CYSTIC FIBROSIS OF THE PANCREAS
Excerpts from a Round Table Discussion
By Paul A. di Sant'Agnese, M.D., and Charles Upton Lowe, M.D.

IN THE COURSE of a review of all features of the disease, the following points were particularly noteworthy:

Incidence
This disease accounts for almost all cases of pancreatic insufficiency in children. The incidence in the population of the United States is between 1 in 600 and 1 in 10,000 live births, with a probable average incidence of 1 in 2,500. There is no sex predominance. There is, however, a difference in racial predilection, being rarely seen in the Negro and never in Mongolians. It is a familial disease, displaying the characteristics of a mendelian recessive gene. This means that in an affected family the disease may occur in approximately 25% of the offspring, that both parents must be carriers of the trait and that two-thirds of the non-affected children are also carriers. Birth order has no effect on the inheritance of this disease. The fact that it is usually a lethal disease indicates that the mutation rate for this gene must be very high; the frequency of the single gene in the population has been calculated to be approximately 1 in 50.

Pancreatic Insufficiency
Clinical evidence of poor digestion and absorption of protein and fat is seen in the increased quantities of these substances in the feces, which causes the feces to be bulky, foul smelling, foamy and greasy. Another clinical effect of malabsorption is seen in the failure of the newborn infant with cystic fibrosis of the pancreas to regain birth weight in the first 10 days of life. In the absence of other evidence of disease, this is a sign suggestive of pancreatic failure.

Studies of nitrogen (protein) absorption in cystic fibrosis of the pancreas have shown that it is not affected by fat intake, though absorption of both is but approximately 60% of normal. However, the nitrogen absorption is directly correlated with the nitrogen intake, i.e., the more ingested, the more absorbed. From a nutritional point of view the patient with cystic fibrosis of the pancreas needs a high protein diet to make up for the deficient absorption. Restriction of fat is theoretically unnecessary except insofar as it improves the character of the stool. The retention of nitrogen can be normal in these patients since they compensate for poor absorption by retaining more of the absorbed nitrogen, and in comparison with normal individuals excrete less nitrogen in the urine.

Focal Biliary Cirrhosis
Focal areas of biliary cirrhosis are seen in the liver in almost all patients coming to necropsy. This is apparently due to concretions in the small biliary ducts with bile stasis and resulting fibrosis.

Focal biliary cirrhosis causes no symptoms or signs in the patients, but the lesions may progress to a diffuse multilobular cirrhosis and become manifest by palpable, hard, nodular, nontender areas in the liver. Further distortion of hepatic architecture may lead to enlargement of the liver, portal hypertension and splenomegaly with eventual clinical evidence of hypersplenism, gastrointestinal bleeding and ascites. Portal

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hypertension may be treated by surgical shunting procedures.

Other Manifestations

Recently a mucoprotein has been isolated from a fraction obtained by precipitating duodenal fluid obtained from patients with cystic fibrosis of the pancreas with organic solvents. This fraction is insoluble in water and has not been reported in the duodenal contents of normal persons. It has been found in some patients in whom the diagnosis of cystic fibrosis of the pancreas was made despite normal or only partial loss of pancreatic function. The relation of this material to the viscid secretions characteristic of this disease has not been established.

Diagnosis

The clinical recognition of this disease rests largely on identification of intestinal insufficiency due to loss of pancreatic enzymes and the presence of chronic pulmonary disease. Despite the protean and subtle manifestations of the disease, the majority (70 to 80%) of patients will have a history of chronic respiratory infection characterized by generalized obstructive emphysema, combined with symptoms of pancreatic insufficiency. Rectal prolapse is not uncommon. Some investigators estimate that about 10% of patients will have overt pulmonary disease while still exhibiting normal or only moderately diminished pancreatic function. Occasionally, patients may present with one of the following syndromes: cirrhosis of the liver with portal hypertension; heat prostration; or vitamin K deficiency with subcutaneous bleeding. The disease process may also be present without producing any clinical symptoms.

