

Revisiting “Respiratory function in emphysema in relation to prognosis”

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DV Bates. Modern classics revisited: Respiratory function in emphysema in relation to prognosis. *Can Respir J* 2000;7(3):271-279.

BACKGROUND: The 1956 paper by DV Bates, JMS Knott and RV Christie, “Respiratory function in emphysema in relation to prognosis” *Quart J Med* 1956;97:137-157 is largely reprinted with a commentary by the first author, Dr David Bates. Although the pathology of emphysema was well recognized at the time, the clinical diagnosis and assessment of its severity were known to be imprecise; physiological measurements assessing and following the clinical course had not been established. The study aimed to follow systematically a group of patients, selected by clinical criteria using standardized clinical and physiological techniques, over four years and correlate physiological and clinical changes in relation to prognosis and eventually to postmortem findings. Fifty-nine patients were recruited to an emphysema clinic at St Bartholomew’s Hospital, London, England. Inclusion criteria were dyspnea without other causes and no cor pulmonale present. Patients’ symptoms were assessed by a standardized questionnaire, and measurements were taken of lung volumes, maximal ventilatory volume, carbon monox-

ide diffusing capacity at rest, exercise and oxygen saturation by oximetry. During the four years of the study, 17 patients died (actuarial expected – four) and 13 presented with signs of pulmonary heart failure. All postmortem examinations (n=9) showed advanced emphysema. A seasonal variation in dyspnea was established (the period included the infamous 1952 London smog). Four patients improved, and the remainder were unchanged or deteriorated. Close relationships were shown between dyspnea and function results, particularly for the diffusing capacity of lungs for carbon monoxide (DLCO). A comparison among a group of patients with chronic bronchitis without dyspnea showed that the DLCO discriminated between them. A loss of the normal increase in DLCO during exercise was shown in emphysema.

IMPORTANCE: The study showed the value of standardized clinical and physiological techniques in following chronic obstructive pulmonary disease patients, and of separating the effects of airflow obstruction from impaired gas exchange function. Impaired gas exchange was shown to be important in influencing prognosis.

Key Words: *Chronic obstructive pulmonary disease; Diffusing capacity; Emphysema prognosis*

Pour le résumé, voir page suivante

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Retour sur l'article « La fonction respiratoire comme facteur pronostique dans l'emphysème »

HISTORIQUE : L'article de 1956 de DV Bates, JMS Knott et RV Christie, « La fonction respiratoire comme facteur pronostique dans l'emphysème » (*Respiratory function in emphysema in relation to prognosis*) *Quart J Med* 1956;97:137-157 est reproduit ici en grande partie, avec un commentaire de l'auteur principal, le Dr David Bates. Bien que la pathologie de l'emphysème ait été bien reconnue à l'époque, son diagnostic et l'évaluation clinique de sa gravité étaient encore imprécis. On n'avait pas établi de mesures physiologiques pour évaluer et suivre le développement clinique de la maladie. Cette étude visait donc à suivre systématiquement un groupe de patients sélectionnés selon des critères cliniques, au moyen de mesures physiologiques et cliniques standardisées pendant une période de quatre ans afin d'établir, le cas échéant, une corrélation entre les changements physiologiques et cliniques et le pronostic, et éventuellement, avec les anomalies découvertes à l'autopsie. Cinquante-neuf patients ont été recrutés dans une clinique de traitement de l'emphysème de l'hôpital St. Bartholomew de Londres, en Angleterre. Les critères d'inclusion étaient la dyspnée, sans autre cause, en l'absence de cœur pulmonaire. Les symptômes des patients ont été évalués au moyen de questionnaires standardisés, et on a enregistré leur volume pulmonaire, leur volume respiratoire maximum, leur capacité de

diffusion du monoxyde de carbone au repos, leur tolérance à l'effort et leur saturation en oxygène par oxymétrie. Au cours des quatre années de l'étude, 17 patients sont décédés (prévisions actuarielles – quatre) et 13 ont présenté des signes d'insuffisance cardiaque pulmonaire. Tous les examens à l'autopsie (n = 9) ont révélé un emphysème avancé. Une fluctuation saisonnière de la dyspnée a pu être établie (la période incluait le célèbre smog qui a touché Londres en 1952). Quatre patients ont vu leur état s'améliorer, chez tous les autres, la situation est restée inchangée ou s'est détériorée. Un rapport étroit a pu être établi entre la dyspnée et les résultats des tests de fonction pulmonaire, particulièrement en ce qui a trait à la capacité de diffusion pulmonaire pour le CO. Une comparaison avec un groupe de patients atteints de bronchite chronique sans dyspnée a révélé que la capacité de diffusion pulmonaire pour le CO permettait de les distinguer. L'absence du phénomène normal d'augmentation de la capacité de diffusion pulmonaire pour le CO pendant l'effort a été démontrée chez les emphysémateux.

