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MORPHOMETRIC STUDIES ON THE PATHOLOGY OF
CHRONIC AIRWAYS OBSTRUCTION.

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THESIS FOR THE DEGREE OF DOCTOR OF MEDICINE
SUBMITTED TO THE UNIVERSITY OF GLASGOW.

RESEARCH CONDUCTED IN THE DEPARTMENTS OF PATHOLOGY
OF THE SOUTHERN GENERAL HOSPITAL, GLASGOW AND THE
UNIVERSITY OF SHEFFIELD.

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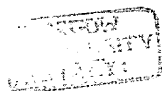


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1. A NECROPSY STUDY OF PULMONARY EMPHYSEMA IN GLASGOW, 1972. Thorax 27, 28
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3. A PATHOLOGICAL STUDY OF THE LUNGS AND HEART IN FATAL AND NON-FATAL CHRONIC AIRWAYS OBSTRUCTION, 1976. Thorax 31, 70
4. QUANTITATION OF THICK WALLED PERIPHERAL LUNG VESSELS IN CHRONIC AIRWAYS OBSTRUCTION, 1976. Thorax 31, 315
5. POST-MORTEM ASSESSMENT OF CHRONIC AIRWAYS OBSTRUCTION BY TANTALUM BRONCHOGRAPHY, 1975. Thorax 30, 405
6. A CLINICO-PATHOLOGICAL STUDY OF FATAL CHRONIC AIRWAYS OBSTRUCTION, 1976. Thorax 31, 693
7. THE CROSS SECTIONAL AREA OF DIAPHRAGMATIC MUSCLE FIBRES IN EMPHYSEMA, MEASURED BY AN AUTOMATED IMAGE ANALYSIS SYSTEM, 1976. Journal of Pathology, 120, 121

A reprint of each of these papers is enclosed at the back of this volume.

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DECLARATION REGARDING WORK UNDERTAKEN IN

COLLABORATION WITH OTHERS

Three of the papers submitted in this thesis involved work in collaboration with other people.

The first paper was written in conjunction with Dr. G.H. Roberts of the Southern General Hospital, Glasgow. Both Dr. Roberts and I collected the material and performed the measurements on the lung slices; one measuring while the other noted the measurements. Both authors contributed to the actual writing of the paper.

The fifth paper was written in conjunction with Dr. G.M. Steiner of the Royal Hospital, Sheffield. I obtained the lungs and together with Dr. Steiner introduced the tantalum dust into them. Both were present when the radiographs were taken. Dr. Steiner was responsible for the majority of the measurements of the radiographs and the author carried out the histological part of the study. The author of this thesis wrote the paper.

The seventh paper was written in conjunction with Mrs. Joyce Hoy, a technician in the Pathology Department, University of Sheffield. The author obtained the diaphragms and selected the blocks for examination. Mrs. Hoy processed these and was responsible for the majority of the measurements made on the Quantimet 720, while I wrote the paper.

SUMMARY

SUMMARY

The work submitted in this thesis consists of seven individual and inter-related studies, all of which are concerned with aspects of the pathology of chronic airways obstruction. This is a disease complex made up of pulmonary emphysema, chronic bronchitis and bronchiolitis. In all the studies quantitation of the extent and severity of the disease processes was carried out.

In the first study the incidence of pulmonary emphysema was established in a series of 50 autopsies on men, performed in a general hospital in Glasgow. Emphysema was present in more than trace amounts in 32 lungs (64 per cent). Centrilobular emphysema was the commonest variety found, being the only or predominant type present in 17 lungs (34 per cent), panlobular emphysema was the only or predominant type in 5 lungs (10 per cent) and in 15 lungs (30 per cent) significant amounts of both centrilobular and panlobular emphysema were present. These results were compared to the published incidences of emphysema in other British industrial centres.

Secondly the incidence of bronchial mucous gland hypertrophy, consistent with chronic bronchitis, was ascertained in 359 consecutive autopsies performed in the same Glasgow hospital. Hypertrophy of the bronchial mucous glands was measured by two techniques which showed good correlation. Using the Reid Index 31 per cent of bronchi showed mucous gland hypertrophy in the chronic bronchitis range as compared to 33 per

cent by a point counting technique. Changes of this degree were commoner in men than women, but were not related to age or smoking habits. The mean Reid Index was significantly greater in smokers (0.46 ± 0.11) than non-smokers (0.41 ± 0.09) and there was a significant relationship between the presence of a chronic productive cough during life and the size of the bronchial mucous glands at autopsy.

The third paper involved a comparison of the changes in the lungs and heart of patients dying from chronic airways obstruction and those with non-fatal chest disease. A series of 50 autopsies was performed in Sheffield, to determine the size of the right ventricle, the amount, type and distribution of emphysema, the size of the bronchial mucous glands and the proportion of the lung occupied by the lumen of small airways of less than 2 mm. in diameter. Eighteen patients died as a result of chronic airways obstruction, 17 had symptoms of chest disease but died from some unrelated cause and 15 had no symptoms related to the respiratory system. A positive correlation was found between the total amount of emphysema, the amount of panlobular emphysema, the reduction in small airways lumen and both the clinical severity of disease and the weight of the right ventricle. No relationship was found between clinical severity and the amount of centrilobular emphysema or the bronchial mucous gland size.

The fourth project was concerned with the changes in the pulmonary arterioles in the same 50 cases.

The number of thick-walled peripheral lung vessels (defined as vessels less than $100\text{ }\mu$ in diameter, which had two distinct elastic laminae) was calculated in all the cases. The mean number of these vessels was found to be significantly greater both in the fatal disease group, as compared to both other groups, and in cases with right ventricular hypertrophy as compared to those with normal hearts. Significant correlations were found between the number of thick-walled vessels and the right ventricular weight, the total amount of emphysema, the amounts of centrilobular and panlobular emphysema and the proportion of the lung occupied by the lumen of small airways.

