Archives of Disease in Childhood, 1971, **46**, 144.

Pulmonary Function and Response to Exercise in Cystic Fibrosis

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Godfrey, S., and Mearns, M. (1971). *Archives of Disease in Childhood*, **46**, 144. **Pulmonary function and the response to exercise in cystic fibrosis.** Results of physiological studies at rest and during exercise in 41 patients with cystic fibrosis of the lungs are presented. The patients were evenly distributed by age between 5 and 21 years, and were grouped into 3 clinical grades corresponding to mild, moderate, and fairly severe disease.

There was a linear relation between tests of lung mechanics such as the FEV_1 and the MVV and the clinical grading. These tests also correlated well with one another. Certain tests, notably those reflecting parenchymal damage such as the TL_{CO} showed a non-linear relation to clinical severity, deteriorating more rapidly from grade 2 to 3 than from grade 1 to 2.

A very specific pattern emerged of enlargement of physiological deadspace even in the mildest cases. As the disease progressed, venous admixture occurred at rest, which was initially returned to normal by exercise. In the severest cases, there was never a complete return to normal. These changes may be explicable in terms of pathology.

Exercise was limited by pulmonary mechanics. Total ventilation was increased to accommodate the increased deadspace so that arterial Pco_2 remained normal. Cardiac output was normal.

Adequate evaluation of the pulmonary physiological abnormality could be obtained by measuring the FEV_1 (or MVV), TL_{CO}, and maximum work load possible, but very useful extra information is obtained by measuring arterial saturation (or venous admixture) and dead space.

Cystic fibrosis is now recognized as the commonest cause of chronic pulmonary disease in childhood, but with improvements in treatment it can be expected that 50% or more of patients will reach the age of 20 years (Warwick and Pogue, 1969). It is accepted that the earlier treatment is started the better the results, and it is therefore of great importance to be able to diagnose and evaluate the condition and to assess the value of various therapeutic regimens. Studies have shown a good correlation between clinical severity and a variety of tests of lung mechanics (Doershuk *et al.*, 1965; Beier *et al.*, 1966; Mearns, 1968; Featherby *et al.*, 1969). These authors are generally agreed that there is airways obstruction which increases as the patient's condition deteriorates. There is less agreement about the ability to transfer CO from lungs to blood (the 'diffusing capacity' TL_{CO}).

In order to study pulmonary efficiency in terms of the balance of ventilation and perfusion within the lung, conventional methods require catheterization of pulmonary and systemic arteries. Though such studies have been performed in patients with cystic fibrosis (Goldring *et al.*, 1964), they are particularly disturbing to children and it may be argued that such procedures are not clinically justifiable. Moreover in cystic fibrosis, when lung damage occurs, a prominent symptom is breathlessness on exertion. Since it is particularly difficult to exercise the patients to a reasonable level during catheterization, this feature of the disease has not been fully studied physiologically.

Recently, techniques have been developed in this department for the investigation of the pulmo-

Received 25 September 1970.

nary and cardiac response to exercise in children by the indirect (CO_2) Fick method (Godfrey and Davies, 1970). These techniques do not involve cardiac or systemic catheterization and are quite acceptable to the children (Godfrey, 1970a). To obtain further information on the physiological disturbances in cystic fibrosis and to see which investigations were the most useful in assessment and management, we have studied a group of patients using these techniques.

Subjects

Studies were made on 41 patients aged 6 to 21·8 years. There were 24 male and 17 female patients and their distribution by age and height centile is given in Fig. 1. The diagnosis of cystic fibrosis was confirmed

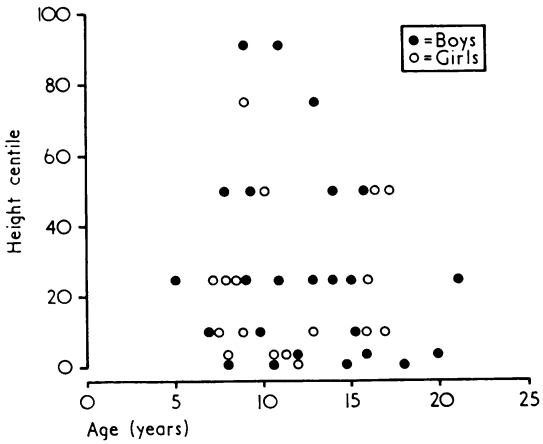

FIG. 1.—*Distribution of subjects by age and height centiles.*

in all these patients by finding the sweat sodium to be above 70 mEq/l. The patients were divided into three grades based on clinical and radiological findings as previously described (Jackson and Young, 1960). In brief these grades are as follows.

