

# Treatment and Prevention of Pulmonary Complications of Cystic Fibrosis in Infancy and Early Childhood

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**Mearns, M. B. (1972).** *Archives of Disease in Childhood*, **47**, 5. **Treatment and prevention of pulmonary complications of cystic fibrosis in infancy and early childhood.** Seventy-six patients with cystic fibrosis seen between 1950 and 1964 were studied, all having been first seen before the age of 1 year. In retrospect, the year 1957 seemed to be a watershed in the treatment of this series of patients, and they were therefore divided into 2 groups. Group A, 30 patients seen before 1957; Group B, 46 patients seen after 1957. The clinical, radiological, and bacteriological findings in the 2 groups at entry were similar as to age of incidence, severity of the initial respiratory symptoms, abnormalities on chest radiographs, and bacteriology of the cultures of cough swabs. Treatment of Group B patients was generally more vigorous, with antibiotics used more efficiently to treat pulmonary infection.

When the patients were followed up and their pulmonary status was assessed clinically and radiologically, at 1 year and at 5 years of age, Group B patients were found to be significantly less severely affected than Group A patients.

It is concluded that vigorous treatment of cystic fibrosis can reduce mortality in infancy, and considerably improve the pulmonary status during childhood.

Cystic fibrosis (CF) was recognized as a disease entity 30 years ago (Andersen, 1938), and during this period the expectancy of life has changed. In 1948 it was reported (Andersen, 1949) that the majority of children with CF died by 1 year of age; in 1964 analysis of data from 31 CF centres in the U.S.A. showed that the probable life expectancy of these patients was then 12 years (Warwick and Monson, 1967). More recently, life tables based on a series of 349 consecutive patients referred to the Cleveland centre between 1958 and 1965 with an average follow-up of only 3.5 years indicated that the probable life of this group of patients would be 21 years (Warwick, 1967), and it is claimed that it was the introduction of mist tent therapy that is the important factor in the improved life expectancy in this group (Matthews, Doershuk, and Spector, 1967).

The disease does not have the same impact on each patient and in analyses it is difficult to match any two patients. The varying clinical picture lends itself to the application of many methods of management, both pharmacological and physical,

so that assessment of results from one clinic to another is difficult. To study the course of this disease and the results of treatment, it is necessary to see these patients early in life before permanent lung damage has occurred, to review them regularly, and to formulate a consistent plan of therapy in which differences in the efficiency of therapy between patients is reduced to a minimum. The purpose of this paper is to report the results of a study of 76 patients with CF started in 1950 by the late Dr. Winifred F. Young that answers the above requirements.

The patients have been seen regularly and none has been lost to follow-up. In 1950 antistaphylococcal drugs were given in short courses but their duration was gradually increased, so that by 1957 antibiotics were used continuously as prophylactic treatment throughout the first year of life. As new and more effective antibiotics became available, these were introduced into the therapeutic regimen. For example, when it became apparent that the staphylococci did not quickly develop resistance to neomycin, this was given by aerosol both in hospital and at home. Erythromycin and novobiocin were found effective in the treatment of staphylococcal

infections in patients with CF and by 1957 these were the most frequently used antibiotics. The benefits of physiotherapy in the seriously ill infant and the continuation of this therapy in the absence of symptoms had also been accepted by this time. The basic management of these patients then remained relatively unchanged until the end of 1963 when synthetic penicillins became available. These penicillins have not been used as routine prophylaxis unless, on sensitivity testing, the staphylococcus is found to be resistant to the other antibiotics. In retrospect, the year 1957 seems to be a watershed in the treatment of this series of patients, since this was the year that effective oral antistaphylococcal antibiotics were introduced. The results in patients admitted before and after this year are considered separately, since this should help assess the relative importance of the various factors in treatment.

### Material

All patients who were under 1 year of age when first seen at the clinic have been included for study but, to give a reasonable period for follow-up, only the 76 patients seen before 1964 are discussed. The oldest patient is 19 years of age and the youngest is 5. During the period of study a total of 125 patients was admitted to the clinic so that approximately 60% (76) of all the patients were seen before 1 year of age. The 76 patients have been divided into 2 groups. In Group A are the 30 patients admitted before 1957, and in Group B the 46 patients admitted after 1957.

