Clinical Manifestations of Cystic Fibrosis Among Patients With Diagnosis in Adulthood*

Marita Gilljam, MD; Lynda Ellis, RN; Mary Corey, PhD; Julian Zielenski, PhD; Peter Durie, MD; and D. Elizabeth Tullis, MD, FCCP

Objective: To define the clinical characteristics and diagnostic parameters of patients with cystic fibrosis (CF) diagnosed in adulthood.

Design: Retrospective cohort study.

Setting: Tertiary care center.

Patients and methods: All patients with a diagnosis of CF made at the Toronto CF Clinics between 1960 and June 2001. Data were collected prospectively and analyzed retrospectively.

Results: There were 73 of 1,051 patients (7%) with CF diagnosed in adulthood. Over time, an increasing number and proportion of patients received a diagnosis in adulthood: 27 patients (3%) before 1990, compared to 46 patients (18%) after 1990 (p < 0.001). The mean sweat chloride level was lower for those with CF diagnosed as adults, compared to those with a diagnosis as children (75 ± 26 mmol/L and 100 ± 19 mmol/L, respectively; p < 0.001) [mean ± SD], and adults were more likely to have pancreatic sufficiency (PS) than children (73% vs 13%, respectively; p < 0.0001). In 46 adults who received a diagnosis since 1990, the reason for the initial sweat test was pancreatitis (2 patients, 4%), pulmonary symptoms (18 patients, 39%), pulmonary and GI symptoms (10 patients, 22%), infertility (12 patients, 26%), and genetic screening (4 patients, 9%). Other manifestations were biliary cirrhosis (one patient) and diabetes mellitus (four patients, 9%). The diagnosis could be confirmed by sweat test alone in 30 of 46 patients (65%), by mutation analysis alone in 15 patients (33%), and by a combination in 31 patients (67%). Nasal potential difference (PD) measurements alone confirmed the diagnosis in the remaining 15 patients (33%).

Conclusion: Patients with CF presenting in adulthood often have PS, inconclusive sweat test results, and a high prevalence of mutations that are not commonly seen in CF diagnosed in childhood. Although most patients have lung disease of variable degrees, single-organ manifestations such as congenital bilateral absence of the vas deferens and pancreatitis are seen. Repeated sweat tests and extensive mutation analysis are often required. Nasal PD may aid the diagnosis, but has not been standardized for clinical diagnosis.

(CHEST 2004; 126:1215–1224)

Key words: adult; cystic fibrosis; cystic fibrosis transmembrane conductance regulator; diagnosis; genotype; ion transport

Abbreviations: CBAVD = congenital bilateral absence of the vas deferens; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; PD = potential difference; PI = pancreatic insufficiency; PS = pancreatic sufficiency

Cystic fibrosis (CF), the most common life-shortening, inherited disease in whites, is described as a disease that manifests primarily in childhood. Most patients with CF will reach adult age, and 48% of patients with CF in Canada are now > 18 years of age. Improved survival has been attributed to advances in treatment. However, increased awareness of the heterogeneous clinical manifestations of CF may have led to an increase in de novo diagnoses of CF in adulthood. A consensus statement defines the diagnostic criteria for CF: at least one typical clinical feature of CF is required, plus either evidence of CF transmembrane conductance regulator (CFTR) dysfunction or confirmation of CF-causing mutations on both chromosomes. During the last decade, we have assessed a large number of patients for possible CF. We have found that patients presenting with CF in adult age appear to be different compared to patients presenting in childhood. They tend to have more subtle findings, and traditional sweat test results may not be positive. Even if superior long-term prognosis may be expected for those with a diagnosis made in...
adulthood, patients with newly diagnosed disease will still have to accept living with a genetic and potentially severe chronic disease. For this reason, it is important to confirm or reject a diagnosis of CF as securely as possible. Given the diagnostic challenges we have encountered, we describe the spectrum of disease manifestations for patients who received a diagnosis in adulthood, and how they differ from patients who received a diagnosis of CF in infancy or childhood. We also describe the role for the various diagnostic parameters for CF including nasal potential difference (PD) measurements.