Grade I: Good general health. May have occasional attack of bronchitis or short periods with cough and sputum. Chest *x*-ray normal or may be a minimal degree of thickened bronchial wall pattern (17 patients).

Grade II: Good general health, with respiratory symptoms as above, but chest *x*-ray showing localized change (12 patients).

Grade III: Persistent pulmonary infection with purulent sputum with or without abnormal findings in the lungs on clinical examination, chest *x*-ray showing generalized changes and with or without impaired general health (12 patients).

Of the 41 children, 31 have been personally followed up at one clinic by M.M. The other 10 children regularly attended another clinic. The clinical assessment of these 10 children was based on the same criteria as the others.

Methods

The patients spent the whole day in the department as outpatients. Adequate rest periods were allowed between studies.

Simple spirometry was performed with a wet spirometer (P.K. Morgan Limited) and the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) were calculated. Lung volumes and airways resistance (Raw) were measured in a whole body plethysmograph by the methods of DuBois, Botelho, and Comroe (1956b) and DuBois *et al.* (1956a). The ratio of the residual volume of the total lung capacity (RV/TLC) as determined in the plethysmograph was calculated. The transfer factor for carbon monoxide (TL_{CO}) was measured by the steady state method of Bates, Boucot, and Dormer (1955).

Exercise studies were performed in exactly the same fashion as described previously for normal children (Godfrey and Davies, 1970). In brief, the patient performed simple progressive exercise seated on a cycle ergometer (Lode), with the work load being increased every minute by an increment depending on height. Pulse and ventilation were recorded. After a rest, a steady state exercise test was performed in which the child was studied at rest and at one-third and two-thirds of the maximum work load achieved in the progressive test. At each level of the steady state test expired gas was collected in a Tissot spirometer and analysed for CO_2 and O_2. Arterialized ear lobe blood was sampled and analysed by the method of Godfrey *et al.* (1971). The mixed venous P_{CO_2} was measured by a rebreathing method using prepared CO_2 in O_2 mixtures (Jones *et al.*, 1967). All data including the electrocardiograph were recorded continuously on a chart recorder (Mingograf 81). The crude data from the studies were fed into a digital computer using a programme written to calculate exercise test results allowing for necessary corrections (Godfrey, 1970b).

After the exercise study, the maximum voluntary ventilation (MVV) was determined by the 15-second sprint method (Clark *et al.*, 1969). The best of several attempts at various frequencies was taken.

Calculations. From the progressive exercise test, the highest level of work completed (W_{max}) and the pulse and ventilation at this level (MExV) were noted. In the steady state test the results at the highest work load were used. Ventilation (Vent), gas exchange, and cardiac output were calculated. The physiological dead space (VD) corrected for instrument dead space (53 ml) was calculated by the equation of Bohr (1890) and the venous admixture (VA) breathing air by the shunt equation (Riley and Cournand, 1949). No correction for theoretical diffusion gradients was applied. No results were available for venous admixture breathing high O_2 because the ear blood P_{O_2} is unreliable at high

levels (personal observations). The VA was also calculated for the steady state rest period.

All values except VA were calculated as percentage of the expected normal values based on height. Normal values for lung volumes and resistance data and for exercise results were those obtained in this laboratory (Godfrey, Kamburoff, and Nairn, 1970b; Godfrey *et al.*, 1970a); the results of Weng and Levison (1969) were used for TL_{CO}.

The abbreviations used in the text appear in Table I.

