Emphysema is defined on an anatomical basis as a disease characterized by structural changes in the lung causing increase, beyond the normal range, in the size of air spaces distal to terminal bronchioles. This anatomical abnormality is commonly found to be associated with increased resistance to airflow in the lungs, varying little either spontaneously or in response to treatment; but this finding is not a defining characteristic.

Knowledge of the causation both of chronic bronchitis and of emphysema is sadly incomplete. There is strong evidence that chronic bronchitis is usually a response to air pollution, both private in the form of cigarette smoking and public in the form of smoke and fumes from domestic and commercial fuel-burning. To what extent and in what way these factors may be concerned also in the pathogenesis of emphysema remains uncertain. Can they directly damage alveoli and cause emphysema? Do the recurrent episodes of infection that commonly occur in the course of chronic bronchitis cause emphysema among other structural changes? Does chronic bronchitis accelerate the progression of emphysema in individuals predisposed to it by some other factor? One form of emphysema is known to be related to exposure to dust. Another form is now known to be associated with a deficiency of α_1-globulin and of the antitryptic activity which resides in this globulin fraction. This deficiency is inherited as a mendelian recessive characteristic (Eriksson 1965). It is rare, and can account for only a small proportion of cases of emphysema; but nevertheless it confirms the suspicion, long held on clinical grounds, that emphysema may in some cases be genetically determined.

In this difficult field, the physician needs to know what the morbid-anatomist can tell him about the anatomical classification and quantification of emphysema. He must be familiar with the pattern of functional defect associated with emphysema, with methods of quantifying it and distinguishing it from the patterns associated with other diseases causing airways obstruction. He must be aware of the contribution which radiology can make, especially of correlations between radiographic appearances and morbid anatomy. His own contribution consists in the integration of all these, and of the evidence derived from long-term clinical and epidemiological studies, to the understanding of the clinical course of the disease and to the problems of individual patients.

REFERENCES
Eriksson S (1965) *Acta med. scand.* **177**, Suppl. 432
Medical Research Council (1965) *Lancet* i, 775
Scadding J G (1967) *Lancet* ii 877

Dr M S Dunnill
(Radcliffe Infirmary, Oxford)

The Classification and Quantification of Emphysema

Definition

Until 1958 there was no satisfactory definition of emphysema, although the term was used extensively by both clinicians and pathologists. It was in that year that the Ciba Foundation held a Symposium on the terminology, definitions and classification of pulmonary emphysema and related conditions (Ciba Foundation Symposium 1959).

Emphysema was defined as 'a condition of the lungs characterized by increase beyond the normal in the size of air spaces distal to the terminal bronchiole either from dilatation or from destruction of their walls'.

One of the main drawbacks to the understanding of the condition was the lack of attention paid to the preparation of lungs before pathological examination. Although Laennec had examined air-inflated and dried lungs it was not until the work of Professor Gough in Cardiff that the importance of inflating the lungs with fixative before examining them was fully appreciated. Several methods of inflating the lung with fixative are available, of which the most sophisticated is that of Weibel & Vidone (1961) using formalin steam. Once such a procedure was adopted certain points with regard to both the normal and pathological anatomy of the lung were clarified. The normal lung may be divided up into three main components (Weibel 1963): (1) A conducting zone, larger airways and blood vessels. (2) A transition zone composed of structures at the level of the terminal and respiratory bronchioles. (3) A respiratory zone, alveoli and capillaries.

The unit supplied by the terminal bronchiole is referred to as the acinus and it is the region of gas mixing by diffusion and gas exchange with the blood. Emphysema is, by definition, a disease of the acinus and, when lungs are examined carefully in the fixed inflated state, it at once becomes apparent that rather than there being just one disease there are several different pathological conditions, and thus it would be more accurate to speak of the emphysemas.

Classification

No satisfactory classification exists. A classification of the disease on an etiological basis is not possible as too little is known of its pathogenesis. The best classification is based on morbid anatomy and depends on the distribution of changes within the acinus. This was proposed by

Table 1
Classification of pulmonary emphysema
(Ciba Foundation Symposium 1959)

(1) *Unselective Distribution Beyond the Terminal Bronchiole*
(*a*) Dilatation alone (e.g. compensatory emphysema, emphysema due to partial main bronchus obstruction)
(*b*) Destruction of the walls of air spaces (e.g. panacinar destruction emphysema)

(2) *Selective Distribution Beyond the Terminal Bronchiole*
(*a*) Respiratory bronchioles affected
(i) Dilatation alone (e.g. focal emphysema due to dust)
(ii) Destruction of the walls of air spaces (e.g. centrilobular emphysema)
(*b*) Alveolar ducts affected