**Materials and Methods**

**Patient Ascertainment**

In Toronto, patients with CF attend the pediatric CF Program until age 16 to 18 years, when they are transferred to the adult CF Program. All patients who received a diagnosis at the Toronto Adult and Pediatric CF Clinics between January 1960 and June 2001, with focus on patients who received a diagnosis in adulthood since 1990 (after the institution of a separate Adult CF Program), were included in the study. Patients with CF diagnosed between 1944 and 1959 (92 children) were excluded due to Program), were included in the study. Patients with CF diagnosis since 1990 (after the institution of a separate Adult CF Program). All patients who received a diagnosis at the Toronto Clinics were excluded.

**Data Collection**

Data for all patients in both the pediatric and adult clinics are stored in a computerized CF patient database. Information on year and age at diagnosis, family history, pancreatic function status, sweat chloride values, genotype, pulmonary function, sputum cultures, severity and duration of symptoms at presentation, and reason for the initial sweat test were extracted from the database. Data available for symptoms at presentation (existence, duration, and severity of pulmonary and/or GI symptoms) were entered in the database as ranked numbers. For patients with CF diagnosed as adults after 1990, we also evaluated the results of nasal PD measurements, and reviewed the hospital charts for more detailed information on symptoms and disease manifestations.

**Mutation Analyses and Tests for Abnormal CFTR Function**

Sweat tests were done on at least two occasions by the urecholine method until the late 1980s, and thereafter by the method described by Gibson and Cooke. Sweat chloride levels < 40 mmol/L were considered negative, levels at 40 to 59 mmol/L were intermediate, and levels ≥ 60 mmol/L were diagnostic of CF. Nasal transepithelial PD measurement was done according to the protocol by Knowles et al. In brief, measurements were performed during perfusion with Ringer lactate (maximum PD) followed by perfusions with amiloride (blocking sodium transport), addition of chloride free solution (generating a chloride gradient), and isoproterenol (cyclic adenosine monophosphate activation of chloride permeability). We found chloride conductance based on the response to chloride free plus isoproterenol to be the primary diagnostic parameter for CF. Perfusion values outside the 99% confidence limit for healthy control subjects in our center (± 7.65 to ± 22.6 mV) were considered to be abnormal. Genomic DNA was isolated from lymphocytes according to standard protocols. Analysis of 31 of the most common CFTR mutations and for the polythymidine tract variant within the intron 8 acceptor splice site was performed in the routine laboratory. If two mutations were not identified, the polymerase chain reaction-based multiplex heteroduplex gel shift analysis on MDE0/00 gel matrix (BMA; Rockland, ME) was utilized for detection of CFTR mutations. The analysis included all the exons, their flanking intron sequences, and the promoter region (approximately 1 kilobase upstream of exon 1). Fragments displaying aberrant migration patterns were further characterized by direct-sequencing analysis using the Thermo Sequenase Radiolabeled Terminator Cycle Sequencing Kit (Amersham-Life Science; Cleveland, OH). Three variants (9T, 7T, and 5T) of the polythymidine tract (T-tract) in intron 8 were also tested. The 5T variant in intron 8 correlates with significantly increased exon 9 skipping (ie, producing incomplete CFTR messenger RNA transcripts missing exon 9) as compared with the 7T and 9T alleles.

**Clinical Evaluation**

A full history of symptoms suggestive of CF was taken, followed by physical examination. Pancreatic function was determined by 72-h dietary records and fecal fat determination and, in some cases, also confirmed by duodenal intubation, pancreatic stimulation with IV hormones, and analyses of pancreatic secretions. Serum trypsinogen was analyzed initially, and then serially in patients with pancreatic sufficiency (PS), in order to detect the onset of pancreatic insufficiency (PI). Spirometry was done according to the American Thoracic Society guidelines, and the FEV₁ was reported as percentage of predicted. Chest radiographic findings were described as normal, minor changes (sole linear scar or bronchiol wall thickening), or bronchiectasis. A modified oral glucose tolerance test was performed in nondiabetic subjects, with measurement of venous plasma glucose levels in a fasting state and 2 h after ingestion of 75 g of glucose, and results were recorded as described by Moran et al.
Statistical Analysis

Statistical analyses were performed for patients with CF diagnosed during the whole study period from 1960 to 2001, and for the subgroup with CF diagnosed between 1990 and 2001. The two-tailed t test was used for comparison between patients with CF diagnosed in adulthood and childhood for sweat chloride values. The \( \chi^2 \) test with Yates correction for continuity was used for comparison between the groups for pancreatic function status, symptoms at diagnosis, and for evaluation of change of proportion of diagnoses in childhood and adulthood over time. Computer software (SAS version 6.12; SAS Institute; Cary, NC) was used for all analyses.

