Cystic fibrosis is a systemic disorder transmitted by autosomal recessive genetics which is still characterized as the most common fatal genetic disease in whites. Approximately 5 percent of the US white population are carriers of the CF gene. Carriers of the CF mutation do not manifest symptoms, a heterozygote advantage has not been demonstrated, and there is at present no carrier test that can be applied to the general population. The basic biochemical abnormality in CF is not known, although rapid progress is being made toward that end. Molecular biologists using recombinant DNA techniques have located the CF gene on a small portion of the long arm of chromosome 7, providing a major step toward isolating the gene itself and finally understanding the biochemical pathways involved in the clinical manifestations of CF.

All fields of medicine may be touched by this disease, and it is possible for the astute physician to find adult patients with CF while evaluating chronic sinusitis, asthma, pancreatic insufficiency, sprue-like symptoms, azoospermia, or cirrhosis and portal hypertension. Similarly, there is great variability in the clinical course of this disease, and deterioration does not occur at the same rate in all patients. Although CF is a systemic disorder, it is the pulmonary disease, recurrent pulmonary bacterial infections superimposed on chronic colonization of the airways and resultant inflammation leading to destructive disease of the airways (bronchiectasis), which causes most of the morbidity. Ninety percent of CF patients die of respiratory failure.

Despite the promise that molecular biology holds for the ultimate therapy for CF, standard care for pulmonary disease due to CF today remains based on prompt initiation of effective treatment of the disease of the airways. In 1988, widespread diagnostic and therapeutic programs have made possible an increased median survival to almost 27 years in CF centers. In the paragraphs that follow, we will present a limited summary of both new and old therapies that remain controversial. The purpose of such a, necessarily, circumscribed review is to highlight therapeutic modalities of promise and to expose common treatments based on inadequate data, in an attempt to provide debate between colleagues, to stimulate clinical trials, and to suggest directions for future clinical investigation.

THE CF PULMONARY LESION

The lungs in CF are morphologically normal at birth, and the onset of pulmonary pathology may occur anytime after birth, with varying severity of the resulting respiratory signs and symptoms. By the time patients with CF enter adulthood, only 2 percent lack evidence of pulmonary disease by history, by chest radiographic examination, and by pulmonary function tests. Recent morphometric work performed on lungs from patients with CF obtained at autopsy indicate that the airway disease and pulmonary remodeling are irregularly distributed and that the upper lobe segments are disproportionately involved. Careful light-microscopic and electron microscopic studies have failed to identify a single lesion specific for CF. In contradistinction to the usual pseudomonas pneumonia, the lesion in CF is largely confined to the airway, with destruction of the wall leading to bronchiolitis and eventually bronchiectasis. As the airway disease becomes established, patchy areas of parenchymal involvement (bronchopneumonia) may become more apparent (Fig 1).

Many adults will have a long history of respiratory infections which started in childhood. Pulmonary disease due to CF may present acutely with staphylococcal pneumonia or insidiously with persistent
cough following an apparent viral upper respiratory infection. The acquisition of mucoid *Pseudomonas aeruginosa* in respiratory secretions marks the beginning of a slow decline in pulmonary function. Respiratory infection in CF follows a smoldering course punctuated by acute exacerbations (in part caused by viral agents) superimposed upon a baseline of chronic productive cough and bacterial colonization, most commonly caused by mucoid *P. aeruginosa*. Curiously, during these airway infections, temperature elevations are uncommon, routine blood cell counts are generally not helpful, and positive cultures of blood are practically unknown. Greater than 90 percent of the deaths due to CF occur during one of these pulmonary infections, and it is a rare occurrence that *Pseudomonas* is eradicated from the sputum, regardless of the antibiotic regimen selected.

Although *P. aeruginosa* is the most common bacterial isolate obtained from the airways of adult patients with CF, recently new multiresistant organisms have emerged. One nonaeruginosa strain, *P. cepacia*, has been associated with increased morbidity and premature death in a subgroup of patients with CF. During acute flare-ups of pulmonary symptoms, 5 to 15 percent of the bacterial strains isolated from samples of sputum may be nonaeruginosa pseudomonas.