The fifth study involved the examination of small airway changes in chronic airways obstruction by a radiographic method. Post-mortem tantalum bronchography was performed on 22 left lungs, 13 of which were in the series of 50 cases previously described. The radiographic changes in the small airways of diseased lungs were irregularity of the bronchial walls, failure of the walls to taper towards the periphery of the lung, areas of narrowing and dilatation and pooling of tantalum at the end of airways. The numbers of small airway branches in the most distal 4 cm. of the lung visualised on the radiographs, and the number of airways of less than 1 mm. in diameter were significantly reduced in patients who died from chronic airways obstruction as compared to those who did not. Histologically the

reduction in small airways filling was due to a combination of acute and chronic inflammation.

The next investigation was of a clinico-pathological nature and concerned 21 patients who died as a result of chronic airways obstruction. Seventeen of the patients were in the fatal disease group in the third study. Thirteen of the patients had been in right ventricular failure for at least one year prior to death and the other eight did not have clinical evidence of right ventricular failure. The patients with failure died at a younger age than those without failure but there were no significant differences between the two groups in the duration of history of chest disease, blood gas estimations, respiratory function tests or the degree of polycythaemia. The group with right ventricular failure had larger right and left ventricles than the group without failure, but there were no significant differences in the amount of emphysema, the size of the bronchial mucous glands, the proportion of small airways lumen in the lung or the number of thick walled peripheral lung vessels, between the two groups. The findings did not support the division of patients with chronic airways obstruction into two groups, broadly defined as 'emphysematous' and 'bronchitic', either clinically or pathologically. Clinical, radiological and electrocardiographic abnormalities were compared to the autopsy findings in the lungs and heart. A clinical history of right ventricular failure correlated well with the finding of

right ventricular hypertrophy at necropsy. Electrocardiographic evidence of right ventricular hypertrophy was found to correspond with the size of the right ventricle, at necropsy, in 66 per cent of cases. The radiographic diagnosis of emphysema proved an accurate assessment when compared to the necropsy findings and radiographic estimations of right ventricular enlargement were accurate in 65 per cent of cases. The most common terminal event in these patients was acute infection in small airways. Pneumonia was an infrequent occurrence.

The final study, was concerned with the changes in the diaphragmatic muscle of patients with chronic airways obstruction. The cross sectional area of the diaphragmatic muscle fibres was measured, with a Quantimet 720 image analysis system, in 18 patients with emphysema and 6 patients with no chest disease. Fourteen of these patients were included in the series of 50 in the third study. The mean cross sectional area of the muscle fibres in the emphysematous group was significantly greater than the normal group. Patients who died from chronic airways obstruction had a larger mean muscle area than those with non-fatal respiratory disease. The increase in muscle fibre size showed a positive correlation with ventricular weight but not with the amount of emphysema in the lungs.

INTRODUCTION

The work included in this thesis commenced with two studies to determine the incidence of both pulmonary emphysema and the pathological changes of chronic bronchitis in an autopsy population. Although similar population surveys had been carried out in other industrial centres in Britain no such investigations had been performed in Glasgow. It was felt to be important to obtain this information and compare Glasgow with other cities in order to discover whether there are aetiological differences between the various towns in Britain and in North America.

As a progression from this a further series of patients was examined to determine why some people die from chronic bronchitis and emphysema and others do not. In the same study an attempt was made to determine whether quantitative differences in the amount of emphysema and bronchitis correlated with the development of right ventricular hypertrophy or not.

The link between the disease process in airways or alveoli and the right ventricle is the pulmonary circulation and so, employing a technique which had previously only been used in experimental animals, changes in small pulmonary arteries were quantitated. The aim was to establish the degree of the vascular changes and to correlate this with the clinical outcome of the patients' disease and pathological measurements on the heart and lungs.

As small airways obstruction is known to be an important factor in the pathology of the chronic

bronchitis and emphysema complex this was studied in detail using the technique of post-mortem bronchography. Using this method the object was to demonstrate the site, extent and nature of the obstructive lesion in small airways.

A group of patients who died from chronic airways obstruction was then examined with a view to establishing clinico-pathological correlations and also determining whether there were differences between those who had long standing right ventricular failure and those who did not. This group of patients was also examined to discover if there are two different patterns of chronic airways obstruction previously described as "emphysematous" and "bronchitic".

Lastly an investigation was carried out to determine if significant changes exist in the major respiratory muscle, the diaphragm, in patients who have emphysema. The cross sectional area of the muscle fibres was therefore measured in a group of patients with emphysema and patients with no chest disease.

HISTORICAL REVIEW.

Laennec, in 1819, is credited with the first clear description of emphysema, although in his treatise (1) he himself acknowledges that a Sir John Floyer described similar changes in the lungs of horses in 1698 and that Baillie recognised the appearances of the dilated air cells in his text on Morbid Anatomy in 1793 (2). Laennec divided emphysema into vesicular and interstitial types and outlined his views on the causes of the disease, in particular, obstruction of small bronchial tubes and air trapping behind the obstruction. He also noted the clinical presentation of the disease, with dyspnoea on exertion, and the fact that patients with emphysema sometimes developed heart disease. In 1862 Waters (3) subdivided vesicular emphysema into lobular and partiallobular types and in 1866, Villemin (4) described the pattern of centrilobular emphysema. Little progress was made until Gough in 1940 (5) demonstrated that the emphysematous lesion in coal trimmers in the Cardiff docks was centrilobular in position as well as being pigmented. Heppleston (6) described the histology of the lesion in coal workers and stressed the importance of the focal accumulation of coal dust around respiratory bronchioles. In 1952 Gough (7) also showed, using the paper mounted whole lung section technique, that centrilobular emphysema was common in the general population and Leopold and Gough (8) described the pathology and commented on the pathogenesis of the disease. The variety of emphysema which involves the whole of the lung lobule was described in 1959 at the Ciba Symposium (9) as

panacinar and by Wyatt in the same year in the United States as panlobular (10). The Ciba Symposium also produced the commonly accepted definition of emphysema as a 'condition of the lungs characterised by increase beyond the normal in the size of air spaces distal to the terminal bronchiole, either from dilatation or from destruction of their walls'. Heard (11) stated that both centrilobular and panlobular emphysema may exist in a distensive and destructive form.

