haziness of the media in a large proportion of diabetics made it difficult to visualize the capillaries in this study. Although, in Fig. 6 B, an arterial injection of fluorescein has shown up zones of capillary closure alongside arteries and scattered small areas of capillary closure (Ashton, 1953), we have been able to discern this phenomenon in only three patients after intravenous injections; usually it is not until microaneurysms and fine new vessels develop that we can show up lesions in the capillary bed with the present intravenous technique.

Besides providing fine anatomical details of the lesions in diabetic retinopathy, fluorescence photography gives information on the permeability of vessels. A proportion of the microaneurysms, segments of the new vessels in the retina, the new vessels projecting into the vitreous and in the retinitis proliferans, all show leakage of fluorescein. It is not surprising that these vessels have abnormally permeable walls because of the alterations in the basement membrane of the endothelium in the microaneurysms (Bloodworth, 1963) and the defective adventitial layers of the new vessels (Ballantyne, 1946; Gartner, 1950).

Hodge and Dollery (1964) have shown that on equilibrium dialysis up to 80% of fluorescein in plasma is bound to the proteins. They infer that this protein-binding is easily reversible because of rapid loss of fluorescein from the blood into the extracellular fluid after an intravenous injection. While it is certain from the photographic studies that free fluorescein (molecular weight of 361) is leaking from these microaneurysms and abnormal vessels, it is possible that fluorescein in the protein-bound form is leaking out as well.

Abnormally permeable vessels could explain the retinal oedema and vitreous haze encountered in some patients with diabetic retinopathy. Retinal oedema, for example, was observed ophthalmoscopically in the young girl whose retinal photographs (Fig. 6 A and B) show numerous fine new vessels with leaking segments. Viterous haze occurs in patients with a rete mirabile or retinitis proliferans, as in the patients whose fundi are illustrated in Figs. 8 and 9. It is often unrelated to previous vitreous haemorrhage, it fluctuates throughout the day, and it is easily discerned by patient and clinician. Continued leakage of plasma proteins from the vessels of the rete mirabile and retinitis proliferans may cause this turbidity of the vitreous.

Information about the circulation rate in the retinal vessels is restricted to direct comparative observations of different vessels in the same field after each injection of fluorescein. We are able to recognize only prolonged filling of some microaneurysms and rapid shunting and delayed drainage of certain vessels, but only relative to neighbouring microaneurysms and vessels.

These preliminary studies have shown that fluorescence photography can reveal the large proportion of small-vessel abnormalities hitherto invisible in the living patient, and can also demonstrate the important functional abnormality of enhanced permeability of these vascular lesions. Further studies may prove useful in elucidating the life-history of specific lesions, as a guide to prognosis in individual patients and in assessing the response to various forms of treatment.

Summary

Retinal photography while fluorescein traverses the retinal circulation has been used to study 41 diabetics with visible retinopathy.

Microaneurysms and fine new vessels were usually shown in far greater numbers and detail than could be observed ophthalmoscopically and with routine retinal photography.

Leakage of fluorescein occurs from a proportion of microaneurysms and segments of the fine new vessels, and more pronounced leakage takes place from the large new vessels and into retinitis proliferans.

No constant or characteristic lesion was seen in retinal vessels adjacent to hard exudates.

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Forced Expiratory Time: A Simple Test for Airways Obstruction

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This paper describes a study of a simple physical sign of diffuse airway obstruction undertaken to see how accurate it is in comparison with more refined methods. Diffuse airway obstruction is a feature of asthma and of the chronic non-specific disease which in Great Britain is commonly labelled as chronic bronchitis and emphysema. Clinical examination as usually practised is not a very good method of detecting or evaluating diffuse airway obstruction: first, because the classical techniques of inspection, palpation, percussion, and auscultation are usually taught with emphasis on the detection of localized or lateralized conditions; secondly, because physical signs which are generally sought, such as the barrel-shaped chest, poor expansion, and diminished cardiac and hepatic dullness, are related to hyperinflation which is secondary to obstruction, and, in any case, they may be present in elderly subjects without chest disease. Direct evidence of obstruction is usually elicited only by listening to the chest; even then the types of rhonchi

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heard depend on the nature rather than the severity of airway obstruction, and the absence of a wheeze does not exclude airway obstruction. Moreover, there is a large observer error in the examination of the chest even among experts (Fletcher, 1952).

