THERAPY OF CYSTIC FIBROSIS OF THE PANCREAS

Harry Shwachman, M.D.
Department of Pediatrics, Harvard Medical School and the Children's Medical Center

GENERAL CONSIDERATIONS

I should like to open my remarks concerning therapy of cystic fibrosis of the pancreas by pointing out that some of the things we do are based on sound physiologic principles, such as salt and pancreatic enzyme replacement. Other therapeutic measures are based on prevention, e.g., the use of water-miscible vitamin A to prevent vitamin A deficiency, the use of vitamin K to prevent prothrombin deficiency, or the use of gamma-globulin to prevent measles in the exposed patient. A number of therapeutic measures have been employed in the management of patients with cystic fibrosis that require further evaluation, as unfortunately the effects produced in many instances are based on the judgment of anxious parents and enthusiastic physicians. Examples of this kind may include the use of trypsin by intramuscular or aerosol routes or the use of adrenal steroids. It is important to keep a proper perspective. We must not discard any form of therapy that offers relief, and on the other hand, we must avoid the use of harmful agents and needless operative procedures.

The first point I should like to make is the importance of being certain of the diagnosis. In the case of equivocal laboratory findings with a clinical picture that is consistent with the disease, I believe therapy should be instituted and the laboratory tests repeated, until the diagnosis can be established or discarded. Figure 1 shows a 9-week-old baby who was first seen about 10 years ago. He had the typical pulmonary picture of cystic fibrosis, yet the duodenal fluid contained adequate proteolytic activity and showed increased viscosity. We felt reasonably certain at that time that he would eventually develop complete pancreatic insufficiency and, as we observed him over the next 3½ years, the duodenal fluid revealed complete absence of all pancreatic enzymes, namely, lipase, amylase and trypsin. He was treated vigorously from the very beginning with antibiotics, which included penicillin and streptomycin by inhalation in addition to Aureomycin® orally. It seems to me that when you suspect cystic fibrosis in such a seriously ill youngster, it is wise to institute therapy immediately and pursue your diagnostic procedures as the condition


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of the patient permits. This patient still attends our clinic.

Make the diagnosis early in the course of the disease. Figure 2 shows an infant at 15 months of age and again at 18 months. He had all the classic manifestations of cystic fibrosis, but the diagnosis was not established until he presented himself to us at the age of 15 months in this advanced stage of the disease. Vigorous therapy brought about a striking though temporary improvement and the youngster succumbed later as a result of extensive bronchiectasis. The point we should like to make here is, attempt early diagnosis before irreversible and advanced pulmonary manifestations appear.

Initial Manifestations

The initial clinical picture varies considerably. Table I shows the initial clinical manifestations as observed by us. It can be seen that the majority of patients have both pulmonary and intestinal symptoms prior to 1

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<th>TABLE I</th>
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<td>Initial Clinical Manifestations</td>
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<tr>
<td>80% of patients have pulmonary and intestinal symptoms under 1 year of age.</td>
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<tr>
<td>15% of patients have predominant pulmonary symptoms with little or no intestinal symptoms. This may occur at any age through childhood. These patients are usually incorrectly diagnosed as having asthma, chronic pneumonia, pertussis, bronchiectasis or even atypical tuberculosis.</td>
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<tr>
<td>5% of patients have meconium ileus at birth.</td>
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<tr>
<td>5% of patients have predominant intestinal symptoms with minimal pulmonary symptoms.</td>
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<tr>
<td>4% of patients may have rectal prolapse as the presenting complaint.</td>
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<tr>
<td>1% of patients may have portal hypertension as the initial manifestation.</td>
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year of age. Approximately 15% have predominantly pulmonary symptoms with few or no gastrointestinal symptoms. These are the patients with partial or no pancreatic insufficiency and are the ones who gave us the most trouble in diagnosis prior to the development of the diagnostic sweat test. A small number of patients have meconium ileus shortly after birth, and this figure may be 5% to 10% of the total number of patients with cystic fibrosis. A small percentage of patients have predominantly intestinal symptoms with no pulmonary symptoms. In recent years we have seen a number of patients with rectal prolapse as the presenting complaint. On rare occasions, portal hypertension may be the initial manifestation. In two small infants, hypoproteinemia, edema and anemia were the presenting picture. Other initial manifestations may include the consequences of excessive loss of salt through the skin. We have also seen vitamin K deficiency with bleeding as an early manifestation of the illness. On occasions, a patient referred because of troublesome nasal polyps may be found to have cystic fibrosis.