PORTÉE : L'étude a donc confirmé l'utilité des techniques cliniques et biologiques standardisées pour exercer un suivi des patients atteints de bronchopneumopathie obstructive chronique et pour faire une distinction entre les effets causés par une obstruction des voies respiratoires et ceux qui sont imputables à des anomalies des échanges gazeux. Les anomalies des échanges gazeux se sont révélées un important facteur pronostic.

Editor's note – *What follows is a commentary by Dr Bates and approximately 75% of the material, including four of the 12 figures, from the Bates et al (1) paper. We have preserved the figure numbering.*

Looking back on this study, one has to marvel at the quantity and quality of data on many topics related to chronic obstructive pulmonary disease (COPD); these include some of the earliest applications of modern methods to this clinical problem, which paved the way for many studies that followed. In addition to the results of studies in a large group of patients, information may also be applied to individual patients.

I believe that this paper may be read again for profit in the following areas: quantitative analysis of symptoms and physical signs; observer error in signs; diagnosis of emphysema; physiological measurements in diagnosis; assessment of disability and prognosis; the value of regular follow-up assessments; and the correlation of clinical and physiological data with postmortem studies.

Norman L Jones
Editor-in Chief
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The 1956 paper by Bates et al (1) reported the results of a five-year follow-up of patients attending an emphysema clinic at St Bartholomew's Hospital in London, England, between 1950 and 1954. The clinic had been started by Dr Ronald Christie, Professor of Medicine, St Bartholomew's Hospital in 1949 with the intention of studying the natural history of what later became known as COPD. These were the days of serious, coal-burning pollution in London, and the infamous smog of December 1952. At least 4000 people died during the episode (a recent estimate is that

the true figure was about 8000 people), and three of the clinic patients died as well (later studies indicated that this figure was probably nearer to 10 patients). The paper documented the worsening of dyspnea that occurred every winter in these cases, with a peak in the winter of 1952.

The study concluded that significant worsening of the disease lead to pulmonary hypertension and right ventricular failure, and that this was associated with a fall in carbon monoxide uptake together with a worsened ventilation distribution and a fall in the 'maximal breathing capacity' (a test of maximal ventilation achievable, which preceded forced expiratory volume in 1 s [FEV₁]). This finding indicated that the progression of lung destruction, or emphysema, was an important factor in the natural history of this condition. This remained a controversial conclusion because other investigators believed at that time that it was the chronic bronchitic element that determined prognosis.

A recent paper (2) used computed tomography (CT) to determine the extent of morphological emphysema during life, and found that both FEV₁ and the diffusing capacity of lungs for carbon monoxide (DLCO) were significantly lower in patients with a greater degree of lung destruction, as indicated by the calculated surface area to volume ratio from the CT scan. In addition, the success of volume reduction surgery in many cases of emphysema supports the view that the extent of lung destruction is an important determinant of disability and prognosis. Our similar conclusion 43 years ago (when all equipment was home-made and primitive) has therefore been strikingly confirmed.

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In the past few years, many articles have appeared on the changes in pulmonary function that are found in chronic emphysema. Most of these have been concerned with the abnormalities of function found in patients with established emphysema compared with normal subjects (3), and few of them have dealt with the sequence of functional change as the disease progresses. Any study of a group of patients with emphysema, over a period of years is faced with a number of problems, none of which can be solved entirely satisfactorily. One of these is the problem of selection of cases. Emphysema cannot be precisely defined clinically, radiological assessment is unsatisfactory, and to define emphysema in terms of function tests might well be considered premature. If, on the other hand, a rigorous clinical definition of emphysema is adopted, the cases selected will inevitably tend to be severe and advanced. The purpose of the present investigation was to select a group of patients, diagnosed according to the criteria set out below, and to follow this group over a period of years both from the clinical and from the functional viewpoint. The results so obtained have been analysed with particular problems in mind, which may be summarized as follows:

1. To confirm or disprove the accuracy of the clinical selection by careful follow-up and post-mortem analysis.
2. To determine the prognosis in emphysema uncomplicated by heart failure.
3. To relate the clinical course of the disease to changes in the function tests.

The answers that have been obtained to some of these questions are suggestive rather than final or definite, but many of the results should be of assistance in planning future studies of this kind on patients with chronic respiratory disorders.

CLINICAL INVESTIGATION

Selection of cases: The criteria adopted in the selection of cases of emphysema to be included in this study were as follows:

1. A history of increasing dyspnoea on exertion, constantly present in both winter and summer.
2. No other apparent cause for dyspnoea. Subjects with a blood-pressure over 140/90 were excluded.
3. A history of chronic bronchitis, though not an essential requirement, was in fact present in all but two cases.
4. No patient was selected in whom there was clinical evidence of cor pulmonale when first seen.

5. Rejection of the subject if he appeared to be an unreliable witness (two cases), or if there were other symptoms not related to the emphysema and thought to suggest the presence of a 'functional overlay' (one case).

