In cystic fibrosis of the pancreas the pathologic lesions and the clinical effects of pancreatic deficiency attracted the attention of the early investigators and gave the disease its name.1-4 From the very beginning, the almost constant association of symptoms of pancreatic deficiency with those of chronic pulmonary disease was recognized. A consideration of these changes and of those of meconium ileus due to obstruction of the small intestine by abnormally inspissated meconium, and the observation at necropsy of a widespread lesion of mucous-secreting glands throughout the body (which were distended by what appeared to be abnormal secretions) led Farber5 and then Shwachman6 to postulate a generalized abnormality of mucous secretion. They suggested that the term mucoviscidosis be adopted. Their position was re-affirmed by Bodian7 when he suggested the term mucosis for this disorder. With the recognition in the last few years of the consistent involvement of the sweat and salivary glands and more recently of the tear glands,8-12 it became evident that cystic fibrosis is in reality a generalized disease in which most, or all, exocrine glands (mucous-producing and others) are affected.

Up to a few years ago the diagnosis was limited to patients with the fully-manifested syndrome—chronic pulmonary disease, pancreatic deficiency and abnormally high concentrations of electrolytes in sweat. In particular the demonstration of absence of pancreatic enzymes in the duodenal contents was required for the diagnosis of cystic fibrosis to be established. In the last 4 or 5 years, and largely due to an improved diagnostic ability resulting from the use of the "sweat test," it has been found that gradation in, or absence of, involvement of organs or glandular systems generally involved in this disorder is characteristic of cystic fibrosis; this has led to recognition of many variations in the clinical and pathologic picture. Incomplete forms of this generalized disturbance exist,13 in which pancreatic function is normal,10,14,15 just as there are patients with virtually no respiratory manifestations, and others in whom the symptoms resulting from cirrhosis of the liver and portal venous hypertension dominate the clinical picture,16 and some in whom high concentrations of chloride and sodium in sweat are the only abnormal findings, and finally those in whom such abnormalities may be found in various combinations.

It may be of interest at this point to mention the percentage of patients who present these varying manifestations. In the total series of more than 550 patients with cystic fibrosis observed at the Babies Hospital since 1939, virtually all have presented pulmonary involvement, although this may not have been present when the patient was first seen. Of the 550 patients only 9 (2%) have had cirrhosis of the liver with portal hypertension, but most of these have...
been seen during the last few years when average age of patients with this disease has been increasing. Out of a total of 254 patients with cystic fibrosis who had the sweat test performed only 2 (0.8%) have presented with sweat electrolytes within the normal range and yet were fully proved to have the disease. In contrast out of a total of 213 patients with cystic fibrosis seen in the last 5 years, 34 (16.4%) had either only reduced or normal pancreatic activity (Table I).

Patients who present with only some, but not all, of the findings of cystic fibrosis, may develop the remaining manifestations later or these may remain in abeyance indefinitely. So far we have seen only three patients with normal tryptic activity of the duodenal contents when first seen, who later developed pancreatic deficiency. While not completely certain, we believe that in one case normal sweat electrolytes in a patient with cystic fibrosis subsequently became abnormally high, and Mendelsohn reports a similar tentative observation.

The basic defect in cystic fibrosis is still unknown and speculation as to its nature has followed various channels. Deficiency in function of the autonomic nervous system and absence of an enzyme or some other metabolic error have been proposed in general terms to explain the generalized dysfunction of exocrine glands. Gochberg and Cooke are the only ones who have put forth a theory concerning the exocrine secretory defect, which they considered might be due to shortage of energy for secretory activity.

### GENETIC STUDIES

Whatever the nature of the basic defect or common denominator of the varying manifestations in cystic fibrosis, there is general agreement that it appears to be genetically transmitted. The published studies available bearing on the mechanism of genetic transmission have been summarized on previous occasions. In the first paper on this subject by Fanconi and Botztein in 1944, no conclusions were drawn. Three subsequent investigations, all reached the conclusion that cystic fibrosis was presumably transmitted as a recessive trait. While two groups concluded that a single recessive gene in the homozygous condition caused the fully-manifested clinical picture, Andersen and Hodges were of the opinion that an uncomplicated recessive trait dependent on a single gene was unlikely.

This problem cannot be resolved with the data on hand, but it must be recognized that while the overall incidence of the disease among siblings is 1 in 4, there are many family groups with an incidence of the disease among siblings much higher than 25%. This may be explained by coincidence alone, or it may indicate the presence of some other factor affecting genetic expression.

