Bacterial Flora of Respiratory Tract in Patients with Cystic Fibrosis, 1950-1971

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Mearns, M. B., Hunt, G. H., and Rushworth, R. (1972). *Archives of Disease in Childhood*, 47, 902. **Bacterial flora of respiratory tract in patients with cystic fibrosis, 1950-1971.** The bacterial flora of the respiratory tract of patients with cystic fibrosis was observed from 1950 onwards. Serum precipitins against *Staph. aureus*, *H. influenzae*, and *Ps. aeruginosa* were determined in the serum of 102 patients.

A trend of change in the bacterial flora was noted; the isolation rate of *Staph. aureus* fell, whether related to age or severity of disease, while after 1964 there was an increased isolation rate of *Ps. aeruginosa* in the most severely affected patients.

Bacterial precipitins were found in 55 of 102 patients. Generally the presence of these correlated with the radiological changes. *Pseudomonas* precipitins were found chiefly in patients with generalized changes, while precipitins against staphylococcus and haemophilus occurred more in patients who had either no radiological change or less severe changes.

These findings have relevance to the management of patients with cystic fibrosis. It is suggested that factors other than bacterial infection may initiate the lung changes in children with cystic fibrosis.

Progressive lung damage in cystic fibrosis is thought to result from bacterial infection, and the role of *Staphylococcus aureus* has been widely discussed since the recognition of this disease by Andersen in 1938. In 1949 Andersen showed that early in the course of the disease cultures of bronchial secretions grew *Staph. aureus* in nearly every case, but in cystic fibrosis with chronic bronchiectasis *Pseudomonas aeruginosa* was commonly associated with the staphylococcus. There is general agreement that in recent years the isolation of pseudomonas has increased in the most severely affected and intensively treated patients, but there is now considerable debate about the role of this species in the pathogenesis of the pulmonary damage in cystic fibrosis. Some have argued that despite this increasing incidence of pseudomonas the clinical course and pathological findings at necropsy have changed little, pseudomonas is not of major pathogenic significance, and *Staph. aureus* is therefore probably still the main agent responsible for the widespread pulmonary changes

(di Sant'Agnese and Talamo, 1967). Others, however, hold the view that efficient antistaphylococcal agents have altered the general course of cystic fibrosis, so that other antibiotic-resistant micro-organisms, e.g. *Ps. aeruginosa*, become the agents responsible for the repeated episodes of pulmonary infection (Doggett and Harrison, 1969).

The present study shows the change in the isolation rates of *Staph. aureus* and *Ps. aeruginosa* from the respiratory tract of patients with cystic fibrosis seen at the Queen Elizabeth Hospital from 1950 to 1971. An attempt has also been made to relate the bacteriology of these patients to their clinical state.

Materials and Methods

Patients. The patients studied all attended the Cystic Fibrosis Clinic. Their management was supervised by the late Dr. Winifred Young until 1969 and since that time by Dr. A. D. Jackson and M.B.M. All were given antistaphylococcal drugs in high dosage when lower respiratory infections occurred and prophylactically at times of upper respiratory infection. They have been analysed below according to age, from 0 to 5 years, 6 to 10 years, 11 to 15 years,

and over 15 years, but the number of patients over 15 years old was too small for useful analysis. Each year a clinicoradiological assessment was made classifying them into 3 groups of increasing severity, I, II, and III, as previously described by Jackson and Young (1960).

Bacteriology. Sputum, if obtainable, or a deep pharyngeal swab, was cultured on blood agar.

The bacterial flora of 140 patients under the age of 1 year was studied on their first admission to hospital between 1950 and 1971—1950 to 1957 (30 patients); 1958 to 1964 (46 patients); 1965 to 1968 (37 patients) and 1969 to 1971 (27 patients). In addition, midsummer (July $\pm$ one month) examinations were made of all patients attending the clinic in the years 1956, 1960, 1964, 1969, 1970, and 1971, these years being selected for the following reasons:

1956—after that year more intensive treatment was given—antibiotics in longer courses and by aerosol with more intensive physiotherapy.

