

also recommended for all pregnant women with detectable plasma viremia in order to optimize treatment for the woman and prevent the transmission of HIV to the newborn. However, to prevent mother-to-infant transmission and to treat patients with an acute primary HIV-infection syndrome, antiretroviral therapy should be instituted promptly, before the results of resistance testing are available. Appropriate changes in the regimen can be made as needed once the results become available.

The study by Little et al. emphasizes the need for new antiretroviral drugs, including agents within existing classes of reverse-transcriptase inhibitors and protease inhibitors, as well as agents that attack HIV at different stages in its replicative cycle. Several nucleoside reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, and protease inhibitors that are active against existing resistant viruses are under development. In addition, new classes of agents — for example, compounds that block the attachment of HIV or its entry into susceptible cells and agents that block the integration of HIV into the DNA in those cells — are in clinical trials. Therapeutic vaccinations and other immunotherapeutic approaches to augment the anti-HIV effects of antiretroviral drugs may also ultimately prove useful in reducing the prevalence of drug resistance.

HIV has proved to be a wily opponent and will most likely develop resistance to any new antiretroviral drug that is introduced. It will be a continuing challenge to develop and use optimally existing and new drug regimens and therapeutic strategies. Our goals should include worldwide access to the most potent antiretroviral regimens, appropriate education about adherence to these complex treatment programs, monitoring of all treated patients for viral suppression and emergence of resistance, and development of long-term strategies to prevent resistance or to treat resistant virus effectively when it develops. Only by achieving these goals can we minimize viral drug resistance and thereby maximize therapeutic options for patients' lifelong battle against HIV.

MARTIN S. HIRSCH, M.D.

Massachusetts General Hospital
Boston, MA 02114

REFERENCES

1. Little SJ, Holte S, Routy J-P, et al. Antiretroviral drug resistance among subjects recently infected with HIV. *N Engl J Med* 2002;347:385-94.
2. Yerly S, Vora S, Rizzardì P, et al. Acute HIV infection: impact on the spread of HIV and transmission of drug resistance. *AIDS* 2001;15:2287-92.
3. Duwe S, Brunn M, Altmann D, et al. Frequency of genotypic and phenotypic drug-resistant HIV-1 among therapy-naïve patients of the German Seroconverter Study. *J Acquir Immune Defic Syndr* 2001;26:266-73.
4. Adje C, Cheingsong R, Roels TH, et al. High prevalence of genotypic and phenotypic HIV-1 drug-resistant strains among patients receiving antiretroviral therapy in Abidjan, Cote d'Ivoire. *J Acquir Immune Defic Syndr* 2001;26:501-6.

5. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet* 1999;353:2195-9.
6. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. *AIDS* 2000;14:F83-F93.
7. Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. *AIDS* 2002;16:209-18.
8. Cohen CJ, Hunt S, Sension M, et al. A randomized trial assessing the impact of phenotypic resistance testing on antiretroviral therapy. *AIDS* 2002;16:579-88.
9. Weinstein MC, Goldie SJ, Losina E, et al. Use of genotypic resistance to guide HIV therapy: clinical impact and cost-effectiveness. *Ann Intern Med* 2001;134:440-50.
10. Duval X, Lamotte C, Race E, et al. Amprenavir inhibitory quotient and virological response in human immunodeficiency virus-infected patients on an amprenavir-containing salvage regimen without or with ritonavir. *Antimicrob Agents Chemother* 2002;46:570-4.
11. Hirsch MS, Brun-Vezinet F, D'Aquila RT, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society-USA Panel. *JAMA* 2000;283:2417-26.
12. The EuroGuidelines Group for HIV Resistance. Clinical and laboratory guidelines for the use of HIV-1 drug resistance testing as part of treatment management: recommendations for the European setting. *AIDS* 2001;15:309-20.

Copyright © 2002 Massachusetts Medical Society.

WHAT IS CYSTIC FIBROSIS?

CYSTIC fibrosis is a heterogeneous recessive genetic disorder with pathobiologic features that reflect mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Classic cystic fibrosis reflects two loss-of-function mutations in the *CFTR* gene and is characterized by chronic bacterial infection of the airways and sinuses, fat maldigestion due to pancreatic exocrine insufficiency, infertility in males due to obstructive azoospermia, and elevated concentrations of chloride in sweat (Fig. 1).¹ Patients with nonclassic cystic fibrosis have at least one copy of a mutant gene that confers partial function of the *CFTR* protein, and such patients usually have no overt signs of maldigestion because some pancreatic exocrine function is preserved (Fig. 1). Although a value of 60 mmol per liter or higher on the sweat chloride test is diagnostic of cystic fibrosis, the concentration of sweat chloride is usually somewhat lower in patients with the nonclassic form of the disease (approximately 60 to 90 mmol per liter) than in those with classic cystic fibrosis (approximately 90 to 110 mmol per liter); moreover, the test result is sometimes borderline (40 to 59 mmol per liter) or normal (<40 mmol per liter) in the nonclassic form.² Some *CFTR* mutations that result in residual *CFTR* function have been linked to disease of one organ, such as late-onset pulmonary disease, congenital bilateral absence of the vas deferens, or idiopathic pancreatitis.³⁻⁵