Badham in 1814 (12) was the first person to use the term bronchitis and he divided it into acute, asthenic and chronic types. Laennec (1) described the clinical and pathological changes in chronic bronchitis, in particular dilatation of the bronchi. He also noted that emphysema sometimes accompanied chronic bronchitis but he thought that this was a rare occurrence. In 1852 von Rokitansky (13) described the most important histological change in chronic bronchitis, that of an enlargement of the mucous glands in the bronchial wall. Florey in 1932 (14) noted an increase in the goblet cells in the surface epithelium of the bronchi in chronic bronchitis. Further research into chronic bronchitis was stimulated by the London "smog" of 1952 when over 4000 people died: most of whom had bronchitis (15). Reid in 1960 (16) devised a method for measuring the enlargement of the bronchial mucous glands and found a clear distinction between normal bronchi and those from subjects with chronic bronchitis. The Reid Index expresses the mucous gland thickness as a fraction of the bronchial wall thickness, measured at the same point. Further work

by Thurlbeck and Angus (17) however showed that the distribution curve of the Reid index was bell shaped, i.e. a normal distribution, and this suggested a gradual change from normal gland size to pathological enlargement of the glands. Complete correlation between clinical evidence of chronic bronchitis and enlargement of the bronchial mucous glands is therefore not possible. Whereas the Ciba Symposium (9) proposed a pathological definition for emphysema, chronic bronchitis was defined in clinical terms: "Chronic or recurrent excessive mucous secretion in the bronchial tree, occurring on most days for at least three months in the year, for at least two years".

The two conditions, chronic bronchitis and emphysema, have long been known to occur together, but the relationship between them has never been completely elucidated. Emphysema has been shown to be more common in bronchitics than in non-bronchitics and bronchitis has been found to be a common occurrence in patients with severe emphysema (18). Mucous gland enlargement has been shown to be commoner in the bronchi of patients with emphysema than in those without it (19). Thurlbeck however found that emphysema can occur without bronchitis and that about one third of bronchitics have no emphysema (18). Because of this confusion it became common following the Ciba Symposium (9) to describe patients as having generalised obstructive lung disease, where widespread narrowing of the bronchial airways, at least on expiration, causes an increase above the normal in resistance to air flow. The term chronic airways

obstructive disease came to be used to describe the clinical state of severe dyspnoea on exertion, not explained by non-pulmonary heart disease and accompanied by suppressed breath sounds throughout the lungs (20). Several attempts have since been made to separate patients with chronic airways obstruction into two or more groups. Burrows et al (21) found two main clinical syndromes which they called Type A and Type B disease. Type A patients were thin, had radiological evidence of emphysema, usually normal blood gases, rarely were polycythaemic and rarely developed heart failure. In contrast, Type B patients were of stocky build, had more evidence of bronchitis and non radiological emphysema, severely disturbed blood gases, and frequently developed polycythaemia and heart failure. There were other patients whom they called Type X who showed intermediate or mixed features. Considerable disagreement still exists over this division of patients and Thurlbeck (22) found that the majority of his patients seemed to fit in neither category or had features of both.

The fact that airways obstruction was a feature of the chronic bronchitics and emphysema disease complex was not of course a new one as Laennec (1) had noted the changes in small airways and advanced the theory of air trapping behind obstruction as a cause of emphysema. Confirmation of organic obstruction in small bronchioles followed in recent times by McLean (23) and Anderson and Foraker (24). This obstructive lesion is thought to follow episodes of infection in small airways i.e.

bronchiolitis. Patients with chronic airways obstruction may therefore have disease in one or all of three sites, large airways, small airways and alveolar sacs. Other theories have been advanced to explain the obstructive element of the disease and Daymen (25) proposed that destruction of alveolar support, due to emphysema, left the bronchioles vulnerable to expiratory check valve closure. Macklem, Fraser and Brown (26) showed that there was obstruction in both large and small airways but Hogg, Macklem and Thurlbeck (27) found that in patients dying of chronic airways obstruction the increase in total resistance to air flow was provided by an increase in the resistance of the smaller passages (less than 2 mm. in internal diameter). The histology of these airways showed mucous plugging, oedema, inflammation and fibrosis.

Having described the development of the various aspects of the airways obstruction disease complex one further aspect remains to be considered. That is the relationship of the respiratory disease to changes in cardiac function and size. Laennec (1) noted that some emphysematous patients developed the changes of congestive cardiac failure and Budd in 1840 (28) stated that right ventricular hypertrophy occurred in emphysema because there was an obstruction to blood flow in a reduced pulmonary capillary bed. Isaaksohn in 1871 (29) confirmed this view and stated that pulmonary hypertension could be entirely explained on the basis of obstruction of alveolar capillaries following atrophy and

disappearance of alveolar walls. The view became generally accepted that right ventricular hypertrophy in emphysema, was roughly proportional to the amount of lung involved by the disease. However, McMichael and Sharpey-Schafer in 1944 (30) showed that insufficient aeration of alveoli led to a reduced arterial oxygen saturation and von Euler and Liljestrand in 1946 (31) found that hypoxia produced a rise in the pulmonary artery pressure. The concept that destruction of alveolar capillaries caused an elevation in the pulmonary artery pressure was no longer tenable and was replaced by a proposed mechanism of direct action on pulmonary arterioles, of reduced oxygen levels, producing vasoconstriction (32).

