Occult Cystic Fibrosis

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OCCULT CYSTIC FIBROSIS*

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Since 1938,¹ when Andersen differentiated cystic fibrosis and coeliac disease as separate pathological entities, cystic fibrosis has been considered as an 'all or none' disease phenomenon. It was usually thought that an affected child in whom the diagnosis could be proven was unlikely to survive many years and that his remaining years would be punctuated by intercurrent respiratory infections, steatorrhea and subsequent malnutrition. It has since become apparent that the disease is a generalized process which may make its appearance in the form of chronic pulmonary infection, a malabsorption syndrome characterized by steatorrhea, foul stools and malnutrition or as meconium ileus in the newborn period.² In 1952, Bodian² reported extensive liver involvement characterized pathologically by biliary cirrhosis and biliary concretions. In 1953, Di Sant'Agnese⁴ and his group demonstrated that sweat electrolyte concentrations were significantly increased in these patients and that this determination had diagnostic value, especially as a screening test, inasmuch as it could be readily done without the insult of duodenal drainage. Webster and Williams⁵ then reported mild disturbances of liver function, Gatzimos and Jowitt⁶ found cystic fibrosis a cause of neonatal jaundice and in 1954, Di Sant'Agnese⁷ reported patients with the disease who showed marked disturbance of liver function. It is now clear that, despite the inadequacy of the term 'cystic fibrosis', the disease is one which often involves many organs and from which a variety of symptoms may arise. Schwachman⁸ and Di Sant'Agnese⁷ have both suggested the concept of 'partial fibrocystic disease' and Schwachman¹⁰ has emphasized the occurrence of dissociation of enzyme activity in pancreatic secretions in these patients. It was further shown that an individual with partial cystic fibrosis and minimal enzyme deficiency might be followed for a number of years and then observed to develop the total disease picture. In 1955, McGrady and Bessman¹¹ studied electrolyte concentrations of saliva in cystic fibrosis patients and found them elevated in much the same way as sweat electrolytes and proposed this method as a screening test for the disease. Our experience at this hospital, has indicated that in our hands, measurement of sweat electrolytes obtained by the collection methods of Shwachman¹² or Barbero¹² is very satisfactory while the collection of suitable samples of saliva from young subjects is fraught with considerable error. It is now generally accepted that, if certain few other diagnostic considerations can be reasonably excluded, sweat chloride concentrations in excess of 60 meq./l. require that cystic fibrosis be ruled out.¹³

Since 1938, then, three basic concepts have arisen regarding cystic fibrosis: first, that it is a generalized disease involving many organs; secondly, that it has a wide spectrum of severity, ranging from barely perceptable secretory dysfunction in several glands to acute intestinal obstruction in the newborn period or suffocating respiratory insufficiency in later childhood; and thirdly, that it is usually a progressive disease though many years may elapse before the patient is much disabled by it.¹⁴,¹⁵,¹⁶

*This terminology is used with reservation. Schwachman² enumerates six synonyms for the disease. Presently there is no generally accepted term for the disease. Cystic and fibrotic changes are seen but the basic biochemical defect has so far eluded definition. Cystic fibrosis now seems to at least have the approval of popular usage with the recent formation of the Cystic Fibrosis Foundation.

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Recently we have had the opportunity to study three patients whose cystic fibrosis has been strikingly characterized by minimal symptomatology and excellent growth and nutrition. The very mild nature of their disease prompted a review of the literature and it was found that few similar patients are reported. For this reason the present cases are reported.