(3) *Irregular Distribution Beyond the Terminal Bronchiole*
(e.g. paracicatricial emphysema, paraseptal emphysema)

the Ciba Foundation Symposium (1959) (Table 1). However, Reid (1967) has put forward a classification based on the presence or absence of airways obstruction and this has much to recommend it, although its details are probably too complex for general use. In fact, there is a considerable body of opinion (Fletcher 1968) which holds that emphysema may be relatively unimportant when compared with airways obstruction in determining a patient's clinical state. The difficulty is that there is no really reliable and consistent way of measuring airways obstruction at autopsy.

Classification of diseases on an anatomical basis is of little use unless it adds to the understanding of the disease and is accompanied by characteristic changes in function and prognosis which are easily recognized by clinicians. In the emphysemas such a stage of sophistication has not been reached and the relationship between structure and function in the various varieties of the disease is ill-understood. Under these circumstances it may be argued that any system of classification is rather meaningless but, in any case, it is important to remember two points: (1) As any pathologist dealing with lung disease will affirm, in many cases of emphysema the anatomical varieties are mixed; this makes it all the more important to study 'pure' cases with great thoroughness. (2) The anatomical classification proposed by the Ciba Symposium, particularly where it concerns 'dilatation alone', implies a knowledge of measurement which, in large part, does not exist.

Methods of Measurement

Essentially three main methods are available for (*a*) the measurement of the volume of normal and diseased lung, (*b*) the measurement of the alveolar surface area, and (*c*) the enumeration of the number of alveoli. It is important, if any comparative measurements are to be made, that lungs should be prepared under standard conditions. They should be inflated and fixed at known pressures. Blocks of tissue for histological examination must be obtained by a recognized method of sampling which ensures that, although only a small quantity of tissue is examined, it is representative of the whole organ (Dunnill 1964). Shrinkage that occurs during processing must be estimated, and measurements in histological sections must be made using recognized random sampling techniques.

The proportions of the lung volume occupied by the conducting bronchi and blood vessels, and by the normal and abnormal parenchyma, can be assessed on gross lung slices using a simple point-counting grid. The procedure entails placing a grid, composed of points placed 1 cm apart at the angles of equilateral triangles, on each 1 cm thick slice of lung and counting the number of points falling into each component. The total number of points in each component is then proportional to the area occupied by that component on the surface of the slice and hence, by the Delesse theorem, to the volume of the component in the lung (Dunnill 1962).

The mean linear intercept principle (Short 1950, Campbell & Tomkeieff 1952) provides a method for determining a mean linear measurement for the air spaces and also, if the volume of the lung parenchyma is known, for determining the area of the air-tissue interface.

Finally, the number of alveoli can be calculated using the method of Weibel & Gomez (1962).

Values for the normal adult lung are shown in Fig 1.

Some Common Varieties of Emphysema

Bullous disease of the lung: Bullæ are referred to in many of the older textbooks of pathology and medicine when describing emphysema. This is because they are easily appreciated radiologically and because they can be seen at autopsy without having to inflate the lung with fixative. They appear as dramatic air-filled cysts most marked at the apices and along the anterior margins of the lungs. If these lungs are inflated and fixed

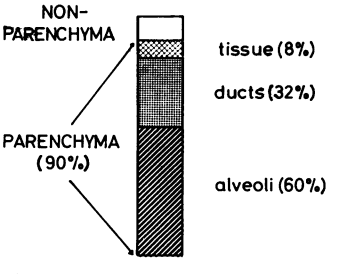

Fig 1 *Morphometric values in normal lung. Number of alveoli* 300×10^6. *Alveolar surface area 70–75* m^2 (*120* cm^2/ml). *Total lung volume 6,000 ml*

Table 2
Bullous disease of the lung

	Case 1	*Case 2*	*Case 3*
Volume proportions of normal parenchyma:			
Alveolar air	66·3	62·6	60·8
Duct air	22·1	25·2	27·5
Tissue	9·9	10·2	9·5
Blood vessels	1·7	2·0	2·2
Number of alveoli (10^6)	280	296	284

before slicing, it will sometimes be appreciated that the lesions are entirely superficial and that the underlying lung parenchyma is normal. Such cases are of importance in that the bullæ may act as space-occupying lesions and compress the normal underlying lung; also, occasionally, a spontaneous pneumothorax may occur. Quantitative studies on 3 cases of this disease are given in Table 2 and the underlying parenchyma has the volume proportions and number of alveoli characteristic of normal lung. Cases where large superficial bullæ are isolated are comparatively rare and frequently bullæ co-exist with other forms of emphysema; thus, Sweet *et al.* (1961) claim that a large percentage of patients with advanced centrilobular emphysema have radiographically visible bullæ and this view is supported by Thurlbeck (1963).