RESULTS

Patients

The number of patients (approximately 550 patients) attending the Toronto CF clinics has remained quite constant over the last 10 years. However, the proportion of adults has increased and now exceeds 50% of the population. Of 1,051 patients (53% male patients) with CF diagnosed in the Toronto CF clinics since 1960, 73 patients (7%) had CF diagnosed in adulthood. The number and proportion of patients with CF diagnosed in adulthood has increased dramatically over the past 3 decades (Table 1).

Clinical Findings at Diagnosis in all Adult Patients With CF Diagnosed Between 1960 and 2001

The mean sweat chloride level was lower for patients with CF diagnosed as adults (75 ± 26 mmol/L) than for patients with CF diagnosed in childhood (100 ± 19 mmol/L, \( p < 0.001 \)) [mean ± SD]. This difference was also seen for the subgroups of children with PI (103 ± 16 mmol/L) compared to adults with PI (93 ± 18 mmol/L, \( p < 0.01 \)), and children with PS (85 ± 26 mmol/L) compared to adults with PS (68 ± 26 mmol/L, \( p < 0.001 \)). PS was more common in adults; 53 of 73 patients (73%) had PS at the time of diagnosis, compared to 124 of 978 patients (13%) with CF diagnosed in childhood (\( p < 0.0001 \)). PI developed after diagnosis in 5 of 53 adult patients (9%) with PS, and in 25 of 124 children (20%) with PS at diagnosis.

Pulmonary symptoms at time of diagnosis, including wheezing, chronic productive or nonproductive cough, hemoptysis, pneumothorax, shortness of breath, bronchitis, and pneumonia, were more common in adults (87%) than in children (64%) [\( p < 0.0002 \)]. A history of > 5 years of moderate or severe pulmonary symptoms was recorded in 34% of adult patients. GI symptoms recorded were abdominal cramps or discomfort, loose and frequent stools, difficulty maintaining weight despite adequate food intake, gastrointestinal reflux with or without esophagitis, cholecystitis, rectal prolapse in childhood, recurrent pancreatitis, and bleeding esophageal varices due to CF-related liver disease. Overall, GI symptoms were less common in patients with CF diagnosed in adulthood (47%) compared to childhood (81%) [\( p < 0.0001 \)].

Characteristics of 46 Adult Patients With CF Diagnosed Between 1990 and June 2001

Since 1990, the mean age at CF diagnosis of 46 adult patients was 32 ± 11 years (range, 16 to 58 years), with no age difference between male (54%) and female patients. The diagnosis was confirmed by two elevated sweat chloride values, or by identification of CF-causing mutations in 31 of 46 patients (67%) [Tables 2, 3]. Only 1 patient was homozygous, and 29 patients (63%) were heterozygous for the ΔF508 mutation. This compares with 49% and 39%, respectively, for patients with CF diagnosed in childhood during the same period of time. Ten additional rare mutations, not included in the 31-mutation screening panel, were detected by extensive mutation analysis. We performed separate analyses, including determination of the polythymidine tract of intron 8, of patients carrying at least one R117H mutation (Table 4). There were 112 sweat tests performed in 46 patients. For 15 patients (33%), with only one elevated or low-intermediate sweat chloride value and nondiagnostic mutations, CFTR malfunction was demonstrated by abnormal nasal PD (Tables 2, 5; Fig 1, 2).

The majority of patients were investigated because of pulmonary and/or GI symptoms (Table 6). All patients with pulmonary symptoms had chronic productive cough and recurrent airway infections requiring antibiotics. Shortness of breath, hemoptysis, and wheezing were other symptoms, and pulmonary lobectomy due to chronic infection had been performed in two patients. Nasal polyposis was recorded for 9 patients and sinusitis for 15 patients. The mean FEV1 was 81 ± 26% of predicted, and bronchiectasis was evident in 26 of 44 patients (59%) with

| Table 1—Proportion of Patients With CF Diagnosed in Adulthood and Childhood* |
|-----------------|-----------------|-----------------|
|                 | Adulthood†      | Childhood       |
| 1960–1969       | 6 (2)           | 276 (98)        |
| 1970–1979       | 6 (2)           | 261 (98)        |
| 1980–1989       | 15 (6)          | 230 (94)        |
| 1990–2001       | 46 (18)         | 211 (82)        |