Eighty-eight cases of emphysema fully satisfied the criteria for inclusion set out above, but 29 of these patients have not been included in the follow-up study because they attended infrequently. The present study therefore includes 59 patients, all of whom were treated with the usual variety of antispasmodic drugs at the discretion of the physician. Many had courses of instruction in breathing exercises. The initial assessment of physical signs, and the follow-up attendance, with the assessment of dyspnoea and bronchospasm, were done by one physician, except for short periods of absence. The physician was not informed of changes in the results of the function tests. All but one of the patients included in this series lived in London within a 15-mile [24 km] radius of the hospital. Another group of 14 cases of "chronic bronchitis" have been included in the present study for comparison with the main group of cases of emphysema. The criterion for the selection of this group was a definite history of recurrent winter bronchitis, without constant dyspnoea on exertion.

The assessment of physical signs: There has recently been a growing awareness of the errors involved in the assessment of physical signs, and of the wide variation customarily found between different observers. Such considerations have quite properly led to scepticism about the value of such observations, but have not produced many suggestions for any practicable alternative ... It is generally recognized that the careful assessment of dyspnoea, by questioning and observation over a period, is more valuable in the diagnosis of emphysema than the presence of any of the individual physical signs of the condition, many of which are found in normal people of the same age group (4). Two points ... call for comment. The first is that, although the observer noted 'cyanosis' in 26 cases, subsequent measurement of the arterial oxygen saturation in 20 of these patients revealed an arterial saturation below 92%, in only one case. This indicates either that most of the patients had peripheral cyanosis, or that the clinical recognition of cyanosis is inaccurate. The work by Comroe and Botelho (5) on the disparity between observed cyanosis and measured arterial saturation would support either of these conclusions. The second point is the general absence of polycythaemia in these patients – a finding which we suspect to be at variance with clinical experience in other countries. A further point of interest is the relatively small number of patients whose occupation had involved hard physical labour, many of the patients having had sedentary clerical work all their lives.

Criteria of dyspnoea and spasm: The degree of dyspnoea was graded by the physician according to the following scale of assessment:

Grade 0. Patient's performance normal for a man of his age.

Grade 1. *Patient capable of light work.* He can walk up

to one mile on the level, and can climb a dozen stairs without undue distress.

Grade 2. *Patient capable of sedentary work.* He can get to and from his place of work; that is, he can walk up to 500 yards on the level without stopping. He can carry out purely sedentary work, and can assist in light household duties.

Grade 3. *Patient capable of no work.* He can move about the house, but is unable to get to and from his place of work. He can assist only in very light household duties, such as laying the table.

Grade 4. Dyspnoea variable – on some days grade 5, on other days grade 3.

Grade 5. Patient bed-ridden. Unable to move without dyspnoea.

The degree of bronchospasm was graded as follows:

Grade 0. No evidence of spasm; no rhonchi.

Grade 1. Slight spasm ;occasional rhonchus.

Grade 2. Moderate diffuse spasm; rhonchi over most of the chest.

One experiment to estimate 'observer error' by Fletcher (6) suggested that fair agreement might be expected between observers in deciding whether rhonchi were present or not. Twenty patients were examined. Eight independent observers agreed on the presence or absence of rhonchi in 10 of them, seven were in agreement in a further two, and six were in agreement in a further six cases. Considering the probable variability in the presence or absence of the sign in some of the patients, this score represented a fair measure of agreement.

Frequency of follow-up visits: As has been stated already, patients who could not attend regularly have not been included in the survey. With one or two exceptions, all those included were seen at least every two months. The average period of observation was three years, and with the exception of some patients who died, none was observed for less than two years. Details of attendance for function testing are given in a later section.

Fatal cases: Table II [not shown] shows the number of patients included in the series who died. It will be seen that the presence of emphysema was confirmed in all those in whom post-mortem examinations were obtained. Three-quarters of the patients who died have shown evidence of right heart failure. From the tables of life expectation it can be calculated that four deaths would be predicted in this group of subjects in a three-year period, and this figure may be compared to the 13 respiratory deaths, and four deaths from other causes, which occurred.

Relationship of the degree of disability to the season of the year: ... Only those patients are included who were seen and assessed several times during the period concerned. Since new cases were being added to the series throughout the five-year period, comparisons are only possible between

the average grade of dyspnoea in the same patient during successive seasons. This figure confirms the clinical impression of worsening of dyspnoea during the winter months. In addition it shows that a peak of disability was reached during the winter of 1952-3, at the time of the severe fog which occurred in December 1952 (7). Three patients in this group died at the time of this fog, and the complaint of increased disability following it was general...

Conclusions:

1. During the course of this investigation 17 of the 59 patients died. Taking their ages and the period of observation into account, only four should have died, if their expectation of life had been as indicated in the insurance tables.
2. Although none of the 59 patients showed evidence of heart failure when first seen, eight, or 13%, died with pulmonary heart failure within two years, and 13, or 22%, within four years.
3. That the diagnostic criteria were reliable was suggested by the fact that all the nine patients on whom a post-mortem examination was performed showed histological evidence of advanced emphysema.
4. There is a demonstrable seasonal variation in the severity of dyspnoea and, to a less extent, in the incidence of rhonchi.
5. Of the patients who survived, four improved during the period of observation, the condition of seven was unchanged, and the remainder showed evidence of deterioration.