### The Heterozygous State

The existence of the heterozygous state has been postulated, and the incidence estimated as being between 2 and 18% of the general population. No way was known for the recognition of heterozygotes until

### TABLE I

| Tryptic Activity* in Duodenal Contents of 213 Patients with Cystic Fibrosis |
|---|---|---|---|---|
| None | Reduced | Normal | Total with Tryptic Activity |
| 0-40 (u/ml) | % of Total | 40-100 (u/ml) | % of Total | >100 (u/ml) | % of Total | Number | % of Total |
| 178 | 88.6 | 11 | 5.2 | 24 | 11.2 | 34 | 16.4 |

* Viscosimetric units per ml (normal values = >100 u/ml).
the demonstration in the author's clinic in 1953\textsuperscript{22} that a significant proportion of relatives (both children and adults) of index cases showed an elevation of electrolytes in the sweat similar to that found in patients with cystic fibrosis.

Several things will be noted from a study of Figure 1 in which the levels of chloride in sweat from four groups of individuals are recorded, and in which 50 meq/l is taken as the dividing line between patients with cystic fibrosis and controls:\textsuperscript{13,23} a) None of 50 adult controls, 21 to 80 years of age, had sweat chloride levels above 50 meq/l and the great majority had much lower concentrations. With three exceptions none of these individuals were normal, but suffered from a variety of conditions not related to cystic fibrosis. None had adrenal insufficiency, renal disease or generalized obstructive emphysema, and none was related to a patient known to have cystic fibrosis. b) Seventeen per cent of parents and 29% of asymptomatic siblings of patients known to have cystic fibrosis had abnormally high sweat electrolytes. c) Most of the parents and siblings of index cases had higher chloride in sweat than either adults or children controls, even when the values fell within normal limits.\textsuperscript{13,23} d) In the parents and siblings of index cases with abnormally high values for chloride in sweat, the concentration was usually lower than in patients with fully-manifested cystic fibrosis.\textsuperscript{13} e) Finally, many individuals who must carry the recessive gene, if the hypothesis is correct, had concentrations of electrolytes in sweat well within normal limits. However, in view of the unexpected behavior of electrolytes of sweat in heterozygotes, which will be discussed later, it is quite possible that under different circumstances or at different times the chloride and sodium concentration in sweat may be abnormal.

In addition, when 24 adults (21 to 76 years old) with obstructive emphysema (Fig. 1) were tested in our institution\textsuperscript{24} it was found that 5 or 20% had elevated chloride and sodium in sweat. All other tests, including assay of duodenal enzymes, were negative in this group and there was no family history of cystic fibrosis. Because up to the present time no other condition has been identified in which sweat electrolytes are increased (with the exception of untreated adrenal insufficiency), it was thought possible that such individuals might in reality have cystic fibrosis with only partial expression of the disease. If patients such as these adults with emphysema were in the pediatric age period, there would be no hesitation in diagnosing.
them as having cystic fibrosis.

Of added interest is the fact that about 20% of parents of patients with cystic fibrosis were found in these same studies to have abnormal spiromgrams, indicating some degree of bronchial obstruction, whether the electrolyte concentration in their sweat test was elevated or not.

In view of these facts perhaps the most acceptable hypothesis at this time, re-emphasized by Childs, presupposes a gene or genes which cause overt disease in homozygotes and partial expression or no expression of the disorder in heterozygotes. The most common partial expression recognized so far is an abnormal electrolyte pattern in sweat, but the finding of abnormal spiromgrams in parents of patients known to have cystic fibrosis suggests that it may not be the only expression.

In considering the studies just described one may wonder whether a substantial number of adults with obstructive emphysema do not belong in this category of heterozygotes, even though they show no other findings suggestive of cystic fibrosis. Following a similar train of thought, a patient in the pediatric age period with chronic lung disease and generalized obstructive emphysema and normal trypsin activity in duodenal secretions, but values for chloride in sweat only slightly below the level of 50 meq/l, may in reality also belong in this category. Faute de mieux, such patients are frequently discharged from many hospitals with the rather vague diagnosis of asthmatic bronchitis.