These physiological findings were supported by the pathological ones of Cromie (33) and Burrows et al (21) who found no direct relation between the severity of emphysema and right ventricular hypertrophy. Leopold and Gough (8) and Hicken, Heath and Brewer (34) advanced the theory that right ventricular hypertrophy may be related to the type, rather than the amount of emphysema. Since these findings were published there have been many other studies confirming and contesting the stated relationships. These have been well reviewed by Thurlbeck (22). Much confusion has also arisen over the use of the term *cor pulmonale*. This was defined by the World Health Organisation expert committee in 1961 (35) as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or the structure of the lung, except where these pulmonary alterations are

the result of diseases that primarily affect the left side of the heart, or of congenital heart disease". However this definition has never had universal acceptance and some authors regard right ventricular failure rather than right ventricular hypertrophy as the criterion of cor pulmonale. Ferrer (36) states that cor pulmonale is now accepted as alteration in structure or function of the right ventricle resulting from disease affecting the lung. As such confusion surrounds this term it has been sparingly used in the present series of studies.

Measuring the extent of disease processes has come late to morbid anatomy, but pulmonary pathology was probably the first field where it found extensive use. The basic principle on which most of the quantitation, in this thesis is based was developed by the French geologist Delesse who stated in 1847 (37) that "in a rock, composed of a number of minerals, the area occupied by any given mineral, on a surface of a section of the rock, is proportional to the volume of the mineral in the rock." This principle, known as differential volumetry is equally applicable to human tissues where the aim is to estimate the volume of normal or diseased tissue in an organ. Several ways of making the area measurements have been used but the one used here was first developed by another geologist, Chayes (38), who proved mathematically that the relative area of a component could be determined by counting the number of random points, on a grid which covered the entire specimen, falling on this component. The more points that are counted the greater the accuracy of the method. Weibel (39) used this method on gross

specimens of lung to quantitate the normal tissues and Dunnill (40) developed a point-counting grid, instead of taking random points, for measuring the amount of emphysema in a whole lung section. The same basic technique was applied to histological material by Chalkey (41) who developed a microscope eyepiece, with four points on it, which he used to determine nuclear cytoplasmic ratios. A modification of this by Dunnill, Massarella and Anderson (42) involved the use of a projection microscope to place the image of a section on a point-counting grid. They used this to determine the proportion of the various components of the normal and diseased bronchial wall. Matsuba and Thurlbeck (43) also used a projection method to determine the relative proportion of the lumen of small airways to other lung tissue, in histological sections.

ESSAY

A CRITICAL ANALYSIS OF THE
PUBLISHED WORK SUBMITTED

The common causes of chronic obstruction to airflow within the lungs are emphysema, chronic bronchitis and some forms of asthma and bronchiectasis (22). The studies in the present series were restricted to chronic bronchitis and emphysema. Each of the seven papers was concerned with a different aspect of the disease complex as it affects the lungs, heart and diaphragm. The pathological processes in all these tissues lend themselves to the recently developed morphometric techniques where an attempt is made to quantify the extent of disease processes in an organ; morphometric techniques were used in all seven studies in this work.

The first two studies performed in a general hospital in Glasgow, were designed to assess the incidence of the two main components of chronic airways obstruction, in autopsy series.

1. A NECROPSY STUDY OF PULMONARY EMPHYSEMA IN GLASGOW

The incidence of pulmonary emphysema was sought in a series of fifty, male autopsies. It is now accepted, following the Ciba Symposium of 1959 (9) that the term emphysema applies to a morbid anatomical condition and therefore the clinical, radiological and functional changes which are commonly associated with it, cannot be used to establish accurately the incidence of the disease. The only method of obtaining an estimate of the frequency of pulmonary emphysema is to study autopsy populations. This is not a truly accurate reflection of the incidence of the disease in the general population as the hospital autopsy population is obviously a highly selected one.

The incidence of emphysema, its amount and the different types present were estimated using three different morphometric techniques: the Heard index (44) a point counting technique (40) and standard chart comparisons (45). The overall incidence of 64 per cent of males in the study having more than trace amounts of emphysema was very similar to the incidence found in other centres: London - 74 per cent (44), Edinburgh - 73 per cent (46) and Cardiff 61.8 per cent (47). There were differences between the different areas when the type of emphysema was considered. In the Glasgow series of 50 lungs, centrilobular emphysema was the type most commonly found (34 per cent of all lungs), a mixture of centrilobular and panlobular emphysema was found in 30 per cent and predominantly panlobular emphysema was found in only 10 per cent. Centrilobular emphysema was the commonest variety in Edinburgh (40 per cent) (46) and in Cardiff (23 per cent) of all lungs (47), but panlobular was the commoner type both in London (80 per cent) (44) and in Birmingham (25 per cent of male patients) (48). This difference may be due to environmental factors but the possibility must be considered that different investigators may place emphysema in different groups due to the subjective nature of the assessment. Considerable observer error in the quantitation of emphysema has been shown by Thurlbeck et al (45) and this applies to differences between observers as well as different estimations by the same observer. Both the point counting method and the Standard Chart comparisons are subject to these errors. Comparison of results from different centres

therefore is fraught with difficulties, but the differences found between centres should stimulate further enquiry into variations in smoking habits and also in industrial air pollution in Britain. This study also provided useful information on the comparison of the three morphometric techniques used. Each of the three methods used has inherent problems which must be borne in mind when comparisons are made. The Heard Index deliberately scores destructive emphysema higher than distensive emphysema and is therefore a measure of the severity of the disease as well as its extent. The point count is the only true quantitative method as it expresses the proportion of the lung involved by emphysema. However as panlobular emphysema involves the entire lobule it generates large numbers whereas with centrilobular emphysema smaller numbers are produced (45). As far as it known this was the first time the standard chart comparison method has been used in this country and it proved a rapid and accurate technique. The deficiencies of this method are that it is not a measure of the amount of lung replaced by emphysema but purely a visual comparison with an arbitrary standard and that as it does not differentiate between different types of emphysema it cannot be used for clinico-pathological correlations. However it is useful in large population surveys and epidemiological studies such as the one reported here. All three methods, although they measured emphysema in different ways, showed a broad correlation in their estimate of the amount of emphysema present in a lung.