**Antibiotics: How Should These Agents Be Administered?**

In large measure, improvement in the survival of patients with CF reflects timely use of newer, more potent antibiotics. The mechanism of action and indications for these antibiotics have been adequately reviewed in recent publications; however, important clinical questions remain unanswered. What is the most effective protocol for administration of these potent antibiotics? Should they be administered orally, by nebulizer, or parenterally? If the parenteral route is selected, should the antibiotics be given only to inpatients, or can these antibiotics be safely administered in the outpatient home setting? Should antibiotics be prescribed continuously or for the first week of each month? Should the choice of antimicrobials be dictated by the results of cultures of sputum? Good answers do not exist for many of these commonly asked clinical questions. Collaborative multicenter studies are needed to quickly provide answers which, with confidence, provide guidance to those caring for patients with CF.

**Ambulatory Intravenous Use of Antibiotics**

Often the limiting factor between in-hospital and at-home treatment is parenteral antibiotics. With improvements in the availability of at-home health care, parenteral antibiotic therapy can be easily achieved at home with success equal to that of in-hospital treatment in selected patients. This can be achieved with either peripheral intravenous access or indwelling central venous access. It should be noted that antibiotics without appropriate attention to concomitant chest physiotherapy and nutrition will have less than optimal results. In a controlled, prospective trial, Donati et al compared at-home and in-hospital antibiotic therapy. The patients (41 in each group) were matched for age, sex, pulmonary function, and arterial blood levels. Intravenous antibiotics, usually a semisynthetic penicillin and an aminoglycoside, were employed with IV catheters ("heparin locks") maintained by registered nurses. The care at home compared

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**Figure 1.** Photomicrographs distinguishing lesion of CF (A, top) from *Pseudomonas pneumonia* (B, bottom). A (top), Intense peribronchial cellular infiltration, glandular hypertrophy (arrowhead) and epithelial desquamation characteristic of CF; alveolar air spaces (arrow) and interstitial structures have minimal alterations (hematoxylin-eosin, original magnification ×250). B (bottom), Complete filling of alveolar spaces with organisms and inflammatory cells, and destruction of interalveolar structures which are pathologic changes characteristic of *Pseudomonas pneumonia* (hematoxylin-eosin, original magnification ×150).
favorably with hospitalization, with both groups demonstrating improvements in the results of pulmonary function tests with similar mean numbers of days of treatment. Moreover, there was no difference in the interval between exacerbations seen in the two groups or between the number of patients requiring further antibiotic therapy; however, care at home was significantly less costly and allowed the individual patient a greater opportunity to participate in work or school.

Winter et al.2 initiated parenteral therapy during hospitalization followed by continuing intravenous antibiotic therapy at home or provided therapy totally at home. There was no difference in mean time until relapse between conventional therapy (ie, antibiotics given entirely in the hospital) and therapy given entirely or partly at home. The major problems recorded with patients participating at home was blockage of the IV cannula, involving 14 cannulas during 116 days of care. No major complications were encountered, eg, thrombophlebitis, extravasation of the antibiotic, or bleeding.

These studies suggest that home-based, intravenous antibiotic therapy can be an effective alternative for selected individuals with exacerbations of their CF-related pulmonary disease. Before implementation of outpatient parenteral antibiotics, the physician must consider the following: (1) the patient’s degree of illness and ability for self-care; (2) the potential for ancillary support, including chest physical therapy and nutritional supplementation; (3) the availability of individuals to care for the IV catheters; and (4) the availability of close medical follow-up, as day-by-day contact with the physician is generally terminated when the patient returns home.

Nebulized Delivery

Several relatively small clinical trials have demonstrated the safety, absence of untoward effects, low rate of development of bacterial resistance, and efficacy of aerosolized antibiotics (Table 1). This route has been used to deliver aminoglycosides, broad-spectrum penicillins, and cephalosporins. A particular advantage is that this therapy may be used at home. This presents an alternative to the rather short list of oral pseudomonicidal agents used in daily outpatient maintenance therapy.

Inhaled antibiotics have been used for over a decade in the treatment of CF-related airway disease caused by *P aeruginosa*, and reported studies are of two types. They examine use of aerosolized antibiotics in the management of acute exacerbations of CF-related pulmonary disease, as well as application of this route on a long-term basis for maintenance therapy. If this mode of delivery is selected, it is advised that the aminoglycoside and broad-spectrum penicillin (carbenicillin; ticarcillin) be administered separately, as gentamicin has been shown to be chemically inactivated by carbenicillin or piperacillin.