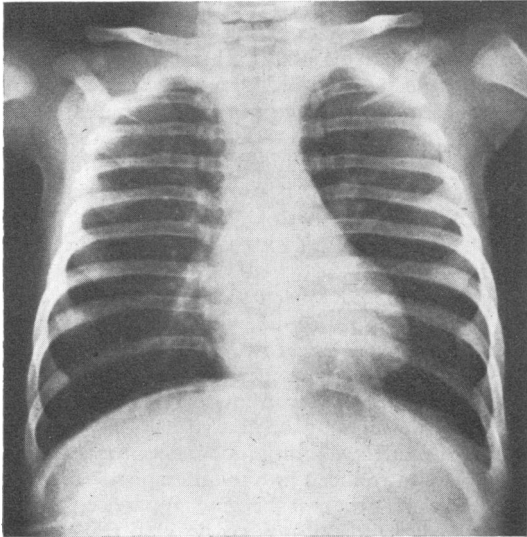


FIG. 1.—Chest x-ray—air trapping—depression and flattening of the diaphragm, horizontal position of the ribs, and increase in intercostal spaces—patient aged 4 months.

### Methods

**Clinical assessment.** The patients were assessed clinically to establish the age of the first respiratory symptoms, the duration of respiratory symptoms before starting treatment at the clinic, and the severity of the respiratory symptoms judged as below.

*Mild* symptoms were as might be expected in any infant of the same age with mild bronchitis; *severe* included evidence of respiratory difficulty as shown by marked intercostal or subcostal recession, dyspnoea, paroxysmal cough, and difficulty in feeding, and *severe with cyanosis* meant that central cyanosis either persistent or in episodes was present in addition to severe symptoms.

**Radiological assessment.** Four main types of change were noted on the chest radiographs: evidence of air trapping as shown by a depressed and flattened diaphragm and by horizontal position of the ribs with widening of the intercostal spaces (Fig. 1), a thickened bronchial wall pattern denoting a parallel-line shadow corresponding to the bronchial walls, both more marked and found more peripherally than in the normal (Fig. 2); collapse/consolidation, either segmental or lobar in distribution; focal disease—small peripheral blob shadow occurring singly but usually in groups, varying in size from 3 or 4 mm to 15 mm in diameter; and generalized focal disease—indicating that these lesions were present in more than one lobe.

**Bacteriological findings.** Since it is difficult to collect sputum from infants and young children, particularly, it was necessary to rely on the culture of cough swabs.

### Clinical Management

The patients were seen at intervals of 4 to 6 weeks, cough swabs were taken at each visit and chest radiographs were taken at 6-monthly intervals or more often if this was indicated clinically. A high calorie, high protein but low fat diet with pancreatic supplements

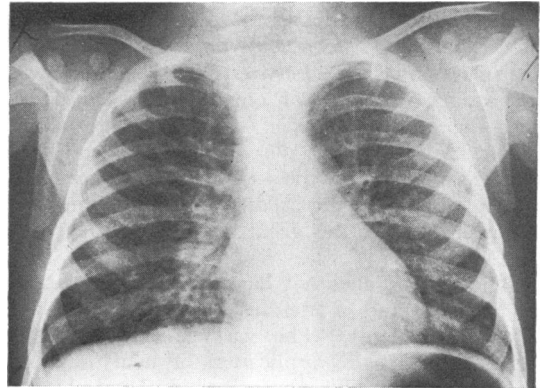


FIG. 2.—Thickened bronchial wall pattern—patient aged 11 months.

and high dosage of vitamins was recommended to maintain optimum nutrition. Parents were instructed in the technique of percussion drainage to clear secretions from the lungs and were instructed to do this twice daily. Infection was controlled by antibiotics, given both orally and by aerosol, the choice of antibiotic was determined by the results of the sensitivity tests on the pathogens cultured from the cough swabs.

Clinical grading of the patients was made at 1 and 5 years of age, the patients being divided into categories I and II.

**Category I.** Patients in Category I had no bronchitis, that is, symptoms and signs of respiration infection, if present in the past, had cleared. Cough if present was minimal and only induced by crying or by exercise. On auscultation of the lungs there were no added sounds, no staphylococcus was cultured from the cough swab on at least 3 consecutive occasions, the swabs being taken at least 3 days apart.

