CHAPTER 5
THE THORAX

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Introduction

There are few conditions in humans that affect most people in the population at some time during their lives, lung inflammation/infection is such a problem. Airways inflammation or infection are a major cause of morbidity and accounts for a large number of visits of patients to their primary care physician. The inflammatory reaction is associated with marked vascular change including hyperaemia and vascular leakiness leading to interstitial oedema. These responses to noxious insults to the lung may lead to damage of the epithelium and due to excess production of mucous and cells to deal with the injury, blockage of airways may occur. The type of initiating injury often determines the type of cellular infiltrate and the response of the individual may be excessive leading to other problems in the lung. The response may affect the airflow and therefore delivery of oxygen and perhaps medication. Therapy to the lungs is often appropriately given via the airways by metered dose inhaler or nebulisers, the mode of this delivery can be studied using radionuclides but is beyond the scope of this chapter and has been reviewed recently [1]. The mechanisms behind the clearance of secretions associated with inflammatory and infective diseases are a further area where nuclear medicine techniques have contributed to the understanding of disease processes. Nuclear medicine studies can therefore contribute to the topic of inflammation and infection in the thorax in terms of understanding pathology, disease progression and management as well as investigating methods to improve therapy.

Infection and inflammation within the thorax is normally associated with either specific symptoms of breathlessness, cough, chest pain (pleuritic, pericarditic or musculoskeletal) or non-specific with fever, lethargy and confusion. The manner in which a patient presents determines the clinician's investigation strategy. The use of nuclear imaging in the thorax for inflammatory/infective disease is to provide diagnostic information to the clinician or at least confirm their suspicion as to the site needing to be treated or

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biopsied. Other radionuclide investigations may provide an opportunity to follow a disease process sequentially or to monitor response to therapy.

Although morphologic imaging such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) provide detailed anatomical information, they have a limited role in evaluating patients with long-term structural abnormalities or functional changes with little structural alteration. Subtle changes to the lung parenchyma having a large functional impact may not be visualised as a structural change. To utilise these modalities effectively a specific question needs to be asked and this may not always be clear in the clinician's mind.

The variety of problems caused by inflammation and infection within the thorax are determined by the structures within the thorax. The techniques used in the detection of inflammation/infection in these structures have been identified in other chapters and include Gallium-67, leucocyte imaging, labelled antibodies including antigranulocyte antibodies, polyclonal immunoglobulin and monoclonal antibodies specifically against Pneumocystis carinii pneumonia (PCP) and various bacteria. The only additional tests used in the thorax are the use of technetium diethylene triaminepentaacetic acid (DTPA) and the use of pyrophosphate or antimyosin antibodies which will be discussed. The measurement of clearance or transfer of ^{99m}Tc DTPA is related to the permeability of the lung epithelium to ^{99m}Tc DTPA and any process which causes disruption of the alveolar and respiratory bronchiole epithelium will increase this permeability. Lung ^{99m}Tc DTPA transfer (permeability, clearance) is measured by assessing the rate of loss of DTPA from the lung after it has been inhaled as an aerosol for 1 - 2 minutes, the particle size should be less than 1 micron. Data is acquired dynamically and the resultant time activity curves analysed to provide a clearance/transfer half time [2].

The investigation of thoracic inflammation and infection will be considered in this chapter by the structures within the thorax and limited to studies performed in human subjects. The areas that are discussed in other chapters e.g. bone infection are only considered here in terms of specific infections within the chest.

Extra Pulmonary Problems.

Skeletal System.

Infection and inflammation in the chest may affect the sternoclavicular joints, the sternum, the clavicles, the vertebrae and less commonly the ribs. Osteomyelitis can affect these areas after trauma, surgery or as a primary site. The most common problem within the ribs is a result of inflammation in costochondral joints. There are rare causes of multiple areas of increased uptake within ribs or of the clavicle which can be seen on conventional bone scanning which may be due to infection and should be questioned in the immunosuppressed patient. These multiple abnormalities in the immunosuppressed patient in the correct clinical setting may indicate bacillary angiomatosis [3]. Other abnormalities include discitis due to acute osteomyelitis or indeed due to tuberculosis, brucellosis etc.

