Ventilatory Function in Infants with Cystic Fibrosis

Physiological Assessment of Inhalation Therapy

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There is little scientific information available concerning respiratory function in young infants with cystic fibrosis. Matthews and Doershuk (1967) reported that they had performed respiratory function studies in infants with cystic fibrosis, but gave no detailed information of their techniques or results. The only other studies have been carried out in older children and adolescents (West, Levin, and Di Sant'Agnese, 1954; Cook *et al.*, 1959; Mearns, 1968).

Intermittent inhalation therapy with nebulized water vapour and propylene glycol is widely used in the treatment of the pulmonary lesions in cystic fibrosis, but no quantitative evidence has been published to substantiate its value.

The present report provides information on these two subjects. Respiratory function studies were performed on groups of infants with cystic fibrosis before there was clinical evidence of infection, and also on those in whom infection had developed. These studies were repeated serially before and during the course of inhalation therapy over a period of months to ascertain the effect of inhalation treatment.

Material and Methods

Included in the study were 18 patients who were less than 9 months of age when first seen. The diagnosis of cystic fibrosis in each patient was based on multiple clinical features of the disease, and confirmed by estimation of sweat electrolyte concentration using the method of Anderson and Freeman (1960).

The initial respiratory function studies were carried out before aerosol inhalation was started. Inhalations were administered by face mask using a Bennett twin jet nebulizer 2814 which produced particles of mean size 3.9μ (Mercer, Goddard and Flores, 1965). The basic inhalation diluent mixture used contained propylene glycol 10% and glycerine 2% in 0.9% saline. Each inhalation treatment consisted of 2 ml. of this

mixture, and 0.25 ml. of 2% orciprenaline administered by a nebulizer 1 to 4 times a day. The treatment lasted 10 to 15 minutes. Antibiotics in appropriate dosage were always added (most commonly neomycin, 500 mg. per inhalation) when there was clinical evidence of chest infection, and in some patients they were continued for most of the study period, even though there was no definite evidence of persisting infection. A mucolytic agent (N-acetyl-cysteine) was used occasionally. Antibiotics were frequently given by mouth to patients with exacerbation of cough or other evidence of infection.

Subsequent respiratory function studies were performed at various intervals (usually monthly) for periods ranging from 6 to 42 weeks. When the infants reached about 9 kg. in weight, these studies became technically difficult and so were discontinued.

The patients are considered in three clinical groups:

Group 1. (*Cases 1-5: 5 newborn infants with meconium ileus initially studied before they developed clinical evidence of chest infection.*) Meconium ileus in 3 patients (Cases 2, 4, and 5) was managed successfully without surgery by means of gastrographin enemas (Noblett, 1969). The other 2 patients (Cases 1 and 3) required ileostomy and segmental ileal resection.

Aerosol inhalation treatment was started in all these patients after relief of the bowel obstruction and before discharge from hospital.

Three patients (Cases 3, 4, and 5) had episodes of 'bronchitis' after leaving hospital, on each occasion improving within a few days of increasing antibiotic administration by mouth and inhalation. Case 5 had had recurrent episodes of this type and was the only patient in the whole study whose latest body weight measurement was less than the 10th centile for age.

Case 4 had persistent bronchitis from about 8 months of age, but he did not receive adequate treatment at home. However, his growth was within normal limits, as was that of the other 3 patients in this group.

Three patients (Cases 1, 4, and 5) received medium-chain triglyceride feeding as randomly selected subjects in a concurrent clinical trial.

Group 2. (*Cases 6-9: 4 older infants studied before*

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they developed clinical evidence of chest infection.) Two of these patients (Cases 8 and 9) presented in the first days of life with meconium ileus: both were treated surgically without complications. Aerosol inhalation treatment was begun at the ages of 2 months and 3 months, respectively, before there was any coughing or other clinical signs of chest infection. This treatment was continued and their subsequent progress at the age of 18 and 19 months was satisfactory.

The other 2 patients (Cases 6 and 7) presented at the ages of 3 weeks and 4 weeks, with a known family history of the disease, but with no cough or clinical evidence of chest disease. Aerosol therapy was begun at this stage, and their progress at the ages of 6 and 4 months was satisfactory, the height and weight being above the 10th centile for age, and physical examination was normal.

