MAINLY ABOUT EMPHYSEMA OF THE LUNGS

A Study On Different Aspects of a Disease

By

Jean Rodger Nairn, M.B.,Ch.B.

Thesis submitted for the degree of Doctor of Medicine

in the University of Glasgow.

December, 1966.

D E D I C A T E D

to the

NAIRN FAMILY

and to the late

DR. SAMUEL JONES GEE

(1839-1911)

who was one of the
first physicians to
draw attention to the
difficulties encountered
in the diagnosis of emphysema

CONTENTS (Vol.I)

PREFACE

Emphysema is a common and disabling lung disease. It is not necessarily generalised in distribution but frequently appears to be predominant in the apices or in the bases.

A recently developed physiological method using a radioactive gas has made possible the study of regional lung function and well established techniques are available for assessing the overall distribution and exchange of respiratory gases. These, coupled with careful clinical and radiological methods, have been used in this study to identify and assess the effect of localised and generalised pulmonary emphysema. Comparison of these methods of examination in a number of patients suffering from emphysema comprises the main subject matter of this thesis. It is hoped that observations made in this way will assist the physician to a better understanding of the different forms of the disease and the resulting functional effect.

Chronic bronchitis cannot be ignored in this study as it frequently complicates emphysema or is complicated by it. The functional effects of bronchitis, like emphysema, are severe airways obstruction and an impairment of gas exchange within the lung. At present there is no radiological or clinical evidence that the effects of bronchitis are localised. It is difficult with present techniques to separate the effects of

emphysema from bronchitis when the two diseases occur together. Therefore, I have tried to evaluate regional and overall lung function in selected cases where there is bronchitis but no evidence of emphysema and emphysema but no bronchitis. By comparing the two groups I hoped to find the functional effects of these diseases separately.

As the aetiology of emphysema is unknown and the nature of the lesion destructive, physicians can only observe and try to prevent complicating infection. In some cases evident localisation of the disease attracts the possibility of surgical intervention. Removal or plication of the affected lung are procedures which are undertaken in this type of case. The criteria for selection of patients, the rationale of the venture and the outcome have not been established. I intend to consider these problems in the light of the results of studies done on a few patients before and after operation.

As there are several different aspects of this study each will be considered in a separate chapter with presentation of the relevant results and discussion. For convenience the tables, figures, appendix with all the data and bibliography are contained in a separate volume.

The work was done at the Institute of Diseases of the Chest and the Brompton Hospital, London, where I held an appointment as research assistant. Full acknowledgement of help and advice from colleagues is placed at the end of this volume.

HISTORICAL NOTES

It has been my privilege in the past year to have ready access to a formidable and interesting collection of historical material on emphysema and bronchitis. Due to this I have been most impressed by the clinical knowledge of these diseases displayed by the 18th and 19th century physicians. I propose to deal only with the early accounts in this chapter and intend to highlight some of the most interesting parts of my reading and those which have a bearing on the subject matter of the thesis.

René Théophile Hyacinthe Laennec (1781-1826) undoubtedly gave the most complete and clear clinical and pathological description of emphysema in the monograph "De l'Auscultation Médiate". He was the first to distinguish between the inter-lobular and vesicular forms of the disease and established it as a clinical and morbid anatomical entity. He described the macroscopic appearances of the lung and compares the different sizes of distended alveoli in the following way "celle du plus grand nombre égale ou surpasse un peu le volume d'un grain de millet; quelques-une atteignent celui d'un grain de chènevis, d'un noyau de cerise ou même d'une fève de haricot ..... "

He stated also that "emphysema may affect both lungs at the same time, one only, or part of one or both".

Contained in the four illustrative cases he described are three where the emphysema was distributed in the following manner - 1) "the great part of the right lung and the lower lobe of the left". 2) "the right lung and only part of the left". 3) "the whole of the left and the upper and middle part of the right".

Clinically he described dyspnoea as being the most striking feature and distinguished it from asthma by the sentence .... "In it the respiration is habitually impeded but is aggravated by occasional paroxysms which are quite irregular in their return or duration" .... In this way he also recognised the attacks of breathlessness from which a patient with emphysema frequently suffers.

He was cognisant also of the frequency of bronchitis accompanying emphysema and stated "In all the cases I have seen there was a slight degree of habitual cough with only slight mucous expectoration".

Laennec invented the stethoscope and described the auscultatory findings in the normal chest and in patients suffering from emphysema. He attributed the respiratory murmur to "the entrance of air into and its expulsion from, the air cells of the lungs" and not to conduction of sound from the larger bronchi through the substance of the lungs to the chest wall. He describes the breath sound in emphysema as "inaudible over the greater part of the chest, and very feeble in parts where it is audible". However, he "found it

difficult to account for the absence of the sound of respiration in a disease which consists essentially in dilatation of the air cells and in which consequently there exists more air than is usual in the lungs". He concluded that the bronchi may be temporarily obstructed and by doing so inferred the presence of "air trapping" as it is frequently referred to to-day.

The stethoscope was viewed in a dubious but now rather amusing light by Sir John Forbes, the translator of Laennec's work into English in 1821 thus:-

"That it will ever come into general use, not withstanding its value, I am extremely doubtful; because its beneficial application requires much time and gives a good deal of trouble both to the patient and the practitioner; and because its whole hue and character is foreign, and opposed to all our habits and associations. It must be confessed that there is something even ludicrous in the picture of a grave physician formally listening through a long tube applied to the patient's thorax, as if the disease within were a living being that could communicate its condition to the sense without. Besides there is in this method a sort of bold claim and pretension to certainty and precision of diagnosis which cannot at first sight, but be somewhat startling to a mind deeply versed in the knowledge and certainties of our art and to the calm and cautious philosophising to which the English

Physician is accustomed".

This is such a contrast to the situation to-day that it shows how very dangerous it is to venture prophetic opinions.

Sir John Forbes was a graduate of Aberdeen University who later studied surgery in Edinburgh. He and C.J.B. Williams were the first consulting physicians appointed at the Brompton Hospital in 1846. The latter was a graduate of the University of Edinburgh and had worked with Laennec for 15 months earlier in his career when he sketched the great man (fig. 1). In his autobiography he says that although he had a high regard for Laennec .. "In hearing his attempted explanations of several of the phenomena of auscultation, I soon found that his knowledge of accoustics was by no means profound: and clever as he had been in teaching the signs empirically, he was not equally successful in explaining them rationally ..". Williams later wrote a book on the .. "Rational Exposition of the Physical signs of Diseases of the Chest" (1835) to help the understanding of auscultation. In it he described the properties and mode of conduction of sound waves, and observed .. "There is a considerable difference in the intensity of the sound of respiration in different individuals; and this depends partly on the thickness of the parietes of the chest but principally on the degree of activity of the respiratory function". By the term "respiratory function" I think Dr. Williams referred to ventilation, and if so I find this comment

particularly interesting as I intend to compare the intensity of sound of respiration in parts of the lung to the underlying ventilation.

Before Laennec there were several morbid anatomical descriptions of emphysema of the lungs which deserve some mention. Bonet (1679), Floyer (1717), Ruysch (1727) and Morgagni (1761) outline pathological appearances which may well have been emphysema but it is confused with asthma, simple distension and emphysema in its subcutaneous form. Two English descriptions are of particular interest. Matthew Baillie, the nephew of John and William Hunter, wrote the first text book on morbid anatomy published in Britain in 1793. He had inherited a large number of specimens from John Hunter and says in the introduction that it gave him "more than ordinary opportunities for examining morbid structures". In this book under the subheading "Air cells of the lungs enlarged" he writes "The lungs are sometimes, though I believe rarely, formed into pretty large cells so as to resemble the lungs of an amphibious animal. Of this I have seen three instances". An example of what he is referring to is contained in a volume of illustrations published at the same time which were drawn by William Clift. Although I have not seen the original plate, the lung is evidently severely affected by emphysema. An added interest is that the lung may be that of Dr. Samuel Johnson, the

literary gentleman (Bishop, 1959) whose various maladies throughout life can be fitted into a clinical picture of emphysema (Larson, 1963).

Even earlier - in 1764, Sir William Watson, a Scotsman, who is mainly remembered for his contributions to electricity and who gave the Duke of Cumberland an electric shock from the point of the sword he used at Culloden, gave "an account of what happened on opening the body of an asthmatic person" to the Royal Society. Although the lungs were described as being "enormously distended with air which no pressure could force back through the wind pipe ..... in several parts the air had formed large bladders", as the patient was only 28 years old and had a short history of only two months of breathlessness I think it is doubtful that this is emphysema but may have been distension due to status asthmaticus.

After Laennec there was a great deal of discussion between Dr. William Tennant Gairdner (1850) and Sir William Jenner (1871) about the aetiology of the disease nearly all of which is speculation. Gairdner was the first to consider bronchitis in relation to the formation of emphysema and postulated that the combination of bronchial obstruction and increased inspiratory pressure was responsible for alveolar dilatation. He described 40 cases of emphysema and in every case there was "some mode or form of condensation of the pulmonary tissue", (i.e. evidence of infection). Edward

Greenhow (1878) agreed with Gairdner and wrote "Emphysema sometimes precedes bronchitis, at other times is concurrent and at others is part of a bronchitic complication".

Another acute clinical observer in that era was Samuel Jones Gee (1839-1911). He was a general physician who published a collection of papers entitled "Medical Lectures and Aphorisms". He had an outstanding gift for succinct description of clinical pictures and dilemmas without getting lost in a morass of detail and current arguments.

He describes the progressive dyspnoea of emphysema thus:- "A man about middle life begins to suffer from slight shortness of breath on exertion; he is short of breath, that is to say the patient cannot inspire so much breath as he seems to need, in a sense like that in which we say that a man is short of money. His breathlessness increases slowly and insidiously until his breath is always short; but no signs of dyspnoea, no laborious or extraordinary movements of respiration, are apparent so long as he is at rest, not until he makes some effort such as that of talking or moving the body. In cases still worse dyspnoea persists even when the patient is at rest. The dyspnoea of emphysema is liable to paroxysms in which the shortness of breath becomes very distressing. These paroxysms are induced by any effort, such as hurrying or even no more than straining at stool, raising a foot to enter a carriage or lifting an arm to shave. A

paroxysm will sometimes occur during sleep and will suddenly awake the patient or will sometimes occur just as he is falling off to sleep. The mere taking of food may be enough to provoke an attack - so will the temperature of air breathed such as occurs on leaving a hot room."

This description could not be improved upon to-day and shows how carefully he must have observed his patients and listened to their histories. Only last year Professor Comroe (1966) put forward a plea to describe the symptom of breathlessness faithfully in the subject's or patient's own words and not invariably call it "exertional dyspnoea". Although early descriptions of symptomatology are at times wordy they compare very favourably with the terse and trite phases employed to-day in hospital records.

Dr. Gee was also aware of the clinical dilemma presented by the patient with emphysema who also has bronchitis and describes it well .... "We are met at the outset by the fact that most of these patients suffer from manifest bronchitis also. These complex cases are not suitable for our present purpose; we cannot disentangle the symptoms of the two diseases so as to be able to say - this is due to emphysema and this to bronchitis; whilst as to the physical signs of emphysema there are none, except in advanced cases, which are always complicated with bronchitis. If we require instances of emphysema quite unattended by catarrh, such instances are not to be found ..."

I intend in this thesis to attempt to disentangle the functional aspects of the two diseases but had the greatest difficulty securing patients with emphysema "quite unattended by catarrh". Indeed, Dr. Gee may well be right and agree with Thurlbeck and Angus (1963) who found that the pathological changes in the bronchial mucosa were present in all patients with emphysema. Some authorities now believe there is such a thing as primary emphysema where there is no bronchitis (Seebohm and Bedell, 1963; Scadding, 1963).

To illustrate the incidence of emphysema Dr. Gee quoted the figures at St. Bartholomew's Hospital from 1894-1897. In 9,928 admissions, 165 or 1·66% were clinically believed to have emphysema but of 1,363 autopsies performed in that period 154 (11·3%) showed evidence of pathological emphysema. My reaction to these figures is that clinical emphysema was as difficult to diagnose then as it is now. It must also be borne in mind that the clinical diagnosis was unaided by radiology and the pathological examinations conducted on uninflated specimens of lung.

The word "bronchitis" was used first by Dr. Charles Badham in 1814. His definition of the disease was:- ..."it is an inflammatory affection of the secreting membrane which lines the bronchial tubes; it is liable to end like other inflammations, in the production of purulent fluid, or more frequently in an excess of the natural secretion of the parts; and death in either case may be occasioned by the

mechanical obstruction which ensues, or by the impediment produced to the reciprocal operations of the air and of the blood upon each other; a state of infinite hazard, from which scarcely any patient is found to recover".

This is a clear description of increased bronchial mucous production and of the ventilation/perfusion disturbance which is marked in bronchitis and is the physiological concept which may underly eventual cardiorespiratory failure.

Badham described the morning cough in chronic bronchitis with attending bouts of paroxysmal cough as the chest is "relieved of the secretion which has accumulated during the night". This is now used as one of the basic requirements for the diagnosis of bronchitis (Medical Research Council, 1960).

Before Badham Hippocrates described pectoral catarrhs and noted the tendency to end in suppuration. Aetius (c 450) and Actuarius (c.1300) also described excess secretion of the bronchial passages which they referred to as "confluence of humours".

Samuel Gee in his usual sensible fashion thought that bronchitis was "the commonest disorder at all ages in the English people in all ranks and conditions in life", an observation which stands very firm to-day. He remarked on the paucity of attention bronchitis attracts on a post mortem table, "where only the severe forms of the disease are recognised without much more minute examination of the bronchial tubes

than they usually receive". This is a point well taken and it is only recently that the pathological microscopic picture of the goblet cells and mucosa of the bronchi has been investigated by Reid (1954) so that less severe forms of bronchitis may be recognised. As for the aetiology of the disorder Dr. Gee remarked .."There are no more potent causes of chronic bronchitis than alcohol and tobacco".

In conclusion it can therefore be said that the clinical and pathological picture of emphysema was well recognised and the symptoms and course of bronchitis defined before 1900. The frequency of occurrence of these diseases separately and together had been noted and the dilemma of separating their clinical effects was quite well known. The aetiology had been discussed. Laennec had described the generalised and more localised forms of emphysema and the problem of diagnosing emphysema during life had been well stated.

These diseases still occur frequently to-day and many of the problems encountered by the 18th and 19th century physicians still exist. In the intervening years interest in these disorders perhaps lagged but during the last 20 years a publication explosion has occurred which seems to increase in intensity and originates from epidemiologists, pathologists, physicians, surgeons and physiologists alike. The modern approach to medicine is more technical and

scientific but clinical observation remains very important. There is a striking contrast between the medical paper of to-day and that of previous centuries. Facts, figures, graphs and statistics are required to prove a point but these are not always applied in a meaningful way to biological problems in modern medicine. Indeed frequently Sir John Forbes' criticism of auscultation can be applied to the conclusions as being a "bold claim and pretension to certainty .....". In his time illustrative cases and the opinion of an experienced physician were adequate grounds for medical knowledge. I think the ideal situation lies between these two extremes and hope that the following thesis will be in keeping with this.

INTRODUCTION

The Definition of Emphysema.

In recent years it became evident that the term 'emphysema' was being used loosely in clinical medicine by physicians, physiologists and radiologists to describe a type of respiratory function disturbance so that the diagnosis bore little constant relation to the pathological findings. Disturbed by this situation a group of specialists in these fields met in 1958 at the Ciba Guest Symposium. They defined emphysema as "a condition of the lung characterised by an increase beyond the normal in the size of the air spaces distal to the terminal bronchioles, with destructive changes in their walls". They further recommended that "clinical use of the word emphysema should only be regarded as presumptive evidence and should only be applied to those cases in which in the observers opinion the defined anatomical changes of emphysema can confidently be asserted to be present". These, or very similar, definitions have gained wide acceptance, (American Thoracic Society, 1962; World Health Organisation, 1961). This symposium was an important milestone partly because it encouraged comparison between the findings during life with morbid anatomy and partly because it indisputably defined emphysema in pathological terms.

Certain pathological types of emphysema are recognised according to the characteristic distribution of the increased

size of the air spaces within the acinus (which is the respiratory unit distal to the terminal bronchioles and includes the respiratory bronchioli alveolar ducts and alveoli). These are: panacinar, periacinar, centriacinar (or centrilobular) and irregular. Not all types of emphysema are necessarily associated during life with disability due to breathlessness and impairment in respiratory function with airways obstruction. By defining the disease according to the size of the air spaces, emphysema now includes a variety of diseases of different aetiology. To illustrate this and to distinguish those types of emphysema with airways obstruction from those without Reid (1965) classified emphysema as in fig. 2.

Although Dr. Reid believes that centriacinar emphysema does not cause air trapping, airways obstruction or disability; there are some who would disagree with her, (Sweet, Wyatt, Fritsch and Kinsella (1961); Bates (1965); Cournand (1965).

It is with emphysema associated with irreversible airways obstruction that this thesis is mainly concerned; in particular primary or essential emphysema and emphysema associated with chronic bronchitis (see fig. 2). Emphysema as found in unilateral transradiancy has also been studied but will be called "unilateral transradiancy" hereafter to distinguish it from the other forms.

The Clinical Definition of Emphysema.

The presumptive clinical diagnosis of emphysema is clearly difficult if anatomical changes are to be asserted to the present. There are only two means of observing the anatomy of the lung during life, one is during a surgical operation or with a biopsy specimen, and the other is by radiology. Surgically, only the exterior of the lung can be seen and the distribution of emphysematous bullae within can only be guessed. A biopsy reveals the microscopic structure of a very small sample of uninflated lung tissue which may be a poor representation of the whole and indeed may be wholly misleading both as to the type of emphysema present and its distribution. Radiology offers a complete view of the lungs, the enclosing chest wall and diaphragm.

Many observations separately, or in combination, have been used to diagnose emphysema on the radiograph by different authorities. Among those under consideration have been the flattening and lowering of the diaphragm, the movement of the diaphragm between inspiration and expiration, the narrow vertical heart, the dilatation of the pulmonary artery, the size of the retrosternal translucent zone, the widening of the rib spaces, hilar pulsations, mid-lung vessel size and peripheral vascular loss.

Whitfield, Smith, Richards, Waterhouse and Arnott (1951) found that "flattening, depression and reduced expiratory

diaphragm excursion was good radiological evidence of emphysema" but did not compare these findings with pathology. Laws and Heard (1962) concluded that the observation of "straightening and stretching and a premature reduction in calibre of the 3rd. to 5th division branches of the pulmonary artery was the most reliable criterion for the diagnosis of emphysema radiologically". By contrast, Sutinen, Christoforedis, Klugh and Pratt (1965) required two of the following four observations to be present, viz. flatness of diaphragm, lowering of diaphragm, deep retrosternal space and irregularity of translucency.

Simon (1964) described three criteria for the diagnosis of emphysema namely excess of air in the lungs, cardiovascular changes and bullae. Contained in the first two of these criteria are a combination of objective measurements and subjective observations in the manner shown in fig. 3. The diagnosis of 'generalised' or 'widespread' emphysema was made when all three or only the first two of these criteria were fulfilled. "Localised" emphysema was said to be present when bullae (localised, relatively transradiant areas with few or no vessel shadows) were present but none of the other criteria.

To verify the different criteria described the pathological findings have been compared with the radiological diagnosis, (Laws and Heard, 1962; Nicklaus, Stowell, Christiansen and Renzetti, 1966; Reid and Millard, 1964). Only the latter group

typed the emphysema, graded the size of the "holes" and described the distribution of these 'holes'. They reported that grades 3 and 4 panacinar emphysema were present in at least $\frac{1}{2}$ to $\frac{2}{3}$ of the lung slice taken through the hilum if 'generalised' emphysema was diagnosed radiologically using Simon's (1964) criteria. Grade 3 emphysema was found to be present in the affected lobe of all the 'localised' radiological group. With this evidence I have accepted the presumptive clinical diagnosis of emphysema on radiological grounds using these criteria; it is possible by doing so to fulfil the Ciba Symposium definition.

It is my intention to investigate the functional picture in 'generalised' and 'localised' emphysema. In addition to define the relationship between lung function tests and some of the separate radiological findings portrayed in figure 3. The general picture of structure and function during life in emphysema will then be more complete and a basis may emerge for a clearer functional evaluation of an individual chest radiograph.

Symptoms and Signs in Emphysema.

Dr. Gee remarked "as for the clinical signs of emphysema there are none". Christie (1944) presented evidence that the symptom of breathlessness on exertion was present in 78% of proved pathological cases of emphysema but the physical

signs of emphysema displayed "in a neat array" in textbooks were unreliable. In particular, the barrel chest phenomenon is not necessarily associated with emphysema (Cabot, 1927; Davidson, 1936). Laennec, in advocating the use of the stethoscope, advised that the new art of auscultation should be learnt in hospital where the morbid anatomical changes which produce the faint breath sounds typical of emphysema could be observed and confirmed. Auscultation is now an accepted mode of examination by every physician in this country and it would be interesting to know how the intensity of the breath sounds heard compare with the ventilation of the underlying lung. This I have attempted to do as an enquiry into the validity of the observation of the intensity of the breath sounds in emphysema.

Lung Function in Emphysema.

Studies of lung function have been done for many years by different investigators (Hutchinson, 1846; Meakins and Davies, 1925). Measurement at the mouth of inspiratory and expiratory flow rates, static lung volumes, diffusing capacity for carbon monoxide, mixing efficiency and airways resistance are now commonly used procedures in hospital practice. It is known that in emphysema there are poor expiratory flow rates, usually a low vital capacity, an increased residual volume and functional residual capacity, a low diffusing capacity, poor mixing efficiency and a high airways resistance (Christie, 1944; Baldwin, Cournand and Richards, 1949; Forster, 1957).

The airways obstruction usually affects most of the lower airways and is irreversible by bronchodilator therapy. Partial closure of the airways results in uneven distribution of inspired gases and uneven ventilation to blood flow ratios within the lungs, which may give rise to arterial hypoxaemia, hypercarbia, and respiratory insufficiency.

The Localisation of Function.

Macroscopically there often appears to be a tendency for the air spaces in emphysema to be more numerous in one part of the lung than in others, (Laennec, 1819; Anderson & Dunnill, 1964). Until recently the only methods available for the physician to discern the distribution of emphysema during life were the comparison in the different parts of the chest of the intensity of the breath sounds, the radiological appearance of the mid-lung vessels and in some centres bronchospirometry.

The modern technique of bronchospirometry was introduced by Carlens (1949) who used a double lumen intrabronchial catheter to measure separately the ventilation and oxygen uptake of the lungs. In 1955 Mattson and Carlens with a triple lumen catheter were able to make similar measurements from the right upper lobe separately from the remainder of the right lung. Smaller, and consequently easier to introduce, less uncomfortable catheters have also been used (Martin, Cline and Marshall, 1953; Martin, Marshall and Cline, 1953).

These made possible the study of ventilation and blood flow in every lobe of the lung if used in conjunction with rapid gas analytical techniques (Martin and Young, 1957; West and Hugh-Jones, 1959, 1961).

Surface counting of radioactive gases, in contrast to gas sampling methods, require no intubation and enable the topographical distribution of ventilation and perfusion to be defined without the dictation of the exigencies of the bronchial tree. This is preferable as the perfusion of the lung has been shown to increase from top to bottom and is influenced by gravity (West, 1962; West, 1966). Soluble oxygen ^{15} (O^{15}) and oxygen labelled carbon dioxide ($C^{15}O_2$) have been used. The count rate after a single inspiration of these gases is proportional to the ventilation and volume of the counting field and the clearance rate of the soluble gases during breathholding measures regional blood flow, (West, Holland, Dollery and Matthews, 1962). O^{15} is prepared in a cyclotron and has a half life of only 2 minutes which limits its clinical application.