A variety of pulmonary function tests have been used for the diagnosis of the condition. The physician of the last century who asked a patient to whistle or blow a candle out was crudely assessing the maximum respiratory velocity (Donald, 1953). Although measurement of airway resistance with the body plethysmograph is the best method for evaluating airway obstruction (Lloyd and Wright, 1963), the forced vital capacity (F.V.C.) and forced expired volume in one second (F.E.V.$_1$) are now well established as the methods of choice among the generally available spirometric techniques. In these tests the volume of air expired by a forcible effort is measured against time by means of a recording spirometer. However, they suffer from the disadvantage that the usual apparatus is cumbersome, although a few portable dry spirometers are now available (McKerrow and Edwards, 1961 ; Vance, 1963). The Wright peak flowmeter (Wright and McKerrow, 1959) has been increasingly used in the last four years and the peak expiratory flow rate (P.E.F.R.) has been shown to have a good correlation with forced expired volume (Higgins, 1957 ; Balgairies, Amoudru, Masure, and Quinot, 1960 ; Lockhart, Smith, Mair, and Wilson, 1960 ; Fairbairn, Fletcher, Tinker, and Wood, 1962).

In a normal person the F.E.V.$_1$ is 70 to 80% of the vital capacity (V.C.). The remaining 20 to 30% of the V.C. takes a further two to three seconds to be expelled. In subjects with airway obstruction this total period is prolonged and air-flow may continue for a long time. Measurement of this time can be of clinical assistance, but its value and limitations are not well documented. This paper describes the relation between a clinical estimate of forced expiratory time (F.E.T.$_c$) and other measurements such as F.E.V.$_1$: V.C.% and P.E.F.R.

Material and Method

The ages of the 95 subjects (65 males, 30 females) studied ranged from 19 to 75 years. The normal subjects came from the staff of the hospital and the abnormal subjects were patients attending the bronchitis clinic, the chest clinic, or the general medical out-patient clinic at the Hammersmith Hospital.

V.C. and F.V.C. were measured with a 6-litre low-resistance spirometer (Bernstein, D'Silva, and Mendel, 1952) with a kymographic speed of 2 cm. per second (Fig. 1). The Wright peak flowmeter (Wright and McKerrow, 1959) was used to measure the P.E.F.R. We calibrated the instrument approximately each day by recording our own P.E.F.R. When the forced expiratory time was measured clinically (F.E.T.$_c$), the subject was asked to take a deep breath and blow it all out as fast as possible. A stethoscope bell was placed over the trachea in the suprasternal notch and the duration of audible expiration was timed with a stopwatch or a wrist-watch with a large second hand. Time was measured to the nearest half second. Practice runs were made before the actual measurement to be certain that the subject understood what to do. At least three consistent records were obtained for each measurement. Widely divergent values were rejected. F.E.V.$_1$, F.V.C., and forced expiratory time recorded spirometrically (F.E.T.$_s$) were calculated from the kymographic tracings (Fig. 1). The best of the three readings of F.E.V.$_1$, F.V.C., V.C., and P.E.F.R., but the mean of three readings of F.E.T.$_c$ and F.E.T.$_s$, were taken. Volumes were converted to body temperature and pressure saturated with water vapour (B.T.P.S.). Some further measurements were made on subjects with airway obstruction before and after inhalation of 1% isoprenaline for two minutes. On two in-patients daily measurements were made over a period of several days.