*Data are presented as No. of diagnoses (%).
†Age ≥ 18 years, or presenting to and receiving diagnosis in the adult clinic. A higher proportion of diagnoses were made in adult age after, compared to before, 1990 (\( p < 0.0001 \)), even after excluding 11 adult patients derived from recent research studies (\( p < 0.0001 \)).
available radiographs, while 13 patients (30%) had normal radiographic findings (Fig 3). Sputum cultures were available for 31 patients (67%); *Pseudomonas aeruginosa* was cultured from 21 patients (68%), *Haemophilus influenzae* from 2 patients, *Escherichia coli* from 1 patient, and *Stenotrophomonas maltophilia* from 2 patients. Three patients had been treated for pulmonary infection caused by *Mycobacterium avium intracellulare* complex; one of them had also been treated for allergic bronchopulmonary aspergillosis.

Loose and frequent stools and abdominal pain were the most common GI symptoms, and PI was confirmed in seven patients (15%). Repeated low trypsinogen levels were recorded for 3 of 39 patients with PS who later acquired PI; 1 of 4 patients with chronic pancreatitis later acquired PI. The pancreatic stimulation test revealed low fluid and bicarbonate secretion but adequate lipase and colipase secretion in five patients with PS and some GI symptoms. Cholecystectomy had been performed in four patients. Only one patient had clinical evidence of liver cirrhosis. From a large group of men with infertility due to congenital bilateral absence of the vas deferens (CBAVD), participating in a genetic study (manuscript in preparation; PR Durie, MD; June 1999), 10 men fulfilled the criteria for a diagnosis of CF. One of these men, a 35-year-old healthy man with PS, abnormal nasal PD, and one elevated sweat chloride value had an older brother with mild CF, the same R334W/R334W genotype, and who acquired PI in adulthood. Results of sweat tests performed in childhood had been negative. A genetic study on patients with recurrent pancreatitis led to the diagnosis of CF in one 17-year-old woman. Genetic screening as part of a planning for pregnancy led to the diagnosis in one man who was subsequently confirmed to be infertile (Table 4). Diabetes mellitus was present at the time of diagnosis of CF in three patients with PS (35 years, 50 years, and 57 years of age, respectively) and confirmed on the first yearly routine oral glucose tolerance test (OGTT) in one 19-year-old patient with PI.

There were two patients with no identified CFTR mutations. A 57-year-old nonsmoking woman, with a lifelong history of productive cough, pulmonary in-

<table>
<thead>
<tr>
<th>Tests</th>
<th>No./Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two sweat chloride levels &gt; 60 mmol/L*</td>
<td>30/46 (65)</td>
</tr>
<tr>
<td>Two disease-causing mutations</td>
<td>15/46 (33)</td>
</tr>
<tr>
<td>Combination of two sweat chloride levels &gt; 60 mmol/L and two disease-causing mutations†</td>
<td>31/46 (67)</td>
</tr>
<tr>
<td>Abnormal nasal PD‡</td>
<td>37/41 (90)‡</td>
</tr>
</tbody>
</table>

*Three patients had only one sweat test performed (chloride levels, 91 mmol/L, 108 mmol/L, and 109 mmol/L, respectively), but CF in a sibling or two CF-causing mutations.
†Genetic analysis was diagnostic for one patient with intermediate sweat chloride values.
‡Change in response to chloride free plus isoproterenol perfusions > 7.65 mV (less negative).
§Nasal PD confirmed the diagnosis for 15 of 37 patients for whom sweat tests and genetic analyses were nondiagnostic.

