

THORAX

Editorials

Diffuse panbronchiolitis and cystic fibrosis: East meets West

Diffuse panbronchiolitis is an intractable disease of adult patients, often elderly, which involves infiltration of plasma cells and lymphocytes with inflammatory hypertrophy of the walls of the respiratory bronchioles.¹ It is predominantly seen in men. The main sites of the chronic inflammation are the bronchiolar and centrilobular regions, and the main symptoms are dyspnoea, cough, and expectoration. The disease was first described in Japan in 1969 and subsequently in Korea and China, and a few cases have been reported outside Asia – notably in Asian emigrants – probably too few as the disease is virtually unknown by physicians in the western world. However, by 1983 more than 1000 cases of probable diffuse panbronchiolitis and 82 histologically confirmed cases had been reported.²

In this issue of *Thorax* two studies are published on patients with diffuse panbronchiolitis.^{3,4} Koyama and colleagues³ have examined the bronchial responsiveness to methacholine in patients with diffuse panbronchiolitis and a group with chronic obstructive pulmonary disease, and also the response to bronchodilators in two larger groups. They found substantial differences in both the methacholine and the bronchodilator response between the two diseases, with much lesser responses being found in the patients with diffuse panbronchiolitis. They suggest that the airflow restriction in bronchiolitis is much more fixed than in chronic obstructive pulmonary disease due to irreversible structural changes within the bronchioles. Tamaoki and colleagues⁴ report the effect of long term inhalation of oxitropium bromide in patients with diffuse panbronchiolitis and a group with chronic bronchitis. After five weeks they reported improved airway flow and decreased sputum quantity, but no change in sputum bacteriology.

The aetiology of the disease, however, is not yet clear. *Haemophilus influenzae* infections occur repeatedly or continuously over a long course and, during this time, the respiratory bronchioles become obstructed and the nearby airway bronchioles become dilated. With these morphological changes superinfection with *Pseudomonas aeruginosa* occurs and the disease becomes intractable.¹ Polymorphonuclear leucocytes become more abundant and free polymorphonuclear leucocyte elastase is present in bronchial fluid and participates in the tissue damage.⁵⁻⁷ Antibodies in serum and sputum against *Ps aeruginosa* are present.⁸ The chronic *Ps aeruginosa* infection is caused by mucoid strains of these bacteria growing as a biofilm which is virtually impossible to eradicate by means of antibiotics.⁹

In 1987 the Research Project team of the Ministry of Health and Welfare for Specific Diseases in Japan found that the 10 year survival rate was 12.4% in cases infected with *Ps aeruginosa* and 73.1% in cases without *Ps aerugi-*

nosa infection.¹ Chronic suppressive treatment with long term daily erythromycin is reported to reduce significantly the symptoms and inflammatory parameters and to increase the 10 year survival to more than 90%.¹ Similar results have been obtained with the new macrolides such as clarithromycin and with fluoroquinolones. The efficacy of macrolides, in spite of their lack of bacteriostatic or bacteriocidal effect against *Ps aeruginosa*,¹⁰ has been studied in vitro and in animal models and it seems that it results from a sub-MIC effect which inhibits the production of proteins such as the exoproteases of *Ps aeruginosa* and from interference with the biofilm matrix.^{9,11} Such effects are not routinely investigated in the clinical microbiology laboratory, and in this respect the ordinary reports of sensitivity testing are of no help to clinicians.¹² In addition, an inhibitory effect of macrolides on polymorphonuclear leucocyte function and TNF- α excretion from monocytes may contribute to their clinical efficacy.^{13,14}

Cystic fibrosis was first described in 1936 and is predominantly found in Caucasians; it is unknown in Japan, China, and Korea. It is a genetic heterogeneous disease which is transmitted as an autosomal recessive trait. The cystic fibrosis gene is located on chromosome 7. More than 300 mutations are known in the gene, probably accounting for the variable symptoms found in cystic fibrosis.¹⁵ The cystic fibrosis gene product is a membrane bound protein called the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This protein is the chloride ion channel which regulates the transportation of chloride ions across fluid transporting epithelial cells.¹⁵ The cystic fibrosis defect of the CFTR protein leads to altered secretions (salty sweat, thick mucus), blocked ducts and thereby reduced mucosal defence¹⁵ which, in turn, leads to recurrent and chronic bacterial infections in the lungs. In small children the bacteria most frequently involved are *Staphylococcus aureus* and *Haemophilus influenzae*.¹⁶ In older children and adult patients these bacteria may still play a part, but the major pathogen is *Ps aeruginosa*.¹⁶ The chronic *Ps aeruginosa* infection is caused by mucoid strains of these bacteria growing as a biofilm which is virtually impossible to eradicate with antibiotics.¹⁶ The most remarkable host response to the infection is the pronounced antibody response which continues to increase over many years, and which is correlated with poor prognosis.¹⁷ The correlation between the antibody response and poor prognosis is due to immune complex mediated chronic inflammation in the lungs of patients with cystic fibrosis.^{17,18} The inflammatory reaction is dominated by polymorphonuclear leucocytes and released leucocyte proteases, myeloperoxidase and oxygen radicals are the main mechanisms of lung tissue damage; in this process the high levels of cytokines (IL-1, IL-6, TNF, and IRAP) in sputum is

probably also important.¹⁹⁻²³ Based on the pathophysiology of the lung tissue damage, a novel and promising therapy has been developed consisting of inhalation of protease inhibitors which, in addition to neutralising the polymorphonuclear leucocyte elastase in the lungs, also inhibits IL-8 production in the bronchial epithelial cells and thereby downregulates this important polymorphonuclear leucocyte chemoattractant.^{22,24,25} Maintenance chemotherapy (chronic suppressive chemotherapy) is used in many cystic fibrosis centres to suppress the number and activity of the *Ps aeruginosa* bacteria in the lungs of patients with cystic fibrosis. More than 90% of the patients now survive for at least 10 years after onset of the chronic infection compared with previously when "on demand" treatment resulted in survival of only 50% for five years. The lung function and inflammatory parameters improve during antibiotic treatment and this effect is still detectable 1-2 months after completion of the treatment.¹⁷ Inhalation therapy with aminoglycosides and β -lactam antibiotics and/or ciprofloxacin treatment is used as an alternative.²⁶

It is obvious that striking similarities exist between the chronic *Ps aeruginosa* infection in diffuse panbronchiolitis and cystic fibrosis. Although the Japanese scientists and clinicians and those in the West have worked independently on two different diseases, the results show that the pathogenesis, therapy, and prognosis of the most important infectious complication in both diseases - chronic pulmonary *Ps aeruginosa* infection - is quite similar. In one important aspect, however, cystic fibrosis research has advanced much further than diffuse panbronchiolitis research, as the molecular genetics of cystic fibrosis has been so well described since the discovery of the cystic fibrosis gene in 1989, whereas the aetiology of diffuse panbronchiolitis is still unknown. Could the pathophysiology of diffuse panbronchiolitis be related to cystic fibrosis? The most common mutation in cystic fibrosis (delta F508) was not found in a recent investigation of 21 patients with diffuse panbronchiolitis,²⁷ but there are no reports on investigations of the occurrence of any other of the more than 300 cystic fibrosis mutations, some of which lead to less severe symptoms. Maybe it is time for scientists and clinicians working on cystic fibrosis and diffuse panbronchiolitis to come together to exchange results and ideas to the benefit of both groups of patients.

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