Group 3. (Cases 10-18: 9 infants with clinical evidence of chest infection before initial study.) The youngest patient (Case 10) presented with meconium ileus on the first day of life. He was successfully treated by gastrographin enema. However, clinical signs of bronchitis were present at the age of 1 week. The other patients presented at various ages, the oldest being 6 months, and all had been given a variety of antibiotics, especially by mouth, before the diagnosis of cystic fibrosis was made.

Two patients presented problems that were difficult to manage. Case 11 developed obstructive jaundice when aged 1 week, and this persisted for 7 weeks. He also contracted staphylococcal septicaemia and pneumonia, and was extremely ill for several weeks, before a diagnosis of cystic fibrosis was established. When discharged from hospital at the age of 4 months his weight was only 3.8 kg. After many months of aerosol therapy his clinical condition gradually improved, his chest signs decreased, and he gained weight to over the 10th centile for age. The other patient who was difficult to manage was Case 15. His mother was severely disturbed psychiatrically so that he was inadequately treated at home. He developed a severe, persistent wheeze and loose cough which improved considerably during a period of intensive aerosol therapy in hospital.

The other 7 patients were seen regularly, the oldest being 20 months at the last visit. All were given regular aerosol therapy, and they were rendered free of chest infection and their height and weight were within normal limits. 3 of these 7 patients were given a medium-chain triglyceride diet as randomly selected subjects in a concurrent clinical trial.

The thoracic gas volume (TGV), which is the volume of air in the respiratory passages at end expiration, was measured with a 49-litre body plethysmograph (DuBois *et al.*, 1956), the method used being similar to that adapted to measure TGV in premature infants (Burnard *et al.*, 1965).

Tidal volume was measured with the infant, partially enclosed in the plethysmograph, breathing room air.

A small piece of Perspex, with a hole 4.5 cm. in diameter for the mouth and nose, was placed over the oval aperture in the lid of the plethysmograph. This was sealed around the nose and mouth and to the lid of the plethysmograph with putty. This method gave a more reliable seal and caused less disturbance to the infant than that of Cross (1949) which uses an inflatable rubber cuff. The tidal volume was measured by recording the pressure change in the plethysmograph with a strain gauge.

Dynamic compliance was measured as the ratio between tidal volume of the infant at rest, measured in the body plethysmograph, and change in intrapleural pressure. Intrapleural pressure was estimated from the measurement of intra-oesophageal pressure with a thin latex balloon 3.5-5.0 cm. long and 2.6 cm. in perimeter, containing 0.2 ml. air (Milic-Emili *et al.*, 1964).

Mean pulmonary resistance was measured as the ratio of total transpulmonary pressure change to the corresponding total change in flow rate between points of equal volume midway in inspiration and expiration (Cook *et al.*, 1957). Pulmonary resistance was also calculated separately for inspiration and expiration. Values for pulmonary resistance pressures were calculated as the differences between observed changes in transpulmonary pressure occurring between the onset of inspiration (or expiration) and mid-inspiration (or mid-expiration) which was near the point of maximal flow rate, and the corresponding elastic component of transpulmonary pressure. The elastic component was estimated from the measurement of compliance and the volume change that occurred between the two points (Frank, Mead, and Ferris, 1957). The transpulmonary pressure was measured with the intra-oesophageal balloon, and the flow rate with the Fleisch pneumotachygraph of resistance 4.0 cm.H₂O/l. per sec.

Satham strain gauges were used to measure all pressures, and the output of the gauges was amplified and recorded using an Electronics-for-Medicine 8-Channel recorder equipped with pressure pre-amplifiers.

The values for TGV were based on the analysis of 5 breaths. There was a constant variation of about 10% in the measurements of TGV, and further statistical analysis of the results was not carried out. 10 breaths were analysed to obtain values for dynamic compliance and pulmonary resistance, and the mean and standard error of the mean of the 10 measurements were calculated.

All patients were mildly sedated with quinalbarbitone given orally in a dose 7-8 mg./kg., and studies were carried out soon after the infants had been fed. With gentle handling, the infants remained lightly asleep during the tests, but quickly awoke if disturbed.

