Pseudomonas aeruginosa and other related species

Robert Wilson, Ruth B Dowling

_Pseudomonas aeruginosa_ was first obtained in pure culture by Gessard in 1882 from cutaneous wounds which had a blue green discolouration and is the major human pathogen from a large genus of strictly aerobic Gram-negative rods which are widely distributed in nature. The majority of _P aeruginosa_ strains produce at least two pigments, a fluorescent yellow pigment and a blue pigment called pyocyanin, which together give the characteristic colour noted above when the bacterium is grown on agar. _P aeruginosa_ is motile by means of a single flagellum and thrives in moist environments; it is extremely versatile biochemically and can grow in many habitats including soil, surface waters, plants and various foods such as vegetables eaten by man. In hospitals _P aeruginosa_ can be found in sinks, respirators, humidifiers, etc, and is occasionally found on the hands of medical personnel.

_P aeruginosa_ is an opportunistic pathogen which only causes disease in patients with impaired host defences. The patient’s defences may be generally weakened by debility or cancer, or there may be specific humoral or cellular defects. Neutropenic patients are especially susceptible to _pseudomonas_ infection and to subsequent septicemia. Alternatively, the body’s defences may be specifically breached as in corneal ulceration or skin burns, or artificially overcome as with assisted ventilation or by an indwelling urinary catheter. Patients with bronchiectasis are particularly prone to chronic infection, and delayed mucociliary clearance may be responsible. The use of broad spectrum antibiotics may kill commensal flora or more antibiotic-sensitive pathogenic species causing infection, and promote colonisation by the intrinsically resistant _pseudomonas_. _P aeruginosa_ is particularly associated with progressive and ultimately fatal chronic respiratory infection in cystic fibrosis. Clues about the biological basis of this host-bacterial interaction which occurs almost inevitably are just being discovered. In this review we will only cover chronic airway infections, although some of the information is relevant to acute pneumonia and septicemia which are most commonly seen in immuno-compromised patients.

Two other _pseudomonas_ species which cause disease in humans will be mentioned briefly. _P (Burkholderia) cepacia_ is a distant relation of _P aeruginosa_ and was first described as a cause of soft rot in onions. It is ubiquitous in the environment and is frequently found in association with soil, water and plants. Like _P aeruginosa_, it is virtually non-pathogenic in healthy people, but it can cause disease in those with reduced host defences, and it has been recognised as an important pathogen in cystic fibrosis. _P cepacia_ may be isolated alone or together with _P aeruginosa_. This may lead to problems in isolating _P cepacia_ because _P aeruginosa_ rapidly outgrows it on agar unless selective media are used. _P pseudomallei_ is widely distributed in the soil and water of rice paddy fields and causes melioidosis, which is a major cause of death from community acquired septicaemia in Thailand and is endemic throughout south east Asia and northern Australia.

Epidemiology

Although the initial isolation of _P aeruginosa_ from sputum may be intermittent in cystic fibrosis and other forms of bronchiectasis, once chronic infection is established it is rarely possible to eradicate it even with intensive antibiotic therapy. A number of longitudinal bacteriological studies of cystic fibrosis patients have shown that most of them harbour the same _P aeruginosa_ clone for many years. Once a particular clone has colonised the lung DNA fingerprinting may reveal shifts in the macrorestriction fragment patterns, indicating subclonal variation, which may result from sequence alterations in restriction recognition sites, genomic rearrangements, and incorporation of extrachromosomal DNA—for example, from bacteriophages. Available evidence suggests that acquisition of _P aeruginosa_ is commonly from the environment, but that patient to patient spread can occur particularly if contact density is high such as can occur at cystic fibrosis centres and recreation camps.