2. AN AUTOPSY STUDY OF BRONCHIAL MUCOUS GLAND HYPERTROPHY
IN GLASGOW.

This paper describes an investigation into the incidence of pathological changes consistent with chronic bronchitis in an autopsy population. Chronic bronchitis is defined in clinical terms (9) but Lynne Reid (16) has shown that there are characteristic changes in the large airways in patients with chronic bronchitis. The most important of these is the increase in size of the bronchial mucous glands and this was measured in the study included here. The left main bronchus was obtained from 359 consecutive autopsies, both male and female, and the sizes of the bronchial mucous glands were estimated using two techniques, the Reid Index (16) and a point counting method (42). In 110 (31 per cent) of the bronchi examined the bronchial mucous glands were enlarged to a degree consistent with chronic bronchitis. This is a higher incidence than that found in London by Reid of 24 per cent (16) and is much higher than the clinical incidence of 12 per cent in a General Practitioners survey of 1,569 patients (49). The incidence of bronchial mucous gland hypertrophy, in the bronchitis range, was higher in men (36 per cent) than women (25 per cent). The General Practitioner survey also showed a higher incidence clinically in men (17 per cent) than women (8 per cent). Even allowing for the increased overall incidence of bronchitis in this pathological study as compared to the clinical one, the number of women in the Glasgow population with severe gland enlargement is remarkably high. The mean size of the bronchial mucous

glands was greater in smokers than in non-smokers, but when these two groups were compared regarding the number of patients with gland enlargement in the chronic bronchitis range, the difference was not significant. 35 per cent of smokers had severe gland enlargement as compared to 25 per cent of non-smokers. Reid (16) in London, found no difference in gland size between those who smoked less than 20 cigarettes per day and those who smoked more than this. Thurlbeck and Angus (17), in Montreal, found that smokers did have a higher incidence of severe mucous gland enlargement than non-smokers and they suggested that whereas cigarette smoking may be an important aetiological agent in chronic bronchitis in North America, air pollution might be more important in the United Kingdom. The results from the present series in Glasgow would tend to support this suggestion as non-smokers had severe hypertrophy as often as did smokers. Also the high number of women with bronchitis, in Glasgow, would confirm this proposition as women generally smoke less than men, but are exposed to the same atmospheric conditions. Patients who had had symptoms of chronic bronchitis during life had, on average, larger bronchial mucous gland than those without symptoms. The degree of enlargement was closer to that found by Thurlbeck in Montreal (17) than Reid in London (16) and this did not confirm the suggestion (17) that a more severe form of chronic bronchitis may exist in the United Kingdom than in North America. The death rate in Glasgow, in 1969, from chronic bronchitis and emphysema was 856 per million

(50). This was exceeded only by deaths from malignant disease, heart disease and cerebro-vascular disease. These two studies described are the first attempt at estimating the incidence of the pathological changes of these diseases in Glasgow. As approximately one third of the autopsy population had changes consistent with chronic bronchitis and approximately two thirds of the male autopsies had significant amounts of emphysema, it is easy to appreciate why the death rate from them is so high in the West of Scotland.

While these studies were in progress it became apparent that patients with chronic airways obstruction fell into two broad groups. There was a group who died as a result of the disease and a group who died from some unrelated cause. A study of the pathological differences between these two groups of patients was undertaken in Sheffield.

3. A PATHOLOGICAL STUDY OF THE LUNGS AND HEART IN FATAL AND NON-FATAL CHRONIC AIRWAYS OBSTRUCTION.

50 patients were included in this series, 18 of these died from chronic airways obstruction, 17 had evidence of chronic chest disease but did not die from it and 15 patients formed a control group as they had no clinical history of chest disease. The amount and type of emphysema and the size of the bronchial mucous glands were compared in these groups but other measurements were also made. The distribution of emphysema in the lung was examined, and the proportion of the lung which was composed of small airways was calculated to obtain a measure of the degree of airways obstruction. Many patients

dying from airways obstruction do so after developing right ventricular failure, with or without right ventricular hypertrophy. The heart was therefore also examined in all these patients and the left and right ventricles were weighed separately. Relationships between all the measurements of airways disease and the size of the right ventricle were sought and also the means of each measurement were compared between the three groups of patients. The morphometric techniques used are described in paper 3 of the series. The total amount of emphysema was found to be greater in the lungs of patients who died from chronic airways obstruction than in the other two groups. A positive correlation was found between the amount of emphysema and the right ventricular weight and when the type of emphysema was considered it was found that the panlobular type was quantitatively related to right ventricular weight but centrilobular was not. As the total amount of emphysema in the lung increased it was found that there was an increase in each of three zones in the lung apical, middle and lower. The proportion of the lung occupied by the lumen of small airways was related to right ventricular weight but the size of the bronchial mucous glands was not. Many studies on various aspects of this subject have been previously reported. The evidence from them is conflicting and in the present discussion only major points of difference between the study in question and the previous work will be developed. In the current work it was found that the amount of emphysema in the lungs was related to the clinical severity of the disease. Patients dying from chronic airways obstruction

had significantly more emphysema than those who had a clinical history of the disease but did not die from it. Also the amount of emphysema had a positive correlation with the degree of right ventricular hypertrophy.