During a pilot study of 12 normal subjects and 12 abnormal subjects, the measurement of F.E.T.$_c$ was made on each subject by two of us (S. L. and A. D. F.). In the normal subjects with an F.E.T.$_c$ of less than 5 seconds no discrepancy greater than 0.5 second was found in the time recorded. In the subjects with an F.E.T.$_c$ of more than 6 seconds, the maximum difference was 1.5 seconds and there was no systematic difference between

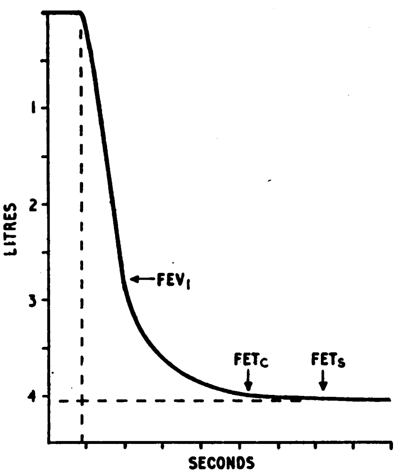

FIG. 1.—Normal spirogram. F.E.V.$_1$ = Forced expired volume in one second. F.E.T.$_c$ = Forced expiratory time measured clinically with a stethoscope over the trachea. F.E.T.$_s$ = Forced expiratory time measured from the spirographic tracing.

the observers. Thereafter all the measurements were made by one or the other of us, each one making approximately half the observations.

Results

Fig. 2 shows the relation between F.E.T.$_c$ and F.E.T.$_s$. Clinical measurements often tended to underestimate the time required for the flow to cease both in normal and in abnormal subjects. The average difference was 0.95 second (S.D. = 1.4).

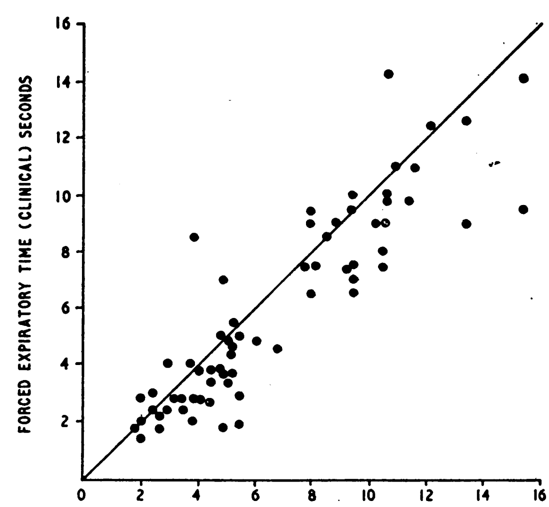

FIG. 2.—F.E.T.$_c$ plotted against F.E.T.$_s$. The oblique line at 45 degrees represents F.E.T.$_c$ = F.E.T.$_s$.

The volume of air expired between the end-point of F.E.T.$_c$ and F.E.T.$_s$ ranged between 20 and 200 ml. in 1 to 5 seconds or a flow rate of 20 to 40 ml. per second in abnormal subjects and 60 to 70 ml. per second in normal subjects. These low flow rates appear not to be detectable by the method, but failure to detect them did not affect the interpretation of the results and would have no clinical significance.

Fig. 3 shows the relation of F.E.T.$_{o}$ to F.E.V.$_1$: V.C.%. There is a significant correlation between the F.E.T.$_{o}$ and F.E.V.$_1$: V.C.% (r = – 0.84), regression of F.E.V.$_1$: V.C.% (y) on F.E.T.$_{o}$ being y = 82.73 – 4.035 x. Of the 50 subjects with an F.E.T.$_{o}$ of less than 5 seconds and in whom the air-flow had ceased, 46 have an F.E.V.$_1$: V.C.% of above 60%. In 42 of 45 subjects with an F.E.T.$_{o}$ of greater than 6 seconds the F.E.V.$_1$: V.C.% was less than 60%, and in all but four cases the air-flow was still continuing until they took the next breath. At a conventional level of F.E.V.$_1$: V.C.% of 65%, if an F.E.T.$_{o}$ of 5 seconds is taken as the upper level of normal, there were seven false negatives ; but there were no false positives above that level.