**Category II.** Patients in this category had added sounds on auscultation of the lungs, persisting cough, and sputum sometimes present and sometimes not.

**Results**

**Comparison of Patients in Group A (seen before 1957) and in Group B (seen after 1957) at Time of Initial Diagnosis**

**Clinical assessment.** (a) *Incidence of respiratory symptoms in first year of life* (Fig. 3). Approximately 60% of the patients in both Group A and Group B (59% : 52% respectively) had had respiratory symptoms in the first 3 months of life. Only 3 patients had their first symptoms after the age of 6 months. 8 of 76 patients had no respiratory symptoms during the first year of life, 2 of these patients being in Group A and 6 in Group B.

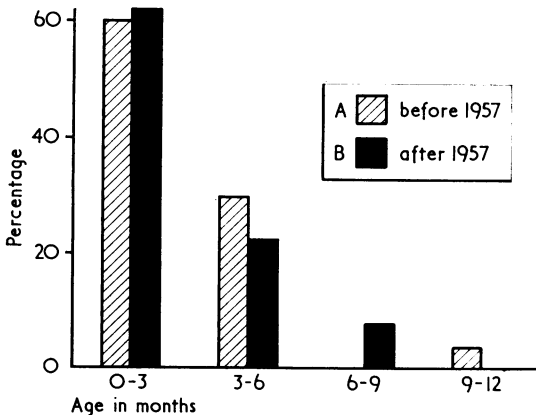


FIG. 3.—Age at first respiratory symptoms.

(b) *Duration of respiratory symptoms before starting treatment* (Fig. 4). Approximately 60% of the patients in both Group A and Group B (60% : 57% respectively) had had respiratory symptoms for less than 2 months before attending the clinic. Nearly 20% of each group of patients

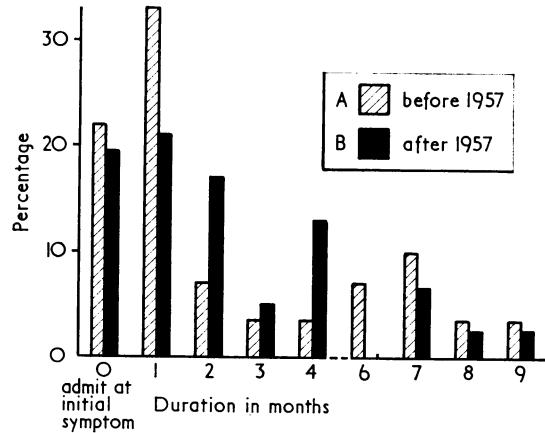


FIG. 4.—Duration of respiratory symptoms before entry to the series.

were seen during their first respiratory symptom. Very few patients in either group had symptoms of more than 6 months' duration.

The results in (a) and (b) above suggest that on admission to the series the patients in Group A and Group B were similar.

(c) *Severity of respiratory symptoms* (Fig. 5). In both Group A and Group B a similar proportion

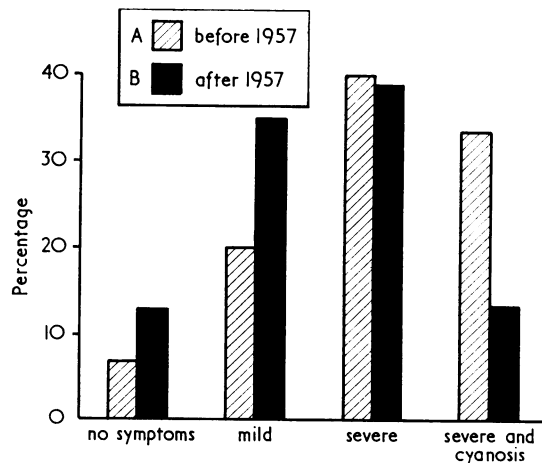


FIG. 5.—Severity of respiratory symptoms in the first year.

of patients had severe symptoms at the time of the initial illness, but in more patients in Group A cyanosis had occurred. Considering the 'severe' and 'severe with cyanosis' together, 10 of the 19 patients (53%) in Group A made a clinical recovery, compared with 17 of the 22 patients (78%) in Group B. The more intensive therapy given to the severely ill infants in Group B may have prevented the occurrence of cyanosis as well as improving their recovery.