The use of poorly soluble ^{133}Xenon (^{133}Xe) in measuring regional ventilation was pioneered by Knipping, Bolt, Venrath, Valentin, Ludes and Endler, (1955). Later, the method was modified to measure regional perfusion also by Ball, Stewart, Newsham and Bates (1962). ^{133}Xe has a longer half life than

O^{15} or $C^{15}O_2$, and being less soluble can be used with a rebreathing procedure so that dynamic events of ventilation can be observed under more physiological circumstances than during breathholding.

Bronchospirometry, lobar gas flow and radioisotope techniques have been used for extracting basic physiological information. Radioisotope studies have also been reported in a large variety of localised lung conditions such as cysts, fibrosis, bronchiectasis, neoplasms, pleural effusions, unilateral emphysema and pulmonary emboli (Ball, Stewart, Newsham and Bates, 1962; Dollery and Hugh-Jones, 1963). Only one group (Bentivoglio, Beerel, Stewart, Bryan, Ball and Bates, 1963) have studied emphysema in more than a few patients.

Measurement of regional lung function has been done in this study with ^{133}Xe in an attempt to be more precise about the localisation of emphysema and to lead to a better understanding in the interpretation of the clinical and radiological features.

Regional and Total Function.

Essentially, the function of the lungs is to closely associate blood and gas in such a way as to allow complete arterialization of venous blood by exchange of oxygen and carbon dioxide. It depends on the ability of approximately 300 million alveoli to do this, and on the air conducting passages to convey air afficiently to the gas exchanging area. In the healthy lung these alveoli are ventilated and perfused

individually in appropriate amounts so that the summated gas exchange results in normal arterial blood gas tensions.

The ventilation/perfusion concept has been known for 50 years and theoretically and qualitatively it has not changed since Haldane, 1922; Krogh and Lindhard, 1917, wrote clearly on the subject. However, the quantitative approach which requires a prediction of the gas composition of the alveolus for any given ventilation and perfusion composition, originated in recent years, (Riley and Cournand, 1949; Riley and Cournand, 1951; Rahn and Fahri, 1965). This presents a great challenge due to the number of alveoli in the lung and the spectrum of ventilation and perfusion (V/Q) ratios in them. In addition, West (1962) has shown a five-fold increase in V/Q ratios from the top to the bottom of the normal upright lung mainly due to a nine-fold increase in perfusion topographically. These differences between ventilation and perfusion are reduced with exercise so that there is a more even distribution from top to bottom of the lung. Regional differences in gas exchange and arterial blood gas tensions at rest under these circumstances is unavoidable in normal subjects, but overall gas exchange is surprisingly unaffected.

In the emphysematous lung the situation is even more complicated. The large underventilated air spaces have a very low V/Q ratio (Briscoe and Cournand, 1962). They are under

perfused in relation to volume and over perfused in relation to ventilation. Therefore, in emphysema there is an even wider spectrum of $\dot{V}/\dot{Q}$ ratios due to these spaces than in normal subjects, while the topographical differences exist as well.

Surface counting radioactive gas techniques measure the summated ventilation and perfusion of an unknown quantity of alveoli which probably amounts to millions in each region surveyed. Some of these will have a high $\dot{V}/\dot{Q}$ ratio and others a very low value. To compute the contributions of these separate alveoli to total gas exchange topographically in the presence of emphysema presents an insurmountable problem at present. However, it is possible to identify regional dysfunction and on basic principles it would seem that total gas exchange is influenced in emphysema by the amount of lung involved.

In this study I intend to consider regional patterns of dysfunction in patients with emphysema side by side with overall lung function and gas exchange. In this way it is hoped that some relationship between the two will be displayed and if so some light may be thrown on the difference in function shown by different patients with different distribution of emphysema.

Cause, Course and Treatment of Emphysema.

The aetiology of emphysema remains unknown. The many attempts which have been made to produce the pathological

change experimentally have been reviewed by Eiseman, Petty and Siden (1959) but all failed to produce much more than acute distension or overinflation of the lung. There is a possibility that primary emphysema may be determined by genetic factors and the familial occurrence of the disease has been demonstrated in a review by Hurst (1959). Until recently no one genetic protein or elastic tissue factor has been identified in an affected family or even in an affected individual. In 1964 Eriksson described a family with a previously unknown type of dysproteinaemia in which there was a marked reduction in one of the main components of the electrophoretic fraction α_1 antitrypsin. This abnormality appears to be associated with severe primary pulmonary emphysema but there is insufficient evidence at present to be absolutely conclusive.

The course and progression of emphysema has not been studied intensively to my knowledge, with the notable exception of the studies of Simpson (1958, and unpublished data). Although an insidious onset and gradual progression to complete disability appears to be the case, the radiological appearance is seldom seen to change in serial radiographs, and has been reported to remain the same for 10 years (Simon and Medvei, 1962; Simon personal communication).

Thus we are faced with a disabling disorder in which the cause and course is unknown. Drugs, such as bronchodilators

and cortico-steroids, as a rule give little relief to the patient who is acutely dyspnoeic. Apart from prevention or prompt treatment of infections, should they occur, the physician can do little. It is in this situation that surgery has been considered and any alleviation of the patient's symptoms under these circumstances seems acceptable treatment.

It has been postulated that removal or plication of localised relatively avascular air containing spaces in the lungs of these patients may allow more normal lung to expand to fill their place so that the relaxation pressure in expiration will be greater and there will be less tendency for airways to collapse and air flow obstruction will be relieved, (Campbell, 1958; Hugh-Jones, 1963). In addition, the 'wasted' ventilation of poorly perfused lung substance will be reduced.

Unfortunately, after these procedures surgeons on the whole seem to be content with a subjective assessment only and there is a lack of convincing objective evidence that surgery is of any assistance in emphysema, (Knudson and Gaensler, 1963). Few functional studies have been done and the criteria for selection of patients for surgical treatment are not yet evident. So I have attempted to consider these matters and have studied some patients post operatively.

Chronic Bronchitis.

Chronic bronchitis, the disease described by Badham in 1819 has lately been redefined as "a condition of recurrent

excessive mucous secretion of the bronchial tree" (Ciba Guest Symposium, 1959). The pathological findings of mucous gland hypertrophy and hyperplasia of the mucous producing elements of the bronchial tree have been described by Reid (1954, 1960). A statistically significant relationship exists between this change and the incidence of smoking or productive cough (Field, Davey, Reid and Roe, 1966) but there is some degree of overlap between the pathological change found in patients who have a productive cough and those who have not (Thurlbeck and Angus, 1963). These changes cannot be seen in a bronchial biopsy and there is no clinical sign which pertains only to bronchitis, so chronic bronchitis is diagnosed during life by historical means and by observation of the sputum produced. It has been stated that any patient with a productive cough which occurs every day for more than 3 months in the year for more than 2 years is suffering from chronic bronchitis, (Medical Research Council, 1960). Defined in this way breathlessness or airways obstruction is not necessarily present. On the other hand, chronic bronchitis alone can be a fatal disease withvery severe airways obstruction and cardio-respiratory failure (Badham, 1814; Simpson, Heard and Lews, 1963). To distinguish this from a simple increase in volume of mucoid bronchial secretion sufficient to cause expectoration, the Medical Research Council Committee on the Aetiology of Chronic Bronchitis (1965) have suggested that when chronic bronchitis is accompanied by

persistent widespread narrowing of the intrapulmonary airways causing increased resistance to air flow it should be called chronic obstructive bronchitis.

Chronic Bronchitis and Emphysema.

As earlier observers had noted chronic bronchitis frequently occurs in a patient with emphysema. In such a patient the clinical dilemma so beautifully stated by Dr. Gee of distinguishing between the signs of the two diseases confronts the physician and the separation of functional effects challenges the physiologist. Because of this throughout this study of patients with emphysema, particular attention has been devoted to the presence or absence of chronic bronchitis. In addition, severely disabled selected patients who suffer from either one or other of these diseases have been compared in the hope that any clinical and functional differences between them will be exaggerated. This has been done before by Fletcher, Hugh-Jones, McNicol and Pride, 1963, and their work will be compared with the data presented.

Unilateral transradiancy:- The apparent localisation of the larger air spaces in this disorder and the different possible aetiology distinguishes it from other forms of emphysema. For these reasons it was particularly studied and is considered separately.

MATERIAL AND METHODS

SELECTION OF PATIENTS

Four groups of patients were studied. They were selected in the following manner,

Group I:- Fifty patients with definite radiological evidence of localised or generalised emphysema using the criteria of Simon (1964). Contained in this group were 14 patients who later had a thoracotomy for emphysematous bullae. They will be called Group Ia.

Group II:- Eight patients with chronic obstructive bronchitis, (Medical Research Council Committee on the Aetiology of Chronic Bronchitis, 1965; Scadding, 1966) who had no radiological evidence of emphysema.

Group III:- Seven patients with the clinical and radiological syndrome of unilateral transradiancy described by Macleod (1954).

None of the patients were studied if there was any evidence of infection in the sputa macroscopically, signs of overt heart failure or reversibility of airways obstruction after isoprenaline inhalation.

The patients in Group Ia were studied on two different occasions - before and 6 months after surgical treatment.

CLINICAL INFORMATION

The history, with particular reference to cough, sputum and breathlessness, was obtained by one observer using a standardised questionnaire (Medical Research Council, 1960) with additional questions about previous history (Fletcher, Hugh-Jones, McNicol and Pride, 1963). The symptoms were graded according to the recommendations of the questionnaire. The form of these questions is in Appendix I.

For the purposes of this study the diagnosis of chronic bronchitis was accepted on the basis of a history of productive cough for more than 2 years, occurring for more than 3 months in the year either during the day or in the morning or at both times.

The age, height and weight of each patient was noted.

The intensity of the breath sounds was recorded by two observers (J.R. Nairn and M. Turner-Warwick) with the stethoscope placed anteriorly and posteriorly on the chest wall over the positions later described as being covered by the scintillation counters corresponding to the upper, middle and lower zones of each lung. The observations were graded in the following way:-

Grade 0 - No breath sounds.

1 - Very weak breath sounds.

2 - Moderate breath sounds.

3 - Normal, good breath sounds.

RADIOLOGY.

A pair of postero-anterior chest radiographs were taken in full inspiration and after full expiration in each patient. The cassette was in a fixed position and the patient was not allowed to move except for the respiratory manoeuvre while the films were taken. Bilateral lateral multisection tomograms and a lateral film were also taken.

Dr. George Simon examined these radiographs in ignorance of the clinical, physiological and surgical findings and recorded the following observations and measurements.

Diaphragm

a. The shape of each dome, i.e. flat or curved.

b. The level, i.e. number of anterior ribs visible above the middle of the right hemidiaphragm on the inspiration film.

c. The movement in cms. of each dome was measured as the difference between the distance from the lower margin of each of the inspiration and expiration films to the middle of each hemidiaphragm (see fig. 4). The sum of the movement of both hemidiaphragms is referred to as diaphragm movement (D.M.) unless otherwise stated.

Heart and Main Vessels.

a. The transverse diameter of heart in cms., (see fig. 4).

b. The transhilar diameter in cms. This measurement is made from the point where the upper lobe vein meets the

descending artery on each side, (see fig. 4).

c. The size of main pulmonary artery, i.e. dilated or normal.

d. The size of hilar vessels, i.e. dilated or normal.

Pulmonary Vessels.

a. The size of the mid-lung vessels in the upper, middle and lower zones of each lung field, i.e. dilated, normal or small in the position shown in fig. 4 .

b. Vessel loss in each zone, i.e. present or absent.

Bullae - These were noted to be present only if clearly demarcated by a surrounding hairline.

a. The location in lobe/segment.

b. The size of diameter in cms. antero/posteriorly and laterally.

Compression of lung

a. The crowding of vessels, i.e. absent or present.

b. Fissure displacement, i.e. absent or present.

Retrosternal translucent zone.

a. The depth (cms.) - This measurement is made "at a point on the ascending aorta which can usually be selected with sufficient fairness to make results reliable"(Simon, 1964).

b. The downward extension (cms.) - This is the distance between the anterior projection of the diaphragm and the lowest extension of the retrosternal translucent area.

Both these measurements are done on the lateral film in the positions shown in fig. 4.

The normal values in most cases for the measurements made are shown below (Simon, 1964).

Level of Diaphragm 6 or $6\frac{1}{2}$ anterior ribs

Movement of each hemidiaphragm 3 cms. or more

Transverse diameter of heart 11·5 cms.

Retrosternal translucent zone. Depth $<$ 3 cms.

Downward extension $>$ 3 cms.

LUNG FUNCTION TESTS

The forced expired volume in one second ($F.E.V._1$) and the forced vital capacity (F.V.C.) were measured in ml. on a fast recording spirometer with a plastic bell. The results are given at body temperature and pressure saturated with water vapour (B.T.P.S.).

The vital capacity (V.C.), functional residual capacity (F.R.C.), residual volume (R.V.) and the total lung capacity (T.L.C.) were measured in litres using the closed circuit helium method (McMichael, 1939). All lung volumes were recorded at B.T.P.S.

The diffusing capacity of the lungs for carbon monoxide ($D_{L_{CO}}$) was measured in ml. CO per minute per mm.Hg. by

the steady state technique with end tidal sampling described by Bates, Boucot and Dormer (1955). This test was performed at rest with the patient seated and again during stepping exercise in the manner described by McNamara, Prime and Sinclair (1959). The minute ventilation at rest and during exercise were recorded and the percentage extraction of carbon monoxide at rest was calculated.

The airways resistance (A.R.) in cms.H_2O/litre/second and the lung volume (L.V.) in litres during panting were measured with the patient seated in a total body plethysmograph by the method described by Dubois, Botelho and Comroe, 1956. The airway conductance which is the reciprocal of airways resistance was calculated only in patients in Group III.

As these techniques are standard and have been well described in the literature no further description seems necessary.

MEASUREMENT OF ARTERIAL BLOOD GASES.

Arterial blood was drawn from the brachial artery in the antecubital fossa under local anaesthesia with the patient lying on a couch at rest breathing air. Another sample was taken within one minute after completion of a 3-minute step test (Hugh-Jones, 1952). Some breathless patients were unable to perform any exercise and some others could not continue for 3 minutes. The amount of work done

during stepping was calculated in the following way:-

$$\text{Work done (Kgm./min)} = \frac{n \times h \times Wt.}{86{\cdot}81}$$

Where n = The number of steps per minute

h = height of step in inches

Wt.= weight of patient in lbs.

During withdrawal of the resting blood sample the expired gas was collected in a previously evacuated Douglas bag and subsequently analysed for carbon dioxide and oxygen content on a Haldane apparatus (Haldane and Graham, 1935). The gas collection was continued for 5 minutes during which the frequency of breathing was noted and the total volume measured with a previously calibrated Wright anemometer.

The measurement of arterial blood oxygen tension (Pa_{O_2}) carbon dioxide tension (Pa_{CO_2}) and pH were done within 2 minutes of blood withdrawal using oxygen, carbon dioxide and pH electrodes respectively which were contained in the one temperature controlled water bath designed in the department (see Fig. 5). Fluids equilibrated with different gas contents which are used to calibrate the electrodes are also contained in the bath. The calibrating fluids have direct access to the electrodes through sleeve valves. The temperature of the bath was kept constant at 38°C. (± ·02°C.). A Stuart Turner, No. 10 electrically operated centrifugal pump ensured

constant and complete water circulation and a supply of air equilibrated water in the bath itself. The electrodes were connected through a switch box to a Vibron pH meter (33-B and C-33-B) supplied by the Electronic Instruments Company Limited. All readings were from the same 100 millivolt scale.

The oxygen electrode was an unstirred modified Clark type. It is shown in diagrammatic form in fig. 6. This instrument was made in the department to give a sufficiently high output voltage to record on the 100 milli volt scale available. A small multiple cathode which consisted of 25 pieces ·001" diameter platinum wire made this possible. The anode made of 6 cms. of ·01" silver wire was wound round the 3·5 mm. outside diameter soda glass tube which contained the cathode. A low permeability membrane of polyvinyladine (Saran Wrap) was used between the sample and the cathode. The nature of the membrane and the small cathode limited the position of the diffusion gradient of the gases within the membrane so that stirring was not required. The electrode was calibrated just before use with air equilibrated water at 38°C., air, and a mixture of one part air and one part 100% nitrogen. These points plotted on linear graph paper against the relevant oxygen tension gave the slope of the electrode. The intercept indicated the residual current of the electrode and should

not exceed 1% of the air reading.

The carbon dioxide electrode was a Severinghaus type (1960). It operated on the principle that the pH of a sodium bicarbonate solution varies in a predictable manner with the carbon dioxide tension with which it is equilibrated. The electrode is shown in fig. 7. Two membranes were used: an inner membrane of woven fibreglass, which provided a thin but stable layer of sodium bicarbonate solution in contact with the glass electrode, and an outer membrane of ·001" Teflon, which allowed the rapid passage of carbon dioxide to the bicarbonate layer. A calomel reference electrode was incorporated in the assembly. The response time of this system was 70 seconds. The electrode was calibrated with 5% CO_2 and 10% CO_2 equilibrated distilled water from the tubes in the heated water bath. The CO_2 contents of the gases used for equilibration were measured on the Haldane apparatus.

The pH electrode was a replaceable capillary electrode supplied by Electronic Instruments Company Limited (S.H.H. 33) with a response time of 1 minute. It is shown in fig. 8. Buffers of 6·840 and 7·384 were used in calibration.

Calculations:- With the arterial blood gas tensions and the results of analysis of expired gas several relevant values can be calculated.

Using the fractional concentration of expired CO_2 and O_2 and Dalton's Law the respiratory exchange value (R) was calculated according to the equation:-

$$R = \frac{F_{E_{CO_2}}}{(F_{E_{N_2}} \times 0.265) - F_{E_{O_2}}}$$ (Douglas and Priestley.1948).

where $F_{E_{CO_2}}$ is the fractional concentration of carbon dioxide in expired gas

$F_{E_{O_2}}$ is the fractional concentration of oxygen in expired gas

and $F_{E_{N_2}}$ is the calculated fractional concentration of nitrogen in expired gas.

The alveolar oxygen tension $P_{A_{O_2}}$ in mm. Hg. was calculated using the alveolar air equation (Comroe, Forster, Dubois, Briscoe and Carlsen, 1964):-

$$P_{A_{O_2}} = P_{I_{O_2}} - P_{a_{CO_2}} \left(F_{I_{O_2}} + \frac{I - F_{I_{O_2}}}{R}\right)$$

where $P_{I_{O_2}}$ = partial pressure of O_2 in mm.Hg. of inspired air

$F_{I_{O_2}}$ = fractional concentration of O_2 in inspired air.

The alveolar-arterial oxygen gradient $(P_{A_{O_2}} - P_{a_{O_2}})$ was calculated in mm. Hg.

The ratio of the physiological dead space (V_D) to the tidal volume (V_T) was calculated from the following

relationship:-

$$\frac{V_D}{V_T} = \frac{Pa_{CO_2} - P_{ECO_2}}{Pa_{CO_2}} \quad \text{(West, 1965)}$$

where $P_{E_{CO_2}}$ is the partial pressure of carbon dioxide in the expired gas.

The percentage saturation of haemoglobin was found using the measured values of Pa_{O_2} and pH and the nomogram of Dill (1944).

MEASUREMENT OF REGIONAL VENTILATION AND PERFUSION.

The method of measuring regional ventilation and perfusion in the lung employed radioactive ^{133}Xenon and an apparatus which recorded impulses picked up from the surface of the chest wall by means of fixed counters. Essentially it consisted of recording zonal distribution of radioactivity after perfusion, after a single inspiration and after rebreathing of ^{133}Xenon. The circuit and procedure were not unlike those described by Ball, Stewart, Newsham and Bates (1962). As this method is not widely used in Britain it will be described in detail.

Chemical and physical properties of ^{133}Xenon.

^{133}Xenon is produced as a fission product by neutron bombardment of uranium ^{235}. Chemically it is an inert gas which is three times as soluble as oxygen and one seventh

as soluble as CO_2 at body temperature. (α = 0·0845 ml. Xenon per ml. H_2O at 760 mm. Hg.). Isotope ^{133}Xenon decays to caesium with a half life of 5·27 days emitting negative particles of maximum energy 0·347 Mev, gamma (γ) rays of 0·081 Mev and by a process of internal conversion X-rays of approximately 0·03 Mev. The β particles are absorbed in less than 1 mm. of tissue and are useless for external counting. The γ and X-rays are detected by surface counting methods but have sufficiently low energy for adequate protection to be afforded by 3/16" lead round the dispensing tonometer and spirometer.

Storage, Dispensing and Precautions using ^{133}Xenon.

The ^{133}Xenon gas used in the test was received as 100 millicurie aliquots contained in 10 cc. sealed glass ampoules every 2 weeks from Radiochemical Products, Amersham, Bucks. In the laboratory the Xenon was stored with 100% CO_2 in a dispensing apparatus which is a slightly modified 30 cc. tonometer enclosed in 3/16" lead shield. This tonometer is shown in fig. 9. Before making the transfer, the tubing and dead space of the tonometer were flushed with 100% CO_2 leaving two thirds of the vessel filled with this gas at atmospheric pressure. The top tap of the tonometer was then opened and the steel cannula advanced up to the top of the ampoule after breaking the inner seal. Mercury passed under

pressure into the ampoule, displaced the radioactive contents through the cannula into the tonometer. The pressure of the tonometer was kept below atmospheric at all times except when the gas was removed for use.

The ^{133}Xe and CO_2 mixture was used in a gaseous form after further dilution with air in a spirometer. For intravenous use the $^{133}Xe/CO_2$ mixture was dissolved with gentle agitation in 10 cc. sterile heparinised saline contained in a glass syringe. Replicates were used throughout this study so when the first syringe has been prepared it was mixed with another 10 cc. of sterile saline until both syringes contain approximately equal radioactivity. The activity of saline prepared in the syringes was measured in a fixed geometric system as shown in fig. 10, using a counting head, from the gantry. Usually a count of 400-500 counts per second (c.p.s.), which was equivalent to approximately 1 millicurie, in each syringe was adequate for the procedure.

The room in which this measurement was performed had an extractor fan which removed the contaminated air. All personnel wore safety monitoring devices which were surveyed monthly. Used glass syringes and other contaminated apparatus were stored in a $^{3}/16$" lead lined box until the isotope was dissipated.

For the complete study it has been calculated that the radiation dosage to the patient is of the order of 40 milli

rads, although it can be 120 milli rads if intrapulmonary mixing is delayed (Ball, Stewart, Newsham and Bates, 1962).

Spirometer Systems.

A spirometer of the Benedict-Knipping type was incorporated in a closed circuit for use during inspiration of the ^{133} Xenon in air mixture. Included in the circuit (as shown in fig. 11) was a soda lime filled cannister to absorb CO_2, a circulating fan and a counting head which recorded the radioactivity of the gas in the circuit through $^1/_{16}$" perspex tube on a separate rate meter and recorder. The circulation time of the circuit when the fan is operating was 3·5 seconds as measured by a bolus of ^{133}Xe. A potentiometer placed on the spirometer pulley relayed the volume changes of the spirometer bell to another recording channel.

Patient access to the spirometer was by lead ringed rubber tubes, a three-way tap and mouthpiece. The dead space of the whole circuit is 2·43 litres and the dead space of the mouthpiece and tap was 65 ml.

To prepare this circuit for the procedure with the patient ^{133}Xe/CO_2 mixture was introduced with a dry glass syringe through rubber tubing with the spirometer bell containing approximately 5 litres until there was a count of approximately 1000 in the mixed circuit. This is an equivalent concentration of approximately 0·4 millicuries/litre. Depending on the freshness of the supply of ^{133}Xenon in store

the volume dispensed to gain the desired spirometer count varied from 0·25 ml. to 2·5 ml. which was withdrawn from the tonometer in a 10 ml. syringe followed by sufficient air to fill the syringe. Accidental loss of radioactivity during transfer to the spirometer was easily avoided in this way.

In addition to this "hot" spirometer, a non-radioactive "cold" spirometer filled with air only with a fast recording light bell rested on top of the lead encased circuit. This spirometer was used during the perfusion of ^{133}Xenon in saline and the volume changes from it recorded on the same circuit as the "hot" spirometer by switching over to it. This enables a simultaneous tracing of the breathholding manoeuvre to be recorded during perfusion.