These results support what has, in recent years, been probably a minority view amongst workers in this field (20, 51-53). The opinion of many, that the amount of emphysema in the lung is not related to the effects of the disease on the right ventricle has many adherents (21, 33, 34, 54-56). The positive correlation found in this series between the amount of emphysema and right ventricular weight may be the result of the inclusion of a whole spectrum of severity of emphysema from zero to almost total lung replacement. In other studies which have shown no such correlation, cases were selected because they had emphysema (34, 54) and also in two other studies (21, 33) the estimation of the size of the right ventricle was made on wall thickness, which is unreliable, rather than weight. Thurlbeck et al (22) give a very clear explanation of the means by which patient selection affects the relationship between emphysema and right ventricular hypertrophy. In a general autopsy population where most patients have no emphysema and a smaller number have progressively increasing amounts of emphysema, a few patients in each group will have right ventricular hypertrophy. This will produce a positive correlation between the amount of emphysema and right ventricular weight. Where patients with symptomatic obstructive lung disease only are included a correlation might still

be expected between the amount of emphysema and right ventricular hypertrophy but where patients are selected purely on the basis of fatal lung disease there should be no simple correlation. This in fact is the case in the present series of studies as will be seen in a later paper.

Secondly the amount of panlobular emphysema, but not centrilobular emphysema was related to death from obstructive airways disease and right ventricular hypertrophy. Several authors have stressed the fact that centrilobular emphysema (34, 38, 57, 58) is more important than panlobular in its effects on the heart. However there have been three North American studies (51, 52, 59) which have found panlobular emphysema to be important in the outcome of the disease as has been shown in the present study. An important technical point in regard to the scoring of emphysema is that using a point counting technique, panlobular emphysema is scored higher than centrilobular emphysema because the holes in the lung are larger (45), and this may contribute to the positive statistical relationship. It should not be inferred from this that centrilobular emphysema does not cause right ventricular hypertrophy but only that there is no quantitative relationship between the two parameters. Hasleton (56) has pointed out that much smaller amounts of lung require to be destroyed by centrilobular than panlobular emphysema to cause right ventricular hypertrophy.

The third important pathological change found to correlate with fatal disease and right ventricular

hypertrophy was the reduction in the proportion of the lung occupied by the lumen of small airways. Bignon et al (60) found a relationship between small airways lumen and right ventricular hypertrophy and a relationship between a reduction in small airways lumen and emphysema has also been shown (8, 61). This study is the first however to show a positive relationship between the reduction in small airways lumen and both death from obstructive airways disease and right ventricular hypertrophy.

In contrast to these findings for small airways the changes in the large airways showed no relationship to the size of the right ventricle. A physiological study (27) has shown that in chronic airways obstruction the increase in total resistance to air flow is provided by an increase in the resistance in the small air passages rather than the larger. The present findings would suggest a similar conclusion and they do not support the concept that chronic bronchitis without emphysema may cause heart failure (62) or that there is a relationship between bronchial gland size and right ventricular hypertrophy (63).

An opportunity was taken during this study to examine the effects of the distribution of emphysema in the lung, on the patient and on the size of the right ventricle. As the blood flow through the lung decreases progressively from the base to the apex (64) it might be assumed that emphysema involving the lower regions of the lung would affect the ventilation/perfusion ratio more than if it only involved the upper lobe. This

would be reflected in the clinical disability of the patients and in the size of the right ventricle. Patients who died from chronic airways obstruction had significantly more emphysema in the lower zone of the lung than those who had only symptomatic disease. However the fatal disease patients also had more emphysema in the upper and middle zones as well and it would appear that as emphysema increases it affects all the areas of the lung rather than affecting the basal area more than the others.

4. QUANTITATION OF THICK WALLED PERIPHERAL LUNG VESSELS IN CHRONIC AIRWAYS OBSTRUCTION.

It is now recognised that the hypoxia caused by chronic airways obstruction has a direct effect on the pulmonary arterioles, causing constriction (32). If this constriction persists it becomes permanent with increase in vessel wall thickness and a rise in the pulmonary artery pressure resulting in hypertrophy of the right ventricle. Pulmonary arterioles were examined, in the 50 cases, which constituted the previous study, for evidence of wall thickening. The proportion of vessels, of less than 100μ in diameter which had a double elastic lamina and a layer of muscle between the laminae, was counted. This was related to the same three clinical groupings as in the previous study and also to the weight of the right ventricle and the measurements of emphysema and bronchitis already described. The complete tables for this study are in Appendix 1, as only abbreviated tables were published in the original

paper. The mean number of thick walled peripheral lung vessels was found to be significantly greater in the group who died of chronic airways obstruction than in the other two groups. A significant positive correlation was found between the number of thick walled peripheral lung vessels and both right ventricular weight and the amount of emphysema in the lung. A significant negative correlation was found with the proportion of the lung occupied by the lumen of small airways. The amount of emphysema and the reduction in the lumen of small airways have been shown to be related to clinical outcome and right ventricular hypertrophy in the previous study. The mechanism of the effect on the right side of the heart is shown to be through the small pulmonary arteries as both of these parameters are related to the number of the vessels which show thickening of their walls.

As far as is known, this technique has not previously been applied to human lung sections, and it proved to be a rapid and accurate method of estimating the degree of small vessel change. The relationship between thick walled muscular pulmonary arterioles and right ventricular hypertrophy, in emphysema, is well established (65, 66, 67), but it has not previously been quantitated.