_P cepacia_ can cause respiratory tract infection in cystic fibrosis, although it is much less common in non-cystic fibrosis bronchiectasis. Strains are usually very antibiotic resistant and have in some studies been associated with rapid clinical deterioration, although this is not always the case. Anxiety has also been increased by reports of cross-infection between patients although not all studies have found evidence of this. Nevertheless, some centres
The mucoid form of *Pseudomonas aeruginosa* does not cause infection in the absence of impaired host defences, yet a wide array of potential virulence factors have been described which may contribute to its pathogenicity in the compromised patient. A review of the literature is summarised in table 1. The failure of the bacterium to infect the healthy lung—or even the mildly compromised defences of, say, a patient with chronic bronchitis—means that no single virulence factor is by itself that potent, but that the whole array should be viewed as contributing to the "pathogenic personality" of the bacterium. Once colonisation of the airways is established, *P aeruginosa* is rarely eliminated despite an exuberant host inflammatory response. 6 21

The mucoid form of *P aeruginosa* produces large amounts of an extracellular polysaccharide called alginate, and this form accounts for up to 90% of isolates from patients with cystic fibrosis. 2 28 Typically, the first time that *P aeruginosa* is isolated it is non-mucoid but after a variable period, often one or two years, it becomes mucoid. Although patients infected by mucoid strains tend to have worse lung function and nutritional state, 6 it is not clear that a shift to the mucoid phenotype is responsible. The mucoid character is chromosomally encoded and is probably selected for by the in vivo environment including sublethal concentrations of antibiotics. 2 The mucoid phenotype is also seen in other chronic infections such as non-cystic fibrosis bronchiectasis and the urinary tract. 7

The attachment of bacteria to mucosal surfaces is considered an important event in the pathogenesis of most infectious diseases. In a histological study of the lungs of patients with cystic fibrosis infected by *P aeruginosa*, most bacteria associated with secretions were intraluminal, while adherence to the epithelial surface occurred when there was cell damage or exposure of underlying connective tissue. 27 The importance of epithelial damage (fig I) in facilitating *P aeruginosa* adherence has been noted in numerous studies, and the bacterium does not seem to adhere to normal epithelium. 29 Cell damage might remove defence mechanisms such as ciliary beating which would otherwise protect the epithelium, 7 and also expose new receptors for bacterial adhesins on damaged cells, on newly exposed surfaces, and on cells that grow to repair the damage. 26 30 Pili have been identified as an important adhesin of *P aeruginosa* 41 52 but do not account for all the adhesive properties and other adhesins such as a protein linked with flagellar biosynthesis, 33 exoenzyme S, 34 and alginate 35 have been identified. *P aeruginosa* has a high affinity for human tracheobronchial mucus in vitro, mucus of organ cultures (fig I) and in the airways. 27 28 36

Bacterial adherence to mucus probably involves both specific and non-specific interactions. 37 40 *P aeruginosa* proteases and rhamnolipid also stimulate mucus production. 41 42 In organ cultures *P aeruginosa* grows as continuous sheets over the mucus surface 28 and it has been shown that growth in such biofilms is resistant to opsonophagocytic killing by neutrophils. 43 44 *P aeruginosa* adherence to mucus, and its lack of adherence to normal epithelium, may explain why it does not infect the normal airway which has efficient mucociliary defences. However, mucociliary clearance is slow in patients with cystic fibrosis 45 and other forms of bronchiectasis, 16 allowing *P aeruginosa* to colonise mucus which is poorly cleared, giving the bacterium time to produce toxins that establish the infection.

There is a special association between cystic fibrosis and *P aeruginosa*, and infection can occur in patients with cystic fibrosis and bronchiectasis before there is significant damage to the lung. 47 48 The recent discovery of cystic fibrosis transmembrane conductance regulator (CFTR) has begun to lead to an understanding of why this might be. 49 Cystic fibrosis epithelial cells in primary culture bind approximately

