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

1. *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 *Traité 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 asymptotically 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 pre-occupation 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 anti-septic and aseptic surgery was reducing post-operative 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-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 refractory 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 precordial 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 co-workers (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 Westermarck (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 Westermarck (1938). He noted that in some cases the affected lung appeared abnormally radiolucent due to oligæmia. 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 Westermarck'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, ($^{15}\text{O}_2$), 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 (^{65}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 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 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 bronchspirometry (Lopez-Majano *et al.*, 1964), standard electromagnetic flow-meter 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 ($^{113\text{m}}\text{In}$) (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 $^{113\text{m}}\text{In}$ 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 ($^{99\text{m}}\text{Tc}$) such as $^{99\text{m}}\text{Tc}$ -MAA (Loken, Telander & Salmon, 1965; Webber, Bennett & Surprenant, 1966) and $^{99\text{m}}\text{Tc}$ -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 $^{99\text{m}}\text{Tc}$ -pertechnetate (10–20 mCi) through the heart and pulmonary vasculature (Kriss *et al.*, 1966; Rosenthal, 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 co-exist. 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 (Poulouse *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, $^{113\text{m}}\text{In}$ (Isawa *et al.*, 1970). Recently, we have obtained inhalation studies of very satisfactory quality using $^{99\text{m}}\text{Tc}$ -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 the 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 rendered

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 delineated from the background radioactivity in the blood. Furthermore, the preparation and use of satisfactory antisera present many difficulties.

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