Many of these protocols have not been properly controlled, but the results document that the emergence of resistant strains is uncommon. It is interesting to note the generally favorable results of these protocols, despite the fact that *P aeruginosa* has been rarely eradicated from the airway secretions. This should not be surprising because we seldom sterilize the sputum with any treatment, including parenteral pseudomonicidal antibiotics delivered in the hospital. Sterilization of secretions in these patients with distorted airways is seldom possible and suggests that an appropriate goal of therapy in patients with CF may be simply reduction of the bacterial burden, rather than eradication of *Pseudomonas*.

Therapeutic clinical trials of aerosolized antibiotics in CF have yielded conflicting results because of the lack of uniformity in grading the severity of the pulmonary disease of the patients with CF enrolled, the variable sizes of particles generated, and the differing antibiotic dosing protocols in each of these studies. Recently, investigators have analyzed an inexpensive, commercially available aerosolizer (Centimist; Intec Corp) and, using an immunoenzymatic assay for gentamicin, calculated that 7.7 percent of the original amount of antibiotic placed in the chamber was deposited in airway secretions. The peak levels in the sputum (mean, 377μg/ml) greatly exceeded MIC and MBC levels for clinical isolates of *P aeruginosa* and, yet, serum levels of the antibiotic were not detected. Therefore, high concentrations of pseudomonicidal antibiotics may be safely and selectively delivered to the airways in CF. In contrast to earlier studies with inhaled antibiotics in the adult ICU, which showed no prevention of pneumonia and selection of resistant organisms,6 the emergence of resistant strains does not occur. Often, clinical improvement is reported when aerosolized antibiotics are used on a long-term basis in maintenance therapy. Our knowledge regarding the physics of the generation and

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**Table 1—Aerosolized Antibiotic Treatment for Pseudomonas in CF Airways**

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>n</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>149</td>
<td>Loss of pseudomonas more commonly observed; improved spirometry; resistance same as systemic usage**</td>
</tr>
<tr>
<td>Broad-spectrum penicillins</td>
<td>26</td>
<td>Subjective improvement; weight gain and fewer hospitalizations; gains in spirometry equivocal; resistance equal to placebo**</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>18</td>
<td>Fewer hospitalizations; improved pulmonary function; resistance equivalent to nonaerosol controls**</td>
</tr>
</tbody>
</table>

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delivery of these droplets has improved greatly in the last six to eight years. Nevertheless, before this mode of therapy can be widely recommended for patients with CF, additional carefully controlled clinical trials should be completed.

**Long-Term Intermittent or Cyclical Therapy**

Because of the ongoing bacterial load in the sputum, many have advocated either long-term continuous or intermittent administration of oral antibiotics. This approach is supported by a double-blind crossover study using cefepime that demonstrated improved growth, fewer pulmonary exacerbations, and less non-pseudomonas organisms in the sputum in the treated group; however, more mucoid Pseudomonas species were isolated in the treated group, suggesting that there may be adverse long-term sequelae of long-term therapy. The change in the predominant flora from Staphylococcus to pseudomonas in patients with CF had been postulated to be due to oral antibiotics selecting for the pseudomonas. Currently, there is a multicenter trial of long-term oral antibiotic therapy underway to help answer the question of whether or not this is beneficial.

There is compelling clinical evidence to suggest oral therapy is beneficial in acute pulmonary exacerbations of CF-related pulmonary disease, despite the fact that until recently there have been no oral antibiotics with strong antipseudomonas properties. While it is entirely possible that improvement is merely coincidental, it may be that suppression or elimination of other sensitive organisms helps decrease the volume and viscosity of the sputum, thereby facilitating mucociliary clearance, without having a primary effect on the pseudomonas. Oral antiviral antibiotics such as amantadine should be considered when acute influenza infections are prevalent in the communities.

**Culture of Sputum in the Selection of Antibiotics**

Several clinical studies have demonstrated that the bacterial species identified in the culture of specimens of expectorated sputum are representative of the bacteriologic findings obtained from resected pulmonary segments, protected catheter brushes, and percutaneous needle aspirates of the lungs of patients with CF. It is our belief that the selection of antimicrobials should be directed by the results of cultures of sputum and the *in vitro* sensitivities, despite the fact that it is well recognized that *in vitro* sensitivity does not necessarily predict success in clearing the airway of the particular pathogen(s) being treated or predict clinical improvement. In fact, some studies have documented improvement despite placebo or "inappropriate" antibiotics.