**THERAPY OF GASTROINTESTINAL MANIFESTATIONS**

In the past, considerable attention was given to the diet. In general, we suggest that the child be offered a normal diet and one which is not too different from that of the rest of the family. We may stress extra calories and a high protein diet. We make little effort to eliminate fat, and the amount of fat allowed in the diet varies according to the tolerance of each individual patient. The majority of patients are able to tolerate the fat in homogenized milk. We may advise the withholding of butter, ice cream, peanut butter, potato chips, french fried potatoes...
and mayonnaise, if these foods produce bulky, frequent or oily movements, or result in cramps or discomfort. In some patients considerable reduction in fat intake is necessary, whereas others may tolerate fat in spite of demonstrable pancreatic insufficiency. In small infants we may suggest the use of protein hydrolysates, particularly if milk curds present a problem, as in surgically-corrected meconium ileus.

For patients with pancreatic insufficiency we routinely recommend the use of a pancreatin preparation, such as Viokase® or Panteric® granules. Viokase® is available in powder and in tablet form. The requirement for one patient may differ from that of another, and the amount given to each patient is regulated according to his individual needs. We may give as little as ¼ to 1 tsp. with each meal, or 2 to 5 tablets per meal. It is much more convenient to provide the older patients with tablets.

A troublesome complaint in relation to the gastrointestinal tract is rectal prolapse. We were surprised, in a review of approximately 400 patients with cystic fibrosis, to find that 22% of the patients had this complaint. In 4% of this group rectal prolapse was the initial complaint. The incidence of rectal prolapse is lower in those youngsters in whom the disease is recognized early and proper consideration given to diet and pancreatin replacement therapy. It is hardly ever necessary to treat this condition by surgery. Conservative measures, including strapping of the buttocks, defecating in the reclining position, and measures designed to reduce the bulk and frequency of the stool are usually successful.

Insofar as vitamin administration is concerned, we usually provide approximately twice the commonly recommended dose. We may add vitamin K to the vitamin supplement of small infants, particularly if they have undergone surgery. We have seen a number of babies with meconium ileus develop prothrombin deficiency, and in one case subdural bleeding occurred. Since this deficiency may cause serious consequences and can be detected and prevented, we now pay close attention to the need for vitamin K. In recent years, signs of vitamin A deficiency have not been reported in patients with cystic fibrosis, although this was a rather common manifestation when the disease was first recognized about 25 years ago. We have seen one clear example of vitamin A deficiency during the past 5 years; the reason we see this so infrequently today is because of the liberal use of water-miscible vitamin A preparations. We have had no experience with vitamin D deficiency in cystic fibrosis. Although laboratory evidence is lacking concerning requirements for the B group of vitamins in patients with pancreatic insufficiency, we recommend supplementation with vitamins of the B complex. More information is needed to define the requirements of these vitamins in the patients under consideration. At the present time we are unable to recognize deficiency of vitamin E by clinical criteria, but this deficiency can be recognized by biochemical investigation and by pathologic alterations of both skeletal and smooth muscle. Since most patients with cystic fibrosis have low levels of vitamin E in the blood, the addition of vitamin E to the diet is recommended.

The excessive loss of salt through the skin which occurs as a result of heat stress must not be forgotten, as the disastrous consequences can be avoided. We have noted that a number of patients with cystic fibrosis actually have a salt craving. The parents should be advised not to curb this craving by withholding salt. The addition of extra salt to the diet during periods of heat stress is advocated.

THERAPY OF PULMONARY MANIFESTATIONS

The greatest therapeutic problem pertains to the management of the pulmonary involvement. There are two major aspects to consider: first, the mechanical effects of thickened secretions; and second, the added effects of infection.
The Viscid Secretions

In the first instance, the altered secretions interfere with the normal mechanism of drainage, affect ciliary action and produce bronchial plugging. In a general way, we attempt to thin the mucus secretions, to establish good drainage, and to prevent and control infection. These measures usually produce improved pulmonary function.

We find iodides of considerable help and often use a saturated solution of potassium iodide, the dose varying with the age of the patient and our estimate of his needs. We may use from 1 to 2 drops three times a day, to as much as 8 drops three times a day. We always inform the parents of the possible undesirable effects when iodides are administered. We also limit their use in order to avoid thyroid enlargement.