5. POST-MORTEM ASSESSMENT OF CHRONIC AIRWAYS OBSTRUCTION BY TANTALUM BRONCHOGRAPHY

As has already been mentioned the site of the obstructive lesion in chronic airways obstruction is

in the small air passages, less than 2 mm. in diameter (27) and the importance of the reduction in the amount of lung occupied by the lumen of small airways, as calculated in histological material, has been shown in studies 3 and 4.

The small airways were also investigated by a different technique: post-mortem bronchograms were performed which allowed the entire distal airways system of any given area to be visualised radiographically. Tantalum bronchograms were made of 22 left lungs: 13 of the lungs used were in the original series of 50 cases previously described and a further nine cases were also included (see Appendix 2 for correlation of the case numbers). Tantalum dust allows investigation of the smallest airways (68, 69) and the radiographs were examined particularly in the most distal 4 cm. of the lung substance. The number of small airways branches in this area and also the number of airways of less than 1 mm. diameter were counted. As in the previous studies the patients were divided into three groups, one with no lung disease, one where the patients died from chronic airways obstruction and the third with non-fatal respiratory disease. In this study patients dying from chronic airways obstruction are described as having cor pulmonale. For the purpose of this paper this was defined as clinical evidence of heart failure due to lung disease. This was the first occasion in which tantalum bronchography had been performed on a series of diseased lungs. The changes found in severely diseased lungs

were irregularity of the bronchial walls, areas of narrowing and diltation of the walls and pooling of tantalum at the ends of airways. The latter change was similar in appearance to that illustrated by Leopold and Gough (70) who made lead bronchograms of lungs but did not quantify the changes. Quantitatively, patients dying from chronic airways obstruction had a significantly reduced number of patent small airways (less than 1 mm. in diameter) compared to both the other groups of patients. They also had a reduced number of small airways branches in the most distal 4 cm. of the lung field. Thus confirmation of the suggested site of obstruction and quantitation of the changes was obtained in a way not previously used in post-mortem material. The study also provided confirmation of the nature of the obstructive lesion, which is a combination of post-inflammatory fibrosis in the walls of airways and mucous plugging of them (23, 21).

There was no significant reduction in the number of small airways filled by tantalum in patients with non-fatal respiratory disease. The numbers of airways counted in this non-fatal group were not significantly different from the group with no chest disease.

It would appear that the loss of the distal small airways function is a part of the disease complex which is closely related to death from chronic airways obstruction.

6. A CLINICO-PATHOLOGICAL STUDY OF FATAL CHRONIC
AIRWAYS OBSTRUCTION

This investigation was concerned purely with

patients who died as a result of chronic airways obstruction. Seventeen of the patients were in the fatal disease group already described in the previous studies and a further four were added to this. The case numbers in this study are the same as in Paper 3. The object of the study was to determine whether there are two different types of patients in this fatal disease group and in particular whether there were differences between those who developed right ventricular failure and those who did not. Clinical and pathological changes were studied and an evaluation of the correlations between clinical impression, investigations during life, and autopsy findings was made. The immediate cause of death in these patients was also noted in this investigation. The two types of patients previously described by Burrows et al (26) as Types A and B have been previously described in the historical review. All the patients in the present series were bronchitics and thus are by definition Type B or Type X (intermediate) in the Burrows classification. However 15 of these patients had radiological evidence of emphysema which is supposed to be a feature of Type A disease. Eight of the patients did not have polycythaemia and eight had never been in heart failure: both features stated to be common in Type B disease. All the patients had significant amounts of emphysema, pathologically; also a feature of Type A disease. This group of patients did not therefore fit into the two types of chronic airways obstruction previously described either clinically or pathologically.

The present group of 21 patients could be divided into two groups simply on the basis of whether they had been in right ventricular failure prior to the terminal admission or not. Thirteen patients had been in right ventricular failure for at least one year, prior to death, and the other 8 patients had never shown signs of right ventricular failure or only developed them during the terminal episode of the disease. There were no significant differences between the two groups in the length of history of the chest disease, blood gas estimations, respiratory function tests or the degree of polycythaemia. The only clinical difference of note, was that patients with heart failure died, at a younger age, on average, than those without it. Pathologically there were no differences of significance between the groups in the amount of emphysema, size of bronchial mucous glands or proportion of the lung occupied by the lumen of small airways. Heart failure in chronic airways obstruction does not appear to be related to quantitative differences in the lung disease. This must be contrasted with the earlier finding in Paper 3 where quantitative changes were related to death from chronic airways obstruction when the fatal disease and symptomatic patients were considered as a single group. This difference is partly caused by patient selection as was explained in Pages 32 and 33. No distinction was made in Paper 3 as to whether patients had heart failure or not, all those dying of airways obstruction being included in one group. Quantitative changes in the lungs and airways would seem to be related

to death from the disease but not to whether a patient develops right ventricular failure or not. The present study does not therefore support the concepts that heart failure is more common in chronic airways disease when emphysema is slight (21) or that it is related more to centrilobular than panlobular emphysema (72). Rather they would confirm Thurlbeck's findings (22) that these patients cannot be readily placed in two distinct groups. This study also provided an opportunity for clinico-pathological comparisons to be made. There was a good correlation between clinical right ventricular failure and right ventricular hypertrophy, with a few exceptions, as found in other studies (22, 73). Patients may have an enlarged right ventricle but not be in right ventricular failure, the myocardium being capable of pumping against the resistance of the pulmonary circulation, but patients who are in clinical right ventricular failure all have large right ventricles. Presumably the myocardium in these patients can no longer cope with the pressure gradient in spite of considerable hypertrophy. Electrocardiographic diagnosis of right ventricular hypertrophy was found to correspond with the weight of the right ventricle, at autopsy, in 66 per cent of cases. The radiographic diagnosis of emphysema proved an accurate assessment when compared to the autopsy findings and radiographic estimations of right ventricular enlargement were accurate in 65 per cent of cases. The degrees of accuracy of these estimations were similar to that of previous studies (22, 35, 74, 75). The most