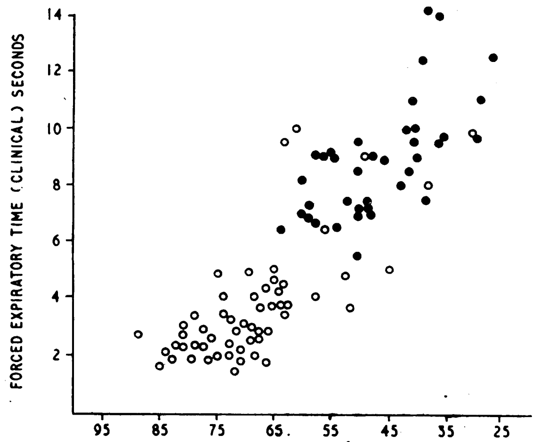

FIG. 3.—F.E.T.$_{o}$ plotted against F.E.V.$_1$: V.C.%. O = subjects in whom air-flow had ceased before the next breath. ● = subjects in whom the flow continued until they took the next breath. r = –0.84. F.E.V.$_1$: V.C. = %82.73 – 4.035 (F.E.T.$_{o}$). F.E.V.$_1$: V.C.% = forced expiratory volume in one second expressed as a percentage of vital capacity.

Fig. 4 shows the relation of F.E.T.$_{o}$ to P.E.F.R. The relation here is obviously not linear. There is a wide scatter of P.E.F.R. value at low F.E.T.$_{o}$ values and a similar wide scatter of F.E.T.$_{o}$ at low values of P.E.F.R. Five out of seven subjects with a low P.E.F.R. and low F.E.T.$_{o}$ had an F.E.V.$_1$: V.C.% of more than 65%, suggesting a restrictive disability.

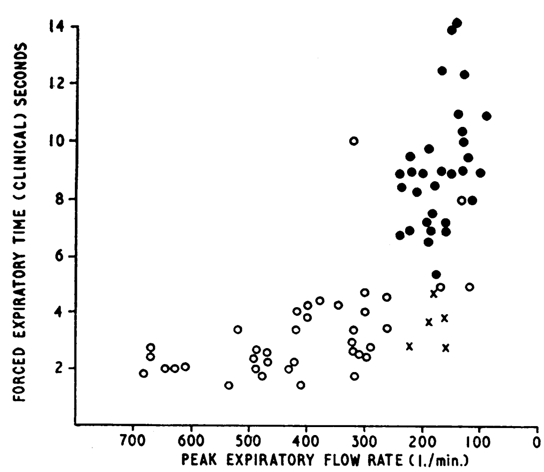

FIG. 4.—F.E.T.$_{o}$ plotted against P.E.F.R. Symbols used are the same as in Fig. 3 with one modification : subjects with an F.E.T.$_{o}$ of less than 5 seconds, and F.E.V.$_1$: V.C.% of more than 65%, and a P.E.F.R. of less than 250 l. per minute are shown as crosses.

In order to assess the value of changes in F.E.T.$_{o}$ as a means of assessing progress in an individual subject both F.E.T.$_{o}$ and F.E.V.$_1$ were recorded repeatedly in two patients with airway obstruction. The results in one patient are shown in Fig. 5. The changes in F.E.V.$_1$ are obviously accompanied by appropriate directional changes in F.E.T.$_{o}$. Fig. 6 shows F.E.V.$_1$ and F.E.T.$_{o}$ before and after bronchodilators on 10 subjects. In all cases there was an increase of F.E.V.$_1$ and a fall of F.E.T.$_{c}$.

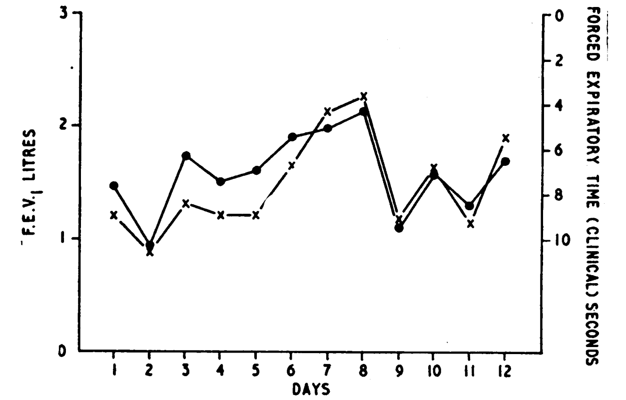

FIG. 5.—Day-to-day change in F.E.T.$_{o}$ and F.E.V.$_1$ in one subject. ●——● = F.E.V.$_1$; ×——× = F.E.T.$_{o}$.