The Counting Apparatus. This is shown in fig. 12.

The counting heads were mounted in two vertical frames which face each other. These frames were suspended from a substantial gantry and could be raised or lowered to suit the height of the patient sitting between them. Six counting heads were disposed on each frame, three of them on either side of the mid line. The upper and lower counting heads could be moved vertically either together or separately within the frame. Each anterior counting head was placed exactly opposite a posterior counting head and the input of impulses to each was simultaneously recorded and eventually summated.

An individual counting head contained a collimator $3\frac{1}{4}$ inches long, a thallium activated sodium iodide crystal of 25·4 mm. diameter and 17·4 mm. thick and a photo multiplier tube.

Six (1810) ratemeters, 12 (1830A) amplifiers selector units, 2 (532D) E.H.T. power packs, 8 servopotentiometers and an eight-channel recorder were incorporated into a bulky tower (fig. 14). All these units were supplied by Isotope Development Company Limited, with the exception of 6 of the servopotentiometers which came from Sangamo Weston (S144.). The connections between these units are displayed on the circuit diagram in fig. 13.

Detection and Enumeration of Radioactive Impulses from the Patient.

The γ and X-rays emitted by the process of decay of ^{133}Xenon strike the crystal after passing through the collimator producing a scintillation according to their appropriate energies, which is in turn detected and amplified in the photomultiplier tube. Only γ rays were used in the ultimate counting of impulses by the ratemeters. X-rays were excluded because counting this less energetic ray would unnecessarily complicate the calculations and also that the use of the γ ray alone would simplify setting up and maintenance. The latter statement stems from the fact that the voltage applied to the photomultiplier tube was inversely proportional to the energy of incident radiation

which it was required to detect and consequently the X-rays and γ rays yielded different plateaus with respect to a given E.H.T. setting and the most clearly defined plateau was that of the γ rays. The E.H.T. supply to the photomultiplier was therefore set for the γ ray plateau only.

From the photomultiplier the impulses passed to an amplifying and selecting circuit which contained a pulse height analyser. The purpose of this device was to two-fold, to reject impulses of low voltage such as cosmic radiation by the use of a discriminator bias and to set an upper limit of acceptance establishing a 'channel width'.

The accepted impulses from one pair of counting heads (i.e. anterior and posterior) were then summated and counted on one ratemeter. This output was relayed to a servopotentiometer which converted a 0-100 millivolt input to a 0-10 milliamp output suitable to the 10 milliamp direct writing recorders.

By experimental determination a discriminator bias of 10 volts and a channel width of 20 volts was found to give optimum definition after the E.H.T. voltage had been set on the plateau for γ rays.

The setting up procedure before each determination required that each of the counting head channels and the "hot" spirometer channel was set at these voltages. Included in this was a comparative calibration of each recording channel on 3 attenuations, i.e. 100 cps, 300 cps and 1K with the same radioactive source.

A more detailed specification of the electronic equipment used in this apparatus is obtainable from a thesis by Mr. Michael Foskett submitted to the Institute of Science and Technology for a qualification of F.I.S.T.

Procedure with the Patient.

The positions of the counting heads on the gantry were arranged and fixed for each patient with reference to a postero-anterior chest film taken in maximal inspiration using the suprasternal notch as an anterior reference point. The upper two counters were placed 1·5 inches from the highest projection of the lung and the lower two counters $\frac{3}{4}$" above the highest projection of the diaphragm. The remaining counters were placed midway between these in the vertical plane. Each counter was placed equidistant horizontally from the mid line, compared with its opposite number on the other side of the chest. The back counters were arranged exactly opposite the front counters. A tracing of the radiograph with the counters position marked was taken in each patient for future reference. Such a tracing is shown on fig. 15.

A size 00 nylon catheter filled with sterile heparinised saline was introduced by the Seldinger technique into the median basilic vein in the right or left antecubital fossa under local anaesthesia. The catheter was advanced until it was intrathoracic and its position is identified by connecting its proximal end to a strain gauge manometer whose output was

displayed on a cathode-ray oscilloscope. When a negative pressure swing on inspiration was recognised the catheter was assumed to be intrathoracic and left in position. The manometer was then removed and replaced by a syringe containing heparinised saline which was strapped to the patient's arm so that he could bend it quite freely. Next, the patient sat on a chair with a low adjustable, semicircular back and arm rests, centrally placed between the two stacks of counters. A foot stool was provided. The stacks were lowered until an anterior reference rod was exactly opposite the suprasternal notch. They were then moved towards the patient until the lower counters almost touched the anterior and posterior aspects of the chest wall but the patient was still able to take a maximal inspiration without discomfort. A mouthpiece attached to the 'cold' spirometer was inserted through a gap in the anterior frame of counters and put in by the patient. A semicircular halter, fixed to the posterior counter frame, was fitted round the sides and back of the patient's neck to help prevent lateral movement. A nose clip was used so that only oral respiration was recorded.

The patient was instructed to take 3 slow maximal inspirations holding the breath in inspiration at the end of the third. While he was doing this the prepared ^{133}Xenon in saline was rapidly injected into the superior vena cava through the nylon catheter, followed by a similar volume of saline. During the breathholding manoeuvre, which lasted

approximately 10 seconds a plateau in each zone was recorded. The patient then removed the mouth piece and breathed air. The radioactive gas was washed out of the alveoli, and the chest counts fell to a background level. This procedure was then repeated after 5 minutes.

After a similar interval, the mouth piece was connected to the "hot" spirometer circuit and the patient instructed to repeat the respiratory manoeuvres. During the first two breaths only air was inspired, on the third the patient took a maximal inspiration of the radioactive gas and held the breath. As soon as a definite plateau in each recording head was seen the patient was allowed to release his breath into the spirometer. Thereafter room air was breathed until the counting rate over the chest had returned to an acceptable background level or for 5 minutes. This breath holding procedure was then repeated.

Finally, the patient rebreathed xenon in air from the "hot" spirometer starting at the beginning of an inspiration. During this procedure oxygen was added at a low rate of flow to keep the volume of the circuit constant. Rebreathing was continued for 6 minutes. Usually at the end of this time the c.p.s. recorded in the spirometer circuit and in the chest leads were constant, indicating that the patient and circuit were near equilibrium. A breathholding manoeuvre at maximal inspiration was then repeated and a further plateau was recorded in each chest lead. Then the patient was allowed

to breathe room air once more. The counting rate fell in all chest zones.

MEASUREMENT OF TRACING.

An example of the tracing recorded after this procedure with a single injection, single inspiration followed by rebreathing ^{133}Xe is shown in fig. 16. Six of these channels represent the summated back and front activity in the 6 zones covered by the counters. The remaining 2 record spirometer counts and spirometer volume.

The plateaus during breathholding in each zone after perfusion and after inspiration of ^{133}Xe are shown at points A and B, respectively. They were measured in c.p.s. minus the height of the background counts in c.p.s. recorded previously in each zone. Figure 17 shows the mode of measurement of such plateaus. The counts per second recorded in each zone after equilibration are measured by taking the height of the plateau during breathholding at point D on fig. 16. As the background counts recorded previous to rebreathing ^{133}Xe are a mixture of tissue and trapped alveolar gas counts, a standard tissue count is subtracted. The standard tissue count is based on the average of 8 normal subjects. The method of obtaining this figure will be explained later. The time taken to wash in 90% of the counts per second recorded at equilibration before the maximal inspiration is calculated and measured in each zone.

Figure 18 illustrates a poor and a good mixing zone with the 90% time marked as A and B respectively.

Calculations.

To evaluate the share each zone receives of the perfusion and ventilation during a single breathholding manoeuvre, the volume of lung which the counters are "looking at" has to be considered. At the end of equilibration mixing is as complete as possible and after a maximal inspiration the geometry of the chest is assumed to be similar to that during the other breathholding manoeuvres; therefore, the measurement of counts per second at that time in each zone reflects the volume of ventilated lung in the field of each counter. The ventilation index (V index) of a zone was calculated in the following way:

$$\text{Zonal V index} = \frac{R_1}{\Sigma R_1} \div \frac{R_E}{\Sigma R_E}$$

where R_1 = c.p.s. in zone during breathholding after a maximal inspiration of Xenon in air.

ΣR_1 = the sum of R_1 in each zone.

R_E = c.p.s. in zone after equilibration and during breathholding after a maximal inspiration of Xenon in air.

ΣR_E = sum of R_E in each zone.

Therefore, the V index of each zone is a measure of the zonal share of ventilation related to the share of ventilatable volume of that zone.

The perfusion or Q index of a zone is the zonal share of perfusion related to the share of ventilatable volume of that zone and is calculated in a similar way, viz.

$$\text{Zonal Q index} = \frac{R_p}{\Sigma R_p} \cdot \frac{R_E}{\Sigma R_E}$$

where R_p = c.p.s. in zone during breathholding after perfusion of ^{133}Xe in saline

ΣR_p = the sum of R_p in each zone.

To express the dynamic events in each zone during rebreathing (C to D in fig. 16) the observed time (t_o) to reach 90% mixing is compared with the predicted time (t_p) for the whole lung to reach equilibrium, assuming perfect mixing. This predicted time t_p can be calculated using the functional residual capacity of the patient (V_{FRC}), the spirometer volume at the beginning of equilibration (V_S), the dead space of the spirometer system (V_{DS}), the alveolar tidal volume (V_{TV}), and the frequency of breathing (f) in the following formula:

$$t_p = \frac{1}{f \log \frac{V_{FRC}}{(V_{FRC} + V_{TV})}} \times \frac{(V_S + V_{DS}) - V_{TV}}{(V_S + V_{DS})}$$

The anatomical dead space was assumed according to body weight. Calculation of the relationship $\frac{t_p}{t_o}$ in each zone yields the zonal "dynamic distribution index", (D.D.I.). This calculation is similar to the dynamic distribution index described by Bentivoglio, Beerel, Stewart, Bryan,

Ball and Bates (1963).

The volume of air entering each zone during the single respiration of ^{133}Xe was also calculated by dividing the inspired volume of xenon and air at the mouth in proportion to the share of inspired counts in each zone.

Predicted Normal Values.

The normal values of the lung function tests were predicted from the data indicated.

1) Lung volumes, diffusing capacity and percentage extraction of carbon monoxide at rest from Bates and Christie, 1964.
2) Diffusing capacity during exercise from McNamara, Prime and Sinclair (1959).
3) Arterial blood gas tensions from Comroe, Forster, Dubois, Briscoe and Carlsen, 1964.
4) Regional ventilation and perfusion indices from Ball, Stewart, Newsham and Bates, 1962.
5) Regional dynamic distribution indices from Bentivoglio, Beerel, Stewart, Bryan, Ball and Bates, 1963.

CRITICAL ASSESSMENT OF METHODS

SELECTION OF PATIENTS

It is essential in a study of this kind to understand the basis of selection of the patients who feature in it. All came from a "hospital population" and therefore the majority had symptoms and are not representative of the population as a whole who suffer from emphysema or from bronchitis or from chronic airways obstruction.

The patients in Group I were selected solely on the basis of radiological features of emphysema so the disablement and symptomatology differed widely between them. There is an inevitable preponderance of radiologically localised emphysema due to the nature of the project. Patients selected for surgical treatment (Group Ia) attended ten different consultant physicians whose opinions differ on the grounds for embarking on such a venture. The type of surgical operation performed varied, as did the surgeon to whom the patient was referred. Such variables were unavoidable, but are important to remember when considering the data which will be presented.

There was a very marked bias in the selection of the bronchitis group (Group II) because they were chosen to compare with some severely disabled emphysematous patients. All had severe airways obstruction, and any radiological features of

emphysema excluded them from the study. This does not imply that those patients had no pathological evidence of emphysema but it is unlikely that Grades III or IV panacinar emphysema was present (Reid and Millard, 1964).

QUESTIONNAIRE.

The use of a series of questions had certain advantages. Questions phrased in identical words, and asked by one observer of a number of patients, are liable to less observer variation than the usual way of recording a case history in hospital notes (Medical Research Council, 1960). Grading the severity of the symptoms made comparison within the population easier. The grades of breathlessness were particularly useful when the subjective result of surgery was considered.

Unfortunately, by standardising the questions and answers the actual sensations and individual idosyncrasies of the patients were ignored. I have been acutely aware of this discrepancy and therefore make no apology for including in this thesis the patients own words which more adequately describe their discomfort associated with breathing.

Although the form of questions devised by the Medical Research Council was used, some sections of the questionnaire were omitted, e.g. the effect of weather.

The prime object of using this standard questionnaire was to have some dividing line between patients with bronchitis and patients without bronchitis.

THE DIAGNOSIS OF BRONCHITIS.

The generally accepted definition of chronic bronchitis is clinical (Ciba Guest Symposium, 1959; World Health Organisation, 1961). Accordingly, I have used the answers to the questions asked about cough and sputum to define the presence or absence of bronchitis. The questions about cough and sputum were asked most pointedly and carefully as it was sensed that men in Britain, particularly those who smoked, seem to regard coughing and spitting as normal events. The answers to these questions were checked by observation and by noting the presence or absence of sputum while the patients were in hospital. Some patients who had ceased to smoke claimed that they no longer had a productive cough. In this event this was recorded regardless of the previous coughing history.

The severity of bronchitis present cannot be gauged in this way, so patients in Group I with a productive cough may or may not be affected functionally by bronchitis. On the other hand in the patients in Group II the functional defect is probably predominantly due to bronchitis.

INTENSITY OF BREATH SOUNDS.

Clinical signs in the chest are liable to considerable observer disagreement (Smyllie, Blendis and Armitage, 1965). In an attempt to measure the extent of this, two observers were used and the variation between their recordings is

described in the data presented.

It is possible that applying grades to an observation which is liable to so much error in itself as intensity of breath sounds has lent on unwarranted exactness to it. At the same time it is pertinent to point out that grading the intensity of breath sounds is different from identifying "diminished breath sounds". Fletcher (1952) suggested that careful definition of some of the signs might result in agreement between observers being increased and the grades applied here are only an attempt at better definition.

The system of grading this sign is very simple and is essentially similar to the usual clinical description of the sounds heard, i.e. absent, weak, moderate and good. Although on some occasions there was doubt in the decision between Grades 2 and 3 on the whole the observers found that the grades could be applied with some confidence.

RADIOLOGY.

The observer variation of the radiological findings has not been investigated in this work. With 4 observers Knott and Christie (1951) found that 25% of cases with "clinical" emphysema were missed but this was on the definitive diagnosis of emphysema and not on separate observations. An effort has been made to record as many objective measurements as possible and thereby separate errors of observation from errors

of conclusion and diagnosis as recommended by Simon (1966).

PHYSIOLOGICAL TESTS.

TOTAL FUNCTION TESTS.

The repeatability of all these tests is dependent on errors inherent in the equipment used, and the patients full co-operation and understanding.

The $F.E.V._1$ and V.C. have been shown to have a repeatability of $\pm$ 110 ml. and $\pm$ 160 ml. respectively by Davidson (1966). Generally, it is accepted in this laboratory that there is a repeatability of less than 10% on repeated observations in the same patient. Exhortation by the observer and clear orientation on the part of the patient is essential.

The measurement of static lung volumes with the closed helium circuit in patients with emphysema and consequently poor distribution of the inspired gas is liable to underestimate the true value as complete equilibration is never strictly attained. A discrepancy of as much as 3·0 litres in lung volumes has been recorded between a test dependent on ventilation (7 minute nitrogen washout) and plethysmographic methods in patients with emphysema (Bedell, Marshall, Dubois and Comroe, 1956). The rebreathing in the helium circuit was continued in some patients up to 30 minutes in an effort to cut down this error with catharometer readings being recorded at minute intervals until no change was shown for 4 minutes.

The lung volumes measured by this method are said to be within ± 200 ml. by Cotes (1965). The helium catharometer in the circuit has a slow response time of 2 minutes with an accuracy of 2% within a range of 0-15% Helium in air.

The diffusing capacity measured by the end tidal sampling method used a carbon monoxide infra-red analyser which has a response time of 10 secs. and an error of 2% of a full scale. The end tidal sampling device has been shown to be satisfactory provided the tidal volume is adequate to clear the instrumental and anatomical dead space (Marshall, 1958).

THE ELECTRODE SYSTEM.

Provided the membranes in the oxygen and carbon dioxide electrode are kept moist and the pH and carbon dioxide electrodes are well cleared of blood and protein particles when not in use the system works well and is reasonably stable.

In addition to the calibration described before use, at monthly intervals the oxygen electrode was specially calibrated with 10% oxygen, 20% oxygen, 30% oxygen and 40% oxygen mixtures in liquid and gaseous form. If the moist gas readings and those using liquid samples were not the same, or if the response was not consistently linear, the electrode was dismantled and reassembled until such a situation was present.

Reasonable maintenance, careful handling and occasional changes of the membranes used have been found to maintain the properties of the electrodes described, for three years. During

this time it has also been shown that it is most important that the calibrating fluids are at the same temperature as the water bath and electrode. The pH electrode is especially sensitive to thermal changes. It is possible to have 2-3°C. temperature change after over-conscientious washings with buffers and cleaning fluids. The latter are unnecessary if the blood sample is not allowed to remain in the electrode chamber for more than 3 minutes.

THE COLLECTION OF ARTERIAL BLOOD AND EXERCISE TEST.

It is recognised that the method used was not ideal and that an indwelling arterial cannula and bicycle ergometer would have been more satisfactory for examining the effect of graduated exercise on the blood gases. These patients had had many tests, were often very disabled, often depressed by constant breathlessness and clinical science had little to offer in their ultimate management. In addition, if surgery was contemplated it was planned to repeat these test with the patients co-operation. For these humane reasons ideal methods were sacrificed and the simpler methods described were used. As a result of this no patient has refused to return to hospital after surgery, nor has there been any loss of rapport consequent upon the collection of arterial blood, a situation which was certainly not present before the present policy was adopted.

The Wright anemometer used to measure minute ventilation during the collection of arterial blood was found to over read by 17% compared with a spirometer and a Donald Paterson gasometer.

Appropriate corrections have been applied. This error is only applicable for intermittent flow rates up to 30 litres/minute. Above 60 litres/minute it was found to over read as much as 80% of the true recording.

MEASUREMENT OF REGIONAL VENTILATION AND PERFUSION.

Movement of the Patient.

The method and calculation infer that the fixed counters are 'seeing' the same position of lung during each manoeuvre. As there were counters both anterior and posterior to the chest wall, movement by the patient forwards or backwards was not so important but lateral movement had to be prevented if possible. To do this the fixed chair with back and arm rests and neck halter were used. In addition, the position of the patient was checked before each breathholding manoeuvre. However, despite these precautions lateral movement cannot be excluded especially in patients of small build as there was room for them to move between the arm rests. The halter served mainly as a guide and was not tightly fixed round the neck. Plastic cushions filled with polythene chips, evacuated to mould round the pelvis of smaller patients, were tried to solve this problem with some success. Vertical movement such as occurred when the patient slouched then sat up straight was also a source of error. During equilibration the patient breathed quietly and tended to relax in the chair; however, during a period of maximal inspiration

and breathholding the disabled patient sat upright, and hunched the shoulders lifting the chest wall. Thus, the volume of lungs 'seen' by the counters must be variable between the equilibration and the other manoeuvres. However, during actual breathholding this variability should be less.

To assess the repeatability of the V and Q indices, duplicate measurements were made in 68 and 65 patients respectively. An analysis of these pairs of observations is contained in table 1. These figures show that there is a close agreement between the pairs of estimate which is probably a reflection of the efforts previously described to prevent lateral and vertical movement by the patient. Hereafter, only the first value of the V and Q indices will be shown.

During breathholding it is difficult to prevent the patient from closing the glottis and performing a Valsalva manoeuvre. This might alter the regional perfusion, (Ball, Stewart, Newsham and Bates, 1962). To minimise this the patient was encouraged frequently to inspire during the breathholding period, as a state of conscious constant inspiration tends to discourage glottis closure.

Rebreathing for 6 minutes will not effect complete mixing or equilibration in a poorly communicating bullous area. However, provided all zones are affected equally in the same patient the share of total volume of any zone at the end of the rebreathing

period will be in the correct proportions. If there are one or two affected zones their volume share will be falsely low. As the V and Q indices of a zone are expressed as a share of zonal counting rates as well as on the "equilibrium" counting rates, they will be to a certain extent dependent on each other and will be falsely high in a zone where the "equilibrium" counts are falsely low.

In contrast to the V and Q indices the zonal dynamic distribution indices are independent of each other in a particular patient and are comparable between patients. For these reasons the D.D.I. is of greater use in indicating the values of absolute intrapulmonary mixing than the V indices.

If mixing is not complete in 6 minutes the 90% mixing time will be too low. However, this error will not be of any great significance as the 90% mixing point will be on the flatter part of an exponential curve, and due to the logarithmic scale the numerical value of this error will be minimised in the lower reaches.

The D.D.I. is partly dependent on the F.R.C. measured by the helium mixing method but it has been calculated that a 10% error in an F.R.C. of 4 litres gives less than a 2% error in the predicted time for complete mixing.

As xenon is not an insoluble gas some is absorbed by body tissues and chest wall. The amount in the tissues is dependent on the length of the rebreathing time and the initial

concentration of xenon in the spirometer. With prolonged rebreathing chest wall counts will tend to obscure the actual alveolar counts present, especially as the chest wall is nearer the crystals than the lung itself. Six minutes was chosen arbitrarily for a rebreathing time as it was found that some zones at least had reached a plateau in this time. In calculating the equilibrium value in each zone a constant number of c.p.s. were subtracted from the observed equilibrium c.p.s. on the tracing to allow for the chest wall tissue contribution. This constant number is based on 8 normal subjects of average build who had the same dosage of xenon, the same procedure and the same time of rebreathing. After the procedure they voluntarily hyperventilated air intermittently for 10 minutes and thereafter the c.p.s. were recorded in each zone. The ^{133}Xe washout was extrapolated backwards and the average tissue count calculated. This did not exceed 10% of the equilibrium c.p.s. in any zone of any patient in this study. Tissue counts vary according to the thickness of the chest wall but this was found to be of the order of 2% in the normal subjects so variations in body size and thickness, fat etc. were ignored.

Technical Difficulties and Errors associated with the procedure.

Recording the radioactivity in each zone directly presented certain difficulties if the margin of error in recording was to be cut to the minimum. The ratemeters recorded on 3 attenuations, counting at 100 c.p.s., 300 c.p.s. and 1,000 c.p.s. per complete scale. In the absence of a tape

recording system the attenuation had to be anticipated correctly to get a reading on scale before the breathholding manoeuvres were performed as there was insufficient time to change them during the manoeuvre. This guess varied with the number of counts in the syringe injected or the number of counts in the spirometer which were known and with the perfusion or the ventilation of the lung zone which were, of course, unknown. Sometimes, mistakes were made which meant that the procedure had to be repeated. During the rebreathing procedure it was more accurate to record on as sensitive a scale as possible, (Ball, Stewart, Newsham and Bates, 1962).

Rapid injection of the xenon in saline solution through a catheter lying in the superior vena cava ensured that the activity arrives in the pulmonary circulation as a bolus, and avoided pooling at the shoulder, an event which necessitated abandoning the procedure on that patient for 24 hours. The long catheter was convenient in timing the injection and breath-holding period as the circulation time did not play such a large part. It was quite common for the upper counter on the side of the catheter to record an off scale deflection while the bolus of xenon passed through that zone before reaching the superior vena cava. This can be misleading for the operator of the ratemeter attenuations as the inclination was to immediately switch to a lower attenuation and record a very low and less accurate plateau when the xenon appeared in the alveoli in that zone. An example of this off scale deflection

is shown in fig. 17. In the same tracing it can be seen that the background counting rate rose before the perfusion of the xenon because of the proximation of the syringe to the counters. This rise was ignored in the measurement of the plateau as the activity causing it was in the lung when the plateau was being recorded.