important single event in precipitating death in this series of patients was acute suppurative bronchitis and bronchiolitis. This was present in 20 of the 21 patients (95 per cent) who were studied. In the past, two authors have stressed the clinical importance of a terminal acute airways infection in chronic airways obstruction (74, 76). The infection is often overlooked clinically as there may be no pyrexia (76) but occlusion of small airways by acute exudate is important in causing respiratory failure in patients who already have chronic chest disease and also it may precipitate right ventricular failure (51, 76). The incidence of acute bronchiolitis in this series is higher than that previously found by Mitchell et al (20) of 41 per cent and by Cullen et al (54) of 88 per cent, in autopsies on patients with chronic airways obstruction. This terminal infection is easily missed at autopsy as the macroscopic changes are not striking. The infection usually remains confined to the airways and bronchopneumonia was an uncommon event in these patients. It is of interest that this lesion which appears to terminate the disease in many patients has the same appearance as the acute bronchiolitis described by McLean (23) as being such an important factor in the initial pathogenesis of emphysema.

7. THE CROSS SECTIONAL AREA OF DIAPHRAGMATIC MUSCLE FIBRES IN EMPHYSEMA, MEASURED BY AN AUTOMATED IMAGE ANALYSIS SYSTEM

The last paper included in this series was concerned with a different aspect of airways obstruction.

The action of the respiratory muscles in chronic chest disease has been studied physiologically but very little work has been done on the pathological changes in the muscles. Intact diaphragms were obtained from 24 patients 14 of whom were in the group of 50 patients included in the third study. Appendix 3 shows the correlation of the case numbers between these two studies. The cross sectional area of diaphragmatic muscle fibres was measured using an automated image analysis system known as a Quantimet 720. The mean muscle fibre size, in a group with emphysema was compared to a group with no chest disease. The emphysematous patients had a significantly larger mean muscle fibre cross-sectional area and patients who died from chronic airways obstruction had a larger muscle fibre area than those who had non-fatal disease. Although it is known that decreased vertical movement of the diaphragm occurs in patients with emphysema, and is probably one of the factors which contributes to their disability, (77)no previous study has measured the changes in the cross sectional area of the muscle fibres. The diaphragmatic muscle fibres may undergo hypertrophy because they are undergoing horizontal shortening when the diaphragm is working at a poor mechanical advantage. Ishikawa and Hayes (78) found an increase in the thickness of the diaphragm in patients with obstructive airways disease but Steel and Heard (79) did not find an increased thickness or muscle volume increase in patients with chronic bronchitis. This difference may be explained by the finding (80) that diaphragmatic movement is related to emphysema but not

to chronic bronchitis. This study was also the first time that a Quantimet system had been applied to muscle fibre measurement. It proved rapid, accurate and gave results which correlated well with methods previously used to perform cross sectional area measurements (81, 82).

ORIGINAL OBSERVATIONS

1.
 - (a) The incidence of pulmonary emphysema in an autopsy population in Glasgow was established for the first time.
 - (b) The prevalence and amount of each type of emphysema was determined in the same autopsy series.
 - (c) The Standard Chart comparison method of estimating the amount of emphysema was used for the first time in a British Series and was found to be a useful technique.
2.
 - (a) The incidence of bronchial mucous gland hypertrophy, to a degree consistent with chronic bronchitis, was established in an autopsy series in Glasgow.
 - (b) Correlations between the size of the bronchial mucous glands and age, sex, smoking and clinical history of chronic bronchitis were obtained in this autopsy series.
3.
 - (a) In an autopsy series in Sheffield the amount of emphysema was found to be related to death from chronic airways obstruction and to right ventricular hypertrophy.
 - (b) The amount of panlobular emphysema, and the reduction in the proportion of the lung occupied by the lumen of small airways were related to death from chronic airways obstruction and

right ventricular hypertrophy.

- (c) The amount of centrilobular emphysema and the size of the bronchial mucous glands were not related to death from chronic airways obstruction or right ventricular hypertrophy.
- (d) The distribution of emphysema in three separate zones in the lung was estimated for the first time, and it was found that as emphysema increases in amount it affects all the areas of the lung but with the apex always showing more disease than the base.

4.

- (a) In the same autopsy series the number of thick-walled peripheral vessels in the lung was found to be related to a fatal outcome of chronic airways obstruction and right ventricular hypertrophy.
- (b) The number of thick-walled peripheral lung vessels showed a positive correlation with the total amount of emphysema and with the amounts of panlobular and centrilobular emphysema and a negative correlation with the proportion of the lung occupied by the lumen of small airways.
- (c) The technique of quantitating thick-walled peripheral lung vessels was used for the first time on human material and produced comparable results to

to previous experiments.

5.
 - (a) Tantalum bronchography was used for the first time in an autopsy series of lungs.
 - (b) Using this technique the number of small air passages in the periphery of the lung were counted and patients who had died from chronic airways obstruction had a significantly reduced number of these airways compared to non-fatal cases.
 - (c) The site of obstruction to air flow in these lungs was shown to be the small airways of approximately 1-2 m.m. diameter.
6.
 - (a) In a group of patients who died from chronic airways obstruction there were no significant differences in clinical or pathological parameters between those who had had long standing right ventricular failure and those who had not.
 - (b) This group of patients did not divide into the two previously described sub-groups: predominantly emphysematous and predominantly bronchitic, either clinically or pathologically.
7.
 - (a) The cross sectional area of diaphragmatic muscle fibres was shown to be significantly greater in patients with emphysema than

in those without it.

- (b) An automated image analysis system was used for the first time to measure the cross sectional area of muscle fibres, and was shown to be more rapid than, and equally accurate to, previous methods.

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