CASE 1. This 13 year old white female was admitted for the investigation of a chronic productive cough of ten years duration. It began with an episode of bronchopneumonia at three years of age and had persisted to the present without progression of severity. Cough was worse on rising in the morning and before bedtime. Occasionally it was productive of yellow sputum but there was no seasonal pattern to the cough. At five years of age, the patient was hospitalized twice for investigation of the cough. On one admission, she underwent adenotonsillectomy and, on the second, nasal polypectomy. Three years before admission to this hospital, she was admitted to a second hospital where extensive studies were carried out and the girl started on a program of bacterial vaccine therapy. Since that time, she had been given extensive antibiotic therapy and hyposensitization without relief. In the year before admission to this hospital, she had lost two months of school attendance because of her chronic cough. Menarche occurred in December, 1955 and menstruation since had been uneventful. Family history revealed no allergy or pulmonary disease.

Physical examination revealed a splendidly nourished, mature, thirteen year old girl who fell in the 50th percentile in reference to weight and the 75th percentile in reference to height on the Iowa Growth Curves. A few, scattered, medium rales were heard in the RML and in the upper part of RUL. Similar, but less marked, findings were noted in the LLL. The liver edge was felt 1 cm. below the right costal margin and the tip of the spleen 2 cm. below the left costal margin. Slight clubbing and cyanosis of the digits and toes was apparent, being less marked in the latter.

Hemogram and urinalysis were normal. Total eosinophile count was 32 per cu. mm. Sedimentation rate (Wintrobe) was 1 mm./hr. L.E. test was negative. Sputum culture showed no growth of fungus but abundant growth of Staphylococcus aureus and Pseudomonas aeruginosa. Total serum bilirubin was 0.33 mg. per cent. Serum cholesterol was 230 mg. per cent, 42% of which was ester fraction. Bromsulphalein test showed 2% retention at 45 minutes and none at 60 minutes. Total serum proteins were 7.2 gm. per cent, 4.3 per cent of which was albumin. Alkaline phosphatase was 7.2 Bodansky units. Glucose tolerance curve was normal. Cephalin-cholesterol flocculation test showed 2-plus reaction. Thymol turbidity test was reported as 4 units, the thymol flocculation test showed 2-plus reaction. Tests for tryp tic activity in the stool on three successive days showed tryp tic activity to a dilution of 1.425. Stool specimens gave a 2-plus reaction for fat when stained with Sudan III. Serum carotene was 50 micrograms per cent. Serum vitamin A level was 16 micrograms per cent. Sweat chloride determinations on samples collected by the patch method of Shwachman yielded values of 164 and 210 meq./l. Similar determination on the patient's father gave a value of 70 meq./l. Her mother was dead. Duodenal drainage was done, the position of the tube checked fluoroscopically and the following results obtained: trypsin 3.8% of normal activity, amylase 6%, lipase 3%. The ph was 5.0 and the viscosity 12.7. A second drainage was done and these results confirmed.
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The patient's chest films are shown in Fig. 1. Films of the paranasal sinuses showed definite haziness of the maxillary sinuses without thickening of the mucosa.

During her hospital course, the patient was placed on oxytetracycline in large doses, iodides, antihistaminics and was given frequent postural drainage. Local therapy was directed towards improving drainage of paranasal sinuses. At the time of discharge, the patient had improved slightly as far as her cough was concerned. She has been followed in the Out-Patient Department and has since been placed on Pancreatin tablets. She has also been provided with Alevaire aerosol equipment for home use. Some improvement of her chronic cough has been obtained with aerosol treatment.

CASE 2. This 7 year old white female was admitted for investigation principally because of the proven existence of cystic fibrosis in a younger sibling. At 6 weeks of age, diagnosis of the disease was suspected in the patient on the basis of a negative test for trypsic activity on one stool. This was not pursued further, however. At 3 years of age, the patient developed a chronic productive cough of mild degree. By 6 years of age, the patient began to be treated periodically with Alevaire-Isuprel aerosols
and iodides for occasional episodes of productive cough without significant fever or illness. Parents noted that iodides afforded especial relief. While stools had not been observed by the parents to be particularly abnormal, except for their bulk, they were noted to be less bulky and odorless after Viokase (4x USP Pancreatin) 1/2 tsp. three times daily was begun a year before admission. Appetite, though good, was never excessive.