Clinicians are best advised to prescribe antimicrobial chemotherapeutic agents at high doses because the serum-airway partition coefficient for many classes of antibiotics has reproducibly been shown to approximate 5:1; that is, the level in the airways will be only 20 to 30 percent of a simultaneously obtained serum concentration (Table 2). The newly released quinolones and the much older agent, chloramphenicol, appear to be exceptions to this formula. Finally, the value of quantitative cultures of sputum in many clinical settings has been argued, but may be of value in the patient with CF. Quantitating the bacterial burden is useful in following the response to therapy and confirming the clinical impressions of worsening or improving in patients with bronchiectasis. The presence of pseudomonas in the sputum has been related to the severity of pulmonary disease as shown by clinical deterioration and death and by pulmonary function tests and chest roentgenograms. Having said this, it is important to emphasize that the greatly distorted airways of these patients continuously harbor bacteria and will infrequently yield a sterile culture of sputum following aggressive antibiotic treatment, although there may be a fall in the density of organisms in the sputum.

**Selection of Nonbactericidal Antibiotics**

Novel use of nonbactericidal antibiotics in an attempt to alter the synthesis and release of pseudomonas virulence factors may be a profitable area for future studies. Preliminary studies by Renneard et al indicate that subinhibitory levels of clindamycin block the ability of *P aeruginosa* to release an inflammatory and destructive bacterial metalloenzym, elastase. Others have reported that subinhibitory concentra-

### Table 2—Antibiotic Classes and Pulmonary Alveolar-Capillary Partition Coefficients

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Percentage of Serum Concentration Achieved in Sputum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>10-30</td>
</tr>
<tr>
<td>Amikacin</td>
<td>20-40</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>20-67</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>20-67</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>6-10</td>
</tr>
<tr>
<td>Sisomicin</td>
<td>4-10</td>
</tr>
<tr>
<td>Penicillins</td>
<td>2.5</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>6-10</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>10-14</td>
</tr>
<tr>
<td>Azlocillin</td>
<td>4-10</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>(5-10)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>2-15</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>200</td>
</tr>
<tr>
<td>Quinolones</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
</tr>
</tbody>
</table>

*Studied in variety of patients with infectious or noninflammatory pulmonary diseases.
tions of clindamycin inhibit production of hemolysin by *Escherichia coli*. Subinhibitory levels of aminoglycosides may have beneficial effects in CF by inhibiting excretion of alginates and the production of siderophores. These and other nontraditional potential mechanisms of antibiotic activity may help explain therapeutic successes.

**Are Corticosteroids Effective in This Airway Disease?**

Corticosteroids have been used in patients with CF in an attempt to abrogate pulmonary inflammation thought to result from type 3 (immune complex-mediated) hypersensitivity reactions. A recently completed randomized, double-blind placebo-controlled study of alternate-day therapy with prednisone (2 mg/kg to maximum of 60 mg) in children with CF (ages 1 to 12 years) concluded after a four-year follow-up that the prednisone-treated group had significant advantages for height, weight, vital capacity, FEV1, peak flow, and number of required hospitalizations.

It remains unclear if the same long-term corticosteroid treatment protocol would prove beneficial in adolescent and adult patients with CF who have a great deal more permanent structural pulmonary damage. It is known that short-term therapy with prednisone (20 to 30 mg/day for three weeks) does not significantly increase pulmonary function in adult patients with CF and may expose the patient with CF to an increased risk of developing pneumothorax.

Although the use of corticosteroids in an alternate-day program appears to be free of potential corticosteroid side effects, it still remains unclear if all patients with CF might benefit from this therapy. An expanded multicenter trial of alternate-day steroids is underway. Future studies could examine other immunomodulators such as the cyclooxygenase inhibitors, eg, ibuprofen. This agent may be expected to decrease airway inflammation mediated by the cyclooxygenase pathway (prostaglandins and thromboxanes).