### Table 1 Virulence factors of *Pseudomonas aeruginosa*

<table>
<thead>
<tr>
<th>Virulence factor</th>
<th>Biological action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucoid exopolysaccharide (alginate)</td>
<td>Adherence to epithelium; barrier to phagocytes and antibiotics; inhibits antibody and complement binding</td>
</tr>
<tr>
<td>Protease enzymes</td>
<td>Tissue damage; epithelial cell tight junction separation; degrade fibronectin; cleave antibodies creating non-functional blocking antibodies; inactivate α1-protease, complement components and cytokines; cleave C3b receptors from neutrophils; stimulate mucus secretion</td>
</tr>
<tr>
<td>Exotoxin A</td>
<td>Cytotoxic by inhibiting protein synthesis; toxic to macrophages; T cell mitogen; inhibits granulocyte and macrophage progenitor cell proliferation</td>
</tr>
<tr>
<td>Lipopolysaccharide</td>
<td>Dominant antigenic determinant on cell surface; loss of sugar unit side chains during chronic infection creates &quot;rough&quot; LPS and serum sensitivity; less potent endotoxin properties than other Gram-negative species</td>
</tr>
<tr>
<td>Pigments eg. pyocyanin, 1-hydroxyphenazine, pyoverdin</td>
<td>Inhibit ciliary beat; siderophores; toxic to other bacterial species and human cells; enhance oxidative metabolism of neutrophils; inhibit lymphocyte proliferation</td>
</tr>
<tr>
<td>Phospholipase C</td>
<td>Haemolysis; tissue damage; destroy surfactant</td>
</tr>
<tr>
<td>Rhamnolipid</td>
<td>Haemolysis; inhibit ciliary beat; stimulate mucus secretion, affect ion transport across epithelium</td>
</tr>
<tr>
<td>Pili</td>
<td>Adherence to epithelium; cytotoxic</td>
</tr>
<tr>
<td>Lipase</td>
<td>Tissue damage</td>
</tr>
<tr>
<td>Histamine</td>
<td>Impair epithelial integrity</td>
</tr>
<tr>
<td>Exoenzyme S</td>
<td>Adherence to epithelium; cytotoxic</td>
</tr>
<tr>
<td>Leukocidin</td>
<td>Cytotox to neutrophils and lymphocytes</td>
</tr>
</tbody>
</table>

Compiled from references 2, 3, 10, 11, 25, 26, 31–35, 41, 42, 49, 64, 68, 78, 81, 82.

have segregated patients carrying *P cepacia*. The benefits of such a policy need to be clearly defined because of the psychosocial implications of segregation and further epidemiological data are urgently needed. 4 25

### Bacterial pathogenesis

*P aeruginosa* does not cause infection in the absence of impaired host defences, yet a wide array of potential virulence factors have been described which may contribute to its pathogenicity in the compromised patient. A review of the literature is summarised in table 1. The failure of the bacterium to infect the healthy lung—or even the mildly compromised defences of, say, a patient with chronic bronchitis—means that no single virulence factor is by itself that potent, but that the whole array should be viewed as contributing to the “pathogenic personality” of the bacterium.

Once colonisation of the airways is established, *P aeruginosa* is rarely eliminated despite an exuberant host inflammatory response. 6 21

The mucoid form of *P aeruginosa* produces large amounts of an extracellular polysaccharide called alginate, and this form accounts for up to 90% of isolates from patients with cystic fibrosis. 2 28 Typically, the first time that *P aeruginosa* is isolated it is non-mucoid but after a variable period, often one or two years, it becomes mucoid. Although patients infected by mucoid strains tend to have worse lung function and nutritional state, 6 it is not clear that a shift to the mucoid phenotype is responsible. The mucoid character is chromosomally encoded and is probably selected for by the in vivo environment including sublethal concentrations of antibiotics. 2 The mucoid phenotype is also seen in other chronic infections such as non-cystic fibrosis bronchiectasis and the urinary tract. 7

