PULMONARY PERFUSION

AND

INHALATION SCANNING -

A HOSPITAL POPULATION STUDY WITH

PARTICULAR REFERENCE TO

PULMONARY EMBOLISM

BY

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THESIS

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THIS THESIS IS DEDICATED TO MY WIFE

EVA

AND MY FAMILY

IN APPRECIATION OF THEIR CONSTANT

UNDERSTANDING, ENCOURAGEMENT

AND SUPPORT

This thesis is of my own composition and is a true record of original work which has not been submitted for the award of any degree or diploma in any university.

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D.J.C.

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CHAPTER `I

GENERAL INTRODUCTION

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The two purposes of this project were:

1. to improve the efficiency of the diagnosis of pulmonary embolism by the use of radionuclides, and

2. To investigate the incidence of pulmonary embolism, especially subclinical embolism in various hospital populations.

1. Improved detection. At various stages use was made of the following techniques:

(a) Rectilinear scanning following administration of iodine labelled macroaggregates (^{131}I MAA).

(b) Blood flow studies following the administration of sodium pertechnetate (Na ^{99m}Tc04), and comparison with (a).

(c) Rectilinear scanning or scintillation camera study following administration of technetium labelled macroaggregates (^{99m}Tc MAFH).

(d) Inhalation scanning - development of new techniques employing aerosols of sodium pertechnetate or indium chloride.

(e) Routine serial pulmonary perfusion scanning and the investigation of abnormal findings by combined inhalation/perfusion scanning techniques.

2. Application of these techniques to clinical situations. The foregoing techniques were used in the following clinical situations to determine the incidence and nature of pulmonary perfusion and ventilation abnormalities in these groups:

(a) A prospective survey of medical inpatients;

(b) A prospective survey of surgical inpatients; and

(c) A group of normal volunteers.

The five chapters which make up this thesis comprise:

I General Introduction

II Historical Introduction

III Subjects, Materials and Methods of Study

IV Prospective Surveys of Medical and Surgical Subjects

V "Selected" Series

The discussion relating to the results obtained in each section has been included at the end of the relevant chapter.

CHAPTER II

HISTORICAL INTRODUCTION

HISTORICAL INTRODUCTION (until 1970)

Summary: Pulmonary embolism was first recognised as an important entity early in the nineteenth century. The evolution of our knowledge of this disorder has been reviewed with particular emphasis on the various diagnostic techniques which have been used to assist in its recognition. These have included physical examination to demonstrate the presence of classical physical signs, electrocardiography, biochemical tests, radiological examinations, pulmonary function tests, ultra-sound and methods employing radionuclides. The wide variety of techniques applied to this problem clearly indicates that no currently available test is entirely satisfactory alone. Probably the most significant advance in recent years has been the development of lung perfusion scanning which has provided at the very least a valuable screening test and a ready method of studying serially the natural history of the perfusion defects produced by thrombo-embolic disease.

I. The pulmonary circulation. The concept of embolism

The first adequate description of the pulmonary circulation was made during the thirteenth century by an Arab, Ibn-An-Nafis. He challenged the orthodox Galenic concept which taught that blood passed from the right heart to the left via invisible pores in the cardiac septa where it mixed with 'pneuma' from the lungs to form the 'vital spirit'. Three hundred years before a comparable

European description he described how, 'in the wisdom of God', blood was carried to the lungs via the pulmonary artery so that 'what seeps through the pores in the branches of this vessel into the alveoli of the lung may mix with what air there is therein and combine with it....the mixture is then carried to the left chamber of the heart by the Arteria Venosa' (the pulmonary veins). This remarkable contribution remained in total obscurity until the early part of this century (Christie, 1969).

It is not surprising therefore, that the significance of obstructions in the pulmonary artery passed unnoticed until after Servetus redescribed the pulmonary circulation and William Harvey in his treatise De Motu Cordis (1628), gave medicine its present concept of the circulation of the blood.

It is surprising, however, that there is no recognisable description in the Bible of pulmonary embolism, a common disease which may have such dramatic manifestations (Bennett, 1887). Galen described a case of sudden death which Cohn (1860) considered to be due to pulmonary embolism but, except for this, the early Greek writings contain no obvious reference to the condition.

The earliest reports of what were probably cases of thrombo-embolic disease date from the seventeenth century when several authors, including Malpighi, described a condition associated with 'asthma, palpitations, inflammation of the chest' and the post-

mortem finding of 'polypus cordis' - a term coined by Vesalius to describe the post-mortem finding of blood clots in the heart (Liebowitz, 1963).

The first clear description of an undoubted case of pulmonary embolism is usually attributed to Hélie (1837). He described a short fat laundrywoman of 65 years who, 2 weeks after being treated in hospital for a sprain and while talking to her neighbours, suddenly developed a violet hue. Her face swelled, her eyes bulged and she lost consciousness. She recovered from this acute attack but died soon afterwards in a similar episode. Examination of her body after death revealed a large heart with well organised clots in the right ventricle and pulmonary artery.

In 1819, Laennec published his Traite de l'Auscultation Médiate. In a chapter entitled Pulmonary Apoplexy he gave an excellent description of the clinical features of pulmonary infarction which he considered to be of non-inflammatory nature, contrary to the accepted views of his contemporaries. He differentiated the condition from such other causes of haemoptysis as bronchogenic malignancy and broncho-cavitary tuberculosis. He noted the central breakdown in many lesions and described 'haemorrhagic pleurisy'. However, Laennec paid scant attention to the involvement of blood vessels and it was Cruveilhier (1829), a contemporary of his, who described in meticulous detail the branching clots which filled the vascular tree leading to these

lesions. Laennec subsequently pointed out that the condition was found most frequently in patients suffering from diseases of the heart with pulmonary congestion and regarded it as being related in some way to cerebral haemorrhage; hence his use of the term 'apoplexy' (Laennec, 1819).

In 1844, Paget, while at St Bartholomew's Hospital, London, described several cases in which old clots were found in the pulmonary artery or its main branches at autopsy. In one case he observed clots in the femoral vein of similar consistency to those in the lung. In the same year, Rokitansky was the first to suggest that pulmonary infarcts were embolic in nature and caused by fragmentation of clots in the veins or in the right heart. In 1845, Egeberg described the case of a woman who died 17 days post-partum of a pulmonary embolus which arose from the veins of the left leg where phlegmasia alba dolens had developed a few days before her death (Gammeltoft, 1952).

During the next decade, Rudolf Virchow carried out the anatomical, experimental and clinical observations which firmly established the concept of embolism. In 1845, he conducted autopsy examinations upon the bodies of seventy-six cases from the Charité Hospital, Berlin, and found formed clots in the pulmonary arteries of eleven, and thrombi in the deep crural veins of eighteen. This had suggested to him the link between the two disorders and and his subsequent studies with artificial emboli showed how such

'bodies' could traverse the veins and chambers of the heart to lodge eventually in one or other branch of a pulmonary artery (Virchow, 1856).

Virchow's concepts were rapidly accepted in the medical world and after 1860, the accounts of pulmonary embolic disease which appeared in medical textbooks reflected his views (Cohn, 1860; Aitken, 1864; Flint, 1867). However, they said little regarding its natural history, prognosis or treatment. It was regarded as an inevitably fatal condition until Pye-Smith (1888) gave a description of several patients who recovered from near fatal attacks, and Welch (1920) recognised that pulmonary embolism could result in chronic ill-health. The contributions of such people as Panum (1864), who demonstrated that pulmonary embolism could be produced asymptomatically in the experimental animal, and Dunn (1920), who documented some of the physiological responses of the of the goat to pulmonary embolism, ensured that at least some clinical and pathological interest became diverted from the general preoccupation with massive and fatal attacks, to a consideration of the less dramatic and poorly recognised manifestations of the disease.

II. Early pathological and clinical studies

(a) Incidence of embolism. At a time when antiseptic and aseptic surgery was reducing postoperative mortality and more extensive operations were being undertaken, it was realised that pulmonary embolism was a common complication of surgical operations

(Lenormant, 1909). However, pathological studies did not confirm the initial clinical suspicion that pulmonary embolism was mainly a postoperative disease.

Pathologists have recognised a high incidence of pulmonary embolism in autopsy material since the nineteen twenties. In 1922, Møller noted eighty-four 'thrombi' in various stages of organisation in the pulmonary arteries in fifty-one of 176 (29%) consecutive subjects studied at autopsy. He concluded that the great majority of these thrombi were embolic in origin.

In the same year Cutler and Hunt (1922) described sixty-three cases of postoperative pulmonary complications, including five deaths, following 1604 operations. Their findings suggested that the majority of such complications were due to pulmonary embolism. They recorded the rapid onset of symptoms and their almost equally rapid subsidence, the involvement of small areas of lung, and the presence of cone-shaped lesions on radiological examination of the chest. They stressed the need for immediate and repeated X-ray examination due to the transience of such changes, advice which has since been often repeated.

In 1935 Brenner, in his detailed survey of the pathology of the pulmonary circulation in 100 consecutive autopsies, listed twenty-eight cases with recent or well organised thrombi in the pulmonary arteries. In thirteen there was an obvious source of embolism and since it was not possible to examine all the systemic

veins at autopsy such sources may have been present in others. He attributed to emboli, numerous changes found in the small vessels which were rarely mentioned at that time in the literature as microscopic investigation of the pulmonary vasculature was unusual.

In 1940 Hampton and Castleman published a paper of great clinical and pathological significance. They correlated the results of post-mortem radiological examination of the chest and the pathological findings in a series of 400 autopsies and compared their results with a larger series of over 3500 autopsies performed in the same laboratory over the previous 10 years. The overall incidence of pulmonary embolism in the retrospective series was 9%; whereas in the combined study group the incidence was 14% - an apparent increase of over 50%. In particular they suggested for the first time that the disease was more common among medical than surgical patients in their general hospital. Indeed one-third of their cases of pulmonary infarction had neither been operated upon nor had any demonstrable cardiac disease.

They described the size, shape and usual locations of the lesions, stressing that pulmonary infarcts are 'always' in contact with a pleural surface and have a convex or 'hump-shaped' cardiac margin (Hampton's hump). In addition, they coined the term 'incomplete infarction' for the syndrome characterised by pleuritic pain or haemoptysis associated with a rapidly appearing

and disappearing infarct-like area of consolidation on chest X-ray.

They demonstrated the similarity of this syndrome to that produced in the lungs of normal animals after embolisation without the development of frank infarction. Their paper indicated that a firm diagnosis of pulmonary embolism could be made although only one of the triad of haemoptysis, pleural pain, and possible site of an embolus was present if it were associated with a 'positive' chest X-ray. Of possibly greater importance they stressed that the diagnosis could be considered in ambulant subjects.

(b) Cor pulmonale. In this atmosphere of increasing interest in the significance of pulmonary embolism, White and Brenner (1933) developed the concept of acute cor pulmonale and attempted to delineate a pattern of physiological and haemodynamic changes which would assist in the diagnosis of embolic disease. Kirschner (1924) had described three extremely useful signs of right heart embarrassment, namely (i) a sharply accentuated second sound; (ii) increased cardiac dullness to the right of the sternum and (iii) *die rote Blutwelle*;* but scant attention

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*Kirschner, while observing a patient apparently dying from a massive pulmonary embolism, noted a red 'arterial wave' pass over the patient's pallid, cyanotic face for a few moments only. A short time later the same phenomenon occurred again. The explanation proposed was that a dislodged piece of the obstructing embolus temporarily permitted an additional amount of freshly oxygenated blood to pass through the lung to the left heart whence it was pumped to the patient's face.

had been paid to them in the English speaking world. In 1935 McGinn and White redescribed the classical findings of acute cor pulmonale when they recorded the clinical features of nine patients with extensive pulmonary embolism and infarction. They emphasised the importance of such signs as pulsation in the second left intercostal space (Litten, 1878); an accentuated pulmonary second sound (Schumacher, 1913); a pseudo- or pleuro-pericardial friction rub; distended jugular veins; increased cardiac dullness to the right of the sternum (Kirschner, 1924); a gallop rhythm heard best in the pulmonary area; and enlargement of the liver (White and Brenner, 1933).

McGinn and White were the first to establish the value of the electrocardiogram in the diagnosis of acute cor pulmonale and to delineate the variety of changes which may be encountered in this disorder. They described the presence of a Q wave and late inversion of the T wave in lead III, together with a gradual staircase ascent of the ST segment in lead II; a prominent S wave and low origin of the T wave in lead I; and an upright T wave associated with inverted P and QRS complexes in lead IV (chest lead). They considered these features to be indicative of dilatation and partial failure of the chambers of the right heart.

Following the work of McGinn and White and Hampton and Castleman, the electrocardiogram and chest X-rays became the main diagnostic tools at the disposal of the clinician. They were useful in so far as they were often able to provide confirmatory

evidence of pulmonary embolism and infarction in cases where clinical suspicion was high. However, it was noted early that McGinn and White's criteria for the diagnosis of acute cor pulmonale were only rarely satisfied (Master, Jaffee and Dack, 1937); while many patients with subsequently proven pulmonary embolism were found to have had either normal electrocardiograms or tracings which showed non-specific changes of doubtful diagnostic significance (Sokolow, Katz and Muscovitz, 1940).

In 1954 DeBakey wrote: 'It becomes increasingly apparent that much of the prevailing confusion on the subject of thrombo-embolism derives from the difficulty of establishing the diagnosis and consequently a firm basis for the disease.' Since then advances have done much to clarify this troublesome problem, particularly those involving the use of angiography and radio-nuclides.

MODERN METHODS OF DIAGNOSIS

I. The scope of the problem: Clinical symptoms and signs.

Recent pathological surveys indicate that pulmonary embolism as well as being a common disorder, is frequently unsuspected until autopsy and contributes significantly to the mortality of hospital populations.

In 1963, Smith, Dammin and Dexter conducted careful arterio-graphic studies in 370 consecutive autopsies. They found that approximately one patient in seven had died of pulmonary embolism;

but the presence of emboli had been suspected in less than one half of the subjects affected. Meticulous examination of the right lung in a post-mortem study of 263 unselected subjects by Morrell and Dunnill (1968) revealed emboli in 51.7% of cases. In 20% of all subjects both old and recent emboli were present. In thirty-seven patients (15%) death was entirely attributable to embolism and considered to have been potentially preventable. These results highlight the difficulties involved in diagnosis.

Diagnosis is difficult partly because the manifestations of pulmonary embolism are so many and varied. Patients may present in acute cor pulmonale; with pleuritic pain and haemoptysis of sudden onset; or, at the other end of the spectrum with neither a symptom nor sign of the disease (Gage, 1953; Owen et al. 1953; Israel and Goldstein, 1957; Sevitt and Gallagher,1961).

In a series of ninety patients, Israel and Goldstein (1957) found the following frequency of symptoms and signs: chest pain 72.2%; dyspnoea 46.7%; haemoptysis 28.9%; fever 78.9%; tachycardia 58.9%; a pleural friction rub 24.4% and phlebitis 64.0%. Variable electrocardiographic changes were noted in just over one-half of the subjects. Sasahara and his collaborators (1967) noted dyspnoea in all seventy-two patients in their series and stressed that dyspnoea is likely to be denied by patients who not acutely ill.

Clinical evidence of thromboembolism may often be obscured

by the presence of coexisting serious disease such as widespread malignancy or advanced cardiac, cerebral, renal or vascular disease. In 1965, Greenberg surveyed the protocols of post-mortem examinations performed upon twelve patients with such diseases dying of pulmonary embolism and found that in nine, pulmonary embolism was recurrent and yet had been diagnosed in only four. He concluded that an important diagnostic sign was a steady worsening in a patient's condition with increasing dyspnoea and orthopnoea refactory to conventional therapy. His findings would suggest that a high index of clinical suspicion is a prerequisite for improvement in the rate of diagnosis.

II. The electrocardiogram

The introduction of multiple chest leads and unipolar limb leads allowed the electrical output of the heart to be recorded more precisely than was possible when McGinn and White, relying on standard limb leads and limited chest leads, published their findings in acute cor pulmonale. Electrocardiography is still the most readily available and simplest means of diagnosing pulmonary embolism. However, only about 20% of patients with the disease develop electrocardiographic changes and a smaller number show diagnostic abnormalities (Sokolow et al. 1940; Goldberger, 1953; Rakov, 1963).

Tachycardia is frequently seen in pulmonary embolism (Rakov, 1963). The basic rhythm usually remains the same as that prior to embolisation; but Duner, Pernow and Rigner (1960) found two

cases of atrial flutter and four of fibrillation occurring at the onset of embolisation in a study of twenty-eight patients, and Webber and Phillips (1966) found atrial arrhythmias in 38.3% (23/60) in subjects following acute pulmonary embolism.

The P wave may be peaked in leads II, III and aVF, but rarely to the extent seen in chronic disease (Wood, 1941). A Q wave may be seen in lead III and may be accompanied by similar changes in lead II and aVF (Sherry, 1967). Right axis deviation, clockwise rotation of the heart (Phillips and Levine, 1950), and right bundle branch block may occur (Durant, Ginsberg and Roesler, 1939). Inversion of T waves over the right ventricle in the precordial leads (Wood, 1941), and S-T segment depression, sometimes excepting lead III, also result from acute strain and dilatation of the chambers of the right heart and are probably the most commonly seen abnormalities (Littman, 1965).

III. Biochemical changes

In recent years, it was hoped that specific biochemical changes might be associated with the development of pulmonary infarction. Unfortunately, to date, there are no biochemical or other laboratory tests which specifically indicate that pulmonary infarction has occurred. Nevertheless, the performance of a profile of enzyme studies may facilitate diagnosis. The studies of Goldstein and Israel (Goldstein, Israel and Seligson, 1956; Israel and Goldstein, 1957), suggested that, in contrast to the

common pattern of events following myocardial infarction, aspartate aminotransferase (AAT; GOT) activity does not increase after uncomplicated pulmonary infarction. Their findings are supported by the experimental results of Agress and his co-workers (Agress, Glassner and Jacobs, 1956). Wacker and Snodgrass (1960) noted a rise in serum lactic acid dehydrogenase (LDH) following pulmonary embolism and proposed that the triad of a normal GOT, elevated LDH and hyperbilirubinaemia would be specific for pulmonary infarction. Such has not been the case. Increased serum LDH activity is found commonly after myocardial infarction, in various forms of liver disease, in renal disease, in progressive muscular dystrophy, occasionally after cerebrovascular accidents and in a variety of other disorders (Snodgrass et al. 1959). Sasahara and co-workers (1967) found the triad of Wacker and Snodgrass to be present in only 18% of their series of fifty-seven patients with pulmonary thromboembolism. More commonly (42%) an elevated LDH was associated with normal GOT and bilirubin levels. These findings have been confirmed in a subsequent study by Polachek et al. (1968).

Recently, Coodley (1969) has suggested that the level of creatine phosphokinase (CPK) is highly specific in differentiating between myocardial and pulmonary necrosis, since the enzyme exists primarily in myocardium, muscle and brain tissue and rarely, if ever, is elevated in the presence of pulmonary infarction without accompanying myocardial necrosis. The value of this observation

remains to be established.

Views differ regarding the usefulness of isoenzyme analysis in the differentiation of pulmonary infarction. Trujillo, Nutter and Evans (1967) found that the only isoenzyme of LDH which was consistently raised in patients with pulmonary infarction and high LDH levels was the hepatic isoenzyme, and this disagreed with the findings of Cohen, Djordjevich and Ormiste (1964).

IV. Radiological investigations

(a) The chest X-ray. There are no pathognomonic radiological signs of pulmonary embolism. Changes when present are often fleeting and even in the presence of massive embolus often unspectacular and non-specific (Kaye et al. 1956). The shadow produced by infarction was described by Westermark (1938) as wedge-shaped with the apex towards the hilum; yet this classical description has been denied by others (Fleischner, 1958). The infarct, as seen in the posterior-anterior projection chest film, may have almost any shape. It may be sharp or ill-defined, regular or irregular, diffuse or mottled (Krause and Silverblatt, 1955). In about one third of cases it is associated with a pleural effusion (Short, 1951).

The first radiological signs of pulmonary embolism in the absence of infarction were described by Westermark (1938). He noted that in some cases the affected lung appeared abnormally radiolucent due to oligaemia. Also, the central pulmonary arteries may appear slightly dilated and end abruptly at the site of

embolisation, a feature that has been amply confirmed by other workers (Shapiro and Rigler, 1948; MacKeen, Landrigan and Dickson, 1961; Sasahara et al. 1964). On the other hand Stein et al. (1959) in a series of ninety cases of pulmonary embolism failed to demonstrate Westermark's sign and others have found it only occasionally.

It has been estimated (Poulose, Reba and Wagner, 1968) that the chest X-ray is diagnostic in fewer than 15 - 20% of cases. The lack of specificity of radiological signs in the disorder is well borne out by a consideration of one of the most frequently seen signs of pulmonary infarction, namely, elevation of the diaphragm on the affected side. This sign, which may be present in up to 70% of cases of pulmonary infarction (Laur, 1963), can arise from an extremely wide variety of pathological disorders ranging from contusion of the chest to epidemic pleurodynia (Fleischner, 1962). However, if considered in conjunction with the presence of such features as the abrupt termination of the vascular pattern of the lung, dilatation of the main pulmonary trunk with narrowing of the vessels below (Davis, 1964), or the occurrence of small bilateral pleural effusions (Fleischner, 1962), it is one of the most valuable indications of the disorder.

(b) Pulmonary angiography. The growing awareness of the less dramatic 'pulmonary embolus minor', the frequently recurrent nature of the disorder, its often fatal outcome, the improved prognosis in persons adequately treated with anticoagulants, and

the availability of such therapeutic procedures as the administration of streptokinase (or urokinase), plication of the inferior vena cava and pulmonary embolectomy, have all accentuated the need to arrive at a correct and precise anatomical diagnosis within a very short time and in a manner safe for the patient. It is now no longer sufficient merely to determine whether or not pulmonary infarction has occurred. Diagnostic endeavour must also be directed towards determining the precise site(s) of obstruction to the pulmonary vascular tree and the site of origin of the embolus.

In 1931, Carvalho and Moniz performed the first pulmonary angiogram, injecting concentrated sodium iodide into the right side of the heart via a catheter (Robb and Steinberg, 1938). The method, although now commonplace, was slow in gaining popularity and for some considerable time the more indirect methods of diagnosis were preferred.

Pulmonary artery catheterisation allows the pressure in the pulmonary artery to be determined indicating the presence or otherwise of pulmonary hypertension (Del Guercio et al. 1964; Chait et al. 1967). During pulmonary angiography, emboli may be identified either as arterial obstructions with abrupt 'cut-off' of the affected vessel, as filling defects, or as localised arterial stasis. Additional indirect signs include diminution or absence of blood flow to a pulmonary segment, poor capillary filling, and diminished or absent venous return from the affected

area (Wiener, Edelstein and Charms, 1966). The additional signs are generally non-specific and have been found in other cardio-pulmonary disorders such as emphysema (Fred et al. 1966), pneumonia and congestive cardiac failure (Ferris et al. 1967).

However, although arteriography gives an excellent anatomical study of the larger pulmonary vessels, it gives only indirect evidence of perfusion abnormalities and involvement of small vessels.

Of considerable importance is the difficulty often experienced in interpreting the angiogram when pulmonary emboli are sought. Superimposition of air in the bronchi may easily cause the false impression that a filling defect is present. This is particularly the case when the left main stem bronchus crosses under the left pulmonary artery. In addition, a significant filling defect may appear transiently in only one or two frames in a consecutive series of fifteen or more pictures. This may be readily missed without the most diligent search by an experienced observer (Freeman et al. 1968).

Problems involved in routine angiography for pulmonary embolism include delays in the performance of a test that requires the availability of theatre facilities, an anaesthetist, cardiologist and other highly trained personnel; as well as the obvious risk of anaesthesia and right heart catheterisation in a seriously ill patient. Nevertheless the performance of an angiogram is, at present, the only means by which the diagnosis of pulmonary thrombo-

embolism can be confirmed beyond any doubt and is thus indicated in all patients who are considered for pulmonary embolectomy (Sherry, 1967) or thrombolytic therapy (Hirsch et al. 1967).

V. Ultrasound

Ultrasound has recently been suggested as a diagnostic tool in pulmonary embolic disease (Miller et al. 1967). Its proponents claim that the technique is simple enough to be performed rapidly and accurately at the bedside by a technician with minimal training. It is claimed that positive 'embolism' tracings, showing marked increased prominence of returning 'echos' can be obtained within 10-15 minutes of the lodgement of an embolus. The value of this technique is yet to be assessed on a large scale.

VI. Radionuclide studies

Blumgart and Weiss were the first investigators to study the circulation in man using radionuclides. In 1927 they injected radium C into the antecubital veins of patients with rheumatic and syphilitic heart disease and detected its appearance in the other arm by means of a modified cloud chamber (Blumgart and Weiss, 1927). However, it was not until the development of sophisticated scintillation counting techniques and the ready availability of suitable short-lived radionuclides that serious investigation of pulmonary blood patterns could begin.

Pulmonary thromboembolic disease, by its very nature, causes a disruption

of normal pulmonary blood flow and this disruption results in alterations in the behaviour of radioactive tracers in a characteristic manner. The clinician is thus able to obtain considerable insight into the nature of his patient's disease without subjecting him to the not inconsiderable hazards of angiography.

Radioactive gases. Regional pulmonary blood flow was first investigated by Dyson and his group at the Postgraduate Medical School, Hammersmith in 1959 using Oxygen-15, ($^{15}O_2$), a short-lived cyclotron-produced radionuclide (Dyson et al. 1960). When inhaled in the form of carbon dioxide this very soluble gas is removed from the pulmonary alveoli by the regional blood supply. The rate at which it is cleared during short breath-holding gives a measure of the local blood flow. Scintillation counters placed over the back of the patient record clearance curves for the $C^{15}O_2$. This 'highly soluble gas technique', as it has come to be called, has serious limitations if used in an endeavour to detect pulmonary blood flow perfusion defects in a clinical situation. It requires the use of an extremely expensive short-lived radionuclide ($T_{\frac{1}{2}}$ = 2 minutes) and thus the diagnostic unit must be situated next to a cyclotron; the resolving power of the system is low, depending on the number of scintillation counters used; and the time available for data storage during the investigation is determined by the patient's ability to hold his breath.

Following the pioneer work of Knipping and his co-workers (1955, 1957) using the reactor produced noble gas xenon 133, Ball and his associates used this radionuclide to measure regional pulmonary blood flow (Ball et al. 1962). Xenon-133 has a half life of 5.3 days and yields an 81 keV gamma ray. The gas is dissolved in saline and injected intravenously. When the gas reaches the pulmonary capillaries, because of its poor solubility, it 'evolves' into the alveoli and remains there as long as the patient holds his breath (Bass, Heckscher and Anthonisen, 1967). The amount of radionuclide evolving in a given segment of lung is a function of the perfusion of that segment; and the subsequent rate of clearance of radionuclide after resumption of breathing is a function of the ventilation of that region. A pictorial representation of the distribution of this radionuclide within the lungs can be obtained using a gamma (scintillation) camera, a static organ-imaging device of high sensitivity. Such a technique is used in some centres for the detection of pulmonary perfusion defects (Loken, 1966; Newhouse et al. 1968). An important advantage of this method is that the radionuclide has a very short biological half-life and most of the radioactivity passes out of the body in one circulation through the lungs. This enables the study to be repeated many times under varying conditions without danger to the patient.

'Microembolic' technique. In 1947 Müller and Rossier injected radiozinc (^{63}Zn) suspended in pectin solution intra-

venously into a patient with pulmonary metastases from a previously treated hypernephroma. They found that the radioactivity remained precisely localised within the lungs and was not detectable elsewhere. They followed this observation with studies employing radiogold (^{198}Au)-labelled charcoal administered during cardiac catheterisation. In 1958 Ernst et al. re-examined Müller's procedure and in a series of eighteen dogs, demonstrated the possibility of outlining pulmonary blood flow patterns by scintigraphy using charcoal particles labelled with ^{198}Au.

The first rectilinear scanners were designed in 1949 for outlining the thyroid gland (Cassen et al. 1951). Such instruments became available commercially shortly afterwards and in the next 10 years it became possible to scan most of the major organs in the body with the notable exception of the lungs. The microembolisation technique using radioactive macrocolloids was apparently to answer this need.

Ariel (1962) reported that inert ceramic microspheres of 60 μm diameter, when injected intravenously, were trapped in the pulmonary tissues. He advocated the use of such particles labelled with beta emitters, such as yttrium-90, in the management of pulmonary metastases. Significantly, he indicated that perfusion lung scans could be obtained if scandium-46 or chromium-51 were incorporated into the irradiating microspheres and their distribution within the lungs defined by rectilinear scanning

techniques similar to those already employed for imaging the distribution of radionuclides in other organs.

Shortly afterwards Haynie and his group demonstrated that obstructions of the pulmonary arteries could be demonstrated accurately by a similar technique using microspheres, 40-60 μm in diameter, labelled with mercury-203 (Haynie et al. 1962, 1963). Pulmonary artery occlusions were produced in dogs at thoracotomy by ligatures placed around various branches of the pulmonary arteries. Lung scans were then performed at intervals of from 1 hour to 5 days after operation. The avascular regions were consistently demonstrated as areas with little or no radioactivity within them.

Meanwhile Gibel and his associates (Gibel, Matthes and Spode, 1962, 1963; Gibel et al. 1962) had conducted similar experiments using charcoal labelled with ^{198}Au and had concluded that their method was a safe and efficient means of detecting localised obstructions to the pulmonary circulation.

In 1963 Taplin and his colleagues (1964a, b, c) initiated the technique of pulmonary scanning after the introduction of microemboli into pulmonary capillaries by the intravenous injection of radionuclide-labelled macroaggregates of serum albumin (MAA). Their studies in animals demonstrated that the procedure had a very great safety margin and that the embolic material was readily metabolised, hence the procedure could be

repeated at relatively frequent intervals. This new radiopharmaceutical was immediately tried in human subjects (Wagner, Sabiston and Iio, 1964a). Wagner et al. (1964b) and Quinn III et al. (1964) reported their initial clinical experience with MAA labelled with iodine-131 (^{131}I) or chromium-51 (^{51}Cr). The size of the particles injected in these studies ranged from 10-70 μm.

Wagner's group described the characteristic pattern of avascularity associated with massive pulmonary embolism in man. The pattern consisted of a gross irregularity of distribution of radioactivity nearly always involving both lungs. They considered that the technique offered a useful and rapid screening procedure without haemodynamic, radiation or immunological hazard to the patient and emphasised its value as a tool in any study of the natural history of pulmonary embolism (Wagner et al. 1964b).

Evidence for the validity of this method of examination of the lungs accumulated rapidly. Good correlations were demonstrated between the distribution of radionuclide within the lung and the results of differential bronchospirometry (Lopez-Majano et al. 1964), standard electromagnetic flowmeter techniques in dogs (Tisi et al. 1968) and the known effects of posture and ventilation on the distribution of pulmonary blood flow in man (Tow et al. 1966). Within a very short time the procedure of lung scanning with ^{131}I-MAA became an accepted routine diagnostic tool in many centres throughout the world, providing useful information concerning

regional lung perfusion which could not be as readily obtained by any other technique. Its popularity has been largely due to the ease of preparation of ^{131}I-MAA, and the dependability of particle size. Albumin macroaggregates have the added notable advantage in that their intravascular life as particles is relatively short. Fragmentation gradually occurs in the obstructed pulmonary capillaries and the small fragments produced are then removed from the circulation by reticuloendothelial tissue and metabolised (Furth et al. 1965; Murphy, Cervantes and Maass, 1967).

In 1966, Kramer and Stern suggested the use of indium-113m (^{113m}In) (a generator-produced nuclide derived from tin-113(^{113}Sn) incorporated into uniformly sized (20-40 µm) particles of iron hydroxide, as a suitable agent for lung scanning (Kramer and Stern, 1966). Its short half-life (1.7 hr) and absence of beta emission allows millicurie quantities to be administered without radiation hazard to the patient. With the usual 200-300 µCi dose of ^{131}I-MAA the absorbed radiation dose to the lungs is of the order of 4-5 rads/mCi, compared with 0.75 rads/mCi using particles labelled with indium (Wagner and Rhodes, 1968). Carrier-free ^{113m}In can easily be incorporated into iron hydroxide particles which can then be sterilised by autoclaving. A drawback to its widespread use has been its relatively energetic gamma photon (390 keV) which renders it less suitable for use with a gamma (scintillation) camera than technetium compounds. Because of tissue penetration by this relatively energetic gamma emission, it may be

difficult to differentiate one lung from the other in a lateral view due to 'shine through' from the opposite side.

The most suitable agents presently available for lung scanning are compounds of technetium-99m (^{99m}Tc) such as ^{99m}Tc-MAA (Loken, Telander and Salmon, 1965; Webber, Bennett and Surprenant, 1966) and ^{99m}Tc-iron hydroxide macroaggregates (Yano et al. 1969; Boyd et al. 1969; Davis, 1970a, b). The energy (140 keV) of the solitary gamma emission of this radionuclide is ideally suited for use with the gamma camera (which is most efficient for energies in the range 100-200 keV) and in our experience is low enough to avoid severe 'shine through' artefacts in lateral lung scintiphotos. In addition, the radiation dose to the patient is less than with any other radionuclide advocated for this purpose.

The great advantage of the 'camera' is the speed with which the distribution of radionuclide within an organ can be visualised. Using a conventional scanner, a minimum of 45 minutes is generally required to obtain a posterior and two lateral views. With the camera, a 10 inch diameter area of the chest is viewed at the one time using conventional collimation, or 13 inches using a diverging collimator. Each scintiphoto requires only 2-5 minutes and the patient can be examined in any posture, a point of considerable importance in dyspnoeic patients who must be 'scanned' in a prone position by most commercially available rectilinear scanners.

Interpretation of pulmonary perfusion defects. It must be emphasised that the demonstration of a pulmonary blood perfusion

defect by such studies is not in itself proof of pulmonary embolism (Moser et al. 1966; Swanson et al. 1966; Poe, Swanson and Taplin, 1967). Perfusion defects may result from such conditions as pneumonia, tuberculosis and bronchogenic malignancy; extrapulmonary displacement of lung tissue, for example, by large pleural effusions or cardiomegaly; intrapulmonary bullae; obstructive airways disease - asthma or emphysema; and pulmonary arterio-venous or bronchial artery-pulmonary artery shunting. In addition, diminished peripheral perfusion may arise as a consequence of alveolar hypoxia and postural gravitational effects (Taplin et al. 1964c). For this reason, it is essential that a very recent chest X-ray should be available for comparison with the perfusion scan and all available information must be taken into account when assessing the significance of perfusion defects. Pulmonary emphysema, in particular, often produces multiple perfusion defects which may be indistinguishable from those caused by multiple pulmonary emboli at first examination. Indeed the two disorders may coexist. Where there is doubt in such a case, repeat examinations may help in differentiating the persisting perfusion defects of emphysema from the changing pattern of pulmonary embolism (Taplin et al. 1964c).

For most purposes, lung scintigraphy in only anterior and posterior projections is inadequate, and perfusion defects visible only in lateral views may be missed (Sasahara et al. 1968). A high speed dual 5 inch detector system which permits simultaneous

anterior and posterior scanning or scanning of both laterals simultaneously helps to reduce the time involved: multiple view gamma camera studies are equally satisfactory (Eaton et al. 1969). In most patients the total area of a lung 'seen' in the lateral projection is nearly double that seen in the posterior or anterior projection. The location, size and shape of an avascular lesion can be more accurately defined with the aid of a lateral view, and frequently the lung segment(s) involved can be accurately identified (Surprenant, 1967). In addition oblique views have been said to assist in differentiating anatomical variants from significant perfusion defects and give better visualisation of the anterolateral and posterolateral costophrenic angles than do straight views (Mack et al. 1969).

Inhalation studies. Bronchoconstriction was first observed in association with pulmonary embolism by Boyer and Curry in 1944. Although it may be extremely severe at times, it is usually of brief duration, hence gross shift in ventilation away from regions with reduced perfusion due to pulmonary embolism is said to be rarely observed (Bass et al. 1967). Nevertheless, many investigators are now re-examining this problem.

Inhalation scanning procedures have been performed using either a radio-aerosol (Pircher et al. 1965; Taplin, Poe and Greenberg, 1966) or a radio-gas (Loken, 1966; Jones, Goodrich and Sabiston, 1967; Newhouse et al. 1968; Shibel, Landis and Moser, 1969). While

the use of a gas would seem preferable on theoretical grounds, the use of such inert gases as ^{133}Xe pose many practical difficulties; particularly with respect to their generation, and contamination of the laboratory.

In the radio-aerosol technique, small particles of the order of 0.5 - 2.0 μm diameter are produced by nebulisation. Such particles are known to be distributed evenly throughout the lower respiratory tract (Taplin et al. 1966). The particles are inhaled, often with the aid of a positive pressure respirator and the patient is scanned in order to determine the distribution of aerosol after inhalation has ceased. Many radiopharmaceuticals have been used including technetium-sulphur colloid, and albumin labelled with radioiodine or technetium (Haynie, 1968).

However, aerosol dispersion in the lungs is dependent upon factors other than diffusion. These include particle size, sedimentation, impaction, rate of air movement, turbulence, the nature and concentration of the radiopharmaceutical employed and the rate of clearance from different parts of the lung. Hence the amount of radioactivity in any portion of a lung is not always proportional to the air flow to that region. Inhalation of a radioactive gas, on the other hand, simulates the usual conditions of ventilation. Areas of poorly ventilated lung can be expected to appear as such on radiogas inhalation, whereas radioaerosol scans may occasionally show such areas as being unventilated (Shibel et al. (1969). Radioactive gas techniques are best suited to gamma

'camera' or multiple fixed probe systems, as the gas washout, unlike aerosol removal, is rapid after inhalation ceases and does not allow time for conventional scanning. However, this technique has been used employing rectilinear scanners by performing the study while the patient re-breathes on a 'closed-system' spirometer containing the gas (Marks et al. 1968).

In a normal subject the inhalation scan image closely resembles the perfusion scan, and in the majority of pulmonary disorders, diminished perfusion is associated with decreased ventilation in the affected areas. However, a perfusion scan defect in the presence of a normal inhalation picture is considered strong evidence in favour of pulmonary embolism (Dore et al. 1968). But this is by no means always the case for, on occasions, there may be little or no air entry into the involved area. The interval which elapses between lodgement of the embolus and the time of study; whether or not infarction occurs; the extent of the involved area and its collateral circulation, are all obviously important in the scan appearances.

Labelling of thromboemboli. Attempts have been made to label thromboemboli in vivo by two separate approaches. The most widely used technique involves the injection of radioiodine-labelled fibrinogen into a subject considered at risk. The rate of clearance of the labelled material is determined, and counting of radio-activity is carried out daily over adjacent sites along the course

of the main veins of both legs. The rapid accumulation of radioactivity at a particular site (or adjacent sites) over the course of a day or two, suggests that a thrombus is developing in the underlying area. This technique has found favour with a number of surgical groups who either inject the radionuclide soon after operation (Hobbs and Davies, 1960; Atkins and Hawkins, 1965) or just prior to operation (Flanc, Kakkar and Clarke, 1968; Kakkar et al. 1970). Although the technique has many proponents and has aroused much interest, I believe its value is limited. A satisfactory label of fibrinogen has yet to be found, preferably one which allows satisfactory imaging of the radionuclide in situ. In my experience, variation in siting of the static probes from day to day renders evaluation of all but the most gross changes difficult. The radiation hazard to the patient, especially if ^{131}I is used as the label, is not inconsequential; and the necessity to block the thyroid must always be taken into account. Most important, the ever present risk of development of homologous serum hepatitis in the course of what is still primarily a research procedure raises a considerable ethical problem. These considerations aside, the very substantial time required to carry out the procedure on every patient each day, mitigates against its adoption as a routine procedure.

An alternative approach involves attempts to label thrombi or emboli after they have formed. To this end, plasmin (fibrinolysin)

(Ouchi and Warren, 1962) and antifibrinogen (Spar et al. 1966) have been used. Employing ^{131}I antifibrinogen, Spar and co-workers demonstrated the presence of intracardiac and intra-pulmonary thromboemboli in a small series of selected patients. Unfortunately, several days are generally required for sufficient radioactivity to accumulate in the thrombus and allow it to be clearly delineated from the background radioactivity in the blood. Furthermore, the preparation and use of satisfactory antisera present many difficulties.

In the following chapters a method is described for assessing pulmonary perfusion and ventilation which is based on radionuclide techniques and is suitable for routinely screening subjects for pulmonary embolism. Using this method an assessment of the incidence and impact of pulmonary embolism in two groups of hospitalised subjects has been obtained. Both symptomatic and asymptomatic embolism are now accessible to study during life and many of the predictions based on autopsy data and clinical experience of symptomatic disease can be examined in the light of more extensive knowledge of the disorder.

CHAPTER III

SUBJECTS, MATERIALS AND METHODS OF STUDY

A. SUBJECTS STUDIED

Subjects from a variety of sources were used in this study. These will be considered in detail in the appropriate sections of the text.

(i) Subjects used for evaluation of techniques. In addition to a group of normal volunteers, patients with known pulmonary pathology and subjects specifically referred to the Division of Nuclear Medicine for lung scanning procedures were used in the evaluation of techniques developed and employed in this study.

(ii) Subjects studied in prospective surveys. Subjects studied in the prospective surveys of medical and surgical patients were all inpatients at the Royal Adelaide Hospital under the care of various visiting and staff specialists.

(iii) Consent. In all studies in which new techniques were involved the subject was informed of the nature of the contemplated procedure and his informed consent was obtained as well as the consent of the attending physician or surgeon prior to the administration of a radiopharmaceutical.

B. MATERIALS

(a) Radiopharmaceuticals.

A wide variety of radiopharmaceuticals was used throughout the study, to assess regional pulmonary perfusion and/or ventilation.

(i) Assessment of perfusion. The radiopharmaceuticals used for the assessment of pulmonary perfusion were:

1. Iodine labelled macroaggregated albumin (^{131}I MAA). (Hoechst AG). Specific activity 0.15-0.3 mCi/mg albumin.
2. Sodium pertechnetate (Na $^{99m}TcO_4$) (Lucas Heights).
3. Technetium labelled macroaggregated ferrous hydroxide (^{99m}Tc MAFH). (Lucas Heights). Specific activity 10-30 mCi/mg Fe^{++}.

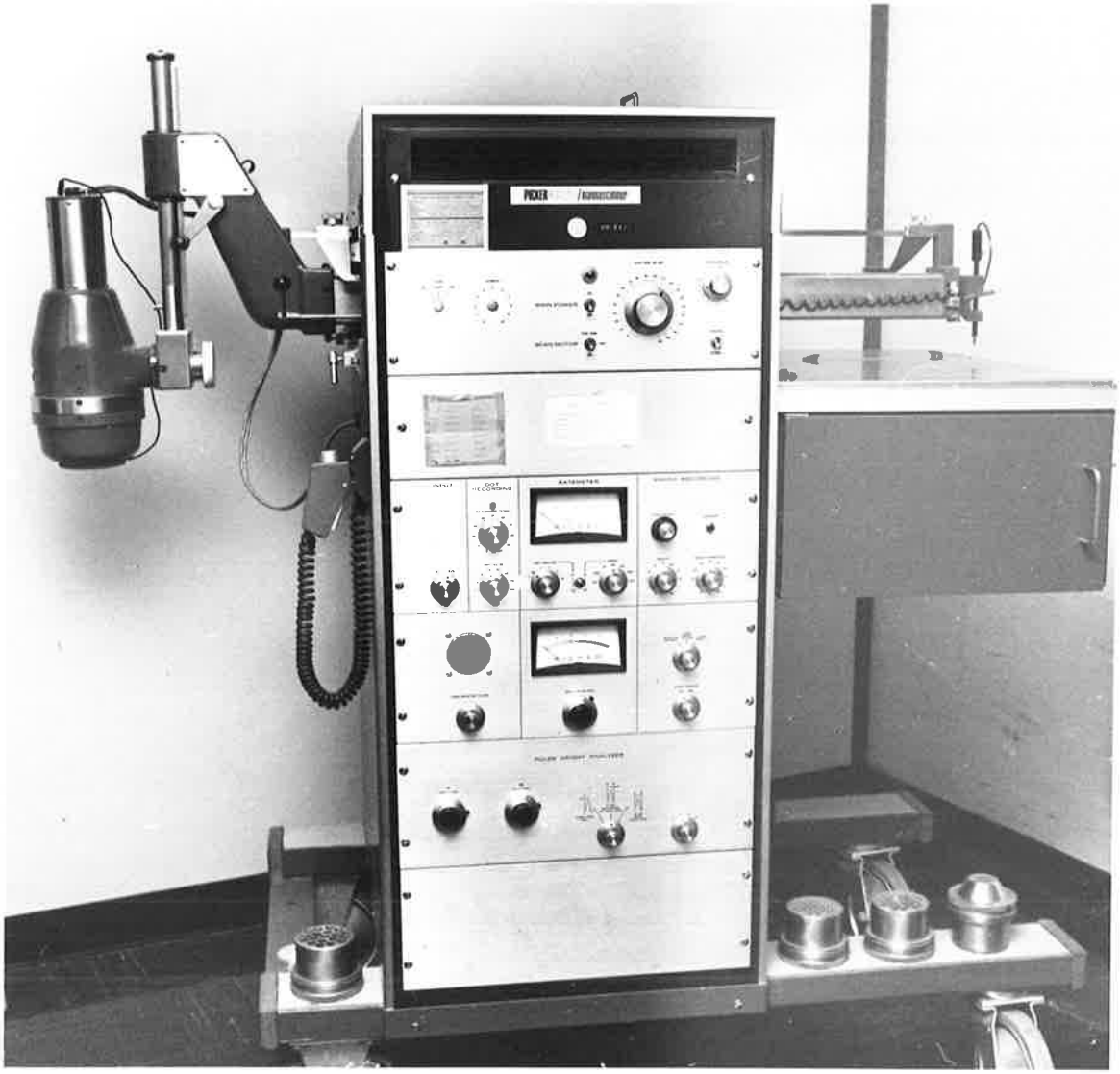
These radiopharmaceuticals were supplied by the Commonwealth Xray and Radium Laboratories (C.X.R.L.) ready for administration (^{131}I MAA and ^{99m}Tc MAFH) or in generator form (sodium pertechnetate).

(ii) Assessment of regional ventilation. The radiopharmaceuticals used for the assessment of regional ventilation were:

1. Sodium pertechnetate (Na $^{99m}TcO_4$) (Lucas Heights).
2. Technetium sulphur colloid ($^{99m}Tc_2S_7$).
3. Technetium labelled human serum albumin (^{99m}Tc HSA).
4. Indium chloride ($^{113m}InCl_3$) (Amersham).

Sodium pertechnetate and indium chloride were made available by the Commonwealth Xray and Radium Laboratories (C.X.R.L.) in generator form [^{99}Mo (Lucas Heights) or ^{113}Sn (Amersham)]. Technetium sulphur colloid was prepared as required from sodium pertechnetate. Both sodium pertechnetate and indium chloride were used while in solution, indium chloride was occasionally used in colloidal form.

Fig. 3:1 Picker Magnascanner (Model 2806-J).


PICKER

(b) Organ imaging equipment. At various stages in this study use was made of a Picker rectilinear scanner, an Ohio Nuclear Dual 5 inch rectilinear scanner and a Nuclear Chicago Pho/Gamma III gamma camera with accessories.

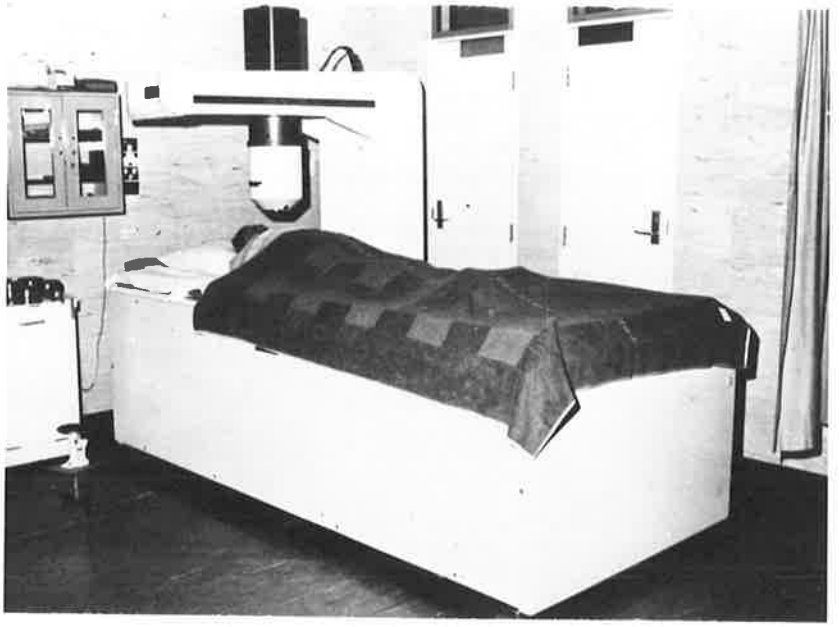
(i) Picker scanner and collimator. A standard Picker magnascanner (model 2806-J) with a 3 inch crystal (figure 3:1) was used for two series of studies. To assess the value of dynamic cardiopulmonary flow studies using sodium pertechnetate and the gamma camera these studies were compared with rectilinear scans using iodine labelled macroaggregated albumin (^{131}I MAA) and the magnascanner with a medium energy focused collimator (2107A).

In a survey of 100 subjects, to compare the scan appearances using a gamma camera and rectilinear scanner when a technetium compound was used, the magnascanner was fitted with a medium energy focused collimator (2107A) (see Appendix f).

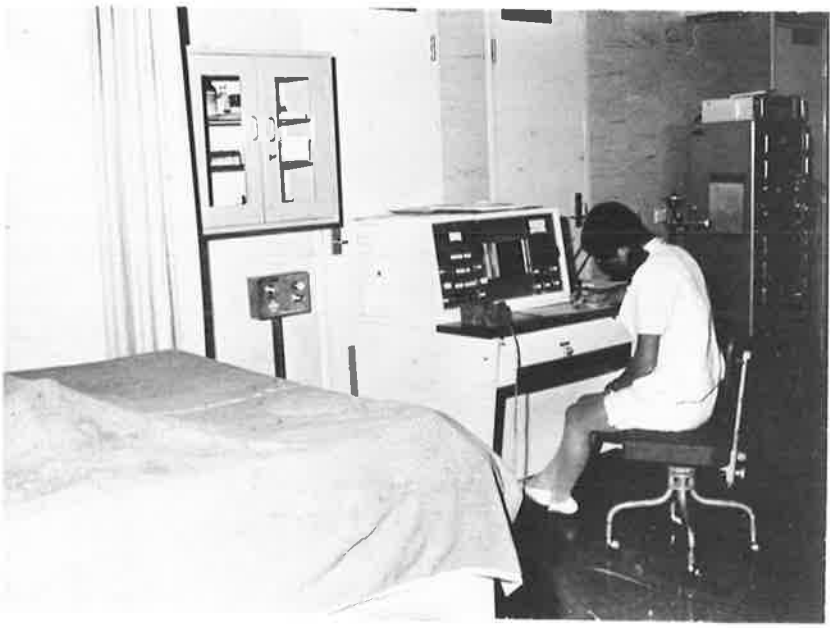
A paper 'dot' and photo printout were obtained in all instances.

(ii) Ohio nuclear scanner and collimators. A standard Ohio Nuclear Dual 5 inch rectilinear scanner (model 84) (figure 3:2) was used at various times in this study but particularly for inhalation scans when 113m indium chloride was used. For this purpose both detectors were fitted with medium energy

Fig. 3:2 Ohio Nuclear Dual 5 inch Rectilinear Scanner (Model 84).



A



B

focused collimators (50 M).

When used for perfusion scans employing a technetium compound (^{99m}Tc MAFH) medium energy (50 M) or low energy (24 L) focused collimators were used.

Minification of the scans in the ratio 2:1 was found to be the most suitable form of output and this was used without exception.

(iii) Scintillation camera. A standard Nuclear Chicago Pho/Gamma III scintillation camera model 6403 was used extensively at all stages of the study. It is illustrated in figure 3:3.

(a) Photomultiplier tubes. The 11 inch crystal of the scintillation camera is viewed by an array of 19 photomultiplier tubes. The early dynamic cardiopulmonary flow studies using sodium pertechnetate were performed while the scintillation camera was fitted with standard photomultiplier tubes (type RCA 4524). These were later changed to higher efficiency bi-alkali photomultiplier tubes with resulting improvement in resolution of studies.

(b) Collimators. When technetium compounds were employed either the standard Nuclear Chicago 4000 parallel hole low energy collimator or the Nuclear Chicago 410 keV diverging medium fine hole collimator was used. The latter was employed when it was considered necessary to view the whole of both lungs

Fig. 3:3 Nuclear Chicago Pho/Gamma III Scintillation Camera (Model 6403) with 1600 word memory (Ridl Model 24-3) and Ampex computer compatible magnetic tape system.

together in the anterior or posterior view as during certain inhalation procedures in larger subjects.

When indium chloride was used the scintillation camera was always fitted with the diverging collimator.

(c) *Data collection and manipulation.*

1. Analogue. A triple lens polaroid camera which produces three separate images with varying degrees of contrast on standard pack type polaroid film (type 107, 3000 ASA) was the most frequently employed form of output.

A time lapse, single lens Nikon camera utilizing 35 mm film (400 ASA) was occasionally used.

2. Digital. The Nuclear Chicago 1600 channel analyser system comprising a 1600 word memory (model 24-3), dual analogue to digital (A/D) converter (model 22-03), and analyser oscilloscope (model 52-56) was used at various stages of the study in combination with an Ampex computer compatible magnetic tape system.

Data accumulated in the 1600 word memory for various time periods was stored on magnetic tape.

Analysis of data was possible by playing the magnetic tape back into the 1600 word memory when it was displayed on the analyser oscilloscope or printed out word by word.

Alternatively the taped data was analysed by computer (CDC 6400,

Fig. 3:4 Diagramatic representation of the simple inhalation system used in inhalation studies. It consists of Bird® Nebulizer (N) to which air is supplied at the rate of 14 litres/min., reservoir bag (B) on which subject breathes via a 20 inch length of corrugated tubing and low resistance valve (V).

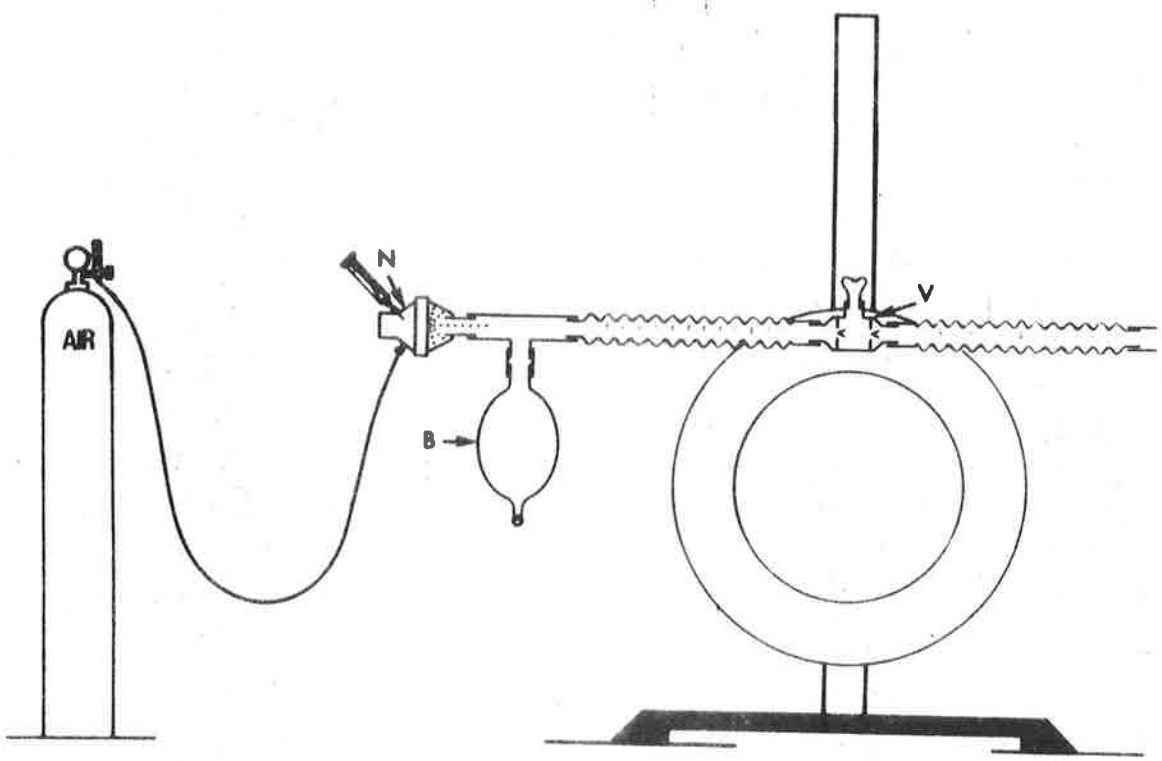


FIG. 3.4

University of Adelaide) when the data was filtered and statistically smoothed to remove spurious data and improve the quality of the information.

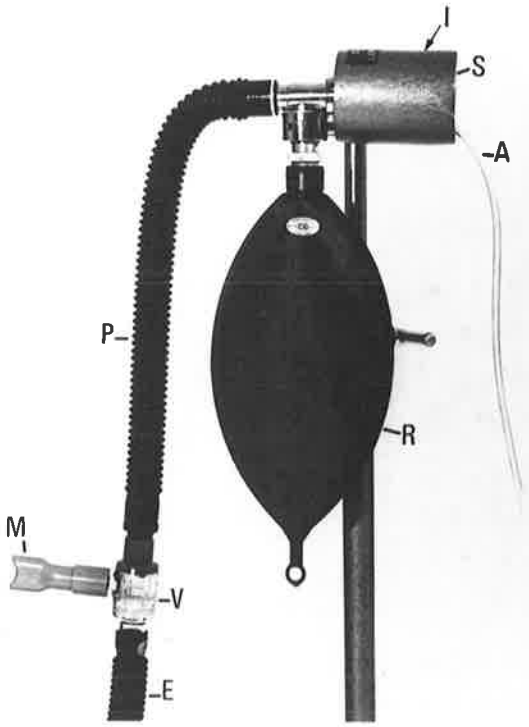
Compensation for irregularity in sensitivity across the crystal of the scintillation camera was achieved by a special programme developed in our own department (O'Reilly et al. 1971) when computer analysis was employed.

(d) Inhalation scanning equipment

i. General. A new aerosol system was developed and used for the determination of regional ventilation. This has been described in detail in the literature (Cook and Lander, 1971e, f, appendix D, E). It comprises a nebulizer, a reservoir and proximal tube, a non return breathing valve and exhaust system. A diagrammatic illustration of the system used is shown in figure 3:4.

ii. Nebulizer. A Bird micronebulizer (model 9993.158) was used to nebulize the radiopharmaceutical administered to the subject. Air was supplied either continuously or intermittently at the rate of 14 litres/minute from a portable source. The nebulizer reservoir was shielded by a heavy lead surrounding envelope in order to reduce the radiation hazard to the subject and operator (figure 3:5). In a small series for purposes of comparison a de Vilbiss ultrasonic nebulizer (model 900) was used (fig. 3:32), the reservoir of the nebulizer being shielded by

Fig. 3:5 The nebulizer and shielding. This comprises the Bird® Micronebulizer (N), heavy lead envelope (S), reservoir bag (R), proximal tubing (P), low resistance valve (V), mouthpiece (M), and efferent tubing (E). Radiopharmaceutical is added to the nebulizer through the shielding (I).


I
S
A
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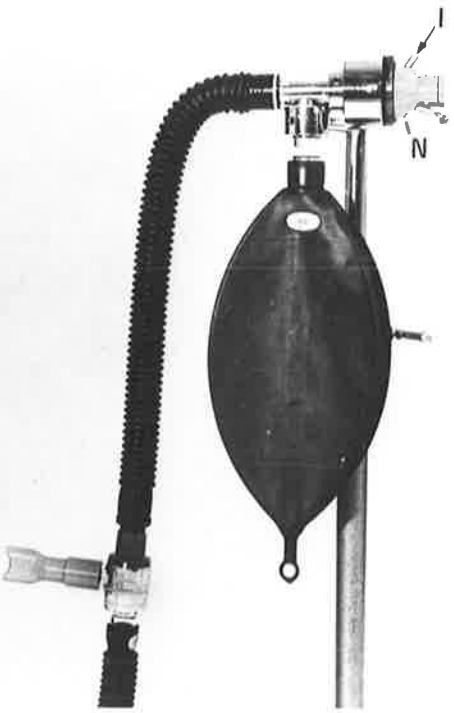

I
N

a lead envelope whenever it contained radiopharmaceutical.

iii. Reservoir and proximal tubing. The outlet of the nebulizer fed, via a T-junction, to a 4 litre reservoir bag and to a 20 inch length of corrugated rubber tubing with an internal diameter of 1 inch (figure 3:4).

iv. Breathing valve. The proximal tubing connected to a low resistance non return valve (Ambu Hesse 201) to which was attached a simple mouthpiece (figure 3:4).

v. Exhaust system. Exhaled material was removed via a large bore low resistance (1 inch internal diameter) tube. This fed into an air conditioning exhaust duct and thence to the outside air. The removal of material from the exhaust tube was facilitated by a venturi system.

C. METHODS

(a) PULMONARY PERFUSION STUDIES.

i. General. Pulmonary perfusion studies refer to any of the processes whereby an assessment of regional pulmonary perfusion was obtained. Three methods were employed and will be described separately. They were:

1. standard rectilinear scanning following the administration of 131 iodine labelled macroaggregated albumin (^{131}I MAA);

2. standard scintillation camera scintiphotography following the administration of 99m technetium labelled macroaggregated ferrous hydroxide (^{99m}Tc MAFH); and

3. dynamic cardiopulmonary blood flow studies following the

administration of sodium pertechnetate ($Na^{99m}TcO_4$).

ii. Rectilinear scanning employing iodine labelled macro-aggregates (^{131}I MAA).

1. Thyroid block. Potassium iodine 100 mg was given orally 30 minutes prior to the administration of radio-pharmaceutical and this dose was repeated four times daily for three days following each test. This served to block the uptake of 131-iodine by the subject's thyroid gland.

2. Method of administration. The radiopharmaceutical was injected into a suitable upper limb vein while the subject lay quietly supine. Up to 300 μCi of ^{131}I MAA was administered, the injection being given over a period of from 5-10 seconds to average out differences in respiratory cycles. Prior to injection venous blood was not withdrawn into the syringe. The scan was begun immediately thereafter.

3. Scanning method. The posterior aspect of the thorax was scanned first while the subject lay prone; this was followed by lateral views. A standard Picker magnascanner was used exclusively for these studies. A window of 100 keV centred on 365 keV was used, background erase was zero for the dot scan and 0-5% for the photoscan. Further contrast enhancement was not employed.

4. Duration of procedure. An average of 60 minutes was required for the three scans.

iii. Studies using technetium labelled macroaggregates (^{99m}Tc MAFH).

1. Thyroid block. Potassium perchlorate 400 mg as a single oral dose was given to all subjects up to 30 minutes prior to the administration of radiopharmaceutical. This served to block the uptake of technetium by the subject's thyroid gland.

2. Method of administration. The radiopharmaceutical was injected into a convenient upper limb vein while the subject lay quietly supine. The dose varied from 1.5 -2.8 mCi. The injection was given over a period of 5-10 seconds and venous blood was not withdrawn into the syringe prior to injection. The scan was begun immediately thereafter.

3. Scanning method. The distribution of radiopharmaceutical in these subjects was determined by rectilinear scan, scintillation camera study or by both techniques in the same individuals for the purposes of comparison (Cook and Lander, 1971a).

(α) Picker rectilinear scanner (Magnascanner). When this instrument was used the posterior aspect of the thorax was scanned first while the subject lay prone; this was followed by both lateral scans. An 80 keV window centred on 140 keV was used. Contrast enhancement was not employed.

(β) Ohio nuclear rectilinear scanner. When the Ohio dual 5 scanner was used the anterior and posterior aspects of the

thorax were scanned first while the subject lay supine; this was followed by both lateral scans obtained at the same time. Variable windows up to 80 keV centred on 140 keV were used; contrast enhancement was not employed.

(γ) Scintillation camera. When the Pho/Gamma III scintillation camera was used scintiphotos were obtained in 4 projections (anterior, posterior and both laterals). The subject was either seated on a swivel chair when the arms were held out of the field of view of the camera during lateral studies, or recumbent during the procedure.

The 10 inch field of view of the scintillation camera does not encompass the full extent of both lungs when they are viewed together. In order that a satisfactory visual comparison of the activity in the two lungs be obtained when they are viewed separately each lung may be "viewed" for a standard time. The following procedure was adopted.

A scintiphoto was obtained which encompassed the whole of one lung, 500 K counts being accumulated in that view. The time taken was noted and the corresponding view of the opposite lung was obtained, counts being accumulated for the time taken to accumulate 500 K counts in the first view. This process was repeated in the remaining projections. A 20% window centred on 140 keV was used in all such studies.

4. Digital data accumulation. On certain occasions

the digital facilities of the 1600 word memory and tape system were used in conjunction with the scintillation camera to store data. Each view was stored separately.

No digital facilities were available for use with the rectilinear scanners.

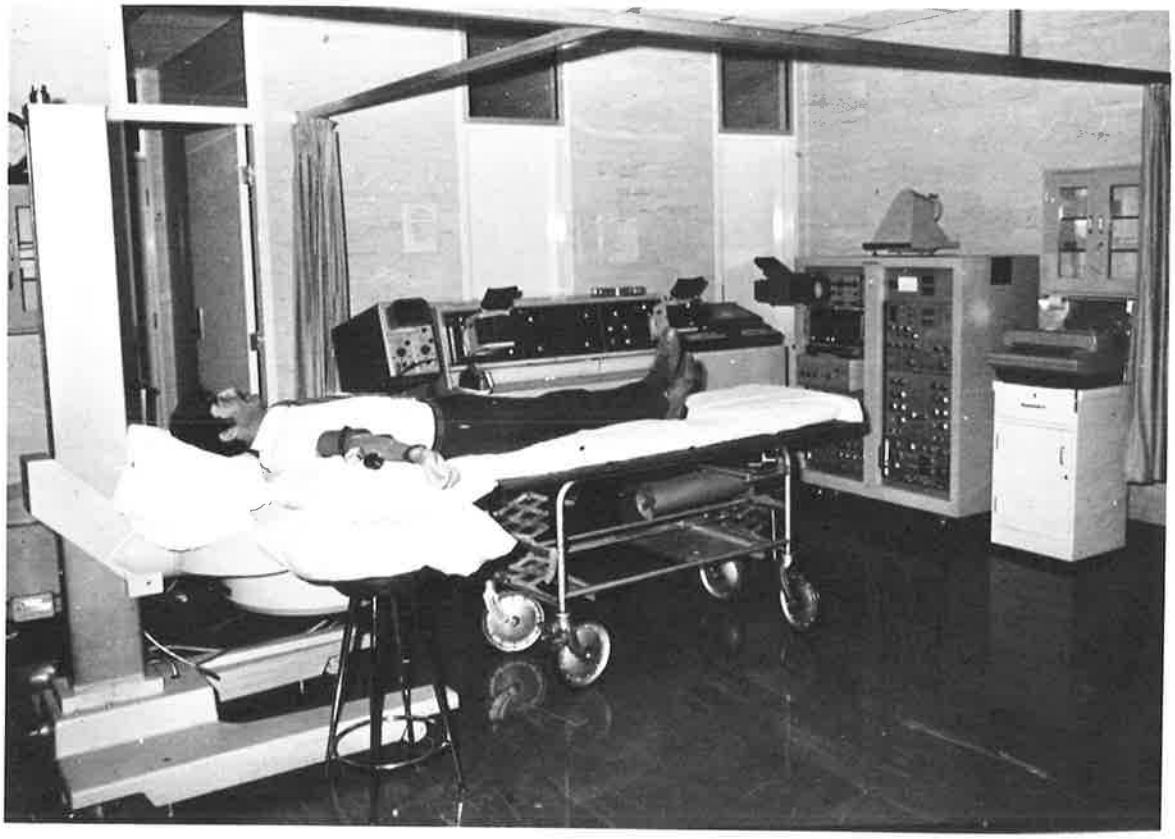
5. Duration of procedure. When the Picker magnascanner was used the duration of the procedure was 45 minutes on average (3 scans). The Ohio Nuclear scanner required 30 minutes (4 scans) and the scintillation camera 20 minutes (6 scintiphotos).

iv. Blood flow studies employing sodium pertechnetate ($Na\ ^{99m}TcO_4$)

1. Thyroid block. Again potassium perchlorate 400 mg as a single oral dose was given to all subjects at least 30 minutes prior to the administration of radiopharmaceutical. This served to block the uptake of technetium by the subject's thyroid gland.

2. Method of administration. Prior to administration of the radiopharmaceutical the subject was positioned accurately lying supine over the surface of the scintillation camera collimator such that as much of the thorax as possible was within the field of view of the camera. This positioning was very much a matter of judgement. However accurate positioning was occasionally facilitated by the use of a transmission disc source containing pertechnetate which enabled the position of the lungs to be determined (fig. 3.6).

Fig. 3:6 Subject lying supine over the gamma camera during flow study.



The radiopharmaceutical was injected into a suitable antecubital vein; the right side was preferred as the intravenous course before reaching the right atrium is shorter on that side, while a sphygmomanometer cuff on the upper arm was inflated to above diastolic pressure. Up to 15 mCi of sodium pertechnetate was used.

The sphygmomanometer cuff was rapidly removed while still inflated and accumulation of data was begun immediately.

3. Data accumulation. Only the scintillation camera was used for data accumulation employing a 20% window centred on 140 keV.

(aa) Analogue. Polaroid films were exposed in rapid sequence, the pictures being pulled by hand at 2 second intervals. A maximum of 8 frames was obtained. Alternatively time lapse 35 mm transparencies were obtained, each frame being exposed for 2 seconds; the number of frames exposed was optional. In both instances a focussed oscilloscope light spot was employed.

(bb) Digital. Digital data was accumulated in the 1600 word memory in a 40 x 40 format and transferred at 2 second intervals (1.8 seconds for data accumulation plus 0.2 seconds recycle time) onto magnetic tape throughout the procedure.

4. Duration of procedure. About 3 minutes was required for the procedure including time for positioning.

(b) INHALATION STUDIES

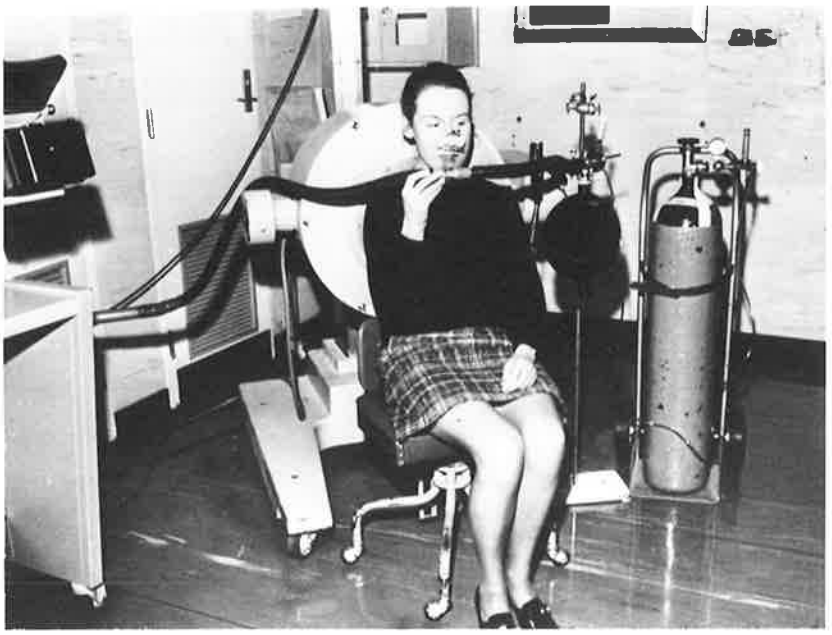
i. General. Inhalation studies were carried out using a new technique and employing either sodium pertechnetate ($Na^{99m}TcO_4$) or indium chloride ($^{113m}InCl_3$) in solution. The procedures have been described in detail in the literature (Cook and Lander,1970a, 1970c, 1971c, 1971e, 1971f; appendices b, d, h, j, k).

ii. Sodium pertechnetate inhalation.

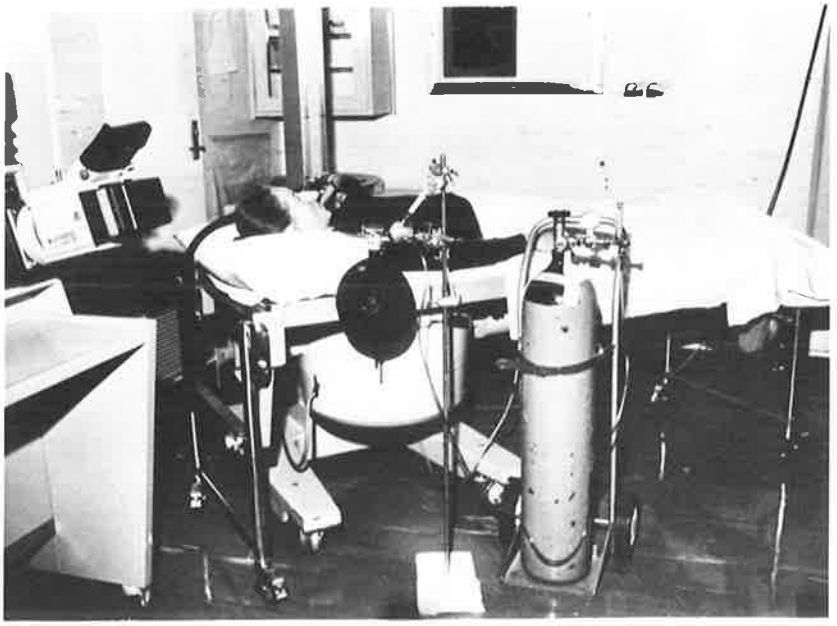
1. Thyroid block. As when sodium pertechnetate is injected intravenously the subject's thyroid gland was blocked by the administration of a single oral dose of potassium perchlorate 400 mg at least 30 minutes prior to the commencement of the procedure.

2. Method of administration. Prior to administration of the radiopharmaceutical the subject was positioned in front of the head of the scintillation camera such that the field of view of the camera encompassed the region of interest in the lungs. The subject was generally either seated or lay supine (fig. 3.7 A, B). His nose was gently clamped and he was permitted a practice period of about 1 minute in which to become accumstomed to the nebulizer system. Up to 15 mCi of the radiopharmaceutical contained in a volume of 2-4 ml was injected into the nebulizer. The nebulized spray was carried to the reservoir and through the proximal tubing by the

Fig. 3:7 The inhalation system in use with subject seated before the head of the gamma camera (A) or lying supine over the collimator face (B) during the procedure.



A



B

continuous or intermittently generated airflow (14 litres/ minute) and was inhaled by the subject. Exhaled material was removed via the exhaust system previously described.

The inhalation of radiopharmaceutical was continued until the nebulizer was dry. While the radiopharmaceutical washed out of the subject's lungs in the post-inhalation phase exhaled material was removed via the exhaust system for up to 30 minutes.

3. Data accumulation. Data was accumulated during the whole of the inhalation phase of the procedure and during the early part of the post-inhalation phase. Only scintillation camera study was performed; a 20% window was used centred on 140 keV.

(aa) Analogue. Analogue data was collected in two ways: (1) Polaroid films were exposed sequentially each for one minute periods during the whole procedure. The subject remained stationary. (2) Polaroid films were exposed for a preset count and then the subject was moved to enable further views to be obtained, again for a preset count.