Other products are available which are aimed at altering the secretions. One such preparation is pancreatic trypsin, which is given intramuscularly or by aerosol inhalation. We are not impressed with the effect of these preparations. However, a buccal tablet containing 10,000 units of streptokinase and 2,500 units of streptodornase, taken three times a day, has proved helpful in a number of patients. We consider this drug to be one that needs further investigation. A word of warning should be mentioned concerning the disastrous effects of liquefying the secretions too rapidly. In this connection adequate suction apparatus should be available at the bedside when the patient is given any form of therapy which may liquefy the retained secretions.

Another method of thinning secretions is by the use of carbon-dioxide inhalations. We have had little experience with this method. An effective method for the removal of secretions is to have the patient sleep in a tent in an atmosphere saturated with a mist. Denton1 has developed satisfactory equipment and has suggested solutions of propylene glycol, glycerine and a detergent which can be used through the night.* The equipment can be readily obtained. We are impressed with the effectiveness of the use of mist in the management of a number of patients who have moderately severe impairment due to thickened bronchial secretions as a result of the disease process itself and the added effects of the infectious process. Many small patients find such a tent comfortable, as it may reduce or eliminate coughing and permit them to sleep through the night.

During the past few years, we have learned a great deal from two experienced English-trained physiotherapists who demonstrated methods of improving pulmonary ventilation by breathing exercises and a fairly sensible approach to achieving effective postural drainage.2 Some of the initial breathing exercises are aimed at increasing the duration of exhalation, followed by teaching correct diaphragmatic, lower costal, and posterior costal breathing. Localized breathing exercises may also be used in attempts to improve function in areas of major involvement or to re-expand areas of atelectasis. In either instance, breathing exercises should be preceded by postural drainage. For postural drainage the physician indicates to the physiotherapist the areas to be drained. The procedures involved are: 1) tipping the patient in a position so that gravity will assist in drainage; 2) clapping with cupped hands over the segment being drained; 3) and vibration over this segment during exhalation. It should be pointed out that the methods employed are in constant use in chest clinics in England.

The Infection

The use of antibiotics to control and prevent pulmonary infection has brought about a marked improvement in the prognosis of children with cystic fibrosis. The administration of antibiotics over prolonged periods of time is often indicated. However, when there is no pulmonary involvement, continuing using a 10% solution of propylene glycol and a 3% solution of NaCl as suggested by Denton and Mathews.

* Since this paper was presented we have been
ous antibiotics are not advocated. Should such a patient develop a respiratory infection, we usually suggest a course of therapy. Unfortunately, the term "prophylactic therapy" has been applied to a number of children in whom pulmonary infection is well entrenched, in which case we prefer to use antibiotics on a more or less continuous basis.

If the pulmonary infection is of a mild degree, we may use as little as 10 to 15 mg/kg/day of a broad spectrum antibiotic, such as chlorotetracycline or oxytetracycline. We take into account the home environment, the number of siblings who are in school and may bring infections home, etc., before deciding what plan of therapy to employ. We often discontinue antibiotics during the summer months in such instances.

When the pulmonary infection is of a moderate degree, we often find that increasing the dosage of broad spectrum antibiotics may in itself not be sufficient to control the infection. In these instances we may employ a combination of antibiotics, such as chlorotetracycline and a sulfonamide preparation or erythromycin. We do not hesitate to use a combination of chloramphenicol and erythromycin in patients with extensive pulmonary involvement. In these instances the antibiotics may be given at approximately 8-hour intervals and the dosage is rarely over 40 mg/kg/24 hours. We have been repeatedly disappointed in trying to decide which antibiotic to use on the basis of sensitivity tests of organisms isolated from the nasopharynx. The two great problems are the appearance of resistant staphylococci and the emergence of pseudomonas as the predominant flora. We seldom employ antibiotics intramuscularly.

When the youngster is severely ill, we give antibiotics by the aerosol route in addition to oral administration. The most common agents used in this way are combinations of penicillin and streptomycin or neomycin and polymyxin. Also we often employ mixtures in the aerosol solution which contain propylene glycol, glycerine, detergents and bronchodilators.

We should like to mention the use of intermittent positive-pressure breathing machines as having a place in the therapy of a select number of patients with cystic fibrosis. Their use should be reserved for those with special training and experience. One cannot overstate the importance of achieving effective bronchial drainage. We believe that when this is successful the use of antibiotics takes a secondary role and may at times be discontinued. The practice of giving antibiotics without attempting to improve pulmonary ventilation and establish bronchial drainage when these are indicated should be discouraged. We think that a frequent change or rotation of antibiotics from month to month is not necessary. When bacteriologic controls are available, it is obvious that the acquisition of new species of bacteria may require a change in antibiotic regimen. The results of cultures of sputum or from the nasopharynx, along with sensitivity tests may at times be a useful guide.