TABLE I

List of Abbreviations Used

TL_{CO}	Transfer factor ('diffusing capacity') for carbon monoxide
FEV_1	Forced expired volume in 1 second
FVC	Forced vital capacity
Raw	Airway resistance
RV	Residual volume
TLC	Total lung capacity
MVV	Maximum voluntary ventilation
W_{max}	Highest workload completed in progressive exercise test
MExV	Highest minute ventilation achieved in progressive exercise test
Vent	Minute ventilation in steady state exercise
V_D	Physiological dead space
VA	Venous admixture ('right-to-left shunt')

Results

The relation between a number of tests and the clinical grade are shown in Table II. Regression equations are given in Table III. There was good agreement between tests of lung mechanics and the clinical grading, airways obstruction increasing with the progression of the disease. Thus the FEV_1, the FVC, and the MVV all decreased significantly from grade 1 to 2 and from grade 2 to 3. The high values for MVV in grade 1 are due to the number of small children in this grade because the SE of the estimate of the expected value is large and the regression on size less exact

TABLE II

Values of Various Measurements in Relation to Clinical Grade: Mean, Standard Error of Mean (SEM) and Number of Observations (n)

		Clinical Grade			Significance of Differences	
		1	2	3	Grades 1–2	Grades 2–3
Age (yr)	Mean	9·51	12·61	15·40		
	SEM	0·72	0·78	1·01	++	+
	n	17	12	12		
FEV_1 (% expected)	Mean	85	67	49		
	SEM	3	6	4	++	+
	n	17	12	12		
FVC (% expected)	Mean	96	82	70		
	SEM	4	4	4	+	+
	n	17	12	12		
RV/TLC (%)	Mean	37	38	54		
	SEM	3	3	3	NS	+++
	n	11	11	12		
TL_{CO} (% expected)	Mean	99	89	70		
	SEM	6	5	6	NS	+
	n	13	11	12		
Raw (% expected)	Mean	251	244	355		
	SEM	19	25	30	NS	++
	n	11	11	12		
MVV (% expected)	Mean	116	89	67		
	SEM	6	4	4	+++	+++
	n	17	12	12		
W_{max} (% expected)	Mean	97	82	69		
	SEM	6	5	4	+	+
	n	15	12	12		
Ventilation (% expected)	Mean	136	141	150		
	SEM	4	7	5	NS	NS
	n	16	12	12		
V_D (% expected)	Mean	226	266	329		
	SEM	16	17	20	NS	+
	n	17	12	12		
VA (rest) (%)	Mean	3·8	5·8	10·3		
	SEM	0·5	0·9	1·1	+	+++
	n	14	12	12		
VA (exercise) (%)	Mean	2·3	2·7	5·6		
	SEM	0·3	0·2	0·7	NS	+++
	n	13	12	12		

Note: Abbreviations are those used in the text but ventilation refers to steady state ventilation. Significance of differences between grades 1 and 2 and grades 2 and 3 are shown (+ = $0{\cdot}05>p>0{\cdot}01$; ++ = $0{\cdot}01>p>0{\cdot}0025$; +++ = $0{\cdot}0025>p$).

TABLE III

Regression Equations for Results

Y	B	X	M	SEY	r	n	Sig.
MVV	0·86	FEV_1	34	21	0·67	39	+ + +
TL_{CO}	0·57	FEV_1	48	20	0·54	34	+ +
W_{max}	0·55	MVV	33	20	0·71	37	+ + +
VD	−1·98	FEV_1	405	64	0·56	39	+ + +
VD	2·86	RV/TLC	152	68	0·48	32	+ + +
VD	13·82	VA	177	135	0·39	36	+ +
Vent.	0·08	VD	120	71	0·30	38	+
MExV	0·36	MVV	25·5	12·3	0·66	35	+ + +

Note: Y = dependent variable, x = independent variable, B = regression coefficient, SEY = standard error of estimate of y, r = correlation coefficient, n = degrees of freedom. Abbreviations are those used in the text. Vent. is ventilation in submaximal steady state exercise and MExV is maximum ventilation achieved at breaking point of simple progressive exercise. Code for significance of regressions is same as in Table II.

in such subjects. There was also good correlation between the various tests of lung mechanics, the best being between MVV and FEV_1 (Fig. 2 and Table III). There was no significant difference between grade 1 and grade 2 for airways resistance but there was a significant deterioration from grade 2 to grade 3.

The transfer factor for CO was normal in grade 1 and was reduced in grade 2 and further reduced in grade 3. The reduction between grades was only significant between grades 2 and 3. There was a significant correlation between TL_{CO} and FEV_1 (Fig. 3 and Table III).