(bb) Digital. When one minute serial scintiphotos were obtained digital data was accumulated in the 1600 word memory and transferred again at one minute intervals onto magnetic tape throughout the inhalation and early post-inhalation phases of the procedure.

iii. Indium chloride inhalation.

1. Subject preparation. No prior preparation of the

subject was required when this procedure was undertaken.

2. Method of administration. Up to 10 mCi of the radiopharmaceutical as eluted from the tin 113 generator and contained in a volume of 5 ml was injected into the nebulizer. The method of delivery of the radiopharmaceutical to the subject and the subsequent removal of the exhaled material was identical to that employed for sodium pertechnetate inhalation studies.

The inhalation of radiopharmaceutical was continued for 10 minutes or, if the accumulation of activity in the lungs was being monitored by scintillation camera, until a count rate of 10 K per minute was obtained.

3. Data accumulation. The distribution of inhaled radiopharmaceutical in these subjects was determined by rectilinear scanner or by scintillation camera or by both.

(aa) Rectilinear scanner. The Ohio Nuclear rectilinear scanner was the only rectilinear scanner used in these procedures. Anterior and posterior aspects of the thorax were scanned first while the subject lay supine after the completion of the inhalation phase; this was followed by both lateral scans obtained at the same time. Variable windows up to 100 keV centred on 392 keV were used; contrast enhancement was not employed.

(bb) Scintillation camera. When the Pho/Gamma III scintillation camera was used scintiphotos were exposed

either during the inhalation phase or as soon as inhalation of radiopharmaceutical had ceased. Because a diverging collimator was always used both lungs were visualised together in the anterior and posterior projections. Fifty thousand to 100 K counts were accumulated in each projection (anterior, posterior and both laterals), the counts obtained being standardised for all views in each subject. A 25% window centred on 392 keV was used.

(γ) Scintillation camera - digital. On certain occasions when combined perfusion-inhalation studies were performed or when changes in activity in the lungs through the inhalation procedure were being monitored the digital facilities of the 1600 word memory and tape system were used in conjunction with the scintillation camera to store data.

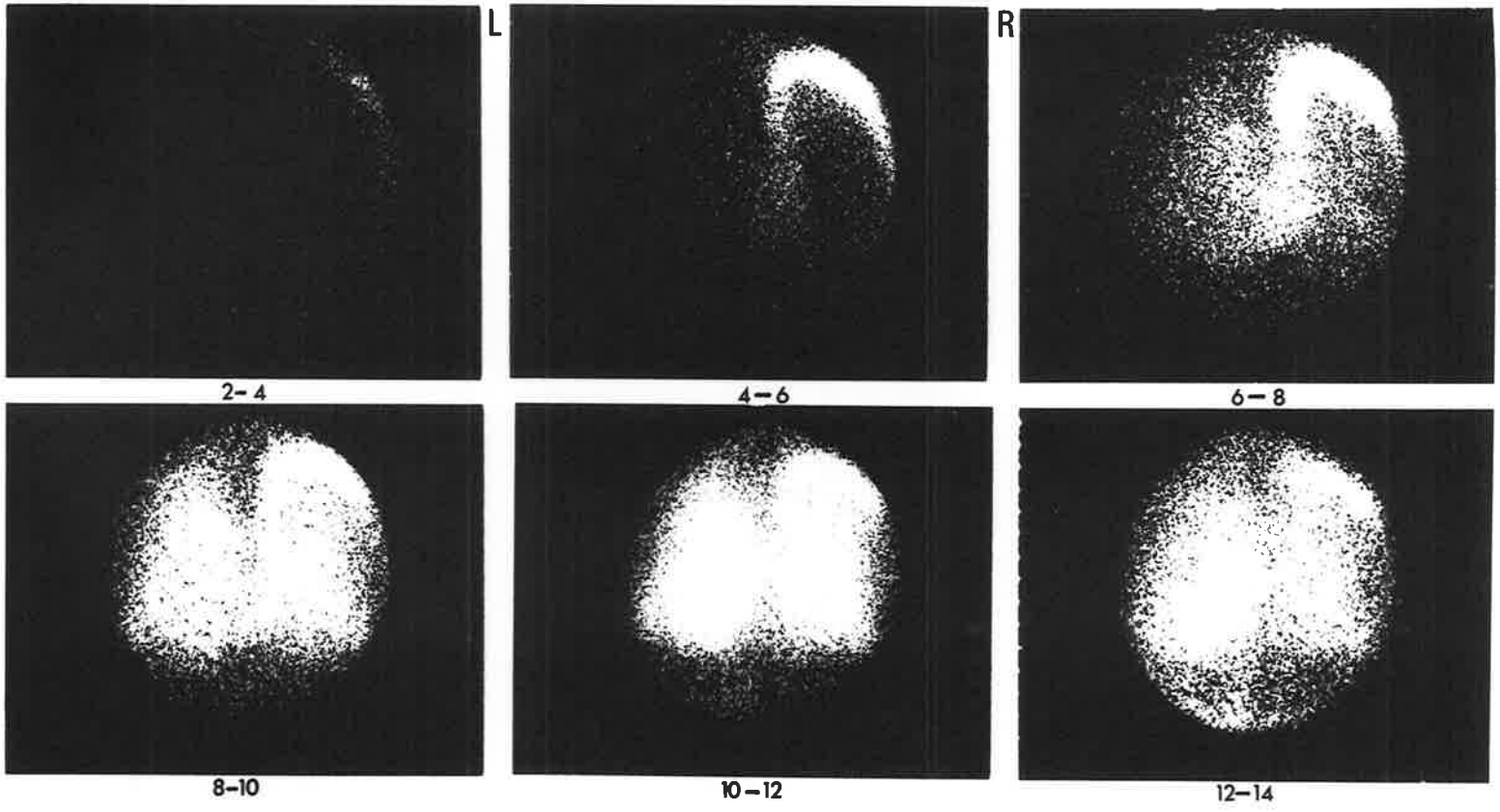
iv. Inhalation of other radiopharmaceuticals. Inhalation studies were performed using technetium sulphur colloid ($^{99m}Tc_2S_7$), technetium labelled human serum albumin (^{99m}Tc HSA) and indium chloride in colloidal form ($^{113m}InCl_3$). The procedures employed were similar to that used with indium chloride solution.

D. GENERAL RESULTS AND CONCLUSIONS CONCERNING METHODS OF STUDY

a. Perfusion Studies.

(i) Using iodine labelled macroaggregated albumin (^{131}I MAA). The results obtained using this widely practised

Fig. 3:9 Normal flow study - frames represent 2 second intervals beginning 2 seconds after injection of radiopharmaceutical. In the initial frame radioactivity is seen in the innominate vein, it is then seen in the superior vena cava and right heart (4-6), passing out through the pulmonary arteries (6-8), in the lungs (8-10, 10-12), then in the left side of the heart and in the aorta (12-14). There is considerable overlap of activity in various sites.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R
2–4
4–6
6–8
8–10
10–12
12–14

standard technique, were similar to those described extensively in the literature (Wagner et al., 1964b; Quinn III et al., 1964; Poulose et al., 1968) when subjects with known pulmonary disease, or subjects referred for routine lung scanning procedures, were studied.

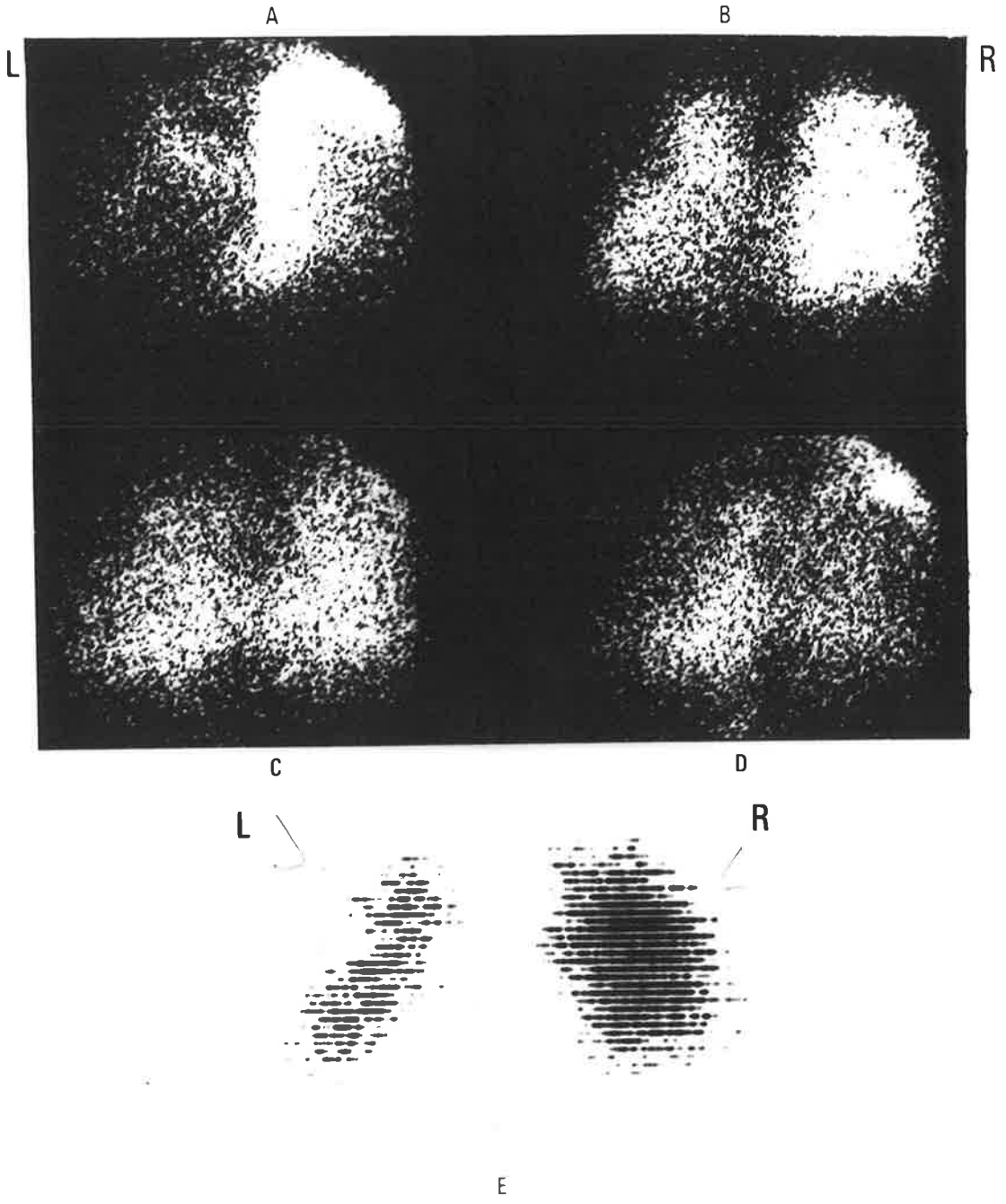
(ii) Using sodium pertechnetate ($Na^{99m}TcO_4$). This method of assessing pulmonary perfusion has been described in the literature (Cook and Lander, 1969) and was used early during the present study. The results in normal subjects without any evidence of pulmonary disease and certain abnormal findings are described to illustrate the results obtained.

(aa) Analogue.

1. Normal (fig. 3.9). The lungs and mediastinum are viewed from the back. Following its intravenous injection the radiopharmaceutical can be seen passing through the innominate vein, superior vena cava and right heart. A great deal of anatomical detail of midline structures is lost because of absorption of some of the gamma energy by the vertebral column.

As the radiopharmaceutical passes out through the pulmonary arteries there is still a considerable amount of activity in the innominate vein. An intensifying blush of activity is then seen in both lungs which later fades as the

Fig. 3:10 Abnormal flow study showing markedly reduced perfusion of the left lung and some irregularity of perfusion on the right. Frame E corresponds to ^{131}I-iodine-MAA lung scan. In later frames activity in the heart obscures the medial portion of the left base.



E

radiopharmaceutical is seen to concentrate in the left side of the heart and appears in the aorta. It is during the phase of maximum pulmonary activity that an assessment of pulmonary perfusion can be made. During that phase in the normal subject the distribution of radiopharmaceutical is quite even.

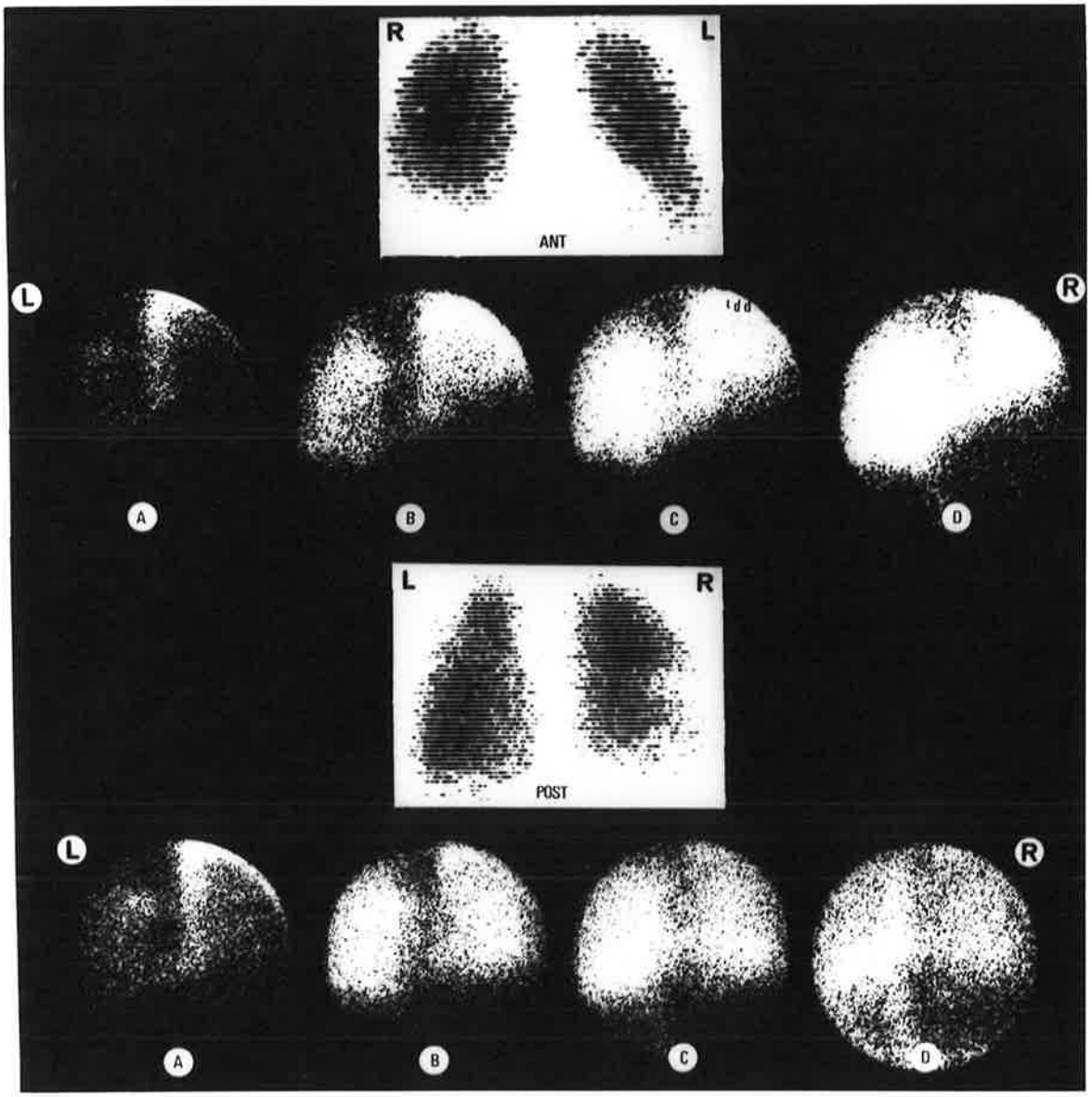
2. *Abnormal.* The initial phases of the procedure are similar in both the normal and abnormal studies provided the innominate vein and superior vena cava are patent. However during the phase of increasing pulmonary activity areas which fail to demonstrate appreciable activity persist (fig. 3.10, 3.11). Later avascular areas in the left lung may be obscured by activity in the heart (fig. 3.11). Only comparatively early in the study can an accurate assessment of pulmonary perfusion be made.

(bb) Digital

1. *Normal.* Digital presentation of normal studies revealed evenly distributed contours of activity during the phase of increasing pulmonary activity.

2. *Abnormal (fig. 3.12, 3.13).* Digital presentation of abnormal studies revealed areas of reduced activity corresponding to the defects seen in the analogue studies. This method of presentation failed to prove superior to analogue studies in the demonstration of perfusion defects; however it did provide more graphic delineation of defects on certain

Fig. 3:11 Two studies on the same subject with an intervening interval of 5 days. The top frame is the anterior perfusion scan - the only view possible because of subject discomfort when lying prone. The corresponding flow study (row 2) revealed a large right basal defect not seen in the scan. A right midzone defect readily demonstrated on subsequent scan (row 3) was not seen in the flow study (row 4).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occasions. The employment of the digital system available with a 40 x 40 channel format was considered of little value in the presentation of this data.

(iii) Comparison of rectilinear scanning using iodine macroaggregates and flow studies using sodium pertechnetate.

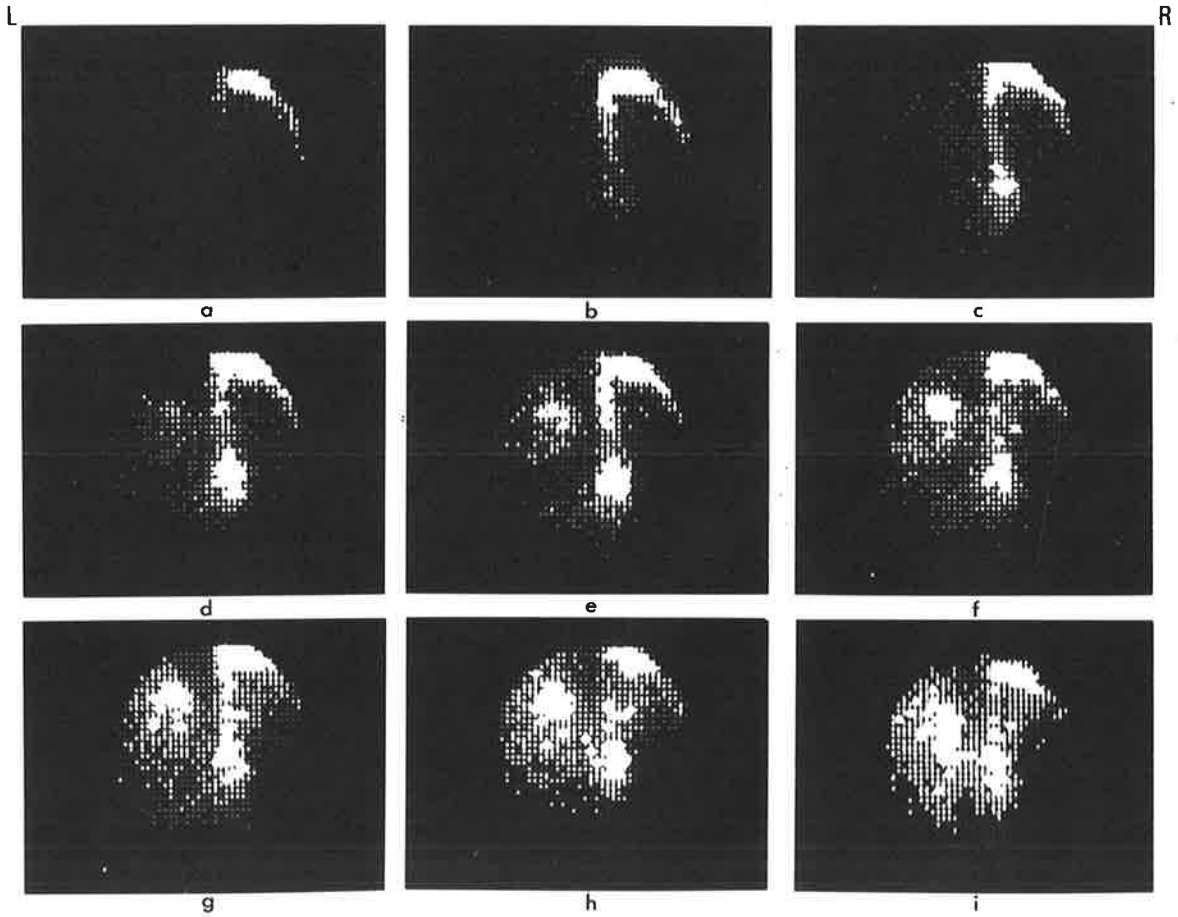
(aa) General. A study of 64 subjects was undertaken to investigate differences between the standard rectilinear scanning technique and flow studies. The administration of iodine labelled macroaggregates and subsequent scanning followed immediately after the flow study in all cases.

(bb) Defect delineation. The rectilinear scans and flow studies were viewed separately by the same observer on two different occasions and were classified as normal, abnormal or unsatisfactory studies. The results are shown in table 4.1.

Table 4.1

	Flow		
Scan	Normal	Abnormal	Unsatisfactory
Normal	20	2	4
Abnormal	7	25	6
Unsatis-factory	-	-	-

Fig. 3:12 Digital flow study, frames at 2 second intervals. The areas of highest activity are shown in solid white, intermediate activity in white dots, lower activity in small dots while areas where activity failed to exceed a set threshold remain black. A large right lower zone defect is demonstrated. (Corresponding scan on following page.)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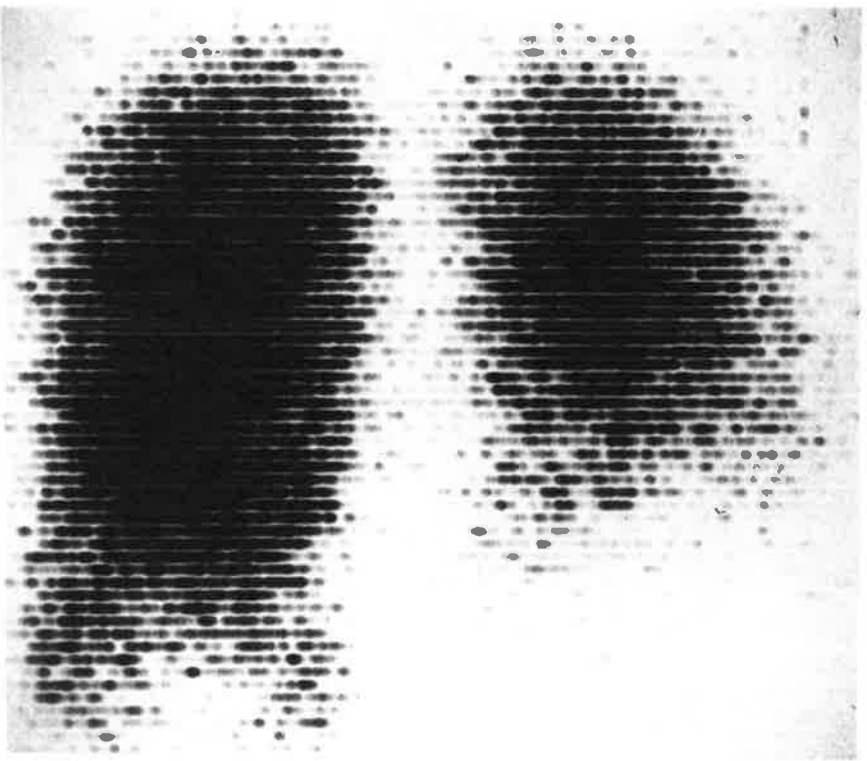


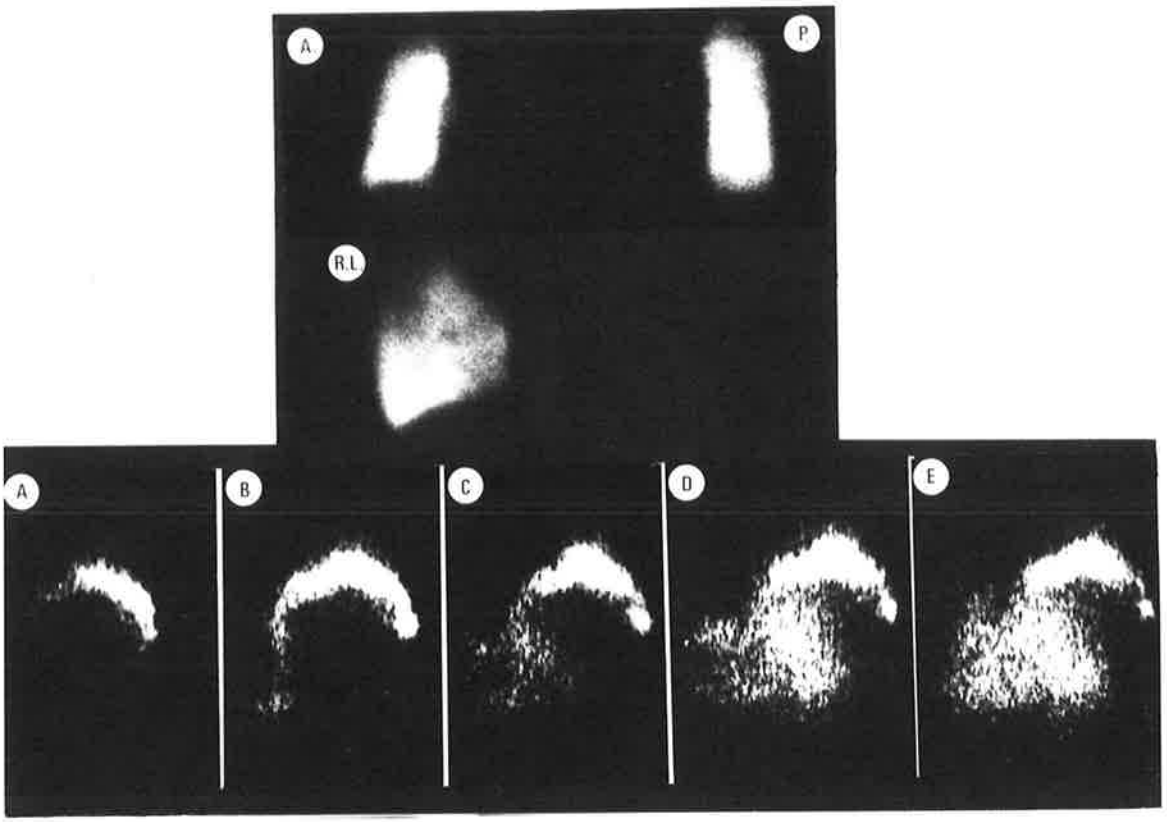
R

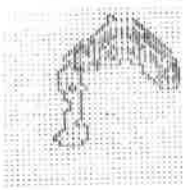
There was only a 62.5% (45/64) agreement level between the two methods in determining normality or abnormality. The 10 unsatisfactory flow studies were either the result of poor positioning, lungs too large to be viewed by the scintillation camera or difficulties encountered with the rapid pulling of polaroid film. Differences between the two methods when studies appeared to be of satisfactory quality were the result of defect position, left basal defects in particular being poorly delineated in the flow study, or size, small non-segmental defects being more difficult to delineate in the flow study.

(cc) Time of study, patient acceptability. The flow study was by far a more rapid procedure (3 min) than the rectilinear scan (15 min plus) and the supine position was greatly preferred to the prone position required for scanning, particularly in subjects who were dyspnoeic or had chest pain.

(dd) Conclusions. Since only one view (normally posterior) of the thorax is obtainable, subject positioning and lung size are of critical importance. Defects in certain areas and of small size were more difficult to resolve than when rectilinear scanning using iodine labelled macroaggregates was employed. The rapidity with which the study could be performed in very sick subjects may warrant its use under some circumstances; however an apparently normal study can only be interpreted as evidence that massive occlusion of the

Fig. 3:13 Four view static perfusion scintillation camera study (top), flow study (centre) and computer analysed digital study (bottom) in a subject with complete obstruction of the left pulmonary artery. The static study demonstrates perfusion of the right lung only. The analogue flow study reveals some activity to the left of the midline, in mediastinal structures and possibly in bronchial vessels. The digital flow study does nothing to simplify the interpretation of the flow study.

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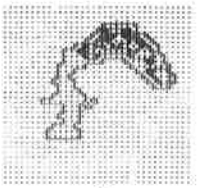
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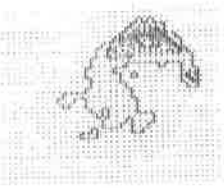
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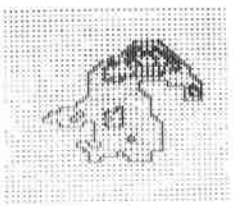
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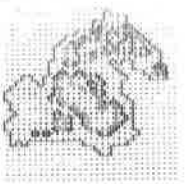
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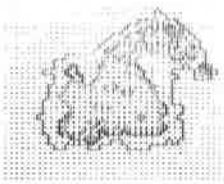
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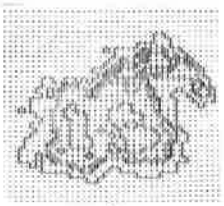
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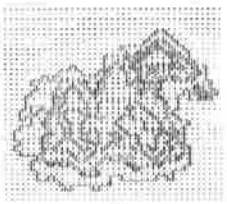

H

pulmonary circulation has not occurred. For these reasons the method was not considered suitable for routine use.

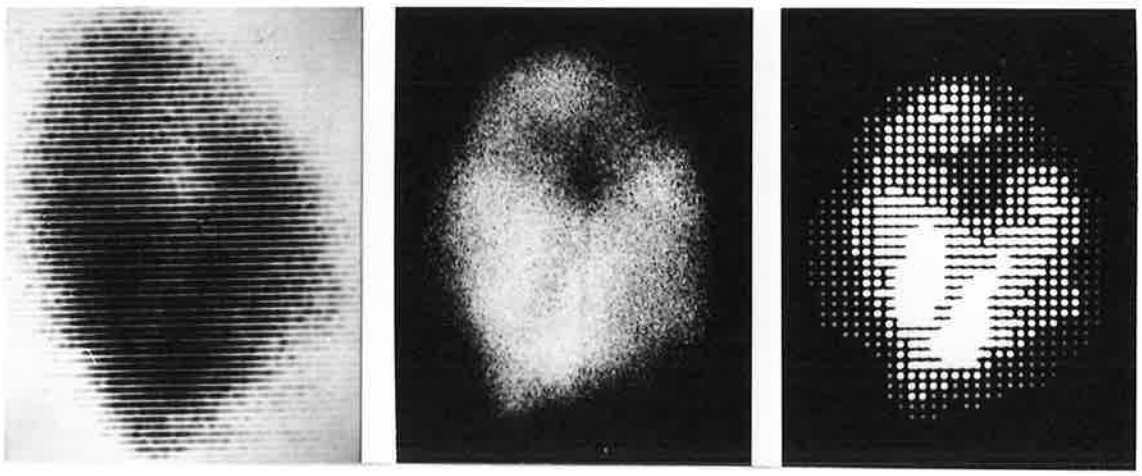
(iv) Using technetium labelled macroaggregated ferrous hydroxide (^{99m}Tc MAFH)

(aa) General. Rectilinear scanning or scintillation camera methods for determining regional pulmonary perfusion using this radiopharmaceutical have been employed extensively since its initial availability (Boyd et al. 1969). A description of rectilinear scans and scintiphotos produced in 100 subjects using this radiopharmaceutical has been published in the literature (Cook and Lander, 1971a, appendix f).

In that investigation pulmonary perfusion studies were carried out on 123 occasions in 100 subjects. Multiple view rectilinear scans and scintiphotos were obtained. Good correlation was found between the two techniques. However scintiphotography was found to have the advantages of speed, reduced incidence of subject movement artefacts and less variation in quality. Differences in the focussing characteristics of the two systems produced slight differences in appearance.

(bb) Digital presentation. The presentation of scintillation camera data in digital form for these studies was found to be of little additional value in delineating perfusion defects (fig. 3.14). Its use was limited to certain instances when combined perfusion and inhalation studies were

Fig. 3:14 Right lateral perfusion scan, analogue scintillation camera study and digital scintillation camera study revealing a defect in the anterior segment of the right upper lobe. The analogue camera study gives the best appreciation of relative activities in various areas in the lung.



performed (see later).

(v) General conclusions

Because of the satisfactory resolution of perfusion defects, speed of study, statistical considerations of photon yield and dosimetry considerations, it was concluded that scintillation camera study using technetium labelled macro-aggregated ferrous hydroxide (^{99m}TC MAFH) was a superior method of examination to either standard rectilinear scanning employing iodine labelled macroaggregated albumin (^{131}I MAA) or blood flow study using sodium pertechnetate (Na $^{99m}TCO_4$). This method was then adopted for the great majority of studies while rectilinear scanning using the same radiopharmaceutical was employed as an alternative procedure in certain instances.

(b) INHALATION STUDIES

i. Using sodium pertechnetate (Na $^{99m}TCO_4$)

(aa) Normal and abnormal subjects. The results obtained in normal and certain abnormal subjects employing this method of examination have been published (Cook and Lander, 1970a, 1970c, 1971f; appendices b, d, k). Illustrative findings are shown in figures 3.15 to 3.19.

(bb) The fate of pertechnetate. Sodium pertechnetate is removed from the airways by three processes - (a) exhalation in the breath, (b) absorption into the perfusing blood supply

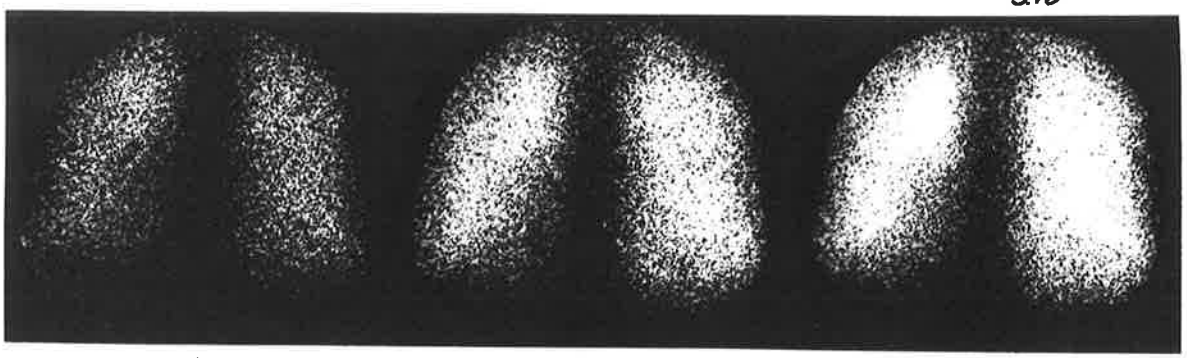
Fig. 3:15 Serial posterior scintiphotos each of 60 seconds exposure and taken at 2 minute intervals during the inhalation of pertechnetate (A,B,C) and at 5 minute intervals during the washout phase (D,E,F). In the normal subject there is even distribution of pertechnetate throughout both lungs and uniform decrease in activity when inhalation ceases. Note that in the later scintiphotos an area of increased activity is seen below the base of the left lung, in the stomach (left lung on the left of scintiphoto).

Fig. 3:16 Scintiphotos taken towards the peak of the inhalation phase using a diverging collimator: 50,000 counts were accumulated in each view. In this normal subject there is some detectable bronchial deposition of pertechnetate seen in the anterior view (top left). Posterior, left and right lateral views are seen in the top right, bottom left and right, respectively.

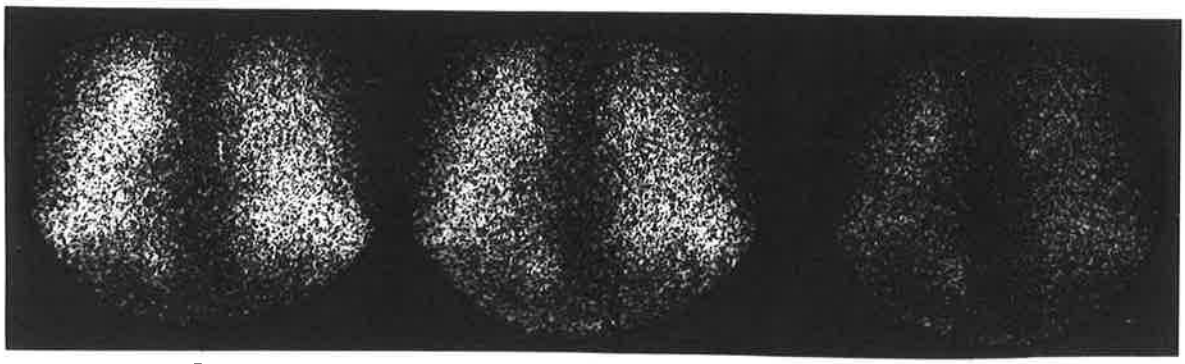
Fig. 3:17 Posterior scintiphotos in a subject with severe obstructive airways disease. On the left a scintiphoto taken towards the peak of the inhalation phase reveals a bizarre distribution of radiopharmaceutical with many apparently unventilated areas and a number of areas of increased deposition. Washout (centre) appears even, and after orciprenaline inhalation and repeat inhalation there is no demonstrable change in pertechnetate distribution.

Fig. 3:18 Serial 60 second posterior scintiphotos taken at 5 minute intervals beginning 10 minutes after the end of the inhalation phase in an asthmatic. The centrally deposited pertechnetate can be followed up the bronchial tree in successive frames until it was eventually coughed up.

Fig. 3:19 (A) Posterior perfusion and (B) inhalation scintiphotos obtained within a short time of each other in a subject with pulmonary embolism. Note the presence of normal ventilation in the regions of decreased perfusion in the right upper zone, midzone and base. Washout was even from all areas without the development of "hot" spots.



A B C



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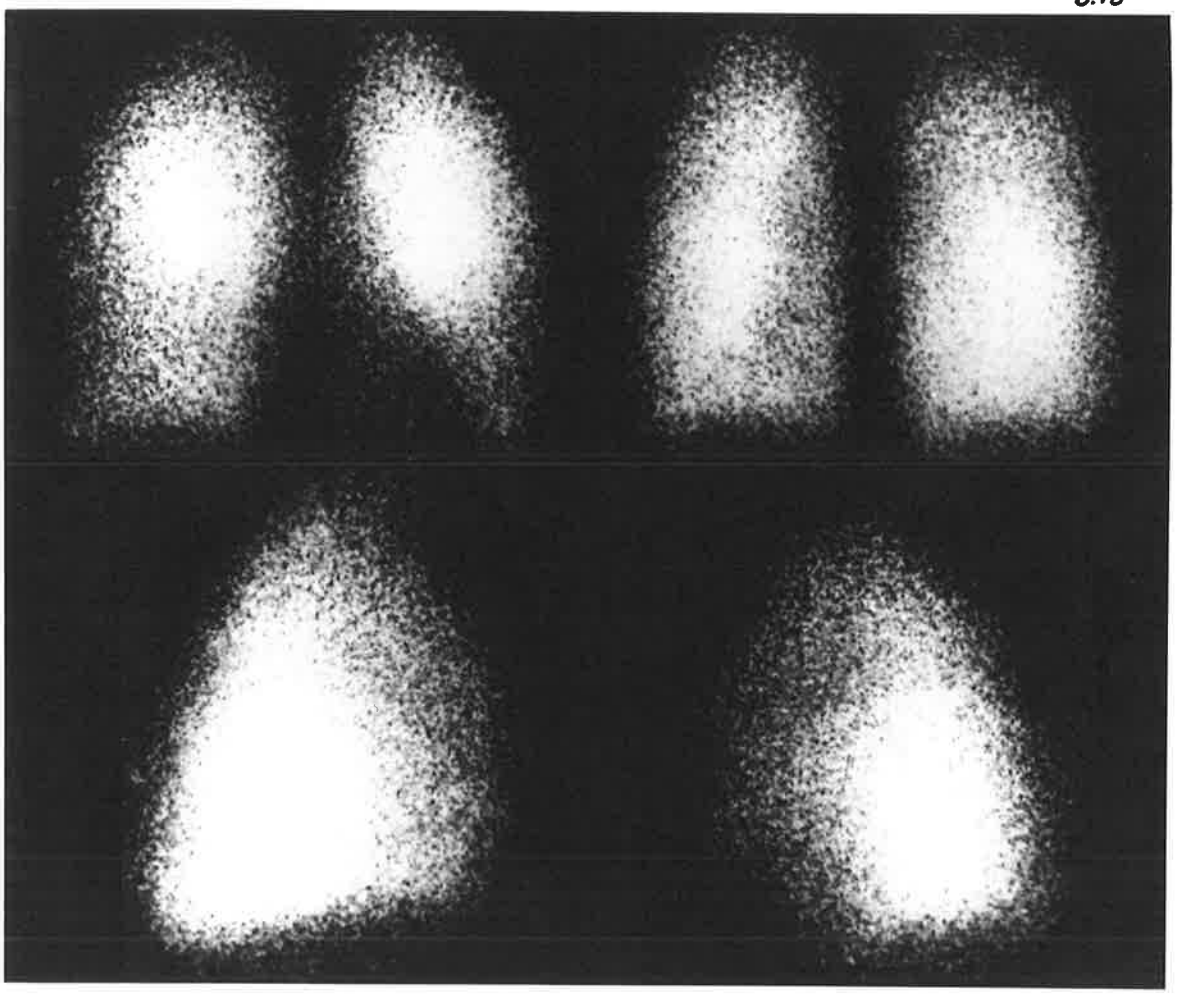
3.16



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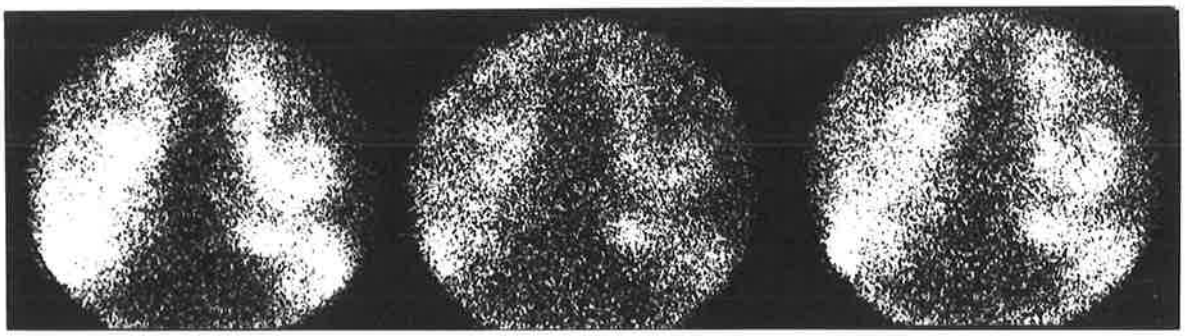

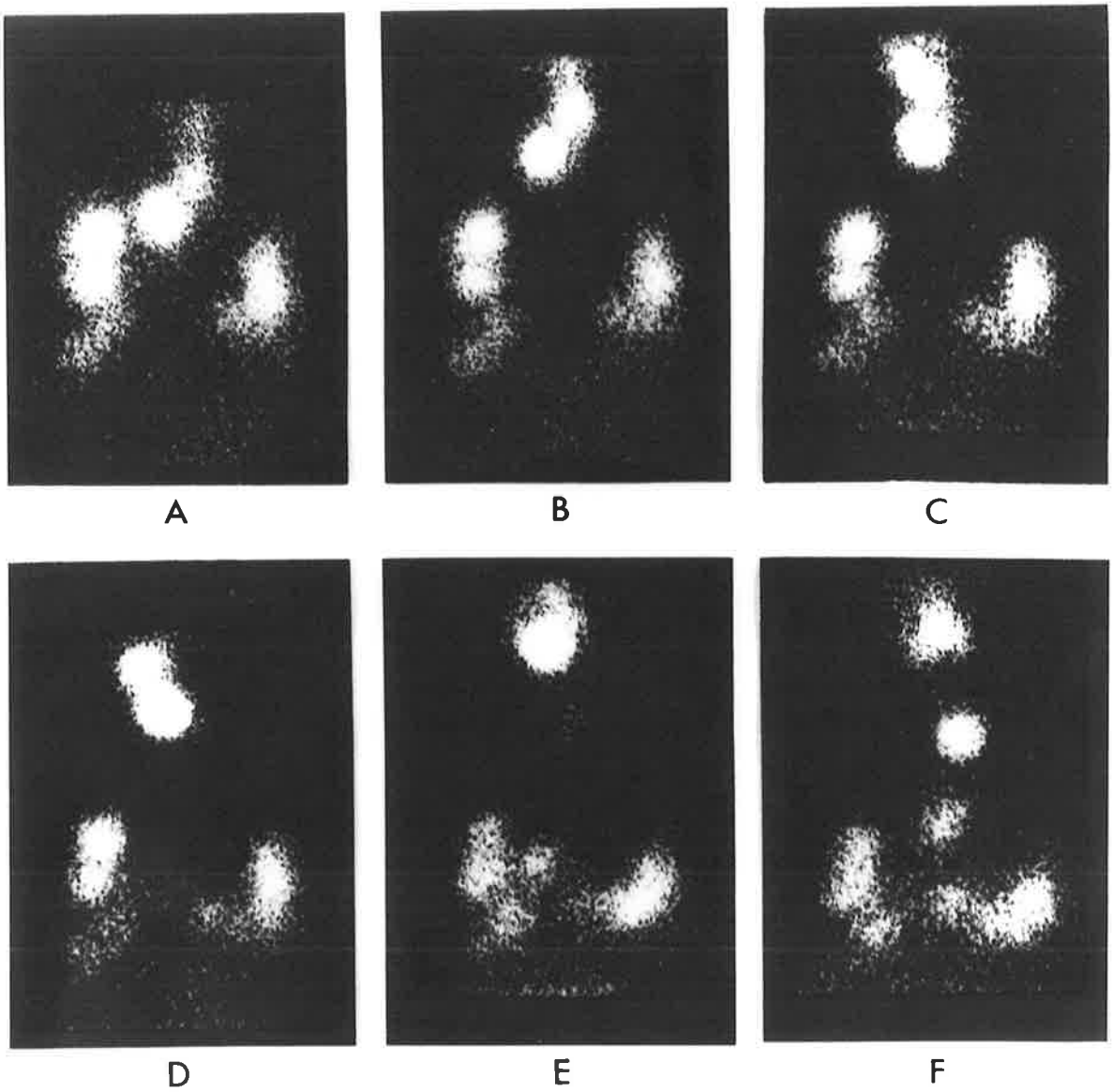

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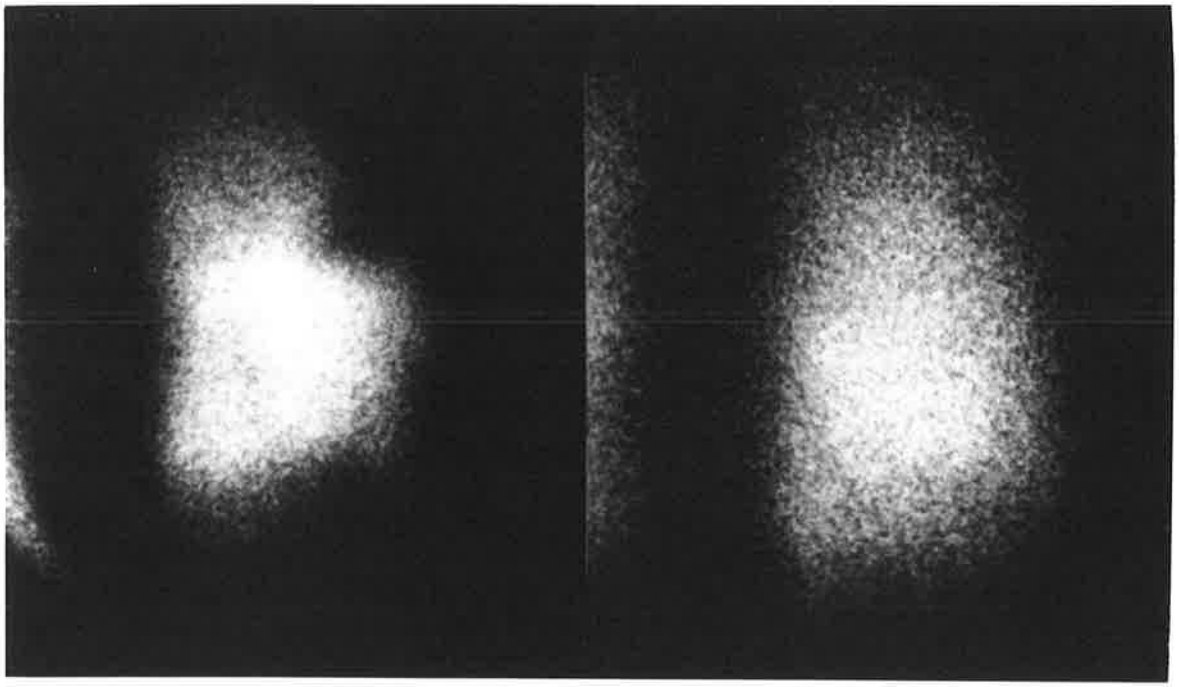
3.19



of the lungs and (c) pertechnetate attached to mucus in the larger airways is removed by ciliary action.

It is unlikely that (c) accounts for much of the decrease in activity noted in the post inhalation phase in the normal subject. However a graphic example of the removal of pertechnetate attached to mucus may be seen in figure 3.18 in an asthmatic with copious sputum.

Efforts were made to quantitate the contributions of the first two processes by trapping and determining the amount of radiopharmaceutical in the exhaled breath and by quantitating the activity in whole blood samples during and following the inhalation phase.

No satisfactory method for quantitating accurately the activity removed from the lungs in the exhaled breath was found as pharyngeal contamination resulted in spuriously high results irrespective of the method of collection. However certain conclusions were made regarding the fate of the inhaled pertechnetate by quantitating the uptake of the radiopharmaceutical in the blood in normal subjects by the following experimental procedure.

EXPERIMENT

Method:

1. Count rate using scintillation camera and disc source containing known quantity (^{Q}A) of pertechnetate noted, reading ^{R}A.
2. Normal inhalation study performed with subjects stationary before head of scintillation camera throughout.
3. Build-up and decline of activity monitored at one minute intervals throughout procedure. Maximum activity recorded = ^{R}M, quantity inhaled ^{Q}M (unknown).
4. Samples of venous blood (5 ml) withdrawn at 2 minute intervals throughout the inhalation phase and at 5 minute intervals thereafter for a total of 30 min. Samples counted against a standard to determine the amount of inhaled radiopharmaceutical each contained (Nuclear Chicago automatic gamma well counting system model 4217).
5. 24 hours later repeat 1, known quantity of radionuclide (^{Q}B) reading ^{R}B.
6. Subject injected with known quantity of technetium labelled macroaggregates (^{Q}C) and using similar geometry to 2, count rate noted (^{R}C).
   It was assumed that these macroaggregates were trapped with 100% efficiency by the lung.

PROPORTION OF INHALED RADIOPHARMACEUTICAL
DETECTABLE IN VENOUS BLOOD

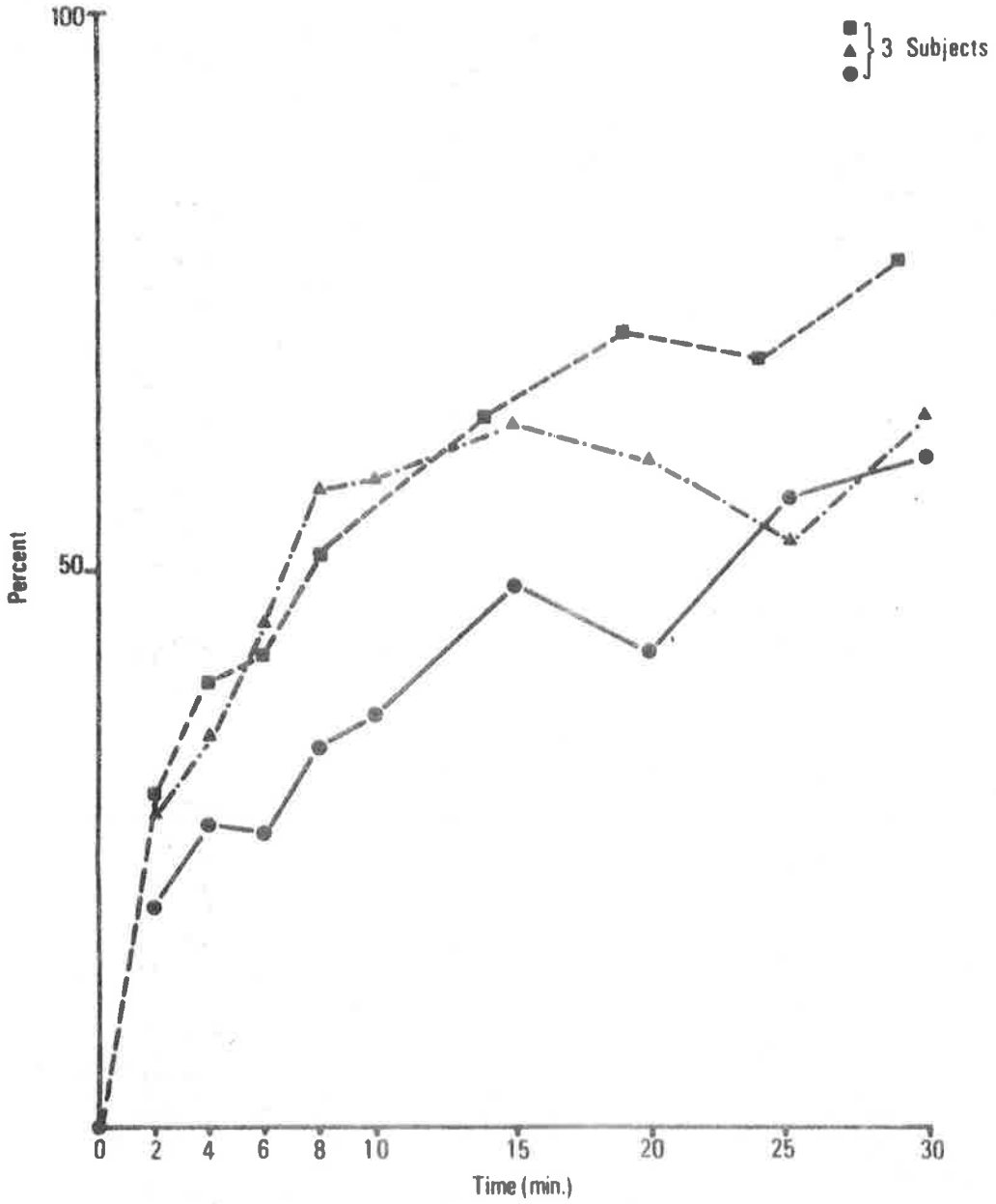


FIG. 3.20

Calculation:

A. Since $\frac{R_A}{Q_A} = \frac{R_B}{Q_B}$, then $Q_M = \frac{R_M Q_C}{R_C}$

The blood volume for each subject was read from a nomogram of blood volume vs height, weight and sex (Hidalgo, Nadler and Block, 1960). Using this value the hypothetical concentration of radiopharmaceutical in the blood assuming Q_M entirely absorbed into the blood stream was calculated C_M. With C_M as 100% the concentration of activity with the blood samples C_1, C_2, ... C_x were plotted against time. The results of such a plot are shown for 3 subjects in figure 3.20. Between 57 and 74% of the inhaled activity was recoverable from the blood.

B. Assuming that 1/3 of the total blood volume during the resting state is within the thorax in a normal individual (Gregg, 1961) activity within the thorax will drop by 2/3 if all the inhaled radiopharmaceutical is absorbed within the

Fig. 3:21 There is a rapid reduction in thoracic activity with time following the inhalation of pertechnetate.

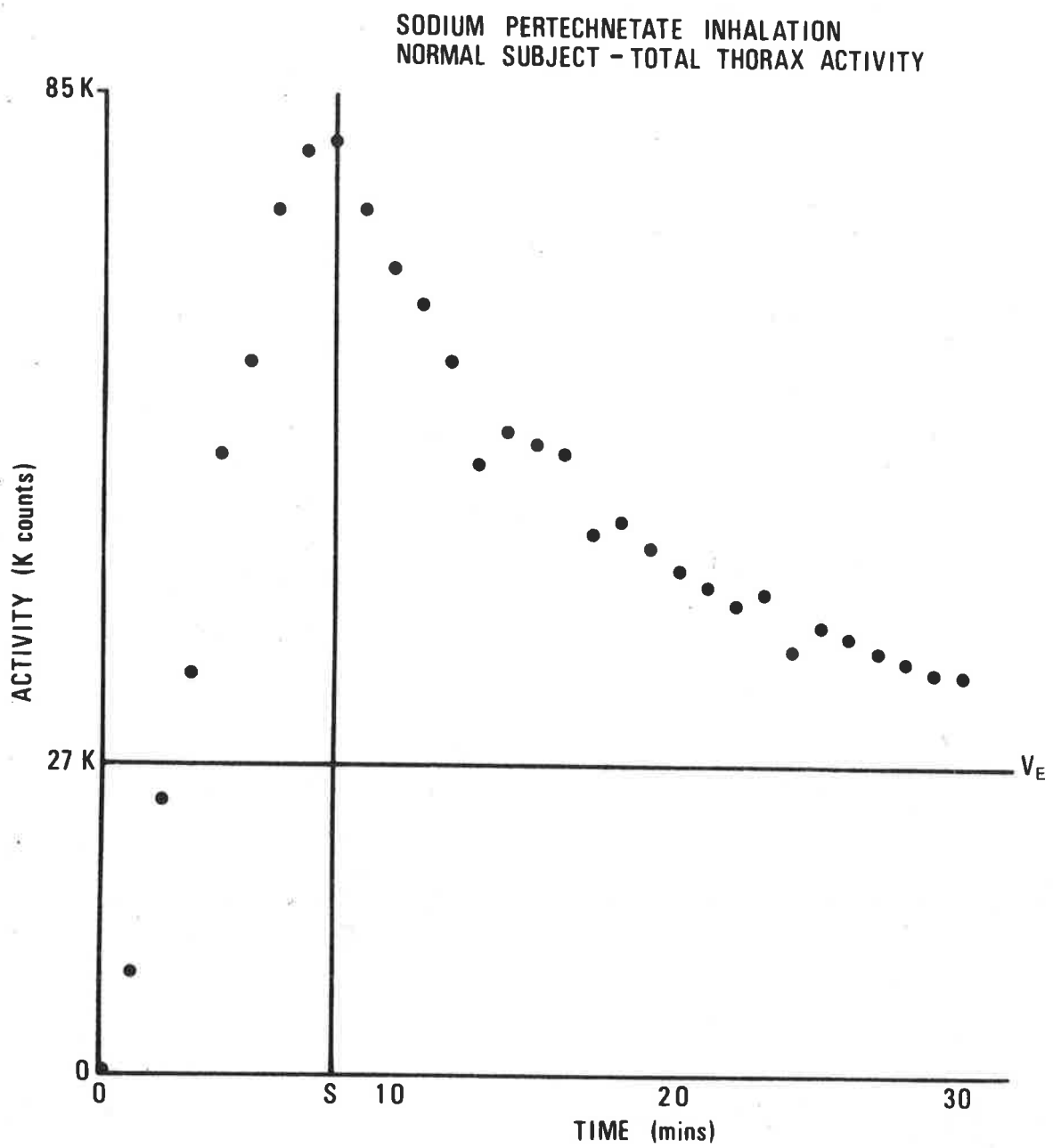

SODIUM PERTECHNETATE INHALATION
NORMAL SUBJECT - TOTAL THORAX ACTIVITY
85 K
ACTIVITY (K counts)
27 K
0
V_E
0
S
10
20
30
TIME (mins)

FIG. 3.21

blood stream and provided it is not excreted. The calculated value for such an endpoint (V_E) is usually approached within 30 minutes of the end of the inhalation phase (fig. 3.21).

Conclusions

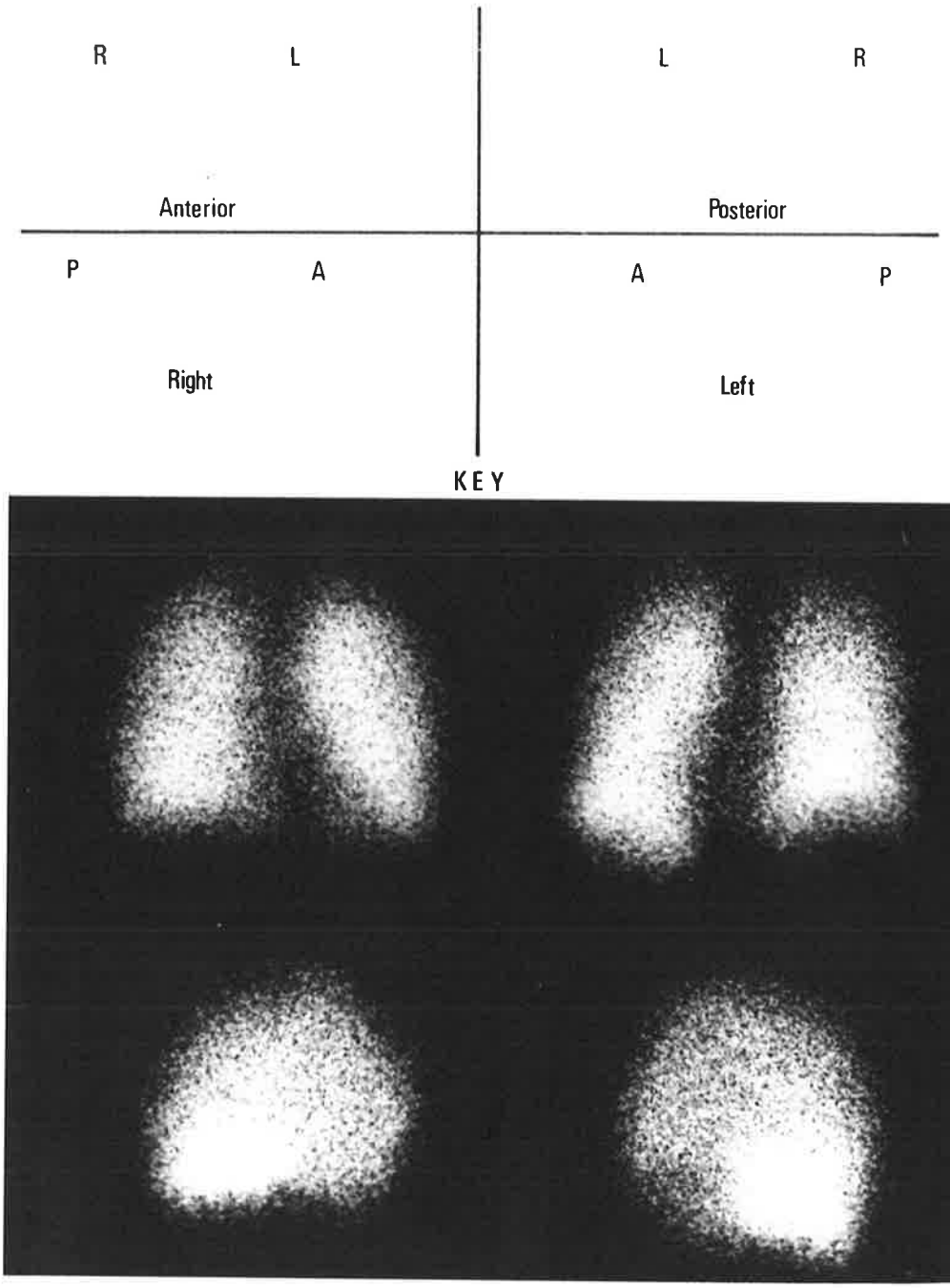
A major proportion of inhaled pertechnetate is absorbed into the blood from where it may be recovered; activity over the thorax falls to about 1/3 maximum within 30 min of terminating inhalation.

ii. Using indium chloride solution $I^{113m}InCl_3$)

(aa) General. The results obtained using this radiopharmaceutical were similar to those obtained using pertechnetate. However indium chloride was found to remain in situ once inhaled and this removed a major source of artefact seen when sodium pertechnetate was used as the inhalant. Multiple view studies were readily obtained using either a scintillation camera or rectilinear scanner.

(bb) Normal subjects. Inhalation studies in normal subjects revealed even distribution of activity throughout both lung fields with minimal bronchial deposition (fig. 3.22).

Fig. 3:22 Normal inhalation study - four views, 50 K counts accumulated in each view. The radiopharmaceutical used was indium chloride.


R
L
L
R
Anterior
Posterior
P
A
A
P
Right
Left
KEY

(cc) Abnormal subjects

1. Localised pulmonary disease. In general subjects with localised pulmonary disease, excluding embolism, exhibited ventilatory defects in the region of the pulmonary abnormality with relatively normal ventilation elsewhere (fig. 3.23).

2. Airways disease

(a) Obstructive airways disease. Bronchial obstruction and chronic obstructive airways disease often resulted in dramatic abnormalities. As with pertechnetate inhalation, proximal deposition of radiopharmaceutical with poor peripheral deposition often resulted in a bizarre picture (fig. 3.24).

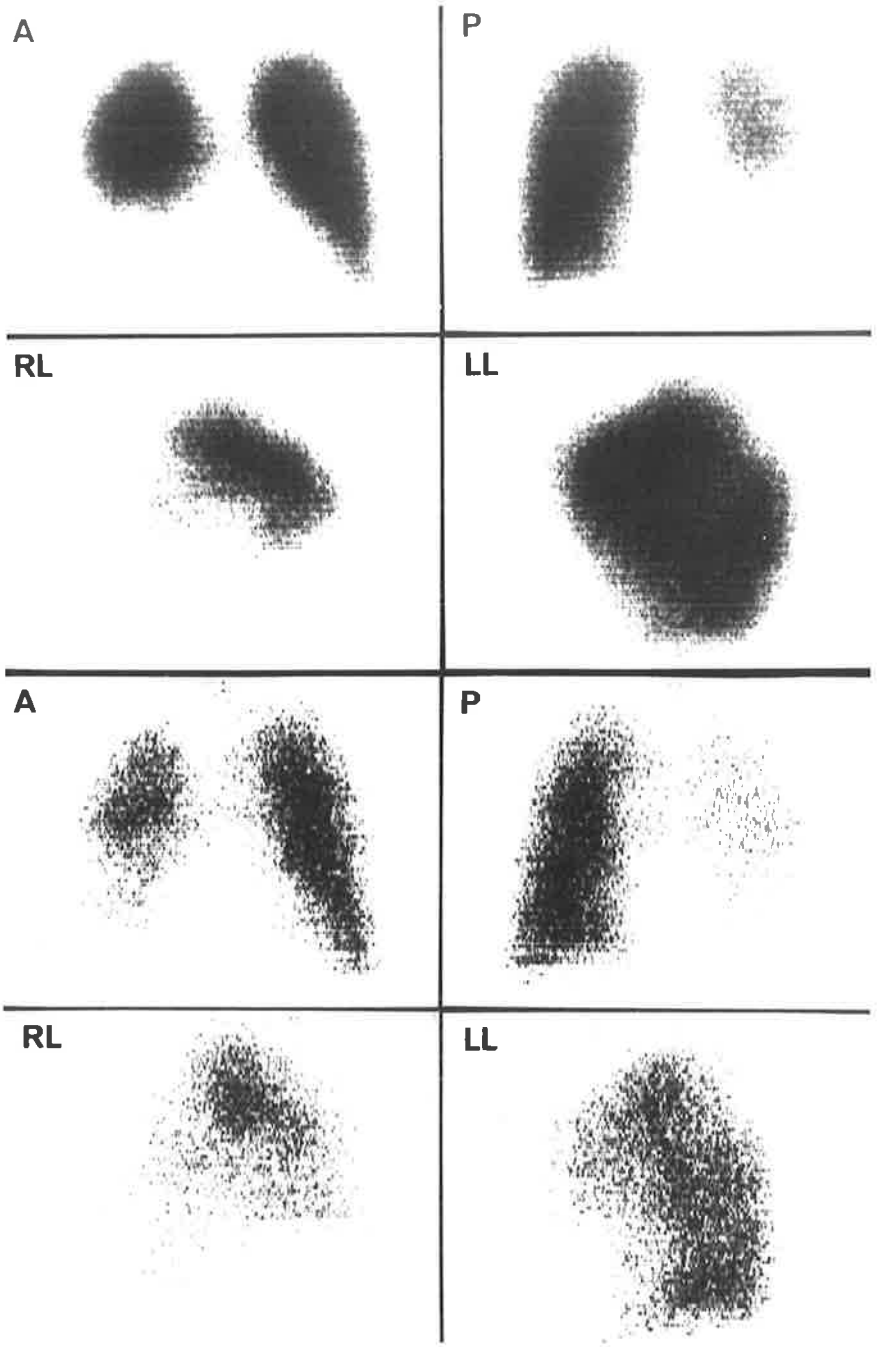
(b) Complete bronchial obstruction. Complete obstruction of a main bronchus by a ball valve tumour resulted in radiopharmaceutical only in the contralateral lung without deposition proximal to the obstruction (fig. 3.25).

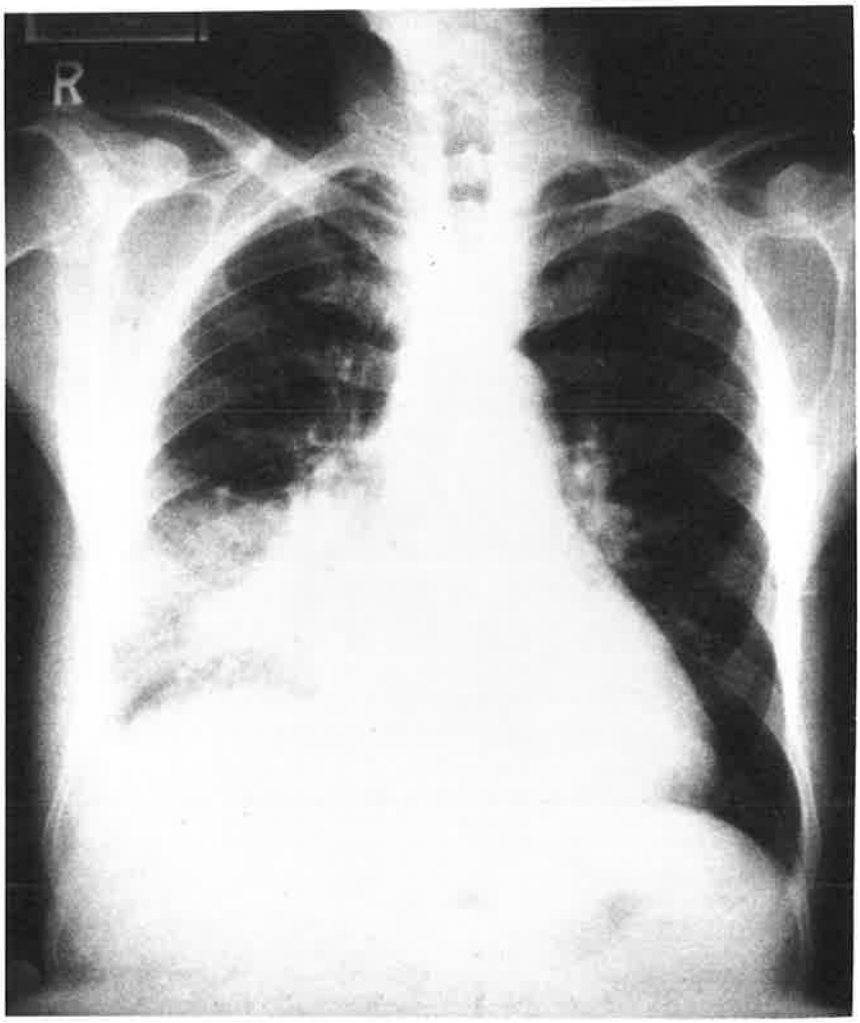
3. Pulmonary embolism

(α) Normal ventilation. In most instances pulmonary embolism did not materially affect the inhalation study but resulted in a relatively normal picture (fig. 3.26).

(β) *Decreased ventilation.* Preexisting lung disease occasionally resulted in an abnormal inhalation study consistent with the preexisting disease process. In such instances the area of embolisation was occasionally demonstrated to be well ventilated.

Fig. 3:23 Subject with cardiomegaly and right lower lobe pneumonia. Perfusion study (above) and inhalation study (below). (Chest Xray on following page.)


A
P
RL
LL
A
P
RL
LL


R

When pulmonary infarction (fig. 3.27) or atelectasis occurred areas so affected showed reduced or absent radiopharmaceutical deposition.

Areas of decreased ventilation secondary to bronchospasm which later in the course of the disease resolve, were not seen at any time.

(γ) Hyperventilation. Areas of hyperventilation associated with embolism were noted when using this technique. In a subject with multiple myeloma and multiple pulmonary emboli the poorly perfused areas of the lungs were maximally ventilated and vice versa resulting in gross perfusion:ventilation inequality and severe blood gas disturbance breathing oxygen. (pCO_2 = 24 mm, $p0_2$ = 72 mm) (fig. 3.28).