**Behavior of Sweat Electrolytes under Stress**

In Figure 2 are depicted some observations on the behavior of electrolytes in sweat following salt restriction and the simultaneous administration (to all but three cases of fully-manifested cystic fibrosis) of either desoxytocorticosterone acetate or 9-alpha-fluorohydrocortisone. Salt restriction and the administration of these compounds decrease electrolyte levels in sweat in normal individuals.

Three groups of patients were studied in this manner: seven children with fully-manifested cystic fibrosis in whom there

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**Fig. 2.** Effect on concentration of chloride in sweat of groups indicated, who were subjected to restriction of salt intake and simultaneous administration of either desoxycorticosterone acetate or 9-alpha-fluorohydrocortisone. (For explanation refer to text.)
was complete pancreatic deficiency, chronic pulmonary disease and high concentration of electrolytes in sweat; eight patients (with what shall be designated for the purposes of discussion as partially-manifested cystic fibrosis) with chronic pulmonary disease and high levels of electrolytes in sweat, but normal values for trypsin activity in the duodenal contents and no complaints referable to the gastrointestinal tract; three adults with chronic obstructive emphysema and abnormally high levels of electrolytes in sweat, all of whom had normal trypsin activity in duodenal secretions.

In the seven patients with completely-manifested cystic fibrosis, the average decrease in chloride in sweat after 5 days of salt restriction was very slight (9 meq/l or 9%). This confirms the observations made by us in 1953,9 that the abnormally high electrolyte concentration in sweat of patients with fully-manifested cystic fibrosis does not vary significantly following a variety of stimuli.

Five of the patients who had cystic fibrosis, but with normal trypsin activity of duodenal contents, behaved in a manner similar to that of the group just discussed. After 5 days of the regimen previously described, the chloride levels in sweat decreased on the average by 30 meq/l or 25%, but remained in a high and abnormal range.

In contrast, three patients with incompletely-manifested cystic fibrosis, after 5 days of salt restriction had an average decrease in the chloride in sweat of 40 meq/l or 50% to reach entirely normal values.

The three adult patients with emphysema, after 5 days of this regimen also had a decrease in the average level of chloride in sweat to 39 meq/l or 56% and had final values for sweat electrolytes well within the average normal range.

Data concerning three parents of patients known to have cystic fibrosis are summarized in Table II. An initial high value for chloride in sweat, obtained some time before this study was undertaken, had already decreased significantly in all; in some cases at least this was presumably a response to hot weather. However, after 5 days of salt restriction and the simultaneous administration of 9-a-fluorohydrocortisone, there was a further decrease in concentration of chloride in the sweat.

In cases 1 and 2 after the test and through

<table>
<thead>
<tr>
<th>Name</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Date</th>
<th>Salt* Restriction</th>
<th>Sweat Chloride (meq/l)</th>
<th>Sodium (meq/l)</th>
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<td>W.A.</td>
<td>39</td>
<td>M</td>
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<td>None</td>
<td>92</td>
<td>124</td>
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<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-18-1957</td>
<td>After Test</td>
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<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7-8-1958</td>
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<td></td>
<td>2-19-1959</td>
<td>None</td>
<td>69</td>
<td>90</td>
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<tr>
<td>A.H.</td>
<td>42</td>
<td>M</td>
<td>1-18-1956</td>
<td>None</td>
<td>82</td>
<td>60</td>
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<tr>
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<td></td>
<td></td>
<td>10-19-1958</td>
<td>Before Test</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10-26-1958</td>
<td>After Test</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
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<td>2-1-1959</td>
<td>None</td>
<td>46</td>
<td>50</td>
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<tr>
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<td></td>
<td></td>
<td>3-10-1959</td>
<td>None</td>
<td>58</td>
<td>94</td>
</tr>
<tr>
<td>M.D.</td>
<td>48</td>
<td>M</td>
<td>5-2-1956</td>
<td>None</td>
<td>88</td>
<td>102</td>
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<td></td>
<td>11-18-1958</td>
<td>Before Test</td>
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<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11-25-1958</td>
<td>After Test</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-17-1959</td>
<td>None</td>
<td>23</td>
<td>43</td>
</tr>
</tbody>
</table>

* And the oral administration of 9-alpha-fluorohydrocortisone.
the winter months there was again a gradual rise to abnormal values for chloride in sweat. Sodium in sweat had in all instances the same behavior as the chloride.