There was a reading error on the tracing of within 2%. A variation between the attenuated scales occurred from day to day but was defined by calibration before each test as described in the previous chapter. This variation was taken into account if itwas more than 2% in any zone at any attenuation change. The recording error attendant on recording from a rectilinear to a curvilinear scale was found to be less than 1%. A one second time constant was invariably used and the maximum reading was given within 3 seconds.

As therewas no absolute standard of radioactive source available in the laboratory it is probable that the absolute values recorded in the tracings varied from week to week. However, as the calculations made on these tracings for reasons of thoracic and geometric asymmetry measure only shares of ventilation and perfusion and the relative efficiency of mixing no absolute values were required.

While considering the technical difficulties with recording and patient handling with which I was principally concerned, it is fitting to mention that throughout the time of this study

we have been constantly beset by electronic failures of the various components of the counting apparatus. Not the least of these has been due to overheating as it was found necessary to keep a constant flow of current running through the amplifiers and servopotentometers to cut down the number of fuses needing replacement and the wear and tear on valves. An extra fan was installed in the tower. In addition to the maintenance costs, the capital cost of this apparatus was in the region of £8,000 and each aliquot of xenon costs £25. This is therefore a very expensive method, a fact which should be borne in mind when considering its value in clinical and research medicine.

THE USE OF ANTERIOR AND POSTERIOR FIXED COUNTERS.

The fixed counting system described here differs from the moving counters described by Dollery and Gillam (1963). The advantage of their method is two-fold: firstly it is cheaper and secondly it accurately localises a small area of dysfunction. I have relied on radiology for identification of the latter. Using fixed counters the dynamic events during the rebreathing process can be observed continuously. An added factor is that after the single inspiration of ^{133}Xe gas and the subsequent breathholding period, the disabled patient is required only to hold the breath while each counter records simultaneously. If the counters were moving the breathholding time would require to be prolonged until a profile from the top to the bottom of the lungs were recorded;which even using

a short time constant would put further stress on a breathless patient.

Ball, Stewart, Newsham and Bates (1962) used only posterior counting devices. By employing counters both at the front and back of the chest wall it was hoped that a larger volume of lung tissue was surveyed and a larger signal gained using smaller dosage of radioactivity. The front, back and adjacent counting fields were judged to overlap sufficiently for it to be justifiable to calculate the actual volume of air inspired into each zone of lung as described in the previous chapter.

CLINICAL ASPECTS OF EMPHYSEMA

PHYSICAL CHARACTERISTICS.

Of 50 patients in Group I, 46 were males and 4 were females. The average age was 54·3 years, the youngest being 37 years and the oldest 70 years at the time of study. Figure 19 shows the height and weight of the 46 male patients, the line depicts the average weight in lbs. according to height in a normal male population between the ages of 50-60 years, (Society of Actuaries, 1959). The mean height of all male patients in Group I was 69 inches. The patients with bronchitis had a mean height of 69·0 inches and those without bronchitis had a mean height of 70·6 inches. As the average height of men in this part of the country is 68 inches (Martin, 1949) it is of interest to note that 11 of the 14 patients without bronchitis were taller than the average whereas only 16 of the 32 patients with bronchitis were over 68 inches in height. All except 2 patients were below the expected weight; it makes no difference in this respect whether bronchitis is present or not. Thirty-five male patients, i.e. 76% of the population, are 20 lbs. or more below their expected weight.

Comment.

The average age of the patients in this group is very similar to that of other investigators, Prime and Westlake,

1954; Bates, Knott and Christie, 1956; Hammond, 1957) despite the wide range of ages which they also report.

Textbooks refer to patients with emphysema as being tall and thin. This view is supported by Fletcher, Hugh-Jones, McNicol and Pride, 1963; and Nash, Briscoe and Cournand, 1965. Certainly, the majority of patients in Group I are underweight but their height seems to me to be more likely to be related to heredity and early environment than present health. In the patients with emphysema and no bronchitis there was a definite tendency to be tall which may be due to a genetic linkage between emphysema and height.

It has been suggested that the weight loss in emphysema is due to an inclination to eat less because of aggravation of dyspnoea by gastric distension (Nash, Briscoe and Cournand, 1965) but I think an added factor might be the depression and worry caused by the breathlessness. One of the commonest findings in depressed patients is loss of weight.

BREATHLESSNESS IN EMPHYSEMA.

'Shortness of breath' and breathlessness on the slightest exercise was the main complaint and clinical feature of the large majority of these patients, even if it was not necessarily of the longest duration. This sensation was variously described as "suffocating",

"stifling" and "never able to get enough breath in". In many it was incapacitating even with minimum exercise, for instance C. Mah, an artist, had had to give up oils and water colours and was only able to do pencil and charcoal drawings sitting in a chair. It was not always associated with exercise as the questionnaire implies: quite frequently the patients volunteered that due to an emotional upset in the household or the anticipation of some exciting event they became breathless. One patient (J.W.) frequently awoke during the night with severe breathless attacks which occurred also at rest during the day, but there was no evidence of left ventricular failure. Attacks of this sensation at rest or during very mild exercise frightened the patients and is obviously very unpleasant. When questioned they said that it was quite different from the breathlessness they used to get when they were younger after exercise. Eighteen patients refused to go into the body plethysmograph because they "wouldn't be able to breathe when shut in a box".

CLINICAL HISTORY FROM QUESTIONNAIRE ANSWERS

Table II shows a summary of the respiratory complaints, duration and previous history of 50 patients in Group I. Individual symptomatology is shown in Appendix II. Thirty-two patients (64%) complained of a productive cough and by definition have bronchitis, 23 (60%) had had a cough longer than breathlessness. Those bronchitic patients have a shorter history either of breathlessness or cough, and are older when they become breathless than patients with emphysema who have no bronchitis although the average age is similar.

Twenty-six (81%) of the patients in Group I with bronchitis were severely disabled and complained of breathlessness when washing, shaving or dressing, whereas only 9 of the 18 patients (50%) with no bronchitis complained of severe breathlessness.

Eighteen (55%) of those with bronchitis had had a chest infection in the past 3 years which incapacitated them for a week or more, compared with only 28% of the patients without bronchitis.

There were no pipe or cigar smokers. All, except 2 were smokers or ex-smokers of cigarettes. Of the 33 ex-smokers, 9 had smoked heavily, 14 moderately and 10 lightly.

Of the 15 smokers, 3 smoked heavily, 8 moderately and 4 lightly.

COMMENT.

These figures give an outline of the incidence, duration and severity of the symptoms in the patients in Group I.

There appears to be a remarkably high incidence (36%) of patients who deny having a productive cough compared with 6% found by Fletcher, Jones, Burrows and Niden (1964). This is easily explained. At one time I particularly looked for patients with evidently uncomplicated emphysema. In addition, this type of patient is more likely to be a suitable candidate for surgery and as such was referred to the laboratory for study.

These patients could be said to be suffering from "primary emphysema". This term was first introduced by Seebohm and Bedell (1963) to describe emphysema in young adults (below 40 years) "without any recognised antecedent",yet in their paper half of the 10 patients described have a productive cough. Other authorities (Scadding - personal communication, Reid, 1965) prefer to use this term only when there is no productive cough in patients with emphysema in this age group. It is therefore interesting to note that in these patients the mean age of onset of breathlessness is younger than in the bronchitic group.

The severity of breathlessness was greater in patients with bronchitis than those without. Although this seems to

indicate a more rapid deterioration in the former group especially in view of the similar age distribution. The progress of these patients can only be ascertained by a long term study. As will be shown later there was no difference in the extent and distribution of emphysema between these two groups radiologically.

The high incidence of chest infections in patients with bronchitis agrees with other reports (Fletcher, Elmes, Fairbairn and Wood, 1959; Elmes, Fletcher and Dutton, 1957). Fewer chest infections had occurred in patients with no bronchitis which was expected but is a point not shown by Fletcher, Hugh-Jones, McNicol and Pride, (1963).

Table III shows the relationship between the smoking history of patients in Group I with that of other investigators. The incidence of ex-smokers, which is high compared with other surveys, is probably partly a tribute to the anti-smoking attitude maintained by most physicians of the hospital. As I have seen a cyanosed patient with hypercapnia, gross airways obstruction, chest infection and cor pulmonale smoking 60 cigarettes a day "to make me feel better", I do not think breathlessness necessarily induces stopping smoking. I have even heard of one patient trying to smoke through a tracheostomy when he had respiratory failure.

INTENSITY OF BREATH SOUNDS IN EMPHYSEMA

Of the several clinical signs in the respiratory system in emphysema dyspnoea on exertion and the diminished intensity of the breath sounds are the most notable, (Christie, 1944; Fletcher, 1952; Fletcher, Hugh-Jones, McNicol, and Pride, 1963). Loss of cardiac dullness, loss of hepatic dullness, and absence of the apex beat are all signs resulting from overinflation of the lungs, a finding which is more accurately displayed on a chest radiograph.

It was through the use of the stethoscope that Laennec verified the "existence of emphysema as well on the living as on the dead subject" and was "led to consider it by no means infrequent". He described the breath sounds heard in emphysema in the following way:

.... "The respiratory murmur is inaudible over the greater part of the chest and is very feeble in parts where it is audible. If the disease is not very severe, the sound of respiration is still audible but in a much less degree than the sound of percussion could lead us to expect...."

In describing the stethoscope and its use he said "I would beg to observe that it is only in a hospital that we can acquire completely and certainly the practice and habit of this new art of observation, inasmuch as it is necessary to have occasionally verified by means of examination

after death, the diagnostics established by means of the cylinder, in order that we may acquire confidence in the instrument ...." In this way Laennec acknowledged that an absolute standard was required to compare with the intensity of the sounds heard through a stethoscope.

The study of the validity of clinical signs is hampered by lack of reliable methods of recording them but they can sometimes be compared with some functional measurement. There has been only one attempt, to my knowledge, to compare a clinical sign in chest disease with a closely related physiological measurement. Comroe and Botelho (1947) measured oxyhaemoglobin saturation and compared it with the clinical sign of cyanosis. A comparison of the intensity of breath sounds with intrapulmonary mixing would be somewhat analagous to this.

The application of 'grades' to the intensity of the breath sounds allows a comparison not only of the grades recorded by the observer to the calculated D.D.I. and the volume of air entering the zone but also it is possible to compare any difference in grading from top to bottom of each lung with the difference in the D.D.I. and volume of air entering between these areas of the lung. In other words, is it possible in emphysema to identify with a stethoscope a zone of lung which is not well ventilated consistently in

different patients and is it possible to discriminate between zones of lung with good and bad ventilation in a single patient by listening to the breath sounds?

RESULTS.

Fig. 20 is a comparison of the grades of intensity of sound in zones of the lung by two observers (J.R. Nairn and M. Turner-Warwick) in 34 patients in Group I. There is complete agreement in 52·3% of zones anteriorly and 42·7% of instances posteriorly. A difference of only one grade between obsdrvers occurred in 40·4% of zones anteriorly and 42·7% posteriorly, i.e. there was complete agreement or only one grade difference recorded in 92·7% of zones anteriorly and 87·4% of instances posteriorly between two observers. The large majority of the zones have been judged to be within grades 1 and 2 by both observers. With M. Turner-Warwick these comprise 67% anteriorly and posteriorly of the total, whereas J.R. Nairn recorded 73% anteriorly and 79% posteriorly as having grades 1 or 2 intensity. J.R. Nairn tended to grade good breath sounds slightly lower than M. Turner-Warwick, i.e. posteriorly J.R. Nairn records 5·4% as grade 3 whereas grade 3 represented 13·2% of the total with M. Turner-Warwick. The breath sounds were noted to be absent or faint (grades 0 and 1) in 99 zones by J.R. Nairn and 93 zones by M. Turner-Warwick but only

in 69 of these zones did the observers agree which is 74% of the least number recorded.

Fig. 21 shows the relationship between the D.D.I. in each zone and the intensity of breath sounds heard anteriorly when recorded by J.R. Nairn in 47 patients from Group I. It is evident that although there is a marked tendency for the D.D.I. to be low when grade 0 or 1 is recorded, there is a wide scatter of the values of the D.D.I. in grades 2 and 3. If the percentage of observations above and below a D.D.I. of 60 units is taken as an arbitrary line of discrimination between good and bad alveolar mixing, the scatter of the grades of breath sounds can be expressed in the following manner:-

GRADE	% of total cases with a D.D.I. above 60 units.	% of total cases with a D.D.I. below 60 units
0	2%	98%
1	22%	78%
2	38%	62%
3	51%	49%

Fig. 22 shows a comparison of the grade of intensity of anterior breath sounds with the calculated volume in ml. entering the zone during maximal inspiration in 47 patients in Group I. There is a wide scatter in grades, 1, 2 and 3. When there are no breath sounds audible, in 44% of instances

there was less than 100 ml. of air entering the zone and in 90% of instances there was less than 400 ml. entering the zone. In 5% of zones when grade 1 was recorded there was less than 100 ml. entering the zone, whereas 79% of zones had less than 400 ml. Grades 2 and 3 intensity of breath sounds were heard in 33% and 59% of zones respectively when the air entering was more than 400 ml.

The observations of M. Turner-Warwick made little difference to these results when considered separately.

Let us now consider the difference in the intensity of the breath sounds heard between the top and the bottom of the lung in individual patients. If there is no difference in grading heard between the upper zone and the lower zone of the lung a 0 is recorded, however if the breath sounds heard at the top of the lung are observed to be grade 2, when those at the bottom are grade 0 then -2 is recorded.

Fig. 23 compares these differences of grades of intensity as recorded by the two observers, J.R. Nairn and M. Turner-Warwick, when listening anteriorly in 34 patients in Group I. There is complete agreement in 45% of observations and only one grade difference in a further 43%. So that in 12% of cases there is marked disagreement between the two observers, i.e. a difference in grading from top to bottom of the lung which is more than one grade different.

It is evident that the majority of the lungs in these patients had breath sounds of a greater intensity at

the top than at the bottom, i.e. most of the points in fig. 23 are on the negative side of the axis.

It is possible now to compare these differences in grades of intensity of breath sounds with differences in intrapulmonary mixing and volume of air entering the top and the bottom of the lungs. Fig. 24 shows the difference in grades of intensity of anterior breath sounds compared with the difference in the dynamic distribution indices between the top and the bottom of the lung. The observer is J.R. Nairn listening anteriorly. The black dots depict observations in 47 patients in Group I and the squares in 7 patients in Group II. Only in 7 lungs, i.e. 6·5% of the total is the difference observed in the breath sounds contrary to that of the D.D.I. from top to bottom of the lung. In the remaining 93·5% of lungs there is either no difference in the breath sounds heard down the lung, or the difference in D.D.I. is in the same direction as the difference heard in the breath sounds, i.e. if there is better intrapulmonary mixing at the top of the lung than at the bottom the breath sounds are of greater intensity there and vice versa. There is a wide scatter evident despite this approximate agreement, as can be seen clearly if the central ordinate is considered. When there is no difference in the grade of intensity of the breath sounds from top to bottom of the lung the D.D.I. has increased by 60 units or

decreased by 105 units. There is no obvious difference in this comparison between patients from Groups I and II. The latter had numerous rhonchi which made listening to the breath sounds more difficult in practice.

Fig. 25 shows a comparison of topographical differences in the lungs of 47 patients in Group I and 7 patients in Group II considering the intensity of the breath sounds and the volume of air entering the zones. Again there is a wide scatter within the quadrants but in only 16 lungs, i.e. 15% of the total, was there marked disagreement shown between the two observations.

DISCUSSION

It is clear that when poor or absent breath sounds are noted in patients with emphysema there is almost invariably poor intrapulmonary mixing in the underlying lung zone. This does not necessarily mean that this clinical sign is diagnostic of emphysema but it does imply that the finding is valid confirmatory evidence of the disease.

In the absence of breath sounds or when faint breath sounds are present it has also been shown that there is less than 400 ml. of air entering the underlying lung zone in 90% of instances. This is only a very approximate figure and of debatable derivation as the breath sounds were observed during tidal breathing and the volume of air entering was

calculated from a maximal inspiration. Nevertheless, there is apparently a definite relationship between a small volume of air entering and faint or absent breath sounds in the same zone.

The observation of moderate and good breath sounds is less valid as a clinical sign of normally ventilated lung.

Detection of a difference in the intensity of the breath sounds between poorly ventilated and more normal lung in the same patient have been demonstrated. Rarely (i.e. $\leq$ 10%) was it shown that the breath sound intensity heard anteriorly belied differences in ventilation between zones in the same lung, although quite frequently (in approximately 30% of instances) there was no difference heard in the breath sound intensity despite a wide variation in the ventilation of the lung between upper and lower zones.

This is a convenient juncture at which to discuss the possible origin of the breath sounds heard in the chest and what influences their intensity in emphysema. Without considering these points it is difficult to see why the breath sounds should bear any relation to intrapulmonary mixing or to the volume of air entering the alveoli.

The breath sounds are a result of turbulence in the air passages. They are audible over the trachea. In the larger bronchi and trachea there is adequate opportunity

for the creation of much turbulence as the walls of these tubes are not smooth, the flow of air is fast, and of constantly changing temperature and humidity. If the sound waves are produced in the upper air passages then the intensity of the sound heard through the stethoscope placed on the chest wall depends on the conduction or reflection of the sound waves through the smaller bronchi and bronchioles to the alveoli and through the walls of the alveoli and the chest wall itself.

Sound waves are conducted best down long straight tubes where there is no interruption. Smaller bronchi or bronchioles which are distorted either from without or within their walls will interrupt the sound conduction, as indeed they will alter distribution of the inspired gas.

Let us now consider sound conduction at the alveolar level. When a ventilated alveolus containing well conducted sound waves is surrounded by other well ventilated alveoli the sound energy emanating will be intensified by each alveolus in every direction. Suppose, however, the well ventilated alveolus is surrounded by large air spaces which are virtually unventilated and therefore contribute little or no sound energy. The energy will be dissipated while traversing this buffer air space so that it will be less intense on arrival at the chest wall. This seems a reasonable hypothesis to explain the faint breath sounds in emphysema and their

association with poor intrapulmonary distribution of air and poor ventilation.

When auscultating a chest there is no standard intensity of sound available in the individual zone or patient which can be used by the observer to compare with what is heard. It is essential when auscultating a patient's chest for the observer unconsciously to establish a scale of intensities of sound heard in all parts of the chest wall. Laennec was well aware of this when he remarked "To judge correctly of the state of respiration, we must not rely on the results of the first moments of examination .... we must allow some seconds to pass before we attempt to form an opinion".

Grading the intensity of sounds heard as was done in this study demands comparison of one zone with another and allows a wider scale of differentiation than simple identification of 'diminished' breath sounds which was the method employed by Fletcher (1952) and Smyllie, Armitage and Blendis (1965). If this data is considered on a two-grade scale (i.e. considering grades 0 and 1 together and 2 and 3 together) there was 74% agreement in anterior breath sounds between the observers in grades 0 and 1. Fletcher, (1952) found 71% agreement and calculated that this could occur purley by chance in 50% of observations. In the population presented, J.R. Nairn and M. Turner-Warwick

individually found approximately half the observations were in grades 0 and 1 so the occurrence by chance of them agreeing on the presence of grades 0 and 1 was 33%.

A further scrutiny of the observer disagreement using a 4-grade scale might be helpful in putting the matter in perspective. If complete agreement or only grade of difference in the observations is accepted, only in 15 instances was there disagreement between observers which is 7·3% of the total. In this population with these observers the random occurrence of disagreement to this extent would be 52 instances or 25%.

It is not claimed that the observer disagreement has necessarily been substantially reduced by using a 4-grade scale, as the present data cannot be further compared with observer disagreement on the 2-grade scale. However, on general principles a multigrade scale is preferable as it allows for shades of difference between observers and between their observations, which cannot be done with only 2 grades or simple identification of "diminished breath sounds".

There was a definite tendency by both observers to record less intense breath sounds in the lower zones of the anterior chest wall than in the upper zones. This is probably partly due to the decreased intrapulmonary mixing in the lower zones in the patients examined and partly to

the more intense breath sounds normally observed in the antero-superior part of the chest wall (Laennec 1821)

In conclusion, these data have shown that weak and absent breath sounds are related to poor ventilation in the underlying lung and that the stethoscope is useful in discriminating between zones of well ventilated and poorly ventilated lung. The observer variation inherent in listening to breath sounds is large but it has been suggested that describing the sounds heard on a numerical 4-grade scale would be a useful epdemiological and clinical practice.

RADIOLOGY AND FUNCTION.

The clinical diagnosis of emphysema is largely based on the radiological features of the disease. There are many and they occur in different combination in different patients. Some are purely subjective observations and others are objective measurements. The empirical criteria chosen by Simon and Galbraith (1953) are well substantiated by morbid anatomical changes (Reid and Millard, 1964) as indicated in the Introduction. In comparison of functional findings with individual radiological features in emphysema, I am not concerned with the correctness of the diagnosis of emphysema but am trying to establish some basis for the functional assessment of an individual chest radiograph.

Simon (1964) distinguishes clearly between 'localised' and 'generalised' forms of emphysema. In the former only cardiovascular changes are present and in the latter all or the first two criteria in figure 3 are fulfilled.

Clinical observation has repeatedly shown that emphysema confined to a small part or the whole of one lung is frequently associated with little functional loss, (Macleod, 1954; Bates and Christie, 1964; Ogilvie and Caterall, 1959). Whereas implicit the term 'generalised' emphysema is that the disease

is widespread throughout the lung. One would therefore expect there to be considerable impairment in lung function. The extent of emphysema radiologically has therefore been defined by the vascular changes and related to function in order to assess the relative importance of the division between so called 'generalised' and 'localised' emphysema and to help in predicting overall functional changes from the radiograph. The following convention was adopted to describe the extent of emphysema present radiologically:- 'Generalised' emphysema was present when the first two, or all three, of Simon's empirical criteria were fulfilled; 'Extensively localised' emphysema was diagnosed when the vascular features were present alone but there was the equivalent of a whole lobe of normally vascularized lung present. When there was equivalent of the whole of a normal lung visible on the radiograph 'localised' emphysema was said to be present. For example, figure 26 is the radiograph of a patient (J.W.) with 'generalised' emphysema and figures 27 and 28 are examples of "extensively localised' emphysema in another two patients, (A.P. and R.G.).

A flat low diaphragm and a large retrosternal translucent zone (indicating evidence of "excess of air" according to Simon, 1964) have been found to be reliable diagnostic signs of emphysema radiologically by many workers (Whitfield, Smith, Richards, Waterhouse and Arnott, 1951; Nicklaus, Stowell, Christiansen and Renzetti, 1966). Calculations of lung volume

made from various measurements on a chest radiograph closely agree with physiologically measured volume in normal subjects and emphysematous patients (Barnhard, Pierce, Joyce and Bates, 1960) but the diaphragm shape or the size of the retrosternal translucent zone was not separately measured. As these features are objective, relatively easy to recognize and evidently found in emphysema it would be valuable to know whether they are indeed related to volume and to what extent they are inter related. This knowledge would be helpful both in the further correlationof structure and function of emphysema and in the rational assessment of the first of Dr. Simon's criteria.

Since the function of the lung depends upon perfusion as well as upon ventilation and volume, the radiological appearance of the blood vessels plays an important part in the qualitative assessment from a chest radiograph. Laws and Heard (1962) state that in the emphysematous lung there is a premature reduction in the calibre of the divisions of the pulmonary artery as well as more peripheral vascular loss. Bentivoglio, Beerel, Stewart, Bryan, Ball and Bates (1963) found that the distribution of abnormal vascular shadows agreed with regional abnormalities of blood flow in 25 out of 32 emphysematous patients whom they examined. These authors did not consider the regional ventilation findings nor the presence of bronchitis in emphysematous patients. Yet in bronchitis, which produces no radiological peripheral vessel abnormality

there must be poor ventilation and poor perfusion which may well have a regional pattern. In this chapter both ventilation and perfusion have been compared with the vascular changes regionally in the radiograph of emphysematous patients, paying particular attention to the effect of bronchitis.

RESULTS.