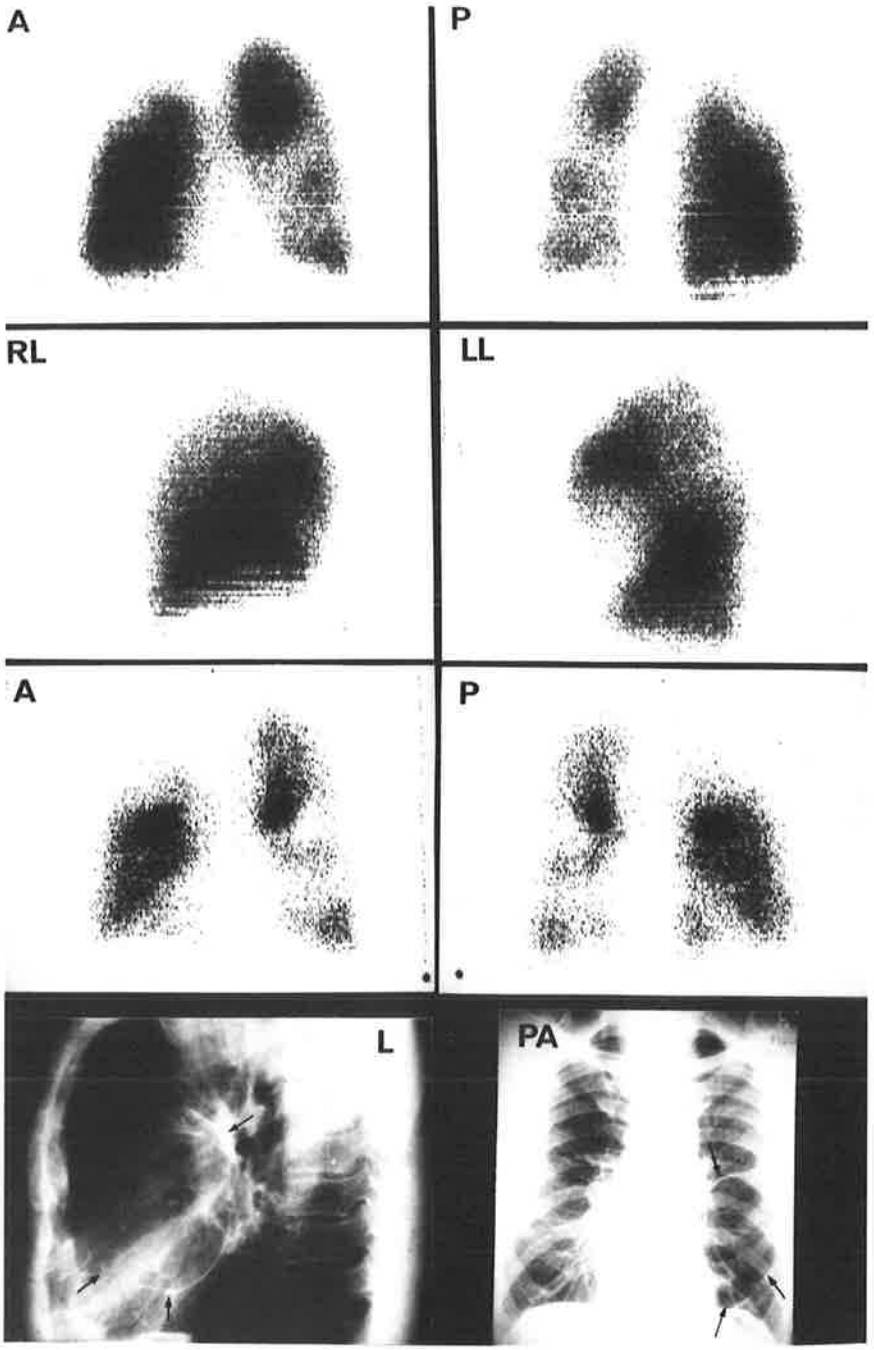
(dd) Fate of indium chloride

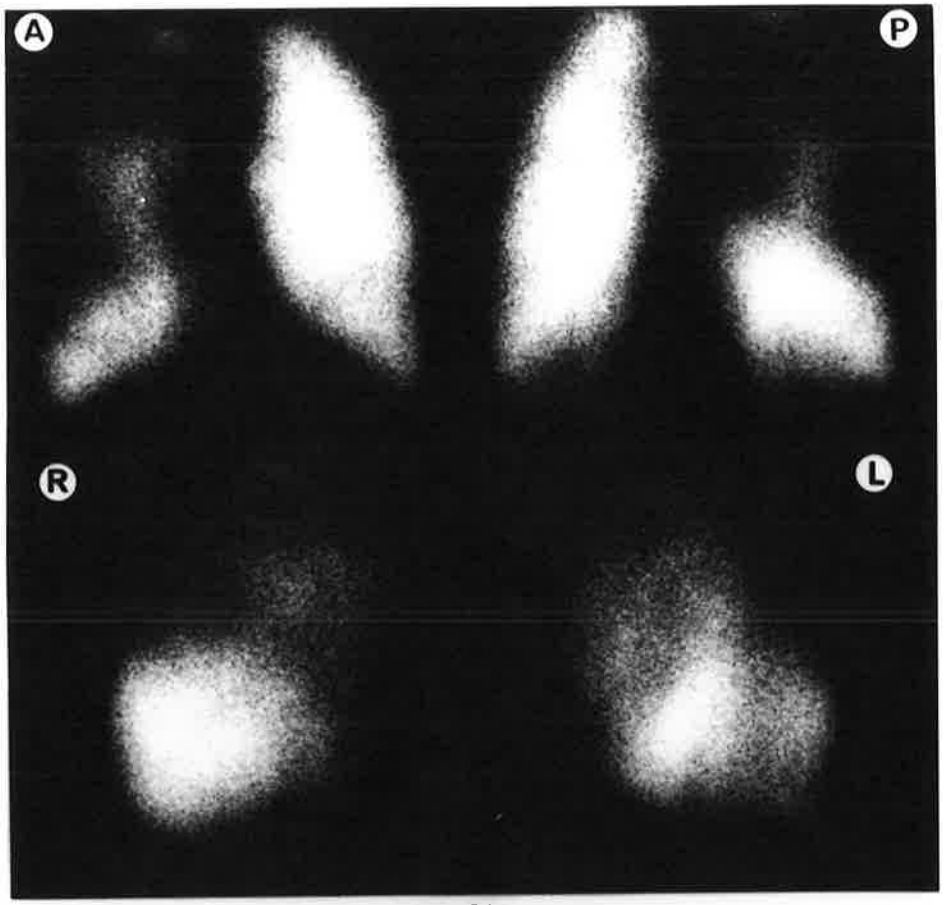
Following its inhalation indium chloride concentration within the lungs remained static (fig. 3.29). No radiopharmaceutical was demonstrable in venous blood samples. The appearances of serial scintiphotos obtained

Fig. 3:24 (a) Obstructive airways disease with bullae. Perfusion study - 4 views (above), inhalation study - anterior and posterior views only (centre), corresponding Xrays (below).

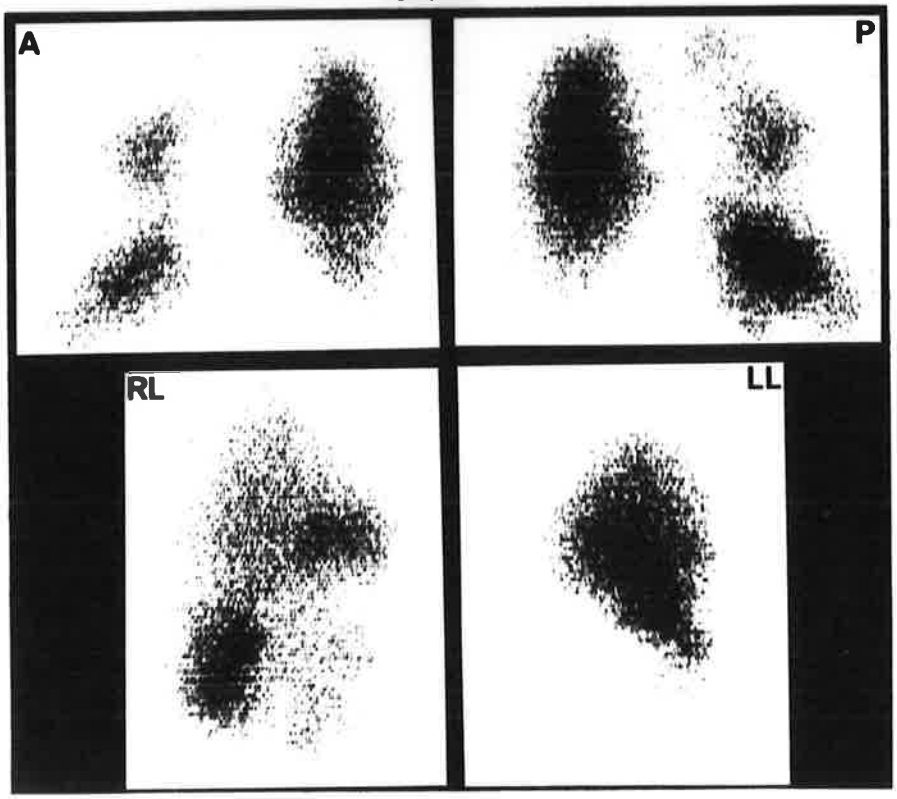
Fig. 3:24 (b) Obstructive airways disease revealing large poorly ventilated perfusion defects and areas of well-perfused and well-ventilated lung. Corresponding chest Xray on following page.

3.24(a)



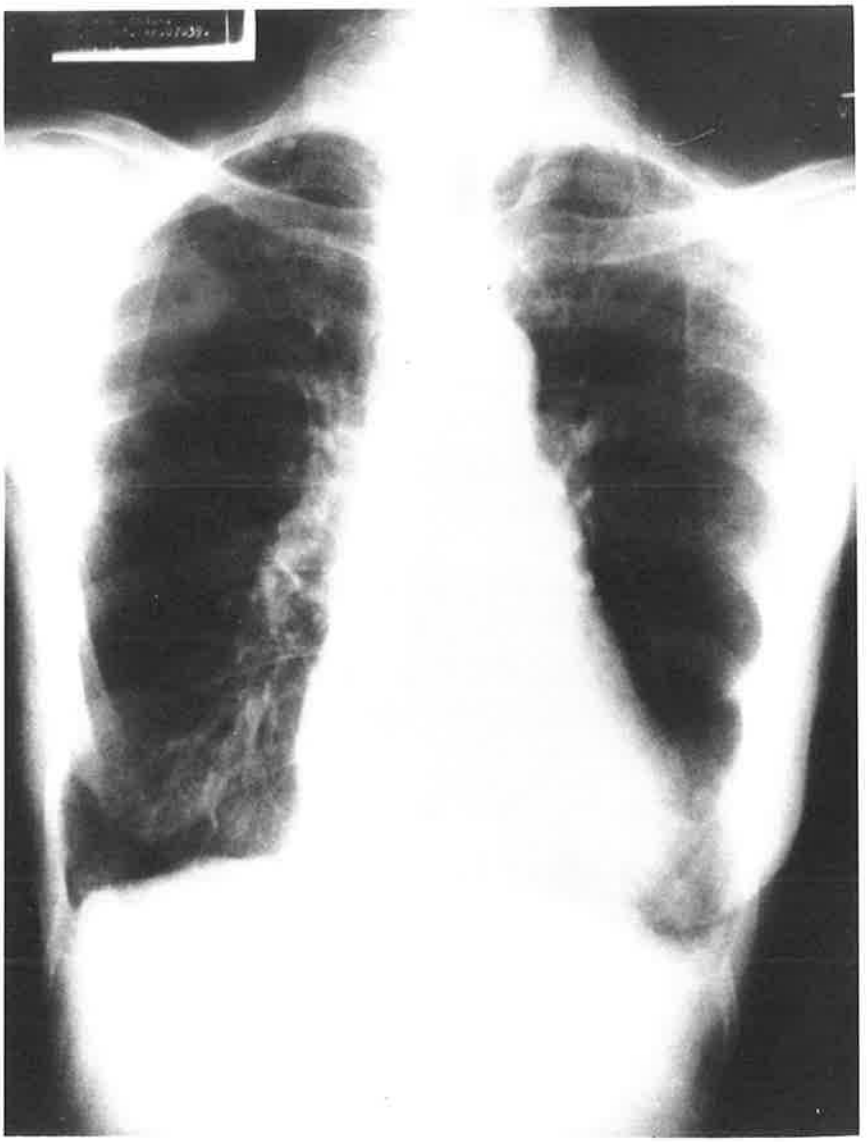


PERFUSION



INHALATION

3.24(6)



over 90 minutes remained unchanged in 2 subjects. These findings led to the conclusion that indium chloride remains in situ once inhaled at least for sufficient time to permit rectilinear scanning or multiple view scintillation camera study.

(c) Combined digital perfusion-inhalation studies. When employed, combined digital perfusion-inhalation studies provided comparable information to that obtained from scintiphotos.

(i) Normal studies. When radiopharmaceutical deposition was even in both the inhalation and perfusion study, contours of activity corresponded in the two studies (fig. 3.30).

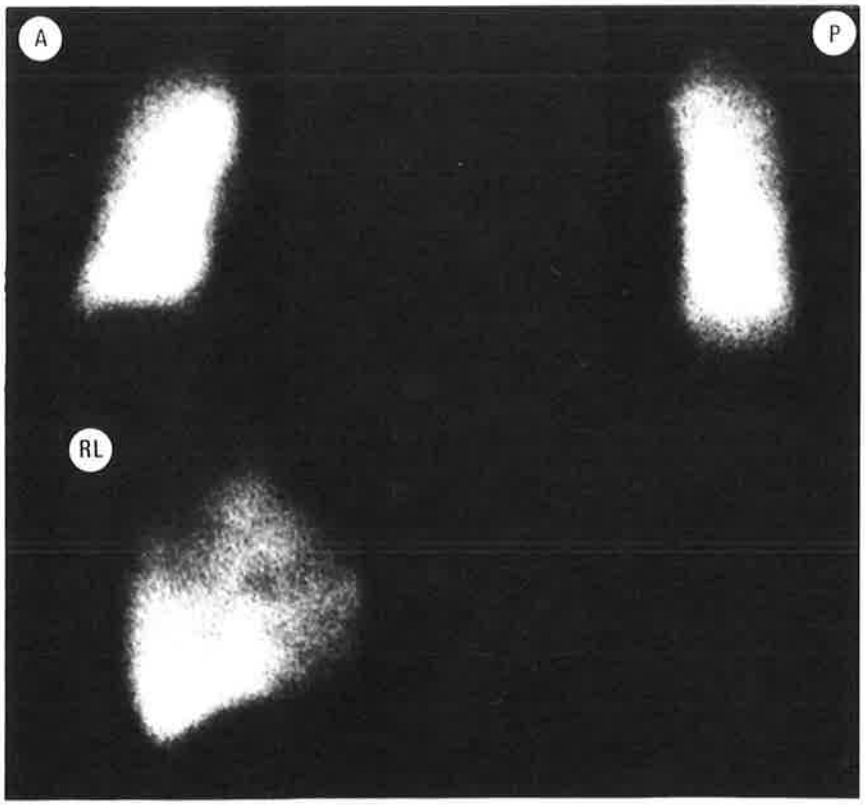
(ii) Abnormal studies. In abnormal studies when the distribution of inhaled and injected radiopharmaceuticals varied, differences in position of contours of activity highlighted the difference between the two (fig. 3.31).

E. DISCUSSION - METHODS

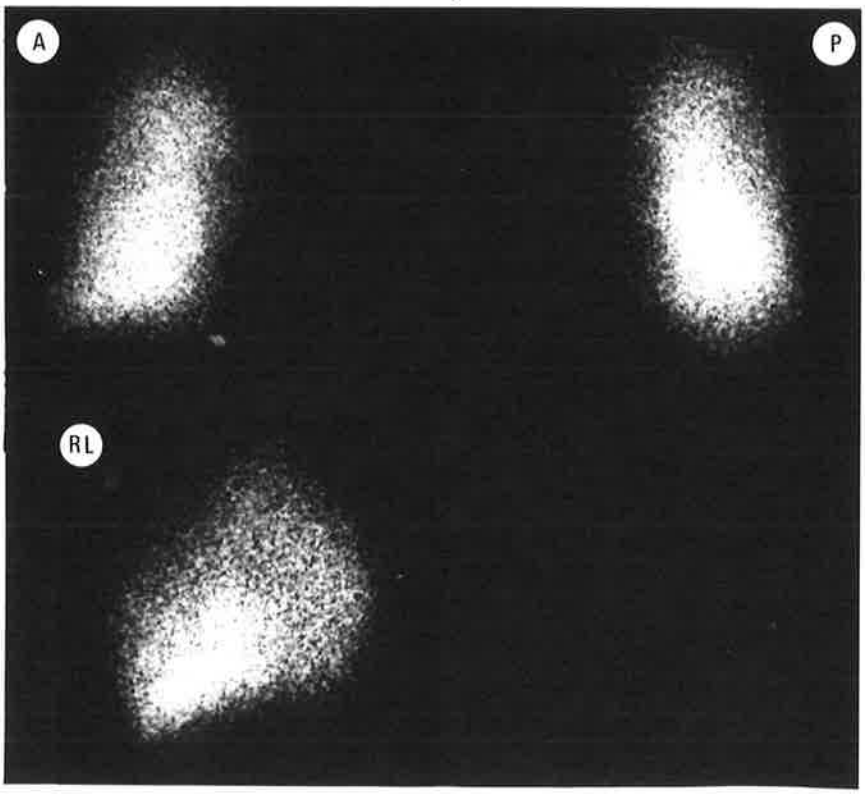
(a) Perfusion studies

(i) Studies employing iodine or technetium labelled macroaggregates (^{131}IMAA or ^{99m}TC MAFH). Perfusion studies employing these radiopharmaceuticals were performed according to a standard technique which is widely used and has been described in the literature (Wagner et al. 1964a; Quinn III et al. 1964; Taplin et al. 1964a).

Fig. 3.25 Complete obstruction of the left pulmonary artery (see fig. 3:13) perfusion study (above), inhalation study (below).



PERFUSION.



INHALATION.

(ii) Studies employing sodium pertechnetate ($Na^{99m}TcO_4$)

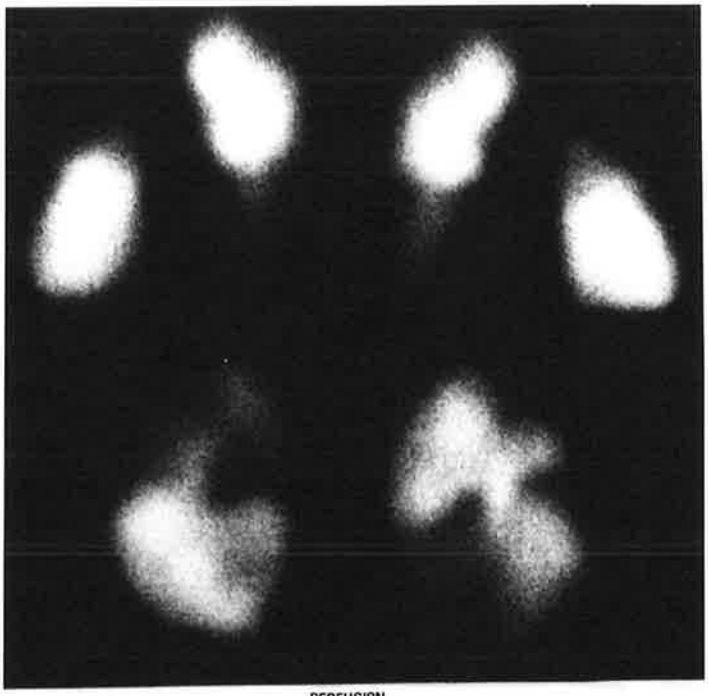
(aa) Reasons for study. Blood flow studies using pertechnetate were investigated at a time when suitable technetium or indium labelled macroaggregates were unavailable for lung scanning procedures and iodine labelled material was used exclusively in our laboratory. While scintillation camera study and rectilinear scanning employing iodine labelled macroaggregates were both time consuming, scintillation camera study lacked the resolution of good rectilinear scanning and the prone position required for performance of a posterior view rectilinear scan was occasionally so uncomfortable that it necessitated cancelling this most important view. The use of sodium pertechnetate flow studies was investigated as a rapid, comfortable means of obtaining information regarding the patency of the lesser circulation.

(bb) Method.

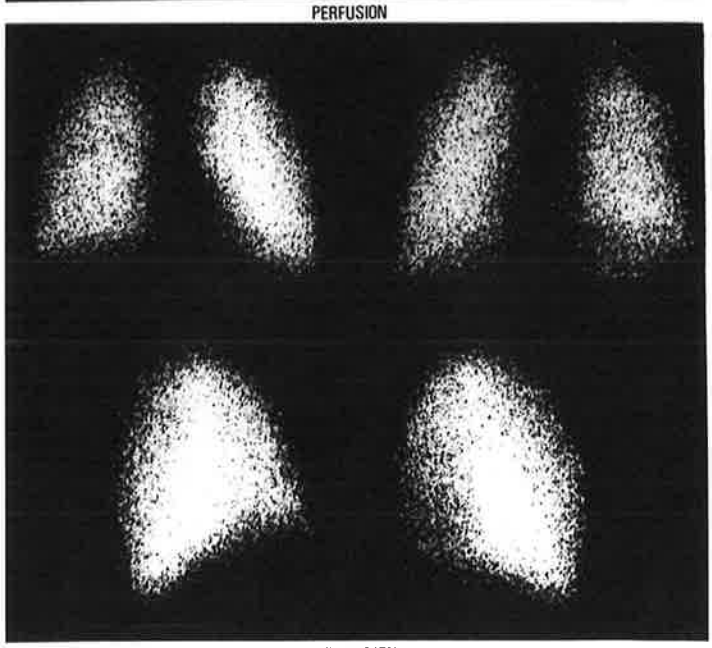
(1) Positioning. The supine positioning of the subject was chosen to incorporate as much as possible of the lungs in the field of the scintillation camera and minimise the contribution of cardiac radioactivity to the picture.

(2) Exposure time. Rapid serial exposure of scintiphotos at 2 second intervals was selected after experimentation as this satisfactorily separated the various phases of the passage of radiopharmaceutical through the heart and

Fig. 3:26 Perfusion (above) and inhalation (below) studies in a subject with multiple pulmonary emboli showing well ventilated perfusion defects.



PERFUSION



INHALATION

pulmonary vasculature and provided sufficient count rates for scintiphotos (4,000 - 20,000 cps).

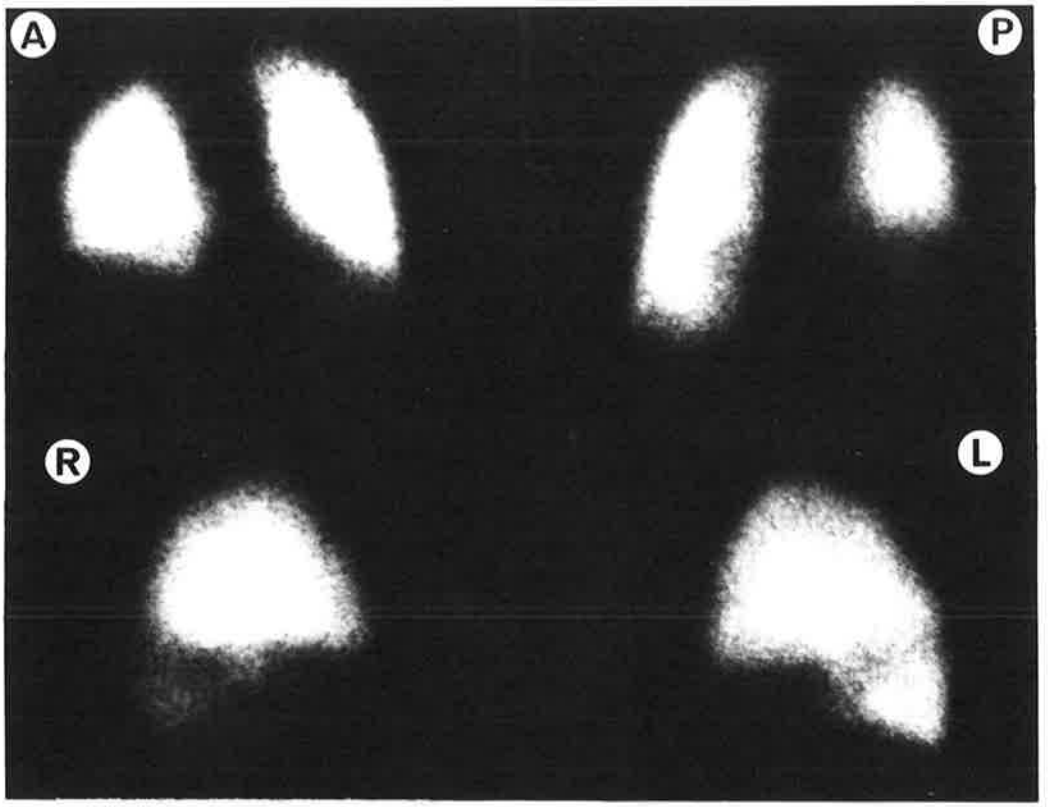
(3) Advantages of method. Increased speed of study, minimal subject discomfort and smaller absorbed radiation dose when compared to study using iodine labelled macro-aggregates [$Na^{99m}TcO_4$, total body dose 0.01 - 0.02 rad/mCi; ^{131}I MAA, total body dose 0.1 - 0.4 rad/mCi; lung dose 4 - 6 rad/mCi (Hine and Johnston, 1970)] were the main advantages.

(4) Disadvantages of the method. Apart from resolution deficiencies and "blind" areas demonstrated in a series of 64 subjects, another major disadvantage in this method of study is the production of only a single view scintiphoto as part of a sequence of scintiphotos each containing varying information. The inability to obtain multiple views of the lung must be a major drawback to this method.

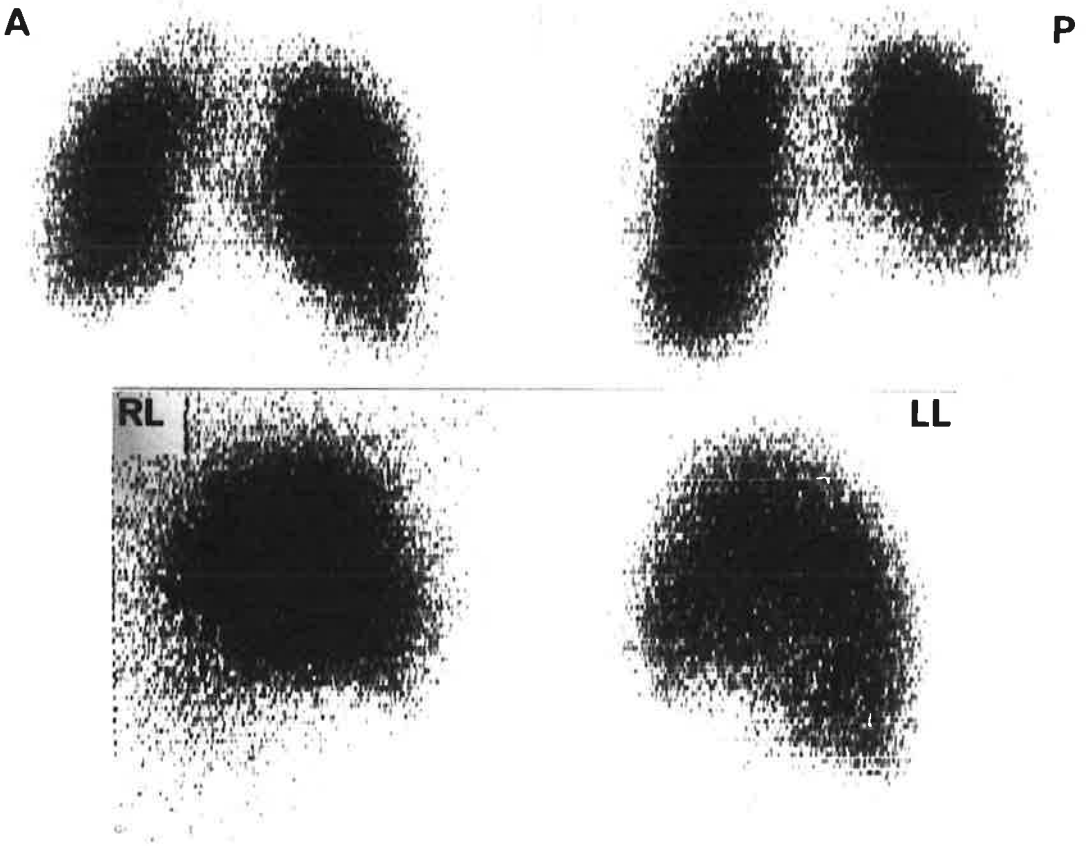
(b) Inhalation studies

Many techniques, some employing radioactive gas and others using radiopharmaceuticals in particulate or liquid forms (Taplin et al. 1966), have been described to investigate regional pulmonary ventilation since Knipping and his group pioneered the use of xenon-133 for this purpose in 1955. In this study an aerosol system was chosen for studies of regional ventilation and a number of technetium and indium compounds were investigated before indium chloride was

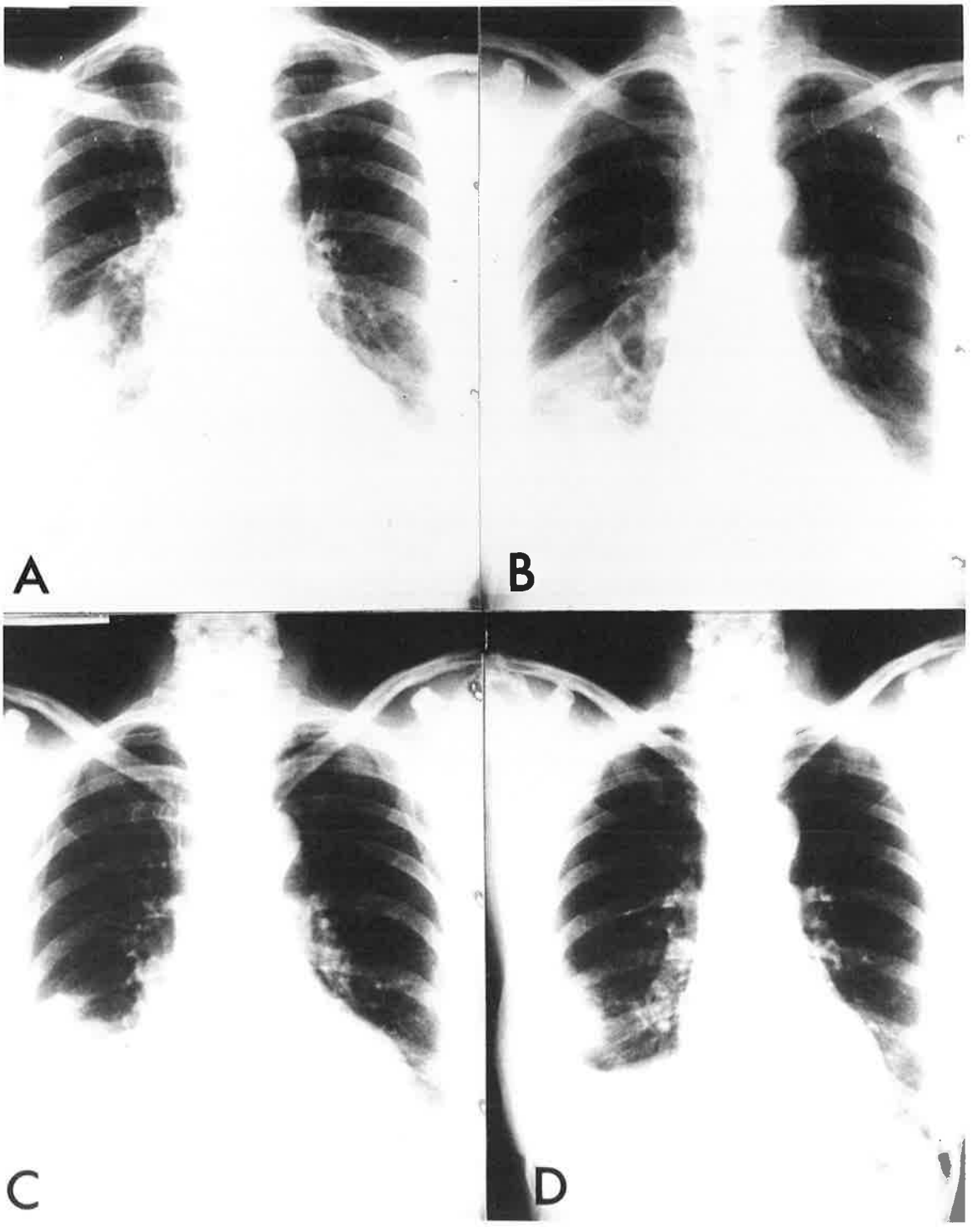
Fig. 3:27 Pulmonary embolism with right lower lobe infarction. There is no demonstrable ventilation in region of the infarct. (Serial Xrays on following page showing "melting iceberg" phenomenon.)



PERFUSION



INHALATION


A
B
C
D

selected as a suitable inhalant for our purposes.

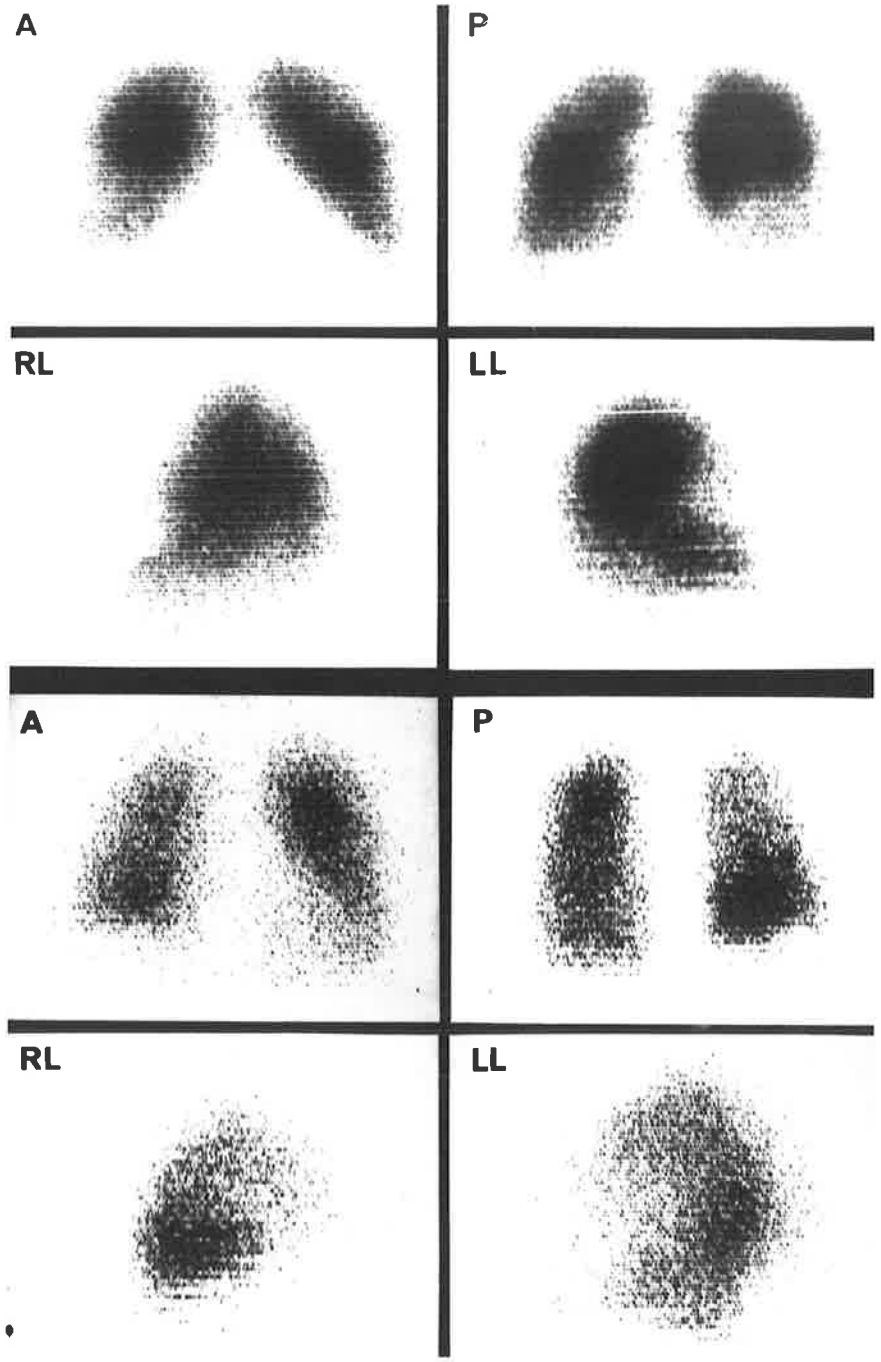
(i) Radioaerosol or radiogas

(aa) Aim of the system. The presence of perfusion defects in the lung is a very nonspecific finding. However most forms of pulmonary disease which cause perfusion defects result in similarly situated areas of decreased ventilation. Pulmonary embolism on the other hand is only rarely accompanied by decreased regional ventilation (de Nardo et al. 1970) when bronchial spasm occurs secondary to acute occlusion of a pulmonary artery (Boyer and Curry, 1944).

To assist in the diagnosis of pulmonary embolism a method which is sensitive to alterations in airway patency is required since the erroneous demonstration of normal ventilation in a subject with suspected embolism will falsely confirm that diagnosis. The occasional erroneous demonstration of abnormal ventilation (false negative study) although undesirable, can be more readily tolerated particularly since decreased regional ventilation is a feature of some cases of embolism.

The practical consideration of patient diagnosis, rather than the production of accurate ventilation:perfusion ratios throughout the lung was the major factor determining the choice of a system for the investigation of regional ventilation in these subjects.

Fig. 3:28 Pulmonary embolism with well ventilated perfusion defects and reduced ventilation in regions of normal perfusion. This is an unusual combination.


A
P
RL
LL
A
P
RL
LL

(bb) Availability of radiopharmaceuticals. The potential for selecting radiopharmaceuticals with gamma energies of different pulse height for perfusion and inhalation studies was an important consideration. A very extensive range of radiopharmaceuticals with widely differing gamma energies, some available in generator systems, were suitable for aerosol inhalation procedures. If a gas was selected the choice was virtually limited to xenon-133, a radionuclide in which less than 40% of the disintegrations are associated with gamma emission, and which can only be satisfactorily used with a scintillation camera or fixed probe system. Its gamma energy is below that considered optimal for use with the scintillation camera (Loken, 1971) and would necessitate prior performance of the ventilation study if a technetium compound was used as the perfusion agent.

Radiopharmaceuticals which do not have the disadvantages of low gamma energy while still being gases, such as xenon 135 (Newhouse et al. 1968) or krypton 81m (Jones, Clark, Hughes and Rosenzweig, 1970; Yano, McRae and Anger, 1970) were not available for use.

(cc) Behaviour of radiopharmaceuticals in the lung. Aerosol droplets are unlikely to be deposited peripherally in the presence of bronchial narrowing or obstruction as turbulence in such situations results in proximal deposition of particles. For this reason the demonstration of peripheral deposition of aerosol can be considered good evidence of

Fig. 3:29 There is no change in thoracic activity following indium chloride inhalation after inhalation ceases. Unlike pertechnetate this radiopharmaceutical is not absorbed into the perfusing blood.

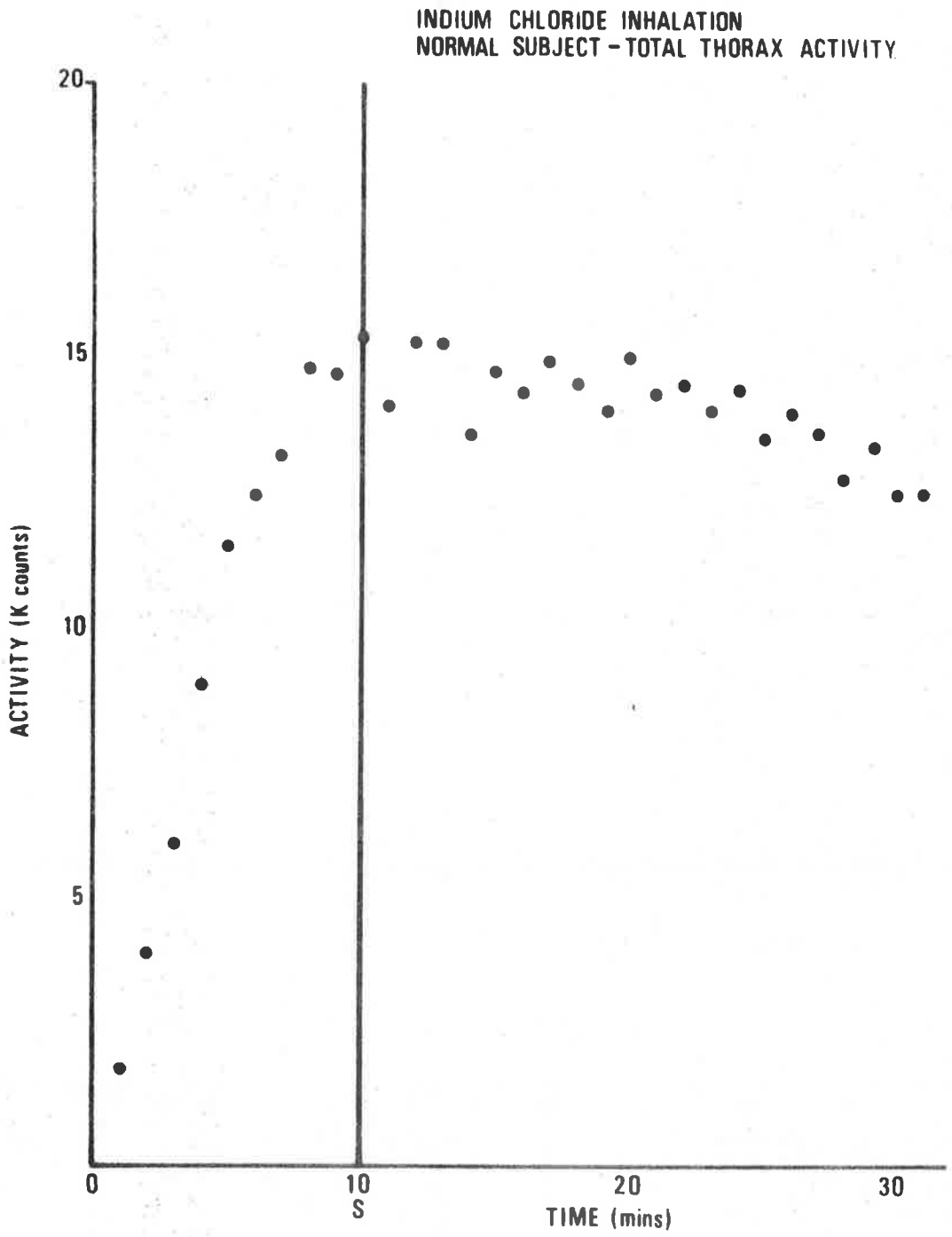

INDIUM CHLORIDE INHALATION
NORMAL SUBJECT - TOTAL THORAX ACTIVITY
ACTIVITY (K counts)
20
15
10
5
0
10
S
20
30
TIME (mins)

FIG. 3.29

airway patency.

With a radiogas on the other hand the recognised effects of slow wash-in of radiogas through partly obstructed bronchi and collateral ventilation through the pores of Kohn may produce falsely normal studies (Wagner et al. 1968).

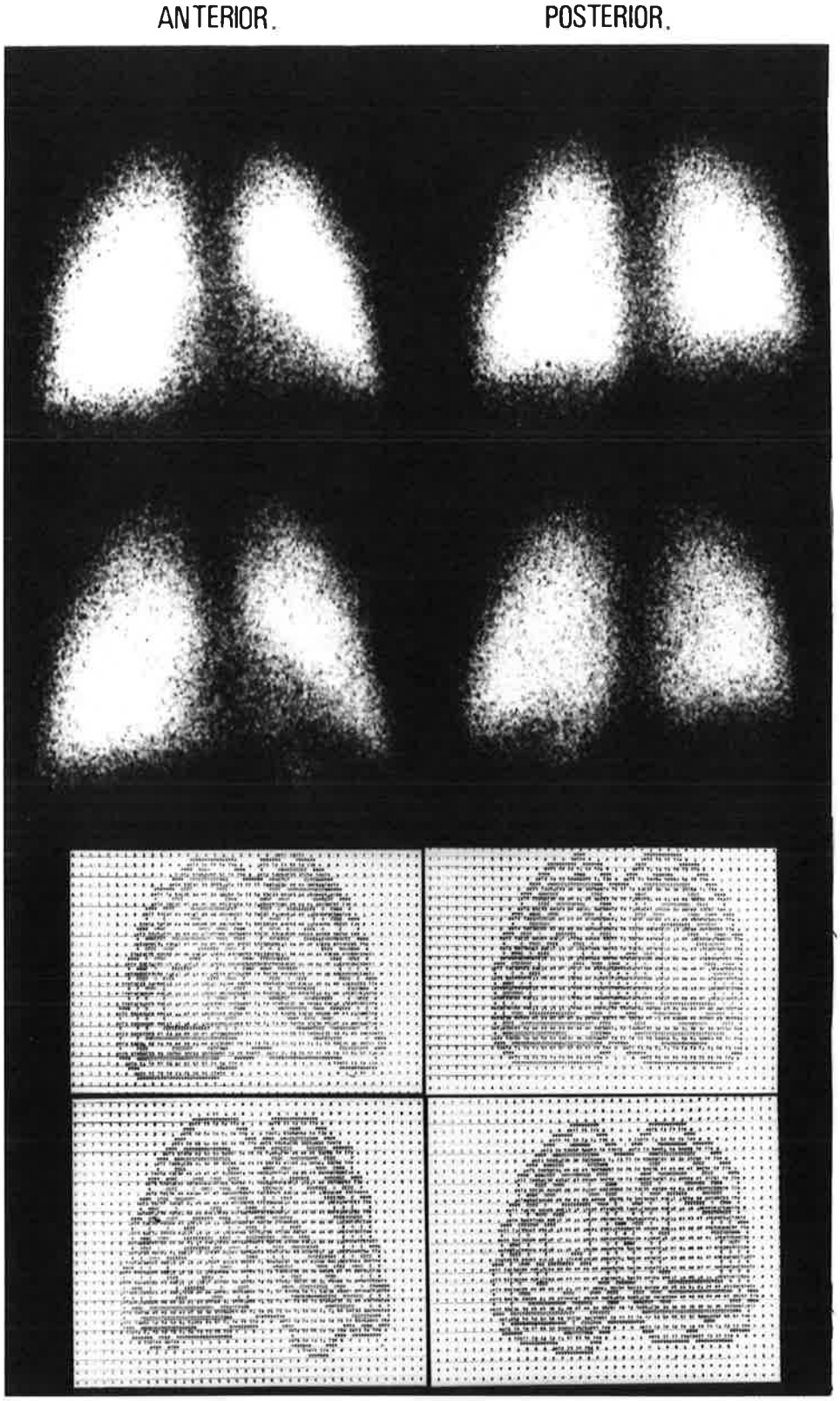
(ii) Radiopharmaceutical

In order that a radiopharmaceutical be suitable for inhalation purposes it must satisfy certain criteria. It must be non toxic, have a suitable gamma energy, and the radiation exposure associated with its use must be within acceptable limits. Other properties which are desirable are ready availability, short half life to permit repeated studies at frequent intervals, it should be non absorbable, lack the necessity for tedious preparation and carry low expense per investigation. In an aerosol system a liquid is probably preferable to a colloid because of its constant physical nature and easier nebulization.

(aa) Sodium pertechnetate ($Na^{99m}TcO_4$)

Sodium pertechnetate satisfies most of the above criteria but it is readily absorbed into the blood on inhalation. In addition, although its gamma energy is very suitable for detection by the scintillation camera and it provides high photon yield, it is unsuitable for use with technetium containing perfusion agents which are increasing in popularity. Nevertheless this agent can be used successfully for inhalation

Fig. 3:30 Normal combined study - analogue and digital. There is great similarity in distribution of radiopharmaceutical when technetium macroaggregates are injected intravenously and indium chloride solution is inhaled. Following inhalation some radioactivity is found in the upper gastrointestinal tract.

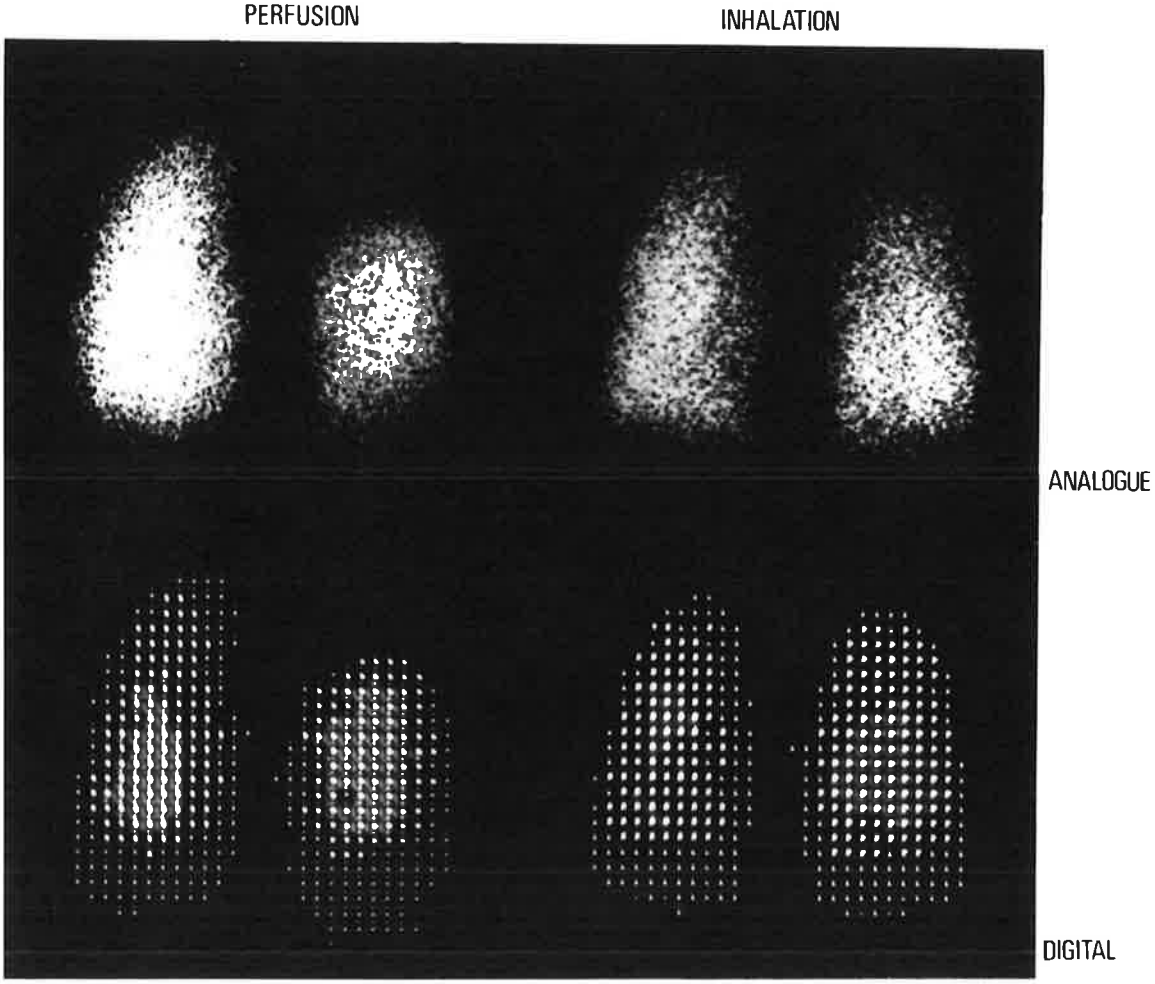

ANTERIOR.
POSTERIOR.
PERFUSION
INHALATION
PERFUSION
INHALATION

studies (appendix k).

(1) Decrease in activity through the upright lung. The apparently even decrease in activity throughout the upright lung cannot be readily explained on the basis of removal by perfusing blood alone as areas of maximum activity should be seen to be cleared fastest. That this phenomenon is not noted may partly be due to a greater return of absorbed activity in the perfusing blood to the dependant areas of the lung as well as to exhalation of some radiopharmaceutical in the breath.

(2) Digital analysis in pulmonary embolism. The possibility was investigated that the removal of radiopharmaceutical by perfusing blood would result in the development of areas of persistent activity in relatively ischaemic zones during the post inhalation phase in cases of pulmonary embolism. Digital comparison of regions which were well ventilated but poorly perfused with 'normal' regions failed to demonstrate such a phenomenon. The removal of radiopharmaceutical by an intact bronchial blood supply may be partly responsible for this finding. The behaviour of an inhaled tracer dose of sodium pertechnetate could thus not be used as a diagnostic test in pulmonary embolism without alternative means of assessing the patency of the pulmonary circulation.

Fig. 3:31 Analogue and digital combined study in a subject with pulmonary embolism showing a well ventilated right upper zone defect.


PERFUSION
INHALATION
ANALOGUE
DIGITAL

(3) Absorbed radiation dose. The absorbed total body radiation dose for intravenously injected pertechnetate is 0.01 - 0.02 rads/mCi (Hine and Johnston, 1970). It is predicted that the total body dose for inhaled pertechnetate would be similar to that figure. Because of its short half time in the lung the absorbed radiation dose to the lung is predicted to be less than 0.1 rads/mCi.

About 10 - 15% of the quantity of radionuclide added to the nebulizer is detectable in the subject's lungs.

(bb) Indium chloride solution ($^{113m}InCl_3$)

(1) General. Indium chloride solution satisfies all the criteria outlined above. In addition, its monoenergetic gamma emission is ideally suited for use with the gamma camera when fitted with a diverging collimator (see appendix aa), and the use of pulse height analysis allows perfusion and inhalation scintiphotos to be obtained virtually simultaneously when a technetium perfusion scanning agent is employed. Its ready availability in a long lived generator system (^{113}Sn: $T_{½}$ = 118 days) makes it potentially constantly available and cost low.

(2) Absorbed radiation dose. Indium-113m decays by isomeric transition and emits a 392 keV gamma ray. When indium ferric hydroxide particles are employed as a perfusion agent the estimated absorbed radiation dose is 0.01 rad/mCi

(whole body) and 0.6 - 0.8 rad/mCi (lung) (Hine and Johnston, 1970). It is expected that the absorbed dose would be similar when indium chloride is inhaled.

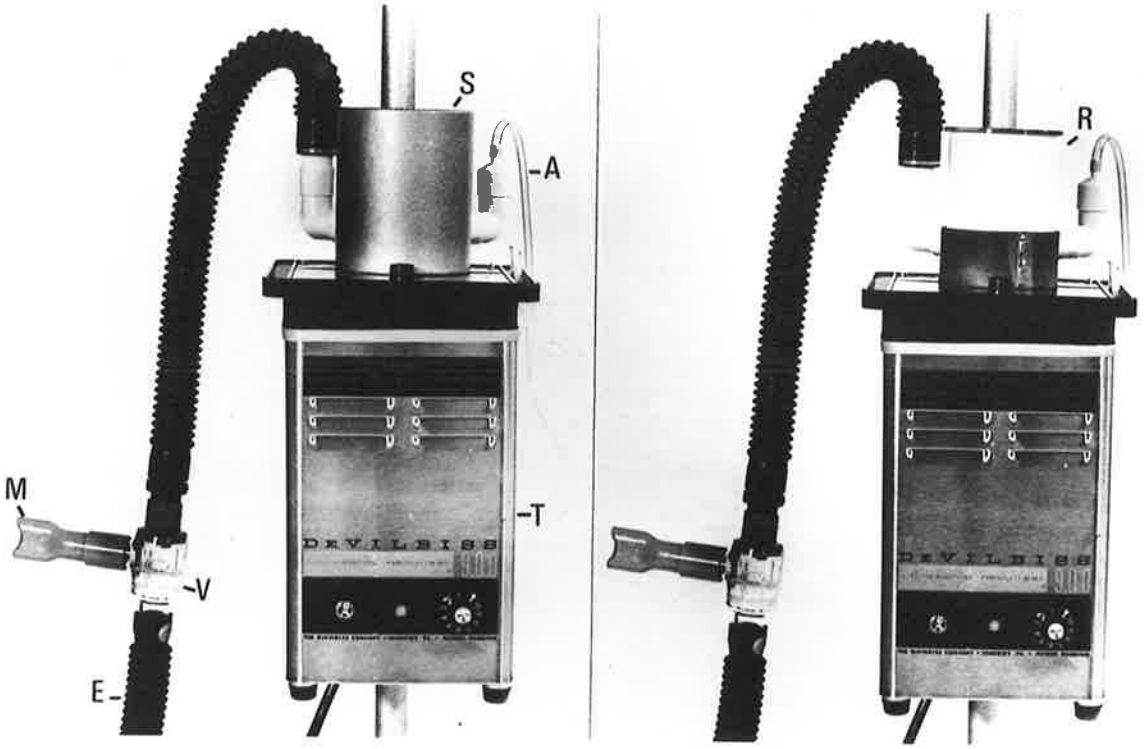
(iii) Apparatus design

(aa) Methods of nebulization. An aerosol spray may be produced either by agitation of a liquid and removal of the droplets which appear over its surface in a stream of air, or alternatively by impacting large liquid droplets on to a solid surface to disrupt them, producing small liquid particles which again are removed by an airstream. The agitation principle is employed in ultrasonic nebulizers and permits greater uniformity of droplet size than does the mechanical disruption of droplets by impaction which produces a wide spectrum of particle sizes.

(bb) Particle size - choice of nebulizer. Particles suitable for inhalation scanning must be in the size range 1 - 5 microns diameter since they must reach the peripheral airways with minimal bronchial deposition (Mitchell, 1960). A number of nebulizing systems were considered for this purpose before a Bird micronebulizer was selected.

The de Vilbiss ultrasonic nebulizer (fig. 3.32) was found to be less satisfactory than the Bird nebulizer because of the large volume of radiopharmaceutical that it was necessary to add to the reservoir for efficient nebulization (about 15 ml). This necessitated either

Fig. 3:32 de Vilbiss Ultrasonic Nebulizer system. This comprises a transducer (T), large reservoir (R), air supply (A), heavy-lead shield (S), and tubing with valve (V) and mouth piece (M).

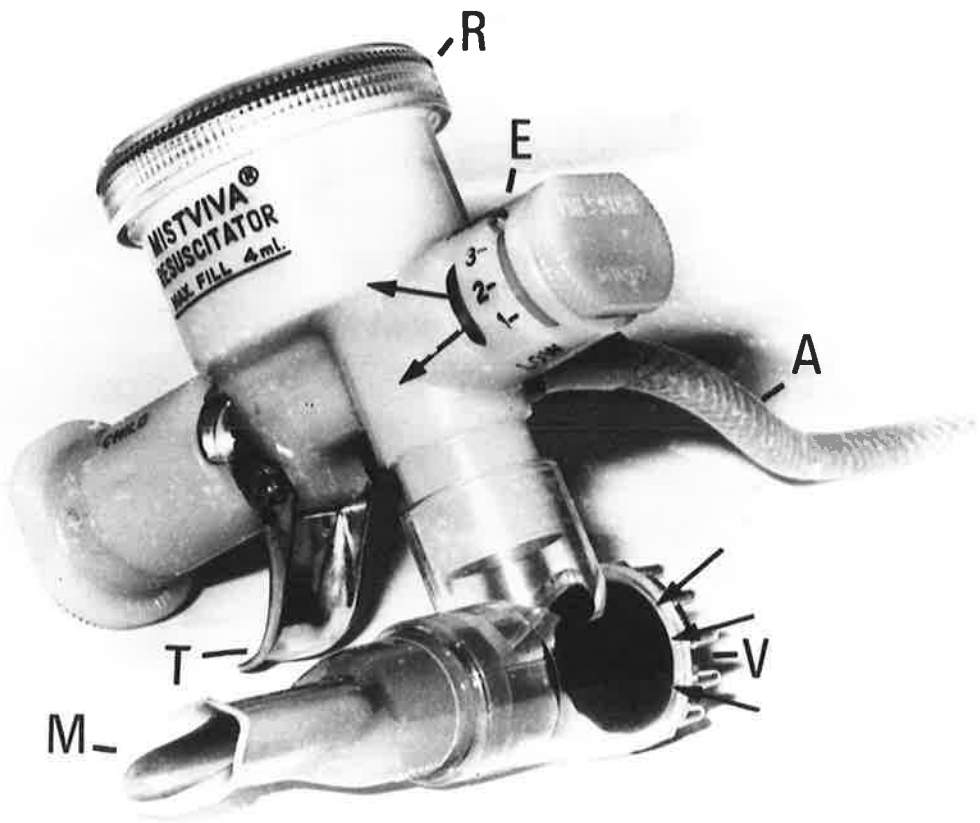

S
A
M
V
T
E
R

considerable dilution of the radiopharmaceutical or addition to the nebulizer of unacceptably large quantities of radionuclide. Studies employing this system were found to be no better than those obtained using the Bird nebulizer and because of radiopharmaceutical dilution they took longer to perform.

The hand held Mist Viva nebulizer (fig. 3.33) was rejected on the grounds that (a) shielding of the nebulizer chamber was likely to be difficult; (b) considerable modification of the nebulizer was necessary to prevent contamination of the laboratory with radiopharmaceutical via a safety valve and (c) a patient activated trigger mechanism was undesirable for routine use in subjects unaccustomed to the handling of nebulizers.

An important factor in the choice of nebulizer was the spectrum of particle sizes it produced. This property was recently investigated by Martin (1969) using a Casella Cascade Impactor in a humidified atmosphere. His results are illustrated in figure 3.34 which shows the droplet count within each of various size ranges < 0.05 microns, 0.5 - 1.0 microns, 1.0 - 2.0 microns, 2.0 - 3.0 microns and > 3.0 microns, for the three nebulizers available. The Bird nebulizer appeared to possess the most suitable characteristics having fewer small particles than the ultrasonic nebulizer and fewer large particles than the Mist Viva nebulizer under the conditions of measurement. Under normal

Fig. 3:33 Mist Viva Nebulizer: This comprises a reservoir (R), trigger mechanism (T), air inlet (A), air valve (V), the air pressure used to produce nebulized particles may be varied by use of a regulator (E). The arrows indicate sites from which contaminated air may escape from the nebulizer.


R
E
A
T
V
M
MISTVIVA®
RESUSCITATOR
FILL 4ml.
3
2
1

NEBULIZER DROPLET SIZE - FLOW RATE 14 LITRES/MIN.

After Martin(1969)

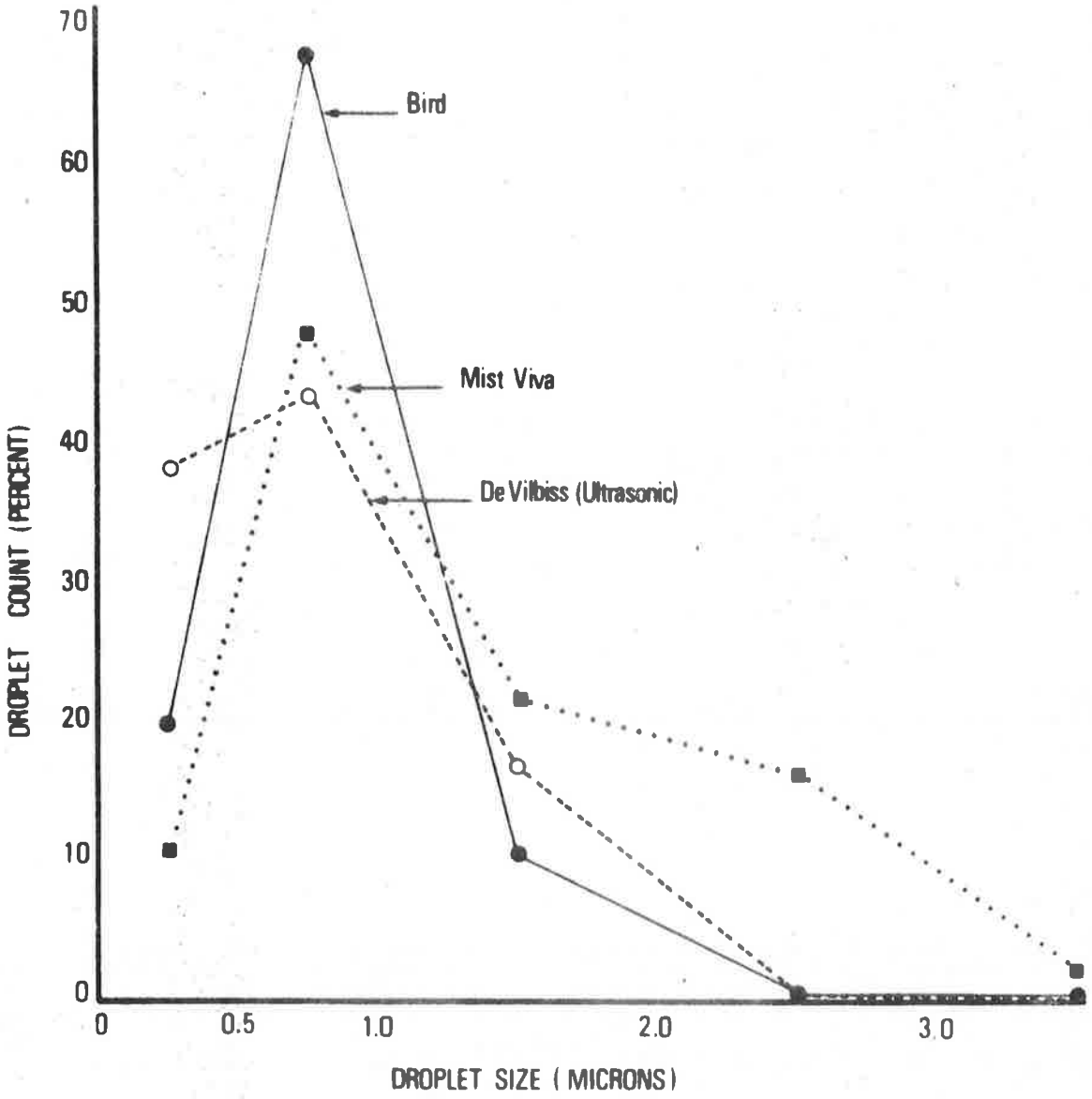


FIG. 3.34

working conditions it is probable that these curves shift to the right.

(cc) Apparatus configuration. The increased tendency of larger particles to fall from the emergent airstream of a nebulizer can be effectively used to filter out droplets of too large a size for inhalation purposes if a wide spectrum of droplet sizes are produced by the nebulizer. The simplest form of such a system is a tube, down which the emergent spray must pass. The larger particles are progressively removed from the airstream leaving only the smaller ones which can be inhaled. Such particles are unlikely to be deposited in the upper airways. Applying this principle to the design of a nebulizing system a suitable configuration was found to be that shown in figure 3.35. A reservoir is situated close to the nebulizer, its purpose is to act as a reservoir, reduce the pressure in the system thus allowing the subject to breathe comfortably, and serves to remove some of the large droplets from the spray. A 1 inch internal diameter corrugated tube is used to deliver the inhalant. A length of 20 inches was found to be optimum. If much longer than this the percentage of nebulized spray actually reaching the subject is greatly reduced. Only 30 - 55% of the dose delivered through a 20 inch tube is delivered through a 36 inch tube. If the tube is shorter bronchial deposition of radiopharmaceutical increases and the nebulizer

Fig. 3:35 Nebulizer (N), reservoir (B) and tubing with breathing valve (V). The proximal tubing and reservoir filter the largest drops from the emergent spray from the nebulizer.

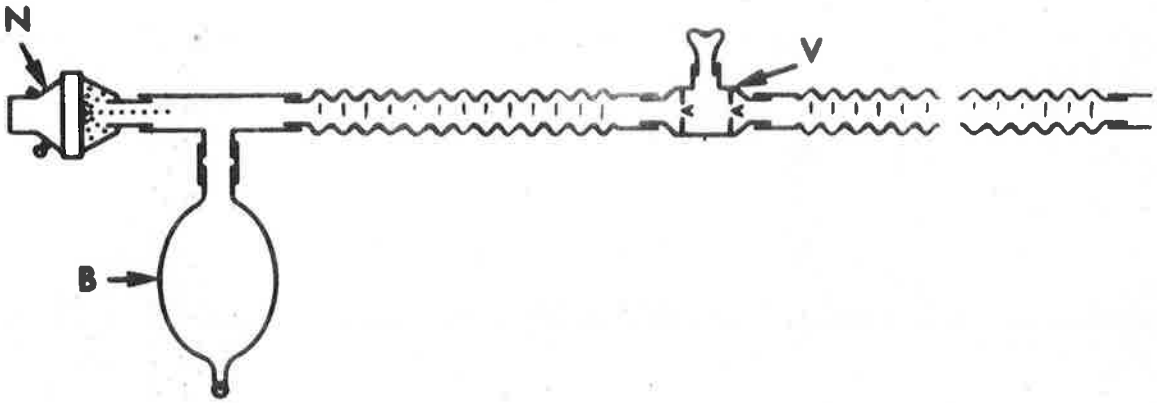


FIG. 3.35

and reservoir are situated too close to the subject's chest for certain imaging procedures to be successfully carried out (i.e. encroaches on the field of view of 'camera').

(dd) Air supply. Delivery of air to the nebulizer at 14 litres/minute is the most satisfactory rate. Lower rates resulted in discomfort and coughing in some subjects. Presumably different rates of airflow alter the conditions of nebulization so that droplets of different size are produced which result in discomfort when they are inhaled. (The rate of evaporation of water in the microdroplets is one factor that may change at different rates of supply of dry air to the nebulizer.)

(iv) Subject acceptability

To the end of 1971 inhalation studies using indium chloride had been performed on 93 occasions in normal subjects and in subjects with a variety of pulmonary disorders. The technique was well tolerated in all instances and has been adopted as a routine procedure for the investigation of regional pulmonary ventilation. The inhalation phase was conducted with subjects supine in the great majority of later studies as most subjects appear more comfortable and less distractable in this position while alterations in radiopharmaceutical deposition due to the physiological effects of different breathing depths are minimised in this position.

CHAPTER IV

PROSPECTIVE SURVEYS OF MEDICAL AND SURGICAL SUBJECTS

GENERAL INTRODUCTION

Post mortem studies have substantiated the frequent existence of undiagnosed pulmonary embolism (Morrel and Dunnill, 1968), yet such studies give little indication of the extent to which embolism occurs in those who may subsequently recover without ever developing recognisable symptoms. Studies of the development of deep venous thrombosis in the legs, particularly those involving the use of radio-iodine labelled fibrinogen have indicated that silent deep vein thrombosis is a common accompaniment of hospitalisation. Such data raise the possibility of asymptomatic embolism occurring from these sites in a significant proportion of hospitalised patients.

These studies of consecutive medical and surgical inpatients during their hospital admission were designed to determine how frequently pulmonary embolism occurs in such a population and the nature of the associated symptomatology and physical signs.

Throughout the study extensive use was made of organ imaging techniques involving the use of radiopharmaceuticals, and a variety of ancillary investigative procedures were employed to increase their specificity. The design of the study has permitted the documentation not only of the incidence and nature of pulmonary embolism in the studied population but also the type of pulmonary perfusion abnormalities

occurring in a wide variety of other disease states.

A. MEDICAL SERIES

Aims:

1. To survey a population of inpatients in a medical ward and document the distribution of their pulmonary perfusion.
2. To correlate the distribution of pulmonary perfusion with other parameters.
3. To document the changes in pulmonary perfusion occurring during hospitalisation.
4. To determine the incidence of pulmonary embolic disease in this population and its nature.

SUBJECTS

i. General: The subjects whose studies form the basis of this investigation were inpatients in medical wards of the Royal Adelaide Hospital between February 1970 and March 1971. All patients admitted to certain preselected units were potential candidates in the study. Only subjects under 20 years of age and pregnant females were excluded; subjects without any clinical indication for perfusion lung scanning were excluded if their stay in hospital was less than six days. Subjects from the preselected units in whom there was a clinical indication for perfusion lung scanning prior to the sixth day of their admission were included at the time of

the original perfusion lung scan.

Some subjects who otherwise satisified the criteria for inclusion were too sick to be moved to the scanning facility at the planned time; in certain instances these subjects were studied later, or not at all if their condition failed to improve. Such occurrences were appropriately noted.

Both the male and female groups were consecutive series. The males were studied from March 1970 to February 1971 and the females from June 1970 to March 1971. The study was halted for one period of 10 days and recommenced; this was the only significant break in the continuity of the study.

ii. Age, sex and recovery rate: Four hundred subjects were studied, 200 male and 200 female. The average age of males was 60.2 years (range 21-91 years) and of females 62.5 years (range 20-89 years). (Table 4.1).

TABLE 4.1

AGE	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
MALE	5	9	17	45	58	43	22	1
FEMALE	8	7	19	22	63	55	28	0

During the course of the investigation 24 subjects admitted to the units being studied died within 6 days of admission. A further 47 subjects who were admitted to those units and remained in

hospital for 6 days or more, were not studied. These subjects were usually too sick to be moved to the scanning facility. Among this group of 71 subjects there was one recorded instance of pulmonary embolism which was discovered at autopsy.

METHOD

On the sixth to eighth day of their admission, or earlier when there was a clinical indication for perfusion lung scanning, each subject included in the investigation was studied in the following manner.

(i) General: A full clinical history was elicited from each subject and a complete physical examination was performed with particular emphasis being placed on assessment of the cardiovascular and respiratory systems. The following investigations were performed routinely. (i) posteroanterior chest X-ray;(ii) biochemical tests - these were performed automatically on an SMA 12 analyser and included determination of total lactate dehydrogenase (LDH); total aspartate amino transferase (AAT or GOT); total bilirubin; (iii) a standard 12 lead electrocardiograph in all subjects over 55 years of age and in all subjects who demonstrated evidence of cardiovascular or respiratory disease; (iv) routine pulmonary perfusion study using ^{99m}Tc MAFH and a scintillation camera. The results of all investigations were noted on a standard pro forma (appendix bb).

(ii) Follow up studies. The perfusion lung scan was repeated routinely at weekly intervals while the subject remained in hospital. Other appropriate investigations were repeated if any change was noted in pulmonary perfusion on these occasions. When significant alterations did occur, or where the clinical condition of the subject indicated, these studies were performed at more frequent intervals.

To determine the cause of significant abnormalities in pulmonary perfusion when this was not evident from the physical, radiological and other routine ancillary examinations, reliance was placed on repeated perfusion scanning to determine the progress of lesions, inhalation scanning using either 99m Technetium (in the pertechnetate form) or 113m Indium chloride to determine airway patency in the region of perfusion defects (see methods, page 47) or pulmonary angiography to determine the extent of large vessel patency.

Many of the early studies in the series of medical subjects antedated the development of the inhalation scanning methods used later. For this reason inhalation studies were not performed on a number of occasions. Reliance in these instances was placed on repeated perfusion scanning coupled with radiological re-examination, and clinical examination to determine the nature of any perfusion defects found.

SCAN CLASSIFICATION

(i) Perfusion studies. In order to facilitate analysis of the perfusion lung scans and comparison between different subject groups, four basic categories have been employed, into one of which all scans were placed. Because of the underlying differences in pulmonary pathology resulting in the various patterns there is not necessarily a progression in the severity of the abnormality in pulmonary perfusion from category A through to category D. The categories are:

Group A: Even distribution of radiopharmaceutical throughout both lung fields: no abnormalities evident.

Group B includes the following appearances: (i) slightly irregular radiopharmaceutical distribution but no discrete defects; (ii) cardiomegaly or just discernible fissures; (iii) relative ischaemia of the lower zones.

Group C includes (i) single or multiple perfusion defects, smaller than segmental size and/or resulting in a "patchy" scan appearance; (ii) perifissural hypoperfusion (marked).

Group D: Defects of at least segmental size in one or both lungs.

The scans were classified blind by the same observer on two different occasions without knowledge of the patient's identitity or diagnosis. In this way it was felt that bias

was reduced. When more than one type of abnormality was present the scan was placed in the category of the major abnormality.

(ii) Inhalation studies. Inhalation studies were employed to determine the extent of demonstrable ventilation in defects noted in the perfusion study. The ventilation of perfusion defects was classified as 'normal' when entry of inhaled radiopharmaceutical appeared unimpaired. When inhaled radiopharmaceutical was noted at the site of the perfusion defect but in relatively decreased concentration, ventilation was classified as 'fair'. When there was no demonstrable radiopharmaceutical deposition in the area it was classified 'poor'.

RESULTS

(i) Age of subjects. The category into which the initial perfusion study was placed and the age distribution of all subjects is shown in table 4.2a.

TABLE 4.2a

AGE	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+	TOTAL
A	7	12	13	17	26	10	6		91
B	2	1	11	21	32	23	5		95
C	2	1	7	18	36	42	21	1	128
D	2	2	5	11	27	21	18		86
TOTAL	13	16	36	67	121	96	50	1	400

In the decades from 60 years of age studies classified into categories C and D are more common than those classified into categories A and B, the proportion increasing from 52% in the seventh decade to 78% in the ninth. (See table 4.2b in which the results are expressed as percentages.)

TABLE 4.2b

AGE	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
A and B	70	81	67	57	48	34	22	-
C and D	30	19	33	43	52	66	78	(100)

(ii) Sex of subjects. The distribution of perfusion study categories and sex of subjects is shown in table 4.3.

TABLE 4.3

	MALE	FEMALE	TOTAL
A	47	44	91
B	41	54	95
C	71	57	128
D	41	45	86
TOTAL	200	200	400

There is not a significant difference between these two groups.

(iii) Diagnoses. Disorders of all organ systems were represented among the 400 subjects studied in this series. The number of major clinical diagnoses involving each system are listed in table 4.4.

TABLE 4.4

DIAGNOSIS	MALE	FEMALE	TOTAL
Respiratory system	79	56	135
Cardiovascular system	72	45	117
Nervous system	35	47	82
Gastrointestinal system	12	20	32
Genitourinary system	6	5	11
Musculoskeletal system	3	7	10
Lympho-haematological system	19	23	42
Endocrine system	20	30	50
Other	6	11	17

Frequently more than one major clinical problem co-existed in the same subject. When this occurred, rather than ignore one disorder and choose what appeared to be the major diagnosis, all diagnoses were noted.