Laboratory aids proposed as screening-tests for the evaluation of pancreatic function include microscopic examination of feces and determination of proteolytic activity of the feces. Neither of these tests is diagnostic. Determination of the concentrations of carotene and vitamin A in the serum is just as useful as a screening test for the steatorrhea due to intestinal insufficiency. Absorption tests measuring response of amino-acid nitrogen in the blood to a protein meal, or absorption of fat-soluble vitamin A from an oily preparation compared with absorption from an aqueous dispersion, will help to differentiate celiac disease from pancreatic insufficiency, but these procedures are generally not necessary. The diagnostic tests which are recommended include determination of the concentration of chloride or sodium in sweat, and the assay of proteolytic enzymes in the duodenal fluid. The determination of the concentration of chloride in sweat is more reliable and simpler than that for sodium. The Andersen-Early method for assay of proteolytic activity is recommended because of simplicity of technique and of materials required as well as a dependability equal to more complicated methods. Determination of the presence of water-insoluble mucoprotein in duodenal juice may be helpful, but is not essential. The use of precipitation with trichloracetic acid in the differentiation of normal and abnormal meconium in infants has been advocated but the results are often difficult to interpret. In summary, the most reliable diagnostic criteria include evidence of pancreatic insufficiency, abnormal concentration of electrolytes in sweat, chronic pulmonary disease with generalized obstructive emphysema and a history of similar disease in other siblings. In the single case some of the criteria may be lacking, as it is now recognized that incompletely manifested cases of cystic fibrosis of the pancreas occur.

Treatment

The treatment of this disease can be divided into three parts: the nutritional aspect, the pulmonary infection and abnormal loss of salt.

Recommended dietary measures include the use of fat-soluble vitamins in amounts about three times that usually recommended. The addition of salt to the food in liberal quantities (2 gm or more per day) is recommended in hot weather. The addition of pancreatic extract is known to decrease
the appetite, and there is no definite proof that it increases nitrogen retention; if used, it is desirable to give 5 to 10 gm/day of a powdered pancreatic extract. Pancreatic supplements may be helpful in controlling the size and character of the stools when these are bothersome. This may also be accomplished by moderate restriction of fat or other foods in the diet which seem to be poorly tolerated. In general, an unrestricted amount of a well-balanced diet is preferable. Restriction of any component of the diet will not improve the nutritional state and may even jeopardize nutrition through creating imbalance or rendering the diet less palatable.

Active treatment of the pulmonary lesion to avoid progressive chronic bronchopneumonia deserves the major emphasis in the treatment of this disease. The need for antimicrobial therapy is based on clinical signs of respiratory infection. A therapeutic course of a broad-spectrum antibiotic orally, or intramuscular penicillin and streptomycin, should last 7 to 15 days. Penicillin and streptomycin may be useful despite laboratory evidence of bacterial resistance, administered either by the intramuscular route or by inhalation. Inhalation therapy is useful as a therapeutic rather than a prophylactic maneuver and requires an air compressor. For inhalation therapy the suggested dosages are: penicillin, 200,000 units, and streptomycin, 200 mg, five times a day. One milliliter of a saline solution containing these amounts of each antibiotic should be added together in a Vaponephrin® nebulizer and nebulized with compressed air flowing at 5 to 6 liters per minute.

The need for continued administration of antimicrobial agents is generally indicated by clinical or roentgenographic evidence of persistent pulmonary involvement. A broad-spectrum antibiotic such as a tetracycline, chloramphenicol or erythromycin, in oral doses of 10 to 20 mg/kg/day, is generally satisfactory. When erythromycin is used, it is suggested that a sulphonamide also be given to provide more complete coverage against the species of bacteria usually incriminated.

Other measures have been tried. Sympathectomy is not helpful. Lobectomy for persistent atelectasis is rarely indicated. Bronchoscopy is difficult in small children, but may be of assistance in older patients. Postural drainage at times is of benefit. The use of wetting agents or enzymes in an aerosol solution has not caused much improvement. Expectorant cough mixtures have not given dramatic results, however, 2% hydrogen peroxide by aerosol inhalation may be of help. It is suggested that gamma globulin be used to prevent measles, and that pertussis vaccination be done in all patients.

For the treatment of heat prostration, replacement of extracellular fluid is of paramount importance. Rapid restoration can be initiated with 10 ml of normal saline/kg intravenously in 15 minutes, with a total equal to 10% of the body weight given as normal saline in the first 24 hours.

The treatment of cor pulmonale must be largely preventive. Once this condition obtains, digitalization results in apparent clinical improvement. Morphine and oxygen should be used with great caution. Morphine does not seem indicated because of its depression of respiration. The role of oxygen is not clear; it may be dangerous despite relief of the anoxia by causing respiratory depression leading to a dangerous elevation of the CO₂ in the blood. If it is used, it is probably safe as long as the respiratory rate stays rapid. Bronchoscopy may occasionally be important as a way of relieving excessive secretions when the cough is ineffective. Under these circumstances it may be required two to three times weekly. There are variable reports of the effects produced by a forced-cough machine. Often it is not beneficial. Some help may be obtained from an abdominal belt to help stabilize the diaphragm.

Other therapeutic measures such as a change in climate, air conditioning, cortisone, and mercurial diuretics are not strikingly helpful.
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