The radiological observations and measurement according to figure 4 in all patients are shown in Appendix II.

Radiological Extent of Emphysema.

The mean values, standard deviations and significance levels of the total lung function tests in patients in Group I according to whether there was 'generalised' 'extensively localised' or 'localised' emphysema present are shown in Table IV. The vital capacity, percentage of predicted vital capacity, % $^{RV}/_{TLC}$ and the resting Pa_{O_2} are significantly different between the 'generalised' and the other two groups. No significant difference was found between the 'extensively localised' and 'localised' groups. All patients with generalised emphysema had severe airways obstruction ($F.E.V._1 \leq$ 1100 ml.), and a low diffusing capacity. The mean value in all the tests is impaired more in the 'generalised' group compared with the 'extensive localised' or 'localised' groups. In each of the latter there are 2 and 3 patients respectively whose $F.E.V._1$

is nearly or above 2 litres and whose V.C. > 4 litres. This is shown in figs. 29 and 30 where these measurements are shown according to the extent of emphysema. Figures 31-33 illustrate the $^{RV}/_{TLC}$, $D_{L_{CO}}$ and resting Pa_{O_2} in a similar way; the patients with bronchitis being distinguished from those without. It is evident that the presence of bronchitis in these patients has no constant effect on these tests.

These findings can be further illustrated by examples of individual patients. A patient with generalised emphysema (J.W.) whose radiograph is shown in figure 26 was very severely breathless and had an F.E.V.$_1$ of 500 ml., a V.C. of 1·80 litres; the $^{RV}/_{TLC}$ was 78% and the total lung capacity over 10 litres. He had no bronchitis.

Differences in function in 2 patients with similar radiological features when the emphysema is partially localised can be shown in the cases of A.P. and R.G. The radiographs are those in fig. 27 and 28. Both patients had 'extensively localised' emphysema with a very similar distribution of small mid-lung vessels and peripheral vascular loss. They have curved diaphragms and one (A.P.) has a normal sized heart. Symptomatically and functionally these patients are quite different. A.P. is severely disabled with gross airways obstruction; R.G. is not breathless except when hurrying and has an F.E.V.$_1$ of over 2 litres. Neither is this difference evidently due to bronchitis as R.G. has a productive cough and A.P. has not.

Shape and Level of Diaphragm.

In 28 patients the diaphragm was flat and in 15 it was curved. In the remaining 6 patients one dome was flat and the other curved.

The relationship between the shape of the diaphragm and the $^{RV}/_{TLC}$, the percentage of predicted T.L.C. and the percentage of predicted F.R.C. in patients in group I is shown in fig. 34 and Table V. There is a large scatter evident in these measurements of lung volume and although there is a significant difference in the values of $\%\ ^{RV}/_{TLC}$ between patients with flat and curved diaphragms, there is none between the other lung volumes. Neither is there any difference when plethysmographic lung volume (L.V.) is considered. The mean L.V. in patients with flat diaphragms is 5·80 litres and with curved diaphragms 5·69 litres.

The shape of the diaphragm is now compared with the T.L.C. as it is observed at full inspiration on the radiograph. The predicted values of T.L.C. have a standard deviation (S.D.) of approximately 10% so the T.L.C. is considered to be increased if it exceeds 120% (or + 2SD.) of the predicted value. Thirteen of the 28 patients (48%) with flat diaphragms had an increased T.L.C. In 6 of the 15 patients (40%) who had curved diaphragms the T.L.C. exceeded 120% of the predicted value. These figures illustrate that the diaphragm shape is not directly related to the volume of air in the lungs.

The level of the diaphragm varied from the 6th anterior rib to the 8th anterior rib; in 26 patients it was low and in 23 it was at the normal level. (It was considered low if the 7th or more anterior ribs were visible above the middle of the right dome). Figure 35 and Table VI show the relationship between the level of the diaphragm and lung volume. The mean values of these volumes are higher in patients with low diaphragms than when the diaphragm is at a normal level and these differences are statistically significant.

In 15 of the 26 patients (58%) with low diaphragms the T.L.C. was increased; this applied to only 5 of the 23 patients (21%) whose diaphragms were at the normal level.

When the combination of the shape and the level of the diaphragm are considered the lung volumes are as shown in Table VII. Flat low diaphragms and curved low diaphragms have the highest mean lung volumes. Curved normal diaphragms have normal or near normal mean lung volumes and flat diaphragms at the normal level have a high % predicted F.R.C. and % $^{RV}/_{TLC}$ but a normal % predicted T.L.C. Differences of significance between these combinations are shown under Table VII.

The incidence of patients with a T.L.C. within the normal range is 37·5% when the diaphragm is flat and low, 85·7% when curved at the normal level, 75% when flat and normal and 37% when curved and low. In other words, the volume of air in the

chest at maximal inspiration is not always increased when the diaphragm is flat and low or when it is curved and low but it is so in the majority of patients. Most of the patients with the diaphragm at the normal level, whether flat or curved, have no "excess volume of air" in their lungs in the maximum inspiratory position when the radiographs were taken.

THE SIZE OF THE RETROSTERNAL TRANSLUCENT ZONE.

Thirty-one patients in Group I had a retrosternal translucent zone of increased depth ($>$ 3 cms.) and in 15 patients it was 3 cms. or less. In the remaining 3 patients whose radiographs were examined this measurement would not be made. Figure 36 and Table VIII shows the relationship between the $\%\ ^{RV}/TLC$, the percentage of predicted F.R.C. and T.L.C. and the depth of this area. This is a large scatter but the mean values are very similar and there is no statistically significant difference between these volumes and the depth of the retrosternal translucent zone. Six of the 15 patients (40%) with a normal depth had an increased T.L.C. compared with 12 of the 31 patients (39%) with a deep retrosternal translucent zone.

The downward extension was only abnormal ($<$ 3 cms.) in one patient with a large lung volume and a normal depth.

If therefore added very little to any relationship held between depth and lung volume.

DIAPHRAGM MOVEMENTS (D.M.)

Of the 45 patients in Group I in which D.M. was measured there were 36 who had poor movement ($<$ 6 cms.). With 2 exceptions all the flat diaphragms moved poorly as did all the low diaphragms, except 3. All the patients with 'generalised' emphysema had a poor D.M.

The $F.E.V._1$ was less than 1 litre in 32 of 36 patients (89%) who had poor D.M., but of the 9 patients with D.M. of $>$ 6 cms. only 2 had an $F.E.V._1$ of $>$ 2 litres.

The vital capacity was less than 2 litres in 26 out of 36 patients (72%) with poor D.M. and of 9 patients with a D.M. of $>$ 6 cms., 6 had a V.C. of $>$ 3 litres.

PULMONARY VESSEL SIZE AND VASCULAR LOSS.

In Table IX and figure 37 the observed vascular pattern in zones in patients in Group I and II is considered in a comparison with the intrapulmonary mixing as measured by the dynamic distribution indices. Patients in Group I with bronchitis are separated in this instance from patients without bronchitis. The number of patients and zones showing the different radiological changes are shown and the percentage of the zones which have dynamic distribution index below the normal value is shown. When there are small lung vessels and evidence of vascular loss in a zone in patients in Group I, there is almost invariably ($>$ 70%) poor intrapulmonary mixing and there is no difference in this relationship whether bronchitis is present or

not. However, there is some poor mixing present when there are normal lung vessels and no evidence of vascular loss in the upper, middle and lower zones of patients in Groups I and II. Patients in Group I without bronchitis (diagnosis - EMPHYSEMA in figure 37 and Table IX) have a lower incidence of poor mixing than patients in Group I with bronchitis (diagnosis - EMPHYSEMA and BRONCHITIS) when the radiograph vascular pattern is normal. This is especially evident in the middle and lower zones. When the patients in Group II are considered, (diagnosis - BRONCHITIS) who by definition have normal vessels in all lung zones, there is poor intra-pulmonary mixing in over 70% in the middle and lower zones. From figure 37 it can be seen that the difference between the ventilation of the zones with a normal vascular pattern in the patients between Group I suggest that it is due to the presence of bronchitis.

Table X shows the relationship between the vascular patterns and the perfusion (Q) index in the patients in Groups I and II considered in the same way as in Table IX. When the vessels are small or absent there is an abnormally low Q index in only the lower zones. The upper and middle zones rarely have poor perfusion despite evidence of a deranged vascular pattern. When there are normal vessels radiologically, the Q index was never low in any zone in the patients in Group I

without bronchitis, whereas 29% of the lower zones in patients in Group I with bronchitis have poor perfusion. There is a greater percentage (69%) of poorly perfused lower zones in patients in Group II (diagnosis - Bronchitis in Table X).

DISCUSSION

It is clear that all patients with 'generalised' emphysema had severe airways obstruction, whereas it was possible for those with only radiological evidence of small pulmonary arterial branches and vessel loss to have nearly normal lung function and only mild symptoms. The combined criteria suggested by Simon and Galbraith (1953) are therefore clinically useful in selecting patients who without doubt have respiratory insufficiency due to their emphysema.

Apart from unilateral transradiancy (Macleod, 1954) there has been little attention paid to patients with 2, 3 or 4 zones of lung with small vessels and vessel loss and no demarcated bullae, who have very nearly normal overall function. There were 5 such patients in this study (F.B., A.H., R.P., R.G., G.F.). The radiograph of one of them (R.G.) is shown in fig. 28. In all of them the upper and middle zones were those showing vascular changes.

None of these patients were disabled by breathlessness. Their radiographs were indistinguishable from patients like

A.P. whose radiograph is shown in fig. 27. For these reasons they constitute an interesting group as they show that the radiological extent of emphysema if it is 'localised' (i.e. without low flat diaphragm etc.) can bear little relation to the overall function of the lung.

It is possible that the distribution of the radiological changes in the upper and middle zones coupled with the maintenance of normal function in the lower zones is the distinguishing feature in these patients. This possibility will be investigated in the next chapter.

Many investigators, notably Baldwin, Harden, Greene, Cournand and Richards, 1950; Laurenzi, Turino and Fishman, 1962; and Ogilvie and Caterall, 1959, have found that patients with single demarcated bullae of unknown origin may have little or no disturbance in function and in others the loss of function is explicable by the thoracic volume occupied by the bulla. Laurenzi, Turino and Fishman (1962) suggested that an added factor in those with severe airways obstruction may be bronchitis. Only 2 patients in Group I had a single demarcated bulla and no other radiological evidence of emphysema (A.M. and T.F.). Both had severe airways obstruction but only one (T.F.) had bronchitis; the cause of the functional impairment in A.M. remains unexplained as the bulla was only (10 x 10) cms. in size.

The difference between the 'generalised' and 'localised' forms of emphysema lies in Simon's (1964) first criteria which includes the shape and level of the diaphragm and the size of the retrosternal space. He states that these indicate the presence of an "excess of air". This term has been taken to mean an increase in the volume of air in the lungs at maximum inspiration, (at T.L.C.) because that is the situation in which the radiographs were taken. However, these data have shown that the shape of the diaphragm is as often flat as it is curved when the T.L.C. is increased in patients with emphysema. Similarly the depth of the retrosternal space bore little relation to the T.L.C. Only the level of the diaphragm was influenced. When the shape and the level of the diaphragm together was considered, this was confirmed. It is reasonable therefore to think of an alternative explanation for the flatness of the diaphragm and the increased depth of the retrosternal space in emphysematous patients.

Macklem and Becklake (1963) showed that there was a decrease in the relaxation pressure at full inspiration in patients with emphysema (-10 cms. H_2O instead of the normal value of - 30 cms. H_2O). This indicates a loss of retractive forces within the lungs. It is possible that this allows the diaphragm to sag so that it appears flat on the radiograph. The same mechanical situation may also permit the sternum to move forward causing an increased depth of the retrosternal space. To my knowledge these pressures have not been compared with the

contour of the diaphragm in patients with emphysema.

I do not deny that most emphysematous patients with a flat diaphragm also have airways obstruction. Indeed all those with 'generalised' emphysema, who by definition have flat diaphragms, had severe airways obstruction. Also there was probably a significant difference between the RV/TLC in patients with flat diaphragms on one hand and curved on the other. This ratio has been shown by Burrows, Kasik, Niden and Barclay (1965) to be the most closely correlated of all the lung function tests to airways obstruction as measured by the $F.E.V._1$. In emphysema airways obstruction is probably partly due to distortion of bronchi and bronchioles by dilated alveoli and partly to lack of elastic support of the walls of the bronchi on expiration. Both these pathological changes contribute to the loss of retractive force present within the emphysematous lung, so it is not surprising to find there is airways obstruction in most of the patients with flat diaphragms. Nevertheless, airways obstruction does not cause the diaphragm to be flat, otherwise all patients with chronic or acute airways obstruction would have flat diaphragms which is patently not the case, (Simon, 1964; Bates and Christie, 1964).

One might expect that the movement of the diaphragm between maximal inspiration and maximal expiration would reflect the volume of air shifted, i.e. the vital capacity,

and there is indeed a rough agreement. However, the role of the diaphragm in this respect is not at all clear. The chest wall and the abdomen also move with respiration. Mead (1966) has shown with a very elegant technique that during a vital capacity manoeuvre approximately 75% of the volume of air moved is accounted for by the change in volume of the rib cage and 25% by change in volume of the abdomen in the standing normal subject. Diaphragm movement can contribute to both these changes in volume. Wade and Gilson (1954) suggested that $\frac{1}{4}$ of the volume of the vital capacity in normal subjects is due to chest expansion and $\frac{3}{4}$ to diaphragm movement. Any relationship which exists between the vital capacity and diaphragm movement in a normal subject is not necessarily applicable to patients with emphysema. In them, as has been shown, the diaphragm is frequently at a low level and/or is flat, so its ability to move either vertically or to expand the base of the thorax is reduced (Campbell, 1958). It is also in a mechanically disadvantageous position to react to external forces either from the abdomen or from the chest wall. In support of these statements is the finding that only 2 flat diaphragms and 3 low diaphragms moved normally.

Now let us consider the relationship between the regional function of the lung and the radiological vessel pattern in emphysema. At first sight it may seem surprising to compare regional intrapulmonary mixing with the size of lung vessels.

This was done for two main reasons. Firstly, the radiological changes are pathognomic of emphysema and poor distribution of gases is bound to be present if there is a significant amount of tissue destruction and disorganization due to emphysema.

Secondly, the dynamic distribution indices, unlike the perfusion indices, are independent of zones in the individual patient. They are comparable between patients as they are standardised for ventilation and volume. For these reasons the dynamic indices are more applicable when separate zones are considered, which seemed the best way to tackle the problem in a number of patients in whom the vascular changes varied from zone to zone.

The results were extremely interesting and of practical significance. If the mid lung vessels are observed to be small and there is evidence of more peripheral vascular loss in a zone of lung, it has been shown that there is poor intrapulmonary mixing in that zone in an average of 83% of cases, This is so whether the patient had bronchitis or not. However, if the vessels are of normal calibre and there is no vessel loss, normal mixing is not always present. This is particularly obvious when bronchitis accompanies emphysema, when the distribution of abnormal intrapulmonary mixing has been shown to be mainly in the middle and lower zones. This leads to the practical point that if a patient has a productive cough and small vessels

in the upper and middle zones the intrapulmonary mixing will be poor throughout the lung in 80% of instances.

The regional ventilation changes in bronchitis will be discussed in full later. It is true that as there were only 8 patients in Group II with severe chronic obstructive bronchitis these results must be regarded with some caution. However, the similarity between the topographical distribution of poor intrapulmonary mixing in them and the normally vascularised zones of 27 patients from Group I with bronchitis is striking.

Scrutiny of regional perfusion in zones with normal vessels revealed a greater incidence of poor perfusion in the lower zones of patients with bronchitis accompanying emphysema than in patients without a productive cough. The difference was not so marked as when intrapulmonary mixing was considered. When small lung vessels were present the Q indices were mainly impaired in the lower zones and very seldom in the upper and middle zones. This is probably due to the very low perfusion values for the upper and middle zones which are included in the normal range in these areas and the wide fields 'seen' by the counters which overlap.

Bentivoglio, Beerel, Stewart, Bryan, Ball and Bates (1963) stated that in 78% of their emphysematous

subjects the perfusion agreed with the vessel changes, but did not specify the location of the disagreement in zones. In this data there is almost total disagreement in the upper and middle zones with small lung vessels and total agreement in these zones when the vessels are normal so in individual patients the agreement shown would depend directly on the incidence of emphysema radiologically in the upper zones.

The reduction in calibre of the mid lung vessels in emphysema is regarded by some to be the only reliable diagnostic sign of the disease (Laws and Heard, 1962) and by others as an essential finding before the diagnosis can be made (Simon and Galbraith, 1953; Simon, 1964). The reason why such vessels appear small on the radiograph is not yet proven but it is pertinent to consider the several possible causes.

In the normal lung the walls of the smaller pulmonary arteries are kept apart partly by intravascular pressure and partly by the framework of the lung tissue itself. In emphysema the transpulmonary pressure is decreased and will exert an extra vascular pressure on the vessel walls, tending to close them. This seems to me to be the most likely explanation but other possibilities must be mentioned.

The cardiac output in emphysema is said to be usually normal and in many cases there is no pulmonary hypertension, (Wade and Bishop, 1962). As the circulating blood volume is also normal, the flow of blood through the pulmonary arteries in the emphysematous lung must also be normal. As these circulatory characteristics are also present even when all the vessels appear small on a radiograph then the size of the vessels is unlikely to be related to flow of blood through them.

Local vascular changes such as hypertrophy of the vessel wall have not been observed in emphysema (Reid - personal communication). If the vessels were small due to vasoconstriction from a reduced Pa_{O_2} one would expect to find the same changes in other pulmonary and cardiac disorders. In any event, these vessel changes have been observed when the Pa_{O_2} was normal in this data.

It is interesting that when inflated and injected, the excised emphysematous lung has vessels of normal calibre (Millard, 1965). This appears to be a contradiction but the pressure used to inject the vessels for this preparation was about 100 mm.Hg. which greatly exceeds the usual pulmonary artery pressure to which this low pressure system is normally subjected. It is not surprising that under these circumstances the vessels were virtually dilated.

In conclusion, this enquiry has shown that in looking at a chest radiograph of a patient with emphysema with function in mind it is useful to decide whether 'generalised' emphysema is present or only the cardiovascular changes of 'localised' emphysema. In the presence of the former, there is invariably severe airways obstruction. The diaphragm shape and the depth of the retrosternal space has been shown not to be related to the volume of air in the lungs at the time the inspiratory film was taken. It is postulated that the cause of these changes is a loss of retractive force in the lungs. The appearance of vessels of small calibre and more peripheral vascular loss in the chest radiograph is closely associated with underlying functional damage but normal vessels do not necessarily mean that that part of the lung is functioning normally. In the presence of bronchitis, the middle and lower zones of lungs have been found to have poor intra-pulmonary mixing despite a normal vessel pattern.

TOTAL AND REGIONAL LUNG FUNCTION IN EMPHYSEMA.

In the following description of the results of total and regional lung function studies in the patients in Group I, two relevant points have been borne in mind which have emerged from comparing the radiographs with function in the previous chapter. First, that several patients in Group I have little overall functional impairment despite considerable radiographic evidence of emphysema. This is surprising. The regional distribution of the radiographic and functional changes are of particular interest in these patients. Secondly, chronic bronchitis has been shown to probably influence regional intrapulmonary mixing but its effect on the total function of the lung in the patients in Group I has not yet been evaluated. This matter demands closer investigation.

Further it is the purpose of this section to compare regional patterns of dysfunction in the patients in Group I with arterial blood gas tensions and overall lung function tests. Indirect methods of assessment indicate gross $\dot{V}/\dot{Q}$ difference in the lungs as a whole in emphysematous patients, (Briscoe and Cournand, 1962). Although it is not possible to measure the $\dot{V}/\dot{Q}$ ratios of different regions of the lung by surface counting methods, zonal patterns of poor intrapulmonary mixing can be defined. These patterns may influence overall gas exchange in different ways according to

the amount and distribution of poorly functioning lung tissue present.

RESULTS.

TOTAL LUNG FUNCTION TESTS.

The detailed values in all patients are shown in Appendix II.

Table XI shows the mean values and ranges of the $F.E.V._1$, static lung volumes and D_{LCO} at rest and during exercise in patients in Group I. On the average, the $F.E.V._1$, V.C. and D_{LCO} measurements are decreased below the expected normal range. No patient had an $\frac{F.E.V.1}{F.V.C.}$ of over 70%. The F.R.C., R.V., T.L.C. and $\%\ ^{RV}/TLC$ mean values were increased beyond the predicted value. The scatter of the $F.E.V._1$, V.C., $^{RV}/TLC$ and D_{LCO} are illustrated in figs. 29-32.

No significant difference was shown between the patients in Group I depending on the presence or absence of bronchitis in the values of $F.E.V._1$, $\frac{F.E.V.1}{F.V.C.}$, the static lung volumes expressed as a percentage of the predicted value, or the D_{LCO} at rest and after exercise. The mean value of the % predicted V.C. was higher in those without bronchitis (69·4% $\pm$ 19·95%) than in patients with a productive cough (62·5% $\pm$ 17·06%). Similarly, there was a small difference in the average value of the F.R.C. (151·4% $\pm$ 42·0% in the bronchitic patients and 145·1% $\pm$ 39·5% in those without bronchitis).

The regional distribution of radiological and functional changes in individual patients in whom these values were not

markedly impaired has been examined.

Only 4 patients had an $F.E.V._1$ of over 2 litres (F.B., R.P., A.H., and R.G.); in 3 of them the radiological evidence of emphysema was confined to the upper and middle zones of the lungs, the remaining patient (R.G.) had also a demarcated bulla at the left base (see figure 28). Intrapulmonary mixing was unimpaired in one or both lower zones in 3 patients and in the fourth (F.B.) all zones had poor mixing.

In 10 patients the V.C. was over 90% of the predicted value; in 7 only the upper and middle zones had radiographic vascular changes and in 5, one or both lower zones had normal intrapulmonary mixing.

Three patients had an F.R.C. below the predicted value, (A.S., T.F., E.Sh.). All had a large demarcated bulla.

The $^{RV}/_{TLC}\%$ was below 50% in 8 patients; 3 had large or multiple demarcated bullae visible on the radiographs (E.Sh., H.K. and N.H.), and in 4 patients only the upper and middle zones had emphysema visible on the radiograph (G.F., R.P., A.H., J.S.); 5 had one or both lower zones with normal intrapulmonary mixing.

The D_{LCO} was over 12·0 ml.CO/min/mm.Hg. in only 3 patients at rest (R.G., T.C., and A.P.), but in 2 of them the % extraction of CO was 26% and 28% so the end tidal sampler may well be in error with them; in the other the emphysema was radiologically localised to the upper and middle zones. Ten patients refused to do any exercise and all except one had a D_{LCO} below 9.0 units (T.C.).

The extraction percentage of CO was above 40% in only 3 patients, 2 of them had a low $D_{L_{CO}}$ (J.M^{c}M., Gl.H.) and generalised emphysema but one (A.P.) had a D_L of 12·6 ml.CO/min/mm.Hg. and the distribution of the emphysema is mentioned above.

The $D_{L_{CO}}$ during exercise exceeded 20 units in only one patient (G.F.) who had emphysema localised to the upper and middle zones.

ARTERIAL BLOOD GAS TENSIONS.

The mean values and ranges of the arterial blood gas tensions, alveolar-arterial oxygen tension differences, alveolar ventilation and V_D/V_T in patients in Group I as shown in Table XII.

The standard deviations and significance level of these values in patients with or without bronchitis is shown in Table XIII. The Pa_{CO_2} and the $\dot{V}_A$ values are significantly different but there is no difference of significance in the other measurements due to bronchitis.

The scatter of the resting Pa_{O_2} is illustrated in fig. 32. This value was above 90 mm.Hg. in 10 patients; in 7 the emphysema was confined radiologically to the upper and middle zones and in 6 there was normal intrapulmonary mixing in one or both lower zones.