Pulmonary embolism was noted in 46 subjects (M:F = 19:27). In only 11 subjects was it the only diagnosis made.

The distribution of initial scan types among subjects presenting with disorders of the various organ systems are shown in table 4.5 where the results are expressed as percentages.

TABLE 4.5

	A	B	C	D
Pulmonary (embolism excluded)	3.4	7.9	55.1	33.7
Cardiovascular (myocardial infarct)	39.5	27.6	22.3	10.5
Cardiovascular (other)	13.9	30.6	27.8	27.8
Nervous system	23.2	32.9	31.7	13.4
Gastrointestinal	35.2	19.4	29.0	16.1
Urogenital	54.5	18.2	18.2	9.1
Musculoskeletal	10	-	80	10
Lymphohaematological	26.2	33.3	19.0	24.3
Endocrine	30	26	28	16
Other	23.5	23.5	41.2	11.8

These results have been presented in detail in the following sections.

(iv) Chest Xray. Radiological abnormalities were seen in the chest Xrays of 241 subjects, 127 men (63.5%) and in 114 women (57%). They have been tabulated in table 4.6.

Frequently more than one abnormality was present.

TABLE 4.6

RADIOLOGICAL ABNORMALITY	MALE	FEMALE	TOTAL
Pulmonary congestion	24	35	59
Pleural effusion	15	14	29
Over inflation	44	16	60
Atelectasis	12	8	20
Pleural thickening	20	13	33
Bullae	6	1	7
Generalised pulmonary fibrosis	3	2	5
Apical fibrosis with calcification	2	1	3
Pulmonary infarction	2	2	4
Oligaemia unrelated to C.O.L.D.*	3	2	5
Pneumonic consolidation	19	13	32
Empyema	1	0	1
Hilar lymphadenopathy	3	3	6
Pulmonary neoplasia (primary)	6	1	7
Pulmonary metastases	0	1	1
"Coin lesion"	0	1	1
Pneumothorax	2	0	2
Cardiomegaly	18	28	46
Kyphoscoliosis (severe)	2	3	5
Fractured rib	1	3	4

*C.O.L.D. = chronic obstructive lung disease.

Certain types of radiological abnormality correlated closely with a given perfusion study classification. However there was a very significant incidence of perfusion abnormalities when the chest Xray was normal (Table 4.7).

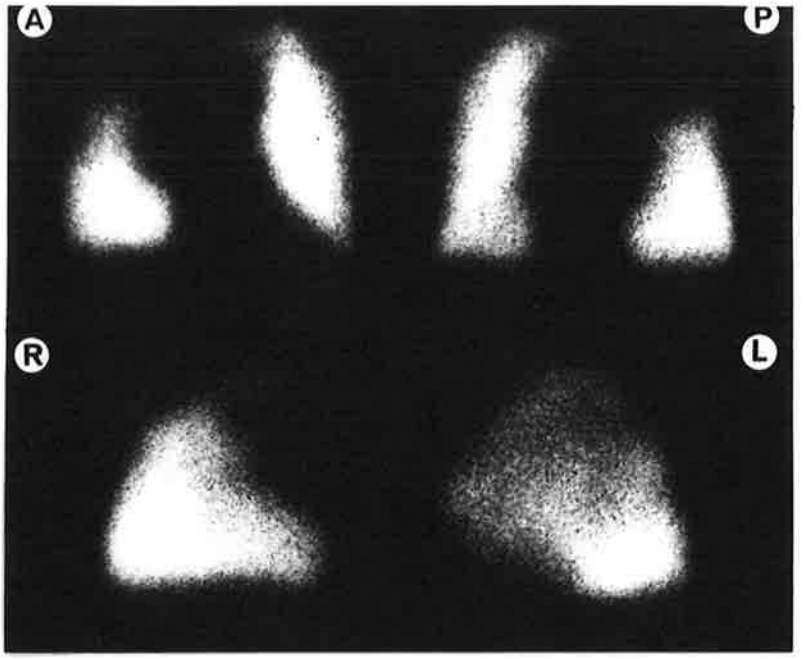
TABLE 4.7

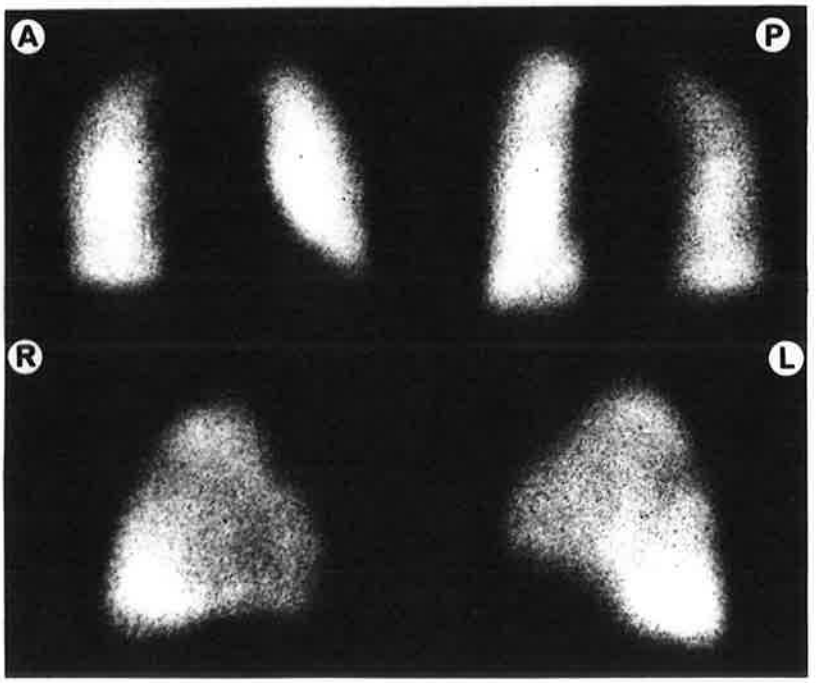
	PERFUSION STUDY CATEGORY				
Chest Xray	A	B	C	D	Total
Normal	66	44	29	20	159
Abnormal	25	51	99	66	241
Congestion	6	14	31	8	59
Over inflation	1	9	34	16	60
Pneumonia	0	2	15	15	32
Neoplasm	0	0	3	5	8

Hyperinflated lungs were associated with a high incidence of category C classification (34/60) i.e. 56.7% as was the radiological finding of pulmonary congestion (31/59) i.e. 52.5%. Chest Xray abnormalities associated with normal or near normal perfusion studies were generally of minor nature.

Hilar lymphadenopathy was accompanied by gross disturbance of pulmonary perfusion in certain instances resulting in large segmental perfusion defects in both lung fields (fig. 4.1).

Fig. 4:1 Gross disturbance of pulmonary blood flow in a subject with mediastinal lymphadenopathy due to lymphoma. Following radiotherapy there was marked improvement of perfusion, particularly to the right upper lobe, within 6 days. (Corresponding chest Xrays on following page.)


A
P
R
L


A
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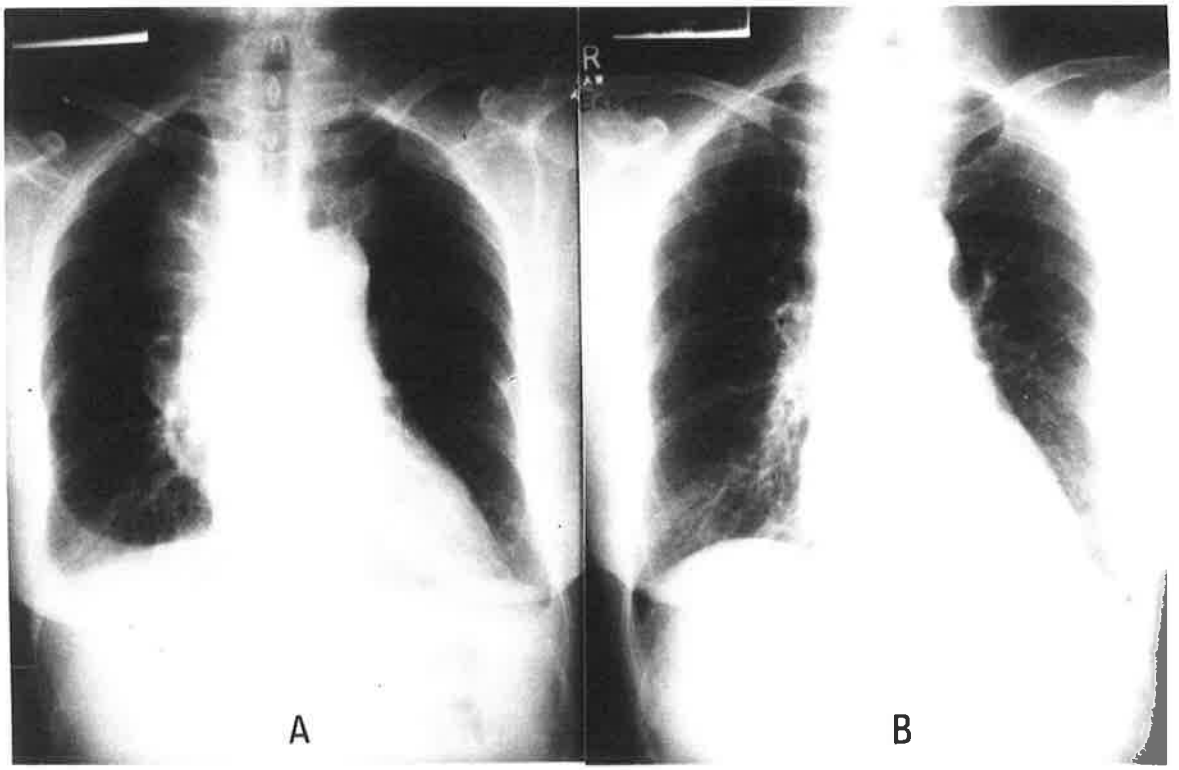
L


A
B

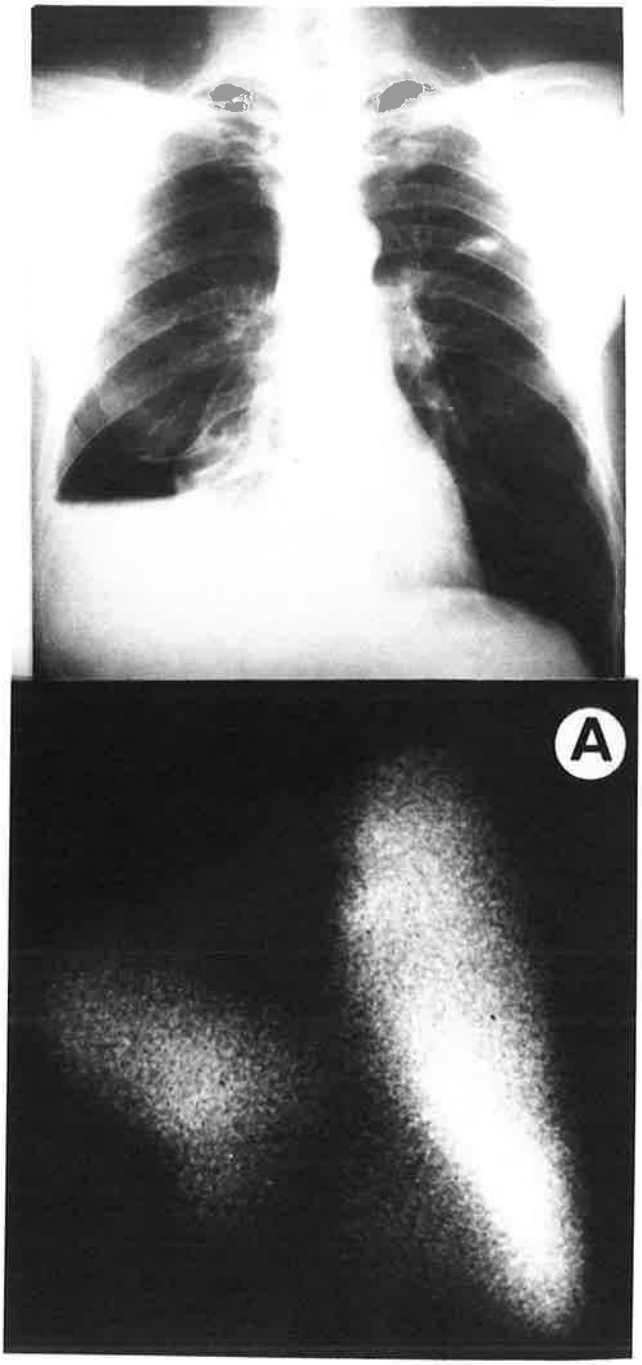
Pneumothorax in one subject was accompanied by an unusual and bizarre picture, the result of a well perfused but collapsed and distorted lung (fig. 4.2).

(v) The respiratory system. The various diagnoses of disorders of the respiratory system are shown in table 4.8 together with the various scan types for each group.

TABLE 4.8

	A	B	C	D	TOTAL
Chronic obstructive respiratory disease	-	-	26	8	34
Asthma	-	2	3	-	5
Pneumonia	1	5	13	15	34
Empyema	-	-	-	1	1
Bronchiectasis	-	-	1	-	1
Pneumothorax	1	-	-	1	2
Pulmonary fibrosis	-	-	2	-	2
"Coin lesion" of the chest	1	-	-	-	1
Carcinoma of the lung (all)	-	-	4	5	9
TOTAL	3	7	49	30	89
Pulmonary embolism	-	-	1	45	46

Fig. 4:2 — P-A chest Xray and anterior perfusion scan in a subject with pneumothorax; perfusion of the collapsed lung results in a bizarre appearance.


A

All subjects who were admitted because of obstructive airways disease had major abnormalities of their lung scans. This group represents those in whom obstructive airways disease was a significant clinical problem. Those with this diagnosis who had large perfusion defects often had bullae or some other pathological process to account for the defect. In three subjects there was coexistent pneumonic consolidation, and in one subject pulmonary embolism was implicated on the basis of changing perfusion scan defects without corresponding radiological change, sudden collapse with chest pain, dyspnoea, haemoptysis and radiologically proven deep vein thrombosis.

The diagnosis of empyema of the lung was arrived at in one subject, an alcoholic asthmatic who collapsed with chest pain and haemoptysis only after a pulmonary angiogram failed to demonstrate occlusion of a pulmonary artery in the region of what was possibly a pulmonary infarct seen on chest Xray.

In obstructive airways disease uncomplicated by other pathology the lung scan generally remained unchanged on subsequent study. In those instances where additional defects were due to other pathology, changes in perfusion in those areas paralleled resolution of the pathological process.

At the time of the initial scan (about 6 days after admission) some subjects admitted to hospital because of

asthma or pneumonia showed only slight abnormalities of their lung scans because of resolution of the pathological process. Larger defects in these subjects generally showed resolution on subsequent study.

Following pneumothorax and reinflation of the lung, perfusion was normal on both occasions this condition was seen.

A "coin lesion" of the chest 2½ cm in diameter situated deep in the lung substance was not seen on scan.

Carcinoma of the lung presented either a picture of patchy perfusion with many nonsegmental defects presumably reflecting pre-existing pathology, or as a large perfusion defect. There was significant abnormality in all the subjects seen in whom this diagnosis was made.

Pulmonary embolism will be discussed in detail under separate heading. This diagnosis was reached in 46 subjects (M:F = 19:27); in 35 subjects thromboembolism was a secondary phenomenon following another medical condition. At the time that the diagnosis was made, segmental defects were noted in 45 subjects while in one subject with a patchy perfusion scan the diagnosis was confirmed by angiography.

(vi) Cardiovascular system disorder. The various disorders of the cardiovascular system and the distribution of perfusion scan types is shown in table 4.9.

TABLE 4.9

	A	B	C	D	TOTAL
Myocardial infarction	30	21	17	8	76
Myocardial ischaemia without infarction	3	4	9	6	22
Hypertensive heart disease	2	7	1	2	12
Valvular heart disease	-	-	4	2	6
Arrhythmia	-	-	1	-	1
TOTAL	35	32	32	18	117

Those with myocardial infarction and those with other cardiovascular disease are discussed separately.

(aa) Myocardial infarction

1. Initial scan normal. The diagnosis of myocardial infarction was confirmed in 76 subjects (M:F = 51:25) by standard 12 lead electrocardiography and serum enzyme studies. In 30/76 subjects (M:F = 21:9) i.e. 39.5%, the initial lung scan was normal.

The radiological findings in these subjects are illustrated in table 4.10.

TABLE 4.10

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	14	7	21
Increased interstitial markings	4	1	5
Marginal cardiomegaly	3	1	4

Some evidence of mild congestive cardiac failure was noted in 8 subjects (26.7%) from this group. Other symptoms and signs, except those specifically related to the time of infarction or associated with deterioration in pulmonary perfusion, were unremarkable.

Deterioration from a normal scan appearance during the period of hospital admission was noted on 7 occasions. The nature of the abnormalities which developed are shown in table 4.11 and the clinical and investigative findings are summarised in table 4.12.

TABLE 4.11

SCAN CHANGE	NO.
Slight irregularity	3
Multiple nonsegmental defects	1
Segmental defects	3

TABLE 4.12

	SEX AGE	SCAN CHANGE	SYMPTOMS	SIGNS	DEFECT CLIN.	VENT. SCAN	C.X.R.	ENZYMES
037432	M 53	A-B	Nil	Nil	Normal	Not done	Normal	
172128	M 52	A-B	Nil	↑ moist sounds	Poor	Not done	Congestion	
084731	M 55	A-B	Nil	Nil	Normal	Not done	Normal	
183862	F 66	A-C	Dyspnoea	Congestive cardiac failure	Poor	Not done	Pulmonary oedema	
182051	F 68	A-D	Nil	Nil	Normal	Normal	Normal	LDH_3↑
166676	M 71	A-D-B	Pleuritic chest pain Haemoptysis	Deep vein thrombosis Cyanosis	Normal	Normal	Congestion	LDH_{1-5}↑
168149	M 68	A-D-B	Pleuritic chest pain Dyspnoea	Congestive cardiac failure Pleural friction rub Deep vein thrombosis	Poor	Not done	Congestion Pleural effusion	LDH_3↑

Two subjects who developed well ventilated defects were considered to have had pulmonary emboli. One subject who developed severe congestive failure with large effusions (UR 168149) retained defects when his congestion and effusions cleared. The presence of a deep vein thrombosis clinically

and pleural friction rub were additional evidence in support of the diagnosis of embolism here also. The remaining changes were associated with increased pulmonary congestion.

2. Initial scan category B. Slight irregularities in perfusion, cardiomegaly or just discernable fissures were seen in 21 subjects (M:F = 14:7) i.e. 27.6%. The radiological findings in these subjects are illustrated in table 4.13.

TABLE 4.13

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	7	3	10
Pleural thickening	2	1	3
Pulmonary congestion	2	4	6
Hyperinflation	2	0	2
Cardiomegaly	2	3	5

Symptoms and signs except those specifically related to the time of infarction or to some degree of congestive cardiac failure, noted in 6 subjects (28.6%), were usually unremarkable in this group. One episode of collapse, chest pain and dyspnoea without E.C.G. change clinically suspected of being due to pulmonary embolism was not associated with scan change.

Deterioration was noted in 2 subjects from this group; one developed multiple nonsegmental defects and the other a segmental defect which subsequently resolved. The clinical and investigative findings are summarised in table 4.14.

TABLE 4.14

	SEX AGE	SCAN CHANGE	SYMPTOMS	SIGNS	DEFECT CLIN.	VENT. SCAN	C.X.R.	ENZYMES
179474	F 55	B-C	Dyspnoea	↓air entry	Poor	not done	Congestion Effusion	-
175100	M 62	B-D-B	Nil*	Nil*	Normal	not done	Normal	LDH_3↑

* = later developed pleuritic pain and deep vein thrombosis

Asymptomatic amputation of the apex of one lung was not associated with symptoms in one subject (UR 175100). A subsequent episode was associated with pleuritic pain and the development of clinically obvious deep vein thrombosis with a palpable venous cord some days after discharge from hospital. The process involved was considered to be pulmonary embolism.

3. *Initial scan category C.* Multiple nonsegmental perfusion defects or prominent interlobar fissures were seen in 17 subjects (M:F = 12:5) i.e. 22.3%. The radiological findings in these subjects are summarised in table 4.15.

TABLE 4.15

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	2	1	3
Overinflation	5	2	7
Bullae	1	0	1
Pleural thickening	3	2	5
Pulmonary congestion	2	4	6
Pleural effusion	1	2	3
Cardiomegaly	2	1	3
Apical fibrosis with calcified lesions	0	1	1

Some degree of pre-existing dyspnoea was complained of by most subjects in this category when questioned closely. There was a history of chronic cough in 7 (M:F = 5:2) which was productive in 4. There was chronic pre-existing chest pain, usually of anginal type in 5 (M:F - 4:1). Other symptoms and signs were related to the episode of infarction or its sequelae.

Change was irregular in this group but resolution of congestion generally resulted in some improvement. No subject whose scan was initially classified into this category subsequently showed normal perfusion.

4. Initial scan category D. Multiple perfusion defects or defects of at least segmental size were demonstrated in the initial scan of 8 subjects (M:F = 3:5) i.e. 10.5%. The clinical and investigative findings in these subjects are summarised in table 4.16.

TABLE 4.16

U.R.	SEX AGE	SCAN CHANGE	SYMPTOMS	SIGNS	DEFECT CLIN.	VENT. SCAN	C.X.R.	ENZYMES	E.C.G.
170939*	F 84	D-B	Crushing chest pain	↓air entry	Poor	Poor	Pulmonary infarct	LDH_{1-5}↑	Pulmonary embolism
152020	F 85	D-D[1]	Dyspnoea	Pleural friction	Good	Not done	Pulmonary congestion	LDH↑ LDH_3↑	LBBB
180486	F 80	D-B	-	↑Moist sounds	Normal	Normal	Normal	LDH↑ LDH_3↑	-
142322	F 76	D-D[1]	Pleuritic chest pain Crushing chest pain	Cyanosis	Good	Not done	Pulmonary congestion Pleural effusion	LDH↑ AAT↑	Atrial fibrillation RBBB
035906	M 52	D-A	Crushing chest pain Dyspnoea	Congestive cardiac failure	Normal	Normal	Pleural thickening	LDH_{1-5}↑	Complete heart block with pacemaker
165528*	M 52	D	Crushing chest pain Dyspnoea	Congestive cardiac failure Deep vein thrombosis	Poor	Not done	Overinflation	LDH↑ AAT↑	Pulmonary embolism
132594	M 75	D	Cough, dyspnoea	↓air entry	Poor	Poor	Overinflation	LDH↑ AAT↑	-
012517	F 75	D	Cough	Congestive cardiac failure	Poor	Poor	Overinflation	LDH↑ AAT↑	-

* : embolism proved by autopsy.

The 6 subjects listed first in table 4.16 were considered to have emboli on the basis of the characteristic perfusion scan findings supported by progress changes, the presence of pulmonary infarction seen radiologically, the demonstration of normal ventilation in the region of the perfusion defect or the postmortem confirmation of the diagnosis. Raised LDH isoenzyme 3 levels were seen in 3 subjects. One subject

(UR 170939) suffered a cerebrovascular accident during the course of her admission.

In the remaining subjects there was clinical evidence of chronic pulmonary disease and decreased ventilation in the region of the perfusion defects.

(bb) Other cardiovascular disease

The diagnosis of cardiovascular disease other than myocardial infarction was made on 41 occasions (M:F = 21:20). The various diagnoses and presenting features are summarised in table 4.17.

TABLE 4.17

DIAGNOSIS AND PRESENTATION	MALE	FEMALE	TOTAL
MYOCARDIAL ISCHAEMIA			
i. Chest pain and congestive cardiac failure	2	4	6
ii. Chest pain	10	2	12
iii. Congestive cardiac failure	2	2	4
HYPERTENSIVE HEART DISEASE			
i. Congestive cardiac failure	4	2	6
ii. For stabilisation of therapy	1	5	6
VALVULAR HEART DISEASE	2	4	6
WOLF-PARKINSON WHITE SYNDROME	0	1	1

The distribution of perfusion scan categories is shown in table 4.18.

TABLE 4.18

DIAGNOSIS	A	B	C	D	TOTAL
Myocardial ischaemia	3	4	9	6	22
Hypertensive heart disease	2	7	1	2	12
Valvular heart disease	-	-	4	2	6
Wolf-Parkinson White syndrome	-	-	1	-	1

1. Initial scan normal. In 5 subjects (M:F = 3:2) i.e. 13.9% the initial scan was normal. The radiological findings in these subjects are summarised in table 4.19.

TABLE 4.19

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	2	1	3
Pleural thickening	-	1	1
Increased interstitial markings	1	-	1

Symptoms related to the presenting complaint in all subjects and there was only slight change in perfusion in any of this group. Electrocardiographic and enzyme studies in each instance were consistent with the underlying pathology.

2. Initial scan category B. In 11 subjects (M:F = 8:3) i.e. 30.6% slightly irregular perfusion was noted. The corresponding radiological findings are summarised in table 4.20.

TABLE 4.20

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	3	1	4
Pulmonary congestion	4	2	6
Pleural effusion	1	1	2
Overinflation	2	0	2

The symptoms and signs noted were generally related only to the presenting condition and electrocardiographic and enzyme studies were unremarkable.

Significant deterioration in perfusion was noted in 3 subjects (M:F = 3:0) whose clinical and investigative features are summarised in table 4.21. Two subjects developed segmental perfusion defects and one subject developed multiple nonsegmental defects.

TABLE 4.21

U.R.	SEX AGE	SCAN CHANGE	SYMPTOMS	SIGNS	DEFECT CLIN.	DEFECT VENT. SCAN	C.X.R.	ENZYMES	E.C.G.
021660	M 62	B-D	Dyspnoea	Congestive cardiac failure	Good	Not done	Pleural effusion	LDH_{1-5} ↑ AAT↑	RBBB
093935	M 52	B-D-B	Crushing chest pain Dyspnoea	Deep vein thrombosis Moist sounds	Normal	Normal	Normal	-	Nonspecific T wave changes
??9694	M 50	B-C	Dyspnoea	Congestive cardiac failure air entry	Poor	Not done	Pulmonary congestion	LDH ↑ AAT↑	Left ventricular hypertrophy

On the basis of the demonstration of normally ventilated perfusion defects in one instance and post mortem confirmation of embolism in another the diagnosis of pulmonary embolism was made in 2 of these subjects. In one of these subjects (UR 021660) low output cardiac failure had been present for some weeks following on earlier myocardial infarction.

3. Initial scan category C. In 15 subjects (M:F = 7:8) i.e. 27.8% patchy perfusion or prominent interlobar fissures were demonstrated. The corresponding radiological findings are summarised in table 4.22.

TABLE 4.22

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	0	5	5
Congestion	4	2	6
Overinflation	4	1	5
Pleural thickening	3	1	4
Effusion	2	2	4

Changes within this group were unspectacular and symptoms and signs related to the presenting condition. Chronic cough was noted in 3 (M:F = 2:1) and some degree of chronic dyspnoea was mentioned by virtually all subjects.

4. Initial scan category D. Ten subjects (M:F = 3:7) i.e. 27.8% had large perfusion defects in their initial scan. In 8 of these (M:F = 1:7) i.e. 88.9% congestive cardiac failure had been or was still a feature of their illness at the time of study. The chest Xray was abnormal in all subjects. These findings have been summarised in table 4.23.

TABLE 4.23

CHEST XRAY	MALE	FEMALE	TOTAL
Cardiomegaly	1	2	3
Congestion	1	4	5
Effusion	0	2	2
Pulmonary opacity	1	0	1
Overinflation	1	0	1
Pulmonary infarct	0	2	2

Symptoms and signs in this group were generally related to the presence of congestive cardiac failure, while one subject without failure who presented with sudden "ischaemic"

chest pain and syncope subsequently developed pleuritic chest pain and clinical evidence of deep venous thrombosis. Ischaemia was diagnosed on the basis of his abnormal E.C.G. and history of angina pectoris.

The principal features of these subjects are summarised in table 4.24.

TABLE 4.24

U.R.	SEX AGE	SCAN CHANGE	BASIC PATHOLOGY	SYMPTOMS	SIGNS	DEFECT VENT. CLIN.	DEFECT VENT. SCAN	C.X.R.	ENZYMES	E.C.G.
177320	M 52	D-B	Valvular disease	Dyspnoea, oedema	Congestive cardiac failure	Good	Not done	Cardiomegally Pulmonary congestion	LDH, AAT, Bil↑	Part RBBB
055861	M 74	D-B	Ischaemia	Pleuritic chest pain Syncope	Deep vein thrombosis	Normal	Normal	Opacity	LDH_{1-5}↑	Atrial fibrillation - normal
180321	M 72	D	Hypertension	Nil	Emphysematous chest	Decreased	Not done	Overinflation	-	Left axis deviation
180486	F 68	D	Hypertension	Pleuritic chest pain Haemoptysis	Congestive cardiac failure ↓air entry Gallop rhythm	Decreased	Not done	Cardiomegally Atelectasis Pulmonary infarct	LDH, AAT↑	LBBB
164113	F 84	D-D[1]	Ischaemia	Dyspnoea, oedema Pleuritic chest pain	Congestive cardiac failure	Good	Normal	Pulmonary congestion	-	Nonspecific T wave changes
102546	F 84	D-B	Ischaemia**	Dyspnoea	Congestive cardiac failure	Good	Not done	Effusion	-	Complete heart block
005375	F 84	D-B	Hypertension	Dyspnoea	Congestive cardiac failure	Decreased	Not done	Pulmonary congestion Pulmonary infarct	LDH_3↑	Nonspecific T wave changes
181434	F 69	D-B	Ischaemia	Crushing chest pain Dyspnoea	Congestive cardiac failure Superficial vein thrombosis - varicose veins	Good	Good	Cardiomegally Pulmonary congestion	LDH, Bil↑ LDH_3↑	Atrial fibrillation
187065	F 65	D-A	Ischaemia	Dyspnoea malaise Crushing chest pain	Congestive cardiac failure	Good	Not done	Pulmonary congestion	LDH, AAT↑ LDH_3↑	Nonspecific T wave changes
168770	F 68	D	Ischaemia	Pleuritic chest pain Dyspnoea	Congestive cardiac failure Deep vein thrombosis	Decreased	Not done	Opacities Effusion	LDH, AAT, Bil↑	Right axis deviation

** digitalis toxicity; *embolism proven at autopsy

One subject (UR 164113) suffered a cerebro-vascular accident during admission. In one subject (UR 181434) admission in congestive cardiac failure followed 3 days after a long plane trip from Europe during which time she was seated

in a soft chair for many hours with little exercise. Oedema of the legs developed during that time. One subject (UR 168776) in this group subsequently died, and extensive thrombosis of peripheral veins and large emboli were found at autopsy.

On the basis of the clinical, radiological and scan findings in these 10 subjects, 9 were considered to have perfusion defects on the basis of pulmonary embolism.

(vii), The nervous system

The recognised major abnormalities of the nervous system are shown in table 4.25 together with the distribution of the various scan types.

TABLE 4.25

DIAGNOSIS	A	B	C	D	TOTAL
Cerebrovascular accident	6	15	15	9	45
Transient ischaemic episode	2	5	2	-	9
Epilepsy	1	2	1	-	4
Encephalitis	1	-	-	-	1
Cerebral neoplasm	-	2	1	-	3
Motor neurone disease	-	-	1	1	2
Parkinson's disease	1	1	-	-	2
Huntington's chorea	-	-	1	-	1
Herpes zoster	1	-	1	-	2
Migraine headache	2	-	-	-	2
Psychiatric disorder	5	2	4	-	11
TOTAL	19	27	26	10	82

Initial scan normal. In 19 of the 82 subjects (M:F = 7:12) i.e. 23.2% the initial lung scan was normal. The corresponding chest Xray was normal in 14 subjects and only minor abnormalities were seen in the remaining chest Xrays. There was little change in perfusion among this group while they remained in hospital. Electrocardiograms and serum enzyme studies were unremarkable.

Initial scan category B. In 27 subjects (M:F = 14:13) i.e. 32.9% the initial scan was classified into category B. The radiological findings are shown in table 4.26.

TABLE 4.26

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	8	9	17
Cardiomegaly	1	2	3
Congestion	1	1	2
Pleural effusion	1	0	1
Overinflation	2	0	2
Pleural thickening	1	1	2
Other opacity	1	0	1

Electrocardiographic and serum enzyme studies were abnormal in 4 subjects (M:F = 3:1) and reflected coexistent myocardial infarction in 3 subjects and myocardial ischaemia

with congestive cardiac failure in 1 subject. Other than in these instances symptoms and signs related to the cardiovascular or respiratory systems were unremarkable. There was little change in perfusion among this group; however the resolution of congestion in 2 subjects and of the opacity (?pneumonic) in one subject was followed by improvement in perfusion.

Initial scan category C. In 26 subjects (M:F 10:16) i.e. 31.7% the initial scan was classified into category C. Radiological findings are summarised in table 4.27.

TABLE 4.27

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	1	8	9
Congestion	1	5	6
Overinflation	8	1	9
Pleural effusion	0	1	1
Pleural thickening	0	1	1
Cardiomegaly	0	2	2

Electrocardiographic and serum enzyme studies were unremarkable except in one subject who had developed co-existent myocardial infarction when electrocardiogram and

serum enzymes reflected the cardiac disorder. Four subjects (M:F = 4:0) had chronic productive cough and some degree of chronic dyspnoea and examination revealed evidence of obstructive airways disease. Moist sounds were heard in the lung bases of most subjects in this group and effort dyspnoea was complained of by 20 subjects (M:F = 9:11) but other symptoms and signs were unremarkable.

Changes in perfusion were marginal when such studies were repeated within this group.

Initial scan category D. The initial scan was classified into category D because of the presence of large perfusion defects in 11 subjects (M:F = 4:7) i.e. 13.4%. The principal clinical features of these subjects are summarised in table 4.28.

TABLE 4.28

U.R.	SEX AGE	SCAN CHANGE	BASIC PATHOLOGY	SYMPTOMS	SIGNS	DEFECT CLIN.	VENT. SCAN	C.X.R.	ENZYMES	E.C.G.
102676	M 55	D-D[1]	Old cerebrovascular accident	Bedridden Pleuritic chest pain	↓air entry	Decreased	Decreased*	Right lower lobe atelactasis	LDH↑ LDH_3↑	Atrial fibrillation
175205	M 61	D-B	Cerebrovascular accident Pulmonary embolism	Pleuritic chest pain Dyspnoea	↓air entry Deep vein thrombosis	Normal	Normal	Atelectasis	-	Atrial fibrillation
163214	M 51	D	Neurosis	Productive cough Dyspnoea	Emphysematous chest ↓air entry	Decreased	Not done	Overinflation Bullae	-	-
180096	M 83	D	Cerebrovascular accident	Dyspnoea	↑Moist sounds	Decreased	Decreased	Pulmonary congestion	-	Nonspecific T wave changes
046060	F 74	D-D[1]	Cerebrovascular accident	Anginal chest pain	-	Normal	Normal	Normal	LDH↑ LDH_3↑	Left ventricular hypertrophy
174087	F 63	D-D[1]	Cerebrovascular accident	Pleuritic chest pain Calf pain	Pleural friction rub	Normal	Not done	Right lower lobe opacity	LDH↑ LDH_3↑	Nonspecific T wave changes
178685	F 70	D-B	Cerebrovascular accident	Aphasic	↑Moist sounds	Normal	Not done	Pulmonary congestion	-	Left axis deviation
177261	F 69	D-D[1]	Cerebrovascular accident	Nil - then collapse	Deep vein thrombosis only-then cyanosis	Normal	Not done	Normal	LDH↑ AAT↑	Q_{III}, ^{a}VF
170939	F 84	D-B	Cerebrovascular accident	Nonspecific chest pain Dyspnoea	↓air entry	Poor	Poor	Pulmonary infarct	LDH_{1-5}↑	Pulmonary embolism
164113	F 84	D-D[1]	Cerebrovascular accident	Dyspnoea, oedema	Congestive cardiac failure	Good	Normal	Pulmonary congestion	-	Nonspecific T wave changes

* ventilation irregular but defect ventilation fair.

One subject (UR 177361) presented with a cerebrovascular accident after a long train trip between Perth and Adelaide lasting 2½ days during most of which time she was seated in a soft chair and had little exercise. Large defects were found on her initial scan, at which time she was relatively asymptomatic. She subsequently developed symptoms of respiratory distress, cyanosis and chest pain associated with the development of further perfusion defects. On the basis of these findings her inferior vena cava was tied but 24 hours postoperatively she suffered a cerebral haemorrhage and died. Permission to perform an autopsy was denied. Another subject (UR 175205) presented initially with pleuritic chest pain and the sudden development of dyspnoea. During the course of his admission he suffered a cerebrovascular accident.

In 9 of the above subjects the available evidence suggested the diagnosis of pulmonary embolism as the cause of the perfusion defects. In one subject (UR 163214) emphysema was the undoubted cause of a large midzone defect and in the other (UR 180096) no progress changes were seen and an accurate diagnosis could not be made.

(viii) Gastrointestinal system disorder

The disorders of the gastrointestinal system and the distribution of the various scan types are shown in table 4.29.

TABLE 4.29

	A	B	C	D	TOTAL
Hiatus hernia	-	1	2	-	3
Ulcer	3	1	3	2	9
Cirrhosis	3	1	2	-	6
Cholestatic jaundice	-	1	-	-	1
Obstructive jaundice	-	-	-	1	1
Gastro-enteritis	1	-	-	-	1
Ulcerative colitis	2	-	1	-	3
Diverticulitis	-	-	-	1	1
Neoplasia	2	2	1	1	6
TOTAL	11	6	9	5	31

Initial scan normal. In 11 subjects (M:F = 4:7) i.e. 35.5% the initial lung scan was normal. The corresponding chest Xrays showed the following features.

TABLE 4.30

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	3	6	9
Cardiomegaly	0	1	1
Pleural effusion	1	0	1

Perfusion was unchanged in those subjects in whom the scan was repeated. Symptoms and signs other than those related to the basic pathology present were unremarkable.

Initial scan category B. In 6 subjects (M:F = 2:4) i.e. 19.4% the initial lung scan was classified into category B. The corresponding chest Xrays showed the following features.

TABLE 4.31

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	1	2	3
Cardiomegaly	0	2	2

Symptoms and signs were generally related only to the basic pathology. However, one subject complained of chronic productive cough and exertional dyspnoea, and moist sounds were heard in 3 subjects on auscultation of the chest. As with those subjects with initially normal studies perfusion remained unchanged in all subjects in this group.

Initial scan category C. In 9 subjects (M:F = 4:5) i.e. 29.0%, the initial lung scan was classified into category C. The corresponding chest Xrays showed the

following features (table 4.32).

TABLE 4.32

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	1	3	4
Cardiomegaly	1	1	2
Overinflation	3	1	4
Pulmonary fibrosis	1	1	2
Pulmonary hypertension	1	0	1

There were symptoms and signs of chronic pulmonary disease in 5 subjects. These are shown in table 4.33.

TABLE 4.33

SYMPTOMS AND SIGNS	MALE	FEMALE	TOTAL
Chronic cough	3	1	4
Productive cough	2	1	3
Dyspnoea	3	2	5
Decreased air entry	3	2	5
Rhonchi	2	1	3

Slight alteration in pulmonary perfusion occurred in one subject from this group but the change was considered of only marginal significance.

Initial scan category D. In 5 subjects (M:F = 3:2) i.e.16.1% the initial lung scan was classified into category D. The corresponding radiological findings are shown in table 4.34.

TABLE 4.34

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	1	1	2
Pulmonary congestion	2	1	3
Pleural thickening	1	0	1
Cardiomegaly	0	1	1
Overinflation	1	1	2

The associated symptoms and signs are shown in table 4.35

TABLE 4.35

U.R.	SEX AGE	SCAN CHANGE	BASIC PATHOLOGY	SYMPTOMS	SIGNS	DEFECT CLIN.	VENT. SCAN	C.X.R.	ENZYMES	E.C.G.
130465	M 71	D-D[1]	Ca Rectum	Pleuritic chest pain Haemoptysis	Pleural friction rub Deep vein thrombosis	Normal	Not done	Pleural thickening	$LDH_3\uparrow$	Right axis deviation Nonspecific T wave changes
147794*	M 65	D	Cirrhosis	Dyspnoea	↓air entry	Decreased	Not done	Overinflation Pulmonary congestion	AAT↑	Atrial fibrillation
001413	M 60	D-A	Diverticulitis	Crushing chest pain Dyspnoea	-	Normal	Normal	Pulmonary congestion	LDH, AAT↑	Nonspecific T wave changes
098306	F 66	D-A	Gastric ulcer	-	-	Normal	Not done	Normal	LDH↑ $LDH_3\uparrow$	Supraventricular extrasystoles
025628	F 62	D	Duodenal ulcer	-	↓air entry	Poor	Not done	Overinflation	-	Nonspecific T wave changes

* = autopsy confirmed pulmonary embolism.

One subject (UR147794) subsequently died and post mortem examination revealed multiple antemortem emboli and a basal pulmonary infarct. The presenting symptoms of collapse with ischaemic type chest pain prompted the initial diagnosis of myocardial infarction in one subject (UR 001412) but scans revealed large segmental well ventilated perfusion defects on the sixth day of admission after clinical evidence of severe diverticulitis was found on day 4. The defects rapidly resolved and the perfusion scan was normal at discharge on day 10. On the basis of the clinical and investigative findings the diagnosis of embolism was made in 2 others, one of whom exhibited no symptoms or signs of the disorder but showed typical scan defects, and the other a bedridden subject with widely disseminated carcinoma (rectal primary) and deep vein thrombosis.

(ix) The urogenital system

The disorders of the urogenital system and the distribution of the various scan types are shown in table 4.36.

TABLE 4.36

	A	B	C	D	TOTAL
Renal failure	-	1	1	-	2
Systemic lupus erythematosus (SLE)	-	1	-	-	1
Renal neoplasia	-	-	-	1	1
Cystitis	4	-	-	-	4
Orchitis	1	-	-	-	1
Klinefelter syndrome	1	-	-	-	1
Bladder neoplasia	-	-	1	-	1
TOTAL	6	2	2	1	11

Eleven subjects (M:F = 5:6) were admitted because of disorders of the urogenital system.

Initial scan normal. The initial scan and corresponding chest Xray were normal in 6 subjects (M:F = 4:2). Follow up scan, obtained in one subject only, remained normal. Symptoms and signs not related to the basic pathology were unremarkable.

Initial scan category B. The initial scan was classified into category B in 2 subjects (M:F = 0:2). Cardiomegaly and congestion were seen in both on chest Xray and in one a small effusion was present. Both subjects complained of exertional

dyspnoea; angina pectoris was present in one subject. No follow up studies were obtained.

Initial scan category C. In 2 subjects (M:F = 1:1) the initial scan was classified into category C. The corresponding chest Xrays showed respectively cardiomegaly and congestion, and pleural effusion. Moist sounds were heard in both subjects on auscultation of the chest, both complained of nonproductive cough and exertional dyspnoea, and orthopnoea was present in one. Follow up study in both subjects revealed no significant change in perfusion.

Initial scan category D. In one subject (M:F = 0:1) the initial and subsequent scans were classified into category D. There was evidence of metastatic involvement of the lung secondary to the renal neoplasia on chest Xray. Apart from exertional dyspnoea and scattered moist sounds in her chest symptoms and signs were minimal. Electrocardiogram and serum biochemistry were normal.

(x) Musculoskeletal system disorders

The disorders of the musculoskeletal system and the distribution of the various scan types are shown in table 4.37.

TABLE 4.37

	A	B	C	D	TOTAL
Polymyositis	-	-	1	-	1
Rheumatoid arthritis	1	-	3	1	5
Osteoporosis	-	-	2	-	2
Pagets disease of bone	-	-	2	-	2
TOTAL	1	-	8	1	10

Ten subjects (M:F = 3:7) had disorders of the musculoskeletal system.

Initial scan normal. In one subject (M:F 0:1) the initial scan and corresponding chest Xray were normal. Symptoms and signs were related only to the basic pathology. No repeat study obtained.

Initial scan category C. In 8 subjects (M:F = 2:6) the initial scan was classified into category C. The chest Xray was abnormal in each instance (table 4.38).

TABLE 4.38

CHEST XRAY	MALE	FEMALE	TOTAL
Cardiomegaly	1	1	2
Pulmonary congestion	1	1	2
Overinflation	1	1	2
Kyphoscoliosis	0	4	4
Consolidation	0	1	1

The following symptoms and signs were noted (table 4.39).

TABLE 4.39

SYMPTOMS	MALE	FEMALE	TOTAL
Exertional dyspnoea	2	3	5
Dyspnoea at rest	1	2	3
Nonproductive cough	0	1	1
Productive cough	1	1	2
SIGNS	**MALE**	**FEMALE**	**TOTAL**
Decreased air entry	2	3	5
Crepitations	2	3	5
Rhonchi	1	0	1
Dullness on percussion	0	1	1

In one subject the electrocardiogram showed complete heart block otherwise electrocardiographic and serum enzyme studies were un remarkable.

Initial scan category D. The initial scan was classified into category D in one subject (M:F = 1:0). There was evidence of basal atelectasis and pleural thickening on chest Xray. This subject had a past history of pulmonary embolism, and had a chronic productive cough. The defect was considered consistent with his previous

pathology. No change was noted on follow up study.

(xi) Lympho-haematological system disorders

The disorders of the lympho-haematological system and the distribution of the various scan types is shown in table 4.40. Disorders of this system were present on 42 occasions (M:F = 19:23).

TABLE 4.40

	A	B	C	D	TOTAL
Anaemia	6	6	5	1	18
Septicaemia	1	2	1	1	5
Myelofibrosis	-	-	1	-	1
Leukaemia	-	1	-	2	3
Lymphoma	2	3	1	5	11
Multiple myeloma	1	1	-	-	2
Haemophilia	1	-	-	-	1
Paroxysmal nocturnal haemoglobinuria	-	1	-	-	1
TOTAL	11	14	8	9	42

The varieties of anaemia present are shown in table 4.41.

TABLE 4.41

ANAEMIA	MALE	FEMALE	TOTAL
Iron deficiency	2	11	13
Secondary to renal failure	-	1	1
Vitamin B_{12} deficiency	1	1	2
Secondary to malignant infiltration	-	3	3
TOTAL	3	16	19

Initial scan normal

In 11 subjects (M:F = 6:5) i.e. 26.2% the initial lung scan was normal. The corresponding chest Xray was normal in 10 subjects (M:F = 5:5) and in one subject there was a small pleural effusion. There was no change in perfusion noted in this group when they were studied subsequently. Symptoms and signs related only to the primary pathology present. Cardiac ischaemia was evident in 2 subjects.

Initial scan category B. In 14 subjects (M:F = 5:9) i.e. 33.3% the initial scan was classified into category B. The corresponding appearances of the plain chest Xray are summarised in table 4.42.

TABLE 4.42

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	2	3	5
Cardiomegaly	1	3	4
Prominent hilum	1	0	1
Atelectasis	1	0	1
Overinflation	0	1	1
Raised hemidiaphragm	0	1	1
Skeletal deposits	0	1	1

Changes in perfusion occurred in 2 subjects - the development of more pronounced irregularity in perfusion was associated with increased pulmonary congestion in both instances. Symptoms and signs reflected the primary pathology. Dyspnoea and ischaemic cardiac pain were present in 3 subjects. Electrocardiographic and enzyme abnormalities of a nonspecific nature were seen in 4 subjects, that is, T wave changes or slight enzyme elevations.

Initial scan category C. The initial lung scan was classified into category C in 8 subjects (M:F = 2:6) i.e. 19.0%. The corresponding radiological findings in these subjects are summarised in table 4.43.

TABLE 4.43

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	0	2	2
Cardiomegaly	0	1	1
Pleural effusion	1	1	2
Pulmonary fibrosis	0	2	2
Consolidation	1	1	2
Kyphosis	0	1	1

The following symptoms and signs were present in these subjects (table 4.44).

TABLE 4.44

SYMPTOMS	MALE	FEMALE	TOTAL
Nonproductive cough	1	2	3
Productive cough	0	2	2
Exertional dyspnoea	2	6	8
Rest dyspnoea	1	2	3
Angina pectoris	2	3	5
SIGNS	**MALE**	**FEMALE**	**TOTAL**
Crepitations	2	6	8
Decreased air entry	1	3	4
Dullness of percussion	1	2	3

Some of these symptoms and signs, for example, anginal chest pain and moist basal sounds, improved when anaemia, if present previously, was corrected. In those subjects in whom repeat studies were obtained perfusion changes were unremarkable.

Initial scan category D. In 9 subjects (M:F = 6:3) i.e. 24.3% the initial scan was classified into category D. The corresponding radiological findings in these subjects have been summarised in table 4.45.

TABLE 4.45

CHEST XRAY	MALE	FEMALE	TOTAL
Normal	2	1	3
Hilar lymphadenopathy	1	2	3
Atelectasis	2	1	3
Other opacity	1	0	1

Severe symptoms of thoracic inlet obstruction due to Hodgkin's disease were present in one subject on admission. At the time of the initial scan multiple segmental defects were present in both lungs, but after radiotherapy these defects rapidly resolved. Dyspnoea and/or cough were present in most subjects in this group and evidence of

decreased air entry or dullness to percussion were found in 6 subjects (M:F = 4:2).

One subject with chronic lymphatic leukaemia presented with chest pain and cough and a peripheral venous thrombosis was demonstrated in one leg. Chest Xray was normal but there was decreased perfusion of the lingula, middle and lower lobes of the right lung; air entry to the area was apparently normal. Electrocardiogram revealed an atrial tachycardia with a 2:1 block; all LDH isoenzyme fractions were elevated, AAT levels were elevated, and sputum and blood cultures grew no pathogens. He died suddenly before follow up. The defect noted was probably embolic in nature (and has been considered as such) though this could not be confirmed as permission to perform an autopsy was denied.

In 4 of the remaining 7 subjects no changes in perfusion were noted on follow up, the defects apparently being the result of pathology other than recent embolism. Electrocardiographic and serum enzyme studies were unremarkable in the remaining subjects.

(xii) Endocrine system disorder

Fifty subjects had evidence of endocrine abnormalities. The vast majority of these (M:F = 18:30) were diabetics, and

the remaining two subjects (M:F = 0:2) had thyroid disorders. Apart from 8 subjects (M:F = 1:7) who presented with uncontrolled diabetes requiring stabilization, the findings in the remaining diabetics have been included in the results relating to abnormalities in other organ systems and this group will not be discussed further. The findings in these subjects are summarised in table 4.46.

TABLE 4.46

	A	B	C	D	TOTAL
Diabetes incidental to other pathology	12	11	11	6	40
Uncontrolled diabetes	3	2	1	2	8
Thyroid disorder	0	0	2	0	2
TOTAL	15	13	14	8	50

Initial scan normal. In 3 subjects (M:F = 0:3) presenting with complications of diabetes mellitus, the initial scan was classified as normal. The corresponding chest Xray was normal in all three. There were no significant symptoms or signs unrelated to the basic pathology and changes in perfusion were not found.

Initial scan category B. In 2 subjects (M:F = 0:2) the initial scan was classified into category B. The

corresponding chest Xray was normal in one and showed cardiomegaly in the other. One subject had angina on exertion and some effort dyspnoea. There were no significant physical signs unrelated to the basic pathology and no changes were noted in perfusion.

Initial scan category C. The initial scan was classified into category C in 3 subjects (M:F = 1:2). The corresponding chest Xrays showed evidence of overinflation (M:F = 1:1) amd pleural thickening (M:F = 0:1). In one subject a retrosternal goitre was present. Two subjects (M:F = 1:1) complained of chronic nonproductive cough, two of effort dyspnoea and one of these suffered dyspnoea at rest. There were moist sounds on auscultation in all subjects. Perfusion remained unchanged in all subjects studied subsequently.

Initial scan category D. The initial scan was classified into category D in 2 subjects (M:F = 0:2), both of whom had been treated in an intensive care area because of diabetic coma with ketoacidosis. The corresponding chest Xrays were normal and the defects seen were well ventilated in both subjects. The features of these two subjects are summarised in table 4.47.

TABLE 4.47

U.R.	SEX AGE	SCAN CHANGE	BASIC PATHOLOGY	SYMPTOMS	SIGNS	DEFECT CLIN.	VENT. SCAN	C.X.R.	ENZYMES	E.C.G.
177878	F 61	D-B	Ketoacidosis	Nil	Nil	Normal	Normal	Normal	-	Normal
040087	F 43	D-A	Ketoacidosis	Syncope	Nil	Normal	Normal	Normal	AAT↑	Nonspecific T wave changes

On the basis of the subsequent perfusion scan changes and the demonstration of normal ventilation, it was concluded that these defects were embolic in nature.

(xiii) Miscellaneous disorders

Seventeen subjects (M:F = 11:6) were admitted because of disorders not readily classified under organ systems. The diagnoses in these subjects are summarised in table 4.48.

TABLE 4.48

	A	B	C	D	TOTAL
Drug overdosage	1	3	5	1	10
Phosgene inhalation	1	-	-	-	1
Electric shock	-	-	1	-	1
Cellulitis	-	-	-	1	1
Erythema nodosum	1	-	-	-	1
Dehydration	1	1	1	-	3
TOTAL	4	4	7	2	17

Initial scan normal. In 4 subjects (M:F = 3:1) the initial scan and the corresponding chest Xray was normal. There were no symptoms or signs other than those relating to the primary pathology. Electrocardiograms and serum enzyme studies were unremarkable. Perfusion was unchanged at follow up in 2 subjects.

Initial scan category B. In 4 subjects (M:F = 4:0) the initial scan was classified into category B. The corresponding chest Xray was normal in 3 subjects and showed increased interstitial markings in one subject. Symptoms, signs and the results of other investigations were unremarkable. Perfusion was unchanged at follow up in 2 subjects.

Initial scan category C. In 7 subjects (M:F = 3:4) the initial scan was classified into category C. The corresponding radiological findings have been summarised in table 4.49.

TABLE 4.49

CHEST XRAY	MALE	FEMALE	TOTAL
Increased interstitial markings	1	2	3
Overinflation	2	2	4
Atelectasis	1	0	1

Two subjects (M:F = 1:1) complained of chronic productive cough and three (M:F = 2:1) of exertional dyspnoea. There was electrocardiographic evidence of ischaemia in 2 subjects and slightly elevated A.A.T. titre in one subject. Perfusion remained unchanged at follow up in three subjects.

Initial scan category D. In two subjects (M:F = 1:1) the initial scan was classified into category D. The corresponding chest Xrays were both abnormal. There was evidence of overinflation in one and fractured rib and atelectasis in the other. In both subjects there was a history of chronic cough, productive in one, and exertional dyspnoea. There was an expiratory wheeze in one subject and areas of decreased air entry were found in both. Serum enzyme studies and electrocardiograms were unremarkable. Both subjects were studied subsequently and no change in perfusion was noted.

(xiv) Pulmonary embolism - primary presentation

From the group of 400 subjects studied, 46 subjects (M:F = 19:27) i.e. 11.5% developed pulmonary embolism. In 11 of these (M:F = 4:7) embolism was the reason for presentation. These subjects presented in a variety of ways: eight subjects presented with a readily recognisable picture of acute embolism, while in the 3 remaining subjects

investigations following admission led to the diagnosis of embolism. In the remaining 35 subjects (M:F = 15:20) embolism was a secondary phenomenon. These latter subjects have been discussed under the headings of disorders of various organ systems and have been summarised in the following section (page 129) together with the subjects initially with embolism.

The clinical and investigative features in the 11 subjects whose reason for presentation was thromboembolism are summarised in table 4.50.

TABLE 4.50

U.R.	SEX AGE	SCAN CHANGE	SYMPTOMS	SIGNS	DEFECT CLIN.	DEFECT VENT. SCAN	C.X.R.	ENZYMES	E.C.G.
027692	F 69	D-D[1]	Pleuritic chest pain	Tender calf	Good	Not done	Basal pleural effusion	LDH, AAT↑ LDH_3↑	-
079863	F 83	D	Pleuritic chest pain	Deep vein thrombosis Hypotension	Good	Good	Bilateral pleural effusion	LDH↑, AAT↑	Atrial fibrillation
183470	F 50	D-B	Pleuritic chest pain Dyspnoea	Right heart failure Hypotension Cyanosis	Good	Good	Normal	LDH↑ LDH_3↑	Q_{III}, aVF, S_I
169053	F 61	D-A	Pleuritic chest pain	Deep vein thrombosis	Good	Good	Pleural effusion	LDH↑ LDH_3↑	Right axis deviation
170544	F 41	D-A	Pleuritic chest pain Dyspnoea	Deep vein thrombosis Hypotension	Good	Not done	Normal	-	Right axis deviation
172562	M 22	D-A	Pleuritic chest pain	-	Poor	Not done	Pulmonary infarct	LDH_3↑	-
013806	M 60	C	Crushing chest pain Dyspnoea	Deep vein thrombosis Hypotension	Poor	Not done	Overinflation Patchy	LDH, AAT↑ LDH_3↑	-
182179	F 75	D	-	-	Good	Good	Normal	-	-
126142	M 74	D-B	Dyspnoea, cough	Deep vein thrombosis Hypotension	Good	Not done	Normal	LDH↑	Nonspecific T wave changes
175205	M 61	D-B	Pleuritic chest pain Dyspnoea	Deep vein thrombosis	Normal	Normal	Atelectasis	-	Atrial fibrillation
155843	F 83	D-B[1]	Pleuritic chest pain (later)	Deep vein thrombosis	Good	Not done	Cardiomegally	-	left axis deviation

The prominent symptoms and signs in this group were pleuritic chest pain (9/11), dyspnoea of sudden onset (3/11), collapse (3/11), deep vein thrombosis (6/11) and increased

pulmonary second heart sound (6/11). The chest Xray was normal in 5/11 and pleural effusions were present in 3/11. In one subject a pulmonary infarct was seen. Serum enzymes were normal in 4/11, total LDH was raised in 6/11, and AAT was raised in 3/11. Isoenzyme 3 (of LDH) was the only fraction elevated and the only enzyme abnormality in 1/11. Except in the subjects with frank pulmonary infarction or patchy radiological opacity defect, ventilation was good. The electrocardiogram was normal in 4/11, right axis deviation was present in 3/11, atrial fibrillation in 2/11, left axis deviation in 1/11 and nonspecific T wave flattening was the only abnormality detected in one subject.

The diagnosis of embolism in the subject (UR 013806) presenting as recurrent pneumonia with patchy opacities on the chest Xray and deep vein thrombosis, was made by pulmonary angiography when characteristic ischaemia and "pruning" of distal vessels was noted.

Two subjects (UR 027692 and 172562) presented with thromboembolic complications of surgery, one 12 days after cholecystectomy and the other 16 days after the removal of a gangrenous appendix.

B. PULMONARY EMBOLISM IN MEDICAL SUBJECTS

(a) Age and Sex Distribution

The distribution of subjects with pulmonary embolism according to their age and sex is shown in table 4.51.

TABLE 4.51

Age	All		Embolism		%	
	M	F	M	F	M	F
20 - 29	5	8	1	-	20	-
30 - 39	9	7	-	-	-	-
40 - 49	17	19	-	3	-	15.8
50 - 59	45	22	5	1	11.1	4.5
60 - 69	58	63	9	10	15.6	15.9
70 - 79	43	55	4	5	9.3	9.1
80 - 89	22	28	-	8	-	28.6
90+	1	0	-	-	-	-

There is not a statistically significant difference in incidence of embolism between the two sexes ($X^2 = 1.2$) and there is no statistically significant difference in incidence on the basis of age alone.

Mode of presentation (fig. 4.3)

(b) Initial diagnosis. Thromboembolism was the reason for presentation to hospital in 11/46 subjects with pulmonary

embolism. In 35/46 subjects embolism was a secondary phenomenon associated with another recognised disorder.

The highest incidence of pulmonary embolism was recognised in association with cardiovascular disorders (table 4.52).

TABLE 4.52

DIAGNOSIS	NUMBER	EMBOLISM	%
All	400	46	11.5
All C.V.S.	117	21	17.9
Myocardial infarct	76	10	13.2
Congestive failure	42	16	38.1
All nervous system	82	6	7.3
C.V.A.	45	6	13.3
All G.I.T.	31	4	12.9
All diabetes	48	7	14.5

Of 117 subjects with disorders of this system 21 (17.9%) developed embolism during admission. The incidence of embolism was particularly high when congestive cardiac failure was noted. Of 42 subjects who developed congestive cardiac failure 16 (38.1%) were noted to develop emboli. Disorders of the nervous system, particularly cerebrovascular accident, were associated with a high incidence of pulmonary embolism. Of 45 subjects with cerebrovascular accidents

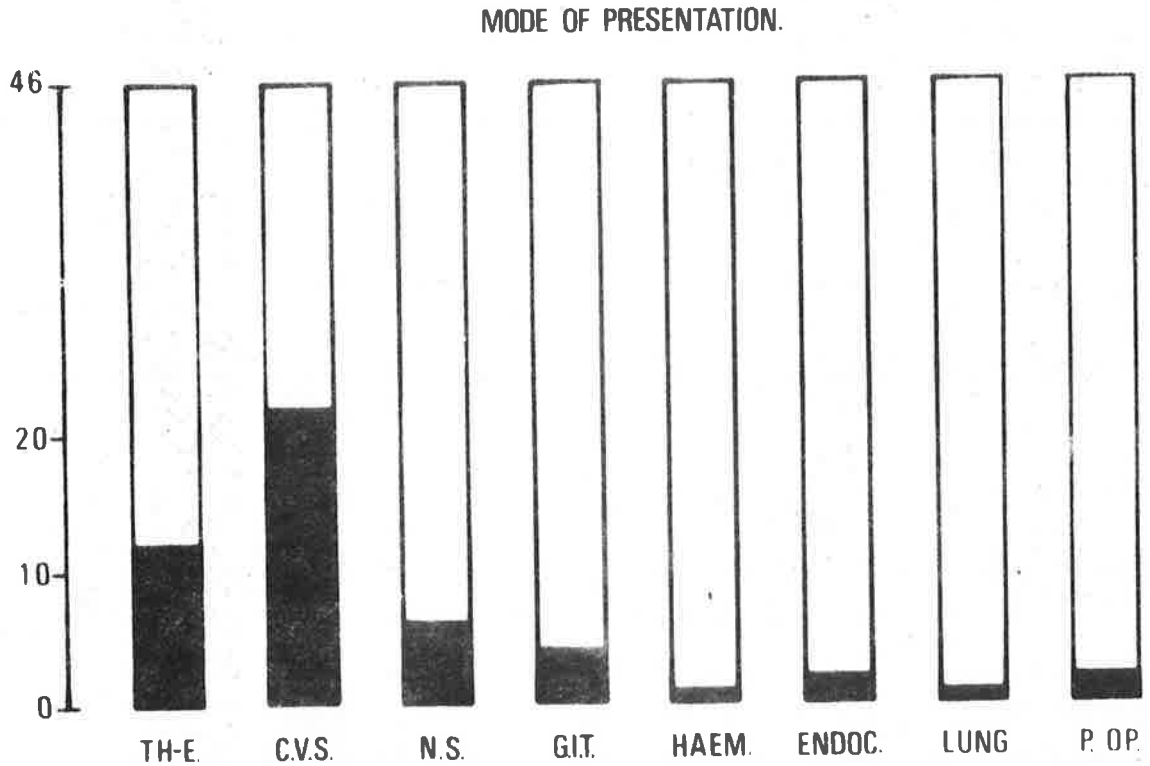


FIG. 4.3. SYSTEM DISORDER

TH-E = THROMBOEMBOLISM PRIMARY DIAGNOSIS
C.V.S. = CARDIOVASCULAR
N.S. = NERVOUS
G.I.T. = GASTROINTESTINAL
HAEM. = LYMPHO-HAEMATOLOGICAL
ENDOC. = ENDOCRINE
LUNG = PULMONARY
P.OP. = POSTOPERATIVE

6 (13.3%) developed emboli.

(c) Clinical diagnosis of embolism. From the total group of 46 subjects, 17 presented a well recognised picture of pulmonary embolism while in 14 the diagnosis was quite unsuspected clinically. In the remaining 15 subjects the diagnosis was considered a possible explanation for the subject's symptom complex prior to definitive diagnosis.

The distribution of clinical types and presenting systems is shown in table 4.53.

TABLE 4.53

System	Obvious	Likely	Unsuspected	Total
Respiratory	-	-	1	1
Cardiovascular	5	10	6	21
Nervous	3	1	2	6
Gastrointestinal	1	1	2	4
Endocrine	-	-	2	2
Lympho-haematological	-	1	-	1
Thromboembolism	8	2	1	11
TOTAL	17	15	14	46

In 12 subjects in whom clinical impression had favoured the diagnosis of embolism no evidence of the disorder was

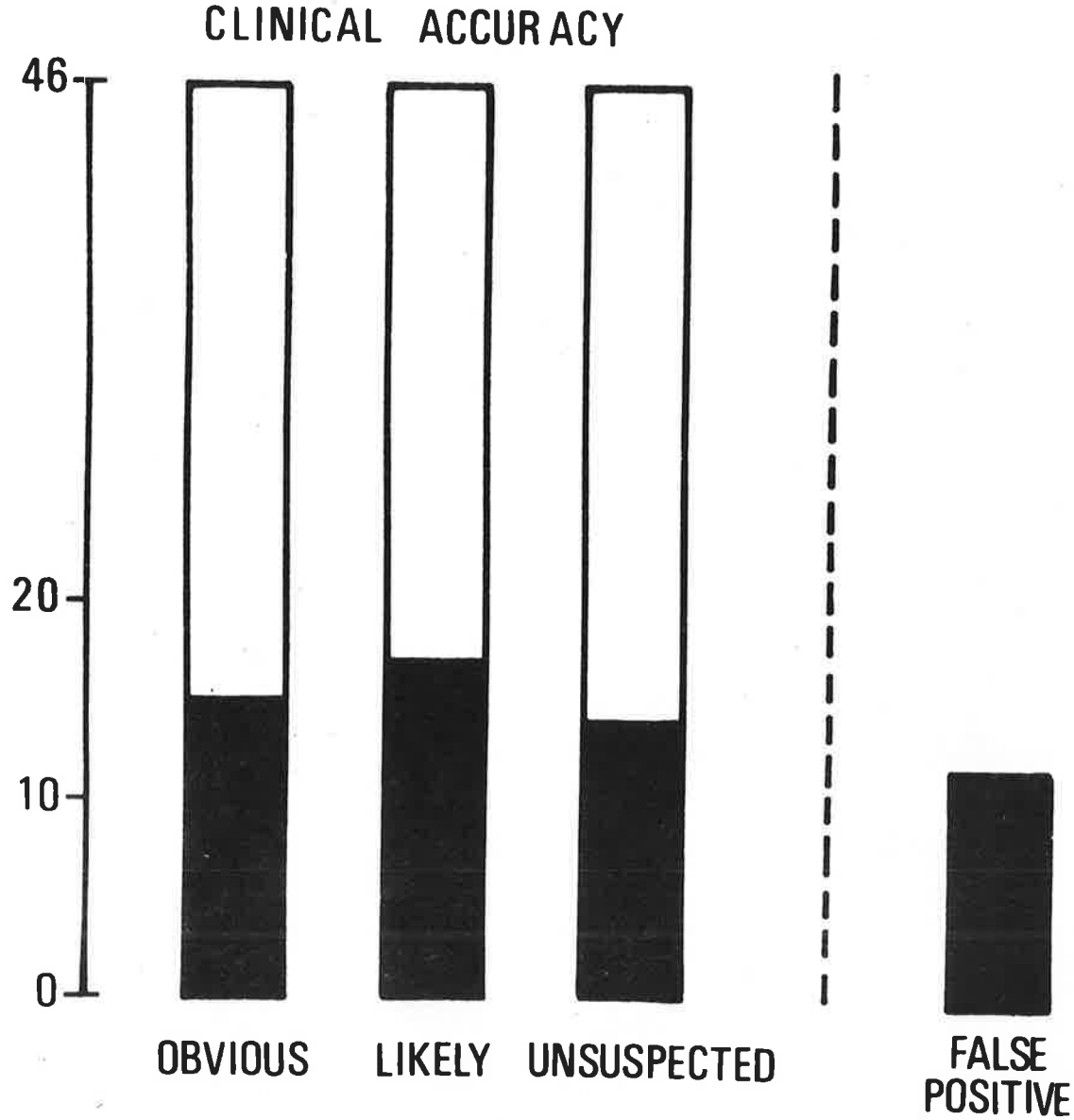

CLINICAL ACCURACY
46
20
10
0
OBVIOUS
LIKELY
UNSUSPECTED
FALSE POSITIVE

FIG. 4.4

found on perfusion scan.(fig. 4.4).

(d) Symptoms. Dyspnoea (28/46) and pleuritic pain (19/46) were the most commonly found symptoms in pulmonary embolism. Cough and haemoptysis were less commonly found (figure 4.5).

Although dyspnoea was the most common finding in embolism it was a relatively common occurrence in the remaining subjects in the study. It was found in 199/354 subjects without embolism (56.2%). Dyspnoea of sudden onset, a less frequent finding in embolism, was found to be more specific being 3.4 times more common in embolism than among all other subjects. Pleuritic chest pain was 12.2 times more common and haemoptysis 3.9 times more common in subjects with embolism, while cough was more common in subjects without embolism (table 4.54).

TABLE 4.54

RELATIVE FREQUENCY OF SYMPTOMS

	EMBOLISM (46)	%	OTHER (354)	%	E/O
Pleuritic chest pain	19	41.3	12	3.4	12.2
Haemoptysis	4	8.7	8	2.3	3.9
Sudden onset dyspnoea	13	28.2	29	8.2	3.4
Rest dyspnoea	21	45.7	109	30.8	1.5
All dyspnoea	28	60.9	199	56.2	1.1
Cough	15	32.6	157	44.4	0.7

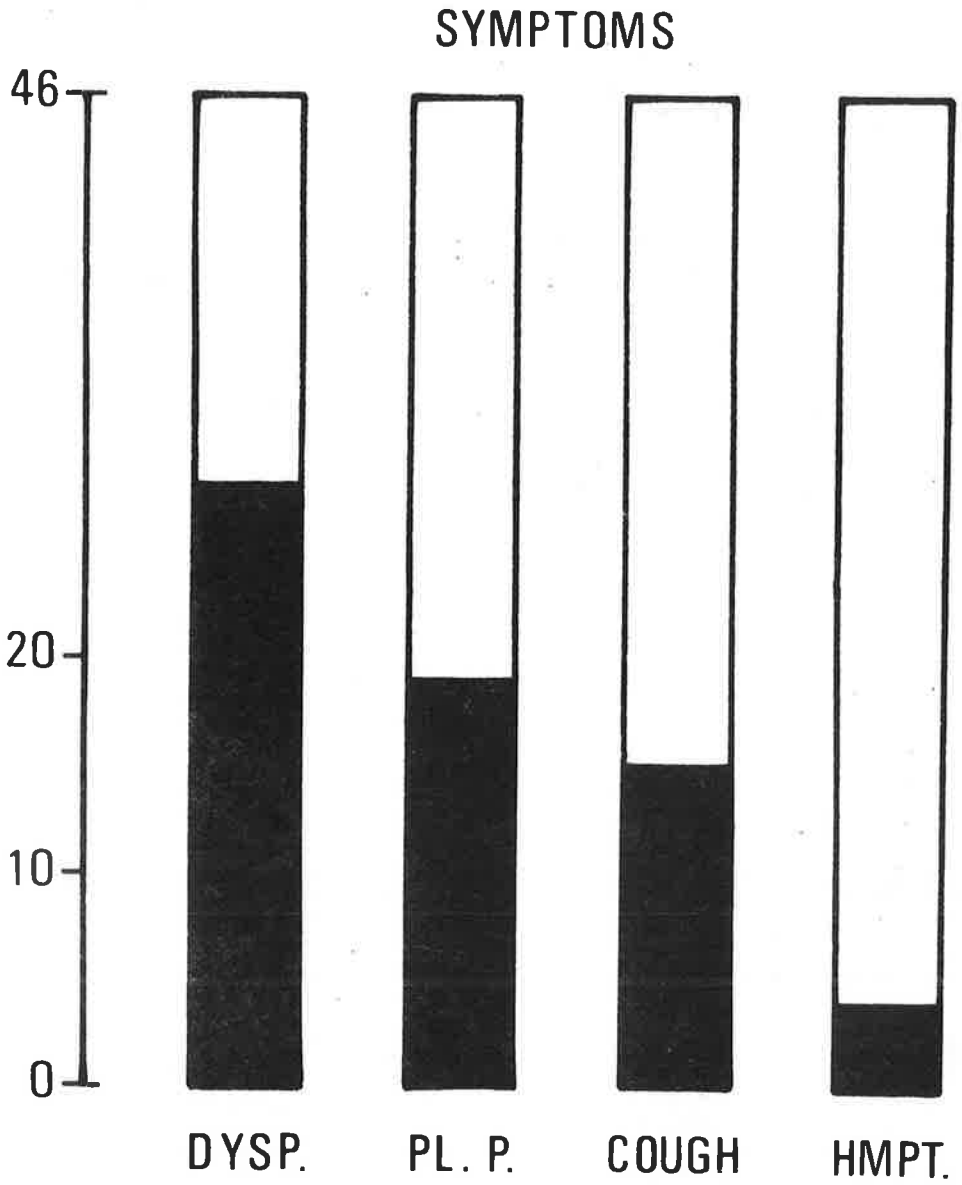


FIG. 4.5

DYSP. = DYSPNOEA

PL.P. = PLEURITIC CHEST PAIN

HMPT. = HAEMOPTYSIS

(e) Signs. Tachypnoea (24/46), increased intensity of the pulmonary second sound (15/46) and deep leg vein thrombosis (15/46) were among the most commonly found physical signs (figure 4.6). A pleural friction rub (6/46), systemic hypotension (5/46) and cyanosis (5/46) were less frequently found. In 16 subjects clinical evidence of congestive cardiac failure was associated with the development of embolism or predated it.