FUNCTION TESTS

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Methods: 1. *Subdivisions of lung volume and mixing efficiency.* The circuit used for these measurements has been described in detail previously (8)...

2. *Maximal ventilatory volume.* The technique followed has been that used by Wright (9), with a low-resistance valve box and two Douglas bags. Details of this circuit and its performance have been recorded elsewhere (10).

3. *Measurement of the diffusing capacity.* Riley and those who have worked with him (11,12), have given much attention to the problem of measuring the diffusing capacity of the lung in patients with respiratory disorder. This measurement is the quantity of a gas, such as oxygen, which can pass per minute from the alveoli into the blood with a pressure gradient of 1 mmHg. In general terms, it is a measure of the ability of the lungs to aerate the blood. For various reasons it is easier to measure the diffusing capacity of carbon monoxide than of oxygen, and since these two gases are believed to behave similarly, the diffusing capacity of the lungs for carbon monoxide has the same functional

significance as that for oxygen. The technique used in making this measurement has been described elsewhere (13)... [The percentage uptake of carbon monoxide was measured, and the diffusing capacity (D_{CO}) calculated as an index of the rate of uptake of the gas per minute per mmHg pressure-gradient between the gas and the blood.] If the 'back pressure' of carbon monoxide in the blood is ignored, as in most cases it can safely be, the diffusing capacity can be calculated by dividing the rate of uptake of carbon monoxide by the mean alveolar tension of carbon monoxide... [Mean alveolar carbon monoxide is calculated from the Bohr equation, using an assumed value for the respiratory dead space.]

4. Arterial oxygen saturation was measured in a number of subjects by the use of an ear oximeter...

Results of function tests: ... The relationship of these tests to the severity of the disease is shown in Figure 3. To avoid biasing the results by frequent repetition of similar findings in one subject, only two series of function tests at the same grade of dyspnoea have been included for any one subject. In this figure are shown also the results in the small group of patients considered to have chronic bronchitis. The 'poor prognosis' group of cases of emphysema comprises those patients who died of emphysema within six months of the last function test. It will be seen that this figure, if read from left to right, represents progressive severity of the disease, as far as that can be assessed clinically. It is apparent that, although the mean results are changing in the expected direction from left to right, there is very considerable overlap between all the groups in most of the tests. Only the test of diffusing capacity (D_{CO}) achieved complete separation between the 'chronic bronchitis' and 'poor prognosis' groups ... This figure suggests that there is general agreement between the severity of the disease as assessed clinically and the tests of respiratory function, the closest agreement being with the diffusing capacity (D_{CO})... Figure 5 shows the effect of exercise on the diffusing capacity of greater degree of discrimination is achieved if the patients are studied on exercise. The normal individual on exercise will usually nearly double the diffusing capacity, but this increase is lost in emphysema.

DISCUSSION OF INDIVIDUAL CASES

Tests of function may be of clinical value either if they are sufficiently discriminating to be useful in diagnosis, or if they are sufficiently accurate and consistent to be useful in prognosis. There can be no doubt of the value of these tests in diagnosis. To assess their value in prognosis it is necessary to determine the consistency of their results in individual patients and, if this is sufficiently accurate, to follow up a number of patients for a sufficient length of time to determine the relationship of changes in function to prognosis. The consistency of these tests as shown in Figure 7 [not shown] is clearly good. The relationship of function to clinical progress

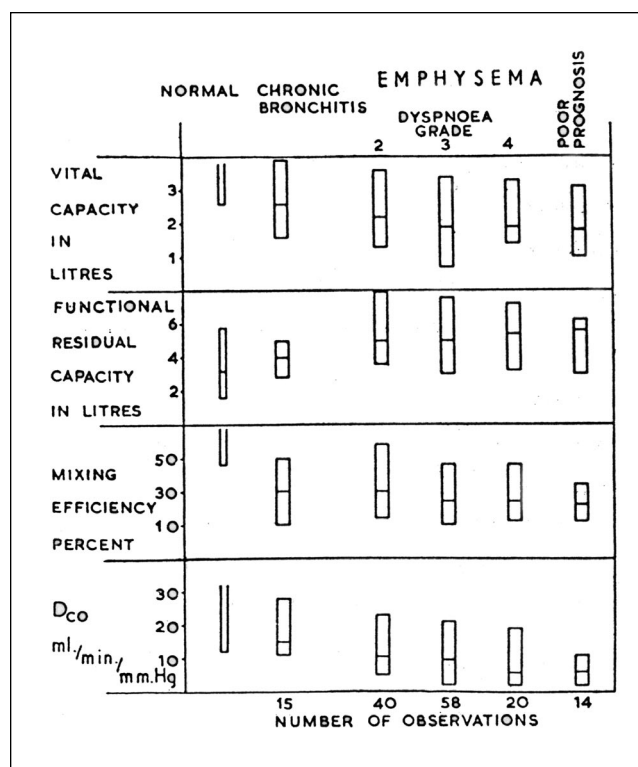


Figure 3) Relationship between function tests and stage or severity of disease. The rectangles indicate range and mean. See text for classification of grades or dyspnoea within the emphysema group. The 'poor prognosis' group consists of patients with emphysema who died within six months of the last function test. There is a general deterioration in the means of the results from left to right - that is, as severity increases. Note that there is no overlap between the chronic bronchitis and 'poor prognosis' groups in the test of diffusing capacity (D_{CO}), whereas there is considerable overlap in all other tests. See text for comment on the high values for D_{CO} and mixing efficiency recorded from some patients

