000 units daily, in four divided doses, and dihydrostreptomycin, 1 gm. daily. In addition she was given 75 units of NPH insulin daily (which she had been taking for several months), a 2,500 calorie diet and calcium iodide (Calcidin) 1.2 gm. four times daily. On October 15, 1957, intermittent positive pressure breathing therapy, three times daily, was begun and an aerosol of 1 per cent phenylephrine and Tergemist.*

On October 24 a fresh stool specimen showed a moderate increase in fatty acid crystals and neutral fat. On October 25 a fecal examination was negative for trypsin activity in all dilutions. On the same day a plain film of the abdomen showed the colon to be distended with fecal material. This was interpreted as corroborative evidence of inadequate digestion of fat. On October 28 duodenal contents were aspirated through a Cantor tube and found to be negative for trypsin activity. With the tube in place, 10 cc. of iodine suspension (Dionosil) was instilled. The following day urine dilutions were negative for iodine, indicating a reduction in fat absorption.[14]

On November 1 a qualitative sweat chloride test[13] was found to be strongly positive. On November 18, 1957, the patient wore a pair of loose fitting, clean, dry rubber gloves overnight, and the sweat collected was analyzed for chloride by the standard serum method of Schales and Schales.[12] A determination of 90 mEq. per liter was made. A sweat sodium determination by flame photometry[4] was 65 mEq. per

*An aqueous solution of the detergent, sodium 2-ethylhexyl sulfate, 0.125 per cent with potassium iodide 0.1 per cent.

liter. Di Sant 'Agnese[7] in 1955 reported a range of from 4 to 60 mEq. (mean 32) for sweat chlorides and from 10 to 90 mEq. (mean 59) for sweat sodium in a large series of control studies.

On November 2 the patient was placed on a regimen of 60 gm. of triple strength pancreatin and 12,500 units of aqueous vitamin A daily. The administration of dihydrostreptomycin and of the other drugs already mentioned was continued and in addition tetracycline phosphate, 250 mg. every four hours night and day, was given.

From this point on the patient improved considerably. By December 12 the body weight had increased 14 pounds and on February 16, 1958, it was 105 pounds. Abdominal distention was decreased. Appetite and food intake had lessened. Stools were much smaller in quantity and bowel movements were reduced from four times to twice daily. The patient was expectorating less than one-half ounce of sputum daily, and the material varied from mucoid to mucopurulent. Pseudomonas remained as the one demonstrable pathogen on sputum culture. The cough became scarcely noticeable. The patient felt "fine" and said that her feeling of fatigue had disappeared. She walked outside the hospital daily. The first follow-up x-ray film of the chest after admission was taken on October 21, 1957 (Figure 4) and was interpreted as showing definite, although minor, improvement in the appearance of the lung fields. The most recent film, taken February 21, 1958, was unchanged.

Other follow-up studies showed improvement. Results of ventilatory pulmonary function studies on February 18, 1958, were: Maximum breathing capacity, 66.45 liters; vital capacity (3 seconds), 1,785 cc. The sedimentation rate (Wintrobe) was 21 mm. in one hour. Leukocytosis has persisted, the number of cells ranging from 13,000 to 14,000 per cu. mm. Results of other studies, which included liver function tests and determinations of blood chlorides, carbon dioxide and nonprotein nitrogen, were within normal limits, as were an electrocardiogram and venous pressure and circulation time determinations.

Because the quantitative sweat sodium and chloride determinations performed on November 18, 1957, were somewhat equivocal, sweat was collected by a different method on February 24, 1958. A two-foot square piece of plastic material was thoroughly cleansed and dried and placed directly on the skin of the patient's abdomen, which had been washed with distilled water and dried thoroughly. Sweating of the abdomen was produced by covering the plastic material with a blanket and a hot water bottle. A specimen of sweat was then collected and analyzed for chloride and sodium by the methods referred to above.[4,7] The following determinations were then made: Chloride, 192 mEq. per liter; sodium, 166 mEq. per liter. On February 25, 1958, the identical procedure was repeated and the following determinations were made: Chloride, 205 mEq. per liter; sodium, 190 mEq. per liter.