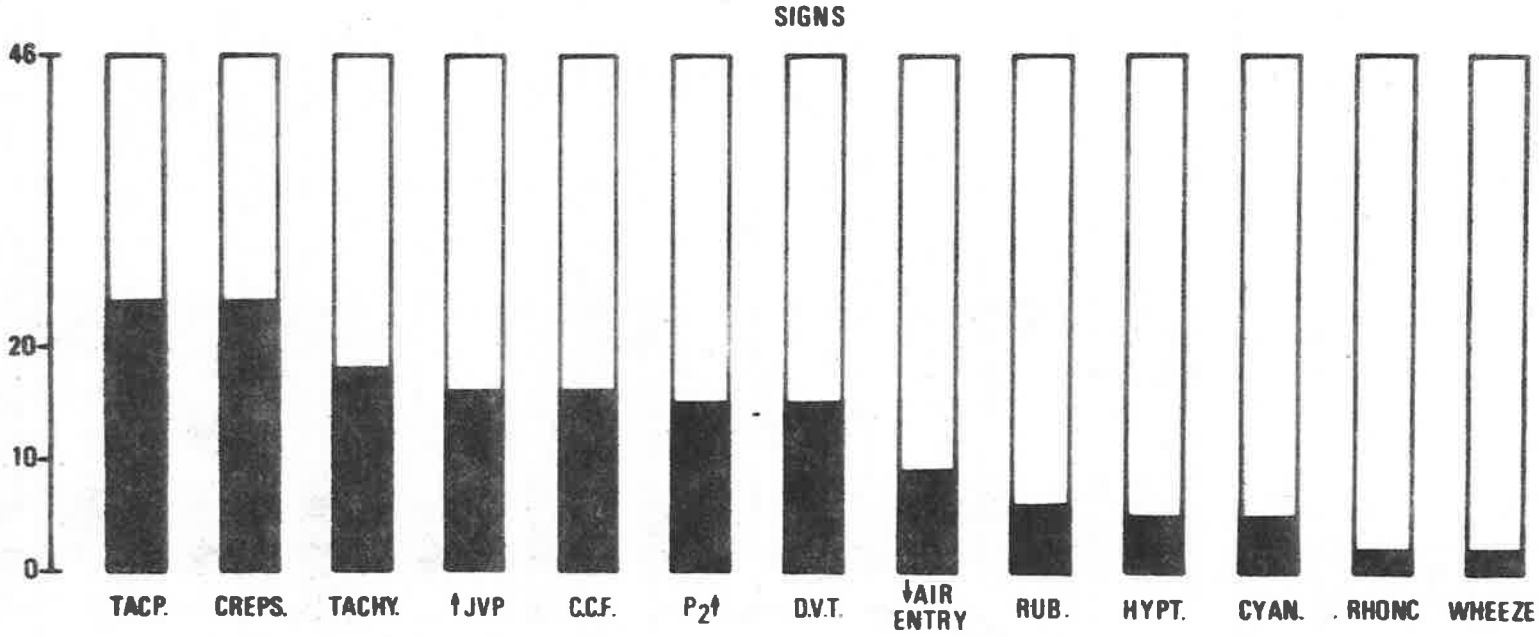
Tachypnoea was 5.3 times more frequently found among subjects with embolism than among the remaining subjects while recent or coexistent congestive cardiac failure was 5.1 times more common in association with embolism. The presence of basal crepitations was no more common in those with embolism than in the other subjects for it was an extremely common finding, being found in just over half of all subjects (table 4.55).

TABLE 4.55

RELATIVE FREQUENCY OF SIGNS

	EMBOLISM (46)	%	OTHER (354)	%	E/O
Increased P_2	15	32.6	21	5.9	5.5
Tachypnoea	24	52.1	35	9.9	5.3
Congestive failure	16	37.4	26	7.3	5.1
Pleural rub	6	13.0	12	3.4	3.8
Tachycardia	18	39.1	43	12.1	3.2
Raised J.V.P.	16	37.4	45	12.7	2.9
Cyanosis	5	10.8	17	4.8	2.3
Basal crepitations	24	52.1	188	53.1	1.0
Reduced air entry	9	19.5	116	32.8	0.6
Rhonchi	2	4.3	29	8.2	0.5
Wheeze	2	4.3	29	8.2	0.5

FIG. 4.6


SIGNS
46
20
10
0
TACP.
CREPS.
TACHY.
↑JVP
C.C.F.
P2↑
D.V.T.
↓AIR ENTRY
RUB.
HYPT.
CYAN.
RHONC
WHEEZE

(f) Radiology. The chest Xray was normal in 16/46 subjects with embolism. The most frequently found abnormalities were pulmonary congestion (12/46) and pleural effusion (9/46) while areas of oligaemia (5/46), atelectasis (5/46), increased prominence of the pulmonary outflow tract (4/46) and frank pulmonary infarction (4/46) were less commonly found. Other miscellaneous abnormalities were seen in 9/46 (figure 4.7).

Pulmonary angiography was performed on 5 occasions when its use was limited to those instances when diagnosis was in strong doubt. In 2 instances a diagnosis of embolism was made.

Pulmonary infarction was found only in association with embolism since its presence was used to confirm the diagnosis. Areas of "atelectasis" and effusion were found significantly more frequently in those with embolism than among the remaining subjects. A normal chest Xray was no more frequent than among all other subjects (table 4.56).

TABLE 4.56

RELATIVE FREQUENCY OF SOME RADIOLOGICAL FINDINGS

	EMBOLISM (46)	%	OTHER (354)	%	E/O
Pulmonary infarct	4	8.7	-	-	-
Atelectasis	7	15.2	13	3.7	4.1
Effusion	10	21.7	19	5.4	4.0
Congestion	12	26.1	47	13.3	2.0
Oligaemia	1	2.2	4	1.1	1.9
Normal	17	36.9	142	40.1	0.9
Cardiomegaly	4	8.7	42	11.9	0.7

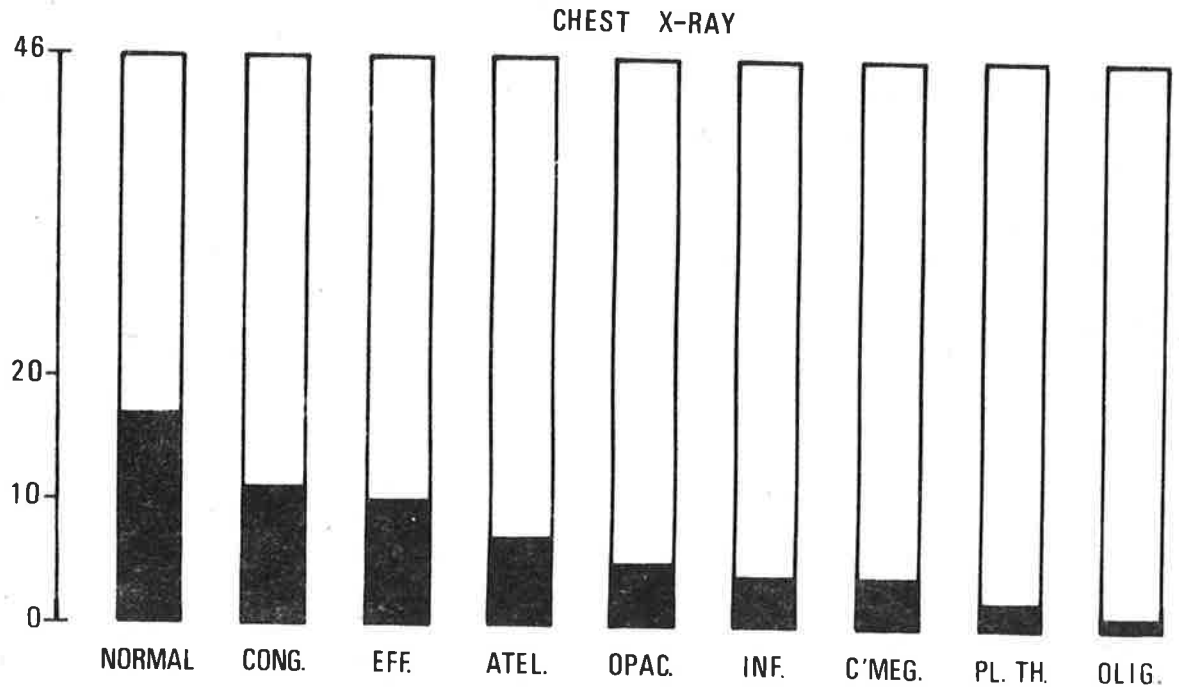


FIG. 4.7

CONG. = CONGESTION
EFF. = EFFUSION
ATEL. = ATELECTASIS
OPAC. = OTHER OPACITY
INF. = INFARCT
C'MEG. = CARDIOMEGALY
PL.TH. = PLEURAL THICKENING
OLIG. = OLIGAEMIA

(g) Electrocardiography. The standard 12 lead electrocardiogram was normal in only 5/46 subjects with embolism. Nonspecific T wave changes were the most commonly found abnormality (15/46) while arrhythmias or evidence of myocardial infarction (10/46) were also frequent findings. Right axis deviation (7.46) and right bundle branch block (4/46) were more commonly seen than left axis deviation (3/46), left bundle branch block (2/46) or complete heart block (1/46). The classical Q3 S1 T3 pattern described by McGinn and White was seen in only 2 subjects (figure 4.8).

It was often not possible to determine whether these changes antedated the appearance of embolism.

Right bundle branch block and right axis deviation were 4.6 and 4.5 times more common in association with embolism than in all other disorders. Arrhythmia (including atrial fibrillation and ventricular ectopic beats) and left bundle branch block were also more common in association with embolism (table 4.57).

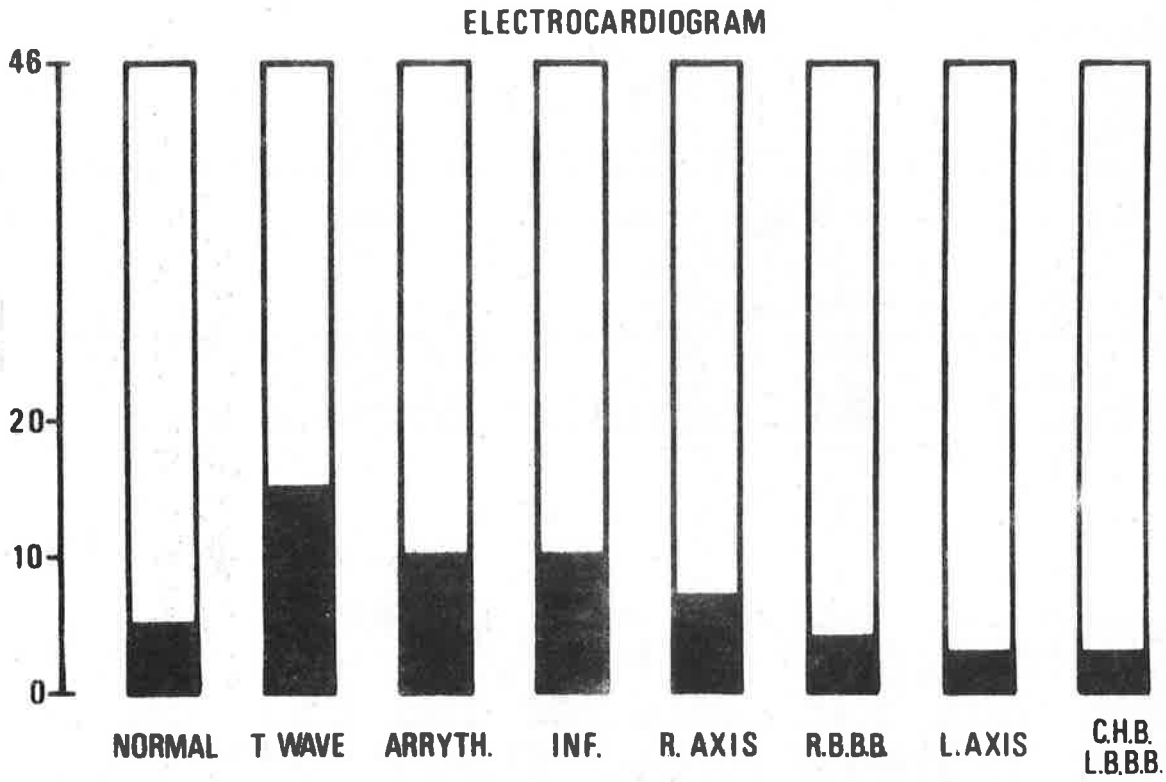

ELECTROCARDIOGRAM
46
20
10
0
NORMAL
T WAVE
ARRYTH.
INF.
R. AXIS
R.B.B.B.
L. AXIS
C.H.B.
L.B.B.B.

FIG. 4.8

TABLE 4.57

RELATIVE FREQUENCY OF E.C.G. FINDINGS

	EMBOLISM (46)	%	OTHER (354)	%	E/O
R.B.B.B.	3	6.5	5	1.4	4.6
Right axis	7	15.2	12	3.4	4.5
Arrhythmia	10	21.7	27	7.6	2.9
L.B.B.B.	2	4.4	7	2.0	2.2
S-T segment changes*	15	32.6	56	15.8	2.1
Other conduction defect	1	2.2	5	1.4	1.5
Myocardial infarct**	10	21.7	74	20.9	1.0
LVH or LAD	3	6.5	39	11.0	0.6

*Not associated with infarction.

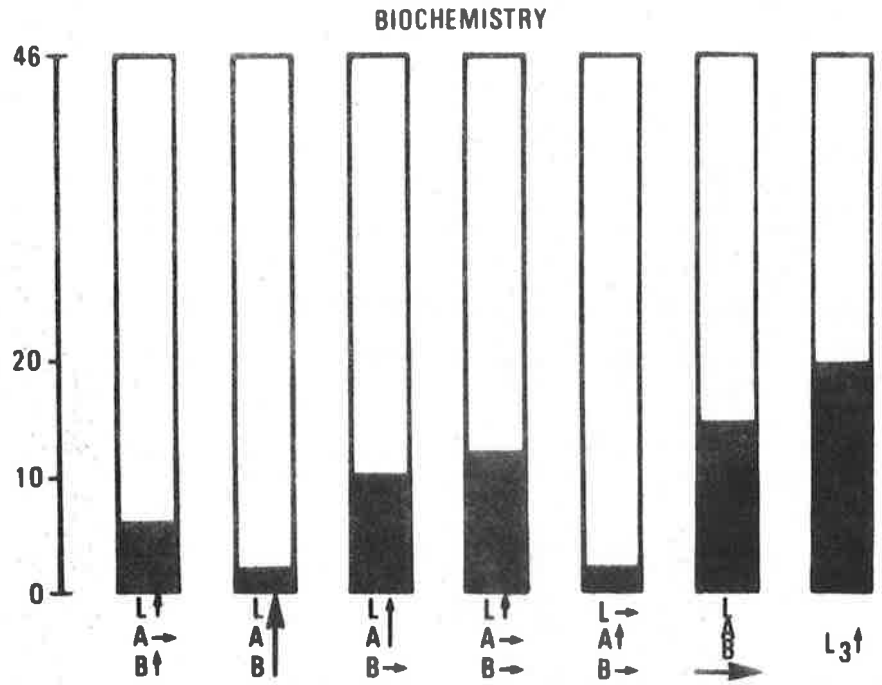
**Old and recent.

(h) Biochemistry. The most frequently seen serum enzyme abnormality was raised total LDH with normal AAT (18/46). Both total LDH and AAT were raised in 12/46 and AAT alone in 2/46). Serum enzymes were normal in 14/46 (figure 4.10).

The most commonly seen abnormal biochemical triad was raised total LDH with normal AAT and bilirubin (figure 4.9).

In 19/46 the titre of LDH isoenzyme 3 was elevated, often in association with elevations of other fractions.

FIG. 4.9



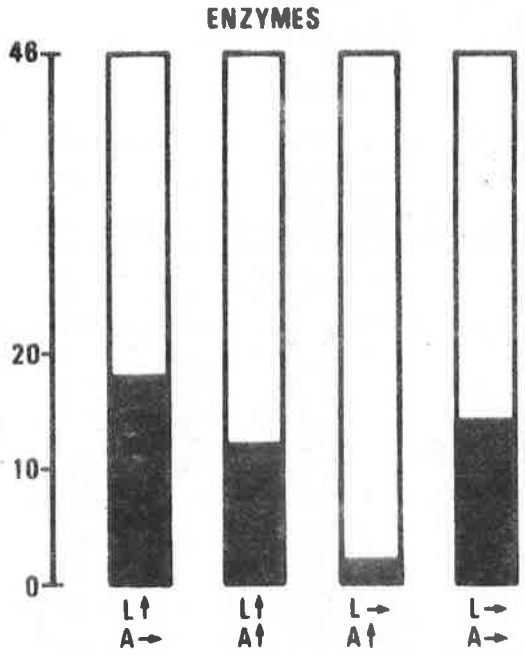


FIG. 4.10

Elevation of only LDH was 3.1 times more common in those with embolism than among those without embolism while other enzyme profiles appeared either as commonly or less commonly in embolism than in all other conditions (table 4.58a).

TABLE 4.58a

RELATIVE FREQUENCY OF ENZYME FINDINGS

	EMBOLISM (46)	%	OTHER (354)	%	E/O
Only LDH raised	18	39.1	45	12.7	3.1
Only AAT raised	2	4.4	16	4.5	1.0
LDH and AAT raised	12	26.1	118	33.3	0.8
LDH and AAT normal	14	30.4	175	49.4	0.6

The results of serum enzyme estimations in pulmonary embolism were compared with those obtained in myocardial infarction (table 4.58b). Raised LDH values alone were found 9.9 times more commonly in embolism than in myocardial infarction while elevation of AAT alone or elevation of both serum enzymes was less common than in myocardial infarction.

TABLE 4.58b

	EMBOLISM (36)	%	EMBOLISM AND MYOCARDIAL INFARCTION (10)	MYOCARDIAL INFARCTION (66)	%	E/M
Only LDH raised	16	44.4	2	3	4.5	9.9
LDH and AAT normal	3	8.3	1	1	1.5	5.5
Only AAT raised	2	5.5	-	4	6.1	0.9
LDH and AAT raised	5	13.9	7	58	87.9	0.2

(i) Outcome. Seven of the subjects in whom the diagnosis of embolism was made died (15.2%). Their diagnoses are summarised in table 4.59.

TABLE 4.59

UR	DIAGNOSIS	MODE OF DEATH	POST MORTEM
170939	Cerebrobascular accident	Cardiac failure	Pulmonary infarcts
168776	Myocardial infarction	Cardiac failure	Massive embolism
177361	Cerebrovascular accident	Cerebral haemorrhage	-
021660	Myocardial ischaemia	Cardiac failure	Pulmonary emboli
147794	Cirrhosis	Liver failure	Pulmonary infarct
165528	Myocardial ischaemia	Cardiac failure	Massive embolism
176466	Lymphatic leukaemia	?Massive embolism	-

In all the above subjects the diagnosis of embolism was made during life.

Thirteen other subjects died after initial study. None was found at autopsy to have evidence of antemortem embolism.

C. PROSPECTIVE STUDY OF SURGICAL SUBJECTS

(a) Subjects

(i) General. The subjects whose studies form the basis of this study were admitted to various general surgical units at the Royal Adelaide Hospital between August 1970 and July 1971. They were 'selected' only in so far as they could be adequately examined prior to surgery and in that their expected surgery was not of a trivial nature. Adequate examination required the availability of a sufficient time period between the times of admission and operation when the patient was not engaged in other examinations, and the availability of both radiopharmaceutical and suitable scanning equipment. No subjects operated on by 'specialised' surgical teams e.g. gynaecology, orthopaedics etc. were included. Circumstances beyond local control such as the failure of radiopharmaceutical production or delivery, and occasional equipment failure also produced breaks in the continuity of the study. These have not been regarded as producing

bias in the series and have been ignored. Suggjects included on operating lists for minor procedures were not included. This category embraced such procedures as check cystoscopy when prostatectomy or other procedure was not contemplated.

(ii) Age. The average age of all subjects was 58.5 years (range 18 - 91) and of those studied serially was 60.2 years (range 18 - 91).

(iii) Sex. A total of 259 subjects were studied pre-operatively and 221 subjects were followed in the postoperative period. The sex distribution is shown in table 4.60.

TABLE 4.60

SUBJECTS STUDIED	MALE	FEMALE	TOTAL
1. Preoperative	123	136	259
2. Postoperative	108	113	221

(iv). Follow up. Three subjects died in the immediate postoperative period, and one subject who suffered a cardiac arrest during the induction of anaesthesia was not studied in the postoperative period. The remaining subjects (34) were not studied later either because of early discharge from hospital (28), or because of temporary instrument failure or administrative error.

For subjects whose operations were on the selected

schedules, inclusion in the study was regarded as routine. In each instance the exact nature of the procedure was explained to them and their consent obtained. Only one subject refused to be included.

(b) Methods

(i) Preoperative studies.

(aa) General. A full clinical history was elicited from each subject and a complete physical examination was performed with particular emphasis being placed on assessment of the cardiovascular and respiratory systems. The following investigations were performed routinely.

1. P-A chest Xray.

2. Biochemical tests - these were performed automatically on an SMA 12 analyser and included determination of the following:

a. Total lactate dehydrogenase (LDH).

b. Total aspartate amino transferase (AAT).

c. Total bilirubin.

3. A standard 12 lead electrocardiograph in all subjects over 55 years of age and in all subjects who demonstrated evidence of cardiovascular or respiratory disease.

4. ABO blood group determination.

5. Routine pulmonary perfusion study using ^{99m}Tc MAFH and a scintillation camera.

In a group of 46 subjects (the last 46 subjects in the series) estimations of lactate dehydrogenase isoenzymes were

obtained preoperatively and at the times of the postoperative studies. The estimation was made by measuring total LDH activity following heat denaturation of LDH fractions by immersion in a water bath for 20 mins at 55°C and then at 65°C.

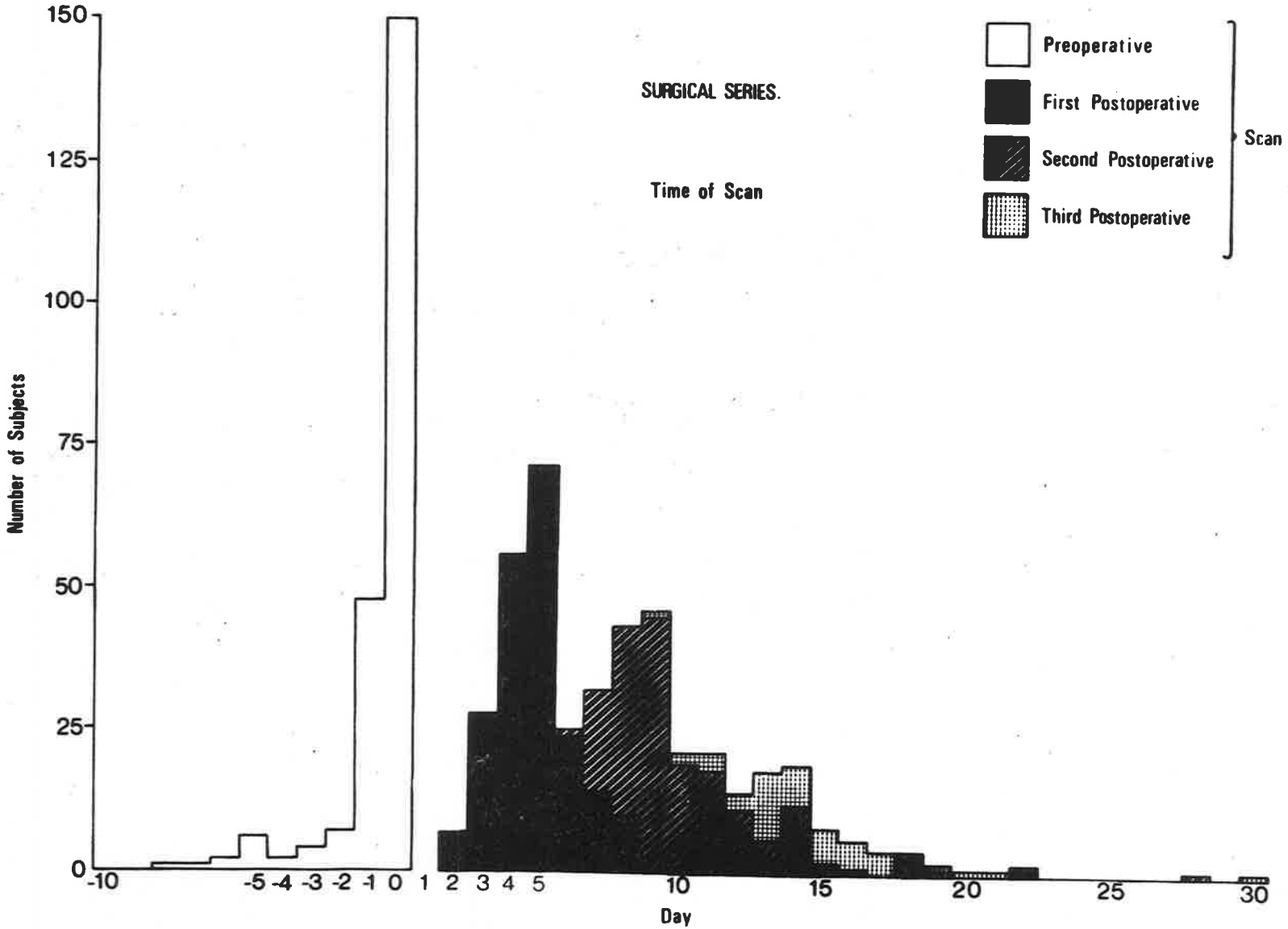
The results of all of these investigations were noted on a standard pro forma (appendix bb).

(bb) Time of study. An effort was made to perform the preoperative studies in the 24 hours prior to surgery and in 90% (198/221) preoperative studies were performed during that period. In the remaining 10% surgery was postponed until a later date for a variety of reasons; the maximum period for such delay was 8 days (figure 4.11).

(ii) Nature of surgery. The nature of the surgery undertaken, its duration and the pathological process involved were tabulated, this information being obtained from the surgeons' and anaesthetists' records (tables 4.71 and 4.72 later).

(iii) Postoperative studies. In the postoperative period perfusion studies were repeated as soon as the clinical state of the subjects permitted from postoperative day 3, and then at 5 day intervals thereafter while they remained in hospital. (The times of postoperative studies are shown in figure 4.11.)

FIG. 4.11


SURGICAL SERIES.
Time of Scan
Preoperative
First Postoperative
Second Postoperative
Third Postoperative
Scan
Number of Subjects
150
125
100
75
50
25
0
-10
-5 -4 -3 -2 -1 0 1 2 3 4 5
10
15
20
25
30
Day

When significant new perfusion defects i.e. development of one or more large defects of at least segmental size, or the development of multiple smaller defects, were found in the postoperative studies their nature was further investigated in the following manner:

1. the subject was questioned closely regarding symptoms referable to the pulmonary system,

2. evidence of thromboembolism or other pulmonary pathology was sought on physical examination,

3. an inhalation study was performed using indium chloride,

4. the chest Xray was repeated,

5. estimations of total LDH, AAT and bilirubin were obtained,

6. LDH isoenzyme activities were estimated, and

7. the perfusion study was repeated at intervals until resolution or no further change was noted.

In 4 subjects inhalation studies were not performed. Pulmonary angiography was performed in 3 of these subjects.

Subjects living in country areas remote from the hospital often could not be followed until resolution of defects was noted.

When a significant abnormality was detected its presence was reported to the clinician responsible for the care of that patient. He made any decision regarding management or

the performance of ancillary investigations (including angiography).

(c) Scan classification

(i) Analysis of perfusion studies. For analysis of the results of the series the scan appearances were placed in four categories. This was done by the one observer (D.J.C.) on two separate occasions without knowledge of each patient's identity. The categories were the same as those employed for analysis of the "medical" subjects. They were:

Group A: Even distribution of radiopharmaceutical throughout both lung fields - no abnormalities evident.

Group B: (a) Slightly irregular radiopharmaceutical distribution but no discrete defects.

(b) Cardiomegaly or just discernable fissures.

(c) Relative ischaemia of the lower zones.

Group C: (a) Single or multiple perfusion defects, smaller than segmental size and/or resulting in a "patchy" scan appearance.

(b) Marked perifissural hypoperfusion.

Group D: Defects of at least segmental size in one or both lungs.

When more than one abnormality was present the scan was placed in the category of the major abnormality.

(ii) Analysis of inhalation studies. Depending on the

nature of radiopharmaceutical deposition in the region of previously demonstrated perfusion defects, inhalation studies were classified as 'normal' or showing 'fair' or poor regional ventilation.

(d) Results

(i) Preoperative studies

(aa) Preexisting disease in initial 259 subjects.

Examination prior to surgery and subsequent investigations revealed the following incidence of preexisting disease in the subjects studied. These statistics have been tabulated under the headings of cardiac disease (table 4.61), respiratory disease (table 4.62), diabetes (table 4.63) and neoplastic disease (table 4.64).

TABLE 4.61

CARDIAC DISEASE

1.	Ischaemia	
	(a) angina pectoris	30
	(b) E.C.G.	
	(i) ischaemia	45
	(ii) previous infarction	12
2.	Hypertension	
	(a) Diastolic b.p. over 90 mm Hg	40
	(b) Regular antihypertensive agents	19
	(c) E.C.G. - left ventricular enlargement/strain	15
3.	Abnormalities in rate or rhythm	
	(a) Sinus bradycardia	1
	(b) Controlled atrial fibrillation	5
	(c) Ventricular ectopic beats	3
4.	Conduction abnormalities	
	(a) RBBB	1
	(b) LBBB	2
5.	Valvular heart disease	
	(a) Mitral	2
	(b) Aortic	2
6.	Cardiac decompensation	
	(a) Recent congestive failure	6
	(b) Radiological cardiomegaly	25
	(c) Digitalised	25
	(d) Long term diuretics	34

TABLE 4.62

PULMONARY DISEASE

1. Symptoms		
(a) Dyspnoea		
(i)	at rest	2
(ii)	on mild exertion	38
(iii)	on extreme exertion only	31
(iv)	bronchial asthma	3
(b) Cough		
(i)	chronic	56
(ii)	usually productive	19
(iii)	occasionally productive	8
(iv)	chronic bronchitis*	22
(v)	haemoptysis	0
2. Signs		
(a)	lung crepitations	70
(b)	decreased air entry	32
(c)	overinflation, decreased air entry and expansion	6
(d)	kyphosis or scoliosis	6
(e)	finger clubbing	3
3. Chest Xray		
(a)	increased interstitial markings	20
(b)	hyperinflation	21
(c)	pleural thickening	12
(d)	atelectasis	8
(e)	bullae	6
(f)	apical fibrosis with calcified lesions	2
(g)	pulmonary metastases	2
(h)	pleural effusion	1
(i)	other	6

*Cough productive of sputum for at least 3 months on at least 2 successive years.

TABLE 4.63

DIABETES

1. Insulin requiring	0
2. Non insulin requiring	14
i. oral agents	8
ii. diet alone	6

TABLE 4.64

NEOPLASTIC DISEASE

Site of primary	
Colon	6
Rectum	6
Pancreas	4
Kidney	3
Prostate	3
Gall bladder	2
Bile duct	1
Breast	2
Skin	2
Parotid	1
Oesophagus	1
Tongue	1
Stomach	1
Lung	1
Adenocarcinoma unknown site	1
Hodgkins or other lymphoma	3
Melanoma	4
Invasive carcinoid	1
Metastases present	10

(bb) Age. The distribution of diagnostic groups A to D (page 144) with age in the 259 subjects studied preoperatively is shown in figure 4.12 and table 4.65.

TABLE 4.65

Scan	0-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+	Total
A	5	11	10	16	13	22	8	-	-	85
B	-	1	3	8	2	21	21	3	-	59
C	-	1	2	7	12	23	35	10	1	91
D	-	-	1	2	2	10	6	3	-	24
TOTAL	5	13	16	33	29	76	70	16	1	259

(cc) Smokers. Smokers were those subjects who had smoked until within 12 months of the date of surgery. Those who had ceased smoking prior to this time were classified as non-smokers.

The distribution of diagnostic groups A to D amongst the smoking and nonsmoking groups is shown in table 4.66.

TABLE 4.66

	A	B	C	D	TOTAL
Smokers	23	24	46	7	100
Nonsmokers	63	35	44	17	159

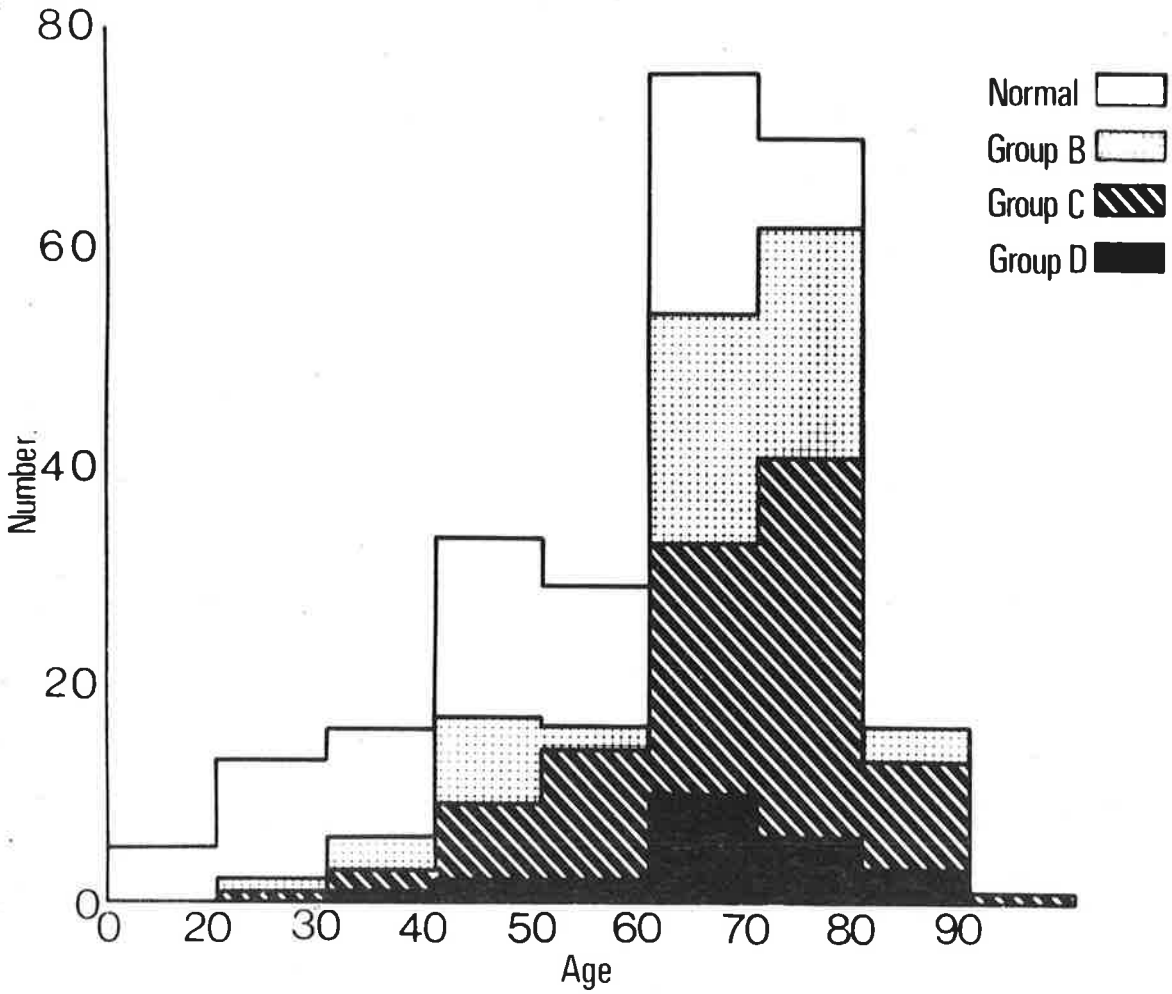

259 Preoperative Subjects
80
60
40
20
0
Number
0
20
30
40
50
60
70
80
90
Age
Normal
Group B
Group C
Group D

FIG. 4.12

There is a significant difference between these groups (rank contingency $x^* = 4.4$, $p < 0.01$). Age and smoking history are shown in table 4.67. The difference in incidence of abnormalities cannot be accounted for on the basis of age alone.

TABLE 4.67

	0-19	20-	30-	40-	50-	60-	70-	80-	90-
Nonsmokers	4	9	9	21	10	46	47	12	1
Smokers	1	4	7	12	19	31	23	3	0

(dd) Dyspnoea. The distribution of scan abnormalities amongst those who complained of exertional dyspnoea is not significantly different from those without dyspnoea (rank contingency $x^* = 1.56$, $p > 0.05$).

TABLE 4.68

	A	B	C	D	TOTAL
Dyspnoea	15	19	32	6	72
No dyspnoea	70	40	59	18	187

(ee) Cough. The distribution of scan categories among those admitting to chronic cough compared to those with no cough is shown in table 4.69. There is a significant difference

between the two groups ($x^* = 3.14$, $p \leq 0.01$).

TABLE 4.69

	A	B	C	D	TOTAL
Cough	7	11	31	7	56
No cough	78	48	60	17	203

(ff) Other symptoms. Other symptoms did not correlate with specific scan findings.

(gg) Perfusion study:chest Xray correlation. Only 57% of subjects whose preoperative perfusion studies were classified into categories C or D had abnormalities of their chest Xray. However when the chest Xray was abnormal there was a high incidence (92%) of scan classification into group C or D (table 4.70).

TABLE 4.70

	SCAN CLASSIFICATION	
	A or B	C or D
Normal chest Xray	138	49
Abnormal chest Xray	6	66

(hh) Neoplasia. Two subjects of those with known neoplasia (46) had pulmonary metastases and one other had a primary pulmonary neoplasm. Areas of decreased perfusion were visualised in the region of the radiological opacity in these subjects.

One subject with Hodgkins disease who had previously undergone mediastinal radiotherapy had an unusual scan appearance with medial decrease in perfusion of both lungs and patchy perfusion elsewhere. This was presumably the result of radiation pneumonitis.

(ii) Other. Scan appearances apart from the above were generally consistent with the subjects' age and known pulmonary disease.

(ii) The surgery

(aa) Nature and duration of surgery. For the 221 subjects who were followed in the postoperative period, the duration of anaesthesia varied from a few minutes to over six hours (table 4.71).

TABLE 4.71

Duration of anaesthesia (min.)	Number
0 - 30	15
31 - 60	55
61 - 120	101
121 - 180	33
181 - 240	14
240+	3

Cholecystectomy and/or exploration of the bile ducts was the most commonly performed procedure. The relative frequency of various operations is shown in table 4.72.

TABLE 4.72

Gastrointestinal surgery		Urological surgery	
Cholecystectomy	66	Prostatectomy	40
Exploration common bile duct	2	Cystoscopy and fulguration	5
Bowel resection	17	and removal calculus	1
Exploratory laparotomy	6	Nephrectomy	3
Appendicectomy	6	Nephrolithotomy	2
Vagotomy and pyloroplasty	5		
Repair rectal prolapse	2		
Sigmoidoscopy and fulguration	2	Minor orthopaedic surgery	5
Hernia repair	18		
		Thyroid surgery	6
Vascular surgery			
		Miscellaneous	23
Bypass graft	9		
Varicose vein stripping	3	TOTAL	221

(bb) Analysis of deaths. There were three postoperative deaths during the period immediately following operation before repeat lung scan was performed. Their course has been summarised in table 4.73.

TABLE 4.73

	Sex	Age	Surgery	Duration	Cause of death	Date
1.	M	58	Hemicolectomy	105 min.	Peritonitis*	Day 7
2.	M	74	Prostatectomy	75 min.	Pulmonary oedema*	Day 5
3.	F	37	Adrenalectomy	45 min.	Multiple metastases*	Day 2

*Confirmed by autopsy.

(iii) Postoperative scan changes

(aa) General. Overall there was irregular change in perfusion postoperatively. In 121 subjects (54.8%, M:F = 53:68) there was no significant change in perfusion pattern. In 76 subjects (34.3%, M:F = 42:34) new defects developed or previously noted defects became more apparent. In 24 subjects (11%, M:F 13:11) there was apparent improvement in perfusion in the postoperative period (figure 4.13).

(bb) Age, sex. There was no correlation between age of subject and the likelihood of showing a change in the post-operative scan (figure 4.13) and there was no significant sex difference (tables 4.74 and 4.75).

TABLE 4.74

SCAN CHANGE	MALE	FEMALE
Static	53	68
Improved	13	11
Deteriorated	42	34
TOTAL	108	113

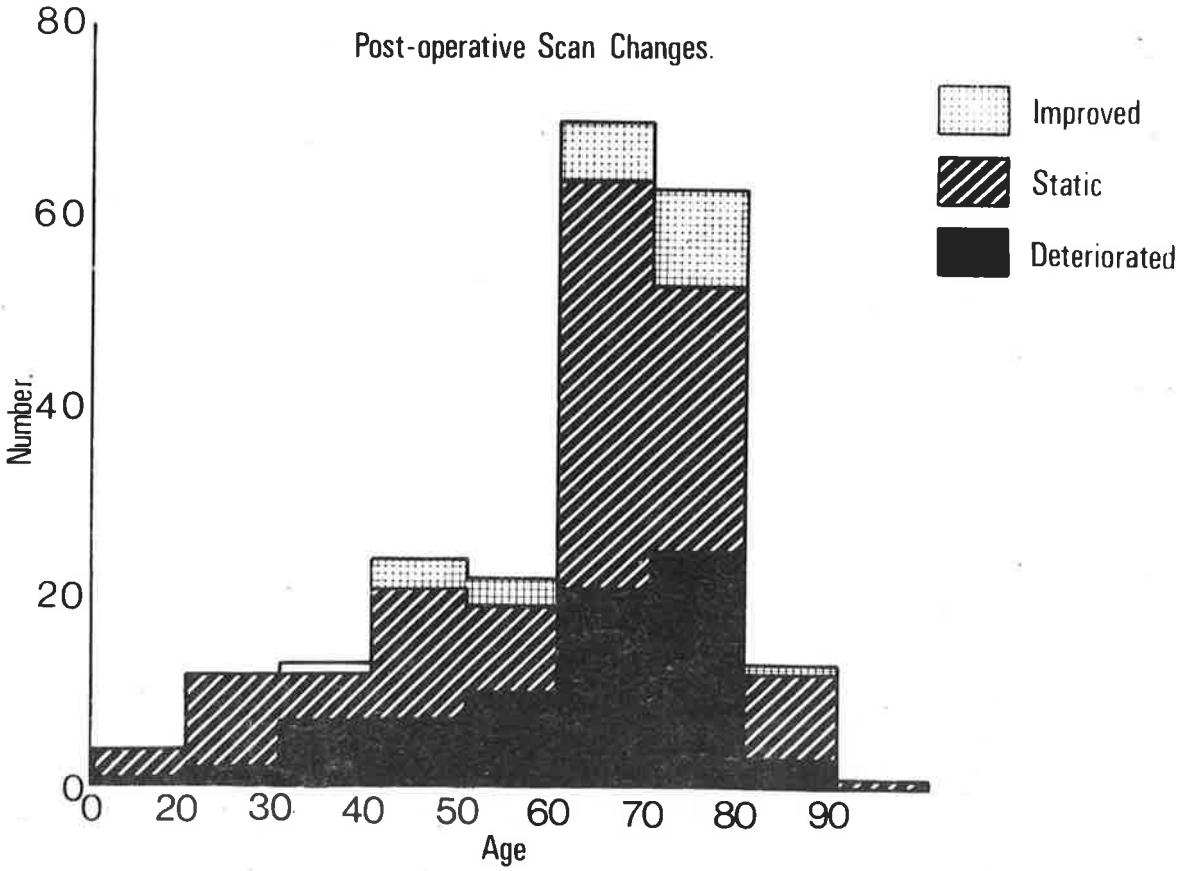

Post-operative Scan Changes.
Improved
Static
Deteriorated
Number.
80
60
40
20
0
0
20
30
40
50
60
70
80
90
Age

FIG. 4.13

TABLE 4.75

SCAN CHANGE	0-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
Static	3	10	5	14	9	42	28	9	1
Improved	-	-	1	3	3	6	10	1	-
Deteriorated	1	2	7	7	10	21	25	3	-

(cc) Smokers. There were 85 smokers and 136 non smokers in the follow up group. Deterioration was noted in significantly more smokers than non smokers - 38/85 smokers (44.7%) and 38/136 non smokers (27.9%) ($x^2 = 5.84$, $p < 0.01$).

(dd) Specific changes. Of the 76 subjects whose lung scan appearances showed some deterioration, 29 subjects developed new perfusion defects of at least segmental size (group D). Normal ventilation was demonstrated by inhalation scan in 15 and intra-arterial filling defects were noted on pulmonary angiogram in another 3. In one additional subject with a large perfusion defect the new defect was clinically well ventilated but no inhalation study was performed. The remaining 10 subjects had defects in ventilation corresponding in position to the areas of decreased perfusion demonstrable on inhalation scan.

(iv) Interpretation of scan findings

The demonstration of large perfusion defects on lung scan together with corresponding inhalation scan defects was considered evidence of bronchial tree obstruction. The nature of the obstruction cannot be determined by scan alone. However in those with productive cough, pre-existing broncho-pulmonary disease, radiological evidence of collapse or undoubted pneumonic consolidation, purely local pulmonary disease was most likely, e.g. bronchial plugging with unexpectorated sputum in a chronic bronchitic. In such situations pulmonary embolic disease was the less likely diagnosis.

The presence of well ventilated perfusion defects on the other hand make pulmonary embolic disease extremely likely, particularly in asymptomatic postoperative patients with little previous history of broncho-pulmonary disease. Those with such defects together with those in whom angiographic evidence of intrapulmonary artery filling defects was obtained, were considered to have suffered pulmonary embolism in the postoperative period.

(v) Pulmonary embolism

(aa) Time of diagnosis. The diagnosis of embolism was made in 20 subjects. The day of diagnosis is shown in table 4.76.

In one subject the diagnosis was made on the day of operation.

In 13/19 remaining subjects the diagnosis was made on the basis of the first postoperative study. In 12/19 this was within 6 days of operation.

TABLE 4.76

	Previous normal postoperative scan	Day of Δ	Further episode	Outcome	Day
1	-	0	no	R	9
2	no	3	yes	PR	9
3	no	4	yes	R	18
4	no	4	no	R	8
5	no	4	no	R	14
6	no	5	no	PR	11
7	no	5	no	R	9
8	no	5	yes	R	9
9	no	5	no	PR	12
10	no	5	no	R	30
11	no	6	no	PR	10
12	no	6	yes	UR	27
13	no	6	no	R	10
14	yes	7	-	not followed	-
15	no	8	no	PR	14
16	yes	9	no	R	15
17	yes	10	no	UR	15
18	yes	10	no	PR	15
19	yes	10	yes	R	16
20	yes	12	yes	PR	16

R = Resolved

PR = Partially resolved

UR = Unresolved

(bb) Subsequent course. In 6/20 subjects further episodes of embolism were diagnosed following deterioration in pulmonary perfusion after the initial diagnosis of embolism.

In 10/20 subjects serial studies were performed until the time of resolution of the lesion. Complete resolution was noted in from 4 to 25 days from time of initial episode. Incomplete (partial) resolution was noted in 7/20 subjects in from 4 to 7 days. It was not possible to follow these subjects further usually because of their residence far from the hospital or their unwillingness to return. Two subjects remained unchanged or worse than the initial abnormal study 5 and 17 days later respectively. One subject was not followed up after initial diagnosis because of discharge to a country centre.

(cc) Age. The age of subjects developing postoperative embolism is shown in table 4.77 and in figure 4.14.

TABLE 4.77

	0-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
Embolism	-	-	1	1	4	3	8	2	-
Total	4	12	13	24	22	69	63	13	1

There were significantly fewer subjects below 50 years of age who developed embolism (2/53) than among those above 50

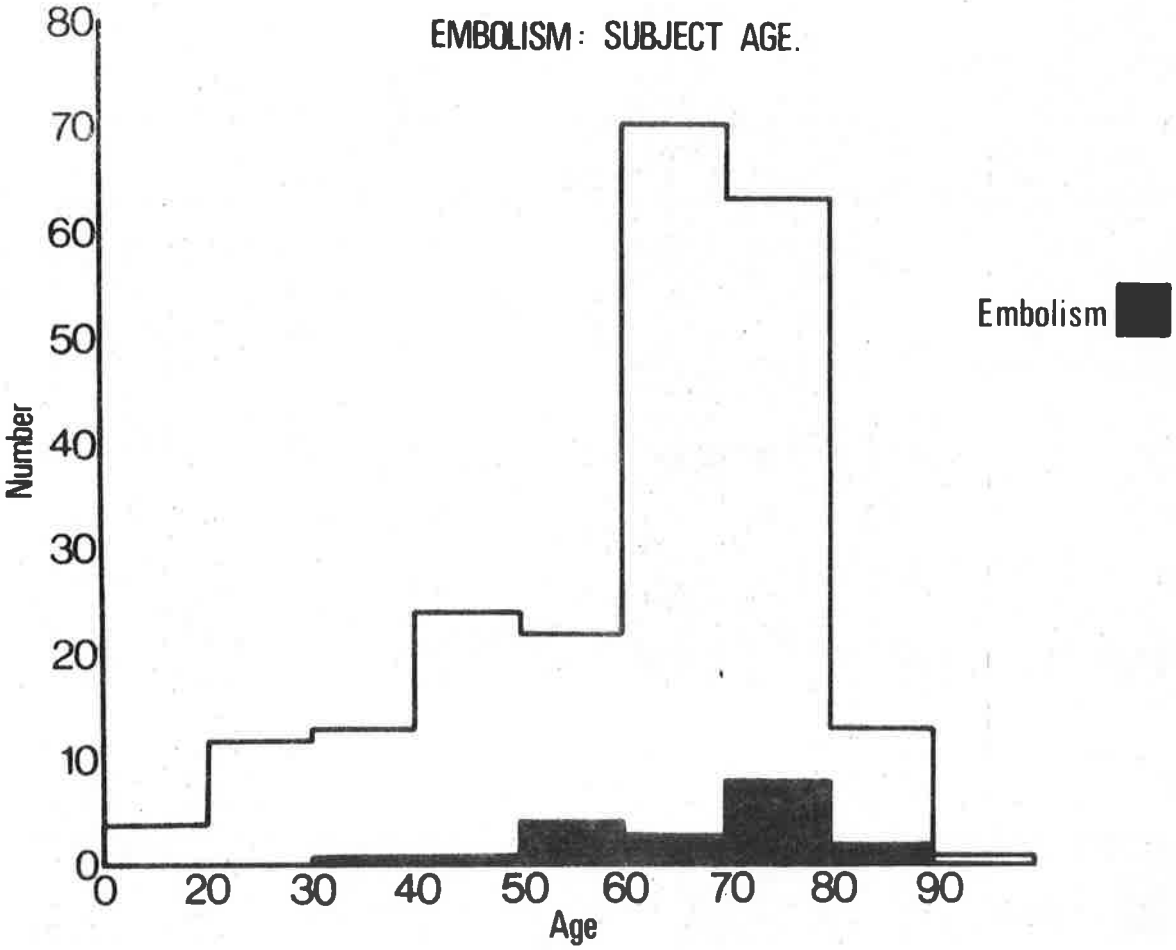

EMBOLISM: SUBJECT AGE.
Number
80
70
60
50
40
30
20
10
0
0
20
30
40
50
60
70
80
90
Age
Embolism

FIG. 4.14

years of age (17/168). (X^2 = 2.95, $p < 0.05$).

(dd) Sex. Six males (6/108) and 13/113 females developed postoperative embolism. There is not a statistically significant difference between these incidences.

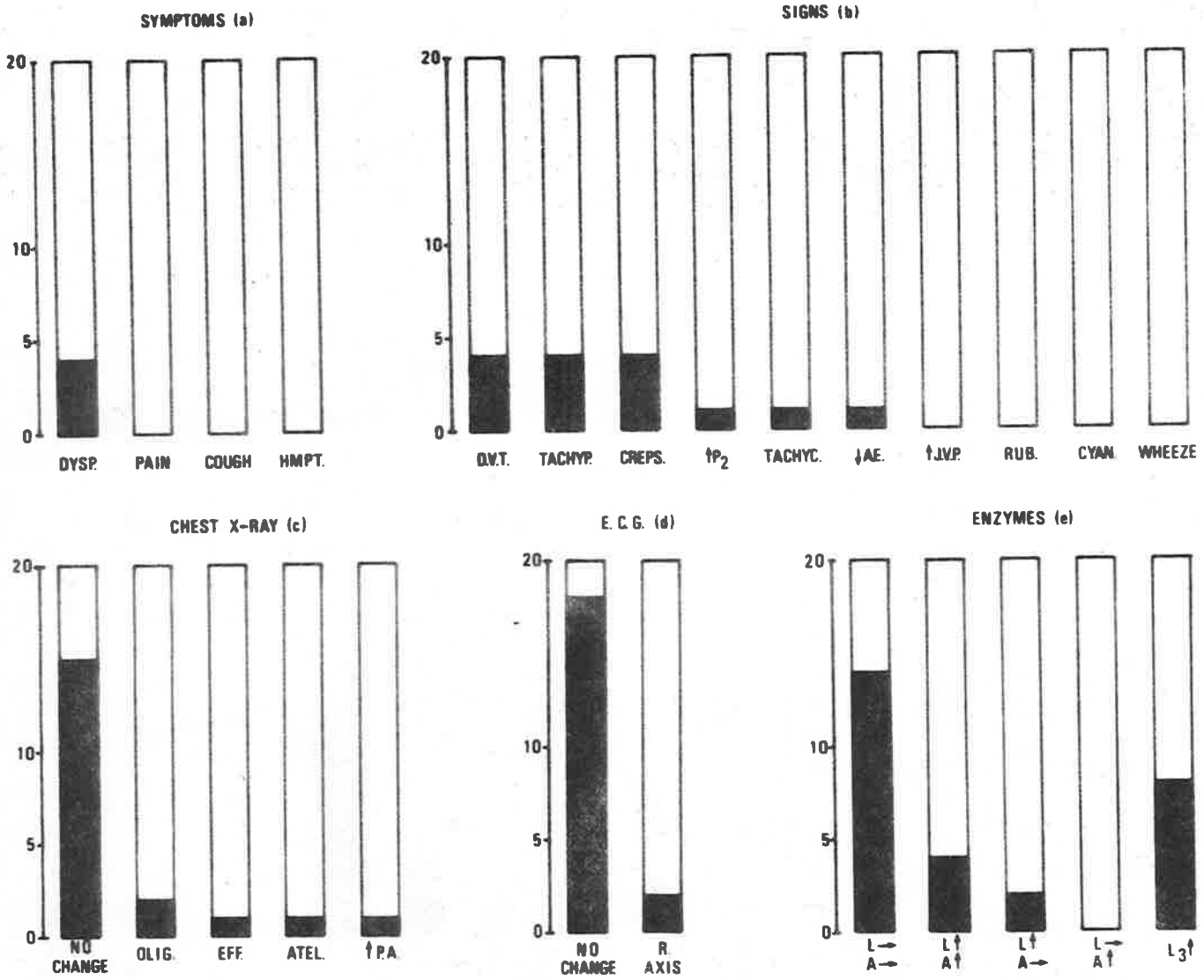
(ee) Clinical features.

α. *Symptoms.* There was a striking paucity of clinical findings associated with the development of embolism in the majority of instances. No subject spontaneously complained of severe symptoms. Pleuritic or anginal chest pain, cough or haemoptysis did not occur. 4/20 subjects developed dyspnoea in association with embolism; in one subject dyspnoea was a spontaneous complaint on mobilisation, but the other 3 subjects denied dyspnoea initially in spite of mild tachypnoea (respiratory rate 25-30 at rest). (Figure 4.15a).

β. *Physical signs.* Deep vein thrombosis was clinically apparent in 4/20 subjects during the postoperative period. In 2 subjects the appearance of embolism ante-dated the clinical appearance of thrombosis. In one subject both embolism and clinical thrombosis were noted on the same day and clinical thrombosis ante-dated the development of embolism in one subject.

There was no clinical evidence of right heart embarrassment or pulmonary hypertension in any subject.

FIG. 4.15


SYMPTOMS (a)
20
10
5
0
DYSP.
PAIN
COUGH
HMPT.
SIGNS (b)
20
10
5
0
D.V.T.
TACHYP.
CREPS.
↑P2
TACHYC.
↓AE.
↑J.V.P.
RUB.
CYAN.
WHEEZE
CHEST X-RAY (c)
20
10
5
0
NO CHANGE
OLIG.
EFF.
ATEL.
↑P.A.
E.C.G. (d)
20
10
5
0
NO CHANGE
R. AXIS
ENZYMES (e)
20
10
5
0
L→ A→
L↑ A↑
L↑ A→
L→ A↑
L3↑

Pyrexia was noted as a transient occurrence in 5/20. Lung crepitations were noted in 4/20 and some decreased air entry in 1/20. No friction rub was noted. (Figure 4.15b).

γ. *Chest Xray.* The chest Xray remained normal or unchanged in 14/19. Changes which occurred in the other 5 subjects were loss of vascular markings at lung base, loss of vascular markings in upper zones, bilateral basal effusions without consolidation or collapse, raised right hemi-diaphragm with subsegmental collapse, and oligaemia plus enlargement of pulmonary artery with cutoff (figure 4.15c).

δ. *Electrocardiograph.* The electrocardiograph showed significant change consistent with embolism in 2 subjects. There was a Q wave in leads II, III and aVF in one subject and there was clockwise rotation in another. There were no other significant changes (figure 4.15d).

ε. *Enzyme changes.* Total lactate dehydrogenase was elevated in 6/20 at the time of embolism. This was associated with raised AAT levels in 4. Four of these subjects had biliary tract disease and preoperative elevation of these enzymes. In 8/20, lactate dehydrogenase isoenzyme III (LDH_3) was elevated following embolism (figure 4.15e).

(ff) Nature of surgery. The incidence of embolism associated with various surgical procedures is shown in figure

4.16. The overall incidence of postoperative embolism was 8.6% (19/221). A high incidence (14.7%) was associated with operations on the biliary tract which was the most commonly performed type of operation.

(gg) Duration of anaesthesia. The duration of anaesthesia and the occurrence of pulmonary embolism are shown in table 4.78. There was only one recorded instance of postoperative embolism in 70 operations lasting one hour or less (1.4%).

TABLE 4.78

DURATION OF ANAESTHESIA (min.)	NO. OF OPERATIONS	EMBOLISM	%
0 - 60	70	1	1.4
61 - 120	101	11	10.9
121 - 180	33	6	18.1
181 - 240	14	1	7.1
240+	3	0	0

The incidence of embolism associated with operations lasting one hour or less was significantly less than that associated with the group as a whole ($X^2 = 5.4$, $p < 0.01$).

(hh) ABO blood group. The ABO blood group of all subjects was obtained during admission. The relative frequency

Post-operative Embolism.

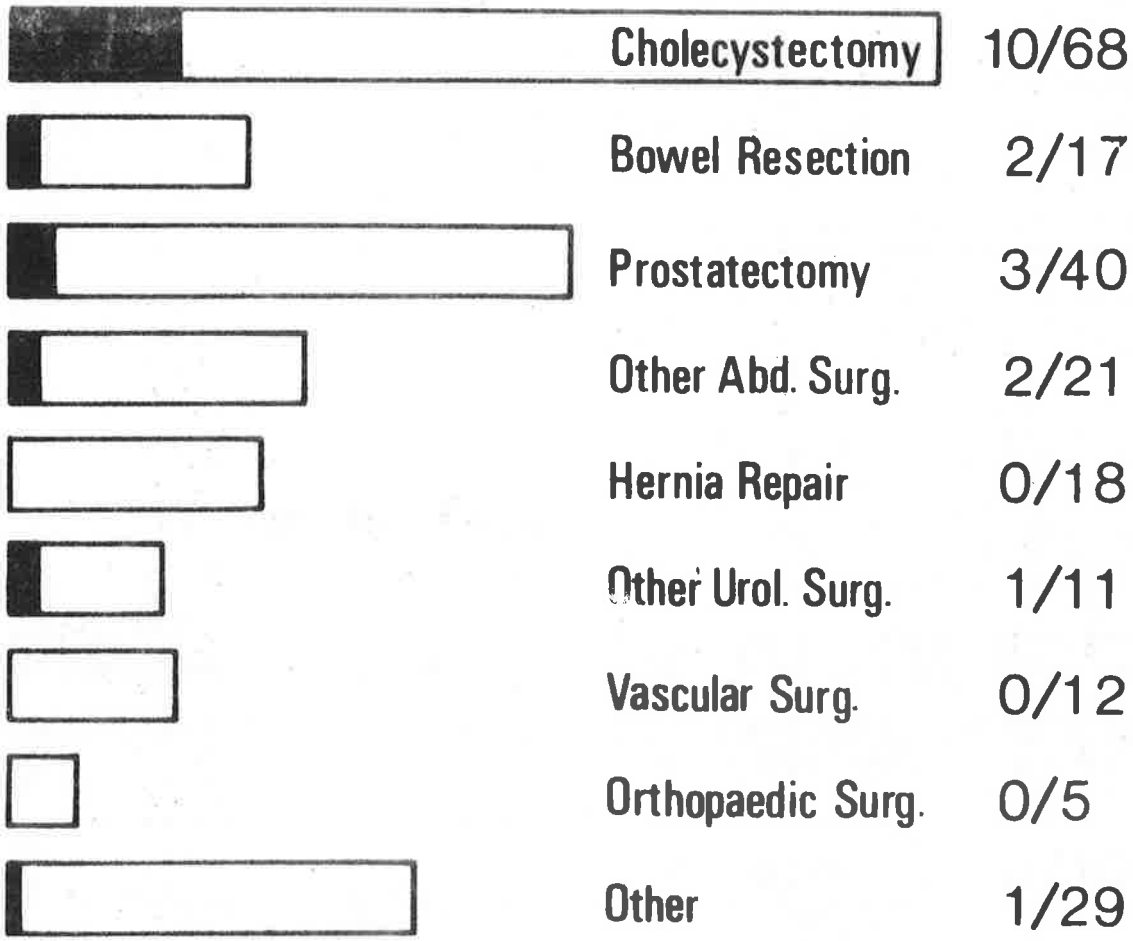


FIG. 4.16

of the various groups and the incidence of embolism associated with each group is shown in table 4.79.

TABLE 4.79

Group	Total	Embolism
O	95	5
A	86	9
B	31	4
AB	8	2

There are relatively fewer subjects of blood group O than expected among those with embolism and relatively more in each of the other groups. However the difference is not of statistical significance.

(ii) Neoplasia. Of the 38 subjects with known neoplasia in the followed up group, 7 (18.4%) developed large perfusion defects which remained well ventilated.

There is a significant difference between the incidence of embolism in this group and the remaining subjects (X^2 = 4.2, $p < 0.05$).

(vi) Perfusion defects not due to embolism

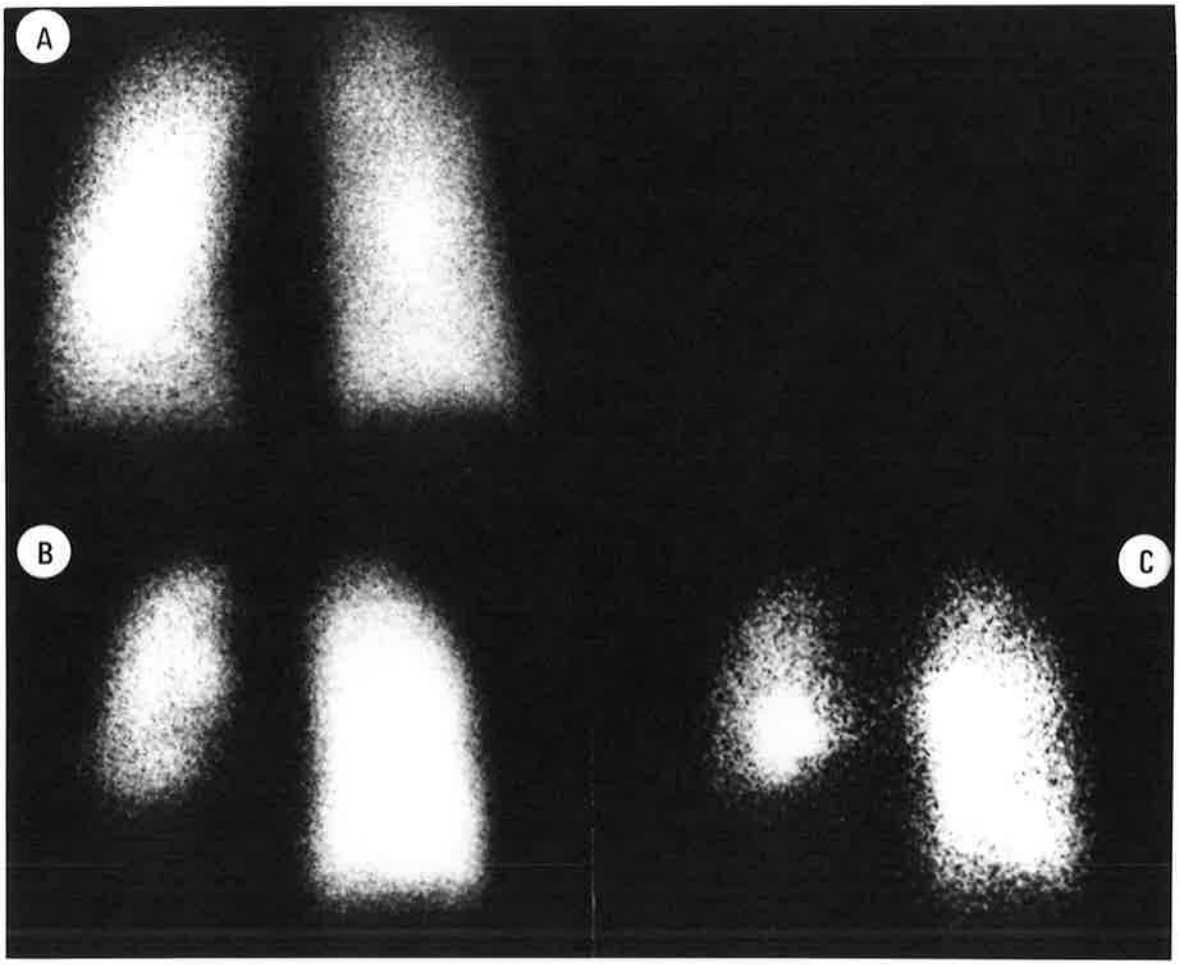
Coexistent perfusion and ventilation defects were found in the postoperative period in 10 subjects (figure 4.17). They

Fig. 4:17 A. Preoperative posterior perfusion scan.

B. Postoperative posterior perfusion scan in same subject 3 days after operation.

C. Postoperative posterior inhalation scan obtained at the same time as B. The area of decreased perfusion in the left base is poorly ventilated and there is proximal deposition of radiopharmaceutical.

The appearances suggest that bronchial obstruction rather than embolism is responsible for the decrease in left lower zone perfusion.


A
B
C

were associated with the following incidence of symptoms, signs and other findings (table 4.80).

TABLE 4.80

Smoker	8
Preexisting pulmonary disease	6
Nonproductive cough	3
Productive cough	4
Dyspnoea	2
Chest pain	3
Tachypnoea	1
Tachycardia	3
Reduced air entry	9
Wheeze	6
Cyanosis	1
Abnormal chest Xray (new)	5
Abnormal electrocardiogram (new)	0
Enzyme abnormality	2

In a bronchitic subject with a recent past history of pulmonary embolism following reconstructive vascular surgery, the sudden onset of dyspnoea, pleuritic chest pain, angina and cough postoperatively was associated with areas of decreased ventilation and perfusion on scan and streaky opacity of his chest Xray. Pulmonary angiogram was not performed. He was treated with antibiotics and physiotherapy and recovery was complete in 10 days. Pulmonary embolism was considered unlikely.

(vii) Symptoms and signs mimicking embolism in other subjects

Sudden onset of pleuritic or anginal chest pain in the postoperative period in 3 subjects suspected of developing

embolism clinically was not associated with changes in pulmonary perfusion. Deep vein thrombosis was diagnosed clinically in 4 subjects in the absence of associated scan evidence of embolism.

(viii) Selected cases

In spite of the few symptoms and signs of embolism noted in this group, the subjects studied represent a wide spectrum of disease with both minor and major impairment of pulmonary perfusion. The following are examples of the clinical course of 3 subjects studied.

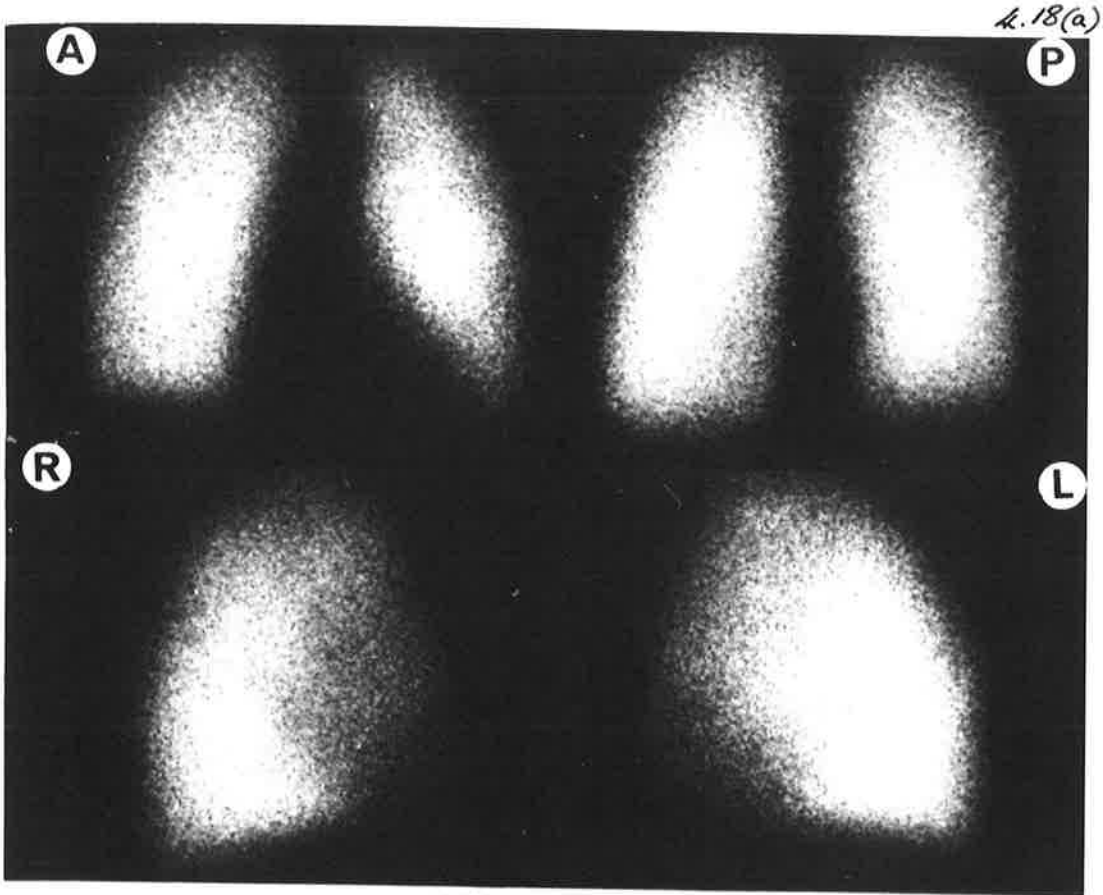
Case 1, Mrs. R.J. 54. Admitted for cholecystectomy following repeated attacks of biliary colic without jaundice. Her past history included a hysterectomy for the removal of uterine fibroids in 1950 and poliomyelitis in 1951. The only residual damage resulting from poliomyelitis was a slightly weakened hand grip and wasting of the left calf which was 2 cm smaller in circumference than the right. On examination there were no abnormal cardiovascular or pulmonary signs. Preoperative lung scan, chest Xray, ECG and biochemistry were within normal limits (figure 4.18a). (LDH 225, AAT 45, bilirubin 0.5). At operation (lasting 100 minutes) a gall bladder containing 2 stones was removed. She made a normal postoperative recovery without obvious

Fig. 4:18a. Subject R.J. Normal initial perfusion study (above). Large left lower zone perfusion defect on day 4 is seen to be well ventilated (below).

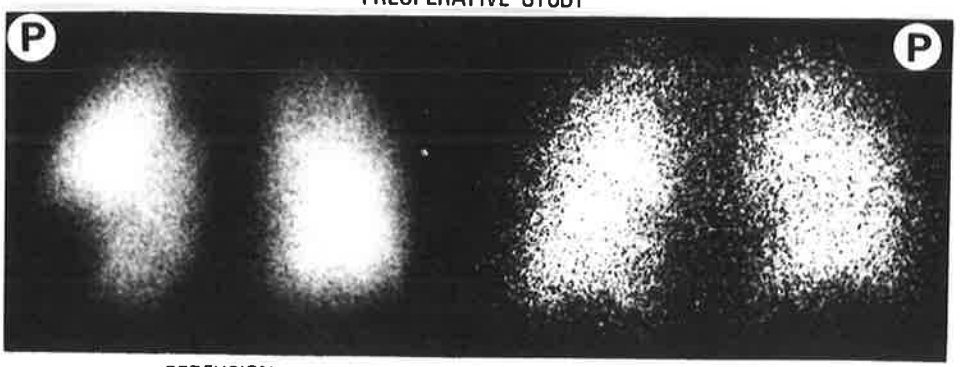
b. Virtually complete resolution with only a small lingula defect on day 7.

P-A chest Xrays taken on day 0 (A) and day 4 (B) were considered normal.

4.18(a)



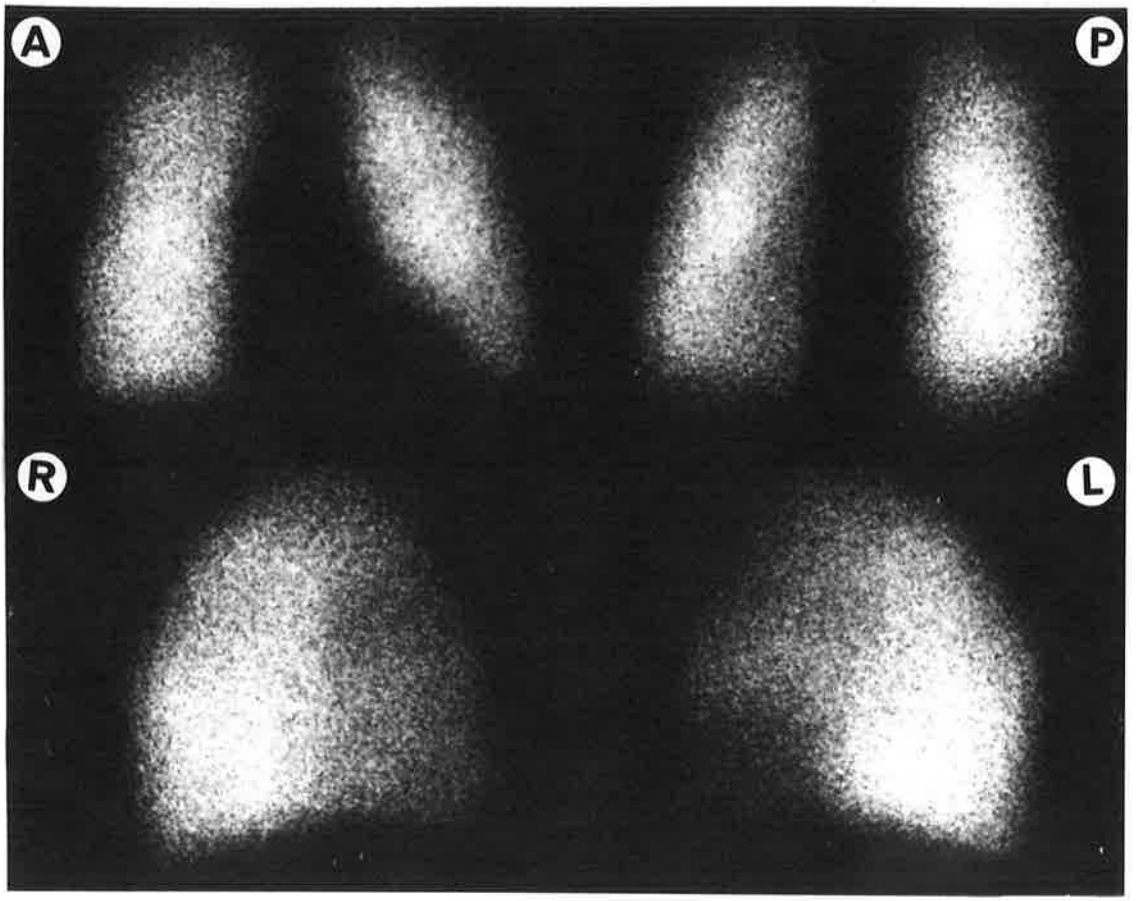
PREOPERATIVE STUDY

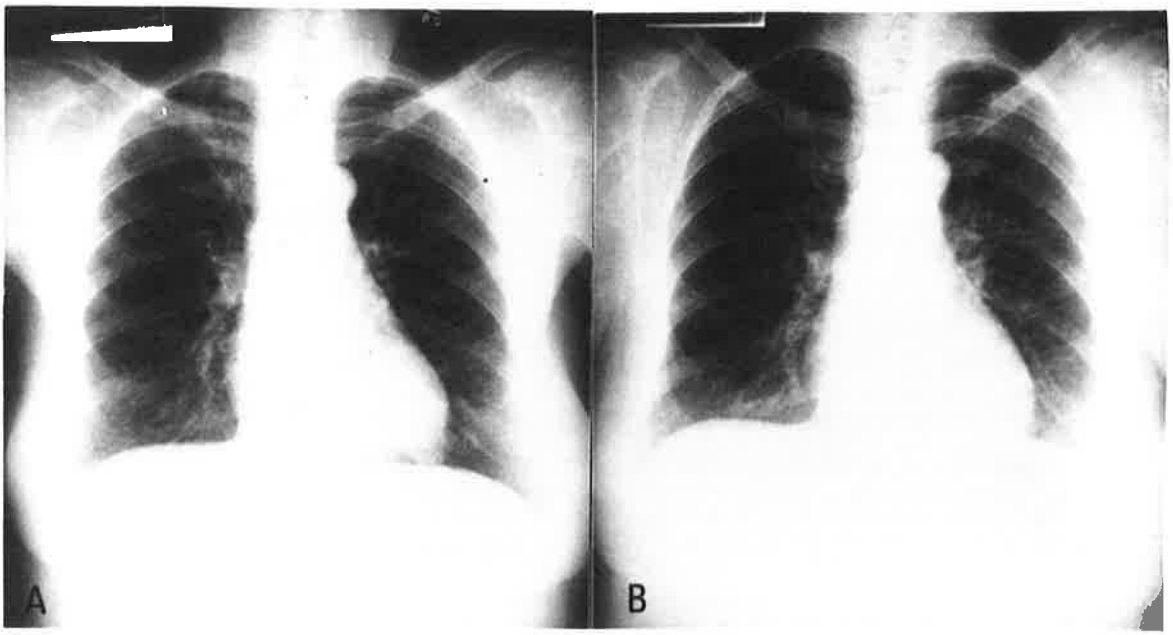


PERFUSION INHALATION

POSTOPERATIVE STUDY

4.18(6)




A
B

incidents.