A singular problem in the thorax is fever in a patient following a sternal split for cardiac bypass graft surgery. The bone scan is invariably positive and the question is whether there is infection present. Sternal wounds following bypass grafting can be investigated by ^{99m}Tc exametazime or ^{111}In labelled cells. Serry et al [4] reviewed 4,124 median sternotomies performed for cardiac surgery. Fifty patients had some form of complication of which 19 had septicaemia and mediastinal abscess in addition to the sternum infection. Therefore the mediastinum has to be viewed in this patient group. Salit et al [5] using gallium to evaluate patients with suspected sternal osteomyelitis found a sensitivity of 86% and specificity of 93% for osteomyelitis. By adding single photon emission tomography (SPET) the mediastinum can be evaluated as well. Cooper et al [6] investigated 29 patients to exclude deep sternal wound infection following coronary artery bypass grafting using ^{99m}Tc exametazime labelling and showed that intense uptake at 4 and 24 hours or increasing uptake between 4 and 24 hours was associated with deep sternal infection (100% sensitive; 89% specific). Superficial sternal infection was not reliably detected. Since the late images were superior to the early images it may be more appropriate to use ^{111}In labelled leucocytes rather than ^{99m} Tc to assess late changes, this study has not been performed. Leucocyte imaging is the most

appropriate method to assess possible sternal osteomyelitis with additional mediastinal infection.

Heart and Great Vessels.

Pericarditis, myocarditis and cardiac transplant rejection.

Most causes of pericarditis and myocarditis are due to viral infection and more rarely due to bacterial, fungal and protozoal infection. The incidence of these diseases is increased in the immunosuppressed patient. Although the history and the clinical signs may strongly suggest the diagnosis, confirmation is sometimes required. Peri-myocarditis may be difficult to diagnose on the basis of the ECG or indeed echocardiography. Pericardial or myocardial pain may be investigated further by nuclear imaging. The utilisation of pyrophosphate, Gallium-67 or ^{111}In antimyosin antibody scanning may help (Fig.1).

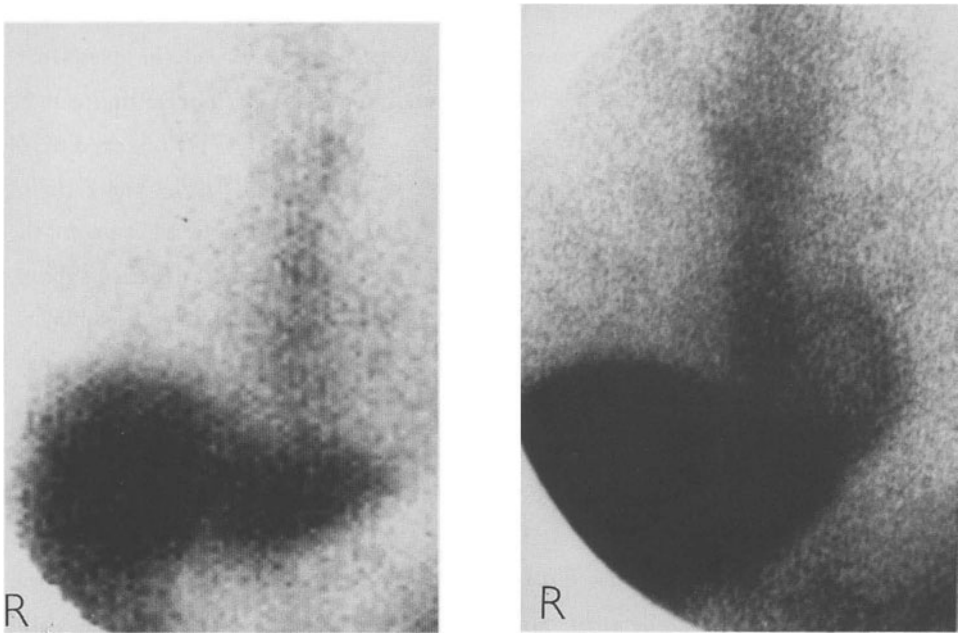

Figure 1. *The scans show a) a normal ^{111}In antimyosin antibody scan at 48 hours and diffuse uptake in the myocardium at 48 hours in a patient with a myocarditis.*

Cardiac problems associated with HIV include cardiomyopathy, myocarditis, Kaposi sarcoma, metastatic lymphoma, pericarditis and endocarditis. Unexpected increased accumulation of gallium-67 in the heart indicates further investigation is necessary; this appearance has been reported in myocarditis [7]. A normal scan however will not exclude a myocarditis. There are isolated case reports on the use of gallium-67 in Kawasaki's disease [8] and a report on the identification of associated myocarditis using ^{99m}Tc exametazime[9]. This latter paper examined 22 infants in the acute phase of Kawasaki's disease and 18 were thought to have myocarditis on the basis of clinical examination, ECG, echocardiogram. The uptake at 24 hours on the leucocyte scan identifed 18 cases of myocarditis whereas the gallium scan was only positive in one case.