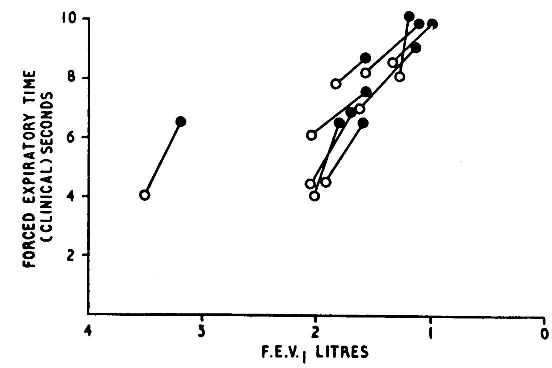

FIG. 6.—F.E.V.$_1$ and F.E.T.$_{o}$ before and after bronchodilators. Ten subjects. ● = readings before bronchodilators. O = readings after bronchodilators. Lines sloping downwards and to the left indicate an increase in F.E.V.$_1$ and a fall in F.E.T.$_{c}$.

Discussion

In normal subjects and patients whose airways are not obstructed the end of forced voluntary expiration occurs relatively abruptly. As a result approximately 70 to 80% of the vital capacity is expelled smoothly and rapidly in one second (Gaensler, 1951) and the remaining 20 to 30% takes only a further two to three seconds (Gross, 1943). However, in patients with diffuse airway obstruction the inequality of the disease process in different airways causes them to narrow irregularly and progressively as the expiration proceeds. The result is that in severe cases less than 40% of the vital capacity is expelled in the first second and the remainder takes much longer. In fact, air-flow may continue for as long as the patient can wait before being forced to take another breath. The time required for maximum forced expiratory effort measured with kymographic tracings is remarkably constant among normal persons of all ages as compared with patients with varying degrees of obstructive disease (Roy, Chapin, and Favre, 1955). Our results, together with those of Rosenblatt and Stein (1962), show that this time can be measured clinically reasonably accurately and that the F.E.T.$_{o}$ gives some idea of the degree of airway obstruction.

F.E.T.$_{o}$ can be measured easily without special equipment, and, although the true forced expiratory time may be slightly underestimated, the difference is clinically unimportant. Rosenblatt and Stein (1962) measured time clinically with a stethoscope on the back of the chest of the subjects but found the end-point difficult to judge and had to depend on a signal by the subject in 5 cases out of 35. We did not encounter this difficulty when using the trachea.

Obviously in subjects who have airway obstruction the end-point of F.E.T.$_c$ depends to some extent on the effort made by the subject to keep going, and this may be the most important factor preventing a better correlation with the degree of obstruction as indicated by the F.E.V.$_1$: V.C.%. We tended to stop encouraging the subjects after about 10 seconds. This probably explains why there are no recorded F.E.T. values of over 15 seconds. We have often found that a really determined patient can be persuaded to maintain air-flow for much longer, and Gilson and Hugh-Jones (1949) observed a subject who took as long as a minute to perform a vital-capacity manœuvre. The results of this study show that when it has been established that a patient's F.E.T.$_c$ is more than 10 seconds there is little to be learned about his ventilatory capacity by prolonging the test.

The results show that airway obstruction can be confidently diagnosed or excluded by accepting the following major subdivisions: an F.E.T.$_c$ of less than 5 seconds with air-flow having stopped suggests an F.E.V.$_1$: V.C.% of more than 60% ; an F.E.T.$_c$ of more than 6 seconds represents an F.E.V.$_1$: V.C.% of less than 50% or if the air-flow continues an F.E.V.$_1$: V.C.% of less than 40%.

In an individual the findings illustrated in Figs. 5 and 6 suggest that the F.E.T.$_c$ can be used as a supplement to other clinical methods in assessment of progress but will of course be dependent on consistent co-operation.