Of the 6 patients with mild symptoms in Group A, 3 made a full recovery, but only 2 of 18 patients in Group B failed to fully recover. No respiratory symptoms developed in 2 patients of Group A and in 6 patients of Group B, and it may be that continuous prophylactic antibiotics given during the first year of life to Group B patients had reduced the incidence of infection, but the number of patients is too small for conclusions (Fig. 6).

**Radiological assessment.** Group A and Group B matched very closely in the incidence of abnormal radiological findings at the time of the initial respiratory illness, especially when these

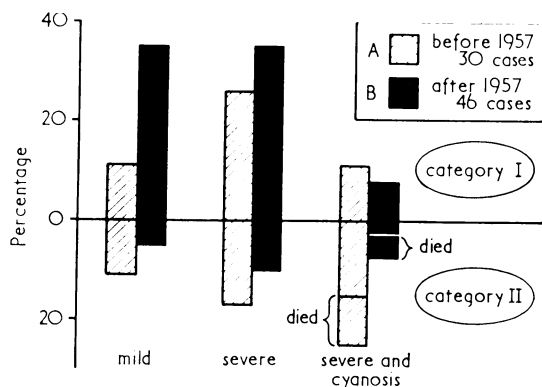


FIG. 6.—Clinical findings at 1 year compared with severity of early respiratory symptoms.

findings were related to the severity of clinical symptoms (Fig. 7). Even in those patients with mild symptoms, more than half showed an area of collapse or collapse consolidation on the chest radiograph, indicating perhaps that the severity of the disease was greater than was apparent clinically.

**Bacteriological assessment.** 86% of Group A patients and 75% of Group B patients had *Staphylococcus aureus* cultured from their cough swabs at the time of their initial symptoms, again suggesting similarity in the patients admitted to each of the groups.

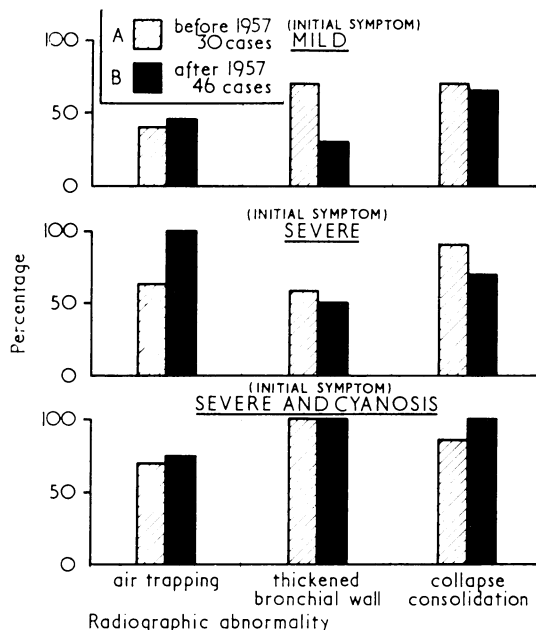


FIG. 7.—Comparison of chest x-ray findings in patients of Groups A and B at time of infection during first year, when related to clinical symptoms.

#### Comparison of Group A Patients with Group B Patients at 1 and 5 Years of Age

**Clinical grading.** At age 1 year 50% of Group A patients and 80% of Group B patients were in Category I, and at age 5 years these percentages were not significantly changed (Table I). 3 of 30 patients from Group A and 2 of 46 patients in Group B died at the time of the initial infection. One more death occurred in each group between 1 and 5 years of age. Thus, there was a 14% mortality rate in the 30 patients of Group A and a 6.5% mortality rate in 46 patients of Group B up to the age of 5 years.