has been determined in all of the 59 patients of the series, and, as the results can only be given in graphic form, it is only possible to discuss illustrative examples.

Cases showing remarkable constancy: From a number of these patients in whom very little change has occurred during the years of observation, one may be selected for illustrative purposes.

Patient JD was 52 years old when first seen in July 1950. He had been employed in a clerical capacity on the Stock Exchange [London] for many years. He gave a history of a chronic winter cough for 10 years, productive of very little sputum, and had noticed progressive dyspnoea for the last two years. When first seen he could manage one flight of stairs, but no more. He had noticed that his chest was more wheezy, and his dyspnoea worse, in foggy weather. Clinical examination revealed a barrel-shaped chest, with a moderate dorsal kyphosis. The area of cardiac dullness was absent. Initially no rhonchi were heard, though bronchospasm was noted to be present on a visit a few months later, and on most of the many occasions on which he was seen during the next five years. His subsequent progress is summarized in Fig-

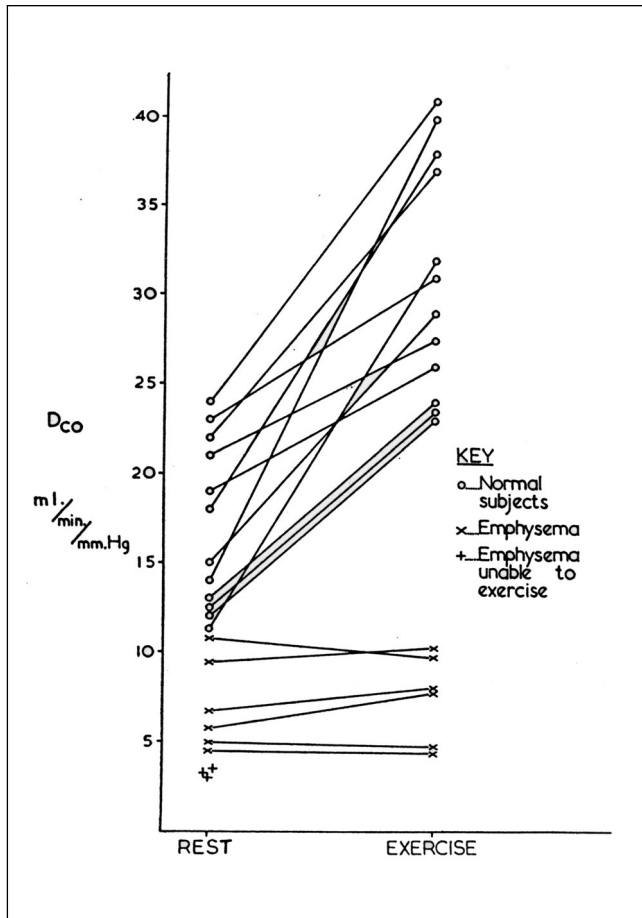


Figure 5) The diffusing capacity on exercise (D_{CO}). The figure illustrates the much greater discrimination between normal persons and patients with emphysema when the diffusing capacity is measured during exercise. Exercise consisted of walking at two to three miles per hour on the level

ure 6 [not shown]. During the period covered by this figure he was seen regularly every month or, occasionally, every other month. He complained of increased dyspnoea during the fog of December 1952, and an increase in the jugular venous pressure was noted after this. In April 1954 he had an acute chest infection, from which he made a satisfactory recovery. The function tests reveal very little change during this period of supervision, and at the end of it this patient was still able to increase the D_{CO} from 6.3 to 8.3 on exercise.

Cases illustrating clinical and functional change: Patient FCW was first seen in March 1950. By trade he was a meter assembler, doing a light factory bench job. He was 32 years old when first seen, and gave a history of one year of non-productive cough, followed by rapidly increasing dyspnoea on exertion, and it was this symptom that brought him to hospital. When first seen he was just able to manage a flight of stairs. There had been no history of asthma either in the patient or in the family. He was a tall, thin man, who had evidently lost weight. An upper dorsal kyphosis was noted, and there were signs of moderate diffuse bronchospasm. The chest X-ray showed flattened diaphragms and 'some evidence of emphysema'. The patient complained of steadily