**How Should Hospitalization Be Used?**

Frequently, hospitalization is necessary despite use of antibiotics, exercise, and daily postural drainage performed as an outpatient. Nonemergency hospitalization may be warranted because of an insidious downhill clinical course including cough, dyspnea, anorexia, weight loss, and lack of energy, making daily activities of work or school impossible. There is no question that aggressive therapy combining antibiotics, chest percussion, and nutritional support leads to subjective improvement, improvement in gas exchange, improvement in pulmonary function, and radiographic improvement in most patients, unless there is severe fixed damage to the airways. Traditionally, this aggressive therapy has been achieved in the hospital. Many CF centers advocate hospitalization only after progressive deterioration on vigorous outpatient regimens, whereas some centers plan routine elective admissions with hopes that this will have a prophylactic effect in slowing the progression of ongoing pulmonary damage. While in-hospital treatment may be considerably more expensive, especially in view of the recent successes with at-home management, supervised therapy in the hospital remains the "gold standard." Patients whose condition fails to improve as outpatients should be given a chance to improve in the hospital. It may be that several factors besides parenteral antibiotics and chest percussion contribute significantly to recovery, such as rest, relaxation, rehydration, and compliance.

Nevertheless, indications for this type of expensive hospitalization and the duration of hospitalization are imprecise. Empirically, hospitalizations have ranged between 10 and 21 days for most patients. The ten-day minimums were selected after repeated failures with stays of five to seven days (as would be customary procedure for an uncomplicated "pneumonia"). By 21 days, most patients have maximized any potential benefit and have made little or no progress in the two or three days just before discharge. Why the ten-day to 21-day period seems to be optimal is uncertain, but it may pertain to factors such as nutritional rehabilitation, muscle fatigue, and accumulation of antibiotics in the airways. Increasingly, as the pulmonary status of patients with CF begins to improve in the hospital, preparations can be made to complete treatment comfortably at home, where usual activities may gradually be resumed. The cost savings for these home-care patients are considerable.

Depending on the timing and intensity of the patient's progressive pulmonary disease, hospitalization may provide long-lasting benefit (months to years) or may only provide a transient respite from ongoing damage. Clinical investigators need to continue studies in search of better parameters predictive of airway inflammation. Preliminary studies have indicated that clinical parameters of CF do not faithfully reflect the destructive inflammatory changes in pulmonary secretions and, hence, when used alone may not be sufficient to judge the adequacy of therapy. Assessment of the bronchoalveolar lavage fluid cellularity, elastolytic activity, IgG concentration, and some assessment of chemotactic activity for neutrophils may complement clinical criteria.

**Does Nutritional Support Improve Pulmonary Function or Prevent Deterioration?**

Patients who have less pancreatic dysfunction and less malabsorption have longer survival; however, it is not clear that nutritional rehabilitation will either reverse or prevent ongoing pulmonary deterioration.
Studies documenting improved nutritional status by either central venous hyperalimentation or by enteral feedings suggest that improved growth contributes to fewer pulmonary exacerbations and perhaps to better results on pulmonary function tests. Appropriate nutrition and control of malabsorption are generally reviewed and emphasized at each visit to the CF clinic, but there are several factors besides malabsorption that can contribute to malnutrition: anorexia due to pulmonary inflammation; increased caloric consumption due to increased work of breathing; dyspnea when the stomach is full; post-tussive emesis; dyspepsia and gastroesophageal reflux; and depression or anxiety. Therefore, simply recommending increased oral caloric intake through larger meals or supplements may not be successful, and a more complex means of nutritional support should be considered.

It has been reported that one month of parenteral nutritional support consisting of a balanced hypercaloric intake in underweight patients with CF results in subsequent improvement in pulmonary function, along with height and weight gain. In the months following this intervention, the rate of airway infection significantly decreased in comparison to that before therapy. Conversely, others report that despite significant increases in weight, height, triceps, skinfold thickness, and midarm circumference, there are no significant changes in spirometric data or pulmonary volumes observed. So nutritional rehabilitation remains a controversial therapy in need of additional carefully designed clinical studies.

Continuous nocturnal feedings either via a nasogastric tube or via a gastrostomy tube can provide the extra calories needed to promote growth. Most children learn to tolerate the nasogastric tube easily and feel good about their improved body habitus. Many adults prefer gastrostomy feeding tubes, which can be inserted by the percutaneous endoscopic technique. It remains to be determined if aggressive nutritional support over the short term can lead to long-lasting nutritional and pulmonary improvement, or whether lifelong support is necessary. It may be that improved nutrition simply lessens the rate of decline in pulmonary function.