The attachment of bacteria to mucosal surfaces is considered an important event in the pathogenesis of most infectious diseases. In a histological study of the lungs of patients with cystic fibrosis infected by *P aeruginosa*, most bacteria associated with secretions were intraluminal, while adherence to the epithelial surface occurred when there was cell damage or exposure of underlying connective tissue. 27 The importance of epithelial damage (fig I) in facilitating *P aeruginosa* adherence has been noted in numerous studies, and the bacterium does not seem to adhere to normal epithelium. 29 Cell damage might remove defence mechanisms such as ciliary beating which would otherwise protect the epithelium, 7 and also expose new receptors for bacterial adhesins on damaged cells, on newly exposed surfaces, and on cells that grow to repair the damage. 26 30 Pili have been identified as an important adhesin of *P aeruginosa* 41 52 but do not account for all the adhesive properties and other adhesins such as a protein linked with flagellar biosynthesis, 33 exoenzyme S, 34 and alginate 35 have been identified. *P aeruginosa* has a high affinity for human tracheobronchial mucus in vitro, mucus of organ cultures (fig I) and in the airways. 27 28 36

Bacterial adherence to mucus probably involves both specific and non-specific interactions. 37 40 *P aeruginosa* proteases and rhamnolipid also stimulate mucus production. 41 42 In organ cultures *P aeruginosa* grows as continuous sheets over the mucus surface 28 and it has been shown that growth in such biofilms is resistant to opsonophagocytic killing by neutrophils. 43 44 *P aeruginosa* adherence to mucus, and its lack of adherence to normal epithelium, may explain why it does not infect the normal airway which has efficient mucociliary defences. However, mucociliary clearance is slow in patients with cystic fibrosis 45 and other forms of bronchiectasis, 16 allowing *P aeruginosa* to colonise mucus which is poorly cleared, giving the bacterium time to produce toxins that establish the infection.

There is a special association between cystic fibrosis and *P aeruginosa*, and infection can occur in patients with cystic fibrosis and bronchiectasis before there is significant damage to the lung. 47 48 The recent discovery of cystic fibrosis transmembrane conductance regulator (CFTR) has begun to lead to an understanding of why this might be. 49 Cystic fibrosis epithelial cells in primary culture bind approximately
Lung damage by inflammatory processes

In cystic fibrosis and most other forms of bronchiectasis there is an exuberant inflammatory response to chronic bacterial infection of the airways.\(^5\)\(^{-}\)\(^{25}\) Large numbers of activated neutrophils are attracted into the airway lumen by host—for example, C5a, LTβ4, IL-8—and bacterial chemotaxins.\(^\text{62}\) There is a strong antibody response in serum, saliva, and pulmonary secretions to many pseudomonas antigens\(^\text{63}\)\(^{-}\)\(^{64}\) and cystic fibrosis patients with chronic \textit{P. aeruginosa} infection have high levels of circulating immune complexes\(^\text{66}\) which are also found in sputum.\(^\text{67}\) There is a strong correlation between severity of lung disease and the titre of anti-pseudomonas antibodies.\(^\text{68}\) This inflammatory response prevents systemic spread of infection but fails to eradicate it from the airways.\(^\text{6}\)\(^{10}\)\(^{11}\)\(^{25}\)

Chronic inflammatory processes cause damage, both to the epithelium\(^\text{69}\) and to the structural proteins of the lung,\(^\text{70}\) which is probably more serious than the damage caused by the bacterium itself. This concept is supported by the observations that cystic fibrosis patients with hypogammaglobulinaemia have significantly less severe lung disease than do patients with normal or elevated levels of immunoglobulins,\(^\text{70}\) and that immunosuppressive agents can benefit patients with cystic fibrosis.\(^\text{71}\)

Activated neutrophils do not differentiate between bacteria and bystander lung tissue. They spill protease enzymes\(^\text{68}\) and oxygen radicals\(^\text{72}\) which, because of the number of neutrophils present, overwhelm the ability of the lung defences to neutralise them. The epithelial damage that ensues, together with stimulation of mucus production by proteinase enzymes,\(^\text{73}\) promotes continued bacterial infection and more inflammation. \textit{P. aeruginosa} produces a low molecular weight factor which stimulates the production of the powerful neutrophil chemotaxin IL-8 from epithelial cells.\(^\text{74}\) Neutrophil elastase in secretions may itself attract more neutrophils into the airway lumen by inducing IL-8 production from the epithelial cells\(^\text{75}\) and impairs opsonophagocytosis by cleavage of complement receptors from neutrophils and complement components from bacteria.\(^\text{76}\)\(^{77}\) Thus, a self-perpetuating “vicious circle” of events is generated.\(^\text{9}\)