To cope with the diagnostic challenges posed by nonclassic cystic fibrosis, a consensus statement has been developed, which defines cystic fibrosis as the

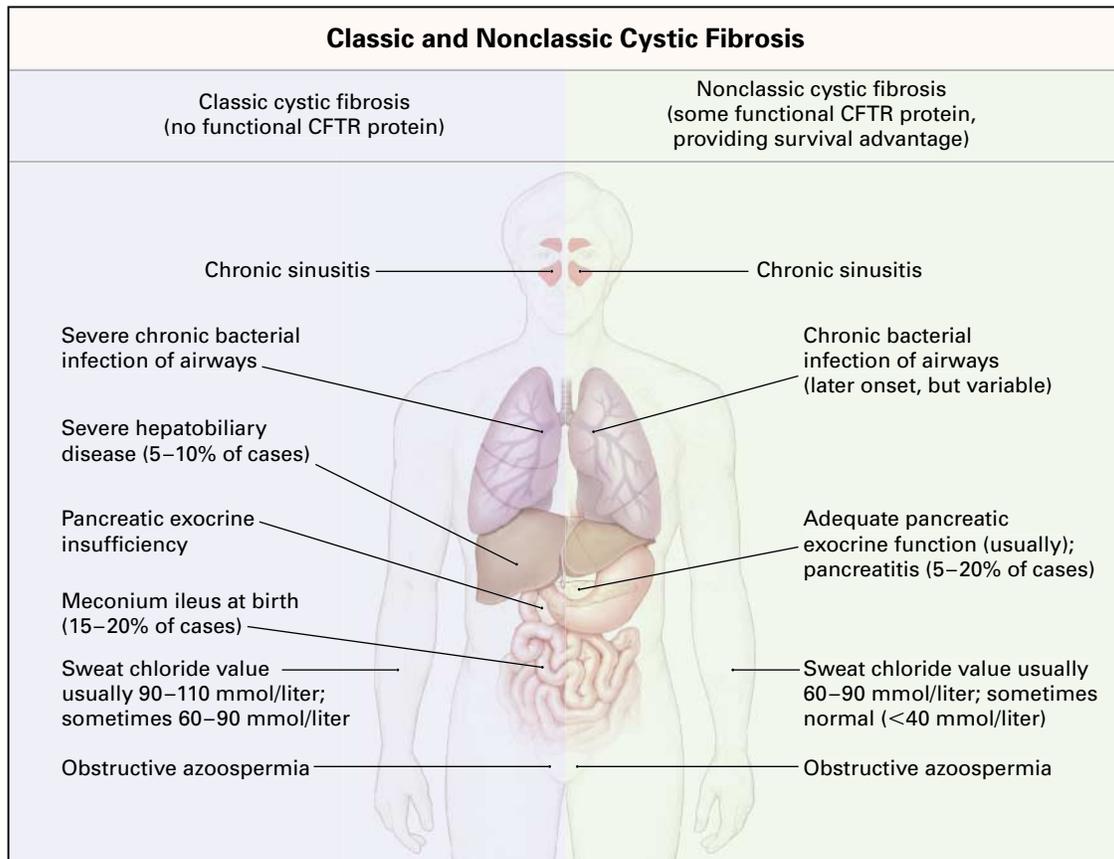


Figure 1. Classic and Nonclassic Cystic Fibrosis.

The findings in classic cystic fibrosis are shown on the left-hand side, and those of nonclassic cystic fibrosis on the right-hand side. Patients with nonclassic cystic fibrosis have better nutritional status and better overall survival. Although the lung disease is variable, patients with nonclassic cystic fibrosis usually have late-onset or more slowly progressive lung disease. Sweat-gland function, as evidenced by the sweat chloride test, is abnormal but not to the extent noted in classic cystic fibrosis. Pancreatitis may occur in patients with nonclassic disease. However, chronic sinusitis and obstructive azoospermia occur in both groups of patients. On the basis of these findings, one can infer that mutations in *CFTR*, perhaps coupled with other genetic or environmental factors, may confer a predisposition to sinusitis, pancreatitis, or congenital bilateral absence of the vas deferens (azoospermia) in the general population.

presence of a coherent clinical syndrome, plus either evidence of CFTR dysfunction (an abnormal value for sweat chloride or nasal potential difference) or confirmation of cystic fibrosis–causing mutations on both alleles.⁶ Patients who have disease linked to mutant *CFTR* with residual protein function but do not meet the diagnostic criteria are considered to have *CFTR*-related disease.