Twelve patients were unable to exercise, 5 of those had a Pa_{O_2} below 70 mm.Hg. at rest; the average Pa_{O_2} of this group was 73·7 mm.Hg. which is lower than the total group. All except one of those unable to exercise had Grade V breathlessness.

In 11 patients the Pa_{O_2} rose > 2 mm.Hg. with exercise; their mean resting Pa_{O_2} was 81·5 mm.Hg. and in 2 patients it was below 70 mm.Hg. In 6 patients the emphysema was confined radiologically to the upper and middle zones of the lungs and 6 patients had one or both lower zones with normal intrapulmonary mixing.

In another 10 patients the Pa_{O_2} fell > 10 mm.Hg.; their mean resting Pa_{O_2} was 82·4 mm.Hg; none were below 70 mm.Hg. but 3 were above 90 mm.Hg. Three of those patients had emphysema confined radiologically to the upper and middle zones of the lungs; only 1 had a lower zone functioning normally, (J.Mc.M.).

The resting Pa_{CO_2} was above 47 mm.Hg. in 11 patients; all had bronchitis. The relationship between $F.E.V._1$ and Pa_{CO_2} is shown in fig. 38 where the presence of bronchitis is indicated. Although the $F.E.V._1$ is invariably below one litre in patients where the Pa_{CO_2} is raised there are 29 other patients in Group I where the $F.E.V._1$ is below one litre but the Pa_{CO_2} is at or below 47 mm.Hg.

The values of Pa_{CO_2} after exercise have not been considered in this data because the arterial blood sample was not withdrawn during exercise and I have observed that the Pa_{CO_2} may change very rapidly with hyperventilation after exercise has stopped and certainly within one minute.

Seven patients had a $\dot{V}_A$ below 3·5 l/min. but only 3 of these had hypercapnia.

Two patients had a V_D/V_T of below 0·40; one (N.H.) had a large, virtually non-communicating bulla and the other (R.P.) had upper and middle zone emphysema radiologically.

REGIONAL LUNG FUNCTION

The results in all patients in Group I are shown in Appendix II.

THE V INDEX AND THE Q INDEX.

Figure 39 shows the relationship between these indices in all zones of patients in Group I. The upper, middle and lower zones are distinguished from each other. There is evidently a definite trend at approximately a 45^0 angle between these indices but there is a wide scatter of points. No obvious difference is discernible between the upper, middle and lower zones. If the transparent cover bearing the normal range of values for each zone is superimposed, it can be seen that very many of the upper zones (triangles) have a great deal higher V and Q index than normal, while almost as many of the lower zones (black dots) have a low V and Q index. This is probably due to the dependence of the V indices and the Q indices separately on each other in a particular patient as they represent shares of ventilation and perfusion.

THE V INDEX AND THE DYNAMIC DISTRIBUTION INDEX.

Fig. 40 shows the relationship between the V index which is a share of a single inspiration during breathholding to a zone,

and the D.D.I. which is measured during tidal breathing. When the D.D.I. is above 60 units the V index is below 0·8 in only one instance. However, when the D.D.I. is low ($<$ 40 units) although in the majority (approx. 145 instances) of the V indices are below 1·0, there are 31 instances where it is above 1·0. Because of this discrepancy which is probably due to the independence of the D.D.I. between zones in an individual on one hand and the interdependence of the V index on the other, the D.D.I. has been chosen to compare the ventilation of zones between patients.

PATTERNS OF REGIONAL IMPAIRMENT IN FUNCTION.

Using the intrapulmonary mixing regional patterns of dysfunction have been found. Table XIV shows these patterns, the number of patients in whom they are displayed and the coding which will be used for reference. Only 10 patients (20%) in Group I have one or both lower zones with normal intrapulmonary mixing. Twenty-six patients (52%) have both lower and middle zones affected and the remaining 14 patients have the lower zones with or without one middle zone with poor mixing.

RELATIONSHIP BETWEEN REGIONAL AND TOTAL LUNG FUNCTION.

The impairment in regional function will be described as coded in Table XIV where 4 approximately equal groups of patients with different patterns have been chosen according to the regional findings.

Table XV shows the mean values, ranges and standard deviations of the total lung function tests in each group of patients with regional impairment patterns. The group which differed from the others significantly contained those patients with one or both lower zones with a normal D.D.I. ($\left.\begin{matrix}221\\220\end{matrix}\right\}$) in the following ways:-

1) The $F.E.V._1$ is higher. (Highly significantly different from 022 and $\left.\begin{matrix}012\\002\end{matrix}\right\}$).

2) The Pa_{O_2} at rest is higher. (Probably significantly different from $\left.\begin{matrix}222\\122\end{matrix}\right\}$ and 022). (i.e. when both middle and lower zones have a low D.D.I. $\pm$ upper zones).

3) The Pa_{O_2} after exercise is higher (Significantly different from $\left.\begin{matrix}222\\122\end{matrix}\right\}$ and 022, i.e. same groups as (2)).

4) The V_D/V_T is smaller (Probably significantly different from 022. i.e. when both lower and middle zones have a low D.D.I. but the upper zones mix normally).

DISCUSSION

The most interesting functional aspect of these emphysematous patients is not the serious degree of regional and total impairment in function of the majority, but the lack of these findings in several who undoubtedly had radiological evidence of emphysema. Many authors have reported poor expiratory flow rates, large static lung volumes, reduced diffusing capacity and disturbances in the blood gases in patients with emphysema. (Baldwin, Cournand,

and Richards, 1959; Bates, Knott and Christie, 1954; Williams and Zohman, 1959; Ogilvie, 1959; Williams and Seriff, 1963; Thurlbeck, Fraser and Bates, 1965; Burrows, Fletcher, Heard, Jones, and Wootliff, 1966; Nash, Briscoe and Cournand, 1965). In all their cases there was evidence of severe airways obstruction, probably because airways obstruction was one of the main requirements for selection for study (Burrows, Fletcher, Heard, Jones and Wootliff, 1966; Nash, Briscoe and Cournand, 1962; Baldwin, Cournand and Richards, 1949. Also, generally speaking in studies done before the Ciba Symposium (1959) the diagnosis of emphysema was made on the purely clinical grounds of unremitting constant dyspnoea and irreversible chronic airways obstruction. By choosing to accept the radiological evidence of emphysema as the basis of the diagnosis in this study, it was not necessary for the patients to have severe airways obstruction.

Ebert and Pierce (1963) discarded the radiological evidence of emphysema "because it does not accurately define the pathologic appearances in emphysema". There is good reason to consider now that the radiological features are well related to morbid anatomy (Laws and Heard, 1962; Reid and Millard, 1964; Thurlbeck, 1963; Thurlbeck, Fraser and Bates, 1964; Burrows, Fletcher, Heard and Wootliff, 1966; Nicklaus, Stowell, Christiansen and Renzetti, 1966). Despite this, Bates and Christie (1964) concluded that "impaired ventilatory flow rates, abnormal inert gas distribution

and impairment of the exercise steady state diffusing capacity must be present before the clinical diagnosis of pulmonary emphysema can be made". There is therefore a possibility that some authorities would not accept that the patients R.G. (fig.26) F.B., R.P., G.F. and A.E., have pulmonary emphysema. On the other hand there is also evidence which indicates that the diagnosis of emphysema is erroneous on purely clinical and physiological grounds because of the resemblence to chronic bronchitis and bronchiolitis (Simpson, Heard and Laws, 1963; Hentel, Longfield, Vincent, Filley and Mitchell, 1963). Indeed, this was one of the main reasons for the Ciba Guest Symposium (1959). In my opinion, the patients in Group I fulfil the Ciba Symposium definition for "clinical emphysema" despite the absence of severe airways obstruction in some of them.

Several clinically and radiologically recognizable forms of pulmonary emphysema have been described by different authors (Bates, 1959; Richards, 1960; Bates and Christie, 1964; Reid, 1965). Among them compensatory emphysema, single demarcated bullae, unilateral transradiancy and multiple bullous emphysema (described as paraseptal by Reid, 1965), have been reported to be unaccompanied by severe airways obstruction. The radiological appearances of the five patients without airways obstruction do not resemble any of these categories. In each case the vascular changes in the radiograph were mainly in the upper and middle

zones but they were of similar extent and distribution to that found in other patients with severe airways obstruction, so as to be radiologically indistinguishable. However, as illustrated in the previous chapter, the normal size of the zonal vessels in the radiograph is not always a very good guide to function particularly when chronic bronchitis is present. When regional function is compared to total function the decisive factor seems to be the function of the lower zones.

It has been shown that patients with one or both lower zones with normal intrapulmonary mixing have a significantly different arterial oxygen tension after exercise from patients with other patterns of regional dysfunction. This is probably simply a reflection of the volume of functioning lung tissue capable of gas exchange in the lower zones compared with elsewhere. Nevertheless, it is of importance as it illustrates that the regional distribution of functional disturbance in the emphysematous lung influences the overall ventilation-perfusion ratio which to my knowledge has not been shown before. Although Bentivoglio, Beerel, Stewart, Bryan, Ball and Bates (1963) stated that "the blood gases in general are more markedly abnormal both in frequency and degree in patients with generalised disease", they did not measure the arterial oxygen tension at rest or after exercise in the emphysematous patients in whom the regional studies had been done.

The failure of the Pa_{O_2} in 22 out of 33 patients to rise with exercise agrees with the data of Jones (1966) who found that 6 out of 9 emphysematous patients Pa_{O_2} fell by a mean of 11.6 mm.Hg. with exercise. He had a superior technique for standardising exercise and measuring blood gas exchange during exercise, nevertheless he also observed that the change in the Pa_{O_2} with exercise bore little relation to the resting Pa_{O_2}, which agrees with the present study.

As Jones (1966) pointed out the lung destruction in emphysematous alevoli has presumably led to a relatively fixed abnormality in their ventilation-perfusion characteristics. Briscoe and Nash (1965) have shown that in a slowly ventilated space with a very low ventilation-perfusion ratio (below 0.1) the saturation of the blood coming from the space is low and relatively insensitive to changes in this ratio. However, it is very sensitive to changes in the saturation of the mixed venous blood. During exercise the mixed venous blood saturation will fall as oxygen consumption increases and in the emphysematous patient the enlarged alveoli will act like a venous arterial shunt. Consequently, the arterial oxygen tension fallls. However, if there are a sufficient number normally ventilated and perfused alveoli whose $\dot{V}_A/\dot{Q}$ ratio is not so low or fixed, the ventilation-perfusion ratio in these alveoli will increase with exercise sufficiently to counteract the effect of the shunt produced by the abnormal alveoli resulting in either a small rise or similar

Pa_{O_2} immediately after exercise compared with the resting level.

It is the relative number of affected alveoli compared with the number of more normal alveoli which will determine the hypoxaemia of a patient with a ventilation-perfusion inequality with exercise and not necessarily the spatial distribution of these alveoli. However, as there are more and smaller alveoli with a larger surface area per unit volume in the lower zones than in the upper zones (Glazier, Hughes, Mahoney, Pain and West, 1966) the normality of intrapulmonary mixing in the lower zones is of greater importance to overall gas exchange.

Before considering the ventilation-perfusion relationship in the emphysematous lung there are several points to bear in mind concerning the V and Q indices. Both are measured when 'looking' at a large number of alveoli, the ventilation and perfusion of which are summated. There is no guarantee whatsoever that the gas and blood 'seen' in these zones meet one another in the alveoli. Even in the normal lung the ventilation-perfusion ratios vary from 0·7 to 2·0 and in the emphysematous from 0·05 to 3·0 (Briscoe and Cournand, 1962), so there is considerable variation at the alveolar level. The assessment of V and Q indices obscures these variations in different alveoli by summation.

Secondly, during a single breathholding manoeuvre (which is a maximal inspiration) as Briscoe (1962) pointed out there is

doubt whether the ventilation and perfusion measured bears any relation to that during normal breathing. Armitage and Arnott (1949) have shown an increase in oxygen consumption during the first deep breath and Nadel and Tierney (1961) have shown that deep breathing decreases the airways resistance. Various changes in the blood circulation during breathholding have been described by Mithoefer (1965).

For these reasons the V and the Q indices themselves are of doubtful value in portraying the ventilation and perfusion in different zones under normal circumstances. Nevertheless, despite these reservations it appears that the V and the Q indices are roughly matched and that generally the underventilated zone is also underperfused. This is in agreement with the observation of the morbid anatomy of the emphysematous lung by Laennec (1821) when he said it looked pale. It also agrees with the findings of Bentivoglio, Beerel, Stewart, Bryan, Ball and Bates (1963) using ^{133}Xe.

It is possible theoretically to derive zonal $\dot{V}_A/\dot{Q}$ ratios based on the V and Q indices if a number of assumptions are made. First, that the fields of the anterior, posterior and adjacent counters overlap so that all of both lungs are surveyed and secondly, that the blood and gas 'seen' actually meet at the alveolar level. A value for the cardiac output can be assumed and the alveolar ventilation measured. These are shared out

between the zones according to the V and Q indices and by interpolation and reference to the oxygen and carbon dioxide dissociation curves and $^{V}/_{Q}$ diagram(West, 1966), predicted alveolar and arterial gas tensions can be gained. Surprising similarity in some patients between the predicted and observed arterial gas tensions has been found but there is a very large discrepancy in others. This is due both to the gross assumptions made and the lack of homogeneity of ventilation and perfusion at the alveolar level which as indicated before is not portrayed by the V and Q indices. Calculations of the zonal $^{V_A}/_{Q}$ ratios have not been included in this thesis for these reasons. Moreover, as little stress as possible has been laid on the indices measured during breathholding and instead the dynamic distribution indices have been used to evaluate the regional function of the lung.

In conclusion, these findings have shown that is is possible to have radiological evidence of emphysema involving the upper and middle zones of the lung with little airways obstruction or disability. The distinguishing feature between those patients and those with severe airways obstruction but similar radiological features lies in the function of the lower zones. In addition, a significantly different degree of hypoxaemia after exercise has been observed in patients with one or both lower zones with normal intrapulmonary mixing compared with those who have poor mixing throughout the lung

CHRONIC OBSTRUCTIVE BRONCHITIS AND EMPHYSEMA

" We are met at the outset by the fact that most of these patients suffer from manifest bronchitis also ..... we cannot disentangle the symptoms of the two diseases so as to be able to say "This is due to emphysema and this to bronchitis"..", Samuel Jones Gee, Lumleian lecture to Royal College of Physicians, London (1899).

Chronic bronchitis, like emphysema, gives rise to airways obstruction. Just how much each disease contributes separately to the functional disturbances in the lungs and heart is very difficult to determine when they occur in the same patient. A reasonable approach to this problem is to study those patients who are severely disabled by apparently only one of these diseases and perhaps some differences in the pattern of clinical and physiological findings will be discernible.

One outstanding study recently has been done in an effort to do this, (Fletcher, Hugh-Jones, McNicol and Pride, 1963). Sixteen patients were selected with severe obstruction of the airways (F.E.V. $<$ 1 litre). They were divided into groups according to the presence of productive cough and the appearance of emphysema on a chest radiograph. Four patients who had the radiographic changes of emphysema but no productive cough were found to be tall and thin, to have little tendency to definite heart failure and no evidence of right ventricular

hypertrophy on an electrocardiograph. The total lung capacity was increased and the single breath diffusing capacity, when divided by the lung volume, D_{LCOSB}/V_A, was decreased. On the other hand 7 patients with normal chest radiographs who complained of a productive cough were of normal build. Compared with the first group, these 7 patients had a higher haemoglobin concentration and packed cell volume, a greater incidence of heart failure and evidence of right ventricular hypertrophy. They were more likely to underventilate and become desaturated and hypercapneic, had a normal D_{LCOSB}/V_A and a normal or reduced total lung capacity.

The residual volume was increased in all the patients but more strikingly in the 4 patients with emphysema. The RV/TLC ratio was similar in both groups of patients.

A complete description of their results is not out of place in this chapter as the same approach in selection of patients has been used. The clinical and physiological findings of Fletchey Hugh-Jones, McNicol and Pride (1963) should be duplicated. The reason for repeating their work and presenting the data separately is three-fold. One, although the intention at the outset of this study was to examine patients with emphysema, many of the patients also had bronchitis, so it seemed logical to investigate patients at the other end of the "spectrum of airways obstruction" (Fishman, 1965) using similar techniques

to complete the picture. In this way it was hoped any differences between the patients with or without bronchitis in Group I which were attributable to bronchitis would be exaggerated. Secondly, there are more patients in each group presented here than in Fletcher, Hugh-Jones, McNicol and Pridds (1963) data. The third reason is that it was of interest to investigate regional ventilation and perfusion in patients with chronic obstructive bronchitis.

SELECTION OF PATIENTS

All the patients had severe irreversible airways obstruction with an $F.E.V._1$ of 1 litre or less.

The first group of 9 patients, 3 females and 6 males, were taken from Group I. Seven of these patients were subsequently subjected to thoracic surgery and the presence of emphysema was confirmed macroscopically. All flatly denied cough and sputum production.

The second group of 7 patients, 2 females and 5 males, were from Group II.

For simplicity, the first group will be called the 'emphysema' group and the second will be the 'bronchitis' group in this chapter.

The two groups comprise patients who, as far as it is possible to tell without pathological examination, have emphysema without bronchitis, and bronchitis without emphysema.

The airways obstruction in each group is comparable and severe.

The detailed radiological findings of the patients in each group are shown in appendix II. Although these form part of the criteria for entry into these selected groups it is worth noting several radiological features in the bronchitic group. With one exception, none of the diaphragms were flat or low. In 6 patients there was poor diaphragm movement. In 2 patients there was an increased depth of the retrosternal space on a lateral film, one of these had kyphosis which may explain this finding. The transverse diameter of the heart was 12·5 cms. or more in all cases: 2 were judged to have enlarged hearts. In 4 cases the pulmonary artery was dilated. There was no evidence of inflammatory changes of any kind in the bronchitis group.

The combination of large hilar vessels, a dilated pulmonary artery, a normal or enlarged heart, normal sized peripheral vessels and a normal diaphragm in a patient with airways obstruction complaining of a productive cough is called by Dr. Simon "chronic bronchitis gone wrong", (personal communication). He claims that these features are found in a definite proportion of patients who are severely affected by chronic bronchitis (Simon, 1966). Four of these bronchitic patients fell in this category, Figure 41 is a postero-anterior chest radiograph of one of these.

RESULTS

Age, Symptomatic and Historical Enquiry (Table XVI):-

The groups are of comparable age but the age of onset of breathlessness is 10 years earlier in the emphysema group than in bronchitis. The groups are similarly disabled by breathlessness. All the bronchitic patients, except one, had had at least two episodes of acute respiratory infection in the past three years of sufficient severity to confine them to bed for a week or more, and in all of them except one cough was the first symptom of which they complained. Four had had one attack of heart failure. On the other hand, only 4 of the 9 emphysematous patients had had an acute infection in the past 3 years and 1 had had slight ankle oedema without other evidence of heart failure. The smoking habits of the 2 groups were similar (see Table XVII).

Routine Clinical Investigations:- While there is a tendency for the emphysema patients to be tall and thin it is noticeable that 5 bronchitics were 20 lbs. or more below weight for their height (fig.42).

Table XVII shows that 3 of the bronchitic group had an increased haemoglobin concentration ($>$ 16·5 gms.%) whereas only 1 of the 'emphysema' group showed this.

Five of the 7 bronchitic patients had definite evidence of right ventricular involvement and 1 had ischaemic changes.

Four of 8 emphysema patients had a normal electrocardiographic pattern.

Physiological Findings:-Table XVIII shows the means and standard deviations of the lung volumes, diffusing capacity, at rest and during exercise, percentage saturation of haemoglobin, arterial blood gas tensions, alveolar ventilation, minute ventilation and V_I/V_T in the emphysema and bronchitic groups. There is no significant difference between these groups when V.C., F.R.C., T.L.C., RV/TLC, D_LCO at rest and during exercise are considered. Expressed as a percentage of the predicted value these measurements are illustrated individually in figs. 43 to 47 , where it can be seen that there is a large overlap in each of these measurements between the groups.

The vital capacity is decreased in all the patients with the exception of one with emphysema (A.V.M.). All exhibit an increase in the functional residual capacity and all except one bronchitic (R.T.) have an increase in the total lung capacity. The increase in the latter figure is not so great compared with the predicted value as the increase in functional residual capacity.

The diffusing capacity at rest is decreased in all the patients. With exercise it increased in 2 bronchitic patients (F.R. and L.M.) and in 4 of the emphysematous; in none of them did it attain a normal exercise value. One

bronchitic and 3 emphysematous patients were unable to exercise at all; all of these had very low diffusing capacities at rest. The percentage extraction of CO from the inspired gas was the same on the average in both groups, but the lowest values were recorded in patients with emphysema.

Table XVIII and fig. 49 show that there is no significant difference between the percentage saturation of oxyhaemoglobin, the $P_{A-a}O_2$, V_D/V_T or minute ventilation in the two groups of patients. However, the mean $PaCO_2$ of the bronchitis group is beyond the upper limit of the normal range at 53·1 mm.Hg,(fig.48) whereas this mean value in the emphysema group is normal (42·4 mm.Hg.). This difference is highly significant. There is a tendency for the alveolar ventilation (V_A) to be low in the bronchitic group, likewise the Pa_{O_2}, however these are not statistically significant. With exercise the Pa_{O_2} rose in two patients in each group. In all the other instances it fell (see fig.49).

The regional ventilation and perfusion findings in emphysema shown in figs. 50 and 51 are in direct agreement in approximately 80% of instances with the size and calibre of the zonal mid line vessels and the evidence of vascular loss seen on the PA radiograph and tomograms. This relationship has been described in detail in an earlier chapter.

In the 7 bronchitics the lower zones have less perfusion than normal in 5 right lungs and 4 left lungs (fig. 53). The upper zones in all except one patient in the right lung and 2 patients in the left lung are apparently overperfused. Intra-

-pulmonary mixing was abnormal in the bronchitic patients; (fig.52) in 11 instances the abnormality was in the lower zone (5 on the right and 6 on the left) and in 9 it was in the middle zone (4 on the right and 5 on the left).

DISCUSSION.

These patients were selected because they were at opposite ends of a clinical spectrum of airways obstruction. The most important finding when the two groups are compared is the lack of any clearly cut distinction between the functional effects of severe bronchitis and severe emphysema, with the single exception of the Pa_{CO_2}. The physiological picture is apparently dominated by airways obstruction. Perhaps, by choosing to include patients whose disability was about the same, the differences between the two groups have been automatically obscured which may have been more marked if the airways obstruction had been less or if serial observations had been made over a long period. It is a valid criticism of enquiries of this kind that they take little notice of the way in which the loss of function has developed and it is precisely in this respect that chronic bronchitis and emphysema differ most.

CLINICAL FINDINGS

A clear difference between the groups has been shown historically in the length of time the patient has complained

of breathlessness and the incidence of chest infections. This point was not shown by Fletcher, Hugh-Jones, McNicol and Pride, (1963). Those patients with emphysema have a long history of breathlessness which gradually becomes worse and this is almost certainly the reason they are more frequently found in hospital practice.

Although there was a tendency for the patients with emphysema to be tall and thin, as commented upon in a previous chapter, it is noticeable that there was also a tendency for the patients with bronchitis to have lost weight. This latter is a point not usually emphasised.

The higher haemoglobin level in the bronchitic group agrees with a similar finding by the other workers (Fletcher, Hugh-Jones, McNicol and Pride, 1963; Nash, Briscoe and Cournand, 1965).

STATIC LUNG VOLUMES

The lack of any obvious or significant difference in the static lung volumes between the groups is at first sight surprising. Many investigators have reported that the T.L.C., $^{RV}/_{TLC}$ and F.R.C. are increased in emphysema but only Fletcher, Hugh-Jones, McNicol and Pride (1963) have investigated "pure" bronchitis when the airways obstruction was so severe. The T.L.C. was increased in both groups of patients studied and the range of values was similar. Although there was a tendency for the F.R.C. to be greater in the emphysematous group it was

also considerably increased beyond the predicted normal value in 6 of the 7 patients with chronic obstructive bronchitis.