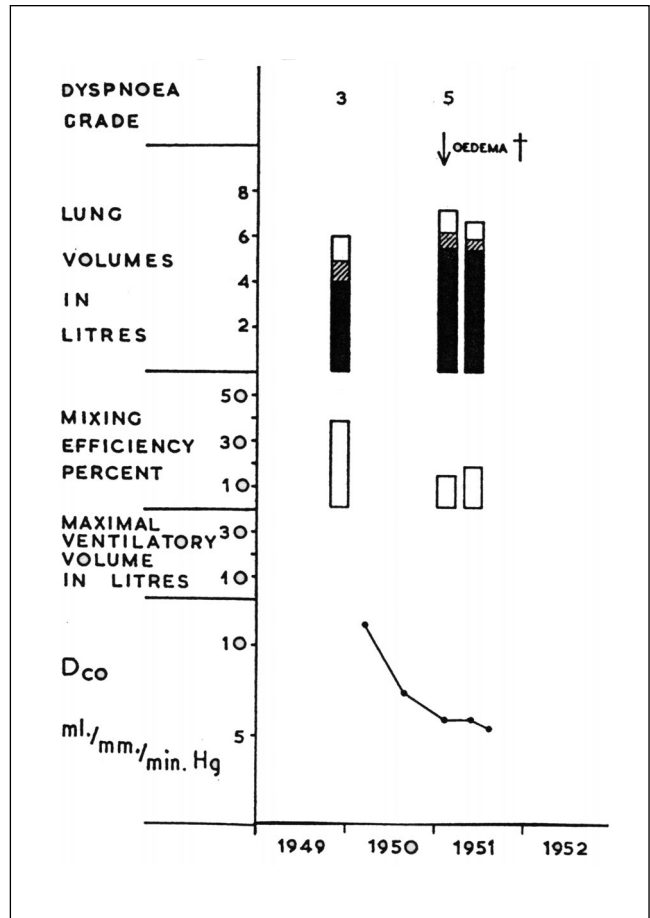


Figure 9) Patient FM. The relatively rapid clinical deterioration before death in December 1951 has been paralleled by adverse changes in all the function tests

increasing dyspnoea up to the spring of 1953. He was made worse by the fog of December 1952, and was admitted to hospital in March 1953 for a course of antibiotics. While he was in hospital all the function tests were repeated every other day for 10 days, and can be seen from Figure 7 [not shown] to show a satisfactory degree of consistency. Their results showed a greater degree of impairment than those obtained previously, but in the spring of 1964 the patient appeared to be better, and this change was paralleled by apparent improvement in the function tests (Figure 8 [not shown]).

Patient FM shows a rather more rapidly progressive course. He was first seen in December 1948, when he was aged 61 years. He was a cook on a railway dining-car. He gave a one-year history of cough with sputum, and of steadily increasing dyspnoea. He said that the amount of sputum had always been scanty. On examination he was found to present the typical features of emphysema, with a barrel-shaped chest, poor air entry at the lung bases, and diffuse 'bronchospasm'. In March 1950 his condition was unchanged, and he was still at work. In November 1950 he had an attack of bronchitis, after which he was noticed to be more dyspnoeic. In February 1951 he was admitted to hospital with heart failure and ankle oedema. The changes in function tests are shown in