Results

In Table I, TGV is related to body weight and to cube of body length, mean conductance (the reciprocal of mean resistance) is related to TGV (specific conductance) and to cube of body length, and compliance is related to TGV (specific compli-

TABLE I

Thoracic Gas Volume Related to Body Weight and Cube of Body Length, Mean Conductance Related to Thoracic Gas Volume (Specific Conductance) and Body Length Cube, and Specific Compliance in Infants with Cystic Fibrosis*

Case No.	Age (wk.)	TGV/Body Weight (ml./kg.)	TGV/Length ³ (ml./cm. ³ × 10 ⁻³)	Specific Conductance (l./sec. per cm.H ₂ O per l. TGV)	Conductance Length ³ (l./sec. per cm.H ₂ O per cm. ³ × 10 ⁻⁶)	Specific Compliance (ml./cm.H ₂ O per ml. TGV)
1	1	64	1.08	0.370	0.400	0.042
	5	31	0.640	0.452	0.291	0.036
	7	32	0.715	0.262	0.259	0.050
	11	33	0.890	0.472	0.416	0.048
	21	26	0.608	0.364	0.222	0.062
2	2	52	1.04	0.293	0.304	0.031
	7	30	0.765	0.268	0.206	0.037
	13	27	0.718	0.286	0.206	0.056
	20	32	0.782	0.244	0.192	0.061
	29	27	0.662	0.330	0.218	0.140
3	3	45	1.32	0.385	0.505	0.042
	7	37	0.952	0.312	0.296	0.054
	16	32	0.805	0.216	0.174	0.046
	29	35	0.955	0.173	0.166	0.036
4	4	29	0.638	0.493	0.318	0.057
	9	23	0.558	0.293	0.100	0.041
	15	36	0.870	0.168	0.147	0.024
	21	32	0.778	0.200	0.156	0.033
	27				0.116	
	44	32	0.816	0.112	0.091	0.023
5	5	39	0.779	0.284	0.220	0.036
	11	41	0.890	0.126	0.112	0.026
	16	43	0.878	0.152	0.136	0.037
	21	42	0.882	0.161	0.142	0.048
	26	34	0.705	0.192	0.135	0.052
	31	40	0.820	0.220	0.182	0.037
	39	40	0.742	0.128	0.095	0.038
	47	28	0.594	0.270	0.161	0.061
6	3	36	0.608	0.270	0.158	0.073
	4	40	0.948	0.185	0.175	0.035
	9	22	0.562	0.243	0.137	0.044
7	6	29	0.750	0.190	0.145	0.048
	12	31	0.840	0.222	0.186	0.053
	20	33	0.839	0.180	0.150	0.046
8	8	29	0.648	0.248	0.162	0.032
	10	31	0.758	0.213	0.162	0.044
	18	25	0.503	0.345	0.174	0.048
	26	23	0.515	0.235	0.128	0.045
	34	27	0.602	0.190	0.133	0.045
9	24	31	0.728	0.068	0.050	0.030
	36	27	0.655	0.114	0.077	0.029
	40				0.135	
10	1	32	0.788	0.167	0.131	0.043
	6	31	0.676	0.252	0.169	0.049
11	8	87	1.56	0.074	0.115	0.008
	12	61	1.22	0.085	0.104	0.022
	24	40	0.975	0.125	0.122	0.020
	32	30	0.841	0.162	0.136	0.041
	44	30	0.695	0.178	0.124	0.038
12	17	46	1.00	0.110	0.110	0.018
	20	40	0.938	0.132	0.124	0.022
	24	33	0.924	0.123	0.114	0.028
	28	38	1.06	0.104	0.110	0.019
	34	37	0.915	0.106	0.097	0.016
	37	31	0.922	0.140	0.129	0.031
	41	27	0.782	0.156	0.122	0.031
	56	25	0.620	0.199	0.124	0.029