Family history was of particular interest and is shown diagramatically in Fig. 2, together with sweat chloride determinations on surviving members.

![Family history, case 2.](image)

Physical examination revealed a pleasant, healthy appearing girl in an excellent state of nutrition. Her height and weight were found to be median for her age when plotted on the Iowa Growth Curves. There were no physical abnormalities.

Hemogram and urinalysis were normal. Total serum bilirubin was 0.5 mg. per cent. Alkaline phosphatase was 5.2 Bodansky units. Total serum protein was 7.0 gms. per cent, 5.0 gms. per cent of which was albumin. Prothrombin activity was 70% of control. Cephalin-cholesterol and thymol flocculation tests showed no reaction. Thymol turbidity test was reported as 1 unit. Glucose tolerance curve was normal for three hours. Tests for tryptic activity on stools for three successive days showed no reaction. Stool specimens gave a 3-plus reaction for fat when stained with Sudan III. 3-plus starch was also found in these specimens. Serum carotene was 15 micrograms percent and the serum vitamin A level 3 micrograms percent. Sweat chloride using the collection method of Barbero et al. was 120 meq./1, and with the patch collection

*Sweat chloride levels on the family of case 2 were obtained by R. G. Cornell, M.D. as part of a study supported by a research grant from the Henry Ford Hospital.
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method of Shwachman was 97 meq./l. Duodenal drainage was done three times, the position of the tube checked by fluoroscope and no activity of trypsin, lipase or amylase was demonstrated in the secretions. The pH was 3.6 and the viscosity 1.79. Sputum culture grew only the normal respiratory tract flora on several specimens, without any dominant organism.

Chest films revealed no abnormalities.

The girl’s hospital course was uneventful and she was discharged following studies reported above on Viokase ½ tsp. three times daily. Previously employed aerosol treatment was to be used as necessary for any episodes of respiratory symptoms during which the use of liberal doses of tetracyclenes was suggested. The patient was referred to her local physician for further care.

CASE 3. This 5 year old white male had been followed in this clinic since the age of three months. His earlier years were quite uneventful except for an episode of salmonellosis which was successfully treated at 3 months of age and adenotonsillectomy performed 2 years before the present admission. At a pre-school examination the child was described by the examiner as being “in excellent condition”.

Present illness began 2 months before admission rather suddenly with the onset of 4-5 bowel movements daily and associated fever and vomiting. This episode lasted 3 days and since that time the boy had passed 4-5 somewhat loose stools daily. Three days before admission, the stools became watery and foul smelling, constant frequent loose stools were passed day and night and, on two occasions, a little fresh blood was observed in the stool.

Physical examination revealed a well nourished boy without physical abnormalities other than moderately hyperactive bowel sounds. When plotted on the Iowa Growth Curves, he was found to fall in the 50th percentile in reference to height and in the 50th percentile in reference to weight. The impression of the admitting physician was ‘possible chronic ulcerative colitis’.

Upper gastrointestinal studies and small bowel studies showed no abnormalities. The barium enema was normal. Chest films revealed no abnormal findings. Sigmoidoscopy to a depth of 23 cm. showed no abnormalities.

The hemogram and urinalysis were normal. The sedimentation rate (Wintrobe) was 1 mm./hr. Agglutinations for typhoid and paratyphoid were negative. Stool culture grew a normal gastrointestinal flora. Two determinations of sweat chloride concentration by the patch method were 127 meq./l. and 214 meq./l. Two successive stool specimens showed tryptic activity to a dilution of 1:425. No evidence of ova or parasites was found in the stool. Duodenal drainage was done and tryptic activity was found to be 23% of normal, lipase 26% and amylase 34%. Viscosity was 2.21 at 4° C. Unfortunately, pH was not determined. Liver function studies were not obtained on this admission.