Postoperative perfusion and inhalation lung scans on day 4 revealed a left lower lobe perfusion defect which was well ventilated. Other defects were noted in the right lower lobe and lingula segment on the left (figure 4.18b). No abnormality was evident on physical examination; in particular, there was no evidence of leg vein thrombosis. Chest Xray revealed normally aerated lungs without any evidence of collapse or consolidation but the lower zones of both lungs were relatively radiolucent, particularly on the left. ECG and serum biochemistry screen were again normal (LDH 195, AAT 45, bilirubin 0.5), and there was no elevation of any of the LDH isoenzymes (1+2 = 60, 3 = 45, 4+5 = 90).

By day 7 the defect in the right lung was no longer visible and partial resolution had occurred on the left, a lingula defect remaining only. The patient remained asymptomatic. (figure 4.18c).

On day 12 further resolution of the lingular defect was noted but a small area of decreased perfusion was noted in the anterior segment of the right upper lobe. Remained asymptomatic.

The patient was discharged from hospital but did not return for follow up scans. Subsequently seen 5 months later at the outpatient department because of persistent diarrhoea; there was no clinical evidence of cardiac or pulmonary pathology and she had remained well following discharge.

Case 2. Mrs. A.D. 65. Admitted for cholecystectomy for biliary dyspepsia following the demonstration of a non-functioning gall bladder. Had many operations for uterine prolapse, but no other significant past history. Dyspnoea was present on abnormal exertion only. She was a nonsmoker. She was obese (82 kg), 5 feet tall and hypertensive (B.P. 230/130). The second heart sound was loud over the praecordium and there was a plainly audible fourth heart sound. Crepitations were present in both lung bases with some pitting oedema of both ankles. The jugular venous pressure was not clinically elevated, and the liver was impalpable. Operation was deferred because of her cardiac status. She was digitalised and given diuretics and on this regime her hypertension and congestive failure improved.

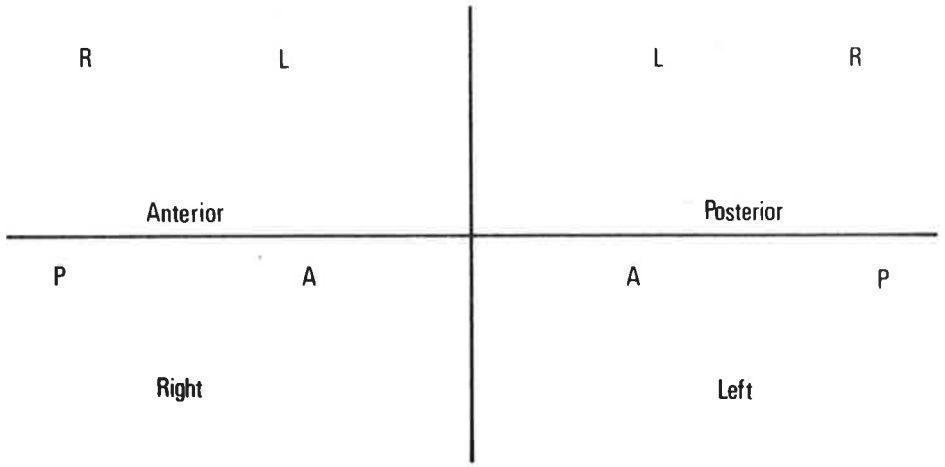
Preoperative perfusion lung scan on the morning of operation was normal (figure 4.19a). ECG showed no specific abnormality. Chest Xray and biochemical screen were normal (LDH 195, AAT 30, bilirubin 0.5). At operation (lasting 105 minutes) the gall bladder was removed. It showed evidence of chronic cholecystitis; there was no evidence of malignancy.

On day 4 postoperatively some slight irregularity of pulmonary perfusion was noted (figure 4.19b) but this was not investigated further at that time. On day 10, multiple defects were noted in both lower zones (figure 4.19c). Chest Xray was considered normal, ECG was normal, biochemical screen

Fig. 4:19a. Subject A.D. Normal initial perfusion study.

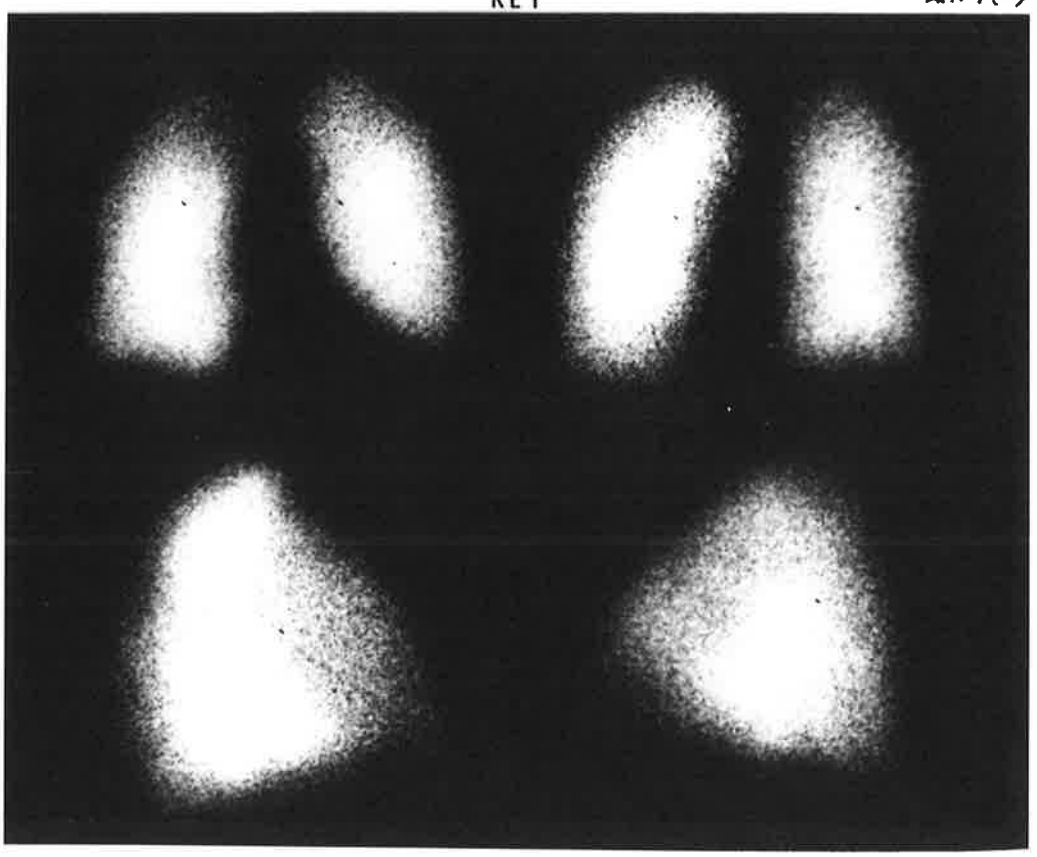
b. Some irregularity in perfusion especially in the region of the right middle lobe and left lower lobe.

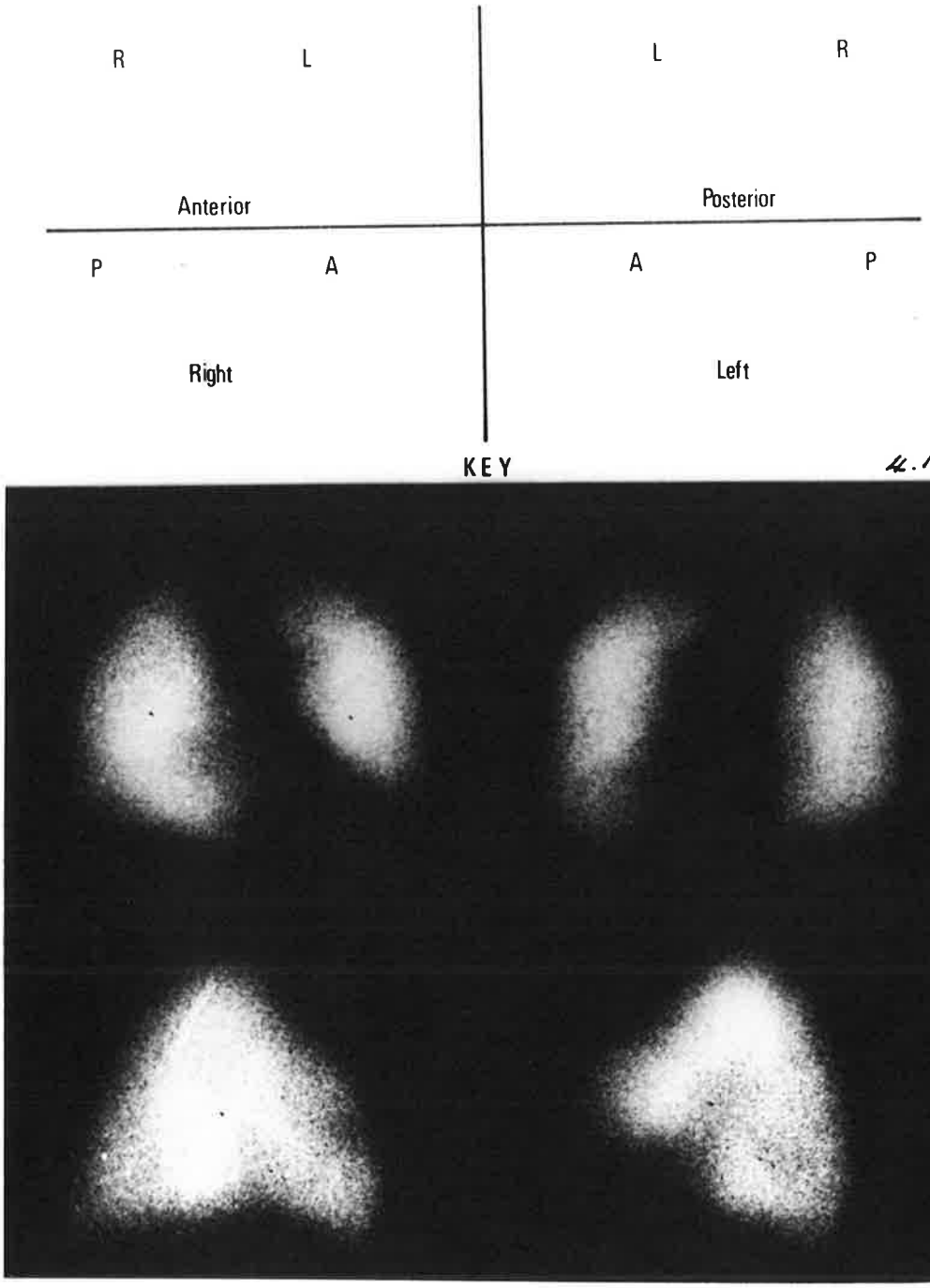
c. Large perfusion defects seen in both lower zones.



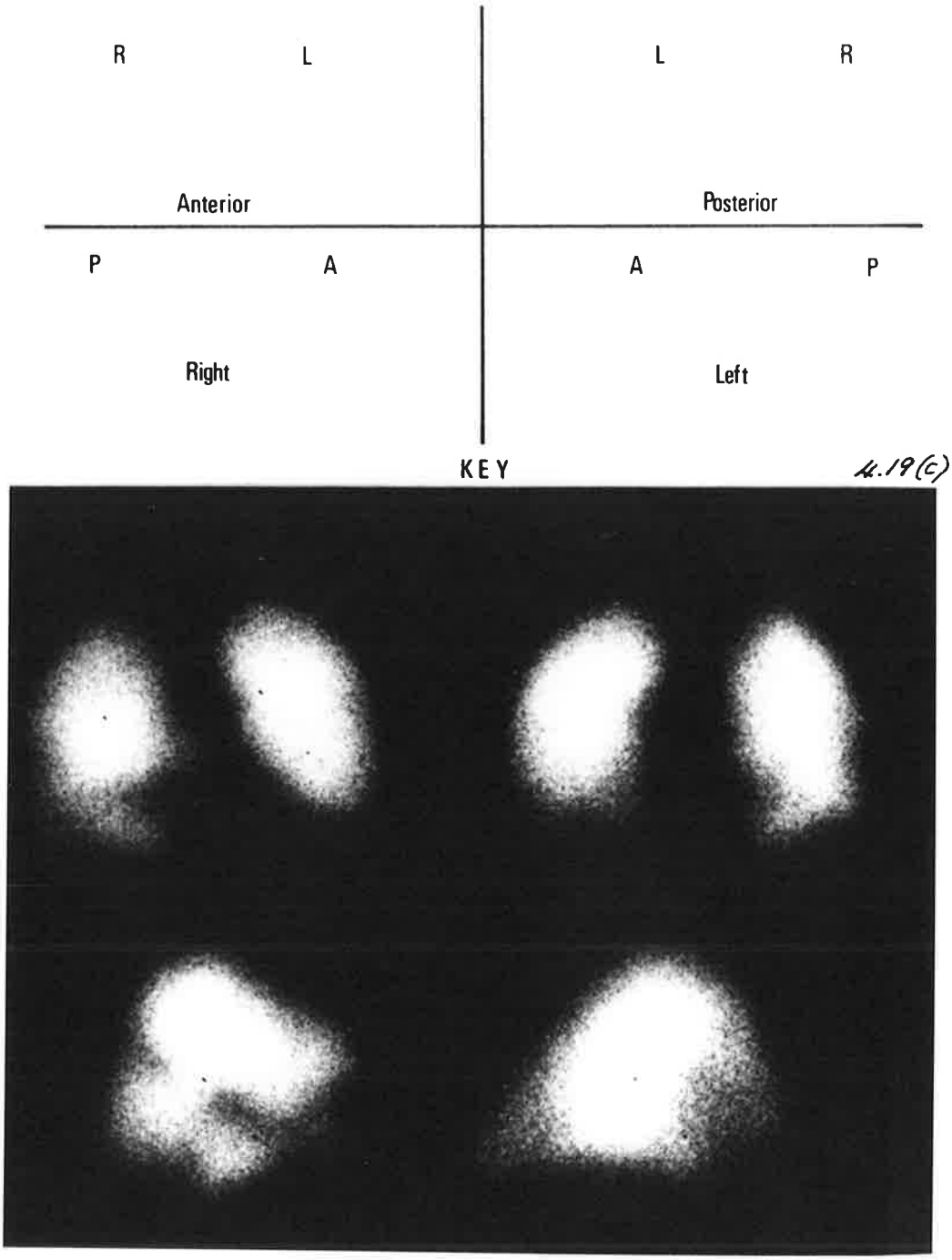
KEY

4.19(a)





4.19(6)



4.19(c)

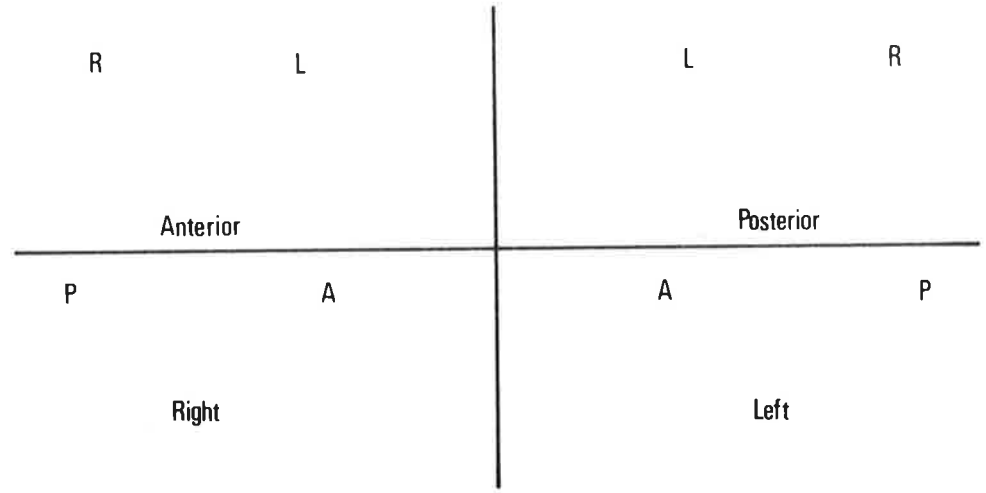
was again normal (LDH 265, AAT 50, bilirubin 0.7) and there were no abnormal pulmonary or cardiac signs. The patient was entirely asymptomatic.

On day 14 a further perfusion defect was noted to have developed at the apex of the right lung (figure 4.19d). Chest Xray showed elevation of the right hemidiaphragm with oligaemia of the right lung field and left lower zone, and prominence and cut off of the right main pulmonary artery. The ECG showed Q wave formation in leads II, III and aVF. Biochemical screen was still normal (LDH 160, AAT 45, bilirubin 0.5) and LDH isoenzymes were not elevated (1+2 = 70, 3 = 50, 4+5 = 40). The patient remained asymptomatic.

Pulmonary angiogram was performed on day 15 and revealed a large filling defect in the right main pulmonary artery and multiple smaller filling defects in other smaller pulmonary arteries in both lungs (figure 4.19e). The patient was still relatively asymptomatic at that time complaining only of slight dyspnoea on walking. Tachypnoea (30/min) was noted transiently for a few hours. There was no clinical evidence of thrombosis. Following pulmonary angiography, streptokinase therapy was instituted and there was gradual resolution of the pulmonary artery obstruction. By day 18 perfusion had returned virtually to normal. She was seen intermittently until 60 days after operation when pulmonary perfusion was noted to be unchanged

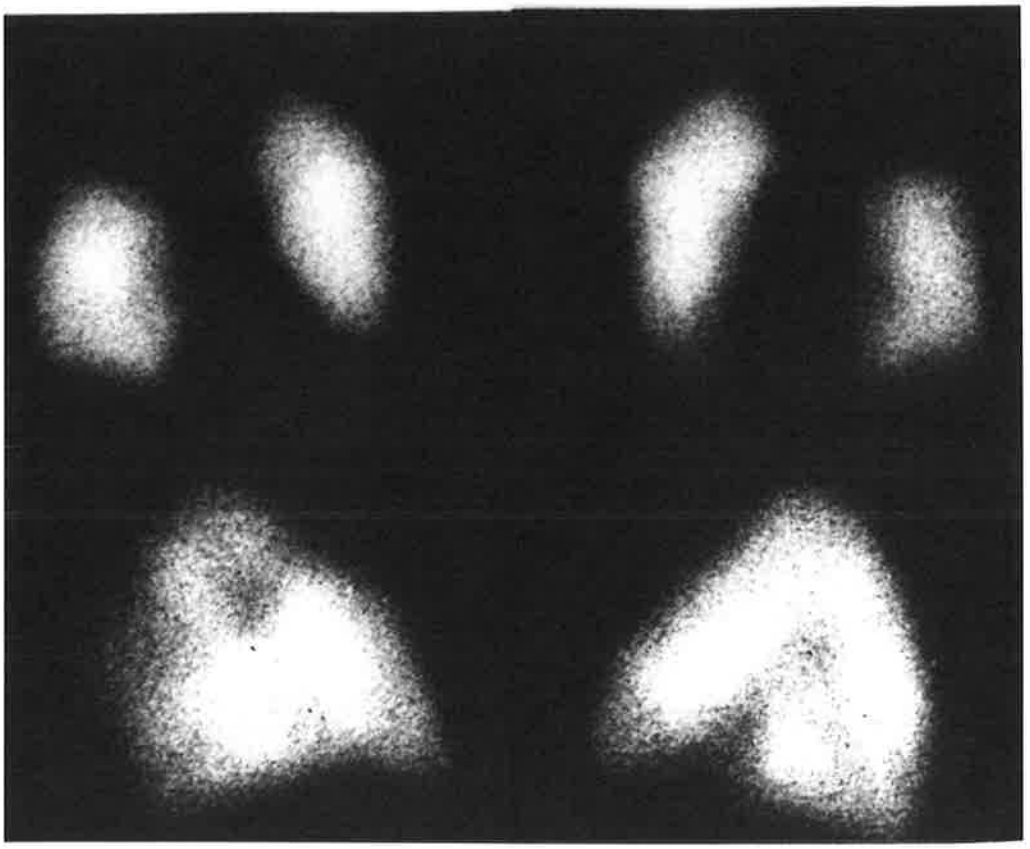
Fig. 4:19 d. Right apical defect has developed, partial resolution of the lower zone defects has occurred.

e. Pulmonary angiogram shows a large filling defect in the right main pulmonary artery and smaller filling defects in smaller vessels in both lungs.

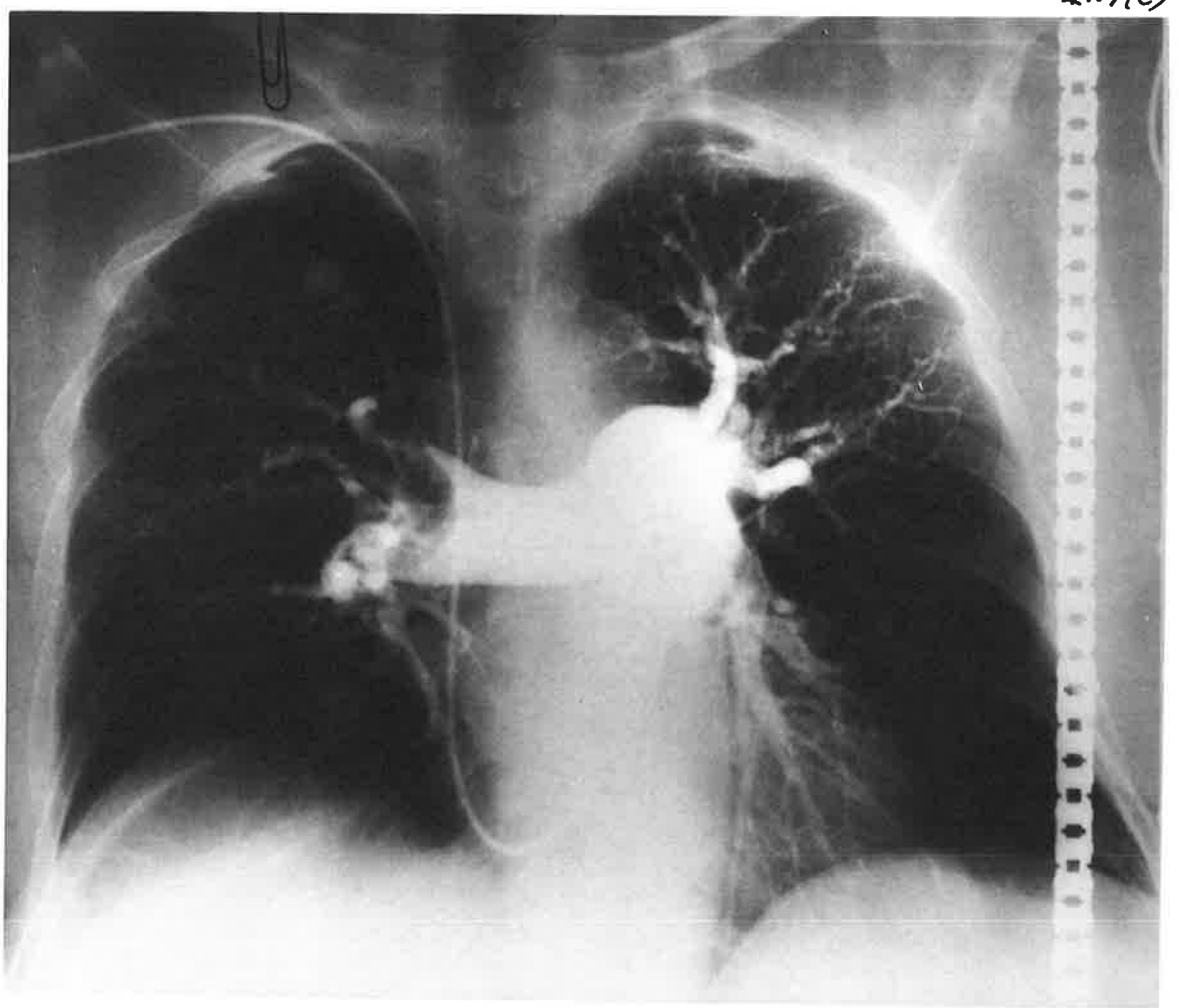


KEY

4.19(d)



4.19(e)



Case 3. Mr. S.B.E. 79. This man presented with a 6 month history of frequency, dysuria, haematuria and difficulty initiating micturition. A large testicular hydrocoele had been present for many years. Significant past history included mild Parkinsonism which was controlled with amantidine.

Some shortness of breath was noticed on climbing stairs or walking uphill but he was not normally dyspnoeic. There were no other significant symptoms. He was a nonsmoker.

Physical examination revealed a soft aortic systolic murmur; there was no abnormality on auscultation of the lungs. He was normotensive and there was slight pitting oedema of the ankles. Jugular venous pressure was not elevated. The liver was impalpable. Hypertrophy of the prostate was found on rectal examination. Routine preoperative investigations were all within normal limits. Preoperative perfusion study revealed slightly irregular perfusion (category B, figure 4.20a).

At operation lasting 120 minutes the prostate was removed by a retropubic approach. Subsequent histology revealed benign fibromuscular and adenomatous hyperplasia.

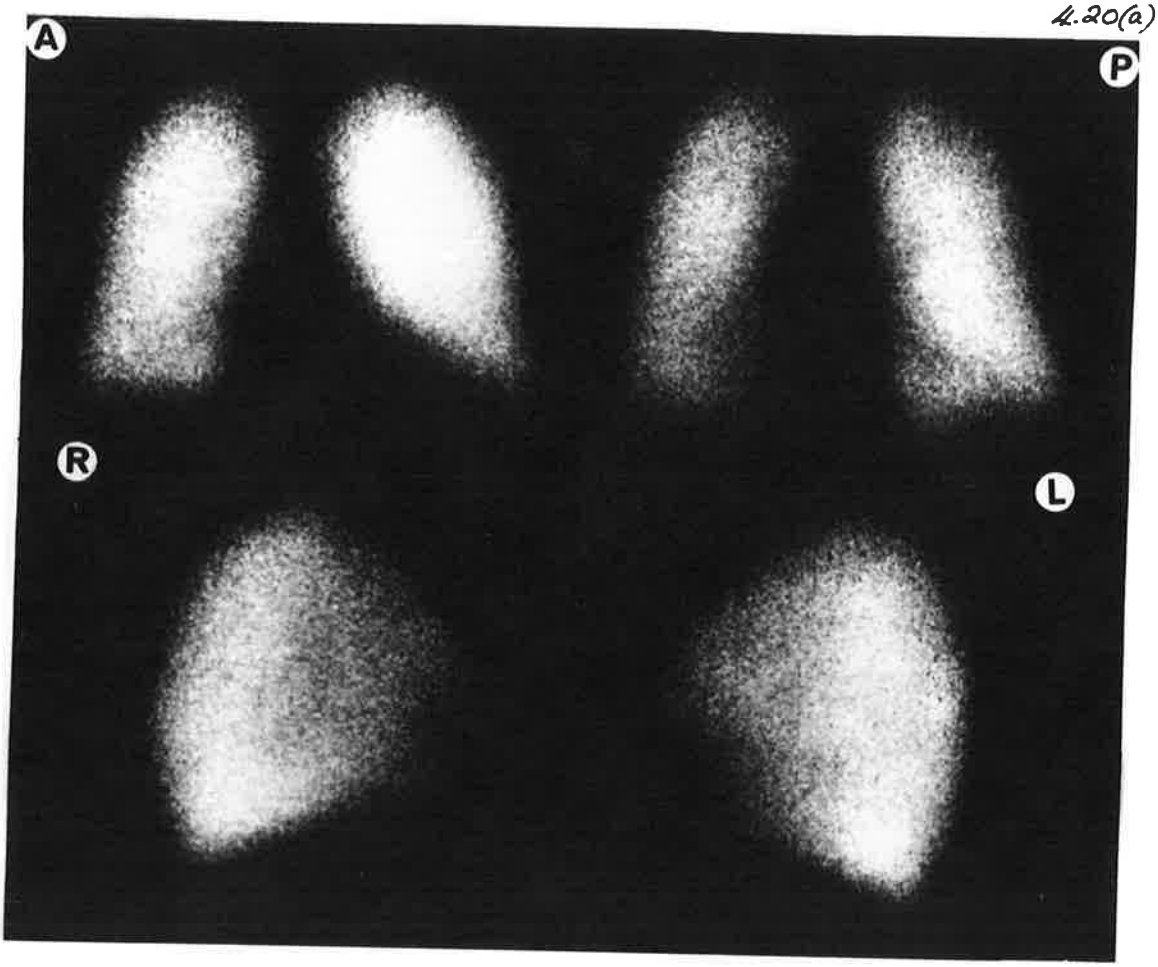
On postoperative day 4 pulmonary perfusion was noted to be grossly abnormal with large segmental defects in both lungs (figure 4.20b). Inhalation study was virtually normal (figure 4.20c). There were no signs of peripheral thrombosis

Fig. 4:20 a. Subject S.E. Preoperative perfusion study.

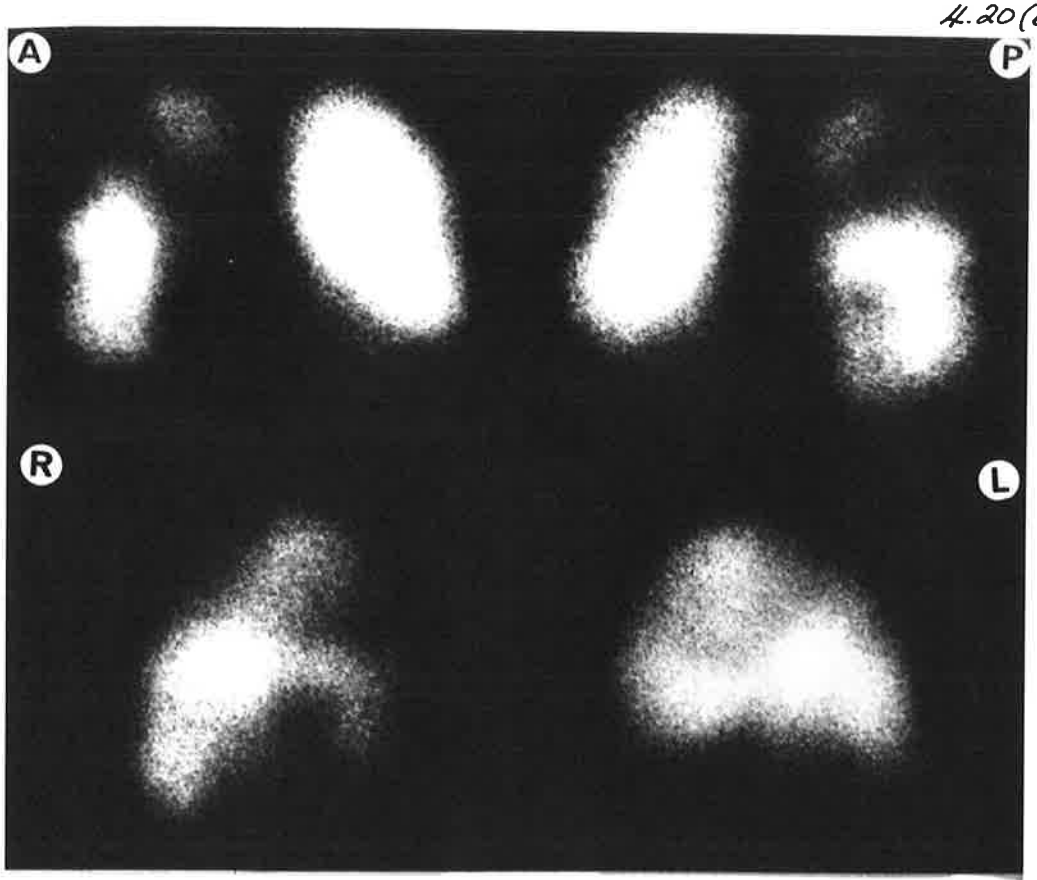
b. Postoperative perfusion study on day 4 reveals large perfusion defects, particularly affecting the right lung.

c. Inhalation study performed at the time of (b) reveals virtually normal ventilation in the underperfused areas.

4.20(a)

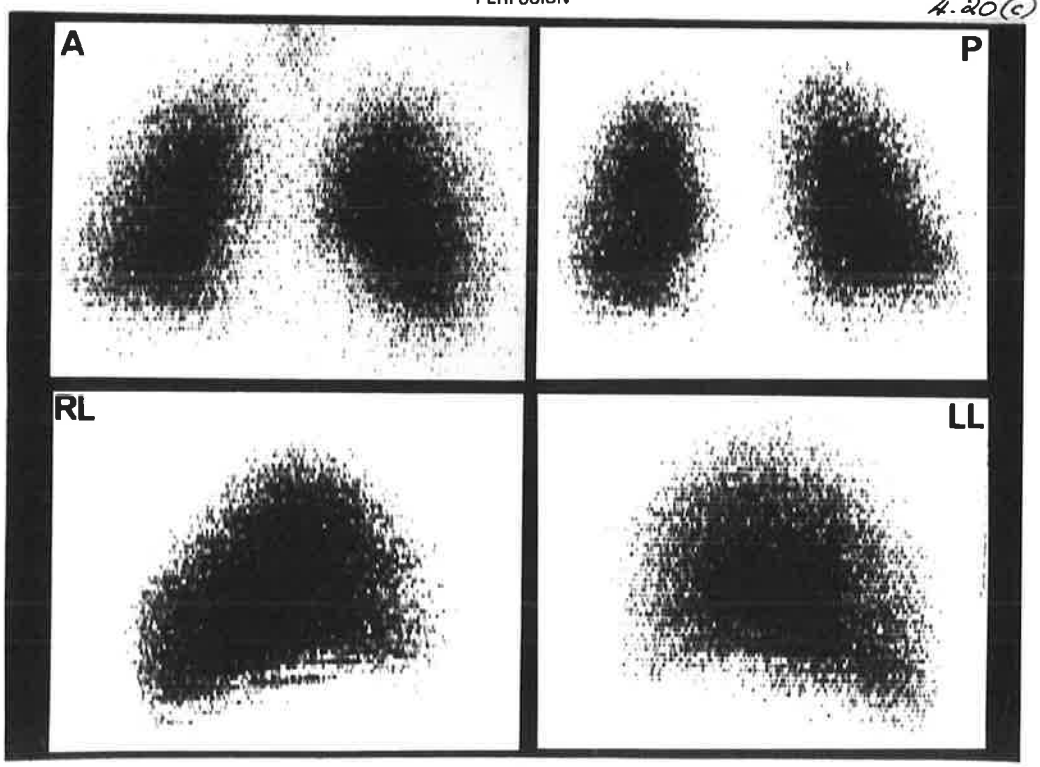


4.20(b)



PERFUSION

4.20(c)



INHALATION

and no abnormal chest signs. Chest Xray, ECG and biochemical screens including LDH isoenzyme estimation were within normal limits. The patient was asymptomatic.

On day 7, perfusion study showed some improvement (figure 4.20d) and he remained asymptomatic and investigations remained normal.

On day 11, a further defect was noted at the apex of the left lung. There was no change in any other parameters (figure 4.20e).

On day 13, further deterioration in perfusion was noted with the development of a perfusion defect in the right lower lobe (figure 4.20f) while ventilation remained normal. On that day he returned to theatre for removal of his hydrocoele. Patient remained asymptomatic.

On day 17, perfusion had returned virtually to normal. He was discharged on day 19. He reported he had remained well when seen 3 weeks after discharge.

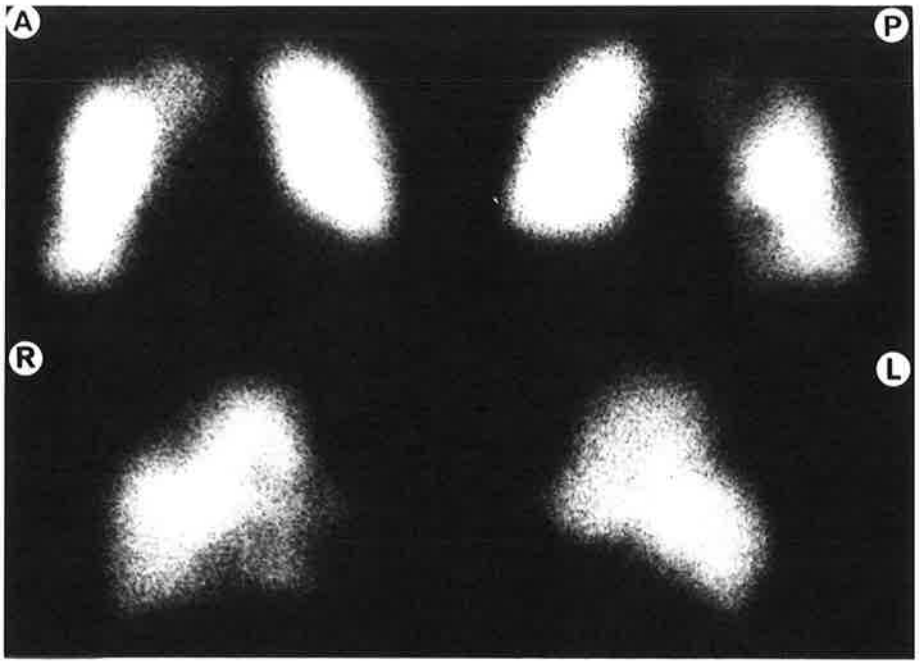
Fig. 4:20 d. Slight improvement in perfusion with possible new defect in the superior segment of the left lower lobe.

e. Definite new defects in the left upper zone.

f. Further right lower lobe defect.

g. Partial resolution of perfusion defects.

4.20(d)



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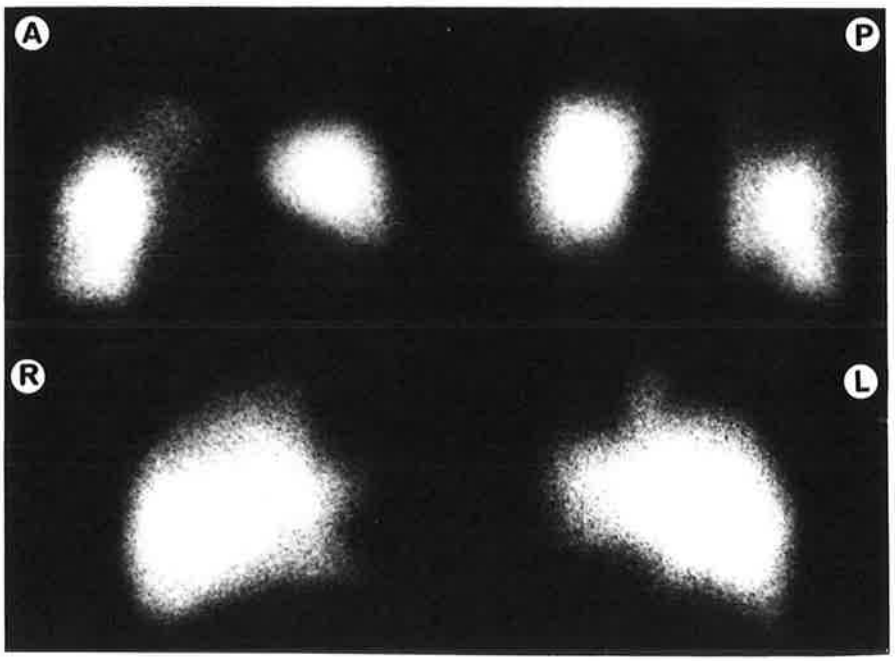
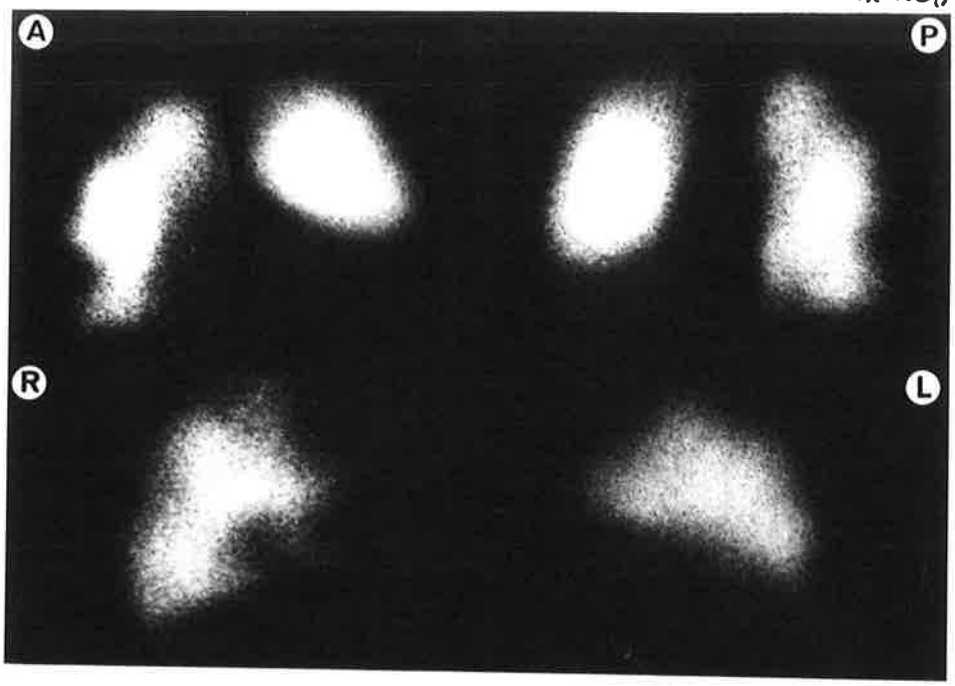
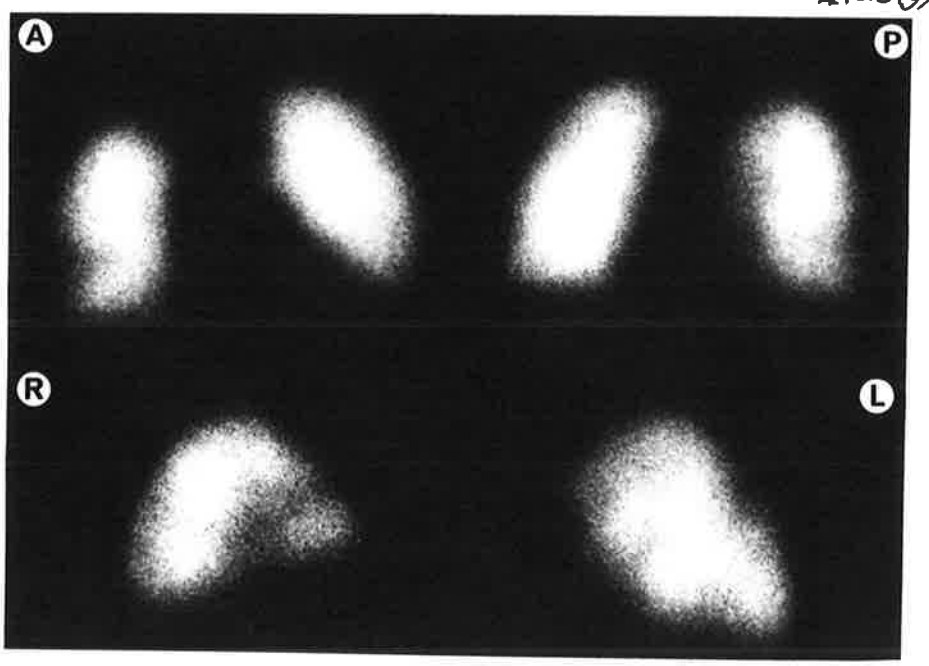


4.20(f)



4.20(g)



D. DISCUSSION OF MEDICAL AND SURGICAL SERIES

(a) GENERAL METHODS

(i) Routine perfusion study. Serial perfusion studies were selected as the most appropriate method for detecting subjects likely to have developed embolism. Besides being a relatively atraumatic procedure it has been shown to be the most sensitive investigation available for the detection of the disorder (Szucs et al. 1971). When the perfusion study is normal there is no likelihood that embolism will be demonstrated by any other method.

The specificity of certain perfusion scan features has recently been demonstrated by Poulose et al. (1970). As a result of a study of 71 subjects with clinically suspected pulmonary embolism they indicate that angiographic proof of embolism can be obtained in 75% of those subjects whose lung scans have perfusion defects corresponding to specific anatomical segments of the lung, providing the plain chest Xray is compatible with embolism, and in 25% of those who show diffuse nonsegmental defects.

When defects of the type associated with a high index of angiographic confirmation in the series described by Poulose et al. were found on routine study, and particularly when such defects were seen to develop in previously normally perfused lung, and no other obvious cause for such defects

were found on clinical examination, pulmonary embolism was strongly suspected and confirmation could be sought on further study.

(ii) Confirmatory studies. Confirmation of the diagnosis of embolism among subjects in this study was obtained by a variety of means. Autopsy confirmation of the diagnosis provided incontravertible evidence in a number of instances, while characteristic pulmonary angiographic changes were seen in others.

Normal ventilation in areas of decreased perfusion has been shown to occur with pulmonary embolism but not with other common types of pulmonary pathology (Medina et al. 1969; De Nardo et al. 1970; Johnson, 1971). The state of regional ventilation is thus an important factor to be determined whenever a pulmonary perfusion defect is found. In this study both inhalation scanning and auscultatory methods were employed. They were considered more accurate than the mere radiological assessment of ventilation using a single postero-anterior chest Xray in full inspiration alone.

Clinical examination of the chest was found to be a useful method of assessment. The results of careful auscultation correlated well with the results of inhalation studies. Particularly when perfusion defects were large, auscultation could be relied upon to confirm or refute the

diagnosis of embolism. Routine meticulous auscultation of the chest in all subjects referred for lung scanning pays rich dividends.

In subjects in whom inhalation studies were not performed, retrospective diagnosis was facilitated by repeated perfusion study when the changing defects of embolism, together with consistent radiological findings, differentiated that condition from other forms of pathology.

(iii) Method deficiencies. The method of examination employed in these series did contain deficiencies in so far as the routine inclusion of certain additional special investigations might have provided valuable extra information regarding individual subjects and made diagnosis in others more straightforward. For logistic, financial and various other reasons these investigations were not included as routine.

The performance of pulmonary angiography in all subjects with scan abnormalities of certain types was not possible because the procedure was regarded as potentially hazardous in certain situations (e.g. post myocardial infarction), and clinicians were generally unwilling to allow this investigation if the outcome of the investigation would not materially affect the therapy of the subject concerned. To be valuable for the assessment of perfusion study

abnormalities, pulmonary angiography should be performed in close proximity to the time of the perfusion study. If this is not done resolution of vascular obstruction may occur resulting in an entirely different situation for the two investigations. Apart from emergency situations, delays of 48 hours or more were unavoidable. This reduced the potential value of the procedure considerably. Similar objections were raised to the routine performance of lower limb phlebography. These investigations were thus only performed in isolated instances.

Routine pulmonary function tests were considered but were not included as a routine because suitable equipment and conditions for their performance, which would enable accurate conclusions to be drawn, were not available.

(iv) Scan classification

The grouping of scan types into only 4 categories has no precedent and represents a considerable simplification. Such a classification was considered justified on a number of grounds. Comparison between heterogeneous groups (e.g. subjects with nervous system disease and subjects with cardiovascular disease) is most easily achieved if the shared characteristics of such groups are collected, categorised and their relative frequencies tabulated. Similarities and differences between the groups then become

apparent; the fewer categories into which the available information is collected the more readily comparable are the two groups. An additional reason suggesting the use of few categories is the improved reproducibility of observer performance in placing scans within categories. If the available choices are few the errors are likewise fewer as dividing lines between categories are less subtle.

For these reasons the minimum number of categories which would allow reasonable separation of major scan types was sought. Besides the normal group, scans showing patchy perfusion, usually representing diffuse pulmonary disease, and scans with discrete defects, usually representing more localised disease, required separate consideration. The remaining scans which showed slight irregularities of perfusion or scan manifestations of such processes as cardiomegaly were grouped together. When more than one abnormality was present the scan was placed in the category of the major abnormality. Deterioration or improvement in perfusion within each group was noted. In this way comparison across the whole spectrum of subjects was facilitated and placement of scans was simplified. Attempts at other methods of classification were less satisfactory.

(b) MEDICAL SERIES.

(i) Subject selection. The method finally adopted for

the selection of subjects was dictated by a number of factors relating to the size and nature of the group to be investigated.

(aa) Long term effects of radiopharmaceuticals. Because of the remote possibility of long term deleterious effects being associated with the radiopharmaceuticals used, subjects below the age of 20 years and pregnant females were not included in the study group.

(bb) Size of study group. Ideally in most surveys of hospitalised subjects, all or a randomly selected group of subjects should be included in the study group at the time of admission to hospital. However, this method of subject selection was not practical in our situation. There are wide fluctuations in the number of daily admissions to the medical clinics of the Royal Adelaide Hospital (0 - 30 subjects) and many of these admissions are for short periods. From the point of view of handling these subjects, i.e. interviewing, examining and scanning, a smaller group of more certain size than the total admission number was considered desirable. The number of subjects was reduced by pre-selecting certain clinics whose patients would be studied and including only those who had been in hospital 6 days.

(ii) Time of study

(aa) Movement to scanning facility. At the time of admission many subjects are acutely ill and their travel within the hospital to various diagnostic facilities must be kept to a minimum. This creates additional problems if subjects are routinely studied on admission and time of initial study would frequently be delayed resulting in little standardisation. Towards the end of the first week in hospital, the proportion who are still acutely ill is greatly reduced, and the great majority of subjects can travel to a scanning facility. In addition, a greater proportion of the day is generally taken up in undergoing intensive investigation earlier in the period of hospitalisation. Additional studies of a non urgent nature are thus more easily performed later during admission.

(bb) Subject transfer. Transfer of patients to other clinics is less likely to occur after the first few days of admission that soon after entering hospital, a factor contributing to the greater 'stability' of a group in hospital for some days.

(iii) Recovery rate

The inclusion in the present study of 400 subjects from a population of 447 who satisfied the criteria for selection (89.5) has been considered a satisfactory recovery rate. It

is possible that those subjects not studied might have carried a higher likelihood of developing embolism than those studied because of their poorer general health and immobility. Had these subjects been included one may speculate that the estimated incidence of embolism would have been higher than that actually obtained.

(iv) Age.

There was a steady increase in the incidence of significant perfusion study abnormalities with age, increasing to 78% of studies for subjects aged 80-89 years. This finding correlates well with the results obtained by Friedman et al. (1970) who found significant perfusion abnormalities in the lung scans of 57 of 80 subjects (71%) in a geriatric nursing unit. The increased incidence of such abnormalities in the current series reflects the higher incidence of cardio-pulmonary disease in the elderly. The development of interstitial fibrosis with distended alveoli in the aging lung, lesions of little clinical significance and not readily detected by plain chest Xray (Simon, 1965), undoubtedly contributes to the picture in the very old.

(v) Chest Xray and perfusion study correlation

(aa) General. In this series an abnormal chest Xray was only rarely accompanied by a normal perfusion study appearance

(25/241) while significant perfusion abnormalities were frequently seen in the presence of a normal chest Xray (49/159). This occurrence may be partly explained by differing sensitivies and resolution characteristics of the two methods of examination. The resolution characteristics of the gamma imaging system employed make discrete lesions smaller than 2 cm in diameter difficult to resolve by this method, though they may be readily resolved by Xray equipment. Other lesions such as small pleural effusions and areas of pleural thickening may be well visualised radiologically, but because they may produce little or no recognisable alteration in pulmonary perfusion they are undetected by perfusion scanning.

The pulmonary perfusion study is a very sensitive method for detecting certain diffuse abnormalities throughout the lung which in certain instances can be detected only with difficulty radiologically. Increased interstitial fibrosis, alveolar distension and even bullous formation may pass radiological examination undetected (Simon, 1965). However such pathology is generally characterised by the presence of perfusion scan defects (Poulose et al. 1968). Pulmonary embolism may present a normal radiological appearance, an occurrence noted in 16 of 46 instances of the disorder in this series, when the perfusion study shows multiple large abnormalities.

In general, lesions accompanied by radiological pulmonary opacity produce corresponding abnormalities in the perfusion study because of decreased pulmonary arterial supply to the area.

(bb) Pulmonary congestion. The demonstration of non-segmental perfusion defects in 31 out of 69 subjects with radiologically evident pulmonary congestion is consistent with the findings of James et al.(1971) who described the occurrence of multiple small ill-defined nonsegmental perfusion defects, corresponding to indistinct opacities in the chest Xray as the most common pattern in congestive cardiac failure. A smaller number (14/69) had less apparent irregularity in perfusion while large defects were noted in 18/69. Increased interstitial pressure in the presence of interstitial oedema with resulting shut down of extra-alveolar vessels is a suggested mechanism for the production of irregular or patchy scan appearance (James et al. 1971). The large defects seen were the result either of confluence of alveolar oedema or other pathology e.g. embolism.

(cc) Overinflated lung. Areas of increased radio-lucency with flattening of the diaphragms characteristic of overinflation of the lungs was generally accompanied by abnormalities in the perfusion study. Pressure by distended alveoli on pulmonary capillaries is probably a major cause for

the occurrence of the small nonsegmental defects which were most commonly seen. Larger defects may be explained by the presence of bullae, while interstitial fibrosis and intra-pulmonary shunting are other possible mechanisms to account for the appearances seen.

(dd) Pneumonia. Relatively little has appeared in the literature regarding the scan appearances seen in pneumonia. Kjellman (1967) studied regional lung function in a small number of children with pneumonia using radioxenon. He found perfusion and ventilation defects corresponding in position to the site of the pneumonia, the defects in ventilation being more extensive than the perfusion defects. When the pneumonia had resolved radiologically, abnormalities in regional lung function persisted. Lopez-Majano et al. (1965) had previously described abnormalities in pneumonia corresponding in position, but generally larger in extent, to the areas of radiological opacity. In the current series many of the subjects with pneumonia showed at least partial radiological resolution by the time of their initial perfusion study. Nevertheless almost half (15/32) showed large perfusion defects and an equal number (15/32) showed multiple nonsegmental defects. The perfusion study abnormality in most instances was more striking than the radiological one. Compression of the pulmonary capillary bed

by interstitial pressure and alveolar exudation are possible explanations to account for this picture. Since all regions showed resolution, tissue necrosis and scarring could not be implicated.

(ee) Pulmonary neoplasia. Many investigators have reported the pulmonary scan findings associated with pulmonary neoplasia (Wagner 1965, Hatch et al. 1965, Tauxe et al. 1970, Maynard and Cowan, 1971). The irregularities in perfusion or large segmental defects seen in subjects with pulmonary neoplasia were consistent with descriptions found in the literature. No subject was found to exhibit complete avascularity or hypoperfusion of one lung. The patchy appearance of the scan away from the site of the lesion in some subjects may represent preexisting diffuse pulmonary disease. Obliteration of pulmonary capillaries by tumour tissue primarily supplied by bronchial vessels, pressure effects on neighbouring pulmonary arteries or invasion of pulmonary arteries by tumour, regional hypoxia and reflex ischaemia due to intrabronchial mass, are possible mechanisms by which the larger defects occur.

(iv) Diagnostic groups

The great majority of subjects presenting with disorders of the pulmonary system showed significant perfusion abnormalities in their initial studies (88.8%). Apart from this group there was no significant tendency towards the

clustering of abnormal perfusion scan types among the various organ system groupings.

Since the perfusion study measures regional pulmonary perfusion it was to be expected that the most frequent demonstration of abnormalities would be among subjects with known pulmonary disease, particularly when the pulmonary disease was considered sufficiently serious to require hospitalisation.

Disorders of other organ systems may have secondary effects on the lung by such mechanisms as the production of interstitial or alveolar oedema as in cardiac or renal failure for example. When present such abnormalities were associated with an increased incidence of perfusion abnormalities and their resolution was followed by improved perfusion. For example, deterioration in perfusion was noted in seven subjects with myocardial infarction whose initial perfusion studies had been entirely normal; in three subjects pulmonary embolism was implicated, while in three others increased moist sounds or radiologically apparent pulmonary congestion suggested pulmonary oedema as the cause.

Many abnormalities in perfusion not specifically attributable to easily identifiable pulmonary disease or pulmonary embolism were related to either subclinical or mild pulmonary disease. Various degrees of bronchitis were

a particularly common cause of irregular pulmonary perfusion in subjects presenting with unrelated pathology. When the 78 subjects presenting with non-respiratory disease whose perfusion studies were classified into category C were examined 28 (36%) complained of chronic cough and 47 (60%) claimed to have exertional dyspnoea.

The previously discussed "degenerative" changes occurring in the pulmonary parenchyma which are primarily the result of aging and are of uncertain clinical significance, presumably account for others. The perfusion studies of 88 subjects presenting with non-respiratory disease were classified into category B. In 44 (50%) no radiological abnormality could be found and significant symptoms were unusual (9.1%). Radiological abnormalities were not found in 24 (31%) of the 78 subjects with non-respiratory disease whose perfusion studies were classified into category C and 16/24 of this group complained of no abnormal symptoms. In the absence of evidence of other disease most of these subjects must be classified into the "degenerative" group.

c. *PULMONARY EMBOLISM IN MEDICAL SUBJECTS*

i. Initial diagnosis. The distribution of subjects with pulmonary embolism according to the system disorder with which they initially presented is not surprising (table 4.81). The high proportion of subjects with pulmonary embolism

secondary to other cardiovascular disease reflects the recognised high incidence of thrombosis and embolism in such subjects (Krause and Silverblatt, 1955). These results are also consistent with recent findings following the use of radiofibrinogen techniques to determine the incidence of leg vein thrombosis after myocardial infarction (Murray et al. 1970; Nicolaides et al. 1971) when an incidence of thrombosis of over 30% was detected.

Nevertheless the very high incidence of embolism in subjects with recent or coexistent congestive cardiac failure (38%) was an unexpected finding. In this situation the subject is presumably predisposed by virtue of venous pooling, stasis and reduced activity. Once embolism has occurred the resulting decrease in cardiorespiratory efficiency further contributes to the perpetuation of the cardiac failure. In certain other subjects with cardiovascular disease and embolism, conditions such as bacterial endocarditis or the presence of an endocardial pacing electrode (Prozan et al. 1968) were probable additional predisposing factors.

The presence of cardiac disease may make the diagnosis of embolism far from straightforward as clinical findings may easily be misinterpreted and explained on the basis of cardiac disease. In all, 72% of subjects with cardiovascular disease and coexistent embolism had symptoms consistent with those of

embolism. However in only one third of these was the diagnosis clinically "obvious". The high incidence of symptomatic embolism in this group probably reflects the poor tolerance to emboli in a group where low cardiac reserve increases the chances of developing significant clinical and haemodynamic changes. This contrasts strikingly with the case of postoperative subjects who develop embolism (see later).

TABLE 4.81

DIAGNOSIS	NUMBER	EMBOLISM	%
All	400	46	11.5
All C.V.S.	117	21	17.9
Myocardial infarct	76	10	13.2
Congestive cardiac failure	42	16	38.1
Nervous system	82	6	7.3
C.V.A.	45	6	13.3
All G.I.T.	31	4	12.9
All diabetes	48	7	14.5
Pulmonary embolism	-	11	-

In the next largest group (table 4.81) those presenting with symptoms which were directly referable to pulmonary embolism, a high proportion naturally presented with symptoms which could be easily attributed to embolism. It is possible to speculate that this group represents only a small fraction of the general population who develop emboli since many of the others may be entirely or relatively asymptomatic and never present to hospitals.

During states of immobilisation the important pumping action of the muscles of the legs on the lower limb veins is lost. This predisposes such subjects to venous stasis. It is unlikely that venous stasis alone is sufficient to explain leg vein thrombosis, the tying of the femoral vein in rabbits seldom results in thrombosis in the absence of tissue damage (Borgstrom, Gelin and Zederfeldt, 1959) and venous thrombosis is uncommon during pregnancy in spite of the compression of the inferior vena cava which occurs (Gordon, Rosenthal and O'Leary, 1952; Sibthorpe, 1955). However, if combined with the other factors in Virchow's triad - damage to the vessel wall or increased coagulability of blood, it may be the deciding factor in determining whether thrombosis occurs. All the subjects with neurological disease who developed emboli were immobilised to some degree by cerebrovascular accidents; embolism was not noted to accompany any other neurological disorders in this series; and undoubtedly venous

stasis was an important factor in the development of these emboli. Symptoms when present were more readily related to embolism in this group than they were in those with cardiovascular disease because symptoms such as dyspnoea and chest pain were less frequently interpreted as manifestations of cardiac disease (table 4.81).

Embolism in the 2/8 subjects presenting with diabetic ketoacidosis and the one subject with benign upper gastrointestinal ulceration was unsuspected. Prolonged immobility was a probable contributing factor to the development of thrombosis in each of these cases while dehydration, an almost universal accompaniment of diabetic ketosis (Winegrad and Clements, 1971) was a possible predisposing factor in the two diabetics (Barker and Priestly, 1942). Well preserved cardiopulmonary function in all instances probably accounted for the lack of recognisable symptoms in this group.

Only 2/32 (6.2%) subjects with neoplasia had evidence of embolism (table 4.82).

TABLE 4.82

SITE OF NEOPLASM	NUMBER	EMBOLISM
Lung	8	0
G.I.T.	6	1
U.G.S.	2	0
Lympho-haem.	16	1
TOTAL	32	2

This is a smaller incidence than the average (11.5%). Although there is a well recognised association between malignant disease and thromboembolic phenomena (Wiernick and Serpick, 1969) neoplasm alone would appear to be a less potent predisposing factor than certain others e.g. congestive cardiac failure. Tumours which have a particularly strong association with thrombotic phenomena, such as those of the pancreas (Sproul, 1938) were not represented in this group.

ii. Specificity of clinical findings. The reported frequency of various symptoms and signs of symptomatic pulmonary embolism take no account of the general frequency of such features among subjects without embolism (Israel and Goldstein, 1957; Sasahara et al. 1967; Szucs et al. 1971). The nature of the present prospective series allows comparisons to be made between all subjects with embolism, both symptomatic and asymptomatic, and those without embolism; and permits the relative frequency of clinical findings to be assessed in the two groups.

When this is done, the lack of specificity of certain symptoms and signs is readily appreciated; and others, while not occurring very frequently, are found to be relatively more specific for embolism. Thus dyspnoea, the most commonly found symptom in embolism (61%) appears to be quite nonspecific (embolism:controls = 1.1:1), while pleuritic chest

pain is found twelve times more commonly in pulmonary embolism than in control subjects. Although certain of the clinical and investigative findings are more commonly found in embolism than in all other subjects they may be even more specifically associated with other conditions, for example, electrocardiographic ST segment changes with myocardial disease. The relative frequencies given can thus only apply to similar groups of medical inpatients selected in the same manner as in this series.

Analysis of serum enzyme changes illustrates the value of total lactate dehydrogenase (LDH) and aspartate aminotransferase (AAT) estimations in separating pulmonary embolism from myocardial infarction. The LDH was raised alone ten times more frequently in embolism than in myocardial infarction, and although normal LDH and AAT values in combination were found less frequently in embolism than among all other subjects (embolism:controls = 0.6:1), this finding was almost six times more common in embolism than it was in myocardial infarction.

The manifestations of pulmonary embolism are protean and they may combine in a wide variety of clinical presentations. While the presence of certain symptoms and signs can do no more than alert the physician to the possibility that embolism has occurred, the extent to which various clinical factors are weighted is very much a matter of individual experience. In the present study a more exact appraisal of the significance of

various factors has been obtained, factors which have been weighted on the basis of "all" and not just "symptomatic" embolism which would otherwise preclude about 30% of subjects from consideration.

(iii) Outcome. Deaths in hospital occurred in twenty subjects in seven (35%) of whom emboli were diagnosed during life, which represents a mortality of 15.2% for pulmonary embolism. However pulmonary embolism was a major contributing factor to death in only two subjects, both of whom had severe cardiac disease. The confirmation of the diagnosis of embolism by post mortem examination in all subjects in whom embolism was diagnosed prior to autopsy, and the failure of post mortem examination to disclose further cases, indicates that diagnosis during life is quite accurate (at least among those who die) if modern diagnostic techniques are correctly applied in a prospective fashion.

(d) SURGICAL SERIES

(i) Subject selection. The study was designed to provide as near an unselected series of subjects undergoing surgery as possible while excluding only those undergoing minor procedures and those operated on by extremely specialised units. This aim was in large part achieved by including in the study all subjects on the preselected operating schedules of general surgical units.

(ii) Time of study. Preoperative studies were used to provide baseline information with which changes occurring in the postoperative period could be compared. By performing preoperative studies very shortly before surgery, changes in scan appearances could be accurately related to the time of operation and the postoperative period.

To determine the full extent of perfusion changes in the postoperative period, a daily assessment of pulmonary perfusion would have been ideal. Only then would some of the more fleeting changes, seen from time to time (Rosenthal, 1968) be recognised. However this was not practicable because of the clinical condition of subjects in the postoperative period, the size of the study group and the properties of the radiopharmaceutical used. Instead the perfusion study was repeated as soon as the subject's condition permitted after operation and at regular intervals thereafter. Such a method did allow relatively long periods during which changes in perfusion might have occurred and resolved. For this reason the estimate of the incidence of pulmonary embolism obtained in the study probably represents a somewhat truncated figure.

(iii) Preoperative studies.

(aa) Age. As in the series of medical subjects, increasing age was associated with an increased incidence of pulmonary perfusion abnormalities. Over 70 years of age more

than half of the subjects had significant perfusion defects (categories C and D). The causes of such defects were probably the same as those resulting in a similar tendency in medical subjects as discussed earlier.

(bb) Smoking history. There is a well recognised aetiological relationship between cigarette smoking and the development of diffuse lung disease such as chronic bronchitis (Hill and Doll, 1957). The increased incidence of abnormalities among smokers presumably reflects this aetiological relationship. In such subjects chronic irritation of the bronchial tree leads to mucous gland hyperplasia and increased bronchial secretions. Casts of these secretions may result in bronchiolar obstruction and repeated infection can cause sub-clinical pulmonary fibrosis both of which may lead to abnormalities in the perfusion study.

(cc) Dyspnoea. The subjective symptom of exertional dyspnoea (table 4.68, page 150) was not a reliable index of pulmonary perfusion abnormality. Exertional dyspnoea was considered present if the subject could not walk at a normal pace on level ground because of shortness of breath but could walk at a slow pace on level ground for up to a mile (Fletcher et al. 1959). Lesser degree of dyspnoea were disregarded. The subject's account of his discomfort involves many factors including intelligence, ability to describe sensations and

threshold for sensory stimuli. It is thus likely that phenomena such as dyspnoea may be reported with little accuracy by subjects untrained in the recognition of abnormal symptoms and their separation from normal sensations. While some who are obviously short of breath on exertion have become so used to their disability that they regard it as 'normal', others are concerned that physiological changes in respiration are quite 'abnormal' and erroneously report respiratory distress. Although a standard question was asked of each subject, observer errors in observation, appreciation and evaluation probably cannot be entirely discounted.

(dd) Cough. Persistent cough was a more reliable index of pulmonary perfusion abnormality than dyspnoea among pre-operative subjects. More than half (38/56) of subjects complaining of this symptom had significantly abnormal perfusion. By far the commonest cause of cough was that associated with cigarette smoking. Wynder, Lemon and Mantel (1965), in a study of the epidemiology of persistent cough, demonstrated that 45% of their population of those smoking 1-10 cigarettes a day, and 70% of those smoking more than 21 cigarettes per day, had persistent cough. In 90% of those with cough it was productive. Cough associated with mucous hypersecretion is a constant feature of chronic bronchitis and may follow exposure to air pollutants. Unless structural

changes have occurred in the lung or bronchial obstruction with inspissated mucous occurs the presence of hypersecretion alone will not be accompanied by perfusion changes. When cough is associated with diffuse parenchymal lung disease, even when clinically mild, it may result in perfusion changes. The abnormalities seen can be expected to vary in severity from slight irregularities to large defects as were seen in emphysematous subjects.

(ee) Chest Xray correlation. The reasons for the type of correlation seen between chest Xrays and perfusion scans has been discussed earlier (see (b) Medical Series (v) chest Xray and perfusion study correlation). As was noted among medical subjects an abnormal chest Xray was rarely accompanied by a normal perfusion scan (8.3%), while a significant number of subjects with normal chest Xray appearances had perfusion abnormalities (26.6%).

(iv) Postoperative studies. A variety of new appearances, whose presence suggested alterations within the bronchial tree or pulmonary vasculature were noted in the first postoperative studies.

Assisted ventilation during anaesthesia with aeration of previously unventilated alveoli may account for the improved perfusion noted in 11% of subjects. Postoperative breathing exercises and physiotherapy may also be partly responsible for

the changes in these subjects.

Deterioration in perfusion occurred 1.6 times more frequently in subjects who had a history of chronic cigarette smoking. Bronchial obstruction consequent upon unexpectorated pooled secretions, followed by reflex vasoconstriction in that area, was the probable mechanism resulting in these changes in most subjects. Inhibition of the cough reflex and voluntary inhibition of cough and deep inspiration in the postoperative period as well as inhibition of the respiratory centre by drugs (e.g. curare and morphine) are potent predisposing factors to pooling of secretions (Warren, 1963). Bronchial secretions are more copious in smokers than nonsmokers. These factors combine to result in a high incidence of postoperative deterioration in perfusion among smokers.

A less common cause of perfusion deterioration in the postoperative period was pulmonary embolism which will be discussed separately.

(e) Thromboembolism in surgical subjects

i. Diagnosis. Since the present study was initiated in February 1970 two smaller series of surgical patients in whom the incidence of pulmonary embolism was estimated in a somewhat similar fashion have been published (Sternlieb, 1970; Allgood et al. 1970). In these series pulmonary embolism was diagnosed on the basis of perfusion scans alone. Such a

technique is not satisfactory as it allows embolism to be diagnosed erroneously when postoperative bronchial obstruction leads to regions of pulmonary ischaemia.

In this present series 10/29 (34.5%) instances of post-operative decrease in perfusion with large defects were accompanied by bronchial tree obstruction as indicated by combined inhalation and perfusion scanning. Without inhalation studies these occurrences would have been regarded as embolic. The very significant number of subjects with non-embolic perfusion defects stresses the necessity of taking account of regional ventilation whenever embolism is sought. Without adequate assessment of this important parameter many diagnostic errors can be made.

(ii) Time of diagnosis

In 13/19 subjects (68.4%) the diagnosis of embolism was made on the basis of the first postoperative study, and in 12/19 (63.1%) the diagnosis was made within 6 days of operation. It is possible that, because of delays in performing perfusion studies in some patients because of their clinical condition, other instances of embolism were missed. Nevertheless a significant number of embolic episodes were recorded early in the postoperative period.

Investigations by other workers using radio-iodinated fibrinogen uptake techniques to detect the development

of thrombosis in the deep limb veins (Flanc et al. 1968; Kakkar et al. 1969) indicate that such thromboses often originate during the period of operation. In a number of such instances fragmentation undoubtedly occurs with the production of pulmonary emboli. The detection of embolism early in the postoperative period by scanning thus correlates well with the published data regarding the natural history of deep vein thrombosis in surgical subjects.

(iii) Subsequent course

In almost one-third (6/19) of the subjects who developed postoperative embolism further episodes of embolism were noted to occur during their stay in hospital, while in the remaining subjects, including the subject in whom embolism was detected preoperatively, no further episodes were noted. Although the characteristic scan finding in symptomatic pulmonary embolism is multiple perfusion defects suggesting multiple episodes (Poulose et al. 1970) the present study indicates that multiple embolic episodes can be detected in only a minority of surgical subjects with embolism. Undoubtedly a group of subjects comprising only those with symptomatic embolism includes a higher proportion of subjects with repeated embolisation than would a group including all embolism since repeated obstruction of the lesser circulation would be more likely to produce recognisable clinical symptoms

than would a single episode.

The rate of resolution noted in some of the detected lesions was faster than has been generally reported as normal (Secker-Walker, Jackson and Goodwin, 1970). However it is consistent with reports of more rapid resolution of pulmonary emboli (Rosenthal, 1968). The rapid resolution noted is consistent with the occurrence of emboli early in the post-operative period when the fragmenting thrombus would be more friable and contain less fibrous tissue than might be expected in older thrombi which have more time to organise. Such friable emboli would be more susceptible to the endogenous fibrinolytic system and persist for a shorter period than the better organised variety.

(iv) Age

Many published autopsy studies stress the effect of advancing age on the development of thrombosis (Carlotti et al. 1947; Towbin, 1954; Sevitt and Gallagher, 1961). Embolism is uncommon in young subjects such as sick soldiers (Allen, Linton and Donaldson, 1945) and when it occurs in children it is rarely due to thrombosis of the leg veins (Emery, 1962). In a clinical study by Morrell, Truelove and Barr (1963) at Oxford, the incidence of pulmonary embolism correlated closely with age and rose steeply after the age of 40 years in both operative and non surgical subjects. In the

present prospective series the findings recognised in symptomatic and autopsy diagnosed embolism still apply. There were significantly more subjects with embolism in the group whose ages were over 50 years. The effect of advancing age may be related to the greater incidence of cardiac and neoplastic disease along older people. In addition when they are confined to bed they tend to be less active than younger persons, a factor which undoubtedly affects the development and propagation of thrombosis.

(v) Sex

In an autopsy series of 351 subjects Hunter and co-workers (1941) found that thrombosis occurred with equal frequency in men and women. Towbin (1954) found a higher incidence of embolism in women (34%) than in men (20%) when he studied a series of 512 subjects who died in an old people's institution. Morrell and co-workers (1963) however could demonstrate no difference in the incidence of pulmonary embolism between males and females in their clinical series. In the present series the incidence in women was double that in men.