continued overleaf

TABLE I—*continued*

Case No.	Age (wk.)	TGV/Body Weight (ml./kg.)	TGV/Length ³ (ml./cm. ³ × 10 ⁻³)	Specific Conductance (l./sec. per cm.H ₂ O per l. TGV)	Conductance Length ³ (l./sec. per cm.H ₂ O per cm. ³ × 10 ⁻⁶)	Specific compliance (ml./cm.H ₂ O per ml. TGV)
13	16	47	1.16	0.080	0.094	0.039
	17	45	1.14	0.151	0.171	0.038
	19	31	0.770	0.184	0.238	0.064
	25	32	0.700	0.226	0.159	0.073
14	18	48	0.940	0.097	0.091	0.034
	19	34	0.721	0.150	0.108	0.064
	20	34	0.723	0.246	0.178	0.064
	46	31	0.670	0.224	0.152	0.051
15	21	41	0.739	0.160	0.118	0.029
	23	33	0.641	0.304	0.192	0.043
	24	33	0.657	0.370	0.242	0.037
	30	35	0.862	0.134	0.112	0.034
	34	42	0.985	0.089	0.088	0.024
	35	35	0.816	0.146	0.120	0.040
	39	38	0.955	0.147	0.141	0.037
	51	31	0.660	0.238	0.157	0.044
16	24	51	1.08	0.078	0.083	0.027
	27	37	0.729	0.244	0.178	0.039
	44	29	0.068	0.166	0.110	0.051
17	28	38	0.833	0.068	0.059	0.026
	32	33	0.756	0.102	0.078	0.041
	40	31	0.705	0.176	0.123	0.053
18	33	38	0.810	0.109	0.088	0.028
	34	36	0.810	0.115	0.093	0.032
	36	33	0.805	0.128	0.103	0.029
	39	33	0.825	0.140	0.116	0.048
	48	22	0.554	0.234	0.130	0.034

* Full details of the measurements of TGV, dynamic compliance, mean pulmonary resistance, inspiratory and expiratory pulmonary resistance will be made available on application to the authors.

ance). In Table II are given the values for these relationships found in a study of 38 healthy infants (Phelan and Williams, unpublished).

The studies carried out before treatment was started showed that there were considerable abnormalities in respiratory function, but the

abnormalities in the 3 groups of patients were not the same.

Of the 5 infants of Group I who presented with meconium ileus and who were first studied before they had developed clinical evidence of chest infection, 3 had raised values for TGV, if the upper limit of normal was taken as twice the SD above the mean for healthy infants. A fourth infant (Case 5) had an abnormal value for TGV when this was related to body weight, but the value related to the cube of body length was within normal limits, and this was probably the better comparison in this infant as he had been ill during the neonatal period from the results of bowel obstruction, and had failed to gain weight adequately. Mean conductance in these 5 infants was within normal limits. Specific compliance was reduced to a value more than 2 SD below the mean for healthy infants in only 1 patient in this group (Case 2).

The 4 infants of Group 2 who were studied before they had clinical evidence of chest infection all had values for TGV that were within normal

TABLE II
Ventilatory Function in 38 Healthy Infants

	Mean	Standard Deviation
TGV/kg. body weight . . .	30 ml./kg.	± 3.3
TGV/body length cubed . . .	0.768×10^{-3} ml./cm. ³	± 0.089
Specific compliance . . .	0.056 l. per cm.H ₂ O per l. TGV	± 0.01
Specific conductance . . .	0.298 l./sec. per cm.H ₂ O per l. TGV	± 0.075
Conductance/body length cubed	0.221×10^{-6} l./sec. per cm.H ₂ O per cm. ³	± 0.066 × 10 ⁻⁶

limits. Conductance related to the cube of body length was abnormal in only 1 infant (Case 9) in this group, if the mean for the whole group of healthy infants is taken as the expected normal value for this group. However, 3 of the infants in this group were considerably shorter and lighter than the majority of healthy infants studied, and one (Case 9) was heavier and longer than the majority of healthy infants. For this reason, it seemed more appropriate to compare these infants with a group selected from the healthy infants who were of comparable length and weight, particularly as the correlation coefficient for the relation of conductance to cube of body length in the healthy infants was only 0.046 and for specific conductance 0.474 . While Cases 6, 7, and 8 all had values for conductance related to body length cubed that were less than 2 SD below the mean value of $(0.259 \pm 0.063) \times 10^{-6}$ for the smaller healthy infants, the mean value for this relation for the 3 infants was $(0.155 \pm 0.009) \times 10^{-6}$, which was significantly different from the mean for the group of smaller healthy infants ($p < 0.001$). Case 9 had a value for conductance related to body length cubed more than 2 SD below the mean value for this ratio for the 9 larger healthy infants $(0.172 \pm 0.031) \times 10^{-6}$. Case 9 was the only one in this group to have an abnormal value for conductance related to TGV (specific conductance). The other 3 infants had values for specific conductance that were less than 2 SD below the mean value of 0.341 ± 0.082 for this ratio for the group of smaller healthy infants. The mean value of specific conductance for the 3 infants of 0.204 ± 0.034 was significantly different from that of the group of smaller healthy infants ($p < 0.001$). Cases 8 and 9 had values for specific compliance that were abnormal, and the other 2 infants had values that were within normal limits.