Another simple test used in assessing airways obstruction is the "match" test (Snider, Stevens, Wilner, and Lewis, 1959), in which the subject is asked to blow out a lighted match held in front of his (wide) open mouth. Marks and Bocles (1960) and Barry (1962) suggested that this test will detect only severer degrees of airway obstruction. Moreover, one hopes carrying of matches is becoming less fashionable.

A by-product of this study has been the provision of further data on the relation of F.E.V.$_1$ to P.E.F.R. These have in the

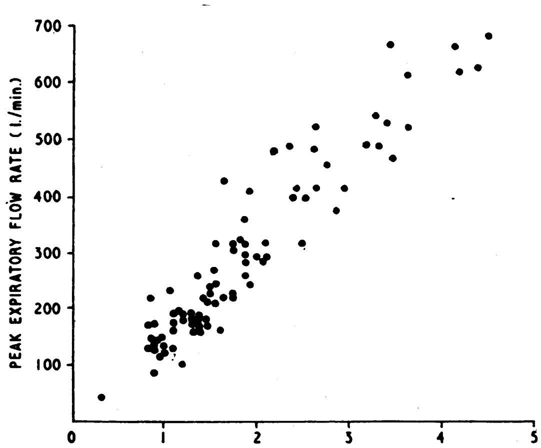

FIG. 7.—F.E.V.$_1$ plotted against P.E.F.R. $r = 0.94$; F.E.V.$_1$ = 0.00567 (P.E.F.R.) + 0.219.

past been shown to have a significant correlation (Higgins, 1957 ; Balgairies *et al.*, 1960 ; Fairbairn *et al.*, 1962). Our results (Fig. 7) substantiate this view. The correlation coefficient (r) for our data is 0.94, the regression of F.E.V.$_1$ (y) on P.E.F.R. (x) for all subjects being $y = 0.00567\, x + 0.219$.

It is worth noting that P.E.F.R. and F.E.T.$_c$ are complementary rather than alternative in that the first is related to F.E.V.$_1$ and the second to F.E.V.$_1$: V.C.%. Reduction of either F.E.V.$_1$ or P.E.F.R. indicates impairment of ventilatory capacity, but neither measure alone indicates whether this is obstructive or restrictive. Measurement of F.E.T.$_c$ enables this distinction to be made. Subjects with a P.E.F.R. of below 250 l. per minute and an F.E.T.$_c$ below 5 seconds have a restrictive impairment of ventilatory capacity.

Recommended Procedure

F.E.T.$_c$ should be measured over the trachea with a stethoscope. The subject should be asked to take a deep breath in and then breathe out as quickly as he can. He should be encouraged to keep on breathing out during the procedure. Three consistent readings should be obtained. An F.E.T.$_c$ of more than 6 seconds suggests airway obstruction. The effect of bronchodilators and day-to-day progress can be assessed reasonably accurately, but it is preferable that the same person make the observations.

Summary

A physical sign of diffuse airway obstruction has been examined. The duration of air-flow during a voluntary forced expiration (the forced expiratory time, F.E.T.) has been measured in 95 subjects, about half of whom were normal and half had diffuse airways obstruction. The F.E.T. as measured clinically with a stethoscope over the trachea (F.E.T.$_c$) was found slightly to underestimate the F.E.T. as measured with a recording spirometer, but the difference was unimportant.

The F.E.T.$_c$ was correlated with the forced expired volume in one second expressed as a % of F.V.C. (F.E.V.$_1$: V.C.%) ($r = -0.84$). The findings show that subjects without airway obstruction have an F.E.T.$_c$ of less than 5 seconds and those with airway obstruction have an F.E.T.$_c$ of more than 6 seconds. The F.E.T.$_c$ mirrors changes in the F.E.V.$_1$ in patients whose airway obstruction is variable.

The F.E.T.$_c$ did not show a linear correlation with the peak expiratory flow rate (P.E.F.R.) because P.E.F.R. is related to F.E.V.$_1$ and not to F.E.V.$_1$: V.C.%. The F.E.T.$_c$ and P.E.F.R. are therefore complementary. Further data on the correlation of F.E.V.$_1$ and P.E.F.R. are reported.

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