Yasuda et al [10] demonstrated increased uptake of ^{111}In antimyosin antibody in patients with myocarditis, but a proportion of these patients had a negative biopsy. A question raised by this study was the magnitude of biopsy sampling error. The use of ^{111}In antimyosin Fab fragment in a large study of patients with suspected myocarditis showed a sensitivity of 83%, but a specificity of only 55% [11]. A proportion of these patients were followed up and 54% of those that had positive scans showed an improvement in their ejection fractions whereas those that had no uptake only 4 out of 22 had a marginal improvement in ejection fraction. The data suggested that endomyocardial biopsy is unlikely to confirm myocarditis in the presence of a normal antimyosin scan. Furthermore it may be concluded that the sampling error of the biopsy may be a major cause of the low specificity of the antimyosin scan.

In heart transplant patients the diffuse increased uptake of ^{111}In antimyosin antibody has been a useful monitor of acute rejection and a guide to those needing biopsy. The scan was positive in 52% of cases with histological rejection, but despite this low specificity it had a 100% sensitivity [12] and therefore may be useful in selection of patients for biopsy. Quantitation of uptake in patients followed up 1 year after transplant, identified those patients with moderate rejection [13]. Carrio et al [14] used quantitation (comparing the heart/lung ratios at 48 hours) in patients with heart transplants and found that the episodes of rejection were identified by the scan but that some scan positive patients did not have rejection confirmed on biopsy. One study challenges the

concept that the anti-myosin scan is correct and biopsies are incorrect due to sampling; Obrador et al [15] looked at the uptake of antimyosin in 21 patients with dilated cardiomyopathy awaiting cardiac transplant. Fifteen patients had abnormal uptake and only 7 had an active myocarditis found in the heart that was removed at transplant surgery. It may still be argued that the histological examination did not include ultrastructural examination and thus minimal damage may have been missed.

The value of antimyosin antibody imaging is perhaps in the evaluation of patients with cardiac type pain or symptoms who do not have a clear diagnosis when the distinction between myocardial infarction and myocarditis is needed. Difficulty with scan interpretation can occasionally arise because of the slow clearance of the Fab fragment from the blood pool and the slow uptake in the myocardium, allowing misinterpretation of the diffuse blood pool activity as a myocarditis. New tracers have been developed to enhance this clearance from the blood pool [16].

Endocarditis.

The sensitivity of Gallium-67 scans in bacterial endocarditis is variable and may be influenced by the use of antibiotics and the site of the disease. Wiseman et al [17] reported positive scans in 6 out of 11 patients scanned at 72 hours, whereas Melvis et al [18] only found increased uptake in 2 out of 28 patients and neither of these identified the valve involved. The difference in the two studies was that the latter study had patients with predominantly right sided endocarditis and in all patients antibiotics has been started.

The use of a murine monoclonal ^{99m}Tc labelled anti NCA-95 antigranulocyte antibody BW 250/183 has been evaluated in 72 patients with suspected endocarditis [19]. Planar scintigraphy and SPET of the thorax were performed at approximately 24 hours. The technique demonstrated true positive scans in 26 patients and false positive in seven demonstrating a sensitivity of 79% and a specificity of 82%. Echocardiography had a sensitivity of 88% and specificity of 97%. The antibody scintigraphy was positive in four patients who had a negative echocardiogram. The repeat studies showed improvement in the scintigraphy paralleling the clinical improvement.

Although the use of SPET leucocyte imaging may have a role in detecting root abscesses it is likely that the mainstay of diagnosis of endocarditis will be the echocardiogram. It is difficult to understand why leucocytes or indeed gallium would localise in vegetations that are essentially intravascular, although interstitial abscesses at the valve roots would allow migration of cells. Whole body imaging detecting metastatic abscesses may however point to a diagnosis of endocarditis

Pleural Disease.

The use of leucocyte imaging in pleural disease is restricted. The diagnosis of pleural pathology usually depends on biopsy or aspiration. However coincidental finding of pleural uptake in patients in whom a source of a pyrexia is being sought is occasionally seen. Diffuse uptake of gallium around the pleura or leucocyte accumulation at a site of prior surgery may indicate a source of infection (fig.2). The difficult area of recurrence of malignant disease after lung resection can be confused with an empyema when ^{18}F-FDG is used as the tracer (fig.3).