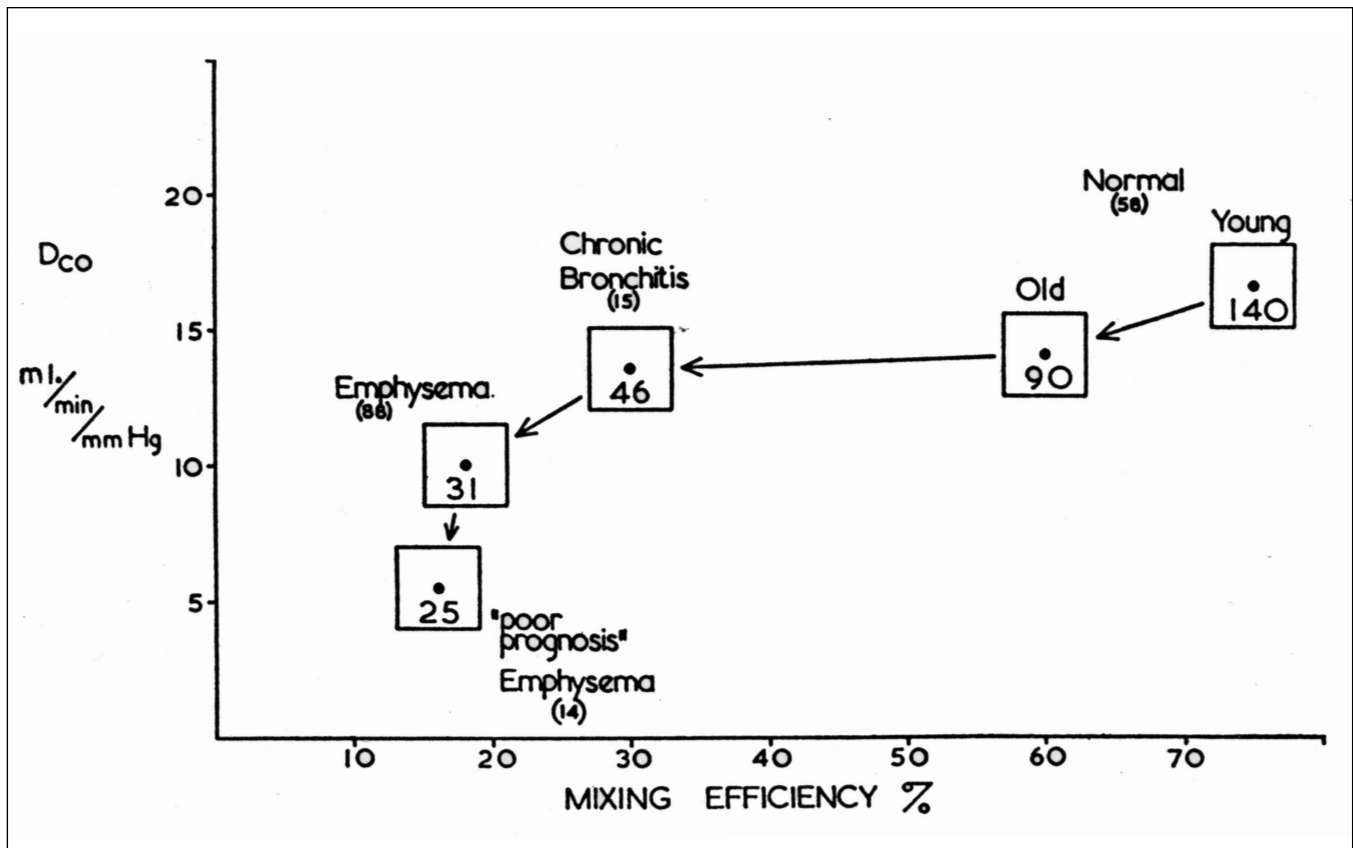


Figure 12) The relationship of tests of function to prognosis. This figure is compiled partly from data in the present study, and partly from data recorded elsewhere (10). The central dot in each rectangle marks the mean value for each group, but the area enclosed by it does not represent the range of values, as there is an overlap between all successive groups. The figure in each rectangle is the mean maximal ventilatory volume for each group (maximum breathing capacity) in litres. The small figures in parentheses are the numbers of subjects in each group. The change which follows the onset of chronic bronchitis is mainly ventilatory, and is concerned with bronchial obstruction; the progression from chronic bronchitis to death in *cor pulmonale* is principally followed by a falling diffusing capacity. See text for criteria of classification

Figure 9. The heart failure responded to treatment, but recurred in June 1951. The oedema again disappeared, but in December 1951, after a slight fog, he was more breathless again, and he died in hospital with oedema and heart failure. Postmortem the lungs showed generalized emphysema; no bullae were larger than about 1 cm in diameter, but only a few small islands of normal alveolar tissue were present in the lungs ...

Only two patients showed evidence of clinical and functional improvement. One of these (WC) showed improvement in a fairly short period of time. He was 49 years old, and on the editorial staff of a London newspaper. He had a long history of recurrent winter bronchitis, and some catarrh. After the fog of December 1952 he became increasingly dyspnoeic, and visited the hospital on account of increasing disability in September 1953. By this time he was too breathless to work, and he was conscious of considerable wheezing in his chest. He was admitted to the ward, where he was found to have a slightly increased jugular venous pressure, but no ankle oedema. There was a considerable increase in the antero-posterior diameter of the chest, and movement was very poor. Generalized rhonchi were heard, with a few basal rales. The electrocardiogram was normal, and the chest

x-ray showed only some 'hypertranslucency'. He was treated with terramycin and antispasmodics, and his progress is shown in Figure 11 [not shown]. It is of interest that the D_{CO} has risen progressively, although there has been no change in the efficiency of gas distribution. There has been a striking decrease in functional residual capacity, which is of interest in view of the general failure of this measurement to correlate with other changes. This case illustrates the occasional finding of improvement, both clinically and by tests of function, in these patients ...

DISCUSSION

The present investigation contains a number of defects, some of which might, in retrospect, have been avoided; others are almost inseparable from this type of study. The difficulty of arranging both clinical and functional assessment on isolated visits has undoubtedly been responsible for some of the wide variations found. Further refinement of the tests is required, and in particular it is clear that studies during exercise would be of much more value than those done while the subject is at rest. The results of this study confirm the general view of the nature of the functional defect in emphysema, namely that there is a gross impairment of the efficiency of

ventilation, and of overall diffusion, within the lung. The nature of the progression from normality to death from pulmonary heart failure is indicated in Figure 12, which is compiled partly from figures in the present series and partly from data recorded elsewhere (10). There appears to be no doubt that the increasing severity of emphysema is related to progressive impairment in gas diffusion.