The ability to exercise was related to clinical grade, W_{max} falling significantly from grade 1 to grade 2 and grade 2 to grade 3 (Table II). In the mildest grade W_{max} was within the normal range (mean ± 18 watts). When comparing W_{max} with the tests of lung mechanics, the best correlation by far was that with MVV (Fig. 4 and Table III). There was also a close correlation between maximum exercise ventilation attained at the limit of the simple progressive exercise (MExV) and MVV (Table III), but it should be noted that exercise ventilation exceeded the MVV at all levels below an MVV of 50 l./min (Fig. 5).

Physiological dead space (VD) was considerably enlarged in all but one child in which it was 122%. In all but 7 children it was over twice the expected value. Even in the fittest children (grade 1) the mean value for VD was 226%. Though it increased progressively with the clinical grading (Table II) the difference between grade 1 and grade 2 was not

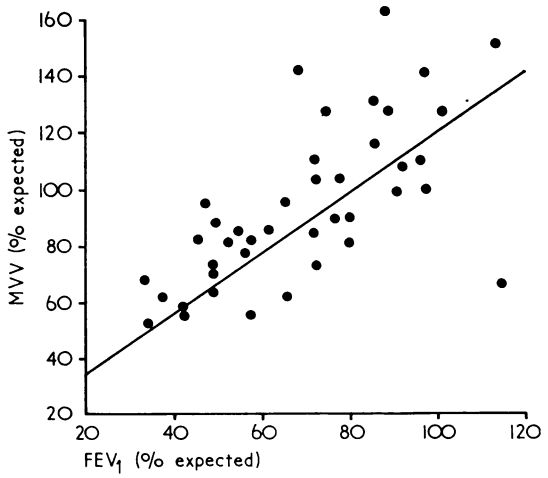

FIG. 2.—*The relation between maximum voluntary ventilation (MVV) and the forced expired volume in 1 second (FEV_1) both expressed as percentage of expected values.*

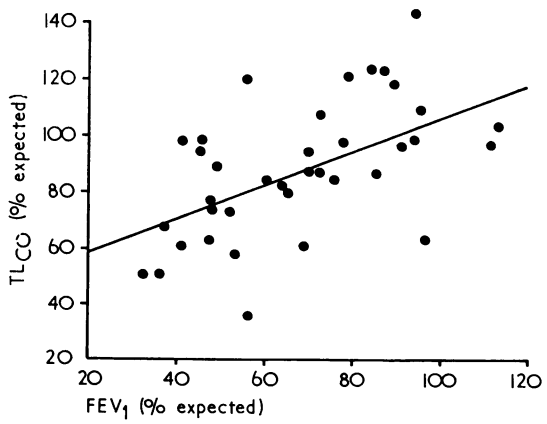

FIG. 3.—*The relation between the CO transfer factor (TL_{CO}) and the FEV_1 both expressed as percentage of expected value.*

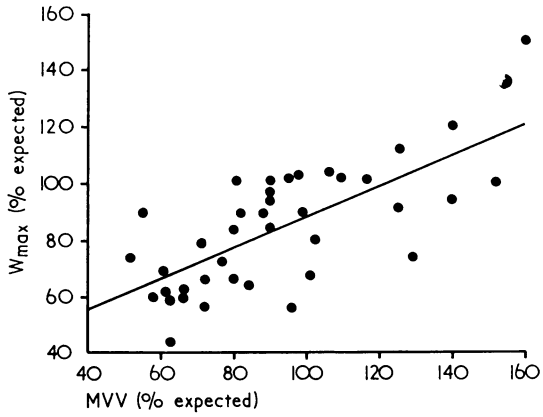

FIG. 4.—*The relation between the highest work level attained on simple progressive exercise (W_{max}) and the MVV both expressed as percentage of expected values.*

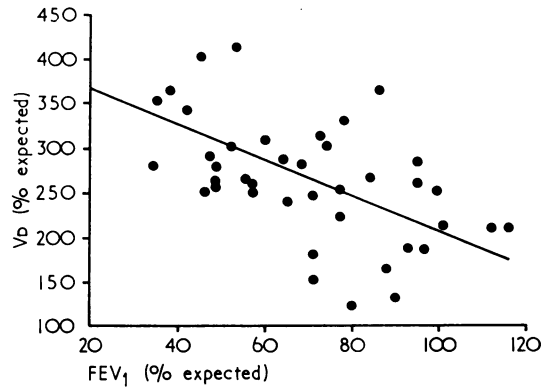

FIG. 6.—*The relation between dead space (VD) and the FEV_1 both expressed as percentage of expected values.*

significant but that between grades 2 and 3 was significant. The enlargement of VD correlated well with the mechanical evidence of airways obstruction as indicated by the FEV_1 or RV/TLC (Fig. 6 and 7 and Table III).