High levels of granulocyte elastase have been found in the sputum of patients with cystic fibrosis and bronchiectasis in several studies.\(^\text{78}\) Older patients with cystic fibrosis, those colonised by \textit{P. aeruginosa}, and those with advanced disease have higher levels than younger patients, those not colonised by \textit{P. aeruginosa}, and patients in good clinical condition.\(^\text{77}\) However, younger patients with cystic fibrosis with good lung function still have raised elastase levels in secretions and signs of ongoing infection and inflammation.\(^\text{79}\) DNA released by degenerating white cells makes secretions more viscous\(^\text{80}\)\(^{81}\) and difficult to clear. \textit{P. aeruginosa} toxins may enhance the damage caused by inflammation—for example, by inactivating α1 antiproteinase\(^\text{82}\) or enhancing neutrophil oxidative metabolism.\(^\text{83}\) The relative
Table 2 Antibiotics used against Pseudomonas aeruginosa

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxypenicillins</td>
<td>Ticarcillin</td>
<td>Greater antipseudomonas activity and less sodium load than carbenicillin</td>
</tr>
<tr>
<td></td>
<td>Temocillin</td>
<td>6 to methoxy substitution gives long half life and more resistance against β-lactamase enzymes</td>
</tr>
<tr>
<td></td>
<td>Azlocillin</td>
<td>Acyl derivative of urea as side chain</td>
</tr>
<tr>
<td>Ureido and piperazine penicillins</td>
<td>Piperacillin</td>
<td>Piperazine side chain; not used in cystic fibrosis because of adverse reactions</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>Ceftazidime</td>
<td>Third generation</td>
</tr>
<tr>
<td></td>
<td>Genumycin</td>
<td>Toxicity of aminoglycosides is based on accumulation, major side effects are on ear and kidney. Measure serum trough and peak levels at third dose, and regularly afterwards</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Tobramycin, amikacin</td>
<td>Only oral antipseudomonal antibiotic</td>
</tr>
<tr>
<td></td>
<td>Meropenem, imipenem</td>
<td>Narrow spectrum of action; Gram-positive superinfection may be a problem if used alone</td>
</tr>
<tr>
<td>Quinolone</td>
<td>Ciprofloxacin</td>
<td>Members of a new class of β-lactam called the thienamycin; imipenem has to be combined with inhibitor cilastatin to block renal metabolism, but meropenem is stable to the renal enzyme</td>
</tr>
<tr>
<td>Monobactam</td>
<td>Aztreonam</td>
<td></td>
</tr>
<tr>
<td>Carbapenem</td>
<td>Meropenem, imipenem</td>
<td></td>
</tr>
<tr>
<td>Beta lactamase inhibitor</td>
<td>Tazocin</td>
<td>Pseudomonas side chain; not used in cystic fibrosis because of adverse reactions</td>
</tr>
<tr>
<td>Polymyxin</td>
<td>Colomycin</td>
<td>Usually given by inhalation because of possible side effects when given parenterally</td>
</tr>
</tbody>
</table>

Compiled from references 2 and 7.