1960—being halfway between 1956 and 1964.

1964—after this time cloxacillin was introduced into the treatment regimen.

1969—supervision of the patients was changed to M.B.M.

1970-71—because of the associated study of bacterial precipitins.

Serum precipitins. During 1969 to 1971 bacterial precipitins against *Staph. aureus*, *Ps. aeruginosa*, and *H. influenzae* were sought in the serum of 102 patients aged 8 months to 17 years. The tests were carried out in the Department of Bacteriology, Institute of Diseases of the Chest. The findings are also incorporated in the series of 195 patients described by May, Herrick, and Thompson (1972), but the latter also includes many older patients as well as others in the same age groups as those described here.

Results

Bacteriology. Study of the babies under 1 year of age shows a progressive decrease in the isolation rate of *Staph. aureus* at the time of initial admission to hospital from 86% of patients in 1950-57 to 30% in 1969-71 (Fig. 1). In comparison, the rate for all patients attending the clinic dropped from 45% in 1956 to 12% in 1971, while the rate for *Ps. aeruginosa* rose from 3% to 28%.

The percentage of patients from whom no recognizable pathogen was isolated remained relatively unchanged at approximately 55%.

Bacteriology related to age (Fig. 2). At all ages the isolation rate of *Staph. aureus* fell during the period of study. In the 0- to 5-year-olds the number of patients from whom no pathogens were isolated increased but there was little change in the isolation rate of *Ps. aeruginosa*. In the patients aged 6 to 10 years the percentage with no pathogens was relatively stable, but after 1964 there was an

FIG. 1.—Bacterial flora of respiratory tract of patients with cystic fibrosis, 1950-1971. The broken line gives the proportion of children under 1 year of age showing positive cultures at first admission.

increased occurrence of *Ps. aeruginosa*. There were progressively fewer patients aged 11 to 15 years with no pathogens but a marked increase in *Ps. aeruginosa* isolations from these subjects.

Bacteriology related to severity of disease (Fig. 3). The isolation rate of *Staph. aureus* fell in all clinical groups during the period of study. The fall was greatest in Group III patients, dropping to less than 10%. Coincidentally in the other two groups there was an increased isolation rate of *Ps. aeruginosa* from approximately 20% to 60%. In Group I pseudomonas isolations did not increase with the decrease in staphylococci.

Bacterial precipitins. No precipitins against any of the bacterial species tested were found in the serum of 47 of the 102 patients examined. Precipitins against *Staph. aureus* were found in 15 patients, against *H. influenzae* in 21, and against *Ps. aeruginosa* in 37. Precipitins against more than one species were found in 15 of the 55 patients with precipitins.

Precipitins related to age (Fig. 4). With increasing age there was an overall increase in the occurrence of precipitins, with no one particular bacterial species predominating.

Precipitins related to severity of disease (see Table). No bacterial precipitins were found in

FIG. 2.—Bacterial flora of respiratory tract of patients with cystic fibrosis related to age.

FIG. 3.—Bacterial flora of respiratory tract of patients with cystic fibrosis related to severity of lung disease.

FIG. 4.—Serum precipitins in 102 patients with cystic fibrosis.

TABLE
Serum Precipitins Against Bacteria Related to Severity of Lung Disease

	Group I (% of 44 patients)	Group II (% of 26 patients)	Group III (% of 32 patients)
No. of precipitins	66	30	31
<i>Staph. aureus</i>	18	11	10
<i>H. influenzae</i>	16	30	19
<i>Ps. aeruginosa</i>	10	50	55

Note: Totals are >100 as some patients had precipitins to more than one bacterial species.

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the serum of 29 of 44 patients (66%) in Group I. The remaining 16 had precipitins divided approximately equally between the three bacterial species investigated. In Groups II and III, 8 of 26 and 10 of 32 patients, respectively (i.e. one-third of each group), had no precipitins to the bacteria tested. While the occurrence of pseudomonas precipitins increased markedly with increased severity of disease, precipitins to the other bacteria tested were not obviously related to the severity of disease.