A number of small clinical trials support the use of intravenous fat emulsions. These emulsions provide caloric supplementation, essential fatty acids and fat-soluble vitamins, and demonstrable improvement in clinical scores when used in patients with CF. Despite improvement in clinical scores, objective changes in pulmonary function, chest roentgenograms, clinical infection, and bacterial growth are inconsistent. The mechanism for the observed clinical improvement after therapy with fat emulsions is not completely clear.

**WILL EXERCISE SUBSTITUTE FOR POSTURAL DRAINAGE?**

In an effort to facilitate mucociliary clearance and to prevent mucus plugging, postural drainage and chest percussion (CPT) have been advocated on a daily basis. While the benefits of this therapy have been documented, routine CPT is inconvenient and time-consuming. It is not known whether CPT will have a prophylactic effect in infants with little evidence of pulmonary involvement at the time of diagnosis. For adult patients, who may not have family members available to assist with percussion, it may be difficult to reach all areas of the lungs. Alternative methods of promoting mucus clearance have been evaluated, usually finding that the traditional methods work best.

Aerosolized β-adrenergic agonists prior to CPT may increase the effectiveness of this therapy by increasing ciliary beat frequency and causing bronchodilatation. Mucolytics are occasionally recommended but without clear evidence of benefit; however, many patients subjectively feel that their sputum is more readily expectorated after N-acetylcysteine. In the face of doubtful effectiveness and potential detriment, mucolytics should be used only for the selected patients who feel the subjective need for them.

Exercise conditioning programs improve exercise tolerance in normal people and in adults with chronic obstructive pulmonary disease not due to CF. Similar results have been obtained with adolescents and adults with CF. An exercise program consisting of three one-hour sessions per week continued for three months produces significant increases in exercise tolerance, lowers heart rate at submaximal workloads, and improves respiratory muscle endurance. A rigorous training program will not improve results of pulmonary function testing, but can improve the sense of well-being, promote good nutrition, and improve respiratory muscle strength; in addition, it may substitute, in part, for chest percussion and drainage. Another proposed benefit of exercise is that deep breathing may facilitate effective clearance of thick respiratory secretions, thereby possibly substituting for more mundane postural drainage.

There are no adverse effects of these exercise programs if patients with CF are cautiously enrolled. Very hypoxic patients with CF who have cor pulmonale should be excluded. Additionally, dangerous falls in oxygen saturations of 5 percent or greater may occur in those patients with CF who have an FEV1 of less than 50 percent of the FVC or have a diffusing capacity for carbon monoxide of less than 80 percent of predicted. Patients with these pulmonary function abnormalities should have supervised exercise testing with ear or pulse oximetry before undertaking an independent exercise program. Preliminary reports...
indicate that the reliability of SaO₂ monitors vary considerably during exercise, depending on the manufacturer of this equipment.⁴⁴

**Is There A Surgical Solution?**

There has been some interest in resectional surgery and, currently, there is great enthusiasm for lung transplantation as dramatic interventional therapies for pulmonary disease due to CF. At present, surgical treatment is reserved for a few specific indications. Under no circumstances should resectional surgery be undertaken without complete mapping of the bronchial tree. This may be accomplished with use of cine-CT or, more reliably, by using selective staged bronchography performed via a flexible fiberoptic bronchoscope.³⁶ Rarely, surgery is indicated for massive pulmonary hemorrhage unresponsive to more conservative therapies (antibiotics, antitussives, and bed rest). Similarly, long-standing segmental or lobar collapse serving as a specific source of illness may not respond to conservative chest percussion or bronchscopy and will force consideration of a surgical approach as well.

Preliminary reports of resectional pulmonary surgery performed for bronchiectasis causing frequent hospitalizations or great disability indicate that a structured system of surgical management including preoperative tracheostomy and unspecified surgical considerations may be beneficial,³⁶ however, we are unaware of a full critical report detailing the benefits of such limited resections in this disease. Furthermore, noting the bilateral diffuse nature of the CF-related destructive pulmonary lesion, it seems unlikely that a surgical approach will find its way into the routine management of the adult patient with CF.