Antibiotic management of pseudomonas lung infections

P aeruginosa is inherently resistant to many antibiotics at concentrations that can be achieved in vivo and, with the notable exception of ciprofloxacin, those to which it is sensitive need to be given intravenously. P cepacia is even more resistant. Bacteria are located intraluminally in association with mucus, or in contact with the epithelium, particularly if the epithelial surface is damaged. To reach the site of infection the antibiotic must therefore penetrate into the bronchial epithelium and secretions. Antibiotic penetration into the mucosa in patients with cystic fibrosis and bronchiectasis may be reduced by thickening and scarring of the bronchial wall. The secretions themselves may provide a barrier to antimicrobial penetration, as may alginate of mucoid strains, and the concentration of antibiotic at the site of infection may therefore be quite different from the concentration in the serum. Antibiotics vary in their ability to penetrate into bronchial mucosa and secretions and, in general, beta lactams, cephalosporins and aminoglycosides penetrate less well than quinolones. Mutations produce strains which are resistant to antipseudomonal antibiotics by mechanisms which include hyperproduction of chromosomal β-lactamase, altered DNA gyrase, and membrane changes reducing drug accumulation.

There appears to be no obvious choice of a particular antibiotic or combination of antibiotics, judging by the large number of reported trials which, unfortunately, often differ markedly in their design, thus making simple comparison difficult. Table 2 lists those antibiotics that have proved to be clinically useful in the treatment of P aeruginosa. A semi-synthetic penicillin or third-generation cephalosporin is usually used in combination with an aminoglycoside antibiotic. The logic of this combination is to obtain additive benefit from antibiotics that have a different mechanism of action, together with the aim of avoiding development of resistance. The pharmacokinetics of cephalosporins and particularly aminoglycosides may be altered in cystic fibrosis. Increased extracellular volume associated with malnutrition, and elevated renal clearance of these drugs in patients with cystic fibrosis, means that higher doses may be needed to obtain adequate serum levels than would be the case in non-cystic fibrosis patients. A number of studies have shown that intravenous antibiotic treatment against P aeruginosa lowers the proteinase concentration in secretions, maintains or improves lung function, and improves survival. For these reasons it has been suggested that courses of intravenous antibiotics should be given at regular intervals in a planned manner, irrespective of exacerbations, in order to reduce lung inflammation presumably by reducing the bacterial burden. Long term oral ciprofloxacin has also been used in patients with bronchiectasis who suffer frequent exacerbations. It improved symptoms and lung function, decreased the number of exacerbations, and reduced hospital admissions. In a number of patients P aeruginosa was eradicated by this long course of antibiotic, but in others resistance developed.

A number of studies indicate that antibiotics may not just benefit patients by killing bacteria. Clinical improvement in cystic fibrosis following antibiotics is often associated with only a small decrease in the viable count of pseudomonas in the sputum or no change at all. The benefit of antibiotic treatment might also be explained partly by reduction in exoprotein production which occurs with subinhibitory concentrations of antibiotic in vitro and from strains isolated from patients after intravenous antibiotic treatment, or perhaps by killing subpopulations of bacteria adherent to the mucosa or infecting the parenchyma. It should be remembered, however, that patients admitted to hospital for intravenous antibiotics also receive supportive care such as physio-
therapy and intravenous rehydration. It will be interesting to compare the results from home intravenous antibiotic programmes when the supportive care may be less good than that obtained in hospital. Because the concentration of antibiotic at the site of airway infection is important, the idea of delivering high concentrations of antibiotic directly onto the mucosa by inhalation is appealing. A number of regimens of nebulised antibiotics, including β-lactams, aminoglycosides and colomycin, either singly or in combination, have been shown to improve symptoms and lung function and reduce hospital admissions of cystic fibrosis patients colonised by P aeruginosa. They are best used in a prophylactic manner to delay relapse, and are less effective during acute exacerbations, probably because they are deposited centrally due to blockage of small airways by secretions and bronchospasm. They should be used after physiotherapy and bronchodilator treatment and prescribed with a suitable air compressor and nebuliser to allow effective dispersal through the bronchial tree. A one-way valve system should be used with an outlet so that exhaled antibiotics can be discharged via a window, preventing exposure of family or other patients to the antibiotic. Continuous erythromycin is commonly used in Japan to treat patients with diffuse panbronchiolitis and other forms of chronic bronchial sepsis involving P aeruginosa. Some recent observations might explain the unexpected benefits that have been reported and justify further clinical studies. Erythromycin reduces exotoxin production by P aeruginosa at concentrations which do not affect bacterial growth, and suppresses biofilm formation. Erythromycin also has anti-inflammatory actions such as inhibition of neutrophil chemotaxis and generation of reactive oxygen species, and is also an inhibitor of mucus secretion in vitro. An important issue which would influence management but remains undecided is the role of P aeruginosa in disease progression in non-cystic fibrosis bronchiectasis. P aeruginosa is associated with worse lung function and worse quality of life, but it is not clear whether chronic P aeruginosa infection causes an accelerated decline in lung function or whether it is simply a marker of those patients whose lung function is already declining rapidly.