In this issue of the *Journal*, Groman et al. report extensive genetic analyses of DNA samples from 74 patients with clinical features suggestive of cystic fibrosis.⁷ Several important observations emerged. First, of the 34 patients in whom standard screening had identified a single cystic fibrosis–causing mutation,

most (26) had a second mutation or the IVS8-5T allele, which was discovered by comprehensive sequencing of the *CFTR* gene. The IVS8-5T allele frequently leads to splicing out of exon 9 of *CFTR*, which may reduce the function of CFTR protein to a level associated with clinical disease.³⁻⁵ Thus, in patients with some clinical features that overlap those of cystic fibrosis, plus one *CFTR* mutation identified by genotype screening, intensive genetic testing of the second allele is likely to identify a second *CFTR* mutation or polymorphism.

Nevertheless, identification of a second mutation or polymorphism in these patients does not conclusively establish the molecular basis of their clinical syndrome.

Missense mutations must be validated as disease-causing mutations by testing the prevalence in a large number of non-cystic fibrosis chromosomes or by conducting functional studies, and the effect of the 5T allele must be assessed with the use of functional assays.⁶ Groman et al. do not report which patients had abnormal values for sweat chloride or nasal potential difference, so it is difficult to determine how many of these patients had cystic fibrosis on the basis of the current diagnostic criteria. Such considerations underscore the limitations of using extensive mutation analysis alone to establish conclusively (or rule out) a diagnosis of cystic fibrosis in unusual cases; extensive clinical and physiological studies are required to complement the genetic data.

The second observation is more provocative. In 40 of the 74 patients who underwent extensive genetic testing, standard screening had shown no *CFTR* mutations. In this group of patients, genetic assays that included Southern blot analysis to detect genomic rearrangements and sequencing of a portion of the promoter region showed two mutant *CFTR* alleles in only three patients and a single mutation in seven patients. In the other 30 patients, there were no *CFTR* mutations. The simplest hypothesis is that mutant *CFTR* was not the basis of the variant clinical syndrome in these 30 patients. The majority of the patients did not undergo extensive testing for evidence of *CFTR*-mediated abnormalities in ion transport. However, the results of linkage (haplotype) analyses of *CFTR* and studies of nasal and sweat-gland ion transport in four patients from two families were consistent with this hypothesis.

It is not surprising that some patients have a cystic fibrosis-like clinical syndrome (“variant cystic fibrosis”) reflecting environmental and genetic influences other than mutations in *CFTR*,^{3,8} and some of the patients in the study by Groman et al. may have had such a variant form of the disease. There have been several reports of mutations in different genes that produce similar clinical phenotypes by acting through common pathways in biologic function, including disorders with clinical features that overlap those of cystic fibrosis.⁹⁻¹²

In the absence of more extensive clinical, radiographic, and physiological information, it is premature to conclude that most (or many) of the patients in this study who did not have any mutations in *CFTR* had a variant form of cystic fibrosis. Since we cannot rely on molecular testing, a diagnosis of cystic fibrosis must be established by ruling out other disorders, because the clinical phenotype is not sufficiently distinct.

Most patients whose DNA was studied by Groman et al. had respiratory symptoms that are common in the general population (recurrent cough and wheezing, pneumonia, reactive airway disease, and chronic

sinusitis). These symptoms may be manifestations of a relatively common disorder (allergic disease or asthma) or a less common disorder (primary ciliary dyskinesia, postinfectious bronchiectasis, hypogammaglobulinemia, or α -antiprotease deficiency) that might be present in this highly selected group of patients. Nor can we rely on the sweat chloride test to confirm the diagnosis. The patient population in the study by Groman et al. was preselected, in part, on the basis of borderline or abnormal sweat chloride values, and there is substantial test and biologic variability in sweat chloride values, particularly those in the borderline range, among normal persons.^{2,7,13,14}

The high prevalence of steatorrhea — in 9 of the 30 patients without *CFTR* mutations — is striking. However, in the absence of a preestablished diagnosis of cystic fibrosis (or any condition known to cause pancreatic insufficiency), studies of fecal fat balance are nonspecific, and the mechanism of excessive fat losses cannot be assigned to maldigestion rather than malabsorption (i.e., a pancreatic cause rather than an intestinal cause).