During his hospital course, no abnormality of bowel habit was noted. The child was completely asymptomatic. He was discharged and presently remains on a 20% protein diet, an aqueous multiple vitamin preparation containing 1000 I.U. vitamin D
and 100 mg. vitamin C plus added B-complex, Pancreatin granules 1 teaspoon three
times daily and penicillin G tablets once daily. His subsequent course is being followed
in the Pediatric Clinic.

DISCUSSION

In Case 1, remarkably slow progression of chronic pulmonary disease is seen and
it was to the tracheobronchial tree that the patient's only symptoms were referred.
In former years, she had been seen in two excellent clinics where the diagnosis of cystic
fibrosis was not considered at the time when the sweat chloride determination was not
available as a screening test. Our attention was directed towards this diagnosis by the
patient's high sweat chloride. At the time she presented for study, this patient
showed definite signs of chronic lung disease in the form of mild clubbing and
cyanosis of the distal extremities. In view of these irreversible changes, the prognosis
regarding this girl's pulmonary status is necessarily guarded. This patient, however,
clearly indicates the necessity of including sweat chloride determinations in the study of
any child or young adult who presents with symptoms suggesting chronic pulmonary
infection. Where these are abnormal, duodenal drainage and assay of the secretions
is indicated. It should be remembered that patients with fibrocystic disease may have
acid duodenal secretions and where these are found, the position of the tube should
be checked fluoroscopically to assure the validity of the test.

It is likely that Case 2 might have gone unrecognized for some time except for
the occurrence of frank cystic fibrosis in a younger sibling. This girl is the most
unusual patient with the disease we have seen in this clinic, being characterized by
excellent growth, nutrition and a completely normal physical examination. Her family
tree is remarkable in that the frequency of afflicted siblings exceed the previously
reported 1 to 4 ratio. A genealogy showing this same feature has been reported
previously from this department. Certainly these and other similar observations
demonstrate that the disease does not follow the simple pattern of a Mendelian recessive.
Two of the patient's surviving siblings, excluding the sibling known to be affected
and under treatment, have been shown to have abnormal sweat chlorides and we hope
to be able to study these children in the near future. Whether the magnitude of sweat
chloride elevation is an index of gene expressivity is presently under study. We have
no clear idea what this girl's subsequent course is likely to be, recorded experience
being lacking in such mild cases. One's only recourse is to the observation that cystic
fibrosis is a progressive disease. It would be speculation to suggest that by age 12 years,
Case 2 might resemble the current status of Case 1.

In Case 3, the possibility of cystic fibrosis was raised by an abnormal sweat
chloride obtained as a part of study for an unexplained diarrhea. Duodenal drainage
was corroborative, though only partial pancreatic insufficiency was demonstrated. The
boy has derived complete control of symptoms from replacement therapy with pan-
creatin and is now completely asymptomatic. In the absence of chronic pulmonary
infection, this situation will probably continue. However, in patients with chronic
pulmonary infection, despite complete enzyme replacement therapy, malabsorption
secondary to chronic infection eventually precludes adequate nutrition. Usually, such
infection is caused by staphylococci and the development of resistant strains is soon
seen with all the attendant problems in treatment they create. For the present, this
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patient is doing splendidly but his subsequent course must remain a matter of conjecture.

The occurrence of such minimal cases of cystic fibrosis as these necessitates revising our thinking regarding the extent of the full spectrum of the disease. Some years elapsed before it was demonstrated that chronic lung disease, meconium ileus, steatorrhea, heat stroke and cirrhosis could all arise from the same generalized disease. It is likely that much further observation will be necessary before the incidence of occult cystic fibrosis in adults, presently only sporadically recognized, can be ascertained.

SUMMARY

1. Three cases of occult cystic fibrosis are reported.
2. The role of the sweat chloride determination as a screening test in the patient with chronic pulmonary infection or unexplained stool abnormalities is emphasized.
3. A genealogy suggesting transmission of the disease other than as a Mendelian recessive trait is reported.

BIBLIOGRAPHY