Organ transplantation is an accepted treatment for many causes of organ failure, including CF-related pulmonary disease. Many US tertiary-care centers have transplantation programs approved for heart-lung transplantation in patients with CF, and it is reasonable to expect that more and more such patients will undergo this surgery. There is a high mortality following transplantation.³⁷ For now, the number of successful heart-lung recipients with CF worldwide numbers in the 20s, and the longest surviving patient is now 2½ years after transplant. Difficulties still to be overcome include the low number of donor organs and the nature of the chronic infection of the upper and lower respiratory tracts of recipients. Preliminary experience suggests that the transplanted lungs do not acquire the CF-related defect. Pioneering work with double-lung (sans heart) transplantation should help to increase the donor organs available.

**Is It Possible To Augment CF Host Defenses?**

Despite new generations of antibiotics, truly effective therapy has not yet been achieved, and immunotherapy has been tried. There are two forms of immunotherapy to consider: (1) active therapy (vaccination); and (2) passive therapies. It is known that parenteral administration of polyvalent pseudomonas vaccines to children before acquisition of pseudomonas and to adults with CF who are colonized with pseudomonas fails to delay the onset of pseudomonas infection in children and does not clear the adult CF airways of this bacterium.³⁶ Similarly, local respiratory immunization by intranasal administration of a pseudomonas antigen preparation to a small number of adult patients with CF who are troubled by chronic pseudomonas infections did not result in clinical improvement or eradication of this pathogen.³⁶ Although many different pseudomonas vaccines are in preparation, it seems unlikely that any will be widely used in the treatment of patients with CF in the near future.

Passive immunotherapy has been widely used in the past to successfully treat pneumococcal and meningococcal diseases. Use of polyclonal antisera still has a role in the short-term management of diphtheria, tetanus, botulism, and viral hepatitis. A number of investigators have described fragmented immunoglobulins in CF airway fluids, and the fact that CF Igs is hypoglycosylated⁴⁰ and, as such, is more rapidly hydrolyzed⁴¹ [Hornick DB, et al Clin Res 341:934a, 1986] provides a rationale for evaluating passive immunotherapy of pseudomonas airway infections in patients with CF. Preliminary work indicates that commercially prepared polyclonal immunoglobulin, modified for safe intravenous use high titers to pseudomonas lipopolysaccharides, is well tolerated by humans, has been shown to be effective against experimental P. aeruginosa pneumonia, and is therapeutic in a burned mouse model; however, pseudomonas in CF airways converts to a smooth, nontypable “O” lipopolysaccharide, making some of the current commercial preparations of pseudomonas antibodies for passive immunotherapy inappropriate. Furthermore as discussed previously (Fig 1), CF is not analogous clinically or pathologically to pseudomonas pneumonia. Because concomitant antibiotic and antiserum therapies appear to act synergistically in treating pseudomonas infections,⁴² therapeutic trials of pseudomonas immune globulin in combination with antibiotics may be worthwhile when the proper replacement antisera become available.

Some additional thought must be given to the proper protocol for administration of passive immunotherapy in the population with CF. Ideally, young patients who are newly identified carriers of P. aeruginosa should be enrolled while the bacterial burden is low and alterations in the architecture of the airways are minimal. Alternatively, patients with CF may receive
pseudomonas immunotherapy administered intravenously monthly as outpatients, beginning immediately following a vigorous inpatient cleanout, and immunotherapy given in combination with oral anti-Pseudomonas antibiotics. Further in vitro studies of this potentially beneficial therapy need to be completed before the risk-benefit analysis for patients with CF can be decided. For now, this remains an experimental therapy which should not yet be applied to patients with CF, but may hold promise for use in the future.

Finally, some mention should be made of passive therapies intended to augment the greatly diminished antiprotease defense screen available in the CF airway. It is known that together the neutrophil serine protease and pseudomonas metalloprotease overwhelm the CF airway antiproteases. These antiproteases, bronchial mucosal inhibitor, α-2-macroglobulin and α-1-proteinase inhibitor, are hydrolyzed by pseudomonas elastase. Unfortunately, aerosolization of a metalloprotease inhibitor (EDTA) did not alter the clinical course of airway infections of children with CF. Presently, α-1-proteinase inhibitor has been prepared from pooled human plasma of normal donors and is available commercially. Infusion of this preparation is known to result in significantly increased antineutrophil elastase capacity in the epithelial lining fluid of the lung; however, studies to date have not successfully demonstrated a clinical efficacy for this preparation in those with acute infectious disease of the airways or chronic inflammatory disease. This seems to be a fertile area for future clinical investigation, especially considering the pathophysiology of ongoing damage to the airways in CF.

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