Only 1 of the 9 infants of Group 3 who had clinical evidence of chest infection before the first study was carried out, had a value for TGV that was within normal limits (Case 10) when TGV was related to body weight. However, if TGV was related to body length cubed, 5 of the infants had values that were within normal limits (Cases 10, 14, 15, 17, and 18). Because of the malabsorption usually associated with cystic fibrosis, body length may be a better measurement with which to relate TGV.

As a group, these 9 infants had a mean value for conductance related to body length cubed of $(0.099 \pm 0.031) \times 10^{-6}$, which was significantly less than the mean value for the group of healthy infants ($p < 0.001$). This group of 9 infants had a

similar scatter of length and weight as the group of healthy infants. Taking the 9 infants separately, each one had a value for conductance related to body length cubed that was more than 2 SD below the mean for the group of healthy infants of appropriate size. Similarly, the mean value for specific conductance for this group of 9 infants of 0.104 ± 0.036 was significantly different from that for the group of healthy infants ($p < 0.001$). Only 2 of the infants (Cases 10 and 15) had a value for specific conductance that was less than 2 SD below the mean value for healthy infants.

Only 2 of the 9 infants had a value for specific compliance that was within normal limits (Cases 10 and 13), if the lower limit of normal was taken as 2 SD below the mean value for the group of healthy infants.

Thus, before treatment for chest involvement was started, the predominant abnormality in respiratory function in the infants presenting in the neonatal period with meconium ileus was increased TGV. In the asymptomatic older infants, it was an increase in airways resistance. In the infants with bronchitis when they were first studied, there was a constant increase in airways resistance, and a variable increase in TGV.

The studies performed after the institution of treatment showed that at the last study most of the abnormalities had been corrected. No infant had an abnormal value for TGV. Only 1 infant (Case 4) had abnormal values for both specific conductance and conductance related to body length cubed, and the treatment he had received had been unreliable. A further infant (Case 16) had a value for conductance related to body length cubed that was abnormal, but the value for specific conductance was within normal limits. Excluding Case 4, the 15 infants who had been treated for longer than 2 months had a mean value for conductance related to body length cubed of $(0.150 \pm 0.033) \times 10^{-6}$ l./sec. per cm. H_2O /per cm. 3 , which was not significantly different from the mean for the larger healthy infants ($p > 0.01$). The mean value for specific conductance of 0.218 ± 0.063 l./sec. per cm. H_2O per l. was also not significantly different from that for the larger healthy infants $(0.236 \pm 0.047$ l./sec. per cm. H_2O) ($p > 0.01$). 5 of the patients (Cases 3, 4, 12, 15, and 18) had values for specific compliance that were abnormal.

The rapidity with which TGV, conductance, and specific compliance returned to normal with treatment was variable. One patient (Case 11), who was the sickest patient in the whole group when first studied, took a number of months

before his measurements of respiratory function were within normal limits. Cases 13, 14, and 15 had measurements within normal limits, after 2 to 3 weeks of intensive treatment in hospital.

The effects of bronchitis on the measurements of respiratory function are seen in Cases 5 and 15. Case 5 developed 2 attacks during the period of the study, one at 9 weeks of age soon after discharge from hospital, and another at about 34 weeks, and Case 15 had bronchitis at about 32 weeks. With bronchitis there was an increase in TGV and a fall in conductance and specific compliance.

Discussion

These results demonstrate a number of important facts concerning chest disease in cystic fibrosis. As pulmonary involvement is responsible for most of the morbidity and mortality in cystic fibrosis, additional information relating to this complication may have considerable implications in the management of these patients.