Table 3—Mutations Identified in 44/46 Adult Patients With CF*

<table>
<thead>
<tr>
<th>Two CF-Causing CFTR Mutations</th>
<th>Two CFTR Mutations</th>
<th>One CFTR Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele 1</td>
<td>Allele 2</td>
<td>Allele 1</td>
</tr>
<tr>
<td>AF508</td>
<td>AF508</td>
<td>AF508</td>
</tr>
<tr>
<td>1717-1G &gt; A</td>
<td>711 + 3A → G†</td>
<td>AF508</td>
</tr>
<tr>
<td>AF508</td>
<td>R117H, 5T†</td>
<td>AF508</td>
</tr>
<tr>
<td>AF508</td>
<td>1898 + 1G → A</td>
<td>AF508</td>
</tr>
<tr>
<td>AF508</td>
<td>R347P</td>
<td>AF508</td>
</tr>
<tr>
<td>AF508</td>
<td>2789 + 5G → A</td>
<td>AF508</td>
</tr>
<tr>
<td>AF508</td>
<td>2789 + 5G → A</td>
<td>AF508</td>
</tr>
<tr>
<td>AF508</td>
<td>A455E</td>
<td>AF508</td>
</tr>
<tr>
<td>G551D</td>
<td>621 + 1G → T</td>
<td>AF508</td>
</tr>
<tr>
<td>AF508</td>
<td>4016insT†</td>
<td>G551D</td>
</tr>
<tr>
<td>AF508</td>
<td>L1077P†</td>
<td>G551D</td>
</tr>
<tr>
<td>R334W,7T</td>
<td>R334W,7T†</td>
<td>G551D</td>
</tr>
<tr>
<td>AF508</td>
<td>3849 + 10kbc &gt; T</td>
<td>G551D</td>
</tr>
<tr>
<td>AF508</td>
<td>2789 + 5G &gt; A</td>
<td>G551D</td>
</tr>
<tr>
<td>AF508</td>
<td>1677delT &gt; A†</td>
<td>G551D</td>
</tr>
<tr>
<td>AF508</td>
<td>5540R†</td>
<td>G551D</td>
</tr>
</tbody>
</table>

*In two patients, no mutations were identified despite extensive analyses.
†Not classified as CF-causing mutations.
‡Not detected by the 31 mutation screening panel.
Table 4—Characteristics of Patients With the R117H Mutation

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Pancreatic Function</th>
<th>Sweat Chloride, mmol/L</th>
<th>Genotype</th>
<th>Nasal PD, Maximum/Chloride Conductance*</th>
<th>Sputum Culture</th>
<th>FEV1, % Predicted</th>
<th>Comment†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>Male</td>
<td>PS</td>
<td>24</td>
<td>ΔF508/R117H,7T</td>
<td>−50/5</td>
<td>S aureus</td>
<td>114</td>
<td>Screening, I</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>Female</td>
<td>PS</td>
<td>114, 106</td>
<td>ΔF508/R117H,5T</td>
<td>−52/2</td>
<td>P aeruginosa</td>
<td>84</td>
<td>P, FH</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>Female</td>
<td>PS</td>
<td>65, 75, 63</td>
<td>ΔF508/R117H,7T</td>
<td>−44/12</td>
<td>P aeruginosa</td>
<td>49</td>
<td>P, BE</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>Female</td>
<td>PS</td>
<td>69, 48</td>
<td>ΔF508/R117H,7T</td>
<td>−62/0</td>
<td>S aureus</td>
<td>65</td>
<td>P, BE, BC, D</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>Male</td>
<td>PS</td>
<td>66, 64</td>
<td>G551D/R117H,7T</td>
<td>−29/8</td>
<td>H influenzae</td>
<td>100</td>
<td>I, P</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>Male</td>
<td>PS</td>
<td>116, 94</td>
<td>ΔF508/R117H,7T</td>
<td>Not done</td>
<td></td>
<td>102</td>
<td>I, P, GI</td>
</tr>
</tbody>
</table>

*Maximum basal PD/change in response to chloride free plus isoproterenol perfusion.
†P = pulmonary symptoms; FH = CF in sibling; BE = bronchiectasis; BC = biliary cirrhosis; D = diabetes mellitus; I = infertility; GI = GI symptoms including pancreatitis and an episode of jaundice.

Discussion

This study demonstrates that the proportion and number of patients with CF diagnosed in adulthood has increased. A large number of these patients presented with subtle symptoms or single-organ disease. The majority had pulmonary disease and PS. In one third of these patients, the diagnosis of CF could not be confirmed by sweat testing, or by analysis of CF-causing mutations based on the current criteria. Nasal PD measurements proved to be an important diagnostic tool for confirmation of abnormal chloride conductance.