Venous admixture (VA) at rest increased significantly from grade 1 to 2 and from grade 2 to 3, but the greatest difference occurred from grade 2 to 3 (Table II). It was rather poorly related to mechanical tests but was significantly correlated with VD (Fig. 8 and Table III). On exercise, the VA fell in all groups but it was still above normal (<3%) for children in grade 3 (Table II). The significant difference in VA between grades 1 and 2 was lost on exercise, but persisted between grades 2 and 3.

Ventilation and pulse rate on exercise were poor guides to clinical state and did not correlate with the maximum working capacity (W_{max}). However, steady state ventilation was above normal in all grades (Table II). It was actually raised in all but one patient, a 7-year-old boy who had a VD of 95 ml, the expected value being 78 ml ± 22 (SE). In the group as a whole there was a significant correlation for the rise of steady state ventilation with the rise of VD (Table III).

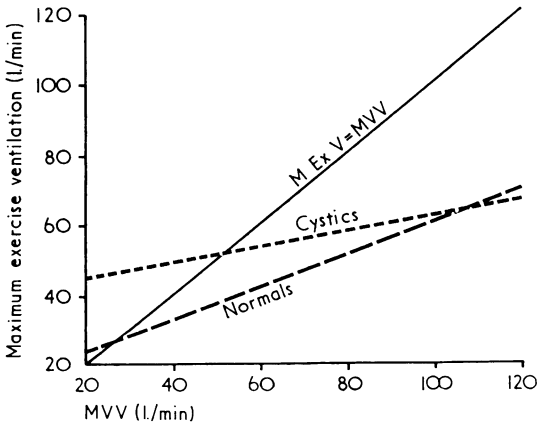

FIG. 5.—*The relation between the highest ventilation attained on simple progressive exercise (MExV) and the MVV. The line labelled 'cystics' refers to the present study and shows that exercise ventilation exceeds the MVV up to 50 l./min. The line labelled 'normals' refers to the normal values found in this laboratory. The line of identity where exercise ventilation = MVV is also shown.*

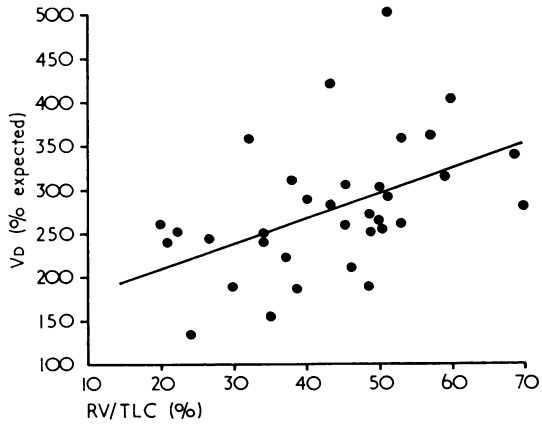

FIG. 7.—*The relation between V_D as percentage expected and the RV/TLC ratio.*

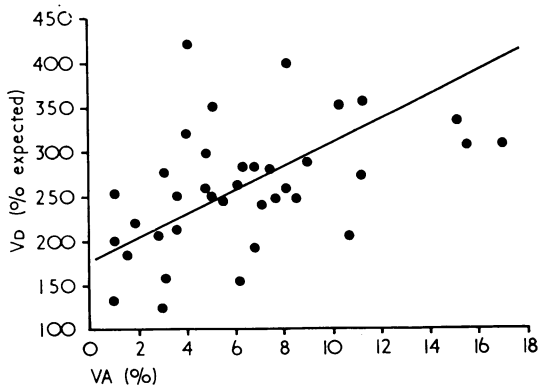

FIG. 8.—*The relation between VD as percentage expected and the venous admixture (or right-to-left shunt).*