Relation between respiratory flora, bacterial precipitins, and radiographic appearances.

Though some patients with x-ray evidence of lung abnormalities had no precipitins to the bacteria tested, generally the presence of precipitins correlated with the x-ray change. Pseudomonas precipitins were found chiefly in patients with generalized changes, while precipitins to staphylococcus and haemophilus occurred mainly in those who had either no abnormalities on x-ray or else only localized changes.

Patients with no precipitins. No pathogenic bacteria were found in the cultures of pharyngeal swabs or sputum of 39 to 47 patients with no serum precipitins, but 11 of these 39 had x-ray evidence of lung abnormalities, 5 localized and 6 generalized. 2 of the remaining 8 patients had localized x-ray changes and both had *Staph. aureus* in culture. The remaining 6 patients all showed abnormalities on x-ray, and *Ps. aeruginosa* with or without other species was isolated in culture.

Patients with staphylococcal precipitins. Precipitins against *Staph. aureus* only were found in 7 patients. 5 patients had clear chest x-rays; *Staph. aureus* was isolated from one and *Ps. aeruginosa* from another, and 3 showed no pathogens in culture. Localized changes on x-ray were present in 2 patients; no pathogens were isolated in either.

Patients with haemophilus precipitins. Precipitins against *H. influenzae* only were detected in the serum of 10 patients but the organism was not isolated from any of them. 4 patients had clear x-rays and no pathogens were shown in culture. Localized x-ray changes were present in 3 patients, *Staph. aureus* being isolated from 2 and the third showed no pathogens in culture. 3 patients had generalized x-ray changes; *Ps. aeruginosa* was isolated from 1, no pathogens were shown in the other 2.

Patients with pseudomonas precipitins. Only 3

of 23 patients with pseudomonas precipitins had clear chest x-rays. 7 had localized and 13 generalized changes. *Ps. aeruginosa* was isolated from 22 of the 23 patients and *Staph. aureus* was isolated from the remaining patient.

Patients with precipitins against more than one bacterial species. Precipitins against more than one bacterial species were detected in 12 patients. 4 patients had clear x-rays, *Staph. aureus* being isolated from one and *Ps. aeruginosa* from the other 3. 6 patients had localized abnormalities on x-ray, *Ps. aeruginosa* being isolated from them all. *Staph. aureus* was isolated in addition in one patient. 6 patients had generalized changes; *Staph. aureus* and *Ps. aeruginosa* were isolated from 4 of these, and *Ps. aeruginosa* only in the remaining 2.

Discussion

By observing the relation between the clinical severity of pulmonary disease, lung changes on x-ray, the bacterial flora of the respiratory tract, and the occurrence of antibacterial precipitins in the patients' serum, an attempt has been made to apportion responsibility for lung damage between *Staph. aureus*, *H. influenzae*, and *Ps. aeruginosa*, which seem to be the commonest pathogens found in cystic fibrosis at the present time (May *et al.*, 1972). This attempt has not been entirely successful, perhaps not surprisingly in a retrospective study such as this, but certain findings have emerged.

Infection by *Staph. aureus*, in contrast to that by *Ps. aeruginosa*, appears at first sight to be unrelated to the severity of disease. Thus, while the isolation rate of staphylococci fell substantially during the period of study in all patient groups, the most striking fall (from over 80% in 1956 to less than 10% in 1971) occurred in the group of patients most severely affected. Similarly, the occurrence of antistaphylococcal precipitins was not obviously related to severity of disease. In contrast, while the isolation rate of staphylococci from the more severely affected patients was falling, that of *Ps. aeruginosa* rose steadily, and the occurrence of serum precipitins against this organism was related especially to patients in Groups II and III. These observations, however, do not prove that the pseudomonas is more likely to cause lung damage than the staphylococcus. Taken in conjunction with the substantially unchanged number of patients from whom neither organism was isolated during the period of study, and the fact that there has been no marked change in the balance of

patients in the three grades of severity, they suggest that *Staph. aureus* and *Ps. aeruginosa* have similar pathogenic significance in cystic fibrosis—indeed Fig. 3 suggests that they are more or less interchangeable in this context.