The studies of the 5 patients who presented with meconium ileus and of the 4 asymptomatic older infants suggest that there may be abnormalities in respiratory function before clinical evidence of chest infection is apparent. The clinical difference between these two groups was not great, and they could have been considered together, despite the fact that all the infants in the meconium ileus group were less than 6 weeks old at the time of the initial study and only 1 of the 4 asymptomatic infants was less than 6 weeks old. However, the two groups showed some differences in the abnormalities of respiratory function. 3 of the 5 infants with meconium ileus had increased TGV, and there was evidence that the 4 asymptomatic infants had increased pulmonary resistance. There has been some doubt whether, in the absence of infection, there are pathological abnormalities in the lungs of infants dying from complications of meconium ileus. Claireaux (1956) considered that there were none, but Esterly and Oppenheimer (1968) noted hypertrophy and hyperplasia of the submucous glands in 6 of the 21 infants dying in the neonatal period, 2 of whom had no evidence of inflammatory changes. Mucous gland hypertrophy in the absence of infection was not seen by Reid and De Haller (1964). Zeulzer and Newton (1949) considered that the plugging of bronchi and bronchioles with secretion was the earliest pathological change if the patients died early in the course of the disease, or if the infection had been of relatively short duration.

While it is impossible to exclude subclinical infection as the cause of the functional abnormalities

in these two groups, the abnormalities could well have arisen from hypertrophy and hyperplasia of the bronchial submucous glands and the presence of excess secretion in the small air passages. It was harder to explain the dissociation between the increased TGV and the increased pulmonary resistance. None of the 9 infants had increases in both measurements. One possible explanation is that in the small neonate hypertrophy and hyperplasia of the submucous glands and increased secretion may have almost completely obstructed some air passages, so that while air trapping occurred as a result, the obstructed air passages were taking practically no part in ventilating the lungs and so were not contributing to the over-all airways resistance. With growth, there may have been opening of these airways with reduction of air trapping, but with the resulting incomplete obstruction contributing to increased pulmonary resistance. In addition, as the weeks passed, there may have been more widespread changes in the mucus glands.

If this theory is correct, some infants might have been expected to have shown an intermediate stage, with abnormalities in both TGV and pulmonary resistance. The number of infants (9) in the two groups without clinical evidence of lung involvement was small, and the absence of one with intermediate changes may have been by chance. While cystic fibrosis is a relatively common disease, affected children comprising 1 in 2500 live births in the community from which these patients were drawn (Danks, Allan, and Anderson, 1965), meconium ileus is seen in only about 10% of patients with the disease in this community, and asymptomatic patients are also uncommon. These 9 patients were the only ones presenting in this way to a unit with special interest in cystic fibrosis during an 18-month period. During the same period, the birth of about 45 children with cystic fibrosis would have been expected within the community from which these patients came. Further investigation of a larger group of patients over a longer period may clarify the association between increased TGV and increased pulmonary resistance in small infants with cystic fibrosis.

The abnormalities found in the group of infants who had clinical evidence of chest involvement at the time of the first study were those expected in a condition in which bronchitis and bronchiolitis are essential pathological features (Zeulzer and Newton, 1949). The increased pulmonary resistance, increased TGV, and reduced dynamic compliance probably resulted from bronchial and bronchiolar

narrowing and obstruction. The changes were similar to those seen in infants with acute viral bronchiolitis, but were not as marked (Phelan, Williams, and Freeman, 1968). The reduction in dynamic compliance probably was the result of the increased airways resistance (Otis *et al.*, 1956).

The changes in the group of symptomatic infants were similar to those reported in older children with cystic fibrosis. West *et al.* (1954) reported increased residual volumes, an increase in the ratio of residual volume to total lung capacity, and reduced maximum breathing capacity which was the only test carried out to provide evidence of airways obstruction. Cook *et al.* (1959) applied more sophisticated techniques to a group of 65 patients with cystic fibrosis aged between 6 and 25 years. They found an increase in residual volume and functional residual capacity, and raised pulmonary resistance and a reduced dynamic compliance in from 75 to 90% of their patients. The least constant finding was the increase in functional residual capacity. Mellins *et al.* (1968) also found a raised pulmonary resistance and reduced dynamic compliance in a group of older children with cystic fibrosis. However, patients reported by these three groups of workers had been treated for varying periods of time before the studies were carried out, and full clinical details were not given, making direct comparison difficult.