Centrilobular emphysema: This represents a selective distribution beyond the terminal bronchiole, involving dilatation of the respiratory bronchioles associated with destruction of the walls of adjacent air spaces. The emphysematous lesions appear in the centre of the acini and of the secondary lobules – hence the name. No matter how large the lesions, they always retain a typical distribution within the lobule and leave a rim of relatively normal alveolar tissue around the periphery. Serial sections show that the spaces are always supplied by a terminal bronchiole or first order respiratory bronchiole, and that third order respiratory bronchioles or alveolar ducts lead out of the spaces to the peripheral alveoli. This disease may be spread throughout the lung substance but is more often distributed in the upper two-thirds of the lung, i.e. upper lobe and apex of lower lobe.

Quantification of this disease (Fig 2) shows a distinctive pattern in that, though almost every acinus may be involved in the condition and thus every molecule of gas passing to the peripheral alveoli has to traverse one of these spaces, the total volume of diseased lung parenchyma, as determined by the point-counting method, may be quite small compared with the total lung volume. The reduction in the number of alveoli in the cases is often surprisingly small and the alveolar surface area is only a little less than in a normal lung.

Panacinar destructive emphysema: This is an unselective distribution of emphysema beyond the terminal bronchiole. It has a uniform distribution throughout the acinus and there is complete destruction of the normal architecture with few, if any, normal alveoli remaining. It is quite distinct from centrilobular emphysema which has involved the entire lobule. Snider *et al.* (1962) and Thurlbeck (1963) consider that its distribution differs from that of centrilobular emphysema in that it is more or less randomly distributed initially but later becomes more severe in the lower zone of the lung. The mean age of patients with this condition is said to be older than those with centrilobular emphysema. In its early stages this disease may be difficult to detect as it consists at first merely of a slight coarsening of the normal sponge-like appearance of the lung. When there is extensive loss of parenchyma recognition becomes simple. It is this difficulty in early recognition which makes the use of the point-counting method on fixed gross slices of lung subject to error. There is often considerable doubt as to whether a point lies in normal or abnormal parenchyma. This is in contrast to centrilobular emphysema where this distinction between normal and abnormal tissues is much more clear-cut. It is in panacinar destructive emphysema, and also in panacinar emphysema, where there is dilatation alone without any destruction of lung tissue, that measurement of the mean linear intercept is of great value.

Thurlbeck (1967) has measured this parameter in 25 normal subjects and obtained a mean value of $2{\cdot}75 \times 10^{-2}$ cm ($\pm 0{\cdot}32 \times 10^{-2}$ cm). The value increases with age. Thurlbeck divides panacinar emphysema into mild, moderate and severe, with mean values for the mean linear intercept of $3{\cdot}04 \times 10^{-2}$ cm, $3{\cdot}69 \times 10^{-2}$ cm and $5{\cdot}17 \times 10^{-2}$ cm respectively. In a series of 11 cases dying with respiratory failure (Table 3), a mean value of $5{\cdot}981 \times 10^{-2}$ cm was found with a range from $4{\cdot}72 \times 10^{-2}$ cm to $7{\cdot}91 \times 10^{-2}$ cm. As the mean linear intercept is increased the total alveolar

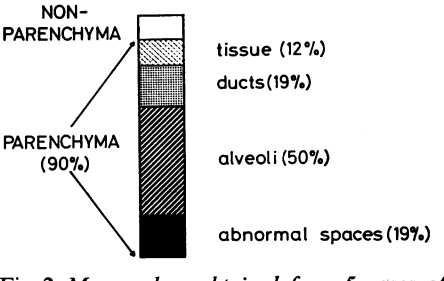

Fig 2 *Mean values obtained from 5 cases of 'pure' centrilobular emphysema. Number of alveoli* 220×10^6. *Alveolar surface area 62* m^2 (*105* cm^2/ml). *Total lung volume 6,500 ml*

Table 3
Panacinar destructive emphysema
(mean values in 11 cases)

Lung volume (ml)	8,000
Volume proportions of parenchyma:	
Alveoli	31
Ducts	12
Abnormal spaces	47
Tissue	8
Vessels	2
Number of alveoli (10^6)	96
Mean linear intercept (10^{-2} cm)	5·981
Area of air-tissue interface (m^2)	49 ($61\ cm^2$/ml)

surface is reduced but this reduction is not as striking as might be supposed because, in these cases, the lung volume is usually greatly increased.