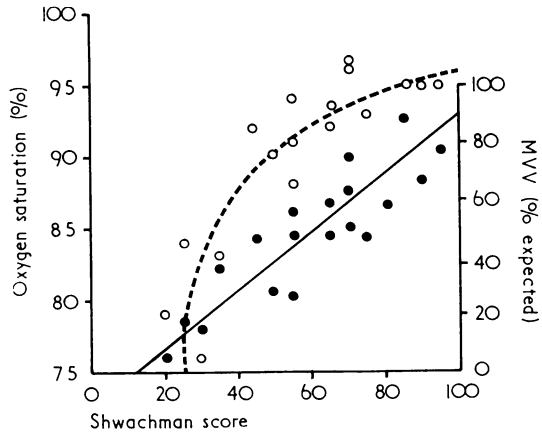

FIG. 9.—*The relation between MVV (solid symbols and right ordinate) and Shwachman score and between arterial saturation (open symbols and left ordinate) and Shwachman score, from the data of Featherby* et al. *(1969). The lines have been drawn as best fits to the data.*

Arterial P_{CO_2} was normal in all but the two eldest patients in whom it was 54 and 49 mmHg respectively.

Cardiac output was within normal limits in all studies.

Discussion

Many studies have now shown the correlation between clinical state and tests of airways obstruction in cystic fibrosis, and this subject has recently been fully discussed (*International Cystic Fibrosis Conference*, 1969). We have confirmed these findings though our method of clinical grading did not employ the Shwachman rating because this rating uses many subjective criteria developed in the Boston Clinic. We felt it would be unreliable arbitrarily to use such a score or to modify it and preferred to use the grading developed in London over a long period. In general terms, the grading proposed by Jackson and Young (1960) which has been used here can be compared with the description of Shwachman and Kulczycki (1958); our grade 1 was approximately equivalent to a Shwachman score of 71 and over, grade 2 to a score of 56 to 70, and grade 3 to a score of 55 or less.

A number of parameters showed little difference between the mild and moderate patients but were significantly worse in grade 3 than grade 2. This applied to the enlargement of RV, the fall in TL_{CO}, the enlargement of VD and the increase of VA on exercise (Table II). Though this might imply that the grading was not even from 1 to 3, many other tests such as the FEV_1 and the MVV showed a smooth deterioration from grade to grade. This finding could imply that recurrent infections result in progressive damage to airways with increasing obstruction, and that parenchymal damage, as shown by abnormalities in the TL_{CO}, VD, and VA, does not occur until a certain level of airways obstruction has been reached.

This discontinuity of some tests and not others can also be seen in the data of Beier *et al.* (1966) where there was an excellent linear correlation for FEV_1 with the Shwachman score but the arterial oxygen saturation (which reflects VA almost linearly over this range) only became abnormal at the lower levels of the clinical score (Fig. 9). The junction between our grades 2 and 3 corresponds approximately to a Shwachman score of 55, and it is just at this level that significant desaturation was noted by Beier *et al.* (1966) (see Fig. 9). We also found that significant VA appeared on passing from grade 2 to grade 3 (Table II). Many studies have shown linear relation between arterial P_{O_2} and clinical score (Matthews *et al.*, 1969; Featherby *et al.*, 1969). It should be realized however that linear correlations between arterial P_{O_2} (as distinct from saturation) and clinical score may well be a physiological artefact because of the non-linear shape of the O_2 dissociation curve. A relatively small increase of venous admixture in a well-saturated patient will cause a larger fall of P_{O_2} than a similar increase (and hence clinical deterioration) in a poorly saturated patient.

Our results have shown up a very consistent pattern of physiological disturbance in cystic fibrosis besides the well-known airways obstruction. In all our patients except one there was a marked increase in VD, even if the clinical condition was considered to be mild. We have not seen this

pattern in other diseases. This increase in VD would necessitate an increase in total minute ventilation in order to keep alveolar ventilation constant; all but 2 patients adopted this pattern, as shown by the normal levels of arterial P_{CO_2}. Our mean arterial P_{CO_2} was 38·6 mmHg, very close to the 39 mmHg found by Featherby *et al.* (1969). They also noted an increase in VD and minute ventilation of a similar order to that found here in their resting studies of 34 children.