No definite conclusions seem possible concerning the contribution made by *H. influenzae* to lung damage in these patients. The organism was not isolated from any patient, but antihaemophilus precipitins were detected in the serum of 21. These tended to occur in older patients with more severe disease, but their significance cannot be assessed because there was often simultaneous infection with *Staph. aureus* or *Ps. aeruginosa*. The findings in this study and in that of May *et al.* (1972) are quite compatible with the concept that *H. influenzae* is an opportunist secondary invader in cystic fibrosis, as it so commonly is in other chronic respiratory disorders.

One of the most striking observations in this study was the remarkable fall in the isolation rate of staphylococci during the past 16 years. It is tempting to conclude that this was the result of improved antistaphylococcal therapy, but the parallel fall in staphylococcal isolations from the babies when first admitted to hospital raises some doubt. It may well be that the finding is a reflection of a general decrease of colonization of the newborn with staphylococci; in some nurseries it has dropped from over 50% to 5% (Light *et al.*, 1968). The coincidental increase in pseudomonas isolations in the older children may reflect the change in recent years in the relative importance of Gram-negative organisms, compared with staphylococci, in hospital-acquired infections (Barrett, Casey, and Finland, 1968).

Because of their implications concerning management, it is of the greatest importance to try and determine the pathogenic roles of *Staph. aureus* and *Ps. aeruginosa* in cystic fibrosis. The prognosis in this disease appears to have improved coincidentally with the introduction of antistaphylococcal drugs (Warwick and Monson, 1967). Lawson (1969) believes that the staphylococcus is always the initial pulmonary pathogen in this condition and that the infection by *Ps. aeruginosa* occurs secondarily when the lungs have been damaged. In order to prevent lung damage he suggests that cloxacillin prophylaxis should be given from the time of diagnosis and continued through life, believing that lung damage, and so pseudomonas infection, will be prevented. However, if children with cystic fibrosis are in fact equally susceptible from birth either to *Staph. aureus* or to *Ps. aeruginosa*, such a policy might

actually lead to an increase of pseudomonas infections at a younger age than that at which they are nowadays commonly seen. In this context, the finding of precipitins against pseudomonas in patients with less than severe lung damage and in the 0 to 5 years group in this series is disturbing. Since 1957 the majority of these patients have been given antistaphylococcal drugs continuously for prophylaxis from the time of diagnosis until their first birthday, and then when clinically indicated, in short or long courses. The low overall incidence of precipitins against *Staph. aureus* could imply that if infection with this bacterium had occurred it was controlled in the majority of patients.

The question of susceptibility to staphylococci and pseudomonas has been discussed by May *et al.* (1972) who believe that any respiratory pathogen may cause the initial bronchopulmonary infection in cystic fibrosis; but it must also be recognized that there is as yet no absolute proof that the lung damage is actually caused by bacterial infection. The presence of radiological disease in the absence of detectable pathogens or bacterial precipitins could be a technical failure but may be an indication to consider that viral infection or even some metabolic disorder, to name just two possible alternatives, could be as, or more, important than bacterial pathogens in initiating the lung changes in children with cystic fibrosis. There can be no doubt though that bacterial infection contributes substantially to progressive deterioration.

The relative importance of staphylococci and pseudomonas in this context cannot be determined from a study of treated patients, but the trend towards replacement of staphylococcus by pseudomonas is a disturbing development because of the difficulty in controlling the latter by chemotherapy.

With the present state of knowledge, treatment of staphylococcal infection is obviously of prime importance but the future prognosis of this disease is still unpredictable. In 1958 Dorothy Andersen wrote, 'the use of antibiotics in these children is far from satisfactory; new agents have appeared so rapidly that evaluation is difficult'. In the ensuing years little advance has been made in the understanding of antibiotic therapy in this disease.

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