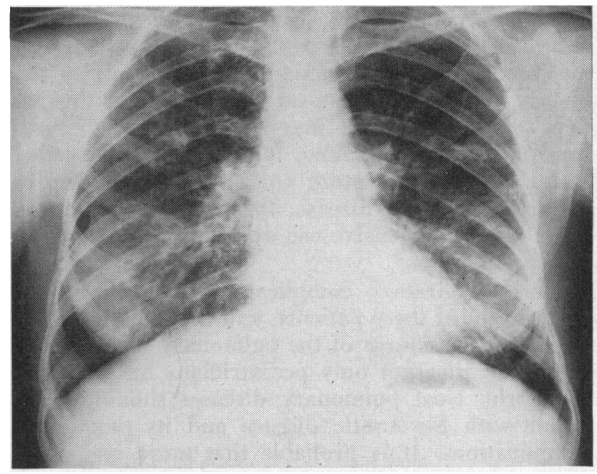

Figure 4.—X-ray film of chest taken October 21, 1957, after two weeks of intermittent positive pressure breathing therapy three times daily, along with antibiotics. This film was interpreted as showing improvement. There was no change from then to the most recent film taken February 21, 1958.

COMMENT

The present-day criteria for diagnosis in cystic fibrosis of the pancreas were met in the case herein presented. Although the patient reached the age of 17 before she received any medical care, which explains the delay in diagnosis, the history from birth through childhood is typical of cystic fibrosis of the pancreas. However, the fact that she reached the age of 24, whether treated or untreated, is most unusual in itself. Apparently in no case reported in the literature did a patient with a diagnosis based on present-day standards reach the age of 24 years.

A second unusual aspect of this case is that in addition to cystic fibrosis of the pancreas the patient had severe diabetes mellitus. These conditions have not, apparently, been previously described together. Di Sant 'Agnese,[5] in describing the microscopic lesions in the pancreas, emphasized that the islands of Langerhans are intact and sugar metabolism is unaltered; he cited this as an example of the coexistence in the same location of two tissues with different functions. Since this patient has apparently lived longer with her disease than any other patient reported in the literature, one is tempted to postulate a common etiology in the two diseases. In the same article cited above, di Sant 'Agnese[5] stated that an important pathological feature of the pancreatic lesion is its progressive nature. Initial lesions are present at birth and become progressively worse over periods ranging from a few months to two or three years. Further studies may provide the answer to this question.

The pulmonary disease in the present case was unusual in that there was no significant roentgenographic evidence of disease on a film taken in 1950, when the patient was 17 years of age. Four years later there were extensive roentgenographic changes and she was disabled because of this respiratory com-

plication. Although this cannot be documented, it seems probable that the patient did not have abnormal roentgenographic changes in childhood, for the history did not suggest such changes and the patient's mother insisted that her childhood diseases were uncomplicated. Also, it is generally conceded that if severe respiratory complications develop in children with this disease, the patients do not recover without intensive use of antibiotics and other therapy.

Since respiratory complications cause death in 90 per cent of these patients, and their fate is determined by the course of the pulmonary disease, it is important that not only pediatricians but all clinicians who treat pulmonary diseases should be familiar with fibrocystic disease and its pulmonary complications. It is probable that more and more of these patients will reach adult life. A simple qualitative screening test[13] for sweat chlorides has been described, and this should be performed in the case of any young adult with obscure chronic pulmonary disease.

The respiratory insufficiency noted in the present case is not unusual. West and co-workers[15] reported in 1954 that both ventilatory insufficiency and alveolar insufficiency may occur, the latter leading to arterial hypoxia and carbon dioxide retention. Bruck[3] analyzed the gas tension in arterial blood and alveolar air in seven patients with fibrocystic disease. He concluded that the primary respiratory disturbance is uneven distribution of ventilation in relation to perfusion. Additionally, he found that when obstruction is generalized, hypoventilation ensues and causes respiratory acidosis. These findings would seem to indicate that intermittent positive pressure breathing therapy is clearly indicated in these patients with severe pulmonary disease complicating fibrocystic disease of the pancreas.

Huang[10] in 1957 found a prevalence of intestinal types of Gram-negative bacilli (*Pseudomonas aeruginosa*, coliform and *B. proteus*) in the bronchial flora of 60 per cent of patients with fibrocystic disease.

Baxter[2] stated that as the respiratory factor becomes worse, infants and children are likely to develop a cor pulmonale, which in the early stages reacts favorably to digitalis therapy. Although there was no objective evidence of this complication in the present case, it must be considered as a probable eventuality should the patient survive the respiratory infection.

SUMMARY

A case of cystic fibrosis of the pancreas (mucoviscidosis) in a 24-year-old woman has been presented. The diagnosis was proven on the basis of present-day diagnostic standards. Apparently, the oldest patient with this disease previously reported in the literature was 19 years of age. In addition to cystic fibrosis, the patient has associated diabetes. These conditions have not, apparently, been previously described together, and their possible relationship has been discussed. Finally, roentgenographic and clinical evidence suggest that the patient's pulmonary disease did not manifest itself until she was 16 years of age. After that it became progressive and disabling. It is probable that this disease will become more common in young adults. Clinicians should consider cystic fibrosis of the pancreas as the primary disease in any young adult with obscure, chronic pulmonary disease.

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