In recent years many studies have demonstrated the increased incidence of thromboembolism following the use of oral contraceptive preparations (Inman and Vessey, 1968; Vessey and Doll, 1968; Vessey and Weatherall, 1968; Vessey and Doll, 1969;

Vessey et al. 1970) and in particular have related the oestrogen content of these preparations to the risk of embolism (Inman et al. 1969; Poller, 1970). None of the subjects in the present series was receiving oestrogens at the time of operation and the majority of those females developing embolism were menopausal or postmenopausal. No ready explanation is available for this result which may be only fortuitous.

(vi) Symptoms and signs

The paucity of symptoms and signs associated with the development of embolism was one of the most striking features of the current study. Dyspnoea when present (4/20) was mild, clinical evidence of deep vein thrombosis was found in only 20% (4/20), and severe symptoms did not occur at all in this group but led to the erroneous clinical diagnosis of embolism in 3 subjects. That it is difficult to fully appreciate the severity of thromboembolic pulmonary vascular obstruction by the usual clinical means was amply illustrated recently by Parmley et al. (1970) in a report of four subjects with relatively asymptomatic massive embolism. The common discovery of multiple perfusion defects in the lung in subjects presenting with single episodes of chest symptoms also suggests that previous episodes of embolism may have occurred which had passed notice. Sasahara et al. (1969) have suggested that the state of the cardiopulmonary system prior to pulmonary embolism may be

a major determinant of the clinical and haemodynamic alterations produced. In some subjects in this series the lack of severe prexistent cardiorespiratory disease may have aided their tolerance to emboli, while in others the relatively minor degree of occlusion brought about by the embolus (less than 15% of the pulmonary circulation) may not be expected to produce severe symptoms in the absence of bronchoconstriction or infarction. However the occurrence of multiple asymptomatic emboli over a period of days in elderly subjects (including illustrated case 3) is difficult to explain on the basis of well preserved cardiorespiratory function or minor occlusion.

It would be expected that emboli occurring later in the postoperative period are more likely to cause symptoms. Being better organised such thrombi are probably less likely to fragment later but if they do the resulting emboli would be larger and less friable because of the increased amount of fibrous tissue. They would thus cause greater disturbance to the pulmonary circulation, both because of their size and their decreased susceptibility to fibrinolysis allowing them to remain 'in situ' longer.

The results of this series indicate that even with most diligent clinical examination many episodes of pulmonary embolism (probably the majority) are going to be missed, as presumably they have been in the past. Although the

efficiency of the method of detection employed in this study cannot be accurately assessed at present, such a technique, if applied routinely even in modified form, would greatly increase the percentage of postoperative embolic episodes detected.

(vii) Nature of surgery. The highest incidence of pulmonary embolism in this series was associated with operations on the biliary tract (14.7%) while prostatectomy was associated with approximately half the incidence of embolism (7.5%).

Almost half a century ago Lister (1927) stressed the high incidence of pulmonary embolism following upper abdominal surgery and considered that good movement of the diaphragm was necessary to maintain adequate venous return from the legs and inhibit venous stagnation, a possible cause of thrombosis. The movement of the diaphragm is least immediately after operation. A detailed study of calf blood flow after operation by Browse (1962) showed that this could be at its minimum immediately after operation or could gradually reach a minimum on about the fifth postoperative day. However no study relating the incidence of embolism or thrombosis to this parameter appears to have been published.

(viii) Duration of anaesthesia

The increased incidence of pulmonary embolism among subjects whose anaesthesia lasted longer than one hour appears to be highly significant. The finding is consistent with recent radiofibrinogen studies (Kakkar et al. 1970) which relate the initial occurrence of leg vein thrombosis to the period of operation. The longer the period of immobility the greater is the risk of developing thrombosis. This thrombus in turn may fragment to result in pulmonary embolism.

The results in this series indicate that operations of short duration, particularly those lasting less than one hour, are relatively free of the risk of postoperative pulmonary embolism (1.4%). This finding is of importance when contemplating prophylactic anticoagulation prior to surgery as has been suggested by some authors (Sevitt and Gallagher, 1961). The group most likely to benefit from such a step would be those whose operations are expected to last in excess of one hour. In many of those undergoing shorter procedures where thromboembolic complications are not a recognised common occurrence the dangers of anticoagulation probably exceed the risks of embolism.

An additional factor which may be of importance is the type of ventilation possible during operation. Hodgson (1964) has shown that positive pressure ventilation during operation causes more stasis in the leg veins than when the patient

breathes spontaneously. During operations in which muscle relaxants are used positive pressure ventilation is necessary. This may play some part in increasing the risks attendant on longer operative procedures.

(ix) ABO blood group. A recent cooperative study revealed a deficit of subjects of blood group O among a population of women developing clinically evident venous thromboembolism (Jick et al, 1969). The association between certain pathological states and ABO blood group is well recognised, particularly those concerned with upper gastro-intestinal lesions such as gastric carcinoma and duodenal ulcer (Vogel and Krugler, 1968). A factor which has been considered in connection with the association of blood group and thromboembolism is the slightly lower levels of anti-haemophilic globulin (A.H.G., factor VIII) in subjects of blood group O (Preston and Barr, 1964). Mechanisms to account for the recognised phenomenon are at present speculative. The findings in this series, although not quite reaching a level of statistical significance, support the observation of Jick et al. (1969) in that there are fewer subjects of blood group O among those with embolism than might be expected if blood group played no part.

(x) Neoplasia. There is a well recognised association between malignant disease and thromboembolic phenomena (Wiernik and Serpick, 1969). In a review of 4,258 consecutive autopsies, Sproul (1938) found that carcinoma was the most frequent systemic condition associated with thrombosis of the veins of the abdomen, pelvis or legs. Barker and Priestly (1942) found that postoperative thromboembolism was two and a half times as common in subjects with carcinoma as in subjects without malignant disease. The finding in the present series that there is a significant increase in the likelihood of developing embolism postoperatively in the presence of neoplastic disease is consistent with the results of Barker and Priestly. In the current series there was 2.3 times the likelihood of developing embolism in the presence of systemic neoplastic disease.

(xi) Implications. The demonstration of asymptomatic emboli in postoperative subjects, some of which herald the occurrence of further, more serious episodes (e.g. illustrated cases 2 and 3), has implications regarding the management of postoperative subjects. Using the results of this study and methods developed for the investigation of peripheral thrombosis (Thomas et al. 1970, Mahaffey et al. 1971) as a basis it is possible to suggest a rational approach to the reduction of mortality from postoperative thromboembolism

which does not involve the use of prophylactic anticoagulation.

All subjects undergoing operation, or only those whose period of anaesthesia is in excess of one hour, are studied by routine perfusion scanning (including plain chest Xray) on the fifth or sixth day postoperative day. Where abnormalities in perfusion are found inhalation scanning is performed. If the presence of embolism is suggested by this method lower limb phlebography including assessment of the patency of the iliac veins and vena cava is performed. Only if venous occlusion is found is definitive therapy commenced in the absence of symptoms. However since small vessel thrombus is unlikely to produce serious effects if embolism from these sites occurs (Mahaffey, Mavor and Galloway, 1971) subjects with only small vessel disease may be omitted from the treatment group. All subjects with embolism are followed by repeated perfusion studies until resolution is noted.

Such a technique would have practical advantages over the use of radiofibrinogen tests used for the detection of thrombosis as it would be less time consuming for staff and facilities and hence could be applied to a larger group of patients. It would not carry any risk of the development of serum hepatitis and would not involve the patient in uncomfortable investigative procedures until later in the post-operative period. The use of contrast radiography to delineate the peripheral and central veins would add the advantage of

demonstrating those subjects with large vessel disease in whom dislodgement of thrombus could produce a life threatening situation. The majority of subjects with embolism experience a benign course, selection for therapy on the basis of peripheral and central phlebography could separate those unlikely to experience further episodes from those who are, and so reduce the necessity for long term medication in the more benign variety of the disease.

CHAPTER V

"SELECTED" SERIES

A. PERFUSION STUDIES IN A NORMAL VOLUNTEER GROUP

The prospective series of medical and surgical subjects revealed a high incidence of perfusion abnormalities, many of which were unsuspected. In addition a high incidence of perfusion abnormalities has been described in association with advanced age (Friedman et al. 1970). Hence, in an effort to determine the frequency with which perfusion abnormalities occur among normal subjects without previous pulmonary disease, a group of 119 volunteers was studied.

(a) Subjects. Volunteers came principally from among the nursing and paramedical staff of the Royal Adelaide Hospital. Subjects were excluded from the study if they had known preexisting pulmonary disease. There were 89 women and 30 men in the survey. Their average age was 25 years (range 18-61). There were 46 smokers and 73 nonsmokers in the group.

(b) Method. A standard 4 view perfusion study was obtained in all subjects using technetium labelled macro-aggregates (^{99m}Tc MAFH) and a scintillation camera. Previous serious diseases were listed on a standard proforma (appendix dd) together with details of oral contraceptive and smoking histories. A chest Xray was obtained for all subjects who had not had a normal chest Xray within the six months prior to the study and in all subjects who had perfusion abnormalities

demonstrated.

The perfusion study was repeated in 25 subjects after periods of up to 3 months.

Perfusion studies were classified "blind" by the same observer on two separate occasions.

(c) Results. The perfusion studies were classified into four groups which corresponded to the classification of the medical and surgical series. The distribution of perfusion study categories is shown in table 5.1.

TABLE 5.1

CATEGORY	NUMBER	PERCENT
Normal (A)	74	62
B	27	23
C	18	15
D	0	0

There were no subjects with defects of at least segmental size and 62% of subjects had normal studies.

The effect of age on the distribution of scan abnormalities is shown in table 5.2 (percentage in brackets).

TABLE 5.2

AGE	SCAN TYPE				TOTAL
	A	B	C	D	
< 20	24 (75)	7 (22)	1 (3)	0	32
20-29	31 (61)	13 (25)	7 (14)	0	51
30-39	8 (40)	5 (25)	7 (35)	0	20
40-49	8 (73)	0	3 (27)	0	11
50-59	1 (33)	2 (67)	0	0	3
60+	2 (100)	0	0	0	2

The results in smokers and nonsmokers are shown in table 5.3 (percentages in brackets).

TABLE 5.3

AGE	SCAN TYPE					
	NONSMOKERS			SMOKERS		
	A	B	C	A	B	C
< 20	14 (100)	-	-	10 (56)	7 (39)	1 (6)
20-29	14 (82)	2 (12)	1 (6)	17 (50)	11 (32)	6 (18)
30-39	4 (44)	3 (33)	2 (22)	4 (36)	2 (18)	5 (45)
40-49	2 (67)	-	1 (33)	6 (75)	-	2 (25)
50-59	1 (33)	2 (67)	-	-	-	-
60+	-	-	-	2 (100)	-	-

The extent of smoking was computed for each subject by multiplying the stated average number of cigarettes smoked per day by the number of years of smoking at that level. This "index" is directly related, albeit roughly, to the total number of cigarettes smoked.

The relationship of the smoking "index" to scan type is shown in table 5.4 (percentages in brackets).

TABLE 5.4

SMOKING INDEX	SCAN TYPE A	SCAN TYPE B	SCAN TYPE C	SCAN TYPE D	TOTAL
0	35 (76)	7 (15)	4 (9)	-	46
1-20	12 (75)	4 (25)	0	-	16
21-100	18 (64)	7 (25)	3 (11)	-	28
100+	9 (31)	9 (31)	11 (38)	-	29

In the 25 subjects in whom perfusion studies were repeated no changes were noted in any subject.

(d) Discussion. The group of 119 volunteers contained relatively few subjects over the age of 40 years. Hence it is not possible to draw valid conclusions regarding the effect of aging on lung scan appearances in a normal population. However a tendency for more abnormalities to occur in other age groups

was noted. The occurrence of previous pulmonary disease, longer exposure to pollutants (such as cigarette smoke, industrial pollutants) all probably play a part in changing the perfusion pattern in certain individuals from normal.

There was an increase in the number of pulmonary perfusion abnormalities with increasing cigarette exposure as expressed as the smoking index. The group studied was small and it was necessary to express widely differing smoking histories in a manner which would facilitate comparison. Thus, for example, a smoker of 20 cigarettes a day for 5 years would have the same "index" as a subject who smoked only 5 cigarettes a day for 20 years. Whether it is entirely valid to consider these two exposures comparable is doubtful. However the use of such an index was considered the most suitable method of expressing the results of this small series. The effect of cigarette smoking on pulmonary perfusion was more pronounced than the effect of age alone. The higher the smoking index the more likely was the perfusion study to be abnormal.

These results suggest a possible causative role for cigarette smoking in the production of nonsegmental perfusion defects and diffuse irregularity in pulmonary perfusion. In certain individuals comparatively low levels of exposure appear to bring about changes in perfusion at an early age. None of the subjects studied admitted to troublesome or persistent chest symptoms. Nevertheless many abnormalities were found indicating

that pulmonary perfusion studies are more sensitive to slight abnormalities in respiratory function than the subjects' own sensory mechanisms! Probable mechanisms underlying the increased incidence of perfusion abnormalities in smokers include increased mucus production resulting in small areas of alveolar obstruction. Alveolar obstruction in turn may result in increased alveolar pressure with resulting collapse of pulmonary capillaries or local vasoconstriction secondary to ischaemia. Changes such as these as well as sequelae of more serious intercurrent episodes of bronchitis common among smokers could account for the various degrees of irregularity in pulmonary perfusion seen more commonly among smokers than among nonsmokers.

Clinical significance

Other authors have attested to the difficulty in interpreting pulmonary perfusion scans in the elderly (Fredman et al., 1970).

Chronic bronchitis and emphysema are also well recognised causes of abnormal pulmonary perfusion (Taplin et al., 1964c). The results of this small study indicate that great care must be taken in interpreting the pulmonary perfusion scans of all smokers, even young ones, as irregularities in perfusion may be related to cigarette smoking rather than to other more acute pathology.

B. LACTATE DEHYDROGENASE ISOENZYME 3 ESTIMATIONS

The confirmation of organ specific diagnosis has been allegedly improved by the availability of electrophoretic and heat stability separation analysis of isoenzymes of lactate dehydrogenase (LDH) (Vessel and Bearn, 1961). In particular it has enabled more confident diagnosis of acute myocardial infarction than was previously possible on the basis of total enzyme estimations (Strandjord, Clayson and Frier, 1962; Peters and Davis, 1969).

LDH_3 isoenzyme is the enzyme most characteristic of pulmonary tissue (Wroblewski and Gregory, 1961) and has been demonstrated to rise to high levels following acute pulmonary embolism in unanaesthetised animals (Bloor, Sobel and Henry, 1970). Others have attempted to demonstrate similar elevations clinically (Batsakis and Brier, 1968; Auvinen and Konttinen, 1971). An experimental situation was thus designed to test the efficiency of the LDH_3 estimate available in our own laboratory in the diagnosis of pulmonary embolism.

(a) Method. The estimations of LDH isoenzyme activity were carried out in the routine biochemical laboratory of the Institute of Medical and Veterinary Science using the following standard technique.

Total LDH activity was first estimated and then sera heated at 55°C for 20 minutes to destroy the heat labile fractions

LDH_{4+5}. Following re-estimation of LDH activity the sera were heated at 60°C for 20 minutes so that only the heat stable portion remained (LDH_{1+2}). A value for LDH_3 can be obtained by subtracting the final estimate of LDH activity from that following initial heating.

Lactate dehydrogenase isoenzymes were estimated in 47 subjects prior to surgery and at the time of routine post-operative perfusion scanning. This estimation was also made at the time of the demonstration of new perfusion defects in all subjects in the surgical series of 221 subjects and in the medical series of 400 subjects.

(b) Results. The results of LDH_3 estimations are shown in figure 5.1. In column 1 are the results of preoperative estimations in 47 subjects (mean ± SD = 50.4 ± 15.1). In column 2 are found the postoperative values in those subjects who did not develop embolism (57.3 ± 21.7). Four subjects from the 47 studied prospectively developed embolism. The estimates of their LDH_3 activity at the time of diagnosis are shown in column 3. Only one episode of embolism occurred in each. In column 3 and 4 are the estimates of confirmed postoperative embolism in 19 subjects made at the time of diagnosis (55.3 ± 24.5). In column 5 are the estimates of LDH_3 activity in 46 "medical" subjects at the time of diagnosis (64.9 ± 26.7).

In figure 5.2 the change in LDH_3 activity from the pre-

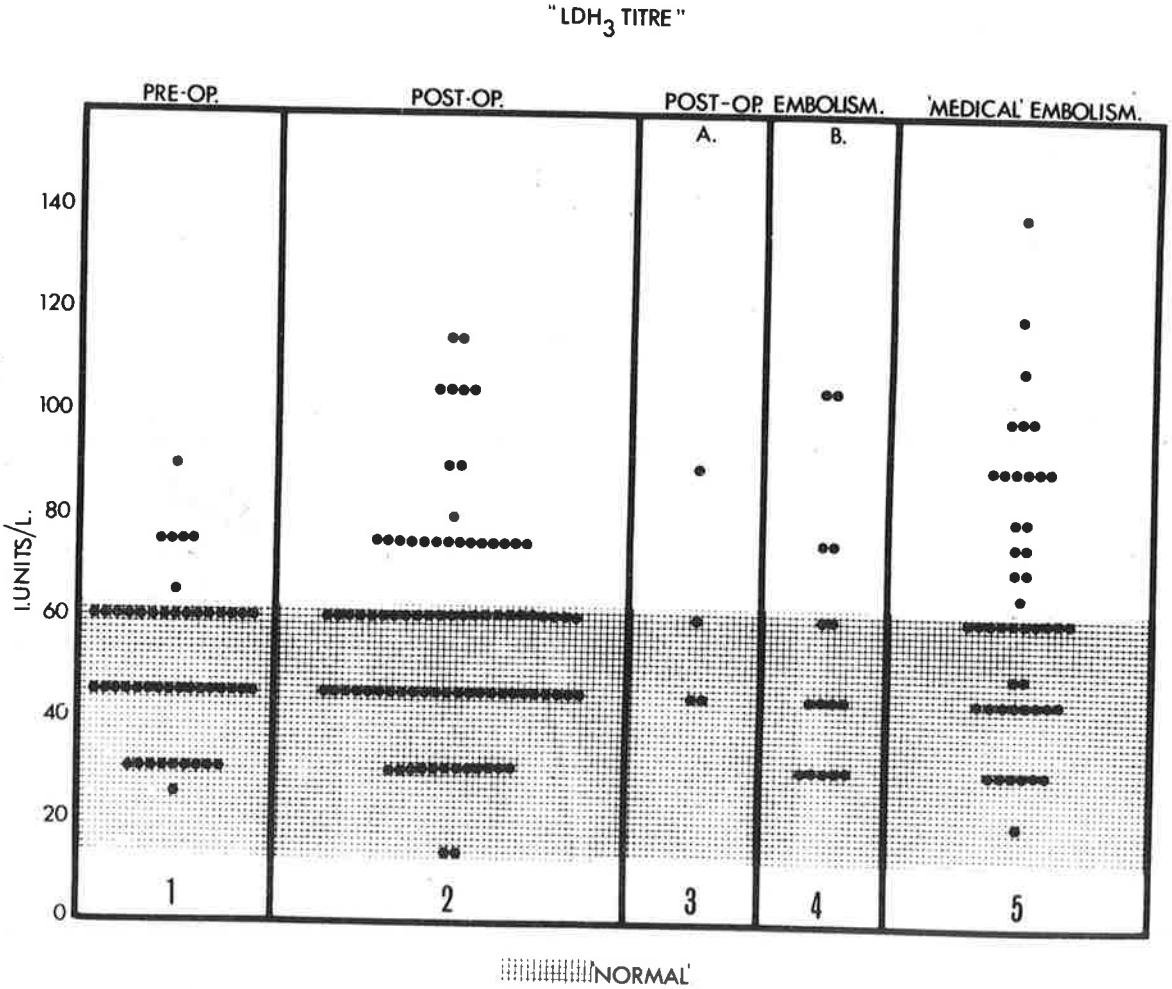


FIG. 5.1

Column 1 Preoperative estimations in 47 subjects

2 Postoperative estimations - no embolism

3,4 Postoperative estimations with embolism

5 Estimations following diagnosis of embolism in medical subjects

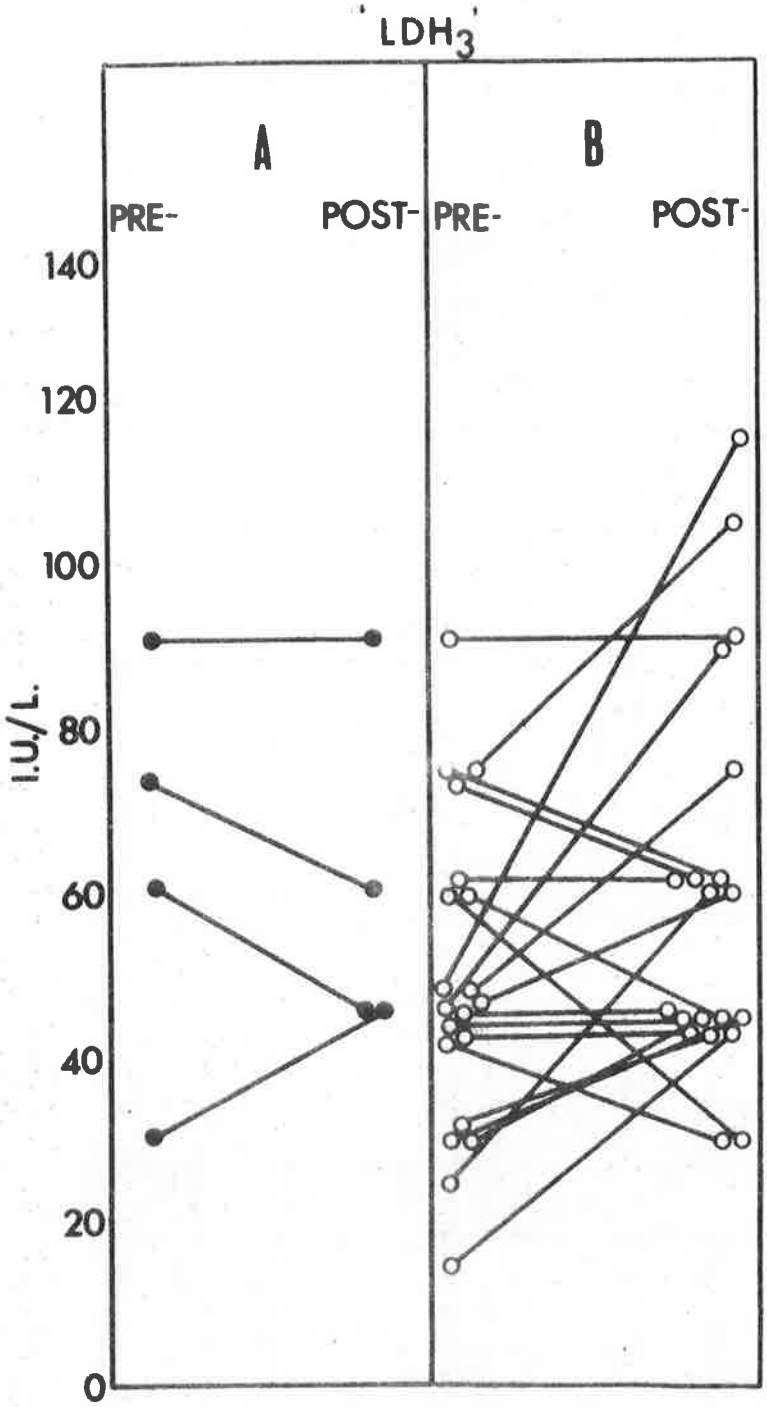


FIG. 5.2 A Change in LDH_3 estimation in 4 subjects who developed pulmonary embolism.

B Change in LDH_3 estimation in 20 consecutive subjects who did not develop embolism.

operative study to the initial postoperative study (whem embolism was diagnosed) has been compared with the change in the first 20 consecutive subjects studied prospectively (columns A and B respectively).

(c) Discussion. It is apparent from inspection of figure 5.1, and from comparison of the mean LDH_3 activity obtained by the method outlined is of little value in separating subjects with embolism from others. There was no evidence that documentation of changing LDH_3 activities was of diagnostic value either. Changes in LDH_3 values were erratic in the "embolic" group as well as in postoperative subjects who did not develop embolism.

It is not known whether the deficiency in this test is related to errors inherent in the method of estimation of the particular isoenzyme fraction or is due to actual fluctuations in LDH_3 values unrelated to the occurrence of embolism.

Animal experiments indicate that the extent of the rise in LDH_3 following pulmonary embolism is related to the size of the embolus and that the rise may be short lived (Bloor, Sobel and Henry, 1970). Although estimates of LDH_3 activity were made in the current study within a short time of the embolic episode in the great majority of instances, the exact time of embolism is unknown. The more evanescent changes might have returned to normal. Other authors (Cohen et al. 1964; Batsakis and Briere,

1968; Goodley, 1969; Auvinen and Konttinen, 1971) have found similar difficulty in differentiating pulmonary embolism from other conditions on the basis of LDH_3 activity and consider the test of doubtful value.

PULMONARY PERFUSION AND INHALATION SCANNING: A HOSPITAL POPULATION STUDY WITH PARTICULAR REFERENCE TO PULMONARY EMBOLISM

SUMMARY

Radionuclide techniques, some newly available and others specifically developed as a part of this project, have been used to assess regional pulmonary perfusion and ventilation in various hospital populations. The aim was to investigate the incidence and natural history of pulmonary embolic disease in two prospective surveys of hospitalised subjects.

A. Methodology

(a) Pulmonary perfusion. Assessment of regional pulmonary perfusion by rapid sequence scintiphotography (scintiangiography) following the intravenous injection of sodium pertechnetate was compared with the results obtained by the usual techniques of pulmonary scanning following the intravenous injection of iodine labelled macroaggregates. However, in a series of 64 subjects scintiangiography was found to offer little advantage beyond speed while major disadvantages included poorer resolution of small defects, inefficient display of the lower zones of the left lung and limitation to a single "view" of the lungsin any one study. When technetium macroaggregated ferrous hydroxide became available in Australia in late 1969 a

comparative study was undertaken of the scintillation camera and a rectilinear scanner in a series of consecutive subjects. On the basis of this study technetium labelled macroaggregates and the scintillation camera were the combination chosen for the assessment of regional perfusion in the prospective surveys.

(b) Pulmonary ventilation. Two techniques, both of which were developed as part of this project, were used for the assessment of regional ventilation. A simple nebulizing system comprising a Bird Micronebulizer®, reservoir bag, breathing valve and delivery tubing was designed to deliver an aerosol spray suitable for inhalation scanning purposes. Initially sodium pertechnetate was used as the inhalant and its behaviour during and following inhalation was observed. Sodium pertechnetate is absorbed into the perfusing blood of the lung following inhalation with $T_{\frac{1}{2}}$ about 15 minutes. Satisfactory scintiphotos of the lung detailing ventilatory patterns could be obtained using this radiopharmaceutical if the scintiphotos were accumulated during the inhalation of pertechnetate and for only 4-5 minutes afterwards.

The inability to perform perfusion and inhalation studies at the same sitting when technetium containing radiopharmaceuticals were used in both investigations led to the use of indium chloride as inhalant. This proved to be a more suitable radiopharmaceutical for combined studies and since it was not

absorbed following inhalation, either gamma camera or rectilinear scanner study was possible.

The behaviour of these two radiopharmaceuticals following inhalation was studied in a variety of conditions. In particular when pulmonary embolism was suspected the diagnosis could be confirmed within minutes by the demonstration of normal ventilation (using indium chloride) in a region of decreased perfusion (using technetium labelled macroaggregates) without moving the subject.

(c) Digital studies. Analysis of blood flow studies and static scintillation camera studies using a 1600 channel analyser, fast magnetic tape system and CDC 6400 computer was investigated. However such manipulation was found to be only of marginal value in the majority of instances.

B. Prospective series

Prospective series of 400 medical and 221 surgical subjects were studied to determine the incidence and natural history of pulmonary embolism in such subjects. Medical subjects were studied at regular intervals from the sixth day of admission and surgical subjects were studied preoperatively and at regular intervals in the postoperative period.

For ease of comparison all perfusion studies were classified as normal or in one of three abnormal groups depending on the type of perfusion displayed.

(a) Medical group. The perfusion patterns noted in the 400 medical subjects were correlated with their radiological appearances and known pulmonary pathology. The results of the investigation were presented according to the organ system disorder with which the patient presented.

Among medical subjects the incidence of embolism was 11.5% (46/400). The incidence was higher in women than in men and was particularly high in association with certain other conditions, particularly those which resulted in prolonged immobility or congestive cardiac failure.

A variety of clinical symptoms, signs and investigative parameters were investigated to determine the relative frequency of some of those features classically described in association with embolism. When their incidence was compared with that in other medical subjects the lack of specificity of certain features was highlighted. Thus dyspnoea, although common in embolism, was equally common among other subjects; while dyspnoea of sudden onset was three times more common among subjects with embolism than among all others. Some pulmonary signs, e.g. wheeze, were less common in embolism than among general medical subjects in this series. Various radiological, electrocardiographic and biochemical features were treated similarly. Of the 46 subjects with embolism a correct confident clinical diagnosis was made in 17 subjects, while the diagnosis was correctly thought likely in 15 subjects. In a

further 14 subjects embolism was unsuspected. Errors in appreciation of embolism generally stemmed from the misinterpretation of symptoms and signs as being entirely due to cardiac disease or to the lack of objective evidence of embolism in subjects with well preserved cardiorespiratory reserve. In 12 subjects an incorrect clinical diagnosis of embolism was made.

Seven subjects who suffered embolism died. In five subjects autopsies were performed and these confirmed the diagnosis of embolism. No macroscopic embolism was discovered at autopsy in any other subjects in this series who died.

(b) Surgical group. A group of 259 subjects was studied preoperatively. The nature of their pulmonary perfusion was correlated with their current radiological chest appearance, the presence of coexisting disease and with a variety of pulmonary symptoms, their age and smoking histories. A high incidence of irregularity in perfusion was associated with the presence of persistent cough and with a history of cigarette smoking, but dyspnoea was a poor indicator of the type of pulmonary perfusion.

Two hundred and twentyone of the subjects studied were followed up in the postoperative period. Irregular changes in pulmonary perfusion were noted following operation, deterioration in perfusion being seen more frequently in chronic cigarette smokers. In 10 subjects non-embolic large perfusion defects were

found which were accompanied by bronchial tree obstruction as seen by combined perfusion-inhalation study. In a further 19 subjects well ventilated perfusion defects or characteristic angiographic changes indicated that embolism had occurred. In 63% (12/19) the diagnosis was made within 6 days of operation, and further episodes were noted to occur during their hospital stay in 6.

The highest incidence of embolism was associated with upper abdominal surgery, 14.7% in operations on the biliary tract. There was a statistically significant increase in likelihood of developing embolism if operations lasted longer than 1 hour. There were relatively fewer males than females in the embolism group and the incidence of embolism among subjects of blood group 0 was low, consistent with the findings of others recently. When neoplasia was present the chances of developing embolism were doubled. Over the age of 50 years the incidence of embolism was increased.

The paucity of symptoms and signs in association with embolism was a striking feature of this series. Symptoms when present were minimal even when there was major obstruction of the lesser circulation. In all instances the course of embolism was benign. However in one subject with a small saddle embolus in one pulmonary artery, streptokinase was used which may have averted more serious disorder.

Implications of these findings for the management of surgical subjects has been discussed.

(c) Selected groups

(i) Normal volunteers. In a normal volunteer group of 119 subjects (average age 25 years) perfusion studies were performed and the results correlated with radiological appearance, smoking habits and age. Chronic cigarette smoking was found to increase the incidence of perfusion abnormalities. Because of poor representation of older age groups in the series no statistically significant age effect could be demonstrated. However a tendency towards a greater degree of abnormality with increasing age was noted.

(ii) LDH isoenzymes. Lactate dehydrogenase isoenzymes were estimated preoperatively and postoperatively in 47 subjects and changes were correlated with the occurrence of embolism. A heat denaturation method was used to estimate levels of LDH_3. It was found that this method is of no value in separating subjects likely to have developed embolism from other postoperative subjects. The results obtained in this group were compared with the values of LDH_3 obtained in other subjects known to have developed pulmonary embolism.

APPENDICES

(Abstracts included in appendices A-M relate to papers delivered at scientific meetings during the course of this project and refer to specific aspects of this work.)

APPENDIX A

COOK, D. J., and H. LANDER, Department of Medicine, University of Adelaide, and the Division of Nuclear Medicine, Institute of Medical and Veterinary Science.

Pulmonary Gammascintiangiography.

Rectilinear scanning of the lungs following the intravenous injection of ^{131}I-MAA (macro-aggregated albumin) or ^{113m}In-Fe(OH)$_3$ is an established technique for the detection of pulmonary perfusion defects. However, it has the disadvantage that only "static" studies are possible. We are thus investigating the value of a new isotopic technique which we are developing, which allows one to obtain "dynamic" and quantitative information of pulmonary blood flow.

^{99m}Tc (as pertechnetate) is injected intravenously and its flow through the pulmonary circulation is detected and followed by a gamma camera (Nuclear Chicago PHO/GAMMA III) linked to a 1600 channel multiparameter analyser and very fast, computer compatible, magnetic tape recording system. In this fashion, events which occur in the lesser circulation from second to second may be visualised and quantitated, and the overall pattern of blood flow in both lungs or in any particular region of a lung may be computed and compared with that in any other region. The technique is simple, rapid, involves virtually no risk or discomfort to the patient and, if desired, can be repeated at frequent intervals. The technique will be illustrated. The results of studies in normal subjects and in patients suffering from a variety of common pulmonary disorders will be presented.

Proceedings of the Australian Society for Medical Research, 2, 303, 1969.

INHALATIONAL PULMONARY SCINTIBRONCHOGRAPHY

D. J. Cook and Harry Lander,

Department of Medicine, University of Adelaide, and Division of Nuclear Medicine, Institute of Medical and Veterinary Science

Using the PHO/Gamma Scintillation Camera and an inexpensive nebulising system which delivers a droplet spray with a particle diameter of 2-4 μ, we have obtained pulmonary inhalation scintiphotos of good quality using ^{99m}technetium as soluble pertechnetate.

Scintiphotos obtained during the inhalation of pertechnetate before and after the administration of a bronchodilator, and during the washout phase after inhalation of the radioisotope had ceased, yielded valuable information concerning airway patency in a variety of pulmonary disease states.

In addition, sequential events in selected regions of both lungs were quantitated by the use of a 1600-channel multiparameter analyser in association with a very fast magnetic tape recording system and the CDC 6400 computer of the University of Adelaide. With this equipment, it was possible to plot sequential isocount profiles for both lungs and to obtain quantitative data on the changes which occur in specific regions of interest in both lung fields.

The method is efficient, safe and causes minimal patient discomfort. It employs an isotope which is readily available in most nuclear medicine laboratories and does not require the manufacture of particles. The results in normal subjects were contrasted with those obtained in a series of patients with chronic obstructive respiratory disease (CORD) and in such conditions as pulmonary embolism and pneumonia.

Australasian Annals of Medicine, 19, 282, 1970.

APPENDIX C

STUDIES OF PULMONARY BLOOD FLOW BY SCINTIANGIOGRAPHY

HARRY LANDER and D. J. COOK,

Department of Medicine, University of Adelaide, and Division of Nuclear Medicine, Institute of Medical and Veterinary Science.

The passage of intravenously administered pertechnetate through the pulmonary circulation may be observed and studied using the Gamma Scintillation Camera. The technique allows recognition of perfusion defects. Resolution is improved by the use of a 1600 channel multiparameter analyser, a fast magnetic tape recording system and the University of Adelaide CDC 6400 computer. This accessory equipment allows the rapid construction of isocount curves related to any predetermined periods in a study and permits serial quantitation of blood flow changes occurring in any selected regions of interest.

The technique has been used to study both normal subjects and patients with a variety of pulmonary disorders. It is relatively simple and entails little discomfort and virtually no hazard to the patient. In contrast to rectilinear scanning, much more information may be collected in a much shorter time.

Australasian Annals of Medicine, 19,282, 1970.

APPENDIX D

Inhalation Scintibronchography Using Nebulized ^{99m}Tc-Pertechnetate BY DAVID J. COOK AND HARRY LANDER, Univ. of Adelaide and Institute of Medical and Veterinary Science, Adelaide, South Australia (Session 20)

A method of examining the lungs using a nebulized spray of technetium as the soluble pertechnetate ion has yielded valuable information concerning airway patency and regional perfusion in both normal subjects and in persons suffering from a variety of pulmonary diseases.

We have used a Pho/Gamma scintillation camera in association with an inexpensive Bird nebulizer and single reservoir system. Ancillary equipment included a 1,600-channel multiparameter analyser, a fast magnetic tape recording system and the CDC 6400 computer of the University of Adelaide.

Information was gathered during inhalation of the radionuclide before and after administration of bronchodilator and during the phase of "washout" from the alveoli. Scintiphotos of good quality were obtained with undetectable bronchial deposition in most patients. Ten microcuries of ^{99m}Tc made up in 3 ml of water and added to the nebulizer resulted in good counting statistics. A counting rate of the order of 100 K/min was obtained over the lung fields.

Sequential events in selected regions of interest in both lungs were quantitated in each study. Isocount profiles have been constructed, and integrated counting rates from selected regions in both lungs in normal and diseased subjects have been plotted against time as an objective measure of airway patency and regional perfusion.

The method is efficient, safe and causes minimal patient discomfort. It uses an isotope readily available in nuclear medicine laboratories. Results in normal subjects will be contrasted with those obtained in patients with chronic obstructive respiratory disease (CORD) and in such conditions as pulmonary embolism and pneumonia. Unlike previous authors who have unsuccessfully attempted to use pertechnetate (and who scanned only after inhalation had ceased) we have demonstrated that important information can be collected if the examination is carried out during inhalation of the radionuclide. Delay after inhalation ceases reduces the value of the examination.

Journal of Nuclear Medicine, 11, 309, 1970.

APPENDIX E

COOK, D. J., and H. LANDER, Department of Medicine, University of Adelaide, and the Division of Nuclear Medicine, Institute of Medical and Veterinary Science, Adelaide.

The Incidence of Pulmonary Embolism in a Medical Inpatient Population.

Pulmonary embolism is recognised as a common postmortem finding. However, the reported incidence of clinical pulmonary embolism remains low. We are presently investigating the incidence and natural history of this disorder in an unselected inpatient hospital population employing serial pulmonary perfusion scintiphotography as a screening procedure. This test is accompanied in each instance by detailed physical examination, and by electrocardiographic, biochemical and radiological investigations.

To date, our attention has been directed solely to the study of medical inpatients admitted to the Professorial Medical Unit at the Royal Adelaide Hospital. Every patient admitted to that Unit who has remained in hospital for 7 days has been included in the series. The initial perfusion study is performed on the seventh day after admission and is repeated every 7 days thereafter while the patient remains in hospital. On each occasion, multiple view gamma camera scintiphotos are obtained after the intravenous injection of 1.5-2.2 mCi ^{99m}Technicium labelled macroaggregated ferrous hydroxide (^{99m}Tc-MAFH). The diagnosis of pulmonary embolism is reached only after consideration of all the evidence obtained on the serial perfusion studies, physical examination and the other ancillary investigations, often including angiography. In several instances the diagnosis has been confirmed at autopsy.

The results of this survey reveal a high incidence of pulmonary embolism in patients not suspected of having the disease. The incidence of pulmonary embolism in the first 100 male medical patients in the series was 13%. Among female patients, the incidence is considerably higher. The significance of these results and the correlation between the occurrence of pulmonary embolism and the various parameters measured will be discussed.

Proceedings of the Australasian Society for Medical Research, 2, 350, 1970.

F.

SCINTIPHOTOGRAPHY AND RECTILINEAR SCANNING OF THE LUNG USING ^{99m}Tc–MAFH (MACROAGGREGATED FERROUS HYDROXIDE)

A Comparison of 100 Subjects

DAVID J. COOK, M.B., B.S., Research Scholar, AND HARRY LANDER, F.R.A.C.P., Reader in Medicine

Department of Medicine, University of Adelaide, and Division of Nuclear Medicine, Institute of Medical and Veterinary Science, Adelaide, South Australia

SCINTIPHOTOGRAPHY AND RECTILINEAR SCANNING OF THE LUNG USING ^{99m}Tc–MAFH (MACROAGGREGATED FERROUS HYDROXIDE)

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Scintiphotography and Rectilinear Scanning of the Lung Using ^{99m}Tc-MAFH (Macroaggregated Ferrous Hydroxide)

A Comparison of 100 Subjects

DAVID J. COOK, M.B., B.S., Research Scholar, AND HARRY LANDER, F.R.A.C.P., Reader in Medicine

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Lung scanning with radionuclide-labelled macroaggregates is an accepted technique for demonstrating pulmonary perfusion patterns. Recently, we began using ^{99m}Tc-MAFH (technetium macroaggregated ferrous hydroxide) as our lung scanning agent and undertook a comparative study of the relative merits of rectilinear scanning and scintillation camera study (scintiphotography) in the same subjects. The purpose of this paper is to compare the results of multiple view rectilinear scanning and scintillation camera studies in 100 subjects using this agent and to underline the great value of the lateral projection in the diagnosis of pulmonary perfusion abnormalities.

MATERIALS AND METHODS

The subjects in this study were patients referred for routine lung scanning, usually because of suspected pulmonary embolic disease. ^{99m}Tc-MAFH prepared by the method described by Boyd *et al.* (1969) is supplied daily to our laboratory by the Australian Atomic Energy Commission. One to two mCi. was administered intravenously to each subject whilst supine.

Following injection, scintiphotos were taken in four projections (anterior, posterior and two laterals) using a Nuclear-Chicago Pho-Gamma III scintillation camera fitted with a 4,000-hole low energy collimator. Separate views of the right and left lungs in the anterior and posterior projections were obtained in most adults. A 20% window was used centred on 140 keV. Ambulant subjects were usually studied while seated, the remainder while lying; 500 K counts were accumulated in each view over 60–200 sec.

All subjects were then scanned in at least three views (posterior and two laterals) using a Picker magnascanner with a 3-in. crystal and medium energy focused collimator (2107A). An 80 keV. window centred on 140 keV. was used. Contrast enhancement was not employed.

The rectilinear scans and scintiphotos were assessed separately by the same observer, blind, on two different occasions. Studies were categorized as normal or abnormal: the extent of any defects was noted, together with the views in which they were seen. The results of the two assessments were then compared.

RESULTS

The appearance of the normal lung scan was recorded in 1964 by Taplin *et al.* Since that time the various features of the normal and abnormal lung scan have been extensively investigated. The relative prominence of certain scan features can be altered by the use of imaging systems with different focusing characteristics, a property which may be used to advantage in the delineation of scan defects.

The Normal Scan and Scintiphoto

In 36 of the 100 subjects studied there was no scan or radiological evidence of lung disease; in one normal subject the study was repeated.

We have found that the scintiphoto differs from the rectilinear scan in a number of features. In the normal subject the anterior view scans and scintiphotos showed uniform distribution of activity over both lung fields. The cardiac impression appeared as an area without any activity on the rectilinear scans, but in the anterior scintiphotos a wedge of activity in the posterior basal segment of the left lower lobe was seen through the heart in the majority of cases (28/36) (Figure 1). There were significant differences in the lateral views presented by the two imaging methods in most subjects. In the lateral projection the activity decreased evenly from the posterior basal region of the lung towards the anterior superior region in the majority of studies. However, this feature was often less pronounced in the scintiphotos. Decreased activity in the region of the middle lobe on the right and lingula on the left, due to cardiac impression, was more prominently

displayed on scintiphotos than on corresponding scans. Hilar structures also were more prominent in the scintiphotos than in the scans (Figure 2). In the 36 subjects the hilum was visualized in 16/72 lateral scintiphotos, but in only 5/72 scans. Posterior scans and scintiphotos were generally comparable.

The Abnormal Scan and Scintiphoto

In 64 subjects perfusion abnormalities were present. In 17 subjects the study was repeated on one or more occasions, a total of 86 studies being performed. Forty-nine subjects had defects considered to be the result of pulmonary embolic disease. Obstructive airway disease accounted for the majority of other abnormal studies. The correlation between the two imaging methods in number of defects detected was close to 100%. However, greater contrast in the rectilinear scans often showed areas of greatly reduced perfusion as areas of absent perfusion and increased the apparent extent of many defects. For this reason it was felt that the scintiphotos appeared to demonstrate more accurately the extent of perfusion abnormalities (Figure 3).

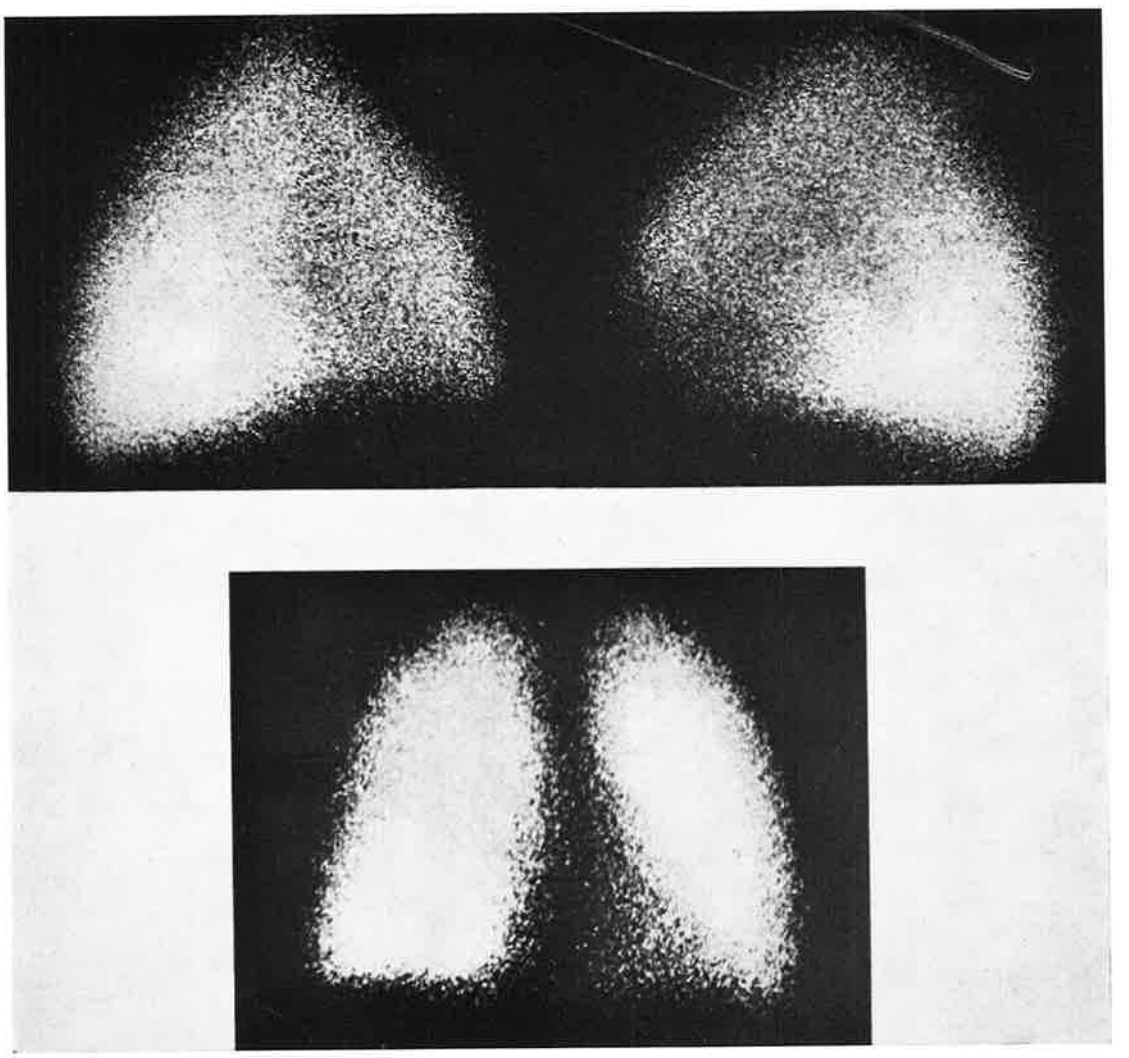

FIGURE 1.—The normal appearance of lateral and anterior scintiphotos. Hilar and cardiac impressions are demonstrated in both lateral views. The heart produces a greater defect in the left lateral projection (top right). *Note :* A lip of activity is seen in the posterior basal segment of the left lower lobe, behind the heart, in the anterior view.

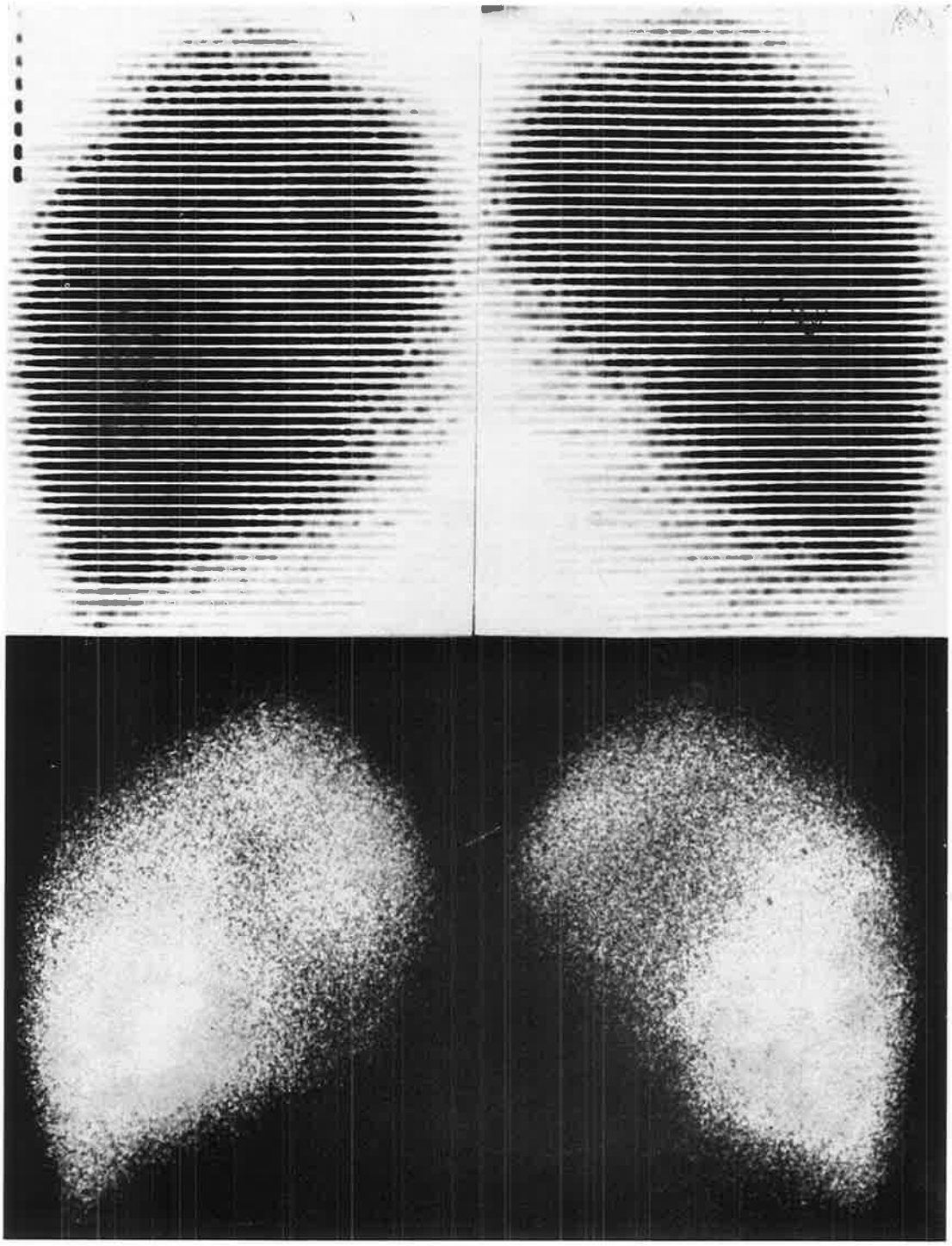

Figure 2.—Due to differences in focusing characteristics of the two systems, hilar and cardiac impressions are more pronounced in lateral scintiphotos than in corresponding rectilinear scans. These should not be confused with pathological defects.

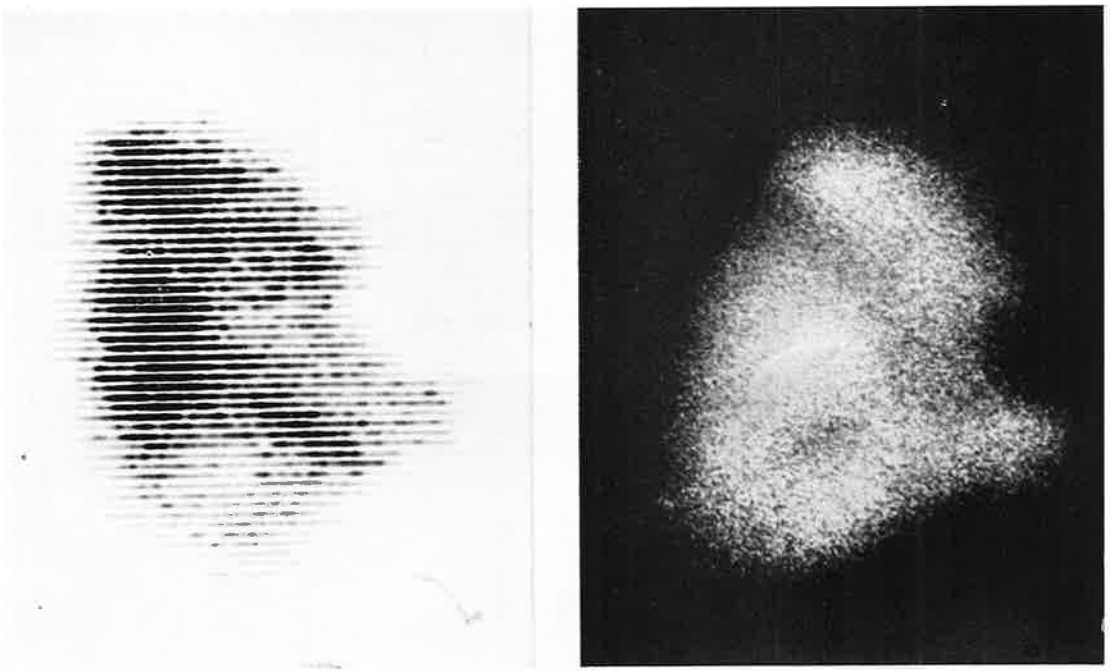

FIGURE 3.—The right lateral projection in a patient with multiple pulmonary emboli. The greater contrast in the rectilinear scan, while not increasing the apparent number of defects, has made them appear more extensive than in the corresponding scintiphoto.

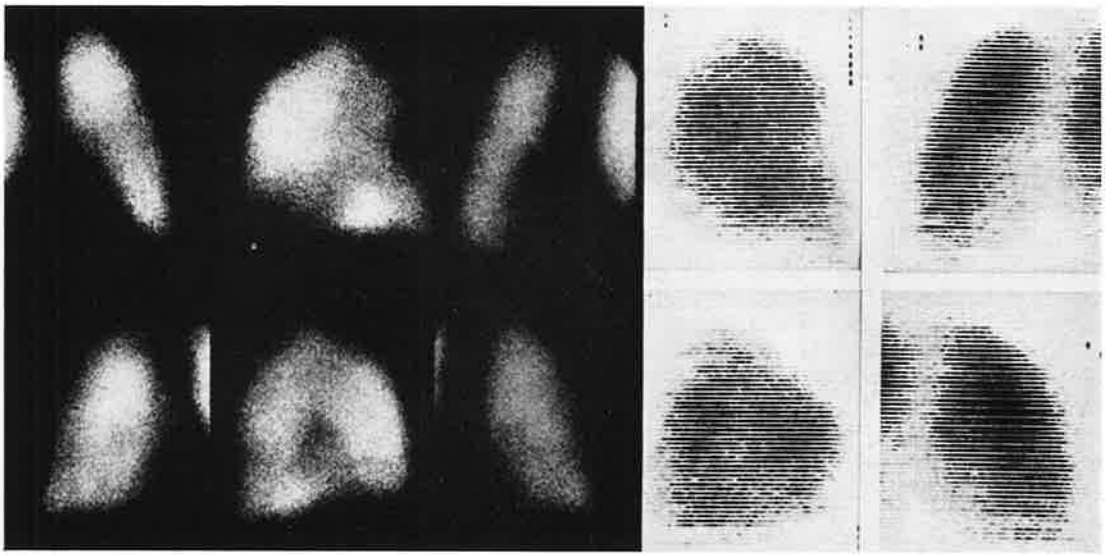

FIGURE 4.—A series of scintiphotos and scans from a patient with pulmonary embolic disease. From the left the projections are anterior, lateral and posterior scintiphotos ; lateral and posterior scans. Both the left lung (top row) and right lung (bottom row) have perfusion defects. Only with the aid of the lateral projection can the precise site and extent of the perfusion defects be ascertained. This is of particular importance when reviewing progress at a future occasion.

The lateral view was of particular value. The cross-sectional area of lung " seen " in this projection is almost twice the cross-sectional area " seen " in either an anterior or posterior projection, and defects not readily detected in either of the two conventional views were often well demonstrated in the lateral view. The full extent of perfusion abnormalities could only be adequately estimated with the aid of the lateral view (Figure 4). Frequently, defects could be localized to precise broncho-pulmonary segments. A confident localization in terms of broncho-pulmonary segment involvement was possible in 62% of subjects (40/64). Such localization was easier on the basis of the scintiphotos than on the basis of the scans.

The pattern of perifissural hypoperfusion described by Eaton *et al.* (1969) and considered to be evidence of microembolization was seen as the only abnormality in four subjects. However, it was more commonly observed in association with discrete defects (10 subjects).

Patient movement artefacts were more commonly encountered using the rectilinear scanner, particularly in the lateral views, when many patients have a tendency to " sag " forwards during the procedure. " Shine through " artefact from the opposite lung in the lateral view was not a more significant problem with either method of examination. Scintillation camera examination was a more rapid procedure than rectilinear scanning. An average of 45 minutes was required for three scans, while scintiphotos took 10–20 minutes for four projections.

To assess the progress of perfusion defects, scans and scintiphotos were repeated on 22 occasions. They yielded similar information. Multiple-view studies were invaluable when reviewing progress as changes were rarely parallel in all projections (Figures 4 and 5). It was easier to compare scintiphotos produced on different occasions than rectilinear scans, for variation in contrast and quality was significantly less in the scintiphotos.

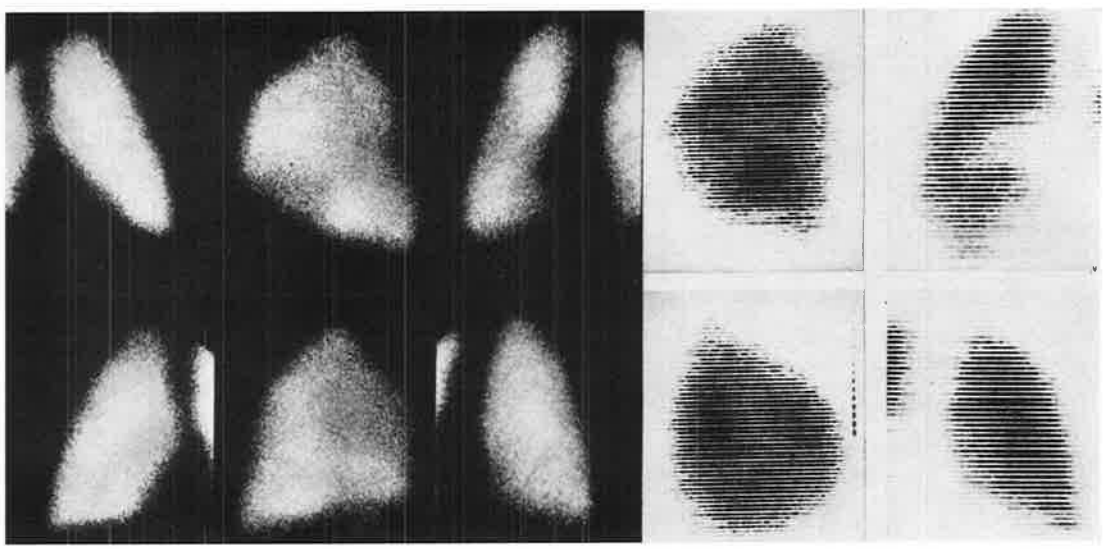

Figure 5.—Follow-up study one week later of patient in Figure 4.

Discussion

Rectilinear scanners with focused collimators deliver their best resolution within a limited depth of field at the geometric focal plane of the collimator in air, and at a shorter distance from the surface of the collimator in tissue (Hine, 1967). The resolution of the scintillation camera is best with the source close to the collimator and decreases linearly as the distance increases (Anger, 1967). The scintillation camera has a better depth of field than the rectilinear scanner and thus good resolution is achieved over a wider range of distances between subject and collimator. This being the case, certain features of the lung may be resolved by the scintillation camera, yet due to their distance from the geometric focal plane of a focusing collimator they remain unresolved by the rectilinear scanner (Gottschalk, 1968). This accounts for

the activity seen in the posterior basal segment of the left lower lobe in the anterior scintiphoto, but not in the corresponding scan.

Although this improved " resolving distance " should facilitate the visualization of perfusion defects, it can complicate the interpretation of lung scintiphotos. This is particularly so when considering the lateral projection, as the contour of the mediastinal surface of the lung may affect the image produced in the scintiphoto to a greater extent than the rectilinear scan. In addition, the distal lung activity might be expected to contribute more to a lateral scintiphoto than to a rectilinear scan. When using ^{99m}Tc-MAFH, the distal (contralateral) lung may be visualized through grossly underperfused areas of the proximal (ipsilateral) lung using either imaging system. However, the contribution of the distal lung is always relatively diffused. This being so, the shape and extent of lesions in the proximal lung can still be confidently estimated under such circumstances using either imaging method.

The use of a 4,000-hole parallel hole collimator on the scintillation camera, as used in this series, limits the effective area of view of the camera to 10 inches and it is thus often necessary to view each lung separately in the anterior and posterior projections. This is a drawback to standard scintillation camera study as there may be no direct visual comparison between the activity in the two lungs and it can be difficult to estimate the relative heights of the hemidiaphragms or apices in many cases without scintiphotos taken specifically to demonstrate them in the one view. Efforts have been made to overcome this disadvantage by the use of a " diverging collimator " (Nuclear-Chicago 410 keV. diverging medium fine hole). In our experience in 21 subjects in whom diverging collimation was compared with parallel hole collimation, although diverging collimation does allow adequate comparison of the activity in both lungs, the resolution is not as good and the efficiency is considerably lower (five to six minutes may be required for a lateral view).

SUMMARY

Lung perfusion studies were carried out using ^{99m}Tc-MAFH (macroaggregated ferrous hydroxide) on 123 occasions in 100 subjects. Multiple-view rectilinear scans and scintiphotos were obtained. Good correlation was found on comparison of the two techniques. However, scintiphotography has the advantage of speed, reduced incidence of patient movement artefacts, and less variation in quality. Differences in focusing characteristics between the two systems produce slight differences in appearance and it is important to recognize these.

The lateral projection was of great value in the delineation of perfusion defects, greatly increasing the efficiency of either method of examination. Changes in scan defects were rarely parallel in all views and the lateral projection was invaluable in assessing defect resolution.

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CLINICAL REVIEWS

The diagnosis of pulmonary embolism: a review with particular reference to the use of radionuclides

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Summary

Pulmonary embolism was first recognized as an important entity early in the nineteenth century. The evolution of our knowledge of this disorder has been reviewed with particular emphasis on the various diagnostic techniques which have been used to assist in its recognition. These have included physical examination to demonstrate the presence of classical physical signs, electrocardiography, biochemical tests, radiological examinations, pulmonary function tests, ultra-sound and methods employing radionuclides. The wide variety of techniques applied to this problem clearly indicates that no currently available test is entirely satisfactory alone. Probably the most significant advance in recent years has been the development of lung perfusion scanning which has provided at the very least a valuable screening test and a ready method of studying serially the natural history of the perfusion defects produced by thromboembolic disease.

Historical introduction

I. *The pulmonary circulation. The concept of embolism*

The first adequate description of the pulmonary circulation was made during the thirteenth century by an Arab, Ibn-An-Nafis. He challenged the orthodox Galenic concept which taught that blood passed from the right heart to the left via invisible pores in the cardiac septa where it mixed with 'pneuma' from the lungs to form the 'vital spirit'. Three hundred years before a comparable European description he described how, 'in the wisdom of God', blood was carried to the lungs via the pulmonary artery so that 'what seeps through the pores in the branches of this vessel into the alveoli of the lung may mix with what air there is therein and combine with it . . . the mixture is then carried to the left chamber of the heart by the Arteria Venosa' (the pulmonary veins). This remarkable contribution remained in total obscurity until the early part of this century (Christie, 1969).

It is not surprising therefore, that the significance of obstructions in the pulmonary artery passed unnoticed until after Servetus redescribed the pulmonary circulation and William Harvey in his treatise De Motu Cordis (1628), gave medicine its present concept of the circulation of the blood.

It is surprising, however, that there is no recognizable description in the Bible of pulmonary embolism, a common disease which may have such dramatic manifestations (Bennett, 1887). Galen described a case of sudden death which Cohn (1860) considered to be due to pulmonary embolism but, except for this, the early Greek writings contain no obvious reference to the condition.

The earliest reports of what were probably cases of thromboembolic disease date from the seventeenth century when several authors, including Malpighi, described a condition associated with 'asthma, palpitations, inflammation of the chest' and the post-mortem finding of 'polypus cordis'—a term coined by Vesalius to describe the post-mortem finding of blood clots in the heart (Liebowitz, 1963).

The first clear description of an undoubted case of pulmonary embolism is usually attributed to Hélie (1837). He described a short fat laundrywoman of 65 years who, 2 weeks after being treated in hospital for a sprain and while talking to her neighbours, suddenly developed a violet hue. Her face swelled, her eyes bulged and she lost consciousness. She

recovered from this acute attack but died soon afterwards in a similar episode. Examination of her body after death revealed a large heart with well organized clots in the right ventricle and pulmonary artery.

In 1819, Laennec published his Traite de l'Auscultation Médiate. In a chapter entitled Pulmonary Apoplexy he gave an excellent description of the clinical features of pulmonary infarction which he considered to be of non-inflammatory nature, contrary to the accepted views of his contemporaries. He differentiated the condition from such other causes of haemoptysis as bronchogenic malignancy and broncho-cavitary tuberculosis. He noted the central breakdown in many lesions and described 'haemorrhagic pleurisy'. However, Laennec paid scant attention to the involvement of blood vessels and it was Cruveilhier (1829), a contemporary of his, who described in meticulous detail the branching clots which filled the vascular tree leading to these lesions. Laennec subsequently pointed out that the condition was found most frequently in patients suffering from diseases of the heart with pulmonary congestion and regarded it as being related in some way to cerebral haemorrhage; hence his use of the term 'apoplexy' (Laennec, 1819).

In 1844, Paget, while at St Bartholomew's Hospital, London, described several cases in which old clots were found in the pulmonary artery or its main branches at autopsy. In one case he observed clots in the femoral vein of similar consistency to those in the lung. In the same year, Rokitansky was the first to suggest that pulmonary infarcts were embolic in nature and caused by fragmentation of clots in the veins or in the right heart. In 1845, Egeberg described the case of a woman who died 17 days post-partum of a pulmonary embolus which arose from the veins of the left leg where phlegmasia alba dolens had developed a few days before her death (Gammeltoft, 1952).

During the next decade, Rudolf Virchow carried out the anatomical, experimental and clinical observations which firmly established the concept of embolism. In 1845, he conducted autopsy examinations upon the bodies of seventy-six cases from the Charité Hospital, Berlin, and found formed clots in the pulmonary arteries of eleven, and thrombi in the deep crural veins of eighteen. This had suggested to him the link between the two disorders and his subsequent studies with artificial emboli showed how such 'bodies' could traverse the veins and chambers of the heart to lodge eventually in one or other branch of a pulmonary artery (Virchow, 1856).

Virchow's concepts were rapidly accepted in the medical world and after 1860, the accounts of pulmonary embolic disease which appeared in medical textbooks reflected his views (Cohn, 1860; Aitken, 1864; Flint, 1867). However, they said little regarding its natural history, prognosis or treatment. It was regarded as an inevitably fatal condition until Pye-Smith (1888) gave a description of several patients who recovered from near fatal attacks, and Welch (1920) recognized that pulmonary embolism could result in chronic ill-health. The contributions of such people as Panum (1864), who demonstrated that pulmonary embolism could be produced asymptomatically in the experimental animal, and Dunn (1920), who documented some of the physiological responses of the goat to pulmonary embolism, ensured that at least some clinical and pathological interest became diverted from the general preoccupation with massive and fatal attacks, to a consideration of the less dramatic and poorly recognized manifestations of the disease.

II. *Early pathological and clinical studies*

(a) *Incidence of embolism.* At a time when antiseptic and aseptic surgery was reducing postoperative mortality and more extensive operations were being undertaken, it was realized that pulmonary embolism was a common complication of surgical operations (Lenormant, 1909). However, pathological studies did not confirm the initial clinical suspicion that pulmonary embolism was mainly a postoperative disease.

Pathologists have recognized a high incidence of pulmonary embolism in autopsy material since the nineteen twenties. In 1922, Møller noted eighty-four 'thrombi' in various stages of organization in the pulmonary arteries in fifty-one of 176 (29%) consecutive subjects studied at autopsy. He concluded that the great majority of these thrombi were embolic in origin.

In the same year Cutler & Hunt (1922) described sixty-three cases of postoperative pulmonary complications, including five deaths, following 1604 operations. Their findings suggested that the majority of such complications were due to pulmonary embolism. They recorded the rapid onset of symptoms and their almost equally rapid subsidence, the involvement of small areas of lung, and the presence of cone-shaped lesions on radiological examination of the chest. They stressed the need for immediate and repeated X-ray examination due to the transience of such changes, advice which has since been often repeated.

In 1935 Brenner, in his detailed survey of the pathology of the pulmonary circulation in 100 consecutive autopsies, listed twenty-eight cases with recent or well organized thrombi in the pulmonary arteries. In thirteen there was an obvious source of embolism and since it was not possible to examine all the systemic veins at autopsy such sources may have been present in others. He attributed to emboli,

numerous changes found in the small vessels which were rarely mentioned at that time in the literature as microscopic investigation of the pulmonary vasculature was unusual.

In 1940 Hampton & Castleman published a paper of great clinical and pathological significance. They correlated the results of post-mortem radiological examination of the chest and the pathological findings in a series of 400 autopsies and compared their results with a larger series of over 3500 autopsies performed in the same laboratory over the previous 10 years. The overall incidence of pulmonary embolism in the retrospective series was 9%; whereas in the combined study group the incidence was 14%—an apparent increase of over 50%. In particular they suggested for the first time that the disease was more common among medical than surgical patients in their general hospital. Indeed one-third of their cases of pulmonary infarction had neither been operated upon nor had any demonstrable cardiac disease.

They described the size, shape and usual locations of the lesions, stressing that pulmonary infarcts are 'always' in contact with a pleural surface and have a convex or 'hump-shaped' cardiac margin (Hampton's hump). In addition, they coined the term 'incomplete infarction' for the syndrome characterized by pleuritic pain or haemoptysis associated with a rapidly appearing and disappearing infarct-like area of consolidation on chest X-ray.

They demonstrated the similarity of this syndrome to that produced in the lungs of normal animals after embolization without the development of frank infarction. Their paper indicated that a firm diagnosis of pulmonary embolism could be made although only one of the triad of haemoptysis, pleural pain, and possible site of an embolus was present if it were associated with a 'positive' chest X-ray. Of possibly greater importance they stressed that the diagnosis could be considered in ambulant subjects.

(b) *Cor pulmonale.* In this atmosphere of increasing interest in the significance of pulmonary embolism, White & Brenner (1933) developed the concept of acute cor pulmonale and attempted to delineate a pattern of physiological and haemodynamic changes which would assist in the diagnosis of embolic disease. Kirschner (1924) had described three extremely useful signs of right heart embarrassment, namely (i) a sharply accentuated second sound; (ii) increased cardiac dullness to the right of the sternum and (iii) *die rote Blutwelle**; but scant attention had been paid to them in the English speaking world. In 1935 McGinn & White re-described the classical findings of acute cor pulmonale when they recorded the clinical features of nine patients with extensive pulmonary embolism and infarction. They emphasized the importance of such signs as pulsation in the second left intercostal space (Litten, 1878); an accentuated pulmonary second sound (Schumacher, 1913); a pseudo- or pleuro-pericardial friction rub; distended jugular veins; increased cardiac dullness to the right of the sternum (Kirschner, 1924); a gallop rhythm heard best in the pulmonary area; and enlargement of the liver (White & Brenner, 1933).

McGinn & White were the first to establish the value of the electrocardiogram in the diagnosis of acute cor pulmonale and to delineate the variety of changes which may be encountered in this disorder. They described the presence of a Q wave and late inversion of the T wave in lead III, together with a gradual staircase ascent of the ST segment in lead II; a prominent S wave and low origin of the T wave in lead I; and an upright T wave associated with inverted P and QRS complexes in lead IV (chest lead). They considered these features to be indicative of dilatation and partial failure of the chambers of the right heart.

Following the work of McGinn & White and Hampton & Castleman, the electrocardiogram and the chest X-rays became the main diagnostic tools at the disposal of the clinician. They were useful in so far as they were often able to provide confirmatory evidence of pulmonary embolism and infarction in cases where clinical suspicion was high. However, it was noted early that McGinn & White's criteria for the diagnosis of acute cor pulmonale were only rarely satisfied (Master, Jaffee & Dack, 1937); while many patients with subsequently proven pulmonary embolism were found to have had either normal electrocardiograms or tracings which showed non-specific changes of doubtful diagnostic significance (Sokolow, Katz & Muscovitz, 1940).

In 1954 DeBakey wrote: 'It becomes increasingly apparent that much of the prevailing confusion on the subject of thromboembolism derives from the difficulty of establishing the diagnosis and consequently a firm basis for the disease.' Since then advances have done much to clarify this troublesome problem, particularly those involving the use of angiography and radionuclides.

Modern methods of diagnosis

I. *The scope of the problem: Clinical symptoms and signs*

Recent pathological surveys indicate that pul-

* Kirschner, while observing a patient apparently dying from a massive pulmonary embolism, noted a red 'arterial wave' pass over the patient's pallid, cyanotic face for a few moments only. A short time later the same phenomenon occurred again. The explanation proposed was that a dislodged piece of the obstructing embolus temporarily permitted an additional amount of freshly oxygenated blood to pass through the lung to the left heart whence it was pumped to the patient's face.

monary embolism as well as being a common disorder, is frequently unsuspected until autopsy and contributes significantly to the mortality of hospital populations.

In 1963, Smith, Dammin & Dexter conducted careful arteriographic studies in 370 consecutive autopsies. They found that approximately one patient in seven had died of pulmonary embolism; but the presence of emboli had been suspected in less than one half of the subjects affected. Meticulous examination of the right lung in a post-mortem study of 263 unselected subjects by Morrell & Dunnill (1968) revealed emboli in 51·7% of cases. In 20% of all subjects both old and recent emboli were present. In thirty-seven patients (15%) death was entirely attributable to embolism and considered to have been potentially preventable. These results highlight the difficulties involved in diagnosis.

Diagnosis is difficult partly because the manifestations of pulmonary embolism are so many and varied. Patients may present in acute cor pulmonale; with pleuritic pain and haemoptysis of sudden onset; or, at the other end of the spectrum with neither a symptom nor sign of the disease (Gage, 1953; Owen *et al.*, 1953; Israel & Goldstein, 1957; Sevitt & Gallagher, 1961).