Dilatation of air spaces without destruction of lung tissue: This occurs in compensatory emphysema and in conditions where there is partial bronchial obstruction such as asthma. The general architecture of the lung is perfectly preserved but all the air spaces are enlarged. At autopsy the lung appears over-inflated and, if there is bronchial obstruction, may fail to collapse on opening the pleural cavities. In these cases the mean linear intercept may provide the only reliable measurement of deviation from the normal. This is illustrated by a case of a man who had had a right pneumonectomy ten years before his death. The left lung was structurally normal but showed generalized over-distension of air space and the mean linear intercept was $4{\cdot}403 \times 10^{-2}$ cm.

In conclusion it must be emphasized that the measurements of parenchymal change in emphysema are of little value unless they are taken in conjunction with measurement of changes in the bronchi and pulmonary blood vessels. How much emphysema contributes to the disability of patients with chronic nonspecific lung disease is unknown and difficult to determine because so many cases show a mixed pathology. It is for this reason that intensive physiological and pathological study of pure forms of the disease is urgently needed.

REFERENCES

Campbell H & Tomkeieff S A (1952) *Nature (Lond.)* **170**, 117
Ciba Foundation Symposium (1959) *Thorax* **14**, 286
Dunnill M S
(1962) *Thorax* **17**, 320
(1964) *Thorax* **19**, 443
Fletcher C M (1968) In: Form and Function in the Human Lung. Ed. G Cumming & L B Hunt. Edinburgh; p 230
Reid L McA (1967) The Pathology of Emphysema. London; p 6
Short R H D (1950) *Phil. Trans. B* **235**, 35
Snider G L, Brody J S & Doctor LeR
(1962) *Amer. Rev. resp. Dis.* **85**, 666
Sweet H C, Wyatt J P, Fritsch A J & Kinsella P W
(1961) *Ann. intern. Med.* **55**, 565
Thurlbeck W M
(1963) *Amer. J. med. Sci.* **246**, 332
(1967) *Amer. Rev. resp. Dis.* **95**, 765
Weibel E R (1963) Morphometry of the Human Lung. Berlin; p 9
Weibel E R & Gomez D M (1962) *J. appl. Physiol.* **17**, 343
Weibel E R & Vidone R A (1961) *Amer. Rev. resp. Dis.* **84**, 856

Dr Gordon Cumming
(Department of Medicine, Queen Elizabeth Medical Centre, Edgbaston, Birmingham)

Disordered Respiratory Function in Emphysema

Normal respiration may be conveniently divided into four parts, which occur together but may be considered seriatim for simplicity.

The first part is that of gas transport down the airways to which the laws of viscous flow in branching tubes are applicable. The linear velocity of flow in the trachea is high, in excess of 100 cm/sec, but as the front of inspired gas passes into the lungs it slows progressively, since the cross-sectional area of the airways increases continuously as the alveolar sacs are approached. In the lobule supplied by the terminal bronchiole flow rates fall to less than 1 mm/sec and at this point linear velocity is no longer the dominant force producing molecular movement. The thermal kinetic energy now dominates, and thus gaseous diffusion laws are applicable.

Thus the second part of the respiratory process concerns the mixing of gases within the distal air spaces.

After inspired gas molecules have gained access to the alveolar spaces, the third phase occurs – that of transfer from the gas phase to the blood phase, which process again invokes the laws of diffusion, but this time across a phase boundary.

The fourth and final aspect of respiration concerns blood flow and principally concerns the manner in which blood is distributed by the pulmonary circulation. The principal determinants of this distribution are the anatomy of the vascular tree, the effects of gravity, and the fact that blood is a non-Newtonian fluid.

Thus the components of respiration may be listed as: gas transport, gas mixing, gas transfer and blood distribution, and we may consider how emphysema affects each in turn.

The emphysematous patient has difficulty in breathing out rapidly, and clearly this constitutes a defect in gas transport. The quantification of such a defect in terms of maximum flow rates, $FEV_{1\cdot0}$ and lung volumes permits some quantification of the extent of the defect. Since these results make a statement about the mechanical efficiency of ventilation, and may have many causes, over-interpretation of the results should be avoided.

In the normal subject one of the consequences of gas transport is regional distribution of ventilation, such that the ventilation of the dependent part of the lung is greater than that of the upper part, due in part to the effects of gravity. As