In Toronto, the number of children with CF diagnosed has decreased slightly over the past 2 decades, probably due to establishment of new CF centers in the surrounding area and, over the last decade, the availability of prenatal diagnosis and option, following genetic counseling, to terminate CF fetuses. In addition, an unexpectedly high number of patients had CF diagnosed in several large families in the 1960s, contributing to the peak incidence. After the discovery of the CFTR...
Several patients followed up for suspected CF had the diagnosis confirmed. For the purpose of this study, such patients were regarded as receiving a diagnosis in childhood, and did not contribute to the increased proportion of patients with diagnoses made in adulthood. Following the discovery of the gene, we launched several studies assessing monosymptomatic clinical manifestations for evidence of CFTR mutations. Consequently, among 46 patients with CF diagnosed in adulthood since 1990, 11 patients (24%) received a diagnosis as a direct consequence of research studies on patients with CBAVD or recurrent pancreatitis. When these patients were excluded, the proportion of patients with CF diagnosed in adulthood remained higher after 1990 compared to preceding years. This suggests that there is an increased awareness that patients with CF can receive a diagnosis in adulthood, as well as recognition that patients may not present with the typical clinical picture seen in children.20–30

Severe CF-related liver disease at diagnosis of CF is an unusual presentation in adults but has been described before.27 There is considerable debate where to draw the diagnostic line between CF and CBAVD.31,32 However, based on the guidelines of the 1998 consensus report of diagnosis of CF, 10 of 47 men participating in a genotype/phenotype study in men seeking medical advice for infertility (results published in part33,34) subsequently had CF diagnosed. Patients with CBAVD should consequently be assessed for possible CF.

CF-related diabetes mellitus is common in adults with CF, and is described to affect as many as 32% of patients > 25 years old.16,35 However, there is a strong association between CF-associated diabetes mellitus and PI. This explains the low prevalence of diabetes mellitus in this selected adult population. Furthermore, two of four adult patients with PS described here with CF diagnosed after 1990 could well have acquired type II diabetes mellitus as opposed to CF-related diabetes mellitus. Unfortunately, it is difficult to clinically distinguish the two entities.

Much research has focused on genotype-phenotype correlation in CF, and possible relations between CFTR mutations and other diseases.36 Increased frequency of CFTR mutations have been reported for patients with idiopathic pancreatitis,37 disseminated bronchiectasis,38 and sinusitis,39,40 but not for patients with severe nasal polyposis.41 An association between mutations in the CFTR gene and allergic bronchopulmonary aspergillosis,42 as well as asthma,43,44 has also been suggested. However, CF-related clinical manifestations in obligate CFTR mutation heterozygotes do not seem to be overrepresented, compared to individuals with a low risk of being carriers.45 With > 1,200 mutations reported to the CF genetic database (www.genet.sickkids.on.ca/cftr) and an increasing number of diseases with reported increased frequency of CFTR mutations, the diagnostic line between CF and other diseases with mutations in the CFTR gene is becoming increasingly blurred. Modifier genes and envi-
vironmental factors probably account for much of the variability of disease, and may also explain associations found between CFTR gene mutation and other diseases such as asthma, sinusitis, and allergic bronchopulmonary aspergillosis.\textsuperscript{36,46} As a consequence, the severity of mutations carried cannot securely predict the severity of disease, especially with regard to pulmonary disease.

The R117H mutation is not generally considered to cause CF disease unless it is combined with the 5T variant on the same allele.\textsuperscript{2} Nevertheless, we diagnosed CF in five patients with R117H,7T in combination with a severe mutation on the other allele. This suggests that the R117H,7T mutation can be associated with variable phenotypic features, including asymptomatic carriers, CBAVD, and CF with variable organ manifestations.

The sweat test remains the hallmark diagnostic test for CF.\textsuperscript{47} We recommend repeated sweat tests when borderline values are obtained and if there is a strong clinical suspicion of CF. Normal or intermediate values do not exclude a diagnosis of CF, especially in older people.\textsuperscript{48,49}

Lower mean sweat chloride levels for adults, compared to children, in patients with PI as well as PS are consistent with the overall picture of milder CF in patients with a diagnosis made as adults. This may be a consequence of differential effects of rare CFTR mutations and/or the modulating effects of non-CFTR genetic variants.