These observations, although in the initial stages, are important in two respects. First, this behavior of sweat electrolytes under stress must be kept in mind in family studies, because asymptomatic relatives of index cases who appear to have normal values for electrolytes in sweat at one time may have abnormal values under different circumstances. Second, patients with completely-manifested cystic fibrosis, who, according to the genetic hypothesis, may be thought of as homozygotes, and asymptomatic parents of index cases, who may be considered as heterozygotes, behave quite differently under stress in regard to sweat electrolytes. Some adults with emphysema, who may in reality be examples of the heterozygotic expression of cystic fibrosis, also behave differently from proven patients and in a way similar to that of parents of index cases. The facts already stated indicate that some of the patients with incompletely-manifested cystic fibrosis also show a marked lability in concentration of electrolytes in sweat. The investigation is not as yet far enough along for us to comment any further on the latter group.

**Differences in Behavior of Electrolytes in Sweat in Homozygotes and Heterozygotes**

As far as electrolytes in sweat are concerned, which is the only way in which we can compare the two groups at the present time, it appears that homozygotes and heterozygotes behave in a different manner in two respects: 1) There is a quantitative difference in values for electrolytes in sweat, being abnormal in both groups under consideration but much higher in most index cases than in their relatives. 2) Known and probable heterozygotes behave like normal individuals in that they are able to conserve salt and decrease the concentration of chloride and sodium in sweat to normal levels after stress, whereas patients with fully-manifested cystic fibrosis show little response to the same procedure and are not able to conserve salt in the sweat.

What is the significance of these observations? Is it possible that the unknown metabolic or enzymatic defect (perhaps concerned with the function of the autonomic nervous system), which may be the common denominator of the generalized dysfunction of exocrine glands in cystic fibrosis, can be present in varying degrees? This certainly is true of other disease entities. For instance in sickle-cell anemia the replacement of 90% of the normal hemoglobin by the abnormal sickle-cell hemoglobin leads to the severe disease in homozygotes, whereas the presence of a smaller amount of abnormal hemoglobin in heterozygotes leads only to the sickle-cell trait. Does a similar mechanism obtain in cystic fibrosis and account for some of the many variations in the degree of involvement and in the severity of the clinical picture? If this were true then all susceptible organs or glandular systems would be affected in all instances, but in varying degrees and at times to an extent too limited to give rise to clinical manifestations. Symptoms may then appear later or remain in abeyance indefinitely.

**CHEMICAL STRUCTURE AND PHYSICOCHEMICAL CHARACTERISTICS OF MUCUS**

As has already been mentioned, abnormalities in structure of mucous secretions have long been thought to be important in the genesis of symptoms in cystic fibrosis. In 1957 it was shown by our group that mucopolysaccharides from duodenal contents of patients with this disease had an abnormal physicochemical behavior and were easily denatured and rendered insoluble. After adding an ethanol-benzene mixture to samples of duodenal contents of patients with cystic fibrosis becomes denatured and yields a precipitate which cannot be resuspended in water, as is the case with mucoproteins from duodenal fluid obtained from normal individuals and from patients with a variety of other diseases. Whereas at first
the chemical composition of these substances was thought to be similar in patients with cystic fibrosis and controls, it is now recognized that there are significant differences.

Dische and collaborators have studied this problem further in recent times by means of fractional precipitation. About 90% of duodenal mucopolysaccharides obtained from controls and most of the material from patients with cystic fibrosis, going in solution after precipitation with the ethanol-benzene mixture, can then be separated into four fractions according to solubility in alcohol. All of these fractions contain a fuco-mucopolysaccharide as the carbohydrate moiety but the distribution of the component sugars, and in particular the distribution of sialic acid and of fucose, among the various fractions varies greatly between patients with cystic fibrosis and controls. In addition, the chemical composition of the carbohydrate moiety of the water-insoluble precipitate that is peculiar to patients with cystic fibrosis and controls. In addition, the chemical composition of the carbohydrate moiety of the water-insoluble precipitate that is peculiar to patients with cystic fibrosis is similar to that of the least soluble fractions. It is felt that these changes in the distribution of sialic acid and fucose may afford one explanation of the decrease in solubility found in specimens obtained from patients with cystic fibrosis.