ILLUSTRATIVE CASES

Figure 4 is a photograph of a patient who was first seen at the age of 16 years in 1950. She was diagnosed as having bronchiectasis at 5 years of age, and a second bronchogram was carried out when she was 10 years old. Although cystic fibrosis was suspected, the diagnosis was not seriously entertained until she was 16 years of age. In favor of this diagnosis was the pulmonary picture, increase in viscosity of the duodenal fluid, and a history of a similar chronic pulmonary process in her younger brother. She did not present clinical or laboratory evidence of pancreatic insufficiency. When the sweat test became available, approximately 5 years later, the sodium and chloride values were elevated, as they were in the case of her younger brother. In the meantime, she had been treated constantly with broad spectrum antibiotics in a dosage of 250 to 500 mg a day. She was able to pursue a college career, subsequently married, and is now a happy housewife at the age of 24 years. An additional feature of her illness is the presence of recurrent nasal polyposis.
Figure 5 shows an 11½-year-old boy who had a very stormy course during his first year of life. He is the first patient with meconium ileus operated upon at the Children's Hospital who survived beyond the immediate post-operative period. Following this successful outcome Dr. Gross and his staff have provided our clinic with approximately 30 additional patients with meconium ileus. We believe that the prognosis in children with meconium ileus, following successful surgery, depends upon the extent and severity of their pulmonary involvement. This patient has had very minimal pulmonary involvement. He has the usual findings of absence of pancreatic enzymes and elevation of electrolytes in sweat. He is not receiving antibiotics.

Figure 6A shows a girl who first appeared at the Children's Medical Center at the age of 3½ years. The diagnosis of cystic fibrosis was readily established, as she had the char-

TABLE II
Ratings of 50 Patients Receiving Antibiotic Therapy Continuously for a Period of 8 or More Years

<table>
<thead>
<tr>
<th>Living</th>
<th>Dead</th>
<th>No. of Pts.</th>
<th>Rating*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Excellent</td>
</tr>
<tr>
<td>Initial score</td>
<td>43</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Present score</td>
<td>43</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Initial score</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
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* See reference 3.
characteristic pulmonary and gastrointestinal symptoms. This child was admitted to the hospital for a brief diagnostic study and the duodenal fluid was typical: it showed complete absence of pancreatic enzymes and increased viscosity. She was given broad spectrum antibiotics on a continuous basis, and Figure 6B shows her appearance 6½ years later. This patient attends school regularly and leads a fairly normal life. Roentgenograms of the lungs reveal the stigmata of cystic fibrosis with fairly marked pulmonary involvement and hilar prominence, diffuse and irregular hyperaeration of both lung fields, an increase in the antero-posterior diameter of the chest, and flattening of the diaphragms and thickening of the peribronchial and interstitial supporting tissues. In spite of her apparent well-being with relatively little to be found on physical examination, this youngster has moderately severe pulmonary involvement, as judged by roentgenograms. Incidentally, the roentgenogram will often show more extensive changes than one could ascertain by physical examination.

Figures 7A and B are roentgenograms of the chest of a patient who began treatment with chlortetracycline in December, 1948. He showed a dramatic clinical response and considerable improvement in the appearance of the roentgenogram. This patient is now 14 years of age.

CLINICAL EVALUATION OF RESULTS

From the few illustrative cases one appreciates the marked variation in severity of the disease. In order to compare patients, a system of clinical evaluation was devised. Our system of clinical rating, developed with Dr. Kulczycki, is presented in Figure 8. The final evaluation is derived from an appraisal of each of four categories: 1) the general activity of the patient; 2) the physical findings; 3) the nutritional status; and
4) the findings in the roentgenogram of the chest. A patient with a rating of above 85 is considered in excellent condition, between 71 and 85 is considered in good condition, etc. We find this system of scoring useful in evaluating the course of any one patient, as well as in comparing groups of patients.

Table II gives our evaluation of 50 patients who received antibiotic therapy continuously for a period of over 8 years. The important point to emphasize is that after 8 years of therapy a number of patients who were in the moderate category have advanced to an improved status. In fact, many are now in better condition than they were when they were originally diagnosed. This is indeed encouraging in a disease which has been considered fatal by those who first described cystic fibrosis about 20 years ago.

REFERENCES
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Harry Shwachman
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