Could some of the patients in this study have had well-defined (but undiagnosed) disorders, such as a gastrointestinal mucosal defect of absorption or the Shwachman–Diamond syndrome, the latter of which is also associated with recurrent respiratory infections? Finally, Groman et al. do not report whether any of the patients had abnormalities that are also linked to slight increases in sweat chloride values, such as malnutrition, adrenal abnormalities, or the skin changes associated with disorders such as hypogammaglobulinemia.¹⁵ Thus, a cystic fibrosis-like constellation of signs and symptoms may reflect, directly or indirectly, the effects of several recognized clinical disorders and their consequences, and labeling such a constellation “variant cystic fibrosis” is a concern.

In theory, some patients may have a variant form of cystic fibrosis without mutations in the *CFTR* gene, although such an entity will be difficult to define, unless an alternative genetic cause is identified, perhaps coupled with diagnostic abnormalities of ion transport. The study by Groman et al. highlights the potential importance of the findings in such patients, which provide an opportunity to gain further insight into mechanisms underlying the pathobiology of the cystic fibrosis phenotype. The study also underscores the challenges encountered in the pursuit of novel pathophysiological insights. These effects will require not only molecular analyses, but also intensive evaluation of patients with the use of standard clinical, radiographic, and biochemical techniques. Moreover, we must broaden our approaches to evaluating ion transport in vivo and use evolving methods (proteomics) to identify biomarkers of other nearly unique features of cystic fibrosis. We look forward to further

definition of the clinical and biologic phenotype in patients such as those described by Groman et al.

MICHAEL R. KNOWLES, M.D.

University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-7248

PETER R. DURIE, M.D.

University of Toronto
Toronto, ON M5G 1X8, Canada

REFERENCES

1. Welsh MJ, Ramsey BW, Accurso FJ, Cutting GR. Cystic fibrosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic and molecular bases of inherited disease*. 8th ed. New York: McGraw-Hill, 2001: 5121-88.
2. Wilschanski M, Zielenski J, Markiewicz D, et al. Correlation of sweat chloride concentration with classes of the cystic fibrosis transmembrane conductance regulator gene mutations. *J Pediatr* 1995;127:705-10.
3. Noone PG, Knowles MR. 'CFTR-opathies': disease phenotypes associated with cystic fibrosis transmembrane regulator gene mutations. *Respir Res* 2001;2:328-32.
4. Chillon M, Casals T, Mercier B, et al. Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens. *N Engl J Med* 1995;332:1475-80.
5. Noone PG, Zhou Z, Silverman LM, Jowell PS, Knowles MR, Cohn JA. Cystic fibrosis gene mutations and pancreatitis risk: relation to epithelial ion transport and trypsin inhibitor gene mutations. *Gastroenterology* 2001;121:1310-9.
6. Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement: Cystic Fibrosis Foundation Consensus Panel. *J Pediatr* 1998; 132:589-95.
7. Groman JD, Meyer ME, Wilmott RW, Zeitlin PL, Cutting GR. Variant cystic fibrosis phenotypes in the absence of *CFTR* mutations. *N Engl J Med* 2002;347:401-7.
8. Mekus F, Ballman M, Bronsveld I, et al. Cystic-fibrosis-like disease unrelated to the cystic fibrosis transmembrane conductance regulator. *Hum Genet* 1998;102:582-6.
9. Pennarun G, Escudier E, Chapelin C, et al. Loss-of-function mutations in a human gene related to *Chlamydomonas reinhardtii* dynein IC78 result in primary ciliary dyskinesia. *Am J Hum Genet* 1999;65:1508-19.
10. Zariwala M, Noone PG, Sannuti A, et al. Germline mutations in an intermediate chain dynein cause primary ciliary dyskinesia. *Am J Respir Cell Mol Biol* 2001;25:577-83.
11. Olbrich H, Haffner K, Kispert A, et al. Mutations in *DNAH5* cause primary ciliary dyskinesia and randomization of left-right asymmetry. *Nat Genet* 2002;30:143-4.
12. Thakker RV. Molecular pathology of renal chloride channels in Dent's disease and Bartter's syndrome. *Exp Nephrol* 2002;8:351-60.
13. LeGrys VA. Assessing quality assurance for sweat chloride testing. *Clin Lab Sci* 1992;5:354-7.
14. Davis PB, Del Rio S, Muntz JA, Dieckman L. Sweat chloride concentration in adults with pulmonary diseases. *Am Rev Respir Dis* 1983;128: 34-7.
15. Rodrigues ME, Melo MC, Reis FJ, Penna FJ. Concentration of electrolytes in the sweat of malnourished children. *Arch Dis Child* 1994;71: 141-3.

Copyright © 2002 Massachusetts Medical Society.

COLLECTIONS OF ARTICLES ON THE *JOURNAL'S* WEB SITE

The *Journal's* Web site (www.nejm.org) sorts published articles into 51 distinct clinical collections, which are listed on the home page and can be used as convenient entry points to clinical content. In each collection, articles are cited in reverse chronologic order, with the most recent first.