The necessity for hyperventilation may be partly responsible for exercise limitation because of the low ventilatory capacity in the more affected subjects. However, the MVV alone is a poor guide to exercise performance, especially in the lower regions as can be seen from the scatter of points in Fig. 4. This is probably because the patients were able to exceed their MVV on exercise (Fig. 5). Mellins *et al.* (1968) showed that patients with cystic fibrosis collapsed their airways and actually reduced airflow during forced expirations, once the driving pressure exceeded certain limits. This could well account for the difference between the MVV test in which high pressures are generated, and the maximum exercise ventilation in which the driving pressure may not have exceeded that needed for maximum flow. We have not noted an increase in peak expiratory flow rate during exercise in cystic fibrosis such as occurs in asthma (Godfrey, 1970c) so that this mechanism is unlikely to be the cause of the greater ventilatory capacity. It is noteworthy that a defect of pulmonary vascularization which could result in a high overall ventilation/perfusion ratio has been noted in pathological studies (Davies, 1969).

In chronic obstructive lung disease in adults areas of lung with high or low ventilation/perfusion ratios are usually present together (Jones, 1966), but in the present study we did not find the degree of VA seen in such adults, even in our most severe patients. Decrease of VA but increase of P_{CO_2} on exercise is seen in the bronchial type of adult chronic airways obstruction, but desaturation occurs in the emphysematous type (Jones, 1966). Thus our patients with cystic fibrosis behave more like the bronchial type but differ from them in the degree of VA and in having a normal arterial P_{CO_2} which does not increase on exercise.

The ability to transfer CO from the alveoli to blood depends on many factors besides alveolar membrane diffusion and is particularly liable to be abnormal in a situation where ventilation/perfusion imbalance occurs (Read, Read, and Pain, 1965). These authors noted that a wide range of TL_{CO} values were obtained by the steady state method in adults with chronic airways obstruction if their arterial saturation was low, but more uniform results were obtained when saturation was high. This could well account for the various conflicting reports about TL_{CO} in cystic fibrosis (Beier *et al.*, 1966; Featherby *et al.*, 1969). Our own study shows that despite these theoretical objections and previous findings, TL_{CO} falls progressively with clinical deterioration, but like VD and VA (which it reflects), the greatest change occurs from grade 2 to grade 3.

We have not been able to make detailed comparisons between different treatment regimens in the present study, but 10 children were treated with a different regimen from the others, and yet we could detect no clear-cut physiological differences. Since they were also in the youngest age group, only time can tell if differences will appear. There was also a clear age difference between children in whom V_D was under 300% expected (9·9 years $\pm$ 1·0 SEM, n = 16) and those in whom it was over 300% (13·6 years $\pm$ 1·1 SEM, n = 25).

In conclusion we feel that there is a basic physiological defect in cystic fibrosis which appears as an enlargement of dead space. It is present even in the mildest affected patients. As the disease progresses, airways obstruction becomes more severe, and eventually venous admixture begins to appear. This initially returns to normal during exercise, but in later stages it is merely reduced. Hyperventilation, whether at rest or on exercise, is a compensation for the increased dead space. The ability to exercise is closely related to the ventilatory capacity and work is probably limited by pulmonary mechanics rather than circulatory factors or hypoxia. There appears to be a point in the clinical progress of the disease where a number of physiological measurements become abnormal or increase for the first time. Simple tests such as the FEV_1 are adequate to follow the progression of the disease but the additional measurement of W_{max} during simple progressive exercise gives a much better idea of reserve. The pattern of physiological disturbance is so characteristic that it could well serve as an aid to diagnosis in doubtful cases, and can be revealed by steady state exercise in the manner described without the use of cardiac or arterial catheterization. Some caution is needed, however, because we have recently studied an 8-year-old boy with chronic pulmonary infection due to hypo-γ-globulinaemia, who showed the pattern of enlarged dead space and increased venous admixture. It may be that the pattern can be produced by early widespread pulmonary infection.

Based on this study we believe that adequate physiological assessment can be achieved with measurement of the FEV_1, TL_{CO}, and W_{max}; the additional measurement of arterial saturation and VD improves the assessment considerably.

We thank Dr. D. Lawson, Dr. J. C. Batten, and Dr. A. D. M. Jackson for allowing us to study some of their patients; Professor Lynne Reid for her advice; and Dr. F. Prime and his staff for carrying out the measurements of TL_{CO} and those using the body plethysmograph. Dr. M. Mearns is in receipt of a grant from the Cystic Fibrosis Research Trust.

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