Commercial genetic screening tests have consid-

![Figure 2](http://journal.publications.chestnet.org/pdaccess.asmx?url=/data/journals/chest/22017/)

**Table 6—Patients With Diagnosis of CF Made in Adulthood Between 1990–2001; Symptoms and Pancreatic Function Status at Presentation in 46 Adults (25 men)**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No.</th>
<th>%</th>
<th>PI/PS, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary only</td>
<td>18</td>
<td>39</td>
<td>0/18</td>
</tr>
<tr>
<td>GI only</td>
<td>2</td>
<td>4</td>
<td>0/2*</td>
</tr>
<tr>
<td>Pulmonary and GI</td>
<td>10</td>
<td>22</td>
<td>7/3†</td>
</tr>
<tr>
<td>Infertility (men only)</td>
<td>12</td>
<td>26</td>
<td>0/12</td>
</tr>
<tr>
<td>Screening/family history†</td>
<td>4</td>
<td>9</td>
<td>0/4</td>
</tr>
</tbody>
</table>

*One patient later acquired PI.
†Two patients later acquired PI.
‡Forty-eight percent of male patients.
§Five other patients with CF in a sibling were investigated because of symptoms.

The R117H mutation is not generally considered to cause CF disease unless it is combined with the 5T variant on the same allele.\textsuperscript{2} Nevertheless, we diagnosed CF in five patients with R117H,7T in combination with a severe mutation on the other allele. This suggests that the R117H,7T mutation can be associated with variable phenotypic features, including asymptomatic carriers, CBAVD, and CF with variable organ manifestations.

The sweat test remains the hallmark diagnostic test for CF.\textsuperscript{47} We recommend repeated sweat tests when borderline values are obtained and if there is a strong clinical suspicion of CF. Normal or intermediate values do not exclude a diagnosis of CF, especially in older people.\textsuperscript{48,49}

Lower mean sweat chloride levels for adults, compared to children, in patients with PI as well as PS are consistent with the overall picture of milder CF in patients with a diagnosis made as adults. This may be a consequence of differential effects of rare CFTR mutations and/or the modulating effects of non-CFTR genetic variants.

Commercial genetic screening tests have consid-
erable limitations as a diagnostic tool in adulthood. The prevalence of different mutations varies between different countries and ethnic populations; therefore, the tests must be adapted for the target population. Screening panels usually include only the more common disease-causing mutations associated with childhood onset of CF. Patients presenting in adulthood frequently carry one or more rare CFTR gene mutations, which are often not included in most commercial screening panels or are not proven CF-causing mutations.

Electrophysiologic investigation using nasal PD may aid in the diagnosis of CF in patients with low or intermediate sweat chloride levels or undetected CF-causing mutations. However, the method has limitations for patients with nasal infection, previous surgery, or polyps, and is technically difficult to perform. The 1998 consensus report suggests that a raised basal PD as well as a low response to perfusion with a chloride-free solution and a β-agonist provide strong evidence for the diagnosis of CF. However, this test has not been standardized for diagnostic purposes, and reference standards have not been established. This test should be limited to research centers with considerable experience with the test. We did not find basal PD to be reliable for distinguishing a CF response, whereas the response to chloride free plus isoproterenol perfusion appeared to be best in discriminating between CF and controls.

The diagnosis may come as a relief and acknowledgment of symptoms for patients with a long history of illness. The psychosocial impact for a young person with mild symptoms, or who has received a diagnosis of CF as a consequence of screening is completely different. It could be argued that these patients do not benefit from knowing their diagnosis. CF can affect multiple organs, and there is a potential for future complications, which could be anticipated or treated earlier with a confirmed diagnosis. Patients with CF diagnosed as adults should be informed that they are different from patients with CF diagnosed in childhood. There is a need for patient information for this unique population, but currently there are inadequate data to provide exact prognostic facts.

In conclusion, we found that patients with CF diagnosed in adulthood present with a wide spectrum of symptoms and severity of disease that does not resemble the characteristic features at presentation in childhood. Furthermore, patients may come to the attention of several different disciplines, including andrologists, gastroenterologists, otolaryngologists, and respiratory physicians. Evaluation with
sweat testing and limited mutation analyses may be nondiagnostic. We advocate referral to a comprehensive multidisciplinary program, with access to more sophisticated diagnostic tools for the diagnosis and care of these patients.

ACKNOWLEDGMENT: The authors thank Sandi Peroff for help with the data collection.

REFERENCES

1 Report of the Canadian Patient Data Registry. Toronto, Ontario: Canadian Cystic Fibrosis Foundation, 2001
36 Zielenskksi J. Genotype and phenotype in cystic fibrosis. Respiration 2000; 67:117–133
47 LeGrys V. Assessment of sweat-testing practices for the diagnosis of cystic fibrosis. Arch Pathol Lab Med 2001; 125:1420–1424