The increase in the F.R.C. and T.L.C. in these patients is probably a result of severe airways obstruction and this would apply whether the airways obstruction was coexistent with destruction of the lung tissue as in emphysema or not. In this connection it is interesting to note the radiological evidence of 'overdistension' (low flat diaphragm and increased retrosternal space) is absent in patients with bronchitis with one exception. This suggests that the lungs could enlarge further in these patients but does not do so. There are good reasons why this should be the case. In emphysema the distension of the lungs seen radiologically is a reflection of gross loss of lung tissue which in turn makes the lungs more easily distensible even if the tissue which remains contains the normal population of elastic fibres. In these circumstances the opposing pull of the chest wall structures stretches the lung until at the new lung volume it is precisely balanced by the tendency of the lungs to collapse. This train of events is especially apparent radiologically in the low position of the diaphragm. In bronchitis, uncomplicated by emphysema, there is no loss of lung tissue and the increased F.R.C., R.V. and T.L.C. are purely an effect of airways obstruction which does not necessarily render the diaphragms flat although it may hinder the diaphragm movement with respiration.

DIFFUSING CAPACITY.

The steady state diffusing capacity at rest and after exercise did not differentiate between the bronchitic and emphysematous group. Fletcher, Hugh-Jones, McNicol and Pride, 1963, and Burrows, Kasik, Niden and Barclay, 1961, have shown that the single breath method of measuring diffusing capacity when it is divided by the lung volume gives low values in emphysema and normal values in bronchitis. First let us consider the differences between the two methods. Cadigan, Marks, Ellicott, Jones and Gaensler (1961) have shown experimentally that the ratio of the single breath diffusing capacity ($D_{LCO\,SB}$) to the steady state diffusing capacity ($D_{LCO\,SS}$) is directly related to increasing unevenness of distribution of inspired gas as measured by nitrogen washout curves in patients with airways obstruction. This implies that an important fraction of the decrease in $D_{LCO\,SS}$ is due to uneven distribution of inspired gas itself. It does not necessarily reflect lung tissue destruction or a decrease in alveolar capillary exchange surface area where there is gross unevenness of distribution present. Even in emphysema the $D_{LCO\,SS}$ has been shown to bear an inverse relationship to the amount of emphysema present pathologically in the lung slice (Williams 1965). In patients with severe airways obstruction whether it is due primarily to bronchitic or alveolar pathology

the uneven distribution will be similar and the effect of this may predominate using the steady state method.

An additional factor is that a raised alveolar pCO_2 has been shown to increase the $D_{LCO\,SB}$ (Rankine, McNeill and Forster, 1961). This occurs only in the bronchitic group and could have only a negligible effect. It could not account alone for the differences between the two groups in Fletcher's (1963) data. The effect of the alveolar pCO_2 on the steady state method is less clear because of the associated increase in minute ventilation (Forster, 1965).

These reasons are sufficient to explain why the single breath D_L should be affected less in bronchitis than in emphysema and why the steady state D_L does not display any differentiation between the two groups of patients.

Bates, Knott and Christie (1956) found that the steady state diffusing capacity was normal in patients with chronic bronchitis. This report appears to directly contradict the present data. However, their patients were selected because of "a definite history of recurrent winter bronchitis without constant dyspnoea on exertion". The mean vital capacity was higher in their study than in the present one and there was no evidence of really severe airways obstruction. Presumably, therefore, their subjects did not have a similar degree of unevenness of distribution of inspired gas and therefore are not comparable to the group of bronchitic patients presented here.

ARTERIAL CARBON DIOXIDE TENSION.

The outstanding and only prominent physiological abnormality found in bronchitis which differed from the emphysema group was the raised arterial pCO_2. This finding is frequently considered to be synonymous with alveolar hypoventilation and indeed separate measurement of alveolar ventilation confirmed that there is alveolar hypoventilation in this group of bronchitics. This agrees with other investigators, (Fletcher, Hugh-Jones, McNicol and Pride, 1963; Smart, Naimi and Capel, 1961).

The highly significant difference in the $PaCO_2$ between these small groups of patients agrees with the significant difference already described in the previous chapter in all the patients in Group I with or without bronchitis. We are now in a position to explore further the relationship between the $F.E.V._1$ and the Pa_{CO_2} in patients in Groups I and II. Fig. 54 shows these values in patients from Group I who had no bronchitis and all the patients in Group II. It seems that the $F.E.V._1$ can be very much less in the former group without hypercapnia than in the latter; if a curve was drawn by eye between the points in each of these groups the bronchitic curve would lie above and to the right of the curve representing the emphysematous patients. Fig. 55 shows the $F.E.V._1/Pa_{CO_2}$ relationship in the patients in Group I <u>with</u> bronchitis. A curve representing these points would lie approximately between

those from fig. 54, tending towards the Group II patients above the normal range of Pa_{CO_2} and towards the Group I patients with no bronchitis when the Pa_{CO_2} were normal. There is obviously a wide scatter round these imaginary curves but nevertheless it is striking that only those patients who have bronchitis have hypercarbia and none who denied having a productive cough have a raised Pa_{CO_2} and it seems to me that the patients represented in fig. 54 have a different $F.E.V._1/Pa_{CO_2}$ relationship from each other.

Burrows, Strauss and Niden (1965) have computed this relationship in 175 patients with chronic airways obstruction but attempted no separation of the patients with or without bronchitis. The wide scatter in their data is represented by a correlation coefficient of 0·47 and they found a curved regression line ($Pa_{CO_2} = \frac{11{\cdot}5}{FEV_1} + 30{\cdot}7$) to be the best fit. The scatter they showed is shown especially well in the patients in fig. 55 and because they draw a curved line I have felt justified in considering the data in this way even with such flimsy evidence.

Howell (1966) has suggested that the raised Pa_{CO_2} found in some patients with an $F.E.V._1$ of more or slightly less than 1 litre contrasted with a normal Pa_{CO_2} in other patients with an $F.E.V._1$ of 500 ml. or lower, is mainly due to a difference in the sensitivity of the respiratory apparatus to CO_2. In addition he has shown that there is an increase in viscous

work in response to a CO_2 load in some patients with chronic airways obstruction and not in others despite a similar ventilatory response to CO_2. Dornhorst (1955) could not explain why some patients retained full sensitivity to CO_2 while others did not, but pointed out that those who are not sensitive to CO_2 suffer "an early and gross decline". As the difference between the two groups of patients selected for this chapter lies in the $PaCO_2$ and as the course of the chronic obstructive bronchitic's illness is one of repeated bouts of chest infection and heart failure it is tem ting to consider that they have lost some central sensitivity to CO_2.

REGIONAL FUNCTION IN BRONCHITIS.

The poor intrapulmonary mixing and the smaller share of perfusion than normal in the patients with chronic obstructive bronchitis in the middle and lower zones is a most interesting finding. To my knowledge this has not been previously reported. There are several possible explanations which I will now enumerate.

Hypersecretion of bronchial mucous coupled with diminished activity of the ciliary apparatus in chronic bronchitis results in mucous accumulation in the bronchi. This will probably gravitate to the small bronchi of the lower zones obstructing these dependent parts in a patchy fashion causing poor intra-pulmonary mixing. The situation may well be aggravated by the

chronically damaged bronchial walls from previous infections. An added factor is the recent finding by Glazier, Hughes, Mahoney, Pain and West (1966) of smaller more numerous alveoli at the bases of the upright lung per unit of lung volume compared with the apices. They also suggested that the air passages are smaller and more numerous at the bases than their apical counterpart. As smaller bronchi and bronchioles are more liable to be completely or partially obstructed with a small quantity of mucous this is another reason why the mixing in the lower zones should be preferentially impaired.

The lower share of perfusion in the middle and lower zones may be caused by vasoconstriction consequent on low oxygen tension locally. Cournand (1957) and Himmelstein, Harris, Fritts, and Cournand (1958) have demonstrated this mechanism in man. Sackner, Will and Dubois (1966) have shown that the site of this vasoconstriction is the greater portion, if not the entire pulmonary arterial tree, in dogs. These investigators were concerned with overall anoxaemia and not the local effects in one or other region of the lung. However, Briscoe and Cournand (1965) have shown that the slowly ventilated space in patients with chronic airways obstruction is also poorly perfused so if these slowly ventilated spaces were at all localised in the lung it is possible that the vasoconstriction would also be localised to that segment of

the pulmonary arterial tree.

It is interesting when considering the regional Pa_{O_2} to note that in the normal upright lung it is much lower (89mm.Hg.) at the base of the lung that it is in the uppermost part (132 mm.Hg.) (West, 1962). Presumably the pulmonary arterial tree is acclimatised to these topographical differences. However, if the vasoconstriction mechanism was a response to an overall drop in Pa_{O_2} it is strange that the bases only should be affected if they are normally at a lower Pa_{O_2}. Indeed regional Pa_{O_2} differences would seem to exclude this possibility.

It should be borne in mind that the normal ranges of the Q index are wide and a large population of alveoli are being surveyed by each counter, but more in the lower than in the upper zones. An overall vasoconstriction may be truly affecting all zones but is only being shown in the lower zones by the method used.

Another homeostatic mechanism which may be responsible for the decreased perfusion, where there is poor ventilation, can be demonstrated in animals (Leibow, 1962) by simple prevention of cyclic respiratory movement by local pressure. The moving lung acts as a pump normally. It may well be that movement of the bases of the lungs is impaired in bronchitis, certainly in the patients studied, 6 of them had poor diaphragm movement.

There is the possibility that despite the absence of radiological evidence of emphysema in these bronchitic patients that mild emphysema (panacinar grades 1 and 2) is actually present and distributed uniformly throughout the lungs (Reid and Millard, 1964).

In this event both the poor ventilation and perfusion would be explicable as a mild disturbance in these functions would be more evident in the middle and lower zones due to the fact that there is more functioning lung tissue in these regions than in the apices.

COMPARISON WITH OTHER STUDIES OF AIRWAYS OBSTRUCTION.

Patients with chronic bronchitis and emphysema who suffer from respiratory insufficiency have been described by Fishman (1965) as a "most perplexing" group. One of the reasons they are so has been shown in this chapter. Patients who have severe airways obstruction evidently stemming from only one of these diseases have been found to display no functional differences which would be of any clinical application except the Pa_{CO_2}. This does not deny the existence of the distinguishable types of functional disturbance described by Baldwin, Cournand and Richards (1959) and Ogilvie (1959) but the diseases as known and recognised clinically as emphysema and chronic bronchitis do not necessarily coincide with the described patterns of dysfunction.

To a certain extent other investigators have solved this problem with a mixture of clinical, radiological and functional criteria (Nash, Briscoe and Cournand, 1964; Burrows, Niden, Fletcher and Jones, 1964). The latter group have divided all the patients with chronic irreversible airways obstruction with two main groups; Type A and Type B. A patient is called Type A if there is radiological evidence of attenuation of the peripheral vessel pattern or with a normal radiograph, severe airways obstruction, no hypercapnia, a reduced $\frac{D_{LCO\ SS}}{V_A}$ and a normal or increased T.L.C. The Type B patient has no vessel changes on the radiograph and at least three of the following:- 1) More than 10 ml. sputum daily.

2) $Pa_{CO_2} > 6$ mm.Hg. above a predicted value from the $F.E.V._1$ described by Burrows, Strauss and Niden (1965).

3) Evidence of "inflammatory changes" in the chest radiograph.

4) T.L.C. $<$ 100% of the predicted value.

5) A normal $\frac{D_{LCO\ SB}}{V_A}$

6) Recurrent or chronic heart failure due to persistent cor pulmonale.

Type A patients have been shown to have widespread emphysema at autopsy while there is much less in Type B, (Burrows, Jones, Heard and Wootliff, 1966). These types have been described as "emphysematous" and "bronchial" types of airways obstruction but the authors point out that a Type B patient is not necessarily

one suffering from chronic obstructive bronchitis. The patients in Group I in this study all fulfill the criteria for Type A because they have radiological evidence of emphysema, however it is unlikely that the patients in Group II could be classified as Type B with the criteria established. None had evidence of inflammation on the chest radiograph, only one had a T.L.C. below the predicted value (98%) and none had a $PaCO_2$ which was sufficiently raised. Five had cor pulmonale. Thus, even if sputum volume had been measured and the single breath D_L had been used, all the patients would have had to produce > 10 ml. of sputum daily and have a normal $\frac{D_L}{V_A}$.

For these reasons the steady state D_{LCO} measurements in these bronchitic patients cannot be compared with that of the Type B patients at rest and during exercise presented by Bedell and Ostiguy(1966); nor can the arterial blood gas results at rest and exercise described by Jones (1966) be compared with the present study in the bronchitics. However, it can be said that the lack of rise with exercise in the steady state diffusing capacity and the $Pa0_2$ in patients with emphysema in this and the previous chapter agrees with their findings in Type A patients.

In conclusion, this comparison between selected patients with severe airways obstruction caused by evidently bronchitis on the one hand and emphysema on the other, has confirmed that the presence of hypercarbia is associated with chronic bronchitis. There were no other obvious differences functionally displayed

in those patients and the physiological findings of Fletcher, Hugh-Jones, McNicol and Pride (1963) were not duplicated; in particular the static lung volumes and $Pa0_2$ were not significantly different. Chronic bronchitis has been found to be associated with poor ventilation and perfusion in the middle and lower zones of the upright lung.

THE PLACE OF SURGERY IN EMPHYSEMA

In 1965 Knudson and Gaensler (1965) in an excellent review on this subject pointed out that although little space in text books has been devoted to it a large variety of surgical procedures have been employed in emphysema in the last 40 years. These were aimed at interfering with different aspects of the disease from the shape of the chest wall to the nerve and blood supply of the lung. Diaphragm reefing, transverse sternotomy, costochondrectomy, resection of the glomus caroticum, hilar denervation procedures, pleurectomy and poudrage have all been used but none with constant or dramatically favourable results. More attention has been paid to 'air spaces' whether demarcated or not radiologically than to any other aspect of emphysema by thoracic surgeons and it is this approach which has been used in the patients I have studied.

Very large isolated demarcated bullae are particularly amenable to surgery but Ogilvie and Caterall (1959) showed that the bulla must occupy more than half a hemithorax before there is a remediable functional effect in the presence of otherwise normal lung. The functional alteration after removal of a large air space has been found to be largely dependent on the condition of the remaining lung and to a

lesser extent upon the size of the air space and degree to which it compresses the surrounding lung substance (Laurenzi, Turino and Fishman, 1962).

Encountered much more often than a single giant bulla is a smaller demarcated bulla which is only a local exaggeration of surrounding emphysematous change or an area of hypo or avascularity which may not be demarcated but appears radiologically localised. The criteria for surgical treatment in this type of patient have yet to be evaluated and it is with this type that I have been principally concerned.

The reason for performing any operation on patients with this kind of emphysema is an attempt to relieve the undue breathlessness which occurs. The question is, is the function of the lung improved in any way? Removal or reduction in size of the 'air space' does not alter the nature of the disease which is essentially destructive, or its course which appears in many cases to be gradually progressive. Neither will it alter bronchospasm or hypersecretion of the bronchial mucosa. Theoretically, one favourable effect may be to so alter the mechanics that the relaxation pressure in expiration of the rest of the lung will be greater and there will be less tendency for the airways to collapse (Campbell, 1958; Hugh-Jones, 1963). This would lessen the degree of airways obstruction. Another effect might be to reduce the physiological

dead space (Hugh-Jones, Ritchie and Dollery, 1966) and thereby allow more efficient gas exchange. Siebens, Grant, Kent, Klopstock and Cincotti (1957); and Jensen, Miscall and Steinberg (1961) thought that compression of surrounding lung contributed to the functional disability and if this was relieved overall function would be improved. This latter hypothesis is in doubt as Davies, Simon and Reid (1966) have shown that subjective improvement is recorded in patients with or without displacement of fissures and crowding of intrapulmonary structure visible radiologically. None of these effects will necessarily alter the symptom of breathlessness, the exact cause of which is unknown.

Determining the results of surgery in these cases is hampered by imprecise definition of the extent of the disease being treated and a lack of post operative evaluation in other than subjective terms. The application of physiological tests to assess the value of surgery has been largely ignored by surgeons (Knudson and Gaensler, 1965). When careful studies have been made the results were inconclusive, (Tabakin, Adhikari and Miller, 1959). However, in some patients there has been a striking improvement as measured by lung function tests and blood gas studies (Hugh-Jones, Ritchie and Dollery, 1966).

In this situation, a careful pre and post operative clinical, radiological and physiological assessment of a few patients with emphysema has been carried out with the aim of

comparing the subjective and functional effects of surgery and with the data to evaluate criteria for selection of these patients for surgical treatment. It was hoped also that the regional function technique would assist in defining the extent of the disease present and that the surgical findings might help in assessing the accuracy of this localisation.

ADDITIONAL METHODS.

Fourteen patients, 3 females and 11 males, who received surgical treatment for emphysema (Group Ia) were studied 6 months or more after operation. The operations performed were either 'plication' or lobectomy; the latter was done in only 2 patients (W.Sh. and A.V.M.). The 'plication' operation consists essentially of progressive ligation of bullous lung after the air has been expelled by pressure. No lung tissue is removed. The surgeon does not confine himself to one lobe of the lung but attempts to reduce the volume of any likely bullae.

The post operative grade of breathlessness was reassessed with the M.R.C. questionnaire and any decrease was used as an indication of subjective improvement.

Regional lung function was measured with the counting heads placed in the same positions as those used prior to operation, using the tracing of the chest radiograph taken at the time as a guide.

RESULTS.

Pre Operative Assessment and Subjective Improvement.

The mean age of the patients was 53·2 years, the oldest being 64 years and the youngest 39 years. All except one (H.B.) had radiological evidence of emphysema. Six had clinical evidence of chronic bronchitis and 5 had the electrocardiographic changes of cor pulmonale. One patient (Gl.H.) had 2 thoracotomies with a 12 month interval between operations. The other patients had only one thoracotomy. Nine patients had grade V breathlessness before operation; 3 had grade IV; 1 grade III and 2 grade II. Six patients fulfilled the criteria for generalised emphysema radiologically and 7 were judged to have only localised emphysema. Six patients had demarcated bullae on the radiograph, but only 3 had evidence of compression.

The relationship between these findings and subjective improvement is shown in tables XIXand XX. For convenience the patients are arranged in order of the subjective improvement in these and all other tables in this chapter. Three patients were improved by three grades of breathlessness, 4 by two grades and 3 by one grade. Five patients felt no better after surgery.

It can be seen that 4 patients with chronic bronchitis felt less breathless whereas 2 did not. Of the 8 patients without bronchitis, 6 showed some subjective improvement. Two of 5 patients with cor pulmonale improved subjectively. The 3 patients who had grades II and III breathlessness before

operation did not feel less breathless. Another 3 with grade IV breathlessness felt better and of 9 patients with grade V breathlessness only 2 did not show some subjective improvement.

Of the 3 patients who had radiological evidence of compression of the lung by a bulla, only 1 showed subjective improvement. Three of the 6 patients with demarcated bullae showed a definite subjective improvement of 2 grades or more, 2 felt one grade less breathless and 1 felt no better after surgery.

Seven operations were done on 6 patients with generalised emphysema. Five were subjectively improved. There was no obvious difference in the subjective outcome if the emphysema was localised.

Table XX shows that the predominance of emphysema by radiological methods was in the middle and/or lower zones in 10 patients. There was no obvious difference in the subjective result of operation depending on the distribution of the emphysema. The ^{133}Xenon findings confirmed the predominantly affected radiological zone in every patient. In addition, the regional dynamic distribution index was found to be low in some zones in 11 patients who had normal mid lung vessels on the radiograph. In 5 patients there was evidence of vascular loss radiologically in a zone which did not show any abnormality of the dynamic distribution index.

PRE AND POST OPERATIVE LUNG FUNCTION.

Table XXI shows the vital capacity and $F.E.V._1$ before operation and change in these measurements after operation. The highest $F.E.V._1$ before operation was 1050 ml. and the lowest 250 ml. The mean $F.E.V._1$ was 696 ml. In 4 patients the $F.E.V._1$ increased by 200 ml. or more and in 4 the $F.E.V._1$ was reduced after operation. All had an $\frac{F.E.V.1}{F.V.C.}$ % of lower than 44% and therefore had evidence of severe airways obstruction. The vital capacity was only 60% of the predicted value or less in 8 patients but was nearly normal (i.e. 90%-100%) in 2 patients. The vital capacity increased 0·20 l. or more in 7 patients but fell in 4 patients after the operation.

The functional residual capacity and total lung capacity before and after surgery are shown in Appendix II. In 7 patients the F.R.C. was more than 150% of the predicted value. In only one patient was it below predicted value (E.S.). This patient had large barely communicating demarcated bullae, so the helium dilution method probably underestimated the F.R.C. After operation in 5 patients the F.R.C. was reduced by more than 0·40 l. and in 5 patients the F.R.C. increased. The highest T.L.C. was 142% of the predicted value and the lowest 71% (E.S.). Seven patients had a T.L.C. of between 100% and 130% of the predicted value. All post operative changes in the T.L.C. were in the samedirection as the change in F.R.C.

with the exception of E.S.

The values of diffusing capacity and arterial blood gases before and after operation are shown in Appendix II. The $D_{L_{CO}}$ in every patient was below the expected range. In no patient did the $D_{L_{CO}}$ change by more than 3·0 units post operatively and this is within the repeatability range of the test.

All the patients had a slight to moderate degree of hypoxaemia at rest before operation (mean Pa_{O_2} = 73 mm.Hg.). After surgery this rose in 7 and fell in 2 patients. Only 4 patients agreed to exercise before operation and the Pa_{O_2} fell in every case. Twelve exercised after surgery and in 11 the Pa_{O_2} fell. Comparison of the change in Pa_{O_2} before and after surgery with exercise in 4 patients showed that 2 (E.Sh. and J.W.) had a similar decrease in Pa_{O_2}; in one, T.P., it fell less after surgery and in one, A.S., it fell further. The Pa_{CO_2} was raised in 1 patient (T.P.) and it fell after surgery by 9 mm. (This patient suffers also from chronic bronchitis so it is possible that the lability of the pCO_2 in this disorder was the reason for the high pre operative value). In no patient was the Pa_{CO_2} outwith the normal range after surgery.

The results of regional lung function studies before and after surgery are shown in Appendix II. In every patient the D.D.I. was below normal limits in the zone of the lung

treated surgically. In 5 patients there is an increase of more than 10 units after operation in that zone and also in the adjacent zone. In only one patient was there deterioration of similar degree (Geo. H.). In 11 patients there was a low Q index in the operated zone; these were all lower zones. After operation, this had improved in 5 patients.

Subjective Improvement and Objective Findings.

Figs. 58-63 compare the subjective improvement with the change in the F.E.V.$_1$, V.C., F.R.C., resting Pa_{O_2} and D.D.I. in the operated zones, the zone adjacent to operation and the sum of both these zones between the pre and post operative values. The relationship between the F.E.V.$_1$, F.R.C. and subjective improvement is not convincing when the repeatability and errors inherent in these tests are considered. In each of the 7 patients who had a subjective improvement of 2 grades of breathlessness or more the vital capacity increased by more than 200 ml. The resting Pa_{O_2} evidently bears little relation to the subjective improvement. However, the mixing indices in the zones which received surgical attention do show an increase in keeping with the patients subjective reports. It is not meaningful with so few patients and so many variables to apply a statistical analysis.

Radiological Changes After Surgery.

Only one patient (R.K.) showed an improvement in the size of the mid line vessels in the lower zone after a plication. This was described by Dr. Simon as "a marvellous improvement". The tomographs before and after surgery are shown in fig. 56 and 57. The peripheral vessel loss recorded pre operatively was no longer evident in 5 patients after operation.

Of the 6 demarcated bullae present before operation: 2 were reduced in size (E.Sh. and A.S.), 2 were removed completely (Geo. H. and W.P.), 1 remained unchanged (A.V.M.), and 1 was replaced by 2 smaller ones (T.P.). Four patients acquired demarcated bullae where previously there were none evident (E.Pl., W.Sh., J.W. and Gl.H.).