Shepard, Cohn, Cohen, Armstrong, Carroll, Donoso, and Riley (14) have recently shown that, in a group of cases of chronic bronchitis and emphysema, there is often a striking disparity between the vital capacity and maximal breathing capacity on the one hand, and diffusion on the other. Our findings are in complete agreement with this conclusion, and scatter-diagrams compiled from our data show no evidence of correlation between the values in question. The evidence in the present series of the prognostic value of the diffusing capacity (D_{CO}) indicates that this measurement, or some refinement of it, is an essential part of any complete assessment of respiratory function. It seems very probable, as Riley has suggested, that the D_{CO} in emphysema is primarily a measurement of the degree of destruction of the lung parenchyma, and presumably this accounts for its value in prognosis. Evidence will be presented elsewhere that bronchospasm alone is, in certain circumstances, capable of lowering the overall diffusing capacity, presumably by reducing the effective surface area of blood exposed to ventilating gas. For clear evidence, therefore, of improvement in gas diffusion in emphysema, it is essential that the effect of a reduction in bronchospasm can be ruled out. In the patient WC (Figure 11 [not shown]), there was an improvement in the overall D_{CO} without any change in mixing efficiency, and although this fact suggests that the degree of bronchospasm had not altered, it is by no means conclusive. We have yet to demonstrate, by combined pressure volume and diffusion studies, that improvement in diffusion can occur without change in bronchospasm. Such an event is of course a theoretical possibility, particularly if any degree of pulmonary oedema is responsible for the lowering of D_{CO} in these subjects.

The clinical and functional findings in this group of cases have led us to certain tentative conclusions. In London, it is true that the majority of cases of advanced emphysema have a long history of chronic bronchitis; in such patients it must be supposed that the progressive damage to the lung parenchyma (that is, emphysema) is a result of the strain of constant bronchiolar obstruction and cough in an ageing lung. A similar sequence of events may occur as a result of asthma, but in the present group of 59 cases of emphysema no patient had a history of allergy or true allergic asthma. It appears that the dyspnoea of emphysema is mainly related to the degree of bronchial obstruction present, at least in the early stages of the disease. The absence of precise correlation between diffusion and ventilatory defect has been noted above. These facts suggest that the two processes of ventilatory defect (bronchospasm) and diffusion impairment (parenchymal change) should be thought of as consecutive processes in one sense, and yet as distinct and individual changes in another.

Certain patients are encountered in whom the diffusing capacity is grossly impaired and ventilatory defect is very slight. We have studied three such patients, who correspond to the patient WBS described by Shepard, Cohn, Cohen, Armstrong, Carroll, Donoso, and Riley (14). It must be remembered that in such cases the bronchial obstruction and ventilatory defect may follow the changes in the lung parenchyma rather than precede them.

The suggestive finding that the onset of evident right ventricular failure is heralded by a falling diffusing capacity is of interest. The reduction in overall gas diffusion in emphysema may be broadly defined as due to loss of effective blood-surface area. Three changes are probably responsible for this loss: (1) actual loss of lung tissue, leading to direct reduction in blood surface; (2) loss of vascular bed in the remaining tissue; and (3) reduction in effective blood-surface area due to inequality of gas distribution. Only the third of these effects seems likely to be potentially reversible, and it is for this reason that the most likely cause of an improvement in overall D_{CO} in these patients, when such a change is found, is relief or partial relief of bronchospasm. It will be realized that patients with advanced emphysema have no reserve of function at all, and the rate of overall gas diffusion is often so impaired as to permit a maximal oxygen transfer of only 300 to 400 mL of oxygen a minute. It is obvious that in these circumstances any additional load, such as acute respiratory infection or an increase in bronchospasm, is likely to prove rapidly fatal. The sequence of events suggested by Figure 12 indicates that careful treatment and supervision of anyone in middle age with bronchospasm might well delay, if not prevent, the changes that are commonly called emphysema. Control of treatment with studies of pulmonary function would add greatly to our knowledge of this group of pulmonary disorders.

SUMMARY

1. Fifty-nine patients considered on clinical criteria to be suffering from pulmonary emphysema have been observed, with respiratory function tests and out-patient supervision, over periods up to five years.
2. Thirteen per cent of this group died with pulmonary heart failure within two years, and 22% within four years. Histological evidence of advanced emphysema was found in all of the nine patients on whom postmortem examinations were made. The overall mortality for this period is more than four times the value predicted from life insurance tables.
3. During the five-year period, 221 estimates of vital capacity, functional residual capacity, and mixing efficiency, and 153 measurements of the diffusing capacity (D_{CO}) were made.
4. Although all these tests of function are of value in diagnosis, only the diffusing capacity (D_{CO}), as measured in this investigation, is a sensitive guide to prognosis.

5. There are two distinct processes in emphysema which usually run concurrently, but which may be independent of one another. The first is bronchial obstruction, and this is mainly responsible for the dominant symptom of this disease, which is dyspnoea. The other, which may be responsible for no symptoms until it leads to heart failure, is the reduction of the pulmonary capillary bed. The latter process, which is most closely related to prognosis, can only be satisfactorily assessed by measurement of the pulmonary diffusing capacity.

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