Matthews, Doershuk, and Spector (1967) mentioned that they found reduced conductance and a variable increase in TGV in infants with cystic fibrosis, some of whom were asymptomatic, but have yet to publish full details.

The studies performed after the institution of treatment showed that the abnormalities in respiratory function were, at least in part, reversible. Only 1 infant (Case 4) in this group had definite evidence of persisting abnormalities in respiratory function at the most recent study. He was not receiving adequate treatment at home. As a group, the other 15 infants who had been treated for periods longer than 2 months had no evidence of persistent increase in airways resistance.

These results provide the first objective evidence that abnormalities in respiratory function in infants with cystic fibrosis can be reversed with treatment. While antibiotics were given orally to most patients in the group for short periods, intermittent inhalation therapy was the only treatment constantly given for chest involvement, and it was probably the important factor in correcting the abnormalities in respiratory function. It was not considered justified to withhold oral antibiotic therapy in the presence

of definite chest infection to measure the effect of inhalation therapy alone. Nor was any attempt made to determine which part of the inhalation therapy was the most important. The aim of the therapy was to control infection by means of antibiotics and to aid the removal of mucus by the addition of water vapour. Mist particles larger than $6-8\mu$ probably do not penetrate the lower respiratory tract, and particles larger than $2-3\mu$ probably do not reach the smaller bronchioles (Mitchell, 1960). The nebulizer used in these infants produced particles of mean size 3.7μ , similar to that of most commercially available jet nebulizers (Mercer *et al.*, 1965). Particles of this size are likely to evaporate and propylene glycol and glycerine were added to stabilize the particles and prevent evaporation (Dautrebande, 1952). However, as that author points out, propylene glycol is hygroscopic and can cause enlargement of the water particles before the small airways are reached. This may not be of major importance, as it has been shown that nebulized isoprenaline in a 50% propylene glycol mixture caused a marked fall in airways resistance after 5 breaths (Lovejoy, Constantine, and Dautrebande, 1960).

Other workers have produced evidence based on clinical, radiological, and respiratory function studies that mist tent therapy is effective in controlling the pulmonary complications of cystic fibrosis. In 36 patients who had been on a satisfactory therapeutic programme for at least 3 years, mean values for vital capacity, functional residual capacity, residual volume, ratio of residual volume to total lung capacity, one second forced vital capacity, and maximum breathing capacity were almost identical to values for normal children (Doershuk *et al.*, 1965). The authors regarded the use of a mist tent at night as one of the most important factors in the treatment of their patients. The patients in their group were older than those included in the present study. In a subsequent paper from the same group of workers, it was shown that abnormalities in vital capacity, functional residual capacity, residual volume, the ratio of residual volume to total lung capacity, and maximum breathing capacity in a group of children with cystic fibrosis could be reversed by the use of mist tent therapy, and that when mist tent therapy was withdrawn there was a deterioration in these parameters, despite the continued use of intermittent aerosol therapy (Matthews *et al.*, 1967). Full clinical details of their patients were not given.

Mist tent therapy is more difficult for both patient and parent than intermittent aerosol therapy. In the group of infants reported here, the intermittent

form of treatment did appear to provide a satisfactory method of controlling pulmonary complications of the disease. However, the tests of pulmonary function applied to the patients may have failed to detect important changes in the lungs, though they were probably more reliable tests than those used by Doershuk and Matthews. Further work is necessary to substantiate the value of intermittent aerosol therapy, but the evidence presented here suggests that it at least is a satisfactory alternative to mist tent therapy in infants.

Summary

Respiratory function studies were carried out in 18 infants with cystic fibrosis who were less than 9 months of age when first seen. In 9 infants who had no clinical evidence of chest infection when first seen, thoracic gas volume was increased in 3 and conductance reduced in 4. The other 9 infants had symptoms of chest infection when first studied, and they too showed an increased thoracic gas volume and reduced conductance. Treatment with intermittent inhalations administered with a nebulizer and face-mask resulted in return to normal of these abnormalities in respiratory function in all infants.

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