#### Clinical grading compared with radiological findings.

**Category I—patients having no bronchitis.** 80% of Group A and 89% of Group B patients who were free from bronchitis had clear chest radiographs at 1 year of age, and at this age clinical and radiological assessment agreed closely. At 5 years of age this correlation was not so close; in Group A, 54% of patients considered free of bronchitis had a clear chest radiograph, while 26% had developed a thickened bronchial wall pattern in the interval. The Group B patients at 5 years continued to be

TABLE I  
Clinical Assessment of Patients

	Group A (before 1957) % of 30 Cases		Group B (after 1957) % of 46 Cases	
	1 yr	5 yr	1 yr	5 yr
<i>At end of 1st year</i>				
Category I	50		80	
Category II	40		16	
Died	10		4	
<i>At 5 years</i>				
Category I	43		78	
Category II	43		16	
Died	14		6	

Note: Both at 1 year and at 5 years Group B contained a higher proportion of Category II cases than did Group A,  $P < 0.05$  at 1 year and  $< 0.01$  at 5 years. The numbers of deaths were not large enough to produce significant differences though they show the same trend, with an advantage in favour of Group B both at the end of 1 year and at the end of 5 years.

satisfactory whether assessed clinically or radiologically (Table II). (In Group B at 5 years, 1 patient had had an area of localized disease—that was persisting collapse with consolidation—removed by lobectomy.)

TABLE II  
Radiological Findings at 1 Year and 5 Years for Category I Cases

	Group A % of 15 cases		Group B % of 37 cases	
	1 yr	5 yr	1 yr	5 yr
Clear radiograph	80	54	89	89
Thickened bronchial walls	7	33	8	11
Localized disease	13	13	3	—
Generalized disease	—	6	—	—

At 1 year, Group B contained a higher proportion of cases with clear radiographs, but the difference was not significant. At 5 years the difference in favour of Group B was highly significant,  $P < 0.001$ .

*Category II—patients with persisting signs.* At age 1 year a thickened bronchial wall pattern was seen on the chest radiograph in 60% of Group A patients and in 72% of Group B patients, but the prevalence of localized disease was similar. At age 5 years the presence of a thickened bronchial wall pattern had increased in Group A, being seen in 83% of patients, but the incidence remained unchanged in Group B patients. The incidence of generalized focal disease at 5 years of age was 44% in Group A patients and only 14% in Group B patients (Table III).

**Bacteriological findings at 1 and 5 years.** *Staphylococcus aureus* was not cultured from cough

TABLE III  
Radiological Findings at 1 Year and 5 Years for Category II Cases

	Group A % of 12 cases		Group B % of 7 cases	
	1 yr	5 yr	1 yr	5 yr
Clear radiograph	27	17	14	14
Thickened bronchial walls	60	83	72	72
Localized disease	17	17	14	14
Generalized disease	—	44	—	14

The proportions with clear radiographs in Groups A and B were not significantly different.

swabs of patients in either Group A or Group B at the time of recovery from the initial acute episode. In Group A patients the staphylococcus recurred more frequently without clinically detectable respiratory symptoms, even when prophylactic antibiotics were continued, than in Group B patients. Persistently positive cultures from cough swabs were not significantly different in Group A and Group B patients (25% : 30% respectively) who were considered to be in Category II. 5 patients died at the time of the initial infection—3 in Group A and 2 in Group B. *Staphylococcus aureus* was cultured from the cough swabs in these 5 patients at the onset of infection, the cultures becoming negative before death in all 5. In all 4 patients examined *post mortem*, *Staphylococcus aureus* was cultured from the lungs. The one patient not examined was in Group B.

**Follow-up at End of 1969**

**Group A patients.** Though these patients had less potent antibiotics and shorter periods of treatment than would be given now, 24 (74%) of the 30 patients of Group A survived to the age of 10 years or beyond. There were 15 patients in Category I at 1 year of age and 12 of these (ages 11 to 15 years) survive, 8 are still free of symptoms. 3 of the 12 patients in Category II at 1 year of age are still living (ages 14 to 19 years) but though they have productive cough they lead normal lives.

**Group B patients.** It is not possible to determine if the improved results observed at 5 years of age in this group are continuing. Only 10 patients could have reached 10 years of age and of these 2 have died at 7 and 9 years. One of these was considered to be in Category I at 1 year of age, and then remained well until 6 years when, after an acute episode of respiratory infection, there was progressive deterioration until death 1 year later.

The other patient who had died and who was in Category II at 1 year of age, gradually deteriorated until death at 9 years.

Seven of the 8 survivors were in Category I at the end of the first year and remain so. The other patient in Category II at 1 year is now 11 years of age and has focal lesions through both lungs on chest radiograph but remains active and leads a normal life.