Surgical Findings.

In 12 patients the surgical findings at operation have been compared with the radiological opinion and the regional ventilation and perfusion data. Both these methods defined the location of the most severely affected zone of the lung in every case. There was disagreement between the radiological and physiological findings when the other zones less affected by emphysema were considered; this occurred in 7 cases.

In the light of observation during operation the ^{133}Xenon technique had indicated the presence of macroscopic emphysema in 5 instances and the radiology in 2.

Morbidity and Mortality.

Five patients suffered from the following illnesses in the immediate post operative period, viz:-

Air leak from plicated lung,
Cardiac arrythmia,
Calf vein thrombosis and shingles,
Pleural effusion and collapse,
Pneumonic consolidation.

No patients required tracheostomy or artificial ventilation. One who is not presented in this section (J.McM.) died 3 months after the operation with staphylococcal pneumonia and therefore was not assessed post operatively. One other patient (Geo. H.) died 15 months after surgery at home, said to be due to coronary thrombosis and "asthma". The first patient who died had bronchitis in addition to severe emphysema but the second denied having a productive cough.

DISCUSSION

From a clinical stand point and as a result of observation of these patients during walking, climbing stairs and conversation there is absolutely no doubt in my mind that the patients who claimed "subjective improvement" of 2 grades or more benefited from the operation. This is almost half the number who received surgical treatment. It is appropriate to record their remarks after the operation here as I think they give a possible clue to the reason they acquired increased exercise tolerance. Several said it was "easier to breathe", and one

that "the sense of discomfort has gone from my chest and breathing is not such an effort now". Three patients who had been breathless for many years said that they no longer got breathless when they were excited and added that they now did not worry about their breathlessness. Breathlessness is a subjective sensation, the specific stimulus for which is unknown. In general terms, it is probably a response to a sense of suffocation which is a "threat to life" (Comroe, 1966). Sufferers from emphysema have this sort of breathlessness as their main complaint and the object of the operation is to alleviate this symptom.

While it is possible to attribute the subjective improvement in this sensation to psychological factors this is not a satisfactory explanation. It may well be that the thoracic distension caused by increased resting lung volume stimulates breathlessness through the proporioceptors in the muscle spindles of the intercostal muscles and joints, (Campbell and Howell, 1963). A reduction in volume or even a local destruction of the nerve pathways during thoracotomy may diminish this signal without increasing the efficiency of gas exchange in the lungs. Accidental exposure of the vagal fibres may have the same effect. Certainly there is no obvious reason which would explain the subjective improvement on physiological grounds in the data presented. Although the regional mixing was improved, overall function was not altered in a convincing manner.

The theoretical grounds for considering surgery were outlined previously. Since neither the airways obstruction as measured by the $F.E.V._1$ nor the efficiency of gas exchange portrayed by the resting $Pa0_2$ showed a consistent change after the operation, one is forced to one of two conclusions. Either these hypothesis are in error or the physiological tests to evaluate the effects of these changes are too imprecise in practice.

In any event even if the $F.E.V._1$ and the resting $Pa0_2$ are increased by surgery the patients do not necessarily feel less breathless.

It is probable that this would have been a more fruitful enquiry into the surgery of emphysema if the effect on breath-holding times at different lung volumes, the pattern of breathing and the response to viscous and elastic loads had been measured before and after thoracotomy in these patients. Guz 1966a, 1966b, has shown that the sensation of breathlessness is altered by infiltration of the vagus with local anaesthetic in the neck and by vagotomy. Therefore, these tests outlined above are more applicable to the measurement of breathlessness than the function tests I have done.

Selection of Patients for Surgical Treatment.

These data can be used for the formation of criteria of selection of patients and I have reached the following conclusions.

Degree of Breathlessness.

As those patients who were not severely disabled did not improve subjectively after the operation only patients with Grade IV or V breathlessness should be referred to a surgeon. To my knowledge this point has not been stressed before.

In this connection, the morbidity and mortality associated with the operation itself should be borne in mind. Even a severely breathless patient may have another 5-10 years of albeit uncomfortable life in front of him without surgery. Those who are not severely breathless may not get any worse.

Bronchitis.

In 2 patients with bronchitis and emphysema (A.S. and R.K.) the operation produced a marked benefit. There was little or no benefit in 4 other cases who had a productive cough. In only 1 of these patients was there hypercapnia (T.P.) and the operation did not help him. Therefore, although bronchitis is not a contraindication to operative interference in emphysema probably if it is sufficiently severe to cause retention of carbon dioxide surgery is not advisable. This is a similar conclusion to that of Davies, Simon and Reid (1966) although no measurement of Pa_{CO_2} was presented in their data.

E.C.G. Findings.

Electrocardiographic evidence of cor pulmonale is not a contraindication to surgery in emphysema. This is an

agreement with Hugh-Jones, Ritchie and Dollery, 1966.

COMPRESSION

The presence or absence of radiological compression makes no difference either to the subjective or objective result. This agrees with Davies, Simon and Reid, 1966.

EMPHYSEMA.

One patient only in this study had no radiological evidence of emphysema (H.B.) and he gained little benefit. On close examination his functional defect was explicable on the grounds of bronchitis alone. Although there was some macroscopic emphysema at operation this was not striking. Clearly, radiological evidence of emphysema is required before contemplating surgery.

Localisation of Emphysema.

Generalised emphysema assessed radiologically is far from being a contraindication to surgery. Some patients do well. In fact, as shown in the comparison of radiological, xenon and surgical observations, so called 'localised' emphysema radiologically according to the lung vasculature had quite extensive functional regional derangement and macroscopically the emphysema is more extensive than indicated on the radiograph. The radiograph invariably picked out the predominately affected zone but failed in 6 cases (which is nearly half of the patients studied) to indicate a lesser degree of emphysema.

Demarcated Bullae.

During this study it has been obvious that surgeons prefer to operate on a demarcated bulla occupying a zone rather than diffusely emphysematous ("candy floss") lung. Although 3 patients out of 7 who showed definite subjective improvement had these bullae, only in 1 of them was it removed completely. In the other 2 patients the bulla was reduced in size (A.S.) or replaced by smaller bullae (E.Sh.). In addition, 3 patients who showed little or no subjective improvement but had demarcated bullae; one of diameter 18 cms. which was completely removed. It was understandable but unexpected to find that 4 patients actually acquired demarcated bullae as a result of the operation.

None of these demarcated bullae occupied larger than 1 zone of the lung, i.e. less than a hemithorax. So it must be concluded that the removal of bullae of this size is unlikely in itself to affect the subjective result. This is in agreement with Ogilvie and Caterall (1959).

Functional Criteria.

Apart from severe airways obstruction no physiological parameter helps in identifying those who will benefit from surgery. The number of zones affected with poor intrapulmonary mixing bears no relation to the outcome, neither does the measurement of the F.R.C, T.L.C. or $Pa0_2$.

In conclusion this study has shown that surgical treatment of emphysema does sometimes benefit the patients' symptoms but the subjective improvement bears no constant relation to an improvement in F.E.V_1, F.R.C., T.L.C., diffusing capacity or overall gas exchange. In the choice of patients with emphysema for surgery, it is advisable that severe breathlessness should be present. Bronchitis without hypercapnia, radiologically generalised emphysema, radiological compression, demarcated bullae occupying less than a hemithorax and electrocardiographic evidence of cor pulmonale do not appear to influence the subjective or objective result of the operation. The mortality and morbidity of surgery must be weighed against the usual prognosis in emphysema of a gradual decline which may take many years.

UNILATERAL TRANSRADIANCY OR MACLEOD'S SYNDROME.

In 1954 William Macleod described a syndrome of clinical signs and radiological appearances in the following words. "The main features are quietening of the breath sounds and lessening of radiographic lung markings with persistently greater transradiancy over one lung, the condition being distinguishable from simple unilateral obstructive emphysema by the small or normal size of the affected side and the absence of evidence of bronchial obstruction". Fig. 64 shows a postero-anterior chest radiograph of a patient with this disorder.

In 1962, Reid and Simon described the histological findings in three patients with this syndrome who had been treated by pneumonectomy. They found that there were enlarged air spaces which were distributed in a patchy fashion throughout the lung. This syndrome therefore is a form of emphysema according to the Ciba symposium definition and has been included in Reid's classification (Fig. 2). It is of particular interest in that the cause may be an obliterative bronchiolitis in childhood (Reid and Simon, 1962). The clinical and radiological findings distinguish it from other forms of emphysema.

Reid and Simon (1962) demonstrated bronchographically that there was no obstruction of the larger bronchi but that the

finer bronchi and bronchioles filled poorly with contrast medium and were irregular or distorted in outline, indicating peripheral obstruction. Microscopic examination revealed distorted bronchioles some of which were obliterated by fibrosis. The main pulmonary arteries were virtually normal but the peripheral branches (at acinar level) were diminished in number. The occurrence of an infection at the bronchiolar level at an age before the development of the gas exchanging area of the lung is complete might arrest subsequent development if there was a failure to ventilate properly through the damaged bronchioles. Such a hypothesis fits the pathological findings and frequently there is a history of severe lung infection in childhood in these patients. Other authors (Belcher, Capel, Pattinson and Smart, 1959) dispute this aetiology but may be confusing the syndrome with simple hypoplasia of the pulmonary arteries.

The evidently unilateral distribution of this disorder has led several investigators (Dornhorst, Heaf and Semple, 1957; Darke, Chrispin and Snowden, 1960) to use bronchospirometry to measure differential lung function. It has been shown in three cases that the transradiant lung is responsible for only 7%, 21% and 26% of the total oxygen uptake (Darke, Chrispin and Snowden, 1960) and that very high pressures are required to inflate this lung when the patient is under general anaesthesia,

after which the lung empties very slowly, (Dornhorst, Heaf and Semple, 1957). The transradiant lung, therefore, plays little part in gas exchange and has severe airways obstruction . Thus, the function of the contralateral or better lung is obviously of great importance in the prognosis of these patients. Although Dornhorst, Heaf and Semple (1957) found that the contralateral lung in 3 patients was normal, Darke, Chrispin and Snowden (1960) reported abnormal mixing in this lung. If the contralateral lung is affected it would be a mistake to consider Macleod's Syndrome as a truly unilateral or localised disorder. In addition, due to the patchy pathological changes caused probably by bronchiolitis obliterans it is possible that the contralateral lung was also affected in childhood but not sufficiently damaged to cause transradiancy.

Most of these patients present clinically in hospital practice with a productive cough (Macleod, 1954) and are said to be prone to frequent chest infections (Dornhorst, Heaf and Semple, 1957; Darke, Chrispin and Snowden, 1960; Fouché, Spears and Ogilvie, 1960). These findings are pathognomic of chronic bronchitis which, if of sufficient severity, would lead to right ventricular strain and failure (Scadding, symposium, 1965). As one lung in this disorder is already severely damaged, bronchitis would have a more serious effect than usual.

Macleod (1954) found that 7 out of the 9 patients he described had shortness of breath. Other authors have reported

"severe" to "moderate" breathlessness, (Darke, Chrispin and Snowden, 1960). However, Bates and Christie (1964) and Bentivoglio, Beerel, Stewart, Bryan, Ball and Bates (1963) state that "there is little if any disability". Probably the degree of disability is linked with the occurrence and severity of bronchitis as much as to Macleod's syndrome.

I have studied seven cases of Macleod's syndrome (Group III) paying particular attention to the incidence of productive cough and the function of the contralateral lung.

In one of these cases (H.S.) the typical lesion is confined to only part of one lung. Whether such a case as this should be included is debatable, but the essential radiological and clinical changes are the same. Scadding has suggested "hypotransradiancy attributable to bronchiolitis obliterans of childhood" as an appropriate description of these changes no matter what their distribution (Symposium, 1965) and because of this I have included this one case who does not have total unilateral involvement.

Results.

The detailed results are shown in Appendix II. Table XXII shows the age, sex, grading of symptoms and history of childhood infection in each patient. Five had a productive cough and one other had a severe non-productive cough (M.E.). Six had had a chest illness within the previous 3 years, Six had breathlessness of varying severity from mild (M.D.) to

quite severe (H.S.). All had either a history of chest trouble dating from childhood (M.E., A.S.) or a history of a definite episode of chest illness at, or before, the age of 8 years.

Fig. 65 shows the intensity of the breath sounds in the transradiant and better lungs compared with the intrapulmonary mixing in the zones where the breath sounds were heard. In only one zone in a transradiant lung was the intensity of the breath sounds recorded as moderate (Grade 2). In all other zones on the transradiant side the breath sounds were absent or weak. However, in the better lung despite a low (below 60 units) dynamic distribution index, the breath sounds were heard to be moderate or good (Grades 2 and 3) in 8 instances.

Table XXIII shows the lung volumes, flow rates and airway conductance data. In 5 of the patients the functional residual capacity is raised beyond the predicted value by a mean value of 780 ml. and the ratio of residual volume to total lung capacity is higher than normal in all cases. Vital capacity is reduced in every instance by a mean value of 1300 ml. and six of the patients have air trapping as shown by the difference between the vital capacity and the F.V.C. In 5 patients the $\frac{FEV_1}{FVC}$ ratio is at or below 40%. The airway conductance is abnormally low in 5 cases and near normal in 2 (H.S. and M.E.).

The values of diffusing capacity at rest and during exercise are shown in Table XXIV. At rest, five measurements

are low and all fail to rise satisfactorily on exercise except one, (D.C.). Percentage extraction is below normal in four patients.

All patients had a normal percentage oxygen saturation and pH. Fig.66 shows that the pO_2 is lower than normal (95 mm.) in 5 patients. In two (A.K. and A.S.) the pO_2 fell with exercise further below this normal value. In two cases the pCO_2 was below the normal range (36-42 mm.), indicating alveolar hyperventilation. In neither case did it rise to within normal limits with exercise. In one further case (A.K.) the pCO_2 rose with exercise to 46 mm.

The regional ventilation and perfusion findings are shown in figs.67 and 68. The dynamic distribution indices are reduced on the transradiant side in all zones in all patients except one (H.S.) where there is normal mixing in the upper zones. In addition, this value is low in 5 patients in at least one region on the opposite side; in two of these (E.L. and H.S.) the whole lung is affected. The perfusion index is below normal limits in all patients on the transradiant side, the lower zones invariably being affected and the middle zones in 2 patients.

DISCUSSION

As these patients were attending a hospital for inpatient or outpatient care they are not typical representatives of all subjects who might exhibit Macleod's syndrome.

This point is relevant in considering their symptomatology. Five out of seven of the cases became short of breath when walking at an ordinary pace on level ground. The two younger patients, (M.D. and M.E.) when questioned admitted to some abnormal limitation of exercise tolerance although this had not been their original complaint. Only 4 of the cases were investigated specifically on account of breathlessness, the others being referred because of the abnormal radiological pattern. Bates and Christie (1964) wrote that "there may be no dyspnoea even on moderate exertion", which does not portray the same clinical picture and seems to be exception rather than the rule among the patients studied here. The widely held opinion that patients who have this condition show symptoms only when the contralateral lung is affected by another disease such as bronchitis cannot be disputed on the evidence shown here but it seems possible that the sound lung has not completely escaped the childhood infection which Reid and Simon think is the initial cause of the condition. In this connection it is interesting to note that all of our patients gave a definite history of childhood chest infection.

Although the breath sounds were found to be weak in the transradiant lung, indeed this is part of the definition of the syndrome, they were not always weak in poorly mixing zones on the contralateral side. There are two possible reasons for this; firstly, that the contrast in intensity of the breath

sounds between the two lungs was noted but not assessed accurately in degree and, secondly that the observer nearly always knew of the clinical diagnosis before listening to the chest.

Five of the 7 patients had a productive cough and could therefore be said to have chronic bronchitis. Both of the other two patients had been subject to recent chest infections. This high incidence of bronchitis may be a reflection of the "hospital population" from which these patients were culled.

The better lung displayed poor mixing in 5 patients in the lower zones in all instances. The middle zone also was involved in one patient and in two, the entire lung. These findings indicate that in these patients Macleod's syndrome is not a truly unilateral functional disorder.

As the function of the better lung is of prime importance to these patients it is worth while using this data to make some deductions in an attempt to proportion the vital capacity and airway conductance between the lungs. Svanberg (1957) has shown using bronchospirometry that the vital capacity is distributed between the lungs in the proportion of 54% to the right and 46% to the left. In table XXV the predicted vital capacity has been apportioned accordingly. The 'calculated' value in table XXV is gained by taking the sum of the counts recorded in each lung after a single inspiration of ^{133}Xenon in air and dividing the vital

capacity measured spirometrically in proportion to these counts. This assumes that the sum of the counts recorded in each lung give an estimate of the amount of air entering each lung. It can be seen that the calculated vital capacity in the transradiant lung in six cases is impaired, and that in four of these cases as the calculated vital capacity in the better lung is near normal, the total impairment in overall vital capacity is apparently only due to the transradiant lung. However, the situation is not quite as simple as that. In cases of this sort where one lung fails to expand normally the other lung may be distended by an unusually negative intrathoracic pressure at maximum inspiration. The extent of such overdistension depends on the compliance of the expanding lung during the measurement of vital capacity. In three cases the calculated vital capacity of the better lung is less than the predicted value (D.C., M.D., H.S.). This partition of the vital capacity is shown on fig. 69.

It is possible also to assess the airway conductance to the lungs separately, bearing in mind two facts. Firstly, Briscoe and Dubois (1958) have shown that the conductance (C) of the normal lung is directly proportional to its lung volume (V) according to the formula:- $C = 0{\cdot}13 \times V$, and secondly that the total conductance of the lung is equal to sum of the conductances of each lung as it is a conducting system connected in parallel. The lung volume at which the

total conductance was measured is divided between the lungs according to the sum of counts observed in each lung at equilibrium. In this way the estimated volume of the better lung is gained. The predicted conductance of the better lung can then be calculated from Briscoe and Dubois' formula on the assumption that the airways are normal in this lung. These figures are shown in table XXVI which shows that the predicted conductance of the better lung is two and three times the observed conductance of the whole lung in 5 patients so even if the conductance of the transradiant lung is negligible, the conductance of the better lung in these patients must be below the normal range. It is quite possible that the observed values for total conductance are largely due to the contribution of the contralateral lung because the rapid shallow breathing used during the measurement of airway conductance will reduce the ventilation of the transradiant lung to the minimum.

The failure of the diffusing capacity to increase significantly during exercise in some of the cases is an important finding. In normal subjects the mechanism of the increase is partly a redistribution of blood in the lung which allows better perfusion of the poorly perfused parts such as the apical regions and it is possible also that alveoli may be opened during exercise that are functionless at rest. The better lung in these patients is probably already working to capacity at rest which leaves it little

scope to increase its efficiency during exercise. In fact, to lend support to this hypothesis using the counts per second recorded in each lung calculation shows that the better lung receives 75% of the available blood flow and 67% of the ventilation.

These studies have therefore shown that there is a high incidence of bronchitis in patients with Macleod's syndrome who are seen in hospital practice. The function of the transradiant lung is invariably abnormal with airways obstruction, poor perfusion and poor intrapulmonary mixing. However, the contralateral lung is frequently also affected. As the prognosis in these patients patently depends on the function of this lung clinical management should be directed towards avoidance of environments or habits liable to cause or exaggerate airways obstruction or chronic bronchitis. A long term study of patients suffering from this syndrome would be interesting, as one would expect that those with severe bronchitis should ultimately suffer from cardio-respiratory failure.

CONCLUSIONS

In the foregoing studies on patients with pulmonary emphysema the following points have been made about the disease.

1. Poor or absent breath sounds are a valid indication that the underlying lung is poorly ventilated but breath sounds of moderate and good intensity are not always related to normal intrapulmonary gas mixing in emphysema.

2. Severe airways obstruction is invariably present when Simons (1964) criteria for the radiological diagnosis of generalised emphysema are fulfilled, but it is possible for there to be bilateral attenuation of the vessel size in the upper and middle zone accompanied by more peripheral vessel loss without severe overall functional derangement.

3. The radiological feature of a flat diaphragm and an increased depth of the retrosternal space are not related to the total lung capacity, whereas the level of the diaphragm is significantly related to this volume.

4. Small mid-lung vessels and peripheral vascular loss as depicted radiologically in zones in emphysematous patients are accompanied by poor intrapulmonary mixing in an average of 83% of instances. However, when the zonal vascular pattern is normal in 20%, 30% and 47% of the upper, middle and lower zones respectively, there is abnormally low mixing, if the patient has no productive cough. When chronic bronchitis accompanies emphysema

there is a higher incidence of poor intrapulmonary mixing in the middle and lower zones when the radiological vessel pattern is normal.

5. Emphysematous patients with normal ventilation of one or both lower zones of the lung have a significantly higher arterial oxygen tension after exercise than patients in whom both lower and both middle zones have poor intrapulmonary mixing.

6. The only significant functional difference between patients with severe chronic irreversible airways obstruction believed to be caused on the one hand by chronic obstructive bronchitis and one the other by emphysema, was the level of arterial carbon dioxide tension.

7. The functional and symptomatic effects of surgery on emphysematous patients bear no convincing relationship to one another with the exception of the regional intrapulmonary mixing. Only severely breathless patients improved subjectively after surgery.

8. The contralateral lung in Macleod's Syndrome frequently shows poor intrapulmonary mixing and perfusion in the lower zone.

These findings should assist the physician in the functional interpretation of the stethoscopic signs and the radiological features in a patient with pulmonary emphysema. They show that overall lung function is affected by regional dysfunction.

In general, tests of lung function cannot be expected to provide a clinical or pathological diagnosis but can indicate

the type and severity of functional disturbance present. This is illustrated clearly in the attempt to find functional differences between chronic bronchitis and emphysema in patients with severe airways obstruction.

Regional lung function measurements have lent a more precise quantitation to the anatomical extent and severity of the impairment in patients with different forms of emphysema than is possible by other means. Perhaps in the future such methods will be of assistance if lung transplantation ever becomes a feasible procedure. At present, although some workers have overcome the technical surgical difficulties (Davies, Rosser and West, 1965), vast immunological problems remain to be solved.

ACKNOWLEDGEMENTS

I am extremely grateful to all my colleagues at the Brompton Hospital and Institute of Diseases of the Chest. I had only to mention the words emphysema and bronchitis and many various contradictory opinions were expressed. These conversations were probably of more value in forcing me to adhere to certain criteria and to critically appreciate other written work on "airways obstruction" than any other single factor.

Dr. Margaret Turner-Warwick listened to many patients' chests at my request and made many helpful criticisms on this and other aspects of the study. Dr. George Simon came into the hospital in the evenings to view the radiographs with me. His opinion I regard as quite invaluable. He has taught me a great deal about the radiology of emphysema. Dr. Malcolm Towers gave me his opinion of electrocardiographs.

I would like to thank the patients themselves who endured the battery of tests with great fortitude and friendliness. They were under the care of the following consultant physicians who permitted me to study them:- Drs. Batten, Citron, Bignall, Lee Lander, Oswald, Zorab, Robson, Nicholson, F. Scadding and Professor J.G. Scadding.

The lung volumes, diffusing capacity, airways resistance measurements and $F.E.V._1$ were measured by Miss Tonia Godfrey and Miss Christine Saunders who are student technicians in the department. They and Mr. M.D. Foskett deserve and receive my extreme gratitude, as without them the study would have been impossible. Mr. Foskett designed the oxygen electrode and water bath, and spent many long hours with the electronic circuitry of the counting apparatus.

Miss Joan Boulton typed the thesis. Dr. W. Wilson of Somerset House gave me some friendly statistical advice. The photographic department of the Royal Marsden Hospital is responsible for the glossy prints. Mr. P. Bishop, the Institute Librarian, was an invaluable help.

To Dr. F.J. Prime I owe a debt of gratitude which I am unable to repay in words for his kindness, patience and valuable advice in the past two years. He has been my mentor and chief critic and has sustained my courage and enthusiasm by continued interest.

This work was done when in receipt of a grant from the Board of Governors of the Brompton Hospital.