Other forms of management

With the successful development of DNA vectors, somatic gene therapy for patients with cystic fibrosis has come closer to reality. However, P aeruginosa lung infections will continue to be a major problem in cystic fibrosis for many years to come. There has been a relative failure of antibiotics to eradicate P aeruginosa or to halt the increased morbidity and mortality following infection. It seems unlikely that any new antibiotic will change this outcome, so preventative strategies and adjunct therapies are very important.

One study has suggested that aggressive antibiotic therapy on first isolation of P aeruginosa may prevent chronic infection. There has been much research into development of an effective pseudomonas vaccine, but most results to date have been disappointing and, in some circumstances, may lead to clinical deterioration, presumably by enhancing inflammation. Recent research has focused on inducing opsonic antibodies which are not readily formed during natural infections. There have been some promising clinical results in small trials, and vaccination prior to P aeruginosa colonisation seems to be a logical approach. A major problem in P aeruginosa bronchial infections is poor clearance of mucus which harbours bacteria and their products, as well as host inflammatory factors. Thus poor clearance perpetuates and enhances the inflammatory response which causes lung damage. Nebulised amiloride may enhance mucus clearance in cystic fibrosis by blocking excess sodium absorption. Recombinant human DNase reduces viscosity of cystic fibrosis sputum with some clinical benefit but results have not been as good in non-cystic fibrosis bronchiectasis, perhaps because the DNA content of the sputum is less.

A number of approaches are being investigated to control the exuberant inflammatory response to P aeruginosa infection. These include oral corticosteroids which may be successful but have unacceptable side effects at the dosage required, non-steroidal anti-inflammatory agents and elastase inhibitors given by inhalation.

I. Introduction


78. Suter S. New perspectives in understanding and manage-
ment of the respiratory disease in cystic fibrosis. Eur J Pa-
79. Konstan MW, Hillard KA, Norvell TM, et al. Bronchoal-
veolar lavage findings in cystic fibrosis patients with stable, clinically mild lung disease suggest ongoing infection and inflammation. Am J Respir Crit Care Med 1994;150:448–
54.
80. Lether MJ, James SL, Marriott C, et al. The origin of DNA associated with mucus glycoproteins in cystic fibro-
83. Lapa e Silva JR, Jones JA, Cole PJ, et al. The immunologi-
90. Hyraud A, Desoures J, Lombard JY. Effects of eryth-
romycin, josamycin and spiramycin on rat polymorphonu-
clear leukocyte chemotaxis. Chemotherapy 1986;32:379–
82.
91. Anderson R. Erythromycin and roxithromycin potentiate human neutrophil locomotion in vitro by inhibition of leukotriactant-activated sphродyne generation and au-
94. Schiifer J, Peet GB, Groot M, et al. Induction of opsonic antibodies to Pseudomonas aeruginosa mucoid exopolysaccharide by an anti-idiotypic monoclonal anti-
99. Rosenstein BI, Eiger H. Risks of alternate-day pred-
102. McElvoye NG, Nakamura H, Birrer P, et al. Modulation of airway inflammation in cystic fibrosis. In vivo suppression of interleukin-8 levels on the respiratory epithelial surface by aerosolization of recombinant secretory leuko-