### Discussion

The first reports of the pathological findings in CF drew attention to the high incidence of staphylococcal infection of the lungs. In the present study it was hoped that it might be possible to prevent permanent damage to the lungs by staphylococcal infection. Persisting 'infection' was defined as 'continuing culture' of staphylococcus from cough swabs in the presence of persistent respiratory symptoms. In the early years of this study this pathogen was not eradicated from the cough swab cultures. This could have been due to the ineffectiveness of the drugs then available, to inadequate dosage, or to too short a course of treatment. Later on the cultures from the cough swabs failed to grow staphylococcus, but this pathogen was cultured from the lungs of the infants who died and so, though the therapy could have been controlling the infection, it was not eradicating it. In recent years after treatment has been started, cultures from the cough swabs are more frequently negative for the staphylococcus, and when antibiotics are discontinued relapse with recurrence of respiratory symptoms is less frequent.

The changes found on the chest radiographs of these patients may also indicate persistence of infection. In other chronic lung disease a thickened bronchial wall pattern has been considered to represent chronic infective changes in the bronchial wall (Hodson and Trickey, 1960). Pathological examination of the lungs of the infants who died during the initial acute illness showed the bronchial wall to be infiltrated by lymphocytes and plasma cells, as well as collapse and epithelialization of the adjacent alveoli and extension of inflammatory cells into the alveolar walls, so increasing the solid zone surrounding the bronchial lumen (Hodson and France, 1962).

In this series, the presence of a thickened bronchial wall pattern on the chest radiograph has been noted to be one of the earliest changes in CF patients with the onset of persistent respiratory symptoms. This change may disappear after episodes of acute infection, but once it has persisted for over 1 year it is unusual for it to clear. The

higher incidence of a thickened bronchial wall pattern at 5 years of age in the patients treated before 1957 was associated with recurrent positive pharyngeal cultures for staphylococci, suggesting that persisting infection may be a factor in producing this radiological change in CF, and also supports the view that the treatment given to patients at this time was not as satisfactory as that given later. This view is further supported by the fact that the patients in the series treated before 1957 had evidence of lung damage at an earlier age and a more rapid progression of the disease than the patients treated after 1957. It is acknowledged that assessment was not as critical in the early years, and that if the patient appeared well and was gaining weight, minimal respiratory symptoms did not receive as much attention, while physiotherapy and antibiotics were discontinued (as would now be considered) prematurely. The more intensive treatment of respiratory symptoms and increasing range of antibiotics has probably slowed down the progression of the disease in those patients treated after 1957 who had persisting signs at 1 year of age.

Lawson (1969) has suggested that prophylactic cloxacillin in full therapeutic dosage from the day of diagnosis should protect against staphylococcal invasion, and that there exists an additional way to judge the efficiency of new methods of treatment, that is by the failure of staphylococcal and other bacterial precipitins to develop in the serum of CF patients so treated (Burns and May, 1968). The majority of patients admitted in early infancy to the present study and treated since 1957 remain free of detectable lung damage assessed clinically and radiologically up to the age of 5 years. They have received continuous antistaphylococcal prophylaxis in the first year of life, and intensive treatment of acute episodes as they occurred after that age. The bacterial precipitins were not studied in these patients, and obviously it is not possible to determine whether the results would have been better if prophylactic antibiotics had been given continuously up to the age of 5 years.

A recent paper (Shwachman, Redmond, and Khaw, 1970) reports the follow-up of 130 patients with CF treated from early infancy. 20 of 25 patients (80%) now aged 0 to 5 years and 33 of 41 patients (80%) now aged 5 to 10 years are considered to have excellent or good physical status. The results reported here follow a similar pattern. It is assumed that bacterial infection is a cause of the lung damage in CF, but it is possible that there are other factors at present undetermined.

The present series shows that vigorous treatment and attempts to control or eradicate infection in

infancy can prevent the majority of these patients from becoming chronic respiratory invalids in early childhood, but this is a chronic disease and surveillance must be continued throughout life. The follow-up in this series, especially of Group B, is too short and the number of patients too small to give any life expectancy figures, but the results show that the mortality in infancy has been reduced and the prognosis in early childhood significantly improved during the past 20 years.

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