In a series of ninety patients, Israel & Goldstein (1957) found the following frequency of symptoms and signs: chest pain 72·2%; dyspnoea 46·7%; haemoptysis 28·9%; fever 78·9%; tachycardia 58·9%; a pleural friction rub 24·4% and phlebitis 64·0%. Variable electrocardiographic changes were noted in just over one-half of the subjects. Sasahara and his collaborators (1967) noted dyspnoea in all seventy-two patients in their series and stressed that dyspnoea is likely to be denied by patients who are not acutely ill.

Clinical evidence of thromboembolism may often be obscured by the presence of coexisting serious disease such as widespread malignancy or advanced cardiac, cerebral, renal or vascular disease. In 1965, Greenberg surveyed the protocols of post-mortem examinations performed upon twelve patients with such diseases dying of pulmonary embolism and found that in nine, pulmonary embolism was recurrent and yet had been diagnosed in only four. He concluded that an important diagnostic sign was a steady worsening in a patient's condition with increasing dyspnoea and orthopnoea refactory to conventional therapy. His findings would suggest that a high index of clinical suspicion is a prerequisite for improvement in the rate of diagnosis.

II. *The electrocardiogram*

The introduction of multiple chest leads and unipolar limb leads allowed the electrical output of the heart to be recorded more precisely than was possible when McGinn & White, relying on standard limb leads and limited chest leads, published their findings in acute cor pulmonale. Electrocardiography is still the most readily available and simplest means of diagnosing pulmonary embolism. However, only about 20% of patients with the disease develop electrocardiographic changes and a smaller number show diagnostic abnormalities (Sokolow *et al.*, 1940; Goldberger, 1953; Rakov, 1963).

Tachycardia is frequently seen in pulmonary embolism (Rakov, 1963). The basic rhythm usually remains the same as that prior to embolization; but Duner, Pernow & Rigner (1960) found two cases of atrial flutter and four of fibrillation occurring at the onset of embolization in a study of twenty-eight patients.

The P wave may be peaked in leads II, III and aVF, but rarely to the extent seen in chronic disease (Wood, 1941). A Q wave may be seen in lead III and may be accompanied by similar changes in lead II and aVF (Sherry, 1967). Right axis deviation, clockwise rotation of the heart and right bundle branch block may occur. Inversion of T waves over the right ventricle in the praecordial leads, and S–T segment depression, sometimes excepting lead III, also result from acute strain and dilatation of the chambers of the right heart and are probably the most commonly seen abnormalities (Littman, 1965).

III. *Biochemical changes*

In recent years, it was hoped that specific biochemical changes might be associated with the development of pulmonary infarction. Unfortunately, to date, there are no biochemical or other laboratory tests which specifically indicate that pulmonary infarction has occurred. Nevertheless, the performance of a profile of enzyme studies may facilitate diagnosis. The studies of Goldstein and Israel (Goldstein, Israel & Seligson, 1956; Israel & Goldstein, 1957), suggested that, in contrast to the common pattern of events following myocardial infarction, aspartate aminotransferase (AAT; GOT) activity does not increase after uncomplicated pulmonary infarction. Their findings are supported by the experimental results of Agress and his coworkers (Agress, Glassner & Jacobs, 1956). Wacker & Snodgrass (1960) noted a rise in serum lactic acid dehydrogenase (LDH) following pulmonary embolism and proposed that the triad of a normal GOT, elevated LDH and hyperbilirubinaemia would be specific for pulmonary infarction. Such has not been the case. Increased serum LDH activity is found commonly after myocardial infarction, in various forms of liver disease, in renal disease, in progressive muscular dystrophy, occasionally after cerebrovascular accidents and in a variety of other disorders (Snodgrass *et al.*, 1959).

Sasahara and co-workers (1967) found the triad of Wacker & Snodgrass to be present in only 18% of their series of fifty-seven patients with pulmonary thromboembolism. More commonly (42%) an elevated LDH was associated with normal GOT and bilirubin levels. These findings have been confirmed in a subsequent study by Polachek *et al.* (1968).

Recently, Coodley (1969) has suggested that the level of creatine phosphokinase (CPK) is highly specific in differentiating between myocardial and pulmonary necrosis, since the enzyme exists primarily in myocardium, muscle and brain tissue and rarely, if ever, is elevated in the presence of pulmonary infarction without accompanying myocardial necrosis. The value of this observation remains to be established.

Views differ regarding the usefulness of isoenzyme analysis in the differentiation of pulmonary infarction. Trujillo, Nutter & Evans (1967) found that the only isoenzyme of LDH which was consistently raised in patients with pulmonary infarction and high LDH levels was the hepatic isoenzyme, and this disagreed with the findings of Cohen, Djordjevich & Ormiste (1964). The value of the estimation of serum hydroxybutyrate dehydrogenase (HBD) activity, proposed as 'a solution to the lack of specificity of LDH determinations' (for the HBD test measures the cardiac isoenzymes of LDH), awaits fuller evaluation.

IV. *Radiological investigations*

(a) *The chest X-ray*. There are no pathognomonic radiological signs of pulmonary embolism. Changes when present are often fleeting and even in the presence of massive embolus often unspectacular and non-specific (Kaye *et al.*, 1956). The shadow produced by infarction was described by Westermark (1938) as wedge-shaped with the apex towards the hilum; yet this classical description has been denied by others (Fleischner, 1958). The infarct, as seen in the posterior-anterior projection chest film, may have almost any shape. It may be sharp or ill-defined, regular or irregular, diffuse or mottled (Krause & Silverblatt, 1955). In about one third of cases it is associated with a pleural effusion (Short, 1951).

The first radiological signs of pulmonary embolism in the absence of infarction were described by Westermark (1938). He noted that in some cases the affected lung appeared abnormally radiolucent due to oligaemia. Also, the central pulmonary arteries may appear slightly dilated and end abruptly at the site of embolization, a feature that has been amply confirmed by other workers (Shapiro & Rigler, 1948; MacKeen, Landrigan & Dickson, 1961; Sasahara *et al.*, 1964). On the other hand Stein *et al.* (1959) in a series of ninety cases of pulmonary embolism failed to demonstrate Westermark's sign and others have found it only occasionally.

It has been estimated (Poulose, Reba & Wagner, 1968) that the chest X-ray is diagnostic in fewer than 15—20% of cases. The lack of specificity of radiological signs in the disorder is well borne out by a consideration of one of the most frequently seen signs of pulmonary infarction, namely, elevation of the diaphragm on the affected side. This sign, which may be present in up to 70% of cases of pulmonary infarction (Laur, 1963), can arise from an extremely wide variety of pathological disorders ranging from contusion of the chest to epidemic pleurodynia (Fleischner, 1962). However, if considered in conjunction with the presence of such features as the abrupt termination of the vascular pattern of the lung, dilatation of the main pulmonary trunk with narrowing of the vessels below (Davis, 1964), or the occurrence of small bilateral pleural effusions (Fleischner, 1962), it is one of the most valuable indications of the disorder.

(b) *Pulmonary angiography*. The growing awareness of the less dramatic 'pulmonary embolus minor', the frequently recurrent nature of the disorder, its often fatal outcome, the improved prognosis in persons adequately treated with anticoagulants, and the availability of such therapeutic procedures as the administration of streptokinase (or urokinase), plication of the inferior vena cava and pulmonary embolectomy, have all accentuated the need to arrive at a correct and precise anatomical diagnosis within a very short time and in a manner safe for the patient. It is now no longer sufficient merely to determine whether or not pulmonary infarction has occurred. Diagnostic endeavour must also be directed towards determining the precise site(s) of obstruction to the pulmonary vascular tree and the site of origin of the embolus.

In 1931, Carvalho and Moniz performed the first pulmonary angiogram, injecting concentrated sodium iodide into the right side of the heart via a catheter (Robb & Steinberg, 1938). The method, although now commonplace, was slow in gaining popularity and for some considerable time the more indirect methods of diagnosis were preferred.

Pulmonary artery catheterization allows the pressure in the pulmonary artery to be determined indicating the presence or otherwise of pulmonary hypertension (Del Guercio *et al.*, 1964; Chait *et al.*, 1967). During pulmonary angiography, emboli may be identified either as arterial obstructions with abrupt 'cut-off' of the affected vessel, as filling defects, or as localized arterial stasis. Additional indirect signs include diminution or absence of blood flow to a pulmonary segment, poor capillary filling, and diminished or absent venous return from

the affected area (Wiener, Edelstein & Charms, 1966). The additional signs are generally non-specific and have been found in other cardio-pulmonary disorders such as emphysema (Fred *et al.*, 1966), pneumonia and congestive cardiac failure (Ferris *et al.*, 1967).

However, although arteriography gives an excellent anatomical study of the larger pulmonary vessels, it gives only indirect evidence of perfusion abnormalities and involvement of small vessels.

Of considerable importance is the difficulty often experienced in interpreting the angiogram when pulmonary emboli are sought. Superimposition of air in the bronchi may easily cause the false impression that a filling defect is present. This is particularly the case when the left main stem bronchus crosses under the left pulmonary artery. In addition, a significant filling defect may appear transiently in only one or two frames in a consecutive series of fifteen or more pictures. This may be readily missed without the most diligent search by an experienced observer (Freeman *et al.*, 1968).

Problems involved in routine angiography for pulmonary embolism include delays in the performance of a test that requires the availability of theatre facilities, an anaesthetist, cardiologist and other highly trained personnel; as well as the obvious risk of anaesthesia and right heart catheterization in a seriously ill patient. Nevertheless the performance of an angiogram is, at present, the only means by which the diagnosis of pulmonary thromboembolism can be confirmed beyond any doubt and is thus indicated in all patients who are considered for pulmonary embolectomy (Sherry, 1967) or thrombolytic therapy (Hirsch *et al.*, 1967).

V. *Ultrasound*

Ultrasound has recently been suggested as a diagnostic tool in pulmonary embolic disease (Miller *et al.*, 1967). Its proponents claim that the technique is simple enough to be performed rapidly and accurately at the bedside by a technician with minimal training. It is claimed that positive 'embolism' tracings, showing marked increased prominence of returning 'echos' can be obtained within 10–15 min of the lodgement of an embolus. The value of this technique is yet to be assessed on a large scale.

VI. *Radionuclide studies*

Blumgart & Weiss were the first investigators to study the circulation in man using radionuclides. In 1927 they injected radium C into the antecubital veins of patients with rheumatic and syphilitic heart disease and detected its appearance in the other arm by means of a modified cloud chamber (Blumgart & Weiss, 1927). However, it was not until the development of sophisticated scintillation counting techniques and the ready availability of suitable short-lived radionuclides that serious investigation of pulmonary blood patterns could begin.

Pulmonary thromboembolic disease, by its very nature, causes a disruption of normal pulmonary blood flow and this disruption results in alterations in the behaviour of radioactive tracers in a characteristic manner. The clinician is thus able to obtain considerable insight into the nature of his patient's disease without subjecting him to the not inconsiderable hazards of angiography.

Radioactive gases. Regional pulmonary blood flow was first investigated by Dyson and his group in Amersham in 1959 using Oxygen-15, ($^{15}O_2$), a short-lived cyclotron-produced radionuclide (Dyson *et al.*, 1960). When inhaled in the form of carbon dioxide this very soluble gas is removed from the pulmonary alveoli by the regional blood supply. The rate at which it is cleared during short breath-holding gives a measure of the local blood flow. Scintillation counters placed over the back of the patient record clearance curves for the $C^{15}O_2$. This 'highly soluble gas technique', as it has come to be called, has serious limitations if used in an endeavour to detect pulmonary blood flow perfusion defects in a clinical situation. It requires the use of an extremely expensive short-lived radionuclide ($T_{\frac{1}{2}} = 2$ min) and thus the diagnostic unit must be situated next to a cyclotron; the resolving power of the system is low, depending on the number of scintillation counters used; and the time available for data storage during the investigation is determined by the patient's ability to hold his breath.

In 1962 Ball and his associates demonstrated that regional pulmonary blood flow could also be measured using the reactor produced noble gas, xenon-133 (Ball *et al.*, 1962). This radionuclide has a half-life of 5·3 days and yields an 81 keV gamma ray. The gas is dissolved in saline and injected intravenously. When the gas reaches the pulmonary capillaries, because of its poor solubility, it 'evolves' into the alveoli and remains there as long as the patient holds his breath (Bass, Heckscher & Anthonisen, 1967). The amount of radionuclide evolving in a given segment of lung is a function of the perfusion of that segment; and the subsequent rate of clearance of radionuclide after resumption of breathing is a function of the ventilation of that region. A pictorial representation of the distribution of this radionuclide within the lungs can be obtained using a gamma (scintillation) camera, a static organ-imaging device of high sensitivity. Such a technique is used in some centres for the detection of pulmonary perfusion defects (Loken, 1966; Newhouse *et al.*, 1968). An important advantage of this method is that the radionuclide has a very short biological half-life and most of the radio-

activity passes out of the body in one circulation through the lungs. This enables the study to be repeated many times under varying conditions without danger to the patient.

'Microembolic' technique. In 1947 Müller & Rossier injected radiozinc (^{63}Zn) suspended in pectin solution intravenously into a patient with pulmonary metastases from a previously treated hypernephroma. They found that the radioactivity remained precisely localized within the lungs and was not detectable elsewhere. They followed this observation with studies employing radiogold (^{198}Au)-labelled charcoal administered during cardiac catheterization. In 1958 Ernst *et al.* re-examined Müller's procedure and in a series of eighteen dogs, demonstrated the possibility of outlining pulmonary blood flow patterns by scintigraphy using charcoal particles labelled with ^{198}Au.

The first rectilinear scanners were designed in 1949 for outlining the thyroid gland (Cassen *et al.*, 1951). Such instruments became available commercially shortly afterwards and in the next 10 years it became possible to scan most of the major organs in the body with the notable exception of the lungs. The microembolization technique using raioactive macrocolloids was apparently to answer this need.

Ariel (1962) reported that inert ceramic microspheres of 60 μm diameter, when injected intravenously, were trapped in the pulmonary tissues. He advocated the use of such particles labelled with beta-emitters, such as yttrium-90, in the management of pulmonary metastases. Significantly, he indicated that perfusion lung scans could be obtained if scandium-46 or chromium-51 were incorporated into the irradiating microspheres and their distribution within the lungs defined by rectilinear scanning techniques similar to those already employed for imaging the distribution of radionuclides in other organs.

Shortly afterwards Haynie and his group demonstrated that obstructions of the pulmonary arteries could be demonstrated accurately by a similar technique using microspheres, 40–60 μm in diameter, labelled with mercury-203 (Haynie *et al.*, 1962, 1963). Pulmonary artery occlusions were produced in dogs at thoracotomy by ligatures placed around various branches of the pulmonary arteries. Lung scans were then performed at intervals of from 1 hr to 5 days after operation. The avascular regions were consistently demonstrated as areas with little or no radioactivity within them.

Meanwhile Gibel and his associates (Gibel, Matthes & Spode, 1962, 1963; Gibel *et al.*, 1962) had conducted similar experiments using charcoal labelled with ^{198}Au and had concluded that their method was a safe and efficient means of detecting localized obstructions to the pulmonary circulation.

In 1963 Taplin and his colleagues (1964a, b, c) initiated the technique of pulmonary scanning after the introduction of microemboli into pulmonary capillaries by the intravenous injection of radionuclide-labelled macroaggregates of serum albumin (MAA). Their studies in animals demonstrated that the procedure had a very great safety margin and that the embolic material was readily metabolized, hence the procedure could be repeated at relatively frequent intervals. This new radiopharmaceutical was immediately tried in human subjects (Wagner, Sabiston & Iio, 1964a). Wagner *et al.* (1964b) and Quinn III *et al.* (1964) reported their initial clinical experience with MAA labelled with iodine-131 (^{131}I) or chromium-51 (^{51}Cr). The size of the particles injected in these studies ranged from 10–70 μm.

Wagner's group described the characteristic pattern of avascularity associated with massive pulmonary embolism in man. The pattern consisted of a gross irregularity of distribution of radioactivity nearly always involving both lungs. They considered that the technique offered a useful and rapid screening procedure without haemodynamic, radiation or immunological hazard to the patient and emphasized its value as a tool in any study of the natural history of pulmonary embolism (Wagner *et al.*, 1964b).

Evidence for the validity of this method of examination of the lungs accumulated rapidly. Good correlations were demonstrated between the distribution of radionuclide within the lung and the results of differential bronchospirometry (Lopez-Majano *et al.*, 1964), standard electromagnetic flowmeter techniques in dogs (Tisi *et al.*, 1968) and the known effects of posture and ventilation on the distribution of pulmonary blood flow in man (Tow *et al.*, 1966). Within a very short time the procedure of lung scanning with ^{131}I-MAA became an accepted routine diagnostic tool in many centres throughout the world, providing useful information concerning regional lung perfusion which could not be as readily obtained by any other technique. Its popularity has been largely due to the ease of preparation of ^{131}I-MAA, and the dependability of particle size. Albumin macroaggregates have the added notable advantage in that their intravascular life as particles is relatively short. Fragmentation gradually occurs in the obstructed pulmonary capillaries and the small fragments produced are then removed from the circulation by reticuloendothelial tissue and metabolized (Furth *et al.*, 1965; Murphy, Cervantes & Maass, 1967).

In 1966, Kramer & Stern suggested the use of indium-113m (^{113m}In) (a generator-produced nuclide derived from tin-113 (^{113}Sn)) incorporated into uniformly sized (20–40 μm) particles of iron hydroxide,

as a suitable agent for lung scanning (Kramer & Stern, 1966). Its short half-life (1.7 hr) and absence of beta emission allows millicurie quantities to be administered without radiation hazard to the patient. With the usual 200–300 μCi dose of ^{131}I-MAA the adsorbed radiation dose to the lungs is of the order of 4–5 rads/mCi, compared with 0·75 rads/mCi using particles labelled with indium (Wagner & Rhodes, 1968). Carrier-free ^{113m}In can easily be incorporated into iron hydroxide particles which can then be sterilized by autoclaving. A drawback to its widespread use has been its relatively energetic gamma photon (390 keV) which renders it less suitable for use with a gamma (scintillation) camera than technetium compounds. Because of tissue penetration by this relatively energetic gamma emission, it may be difficult to differentiate one lung from the other in a lateral view due to 'shine through' from the opposite side.

The most suitable agents presently available for lung scanning are compounds of technetium-99m (^{99m}Tc) such as ^{99m}Tc-MAA (Loken, Telander & Salmon, 1965; Webber, Bennett & Surprenant, 1966) and ^{99m}Tc-iron hydroxide macroaggregates (Yano *et al.*, 1969; Boyd *et al.*, 1969; Davis, 1970a, b). The energy (140 keV) of the solitary gamma emission of this radionuclide is ideally suited for use with the gamma camera (which is most efficient for energies in the range 100–200 keV) and in our experience is low enough to avoid severe 'shine through' artefacts in lateral lung scintiphotos. In addition, the radiation dose to the patient is less than with any other radionuclide advocated for this purpose.

The great advantage of the 'camera' is the speed with which the distribution of radionuclide within an organ can be visualized. Using a conventional scanner, a minimum of 45 min is generally required to obtain a posterior and two lateral views. With the camera, a 10 in. diameter area of the chest is viewed at the one time using conventional collimation, or 13 in. using a diverging collimator. Each scintiphoto requires only 2–5 min and the patient can be examined in any posture, a point of considerable importance in dyspnoeic patients who must be 'scanned' in a prone position by most commercially available rectilinear scanners.

Blood flow studies. The great sensitivity of the 'camera' can be utilized to obtain rapid sequential exposures and to visualize the flow of an intravenously injected bolus of ^{99m}Tc-pertechnetate (10–20 mCi) through the heart and pulmonary vasculature (Kriss *et al.*, 1966; Rosenthall, 1967; Cook & Lander, 1969).

The use of a multiparameter analyser, fast digital magnetic tape recorder and, if available, a suitable computer enable a 'digital' representation of the gamma camera data to be obtained which may assist in the delineation of perfusion defects in certain cases (Cook & Lander, 1969; Lander & Cook, 1970).

Interpretation of pulmonary perfusion defects. It must be emphasized that the demonstration of a pulmonary blood perfusion defect by such studies is not in itself proof of pulmonary embolism (Moser *et al.*, 1966; Swanson *et al.*, 1966; Poe, Swanson & Taplin, 1967). Perfusion defects may result from such conditions as pneumonia, tuberculosis and bronchogenic malignancy; extrapulmonary displacement of lung tissue, for example, by large pleural effusions or cardiomegaly; intrapulmonary bullae; obstructive airways disease—asthma or emphysema; and pulmonary arterio-venous or bronchial artery-pulmonary artery shunting. In addition, diminished peripheral perfusion may arise as a consequence of alveolar hypoxia and postural gravitational effects (Taplin *et al.*, 1964c). For this reason, it is essential that a very recent chest X-ray should be available for comparison with the perfusion scan and all available information must be taken into account when assessing the significance of perfusion defects. Pulmonary emphysema, in particular, often produces multiple perfusion defects which may be indistinguishable from those caused by multiple pulmonary emboli at first examination. Indeed the two disorders may coexist. Where there is doubt in such a case, repeat examination may help in differentiating the persisting perfusion defects of emphysema from the changing pattern of pulmonary embolism (Taplin *et al.*, 1964c).

For most purposes, lung scintigraphy in only anterior and posterior projections is inadequate, and perfusion defects visible only in lateral views may be missed (Sasahara *et al.*, 1968). A high speed dual 5 in. detector system which permits simultaneous anterior and posterior scanning or scanning of both laterals simultaneously helps to reduce the time involved: multiple view gamma camera studies are equally satisfactory (Eaton *et al.*, 1969). In most patients the total area of a lung 'seen' in the lateral projection is nearly double that seen in the posterior or anterior projection. The location, size and shape of an avascular lesion can be more accurately defined with the aid of a lateral view, and frequently the lung segment(s) involved can be accurately identified (Surprenant, 1967).

A recent study of seventy-one patients with clinically suspected pulmonary embolism has indicated that angiographic proof of pulmonary embolism can be obtained in up to 75% of those patients whose lung scans have perfusion defects corresponding to specific anatomical segments of the lung, providing the plain chest X-ray is compatible with embolism. Specific angiographic abnormalities diagnostic of embolism were found in 25% of those

patients whose scans showed diffuse, patchy and non-segmental defects (Poulose *et al.*, 1970). This finding suggests that certain scan defects have a degree of specificity not previously appreciated. The lung scan may, in certain cases, be sufficiently diagnostic of embolism to form a sound basis from which to carry out definitive treatment.

Inhalation studies. Bronchoconstriction was first observed in association with pulmonary embolism by Boyer & Curry in 1944. Although it may be extremely severe at times, it is usually of brief duration, hence gross shift in ventilation away from regions with reduced perfusion due to pulmonary embolism is said to be rarely observed (Bass *et al.*, 1967). Nevertheless, many investigators are now re-examining this problem.

Inhalation scanning procedures may be performed using either a radio-aerosol (Pircher *et al.*, 1965; Taplin, Poe & Greenberg, 1966; Cook & Lander, 1970a, b; Isawa, Hayes & Taplin, 1970) or a radio-gas (Loken, 1966; Jones, Goodrich and Sabiston, 1967; Newhouse *et al.*, 1968; Shibel, Landis & Moser, 1969; Jones et al. 1970; Isawa *et al.*, 1970). While the use of a gas would seem preferable on theoretical grounds, the use of such inert gases as ^{133}Xe pose many practical difficulties; particularly with respect to their generation, and contamination of the laboratory.

In the radio-aerosol technique, small particles of the order of 0·5–2·0 μm diameter are produced by nebulization. Such particles are known to be distributed evenly throughout the lower respiratory tract (Taplin *et al.*, 1966). The particles are inhaled, often with the aid of a positive pressure respirator and the patient is scanned in order to determine the distribution of aerosol after inhalation has ceased. Many radiopharmaceuticals have been used including technetium-sulphur colloid, albumin labelled with radioiodine or technetium (Haynie, 1968) and, most recently, ^{113m}indium (Isawa *et al.*, 1970). Recently, we have obtained inhalation studies of very satisfactory quality using ^{99m}Tc-pertechnetate as a fine aerosol. Scintiphotos produced during inhalation of aerosol and during the washout phase after inhalation has ceased, give a pictorial representation of airway patency which is rapid and simple to produce (Cook & Lander, 1970a, b).

However, aerosol dispersion in the lungs is dependent upon factors other than diffusion. These include particle size, sedimentation, impaction, rate of air movement, turbulence, the nature and concentration of the radiopharmaceutical employed and the rate of its clearance from different parts of the lung. Hence the amount of radioactivity in any portion of a lung is not always proportional to the air flow to that region. Inhalation of a radioactive gas, on the other hand, simulates the usual conditions of ventilation. Areas of poorly ventilated lung can be expected to appear as such on radiogas inhalation, whereas radioaerosol scans may occasionally show such areas as being unventilated (Shibel *et al.*, 1969). Radioactive gas techniques are best suited to gamma 'camera' or multiple fixed probe systems as the gas washout, unlike aerosol removal, is rapid after inhalation ceases and does not allow time for conventional scanning. However, this technique has been used employing rectilinear scanners by performing the study while the patient re-breathes on a 'closed-system' spirometer containing the gas (Marks *et al.*, 1968).

Most recently, combined inhalation-perfusion scanning has been developed to allow comparison of regional blood flow with ventilation in the same area in an attempt to aid differentiation of pulmonary embolism from other causes of diminished perfusion (Isawa *et al.*, 1970). In a normal subject the inhalation scan image closely resembles the perfusion scan, and in the majority of pulmonary disorders, diminished perfusion is associated with decreased ventilation in the affected areas. However, a perfusion scan defect in the presence of a normal inhalation picture is considered strong evidence in favour of pulmonary embolism (Dore et al., 1968; Isawa *et al.*, 1970). But this is by no means always the case for, on occasions, there may be little or no air entry into the infarcted area. The interval which elapses between lodgement of the embolus and the time of study; whether or not infarction occurs; the extent of the involved area and its collateral circulation, are all obviously important in the scan appearances.

Labelling of thromboemboli. Attempts have been made to label thromboemboli *in vivo* by two separate approaches. The most widely used technique involves the injection of radioiodine-labelled fibrinogen into a subject considered at risk. The rate of clearance of the labelled material is determined, and counting of radioactivity is carried out daily over adjacent sites along the course of the main veins of both legs. The rapid accumulation of radioactivity at a particular site (or adjacent sites) over the course of a day or two, suggests that a thrombus is developing in the underlying area. This technique has found favour with a number of surgical groups who either inject the radionuclide soon after operation (Hobbs & Davies, 1960; Atkins & Hawkins, 1965) or just prior to operation (Flanc, Kakkar & Clarke, 1968; Kakkar *et al.*, 1970). Although the technique has many proponents and has aroused much interest, we believe its value is limited. A satisfactory label of fibrinogen has yet to be found, preferably one which allows satisfactory imaging of the radionuclide *in situ*. In our experience, variation in siting of the static probes from day to day renders

evaluation of all but the most gross changes difficult. The radiation hazard to the patient, especially if ^{131}I is used as the label, is not inconsequential; and the necessity to block the thyroid must always be taken into account. Most important, the ever present risk of development of homologous serum hepatitis in the course of what is still primarily a research procedure raises a considerable ethical problem. These considerations aside, the very substantial time required to carry out the procedure on every patient each day, mitigates against its adoption as a routine procedure.

An alternative approach involves attempts to label thrombi or emboli after they have formed. To this end, plasmin (fibrinolysin) (Ouchi & Warren, 1962) and antifibrinogen (Spar *et al.*, 1966) have been used. Employing ^{131}I antifibrinogen, Spar and co-workers demonstrated the presence of intracardiac and intrapulmonary thromboemboli in a small series of selected patients. Unfortunately, several days are generally required for sufficient radioactivity to accumulate in the thrombus and allow it to be clearly delinated from the background radioactivity in the blood. Furthermore, the preparation and use of satisfactory antisera present many difficulties.

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APPENDIX H

THE USE OF INDIUM-113m CHLORIDE FOR INHALATION SCANNING IN THE DIFFERENTIAL DIAGNOSIS OF PULMONARY EMBOLISM

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Pulmonary perfusion scan defects in the absence of significant radiological abnormality are found with increasing frequency with advancing age. Determination of airway patency in the area of perfusion defect(s) enables pulmonary embolism to be differentiated from other causes of abnormal perfusion patterns, in particular from obstructive respiratory disease.

Until recently, technetium in the pertechnetate form has been used for inhalation studies in our laboratory. However, this has certain disadvantages, especially if one wishes to use a technetium-labelled radiopharmaceutical for perfusion scanning. If a defect is found under such circumstances, it is necessary to wait at least 24 hours before an inhalation study can be performed. In addition, pertechnetate is unsuitable for use with conventional rectilinear scanning devices as it is rapidly cleared from the lungs when inhalation ceases.

We have recently found $^{113m}InCl_3$ to be a satisfactory radiopharmaceutical for inhalation scanning used either alone or when a technetium compound is used for the perfusion study. The indium is inhaled from a simple nebulising system, which has been described previously, without further manipulation after milking from a ^{113m}Sn generator. Once inhaled, the ^{113m}In remains *in situ* permitting either conventional rectilinear scanning techniques to be employed or multiple view gamma camera scintiphotos to be obtained.

The use of these two radiopharmaceuticals with widely separated gamma emissions enables differentiation of the radionuclides by pulse height analysis and thus allows perfusion and inhalation studies to be obtained virtually simultaneously. The short half-lives of technetium and indium permit repetition of the studies at frequent intervals, if desired.

The method is simple and inexpensive. It causes no patient discomfort, requires no complex radiopharmaceutical preparation and often enables a firm diagnosis of the nature of the perfusion defect to be made within minutes. It is a most suitable procedure for any small Nuclear Medicine laboratory.

Australian and New Zealand Journal of Medicine, 1, 290, 1971c.

APPENDIX I

THE VALUE OF ROUTINE SERIAL PULMONARY PERFUSION SCANNING IN THE DETECTION OF POSTOPERATIVE PULMONARY COMPLICATIONS

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Perfusion scanning is a sensitive method of detecting pulmonary embolism and other disorders of the lung which are known to occur with increased frequency in postoperative patients. We are presently conducting a survey to determine the incidence of pulmonary perfusion defects in a population undergoing elective surgery and to elucidate the nature of the pathological processes underlying these defects. Perfusion scans are performed prior to operation and routinely at intervals of three to five days postoperatively as long as the patient remains in hospital. Physical examination, certain biochemical tests, electrocardiographs and chest X-rays are performed on all patients before surgery and repeated if any abnormality is detected in a post-operative study. When necessary to elucidate the nature of any defect(s), repeated perfusion scans are performed in conjunction with inhalation scans, pulmonary angiography and other investigations which may be considered appropriate.

The demonstration of scan abnormalities characteristic of pulmonary embolism is frequently the only or earliest evidence of the disorder. In a group of 80 consecutive surgical patients studied serially so far, nine (11%) have developed pulmonary emboli; but in only one was the disorder suspected clinically.

In a further five patients, large defects indistinguishable from those seen in embolism were detected. However, ancillary investigations, including inhalation scanning studies, suggested that the defects were primarily associated with airways obstruction. Cholecystectomy was the most commonly performed operation (24/80) and accounted for five instances of postoperative embolism.

If it is accepted that postoperative pulmonary embolism is a serious disorder requiring early and vigorous therapy, the high incidence of otherwise unsuspected disease indicates that routine serial pulmonary perfusion scanning has an extremely important role to play as a screening procedure in patients undergoing elective surgery.

Australian and New Zealand Journal of Medicine, 1, 291, 1971.

INHALATION LUNG SCANNING USING CARRIER-FREE ^{113m}In

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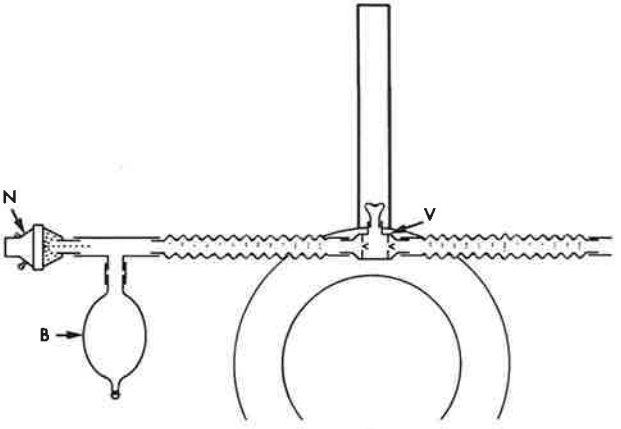
Dual-isotope techniques (*1*) or the use of certain radioactive gases (*2*) permit estimates of both pulmonary perfusion and ventilation to be carried out simultaneously in the same study. However, the inconvenience involved in the preparation of radionuclide-labeled pharmaceuticals and the expense and difficulty in handling radioactive gases prompted us to investigate simpler methods of obtaining inhalation studies of good quality.

We have previously described a method using technetium in the pertechnetate form which yields information of high quality (*3,4*). However, it is not possible to perform perfusion and inhalation studies simultaneously if one also desires to use a technetium-labeled compound (e.g. macroaggregated albumin, MAA, or macroaggregated ferrous hydroxide, MAFH) for the perfusion study. To overcome this, we have recently used carrier-free indium in a nebulized spray generated by the same simple nebulizing system we employ for pertechnetate inhalation studies.



METHOD

The system (Fig. 1) consists of a Bird(R) micronebulizer through which a stream of air is passed at the rate of 14 liter/min to a 5-liter reservoir bag. Sterile ^{113m}In is eluted from a ^{113}Sn-containing generator using 0.05 *N* hydrochloric acid. This is added to the nebulizer without the addition of buffer in a concentration of 10–15 mCi in 5 ml. The subject inhales the nebulized spray from the 5-liter reservoir via a 20-in. length of corrugated rubber tubing (i.d. 1 in.) to the end of which is attached a mouthpiece fitted with a non-return valve. Exhaled material is removed by a large-bore, low-resistance tube. The study is generally carried out with the subject seated before the head of a gamma camera (Nuclear-Chicago Pho/Gamma III fitted with a diverging collimator. Inhalation of the indium causes no discomfort. Of the activity added to the nebulizer, 10–15% is detectable in the patient's lungs. Counts may be accumulated during inhalation or after inhalation ceases because the ^{113m}In is not cleared rapidly from the lungs. A counting rate of about 15 kcpm is obtained after 5-min inhalation. Rectilinear scanning of the lungs after inhalation produces equally satisfactory results.

Unlike technetium in the pertechnetate form which is rapidly removed from the lungs when inhalation ceases (*3, 5*), the indium appears to remain in situ

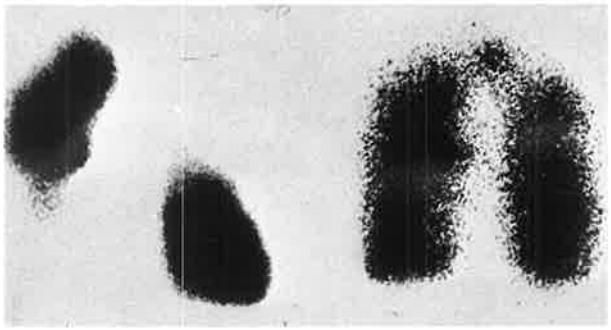


FIG. 2. Posterior projection scintiphotos of patient with right upper and left lower zone pulmonary emboli. Perfusion study on left (^{99m}Tc-MAFH) and inhalation study on right (^{113m}In-$InCl_3$) were obtained at the same sitting. Scintiphoto on right was taken during inhalation of radionuclide. "Hot" area between apices of lungs represents activity in breathing valve and tubing.

the simple, small Bird(R) nebulizer instead of an ultrasonic model enables much smaller volumes of radiopharmaceutical to be nebulized. This permits more rapid accumulation of activity in the lungs and thereby reduces the time required for inhalation.

This system may be used in combination with pulmonary perfusion studies employing technetium-labeled compounds. Both radionuclides have a monoenergetic gamma emission (^{113m}In, 392 keV; ^{99m}Tc, 140 keV) and can thus be readily separated by pulse-height analysis. This property allows both perfusion and inhalation studies to be performed virtually simultaneously in any position without movement of the patient. Accurate assessment of ventilation/perfusion relationships throughout both lung fields is thus possible (Fig. 2).

Important advantages are that both radionuclides persist in the lungs for sufficient time to allow either scintiphotographic or conventional rectilinear scanning techniques to be performed; and both have sufficiently short half-lives to allow repetition of the studies at frequent intervals if desired with the minimum of discomfort and hazard to the patient.

ACKNOWLEDGMENTS

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INHALATION PULMONARY SCINTIPHOTOGRAPHY USING PERTECHNETATE

BY

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INHALATION PULMONARY SCINTIPHOTOGRAPHY USING PERTECHNETATE*

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THE use of radionuclide labeled aerosols in conjunction with modern developments in organ imaging techniques has facilitated the study of regional pulmonary ventilation in a safe and simple manner and enables a graphic representation of ventilation patterns to be readily obtained. A wide variety of radiopharmaceuticals have been used.[5,9] However, prior to earlier brief reports by us,[2,3] no successful method had been described using an aerosol of technetium in the pertechnetate form, the most readily available radiopharmaceutical in nuclear medicine laboratories.

The purpose of this paper is to detail the simple method we use to obtain pulmonary inhalation scintiphotos using an inexpensive nebulizing system with pertechnetate, and to describe some of the properties of the system.

MATERIAL AND METHOD

The apparatus employed is illustrated in Figure 1. The aerosol of pertechnetate is generated by a Bird micronebulizer. Ten to 15 mc of the radiopharmaceutical, contained in a volume of 2 ml., is injected into the reservoir of the nebulizer (N) to which air is then supplied at the rate of 14 liters per minute. The nebulized spray is generated as required and is collected in a 5 liter reservoir bag (B) from which the patient breathes via a 20 inch length of corrugated rubber tubing (internal diameter 1 inch) and a low resistance non-return valve (V).* A simple mouthpiece is used. Exhaled material is removed via a large bore, low resistance efferent tube which may feed either into an exhaust duct or directly to the outside air.

It is our practice, after the oral administration of 400 mg. of potassium perchlorate, to seat the subject on a swivel chair in front of the detector of the gamma camera† with his back towards the crystal. The reservoir bag is filled with air. The subject's nose is then clamped gently and he is instructed to breathe as evenly and normally as possible through the mouthpiece. We generally allow each subject to inhale air alone for several minutes before the radionuclide is added to the nebulizer, so that he may become accustomed to the procedure as far as possible before the test is commenced. Considerable care must be taken

† Nuclear Chicago Pho/Gamma III.

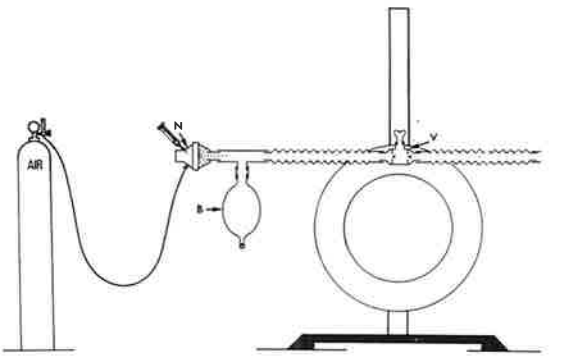

FIG. 1. Diagrammatic representation of the inhalation system employed. Air is supplied to the Bird micronebulizer (N) near the center of the diagram. The subject breathes from the reservoir bag (B) via a 20 inch length of corrugated tubing and low resistance valve (V), while seated in front of the detector of the gamma camera. Exhaled material is removed by an exhaust duct.

* Ambu® Hesse 201.

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‡ Reader in Medicine, University of Adelaide.

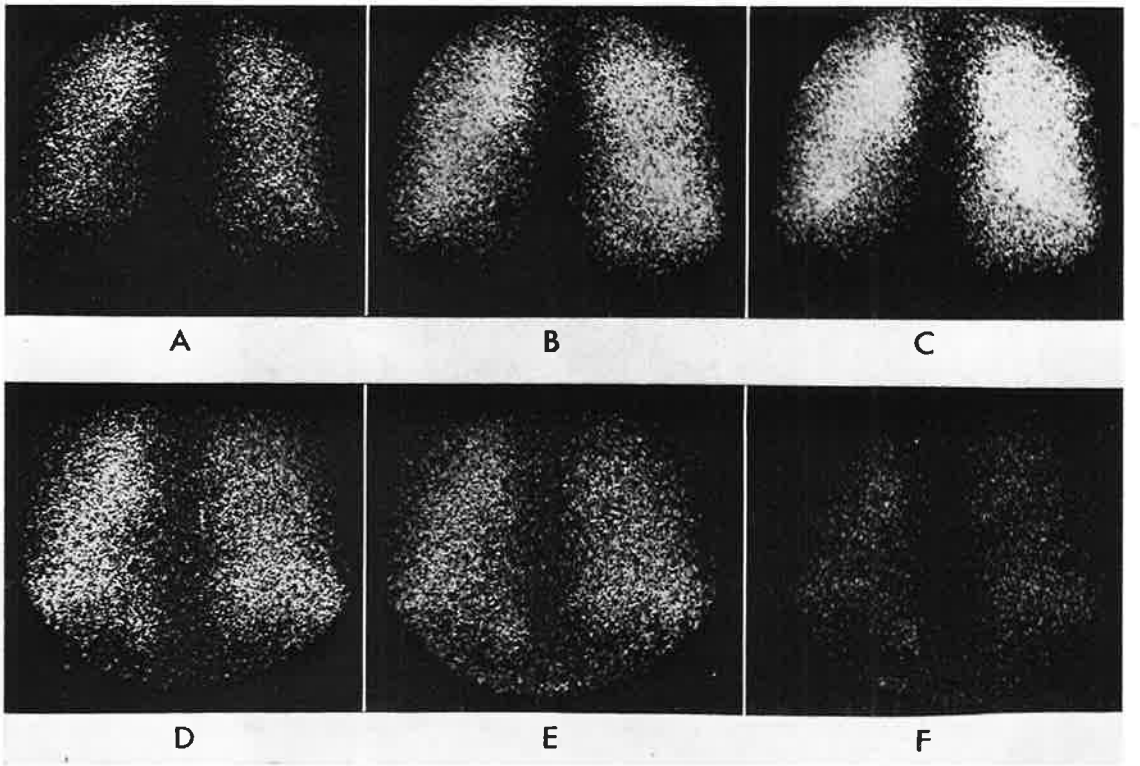

Fig. 2. Serial posterior scintiphotos each of 60 seconds exposure and taken at 2 minute intervals during the inhalation of pertechnetate (*A*, *B*, *C*) and at 5 minute intervals during the washout phase (*D*, *E*, *F*). In the normal subject there is even distribution of pertechnetate throughout both lungs and uniform decrease in activity when inhalation ceases. Note that in the later scintiphotos an area of increased activity is seen below the base of the left lung, in the stomach (left lung on the left of scintiphoto).

in positioning the patient at this stage to ensure that both lungs will be entirely visualized. If necessary, a diverging collimator may be used.

The pertechnetate is added to the well of the nebulizer by means of a syringe, and serial scintiphotos, each of 1 minute exposure, are commenced and continued for 5–10 minutes by which time a consistent scintiphoto image of the distribution of radionuclide within the lungs is usually obtained. When the inhalation phase has been completed, the mouthpiece is withdrawn and, if desired, the patient is rotated to obtain anterior and lateral scintiphotos. As the pertechnetate disappears rapidly from the lungs after inhalation of the radionuclide has ceased, it is important that any additional views required at this stage are obtained with the minimum of delay. Alternatively, once a satisfactory posterior projection scintiphoto has been obtained, the patient may be rotated to obtain further views during the inhalation phase with little inconvenience. Additional useful information may be gained by continuing observation during the washout phase. It has been our practice to collect such data for at least 15 minutes.

Whenever possible, we prefer to use the standard 4,000 parallel hole, low energy collimator because of its adequate resolution, sensitivity and lack of distortion. However, the 10 inch diameter circular field of view visualized with this system is not large enough to encompass the full extent of both lung fields in most subjects. Because of the larger field of view it offers, a diverging collimator* is frequently used;

* Nuclear-Chicago, 410 Kev. diverging medium fine hole.

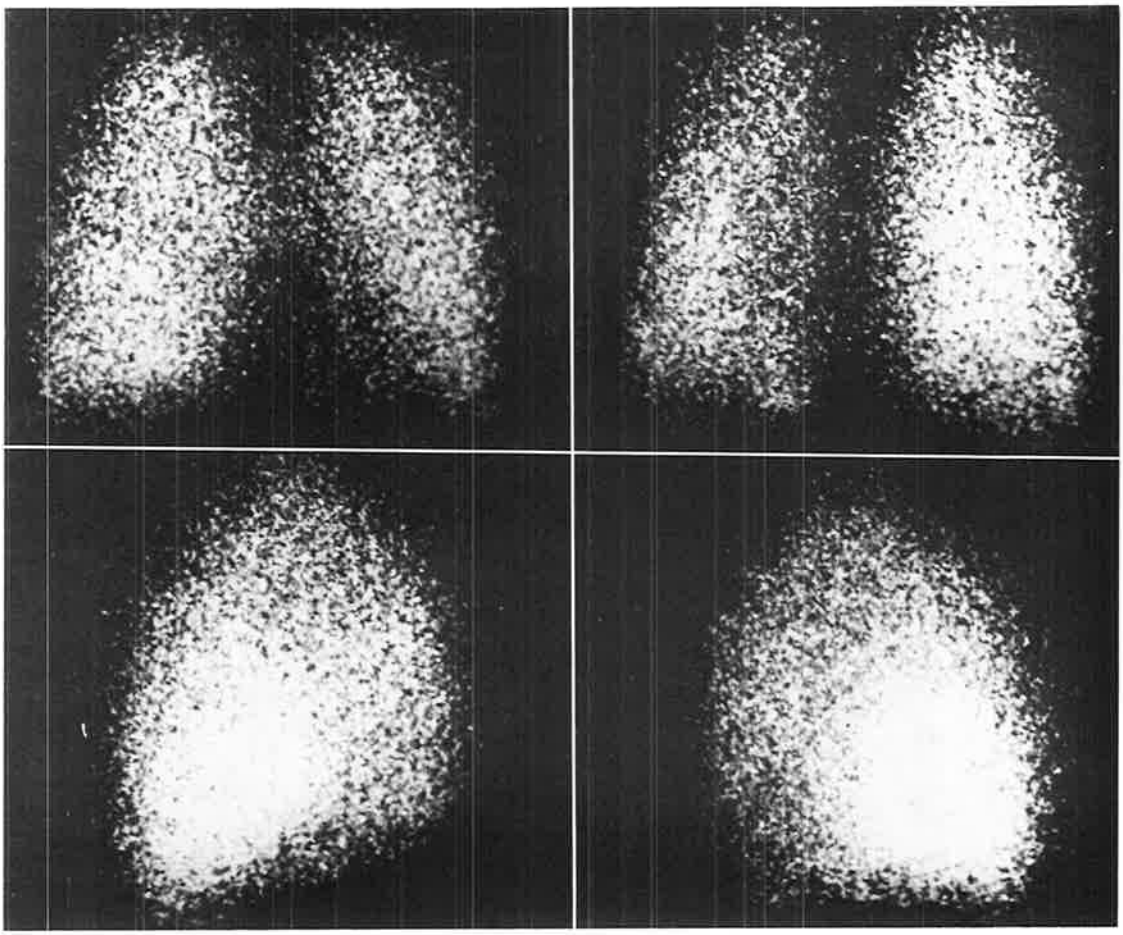

FIG. 3. Scintiphotos taken towards the peak of the inhalation phase using a diverging collimator: 50,000 counts were accumulated in each view. In this normal subject there is some detectable bronchial deposition of pertechnetate seen in the anterior view (top left). Posterior, left and right lateral views are seen in the top right, bottom left and right, respectively.

however, this has the disadvantage of lower sensitivity and resolution with increasing distortion as one approaches the periphery of the field.

Irrespective of the collimator employed, we have used a 20 per cent window centered on 140 kev. With the standard parallel hole collimator, a maximum count rate of approximately 80 K/minute is generally obtained towards the end of the inhalation phase in normal subjects; with the diverging collimator a rate of 50 K/minute is obtained. The over-all efficiency of the system is not high, for only 10–15 per cent of the nebulized spray is detectable in the lungs; the remainder "rains out" in the reservoir and proximal tubing.

During the entire procedure, we have accumulated the data generated by the camera in a 1,600 channel multiparameter analyzer* and "dumped" it at intervals of 1 minute, by means of a recorder,† on to digital magnetic tape to be subsequently processed by computer.‡ Before comparing activities in various regions of interest, we have corrected first for nonuniformity of response across the crystal face. A program

* RIDL®.
† Ampex®.
‡ CDC 6400.

for this purpose, which has been developed in our laboratory, is described elsewhere.[6]

This paper records the results obtained in 15 normal subjects and in 51 patients suffering from a variety of pulmonary disorders.

RESULTS

STUDIES IN NORMAL SUBJECTS

In normal subjects, inhalation of pertechnetate is consistently followed by uniform distribution of activity throughout both lung fields (Fig. 2, *A–C*). Static scintiphotos taken towards the peak of the inhalation phase (Fig. 3) demonstrate the usual features seen in inhalation scans employing a radiogas (for example, Xe^{133}) or other radio-aerosols. The distribution of technetium is uniform throughout all areas, the vertebral column and cardiac outline are clearly delineated and there is negligible bronchial precipitation of the material.

Quantification of the radioactivity reveals that it accumulates rapidly in all areas. Data obtained in one study in which the upper and lower zones of both lungs are compared are illustrated in Figure 4. When inhalation of radio-aerosol ceases, the rate of decrease of activity in each zone is relatively uniform throughout the normal upright lung (Fig. 2, *D–F*). After 15–20 minutes in the majority of normal subjects, relatively little radioactivity remains localized in the lung fields, but increasing background radiation is evident from circulating radionuclide which has been absorbed, and an area of increased activity generally becomes evident in the region of the stomach (Fig. 2*F*). There is very seldom any accumulation of activity in the main bronchi. Thirty minutes after inhalation has ceased, the pulmonary outline is usually no longer discernible in the scintiphotos.

STUDIES IN ABNORMAL SUBJECTS

As in normal subjects, the appearances obtained using pertechnetate in nebulized form are similar to those obtained using other radiopharmaceuticals. In patients with such localized disorders as lobar pneumonia or bronchogenic malignancy, activity in the affected area is usually reduced or even absent; elsewhere, in the absence of underlying chronic obstructive lung disease, an essentially normal pattern is seen.

Patients with generalized disease, especially obstructive airways disease, frequently demonstrate quite bizarre patterns with a tendency to more proximal deposition of pertechnetate and many apparently

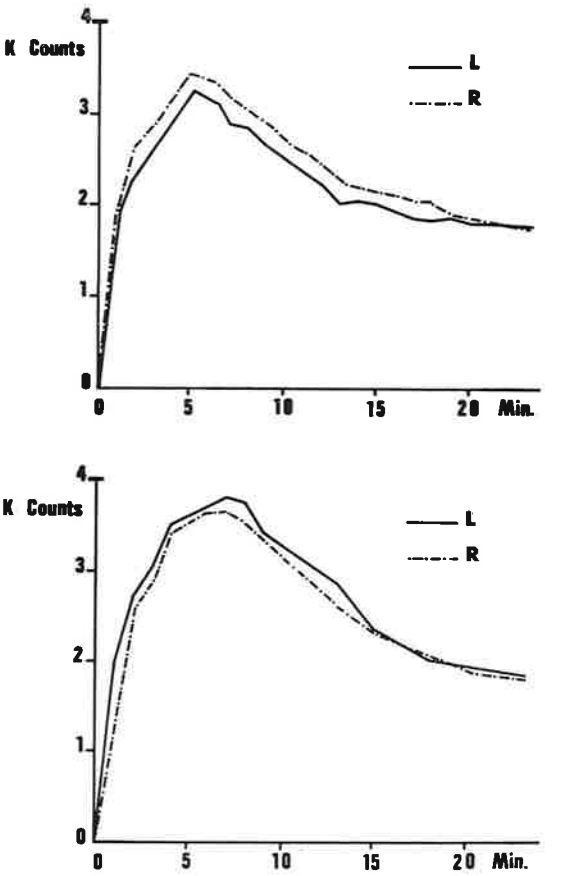

Fig. 4. Quantitation of the activity for 60 second intervals over 4 equally sized regions of interest at the apices (top graph) and bases (bottom graph) of the lungs during a 6 minute inhalation period and 18 minute washout phase reveals a rapid build-up of activity followed by an even reduction in all areas on ceasing inhalation.

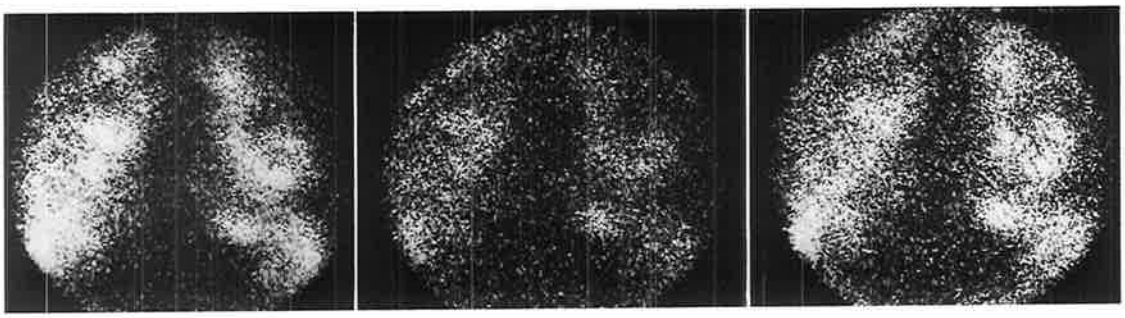

FIG. 5. Posterior scintiphotos in a subject with severe obstructive airways disease. On the left a scintiphoto taken towards the peak of the inhalation phase reveals a bizarre distribution of radiopharmaceutical with many apparently unventilated areas and a number of areas of increased deposition. Washout (center) appears even, and after orciprenaline inhalation and repeat inhalation there is no demonstrable change in pertechnetate distribution.

under- or non-ventilated areas. In such cases, the clearance of radionuclide from the lungs tends to be retarded and may vary quite considerably from one area to another. After allowing time for clearance of pertechnetate from the lungs in 4 subjects, orciprenaline* was administered and the procedure repeated (Fig. 5). In none of the subjects was there any obvious alteration in distribution of the inhaled pertechnetate, although 2 subjects reported diminished respiratory discomfort.

We studied 3 asthmatics during recovery from severe attacks of asthma. In each case there was marked central deposition of radiopharmaceutical, the majority of the inhaled dose apparently failing to reach the alveoli. In 2, after removal of what pertechnetate did reach the alveoli, many "hot" areas remained in the mainstem and lower order bronchi and their course could be followed up the trachea until they were eventually coughed up (Fig. 6).

Twenty-five patients in whom there was clinical and investigative evidence of pulmonary embolism were included in our abnormal group. In 20, no abnormality was evident in the inhalation studies, despite the existence of some quite extensive defects in pulmonary perfusion (Fig. 7, *A* and *B*). In these patients, washout of pertechnetate appeared to occur evenly throughout all areas. Three of these subjects failed to show adequate ventilation of the ischemic areas seen on perfusion scan and 2 had coexisting obstructive airways disease resulting in bizarre patterns.

* Alupent® inhaler.

DISCUSSION

If the 2 critical parameters of particle size and time of "imaging" are controlled, the pertechnetate form of technetium is suitable for inhalational lung scintiphotography.

Particle Size. The Bird micronebulizer generates a fine mist of particles of greatly varying size. Approximately 20 per cent of the particles are smaller than 2 μ in diameter and the remainder have a diameter of 2–4 μ.[4,7] The reservoir and tubing proximal to the patient, which serve to collect and store the intermittently generated spray, reduce the pressure and turbulence in the system. In addition, it removes the largest droplets which precipitate on to the walls. This filtering effect of the proximal tubing ensures that only the smaller particles are inhaled. These are less susceptible to removal by impaction in the upper airways and there is very little bronchial deposition in normal subjects.

We have not been able to measure satisfactorily the size of the particles likely to be inhaled. However, we have compared the scintiphotos obtained in the same normal and abnormal subjects using our pertechnetate aerosol, with those obtained

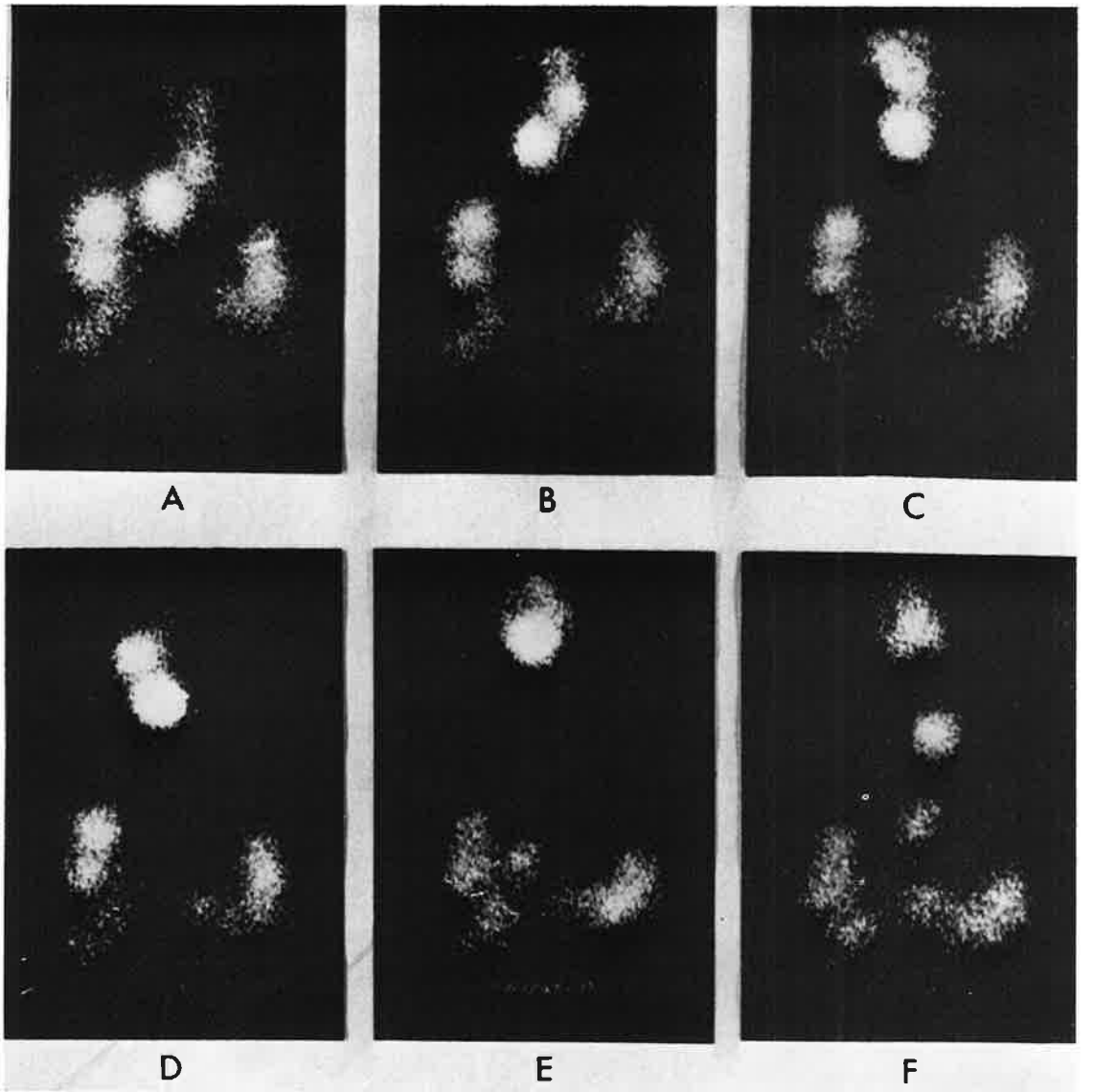

Fig. 6. Serial 60 second posterior scintiphotos taken at 5 minute intervals beginning 10 minutes after the end of the inhalation phase in an asthmatic. The centrally deposited pertechnetate can be followed up the bronchial tree in successive frames until it was eventually coughed up.

using aerosols of Tc^{99m} sulphur colloid (with a particle size of less than 1 μ) and/or Tc^{99m} HSA. There was no significant difference in the images obtained with the different preparations, except that 70–80 per cent of the markers were still detectable in the lungs of normal subjects after 24 hours. It would thus seem that a major portion of the output of our system passes beyond the ciliated epithelium of the bronchial tree which is normally cleared of particles within 18 hours.[1]

Time of Imaging. Previous investigators have been unable to obtain satisfactory inhalation images using pertechnetate[5,8] for they have used scanning techniques after inhalation has ceased. In our studies, scintiphotos are taken with a gamma camera during inhalation of the aerosol. Only then and in the first few minutes after

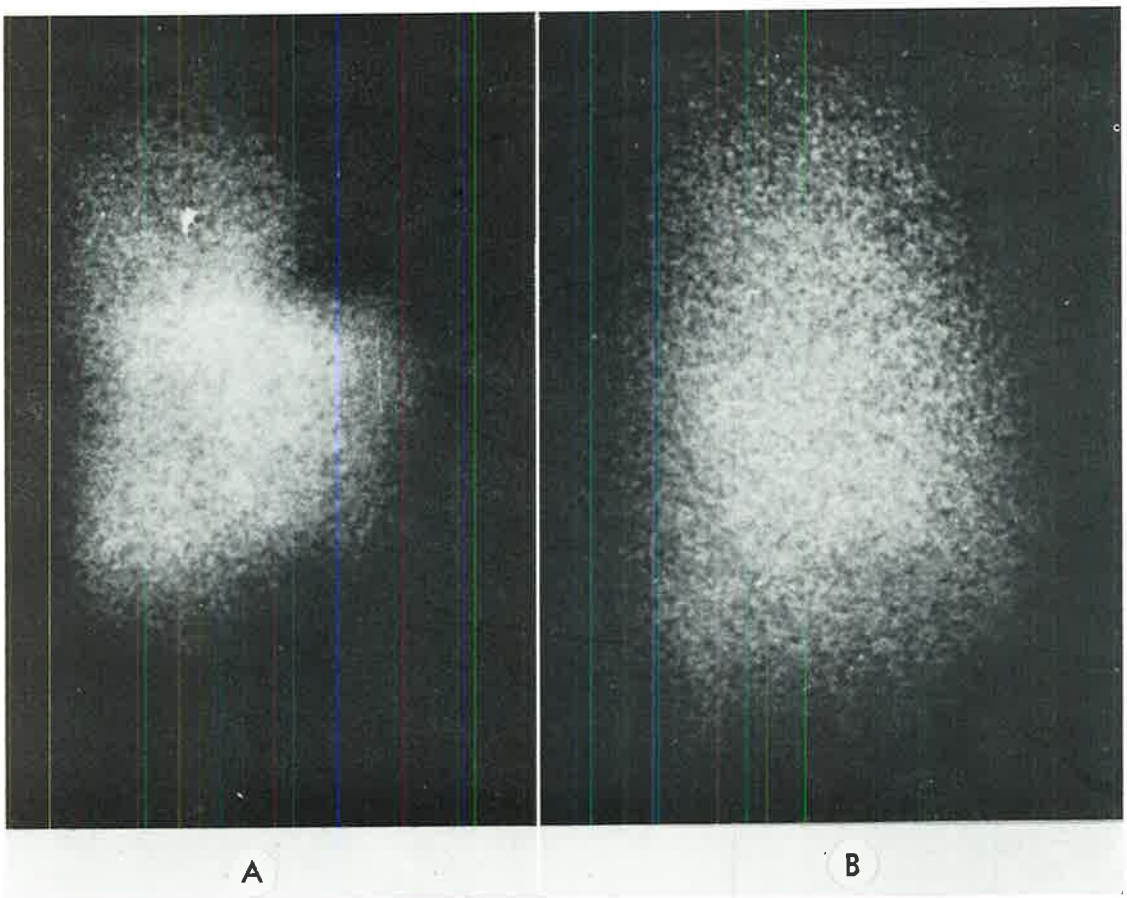

FIG. 7. (*A*) Posterior perfusion and (*B*) inhalation scintiphotos obtained within a short time of each other in a subject with pulmonary embolism. Note the presence of normal ventilation in the regions of decreased perfusion in the right upper zone, midzone and base. Washout was even from all areas without the development of "hot" spots.

inhalation of the aerosol has ceased can scintiphotos of good quality be obtained for, as demonstrated above, pertechnetate is removed rapidly from the lungs.

Fate of Pertechnetate. The prompt clearance of pertechnetate from the lungs initially suggested to us that local perfusing blood might account for the removal of a significant proportion of the inhaled material and that the technique might thus provide information regarding regional perfusion. However, this has not been the case. In none of our studies of patients with pulmonary embolism have we observed the evolution of residual "hot" areas, as the radionuclide is removed from normally perfused lung at a more rapid rate than from ischemic lung.

Several factors probably contribute towards this finding. We have observed that the rate of decrease of radioactivity with time is similar in all areas of the upright normal lung; there is not a more rapid decrease in the bases, where blood flow per unit volume of lung is greatest.[10] Quantification of the pertechnetate in exhaled breath indicates that 55–75 per cent of the reduction from maximum radioactivity over the lungs is lost by this route within 30 minutes of the cessation of the inhalation phase. Disappearance of the remaining radioactivity from the lungs is associated

with a build-up of background circulating blood activity and this would tend to obscure the development of any visually apparent residual "hot" area. Clearance of activity undoubtedly occurs also from both normal and "non-perfused" lung via the bronchial circulation. Nevertheless, it seems likely that in at least some cases of extensive pulmonary embolism with preservation of airway patency that "hot" areas might be found.

SUMMARY

Inhalation lung scintiphotos of good quality with a minimum of bronchial deposition have been obtained using a simple, inexpensive nebulizing system and technetium in the pertechnetate form.

The method described is a rapid means of obtaining useful information regarding airway patency with no radiopharmaceutical preparation.

Pertechnetate is a suitable radiopharmaceutical for inhalation lung studies providing scintiphotos are obtained during the inhalation phase and not exclusively after inhalation ceases, when pertechnetate is rapidly cleared from the lungs.

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APPENDIX L

COOK, D. J., and HARRY LANDER, Department of Medicine, University of Adelaide, and Division of Nuclear Medicine, Institute of Medical and Veterinary Science.

Observations on the Criteria for the Diagnosis of Pulmonary Embolism.

The diagnosis of pulmonary embolism is suggested by the combination of a series of common respiratory symptoms and signs and by the development of a variety of "characteristic" electrocardiographic, radiological and biochemical changes. Nevertheless, judging by autopsy studies, its true incidence is considerably underestimated during life.

A series of 221 (108 males; 113 females) surgical patients, aged 18-91 years, were studied before and at frequent intervals after surgery by serial pulmonary perfusion scintiphotography. In those subjects in whom a defect was observed, a radionuclide inhalation study or angiogram was performed. Pulmonary embolism was detected in 19 [8.6%] (7 males; 12 females) of the subjects postoperatively, and in 1 preoperatively. In 12, embolism occurred within 6 days of operation and in 6, more than one episode of embolism was observed. No subject complained spontaneously of severe symptoms: none developed pleuritic pain, cough or haemoptysis. A transient pyrexia occurred in 5 and tachypnaea in 4. Deep vein thrombosis was evident clinically in 4. No subject evinced right heart embarrassment.

In 15/19 the chest X-ray remained normal or unchanged; in 4, changes consistent with embolism were observed. Significant ECG changes were noted in only 2 subjects. In 6, the total serum lactic dehydrogenase (LDH) level was elevated, and in 8, the level of the isoenzyme LDH_1 was increased.

Pulmonary embolism occurs more frequently than is usually diagnosed and is most commonly asymptomatic. Symptoms and signs suggestive of the disorder frequently develop in the absence of embolism.

Proceedings of the Australian Society for Medical Research, 2, 480, 1971.

APPENDIX M

LANDER, HARRY and D. J. COOK, Department of Medicine, University of Adelaide, and Division of Nuclear Medicine, Institute of Medical and Veterinary Science, S.A.

The Detection of Pulmonary Embolism by Combined Radionuclide Serial Pulmonary Perfusion, Ventilation and Blood Flow Studies.

Pulmonary perfusion scanning using radionuclide labelled macroaggregates is a sensitive technique for the detection of pulmonary embolism, but lacks specificity. Additional information may be gained by repetition of the study at frequent intervals and observing the evaluation of changes. In a series of 221 surgical cases, we have further enhanced its diagnostic value by routinely undertaking baseline preoperative studies (in which a high incidence of abnormalities has been detected) and by repeating the test at regular and frequent intervals after operation. ^{99m}Tc-MAFH (macro-aggregated ferrous hydroxide) was used in these studies.

Whenever a perfusion defect was observed, inhalation studies were performed using an aerosol of either pertechnetate or carrier-free $^{113m}InCl_3$. Additional useful information was obtained in certain cases by the intravenous injection of a bolus of pertechnetate and observation of its passage through the pulmonary and bronchial circulations.

Combined studies, particularly if performed at intervals, are of much greater diagnostic value than the performance of any single study alone, particularly in the provision of information concerning discrepancies in regional ventilation/perfusion; and in this respect the ^{113m}In-aerosol technique has many practical advantages over the use of a radioactive gas. In our series of surgical patients, the combined technique described provided a simple, safe and reliable method for the early detection of asymptomatic pulmonary embolism. In one subject, pulmonary embolism was detected prior to surgery.

Proceedings of the Australian Society for Medical Research, 2, 481, 1971.

APPENDIX (aa)

THROMBOEMBOLISM INDEX

Name: Age: Sex: UR:

CLINICAL DIAGNOSIS:

HISTORY

Chest pain	No	Sudden onset		Pleuritic	Rec. Angina
Dyspnoea	No	Sudden onset		At rest	On exert.
Haemoptysis	No	Yes	Cough	Productive	Chronic
Surgery	No	Yes	Nature		
Recumbency	No Yes	Duration		Smoker	Yes:No Number:
CVS disease	No	Yes	Nature		
"Pill"	No	Yes			

Other drugs:
P.H. thromboembolism No:Yes
Other:

EXAMINATION

Thrombosis:	No	Sup. thrombophlebitis					
		Dvt	Cord	Swelling	Homman's	Pain	
Embolism:	No	Cyanosis	Red. A.E.	Tachyc.	Fr.rub	Inc.P2	
		Hypotens.	Wheeze	Creps	Tachyp.	Tachyc.	
		JVP	Pyrexia				

INVESTIGATIONS

CXR:	Normal	Prom.PA.	Eff.	Atelect.	Oligaem.	Infarct
		Cardiomeg.		Pulm.oed.	Other	
ECG:	Normal	R axis	Arrhythmia	ST changes	Infarct	Q_{III}
		S_1	Other			
Biochem:	Normal	LDH	AAT	Bili.	Isoenz.	1+2
						3
						4+5

Other investigations:

APPENDIX (bb)

SURGICAL THROMBOEMBOLISM

Name: Age: Sex: UR:
Clinical diagnosis:

HISTORY:

Chest pain	No	Yes	Nature
Dyspnoea	No	Yes	Nature
Haemoptysis	No	Yes	
Recumbency	Comp.	Part.	Dur.
C.V.S. dis.	No	Yes	Nature
Neoplasia	No	Yes	Nature
Pill	No	Yes	Other drugs:
P.H. thromboemb.	No	Yes	Cig.smoke:
Other			

EXAMINATION

Thrombosis	No Yes Evidence
Chest pathology	Cyan. A.E. Tachyc. Frict.R. Pyrex. Hypoten. Wheeze Creps. Tachypn. Other
Scan 1 (preop)	Normal Abnorml Description:

INVESTIGATIONS

CXR: Date:	Normal	Prom.p.a.	Effusion	Atelect.	Oligaem.
		Infarct	Hampton's H.		Other
ECG: Date:	Normal	R axis	Arrhythmia	ST changes	
		Other			
Biochem: Date:	Normal	LDH	Isoenz.	SGOT	Bili.

APPENDIX (bb) contd.

Scan 2 (postop)	Normal	Abnormal	Consist.known pulm.dis. Consist.P.E. Mult.def. Sing.def.
	Defect sites: Comment:		
Scan 3	Normal	Abnormal	Consist.known pulm.dis. Consist.P.E. Mult.def. Sing.def.
	Defect sites: Comment:		
Scan 4	Normal	Abnormal	Consist.known pulm.dis. Consist.P.E. Mult.def. Sing.def.
	Defect sites: Comment:		

HISTORY

Date	Chest pain	No	Yes	Nature
	Dyspnoea	No	Yes	Nature
	Haemoptysis	No	Yes	
	Recumbency			

EXAMINATION

Date	Thrombosis	No	Yes	Evidence		
	Chest path.	Cyan.	A.E.	Tachyc.	Frict.R.	Pyrexia
		Other				

INVESTIGATIONS

CXR:	Normal	Prom.p.a.	Effusion	Atelect.	Oligaem.
Date		Infarct	Hampton's H.		Other
ECG:	Normal	R axis	Arrhythmia	ST changes	
Date		Other			
Biochem.	Normal	LDH	Isoenz.	SGOT	Bili.
Date					

Angiogram:

ABO blood group:

APPENDIX cc

STATISTICAL METHODS

Chi-square estimations and analysis of groups by rank contingency were carried out according to the methods outlined in

> *"Biostatistics - An Introductory Test"*
> A. Goldstein, The Macmillan Co., New York, 1964

and employing the tables included in that text.

APPENDIX dd

A number of factors contribute to the improved resolution of the gamma camera with diverging collimation when 113m indium is used. These are discussed below.

CAMERA RESOLUTION WITH DIVERGING COLLIMATOR AT 392 keV AND 140 keV

Since there is no appreciable septal penetration in the 410 keV medium fine hole diverging collimator (Nuclear Chicago) resolution at these energies is not affected by the characteristics of the collimators.

Features of the crystal and electronics of the gamma camera are entirely responsible for resolution differences.

1. At low gamma energies primary photoelectric interactions are the main contributors to the photo peak in sodium iodide (Anger, 1967).
2. At higher energies multiple Compton-photoelectric events are the main contributors to the photo peak (Anger, 1967). Thus at low energies in sodium iodide the scintillation is more likely to be situated in the path of the incident gamma ray. At higher energies the computing circuit of the camera will place a single flash at the centre of luminous intensity of the scintillations when multiple Compton-photoelectric events occur. Alternatively at higher energies if the secondary gamma ray escapes the scintillator, the Compton interaction does

not contribute to the photopeak because it produces a weak scintillation. The overall result is slight degrading of the resolution at higher energy due to these factors. However the effect is slight.

3. (a) The accuracy with which the photo multiplier array can determine the position of scintillations in the crystal is limited by the statistics of electron production in the photo tubes. The loss of resolution from this cause is inversely proportional to the square root of the brightness of the scintillation (Anger,1967).

(b) The number of luminescent quanta produced by an electron is proportional to its energy loss in the scintillator (Hine, 1967).

(c) The number of electrons emitted from the photo cathode of the photo multiplier tube is proportional to the number of luminescent quanta in the scintillator.

Thus loss of resolution $\alpha \sqrt{\frac{1}{E}}$

At higher energies the loss of resolution of the camera due to the statistics of electron production is reduced. This is a major factor in improved inherent resolution distance at 364 keV (0.25") compared with 160 keV (0.37") for the camera (Anger, 1967) and will be the major factor operating at 392 keV.

$$\left[0.370 \times \sqrt{\frac{160}{364}} = 0.245\right]$$

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