In Table III are represented the results in 126 patients with cystic fibrosis who were tested for the presence of the insoluble mucoprotein in duodenal fluid. In both Group I (patients with no tryptic activity in duodenal secretions) and in Group III (patients with normal tryptic activity in the duodenal contents and without symptoms referable to intestinal insufficiency) there are individuals in whom the insoluble mucoprotein was present in duodenal secretions and some in whom it was absent. This mucoprotein fraction is therefore presumably independent of the presence or absence of pancreatic juice and is apparently not affected by tryptic activity, a fact borne out also by in-vitro experiments. However, the distribution of patients according to the presence or absence of this mucoprotein fraction is totally different in these two groups. In Group I, 92 patients presented this fraction and only 2 did not. Conversely, in Group III, 19 did not show the abnormal mucoprotein, while only 6 did.

If it is assumed that a similar abnormal composition of mucoids may be present in mucous secretions throughout the body in patients with cystic fibrosis, then the increased susceptibility to denaturation of one part of the mucoid in the duodenal fluid may give a clue as to the genesis of many of the symptoms of this disorder. It is possible to speculate that a change in the physicochemical environment of these mucous secretions might cause irreversible precipitation of the mucoproteins in organs such as the pancreas, the liver and others, thus initiating the chain of clinical events. The presence of this easily denatured substance, according to this hypothesis, would be the forerunner of further difficulties and not a consequence of them.

**BACTERIOPHAGE TYPING OF STAPHYLOCOCCUS AUREUS ISOLATED IN CYSTIC FIBROSIS**

The striking association between Staphylococcus aureus hemolyticus and the pulmonary involvement in cystic fibrosis is well known. The presence of this organism

*After this paper was written, another study on mucoproteins in this disease appeared to which the reader is referred for further data and discussion.*

---

**TABLE III**

<table>
<thead>
<tr>
<th>Duodenal Contents</th>
<th>Mucoprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptic Activity</td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>absent</td>
</tr>
<tr>
<td>Group II</td>
<td>reduced</td>
</tr>
<tr>
<td>Group III</td>
<td>normal</td>
</tr>
<tr>
<td>Total No. of cases</td>
<td>22</td>
</tr>
</tbody>
</table>

**BACTERIOPHAGE TYPING OF STAPHYLOCOCCUS AUREUS ISOLATED IN CYSTIC FIBROSIS**

The striking association between Staphylococcus aureus hemolyticus and the pulmonary involvement in cystic fibrosis is well known. The presence of this organism

*After this paper was written, another study on mucoproteins in this disease appeared to which the reader is referred for further data and discussion.*
as the sole or predominant one in cultures from the lungs of patients at necropsy or from cultures of the sputum or nose and throat has long suggested a metabolic relation between this microorganism and cystic fibrosis. To date it has not been possible to prove such a relationship, although preliminary experiments in this direction have been carried out in our institution. It was logical to wonder whether the recently developed bacteriophage typing of this organism would offer any information and whether any one phage type of staphylococcus was associated with cystic fibrosis. Table IV, modified from a forthcoming paper,\textsuperscript{3} gives the results of phage typing of 174 strains of Staph. aureus isolated from 75 patients with cystic fibrosis. It can be seen that the distribution of organisms falling within phage types I, III and miscellaneous types is not significantly different from that found in other patients who are frequently hospitalized. These observations indicate that there is no one phage type playing a greater role than others in the respiratory involvement of cystic fibrosis.

### SUMMARY

The pathogenesis of cystic fibrosis, the common denominator responsible for the widespread dysfunction of so many or perhaps all exocrine glands, is not known. The basis defect, whatever its nature, is genetically transmitted and there is suggestive evidence that it may be present in varying degrees and so affect the variety and severity of clinical manifestations in different individuals. There are accumulating data to indicate that the heterozygous state may be identified by biochemical or physiologic tests.

The abnormal chemical structure of mucoproteins in duodenal contents of patients with cystic fibrosis tends to decrease the solubility, while the abnormal physicochemical behavior shows that these mucoproteins are easily denatured and rendered insoluble. If this were true of mucous secretions throughout the body it would be possible for a change in the physicochemical environment of these mucous secretions to cause irreversible precipitation of mucoproteins in organs such as the pancreas, liver and others, thus initiating the chain of clinical events and leading to many of the symptoms manifested by patients with the disease.

Despite the almost constant and striking association of Staphylococcus aureus and the respiratory involvement in cystic fibrosis, the distribution of bacteriophage types of this microorganism resembles that found in other hospitalized patients.

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Paul A. di Sant'Agnese
Pediatrics 1959;24;313

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