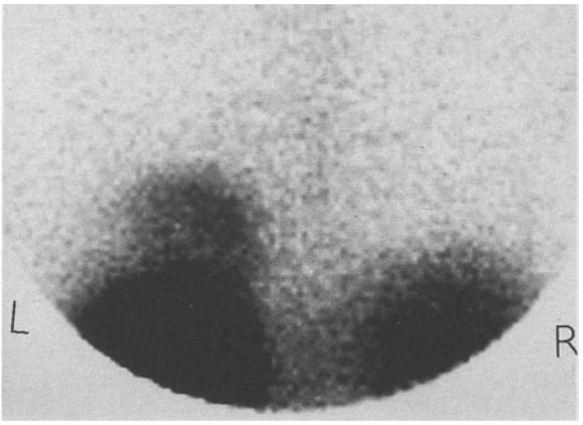

Figure 2. *The scan appearances show increased uptake of ^{111}In oxine labelled leucocytes in an empyema in the left lower chest.*

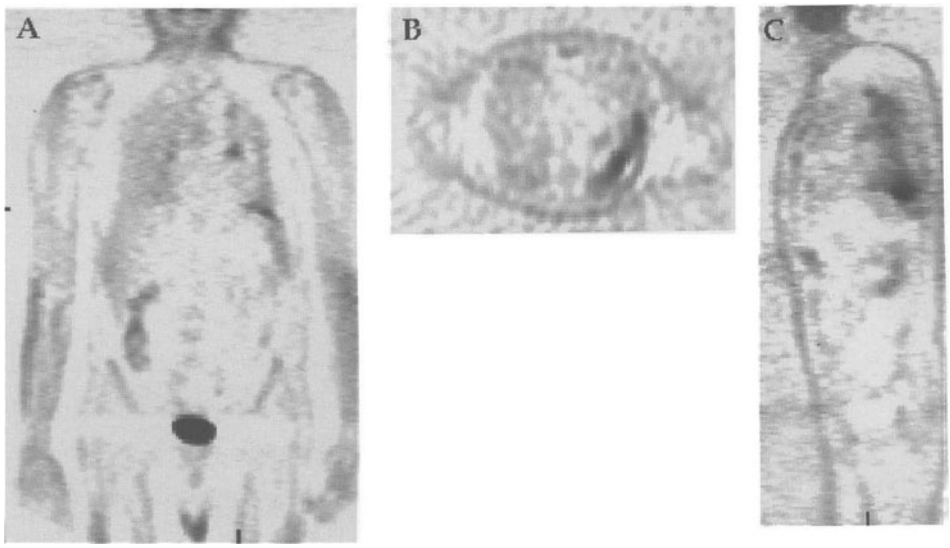

Figure 3. *A half body ^{18}F Fluorodeoxyglucose PET scan showing A) coronal B) transaxial and C) sagittal cuts through the left lower lobe empyema and regional hilar lymph node accumulation of DFG. This presents potential difficulty in distinguishing a pleural carcinoma and a hilar metastasis.*

Lymph node disease.

Lymph nodes in the hila, mediastinum and the subcarinal structures may demonstrate reactive change associated with infection within the lung or direct involvement in granulomatous processes e.g. sarcoidosis or mycobacterial infections. Lymphadenopathy can be assessed using Gallium-67, ^{18}F-fluorodeoxyglucose (FDG) or the combination of Thallium-201 and Gallium-67 to assess whether disease is inflammatory or malignant in nature. Discussion about the distinction between tumour and inflammation is beyond the scope of this chapter. Assessment of sarcoidosis may include high uptake in the mediastinum and hilum which may be associated with uptake in the parenchymal tissue and is discussed below under parenchymal lung disease. The utility of these diagnostic agents are discussed below. The agents are not normally used to assess known

lymphadenopathy, but rather lymphadenopathy is found during whole body assessment of patients with a pyrexia of unknown origin or suspected malignancy.

Pulmonary disease.

The lung parenchyma provides an enormous exposed surface to the air. Approximately 20,000 litres of air pass over the epithelial surfaces of the lung per 24 hours. These air exchanges allow particles of bacteria, viruses, antigens and various chemicals to come into direct contact with the lung surface and potentially irritate or cause severe disease. These disease processes can be evaluated by a number of imaging techniques. A variety of diseases e.g. collagen diseases have secondary efects on the lung and these may result in problems for the patient.

Inflammatory lung disease.

Alveolar and interstitial diseases.

This group of patients tend to have diffuse disease affecting both lungs. Normally the patient will present with breathlessness, a cough and possibly fever, with the chest radiograph often abnormal although not invariably. An indication of the cause of the underlying disease may be given by the patient's occupation, hobbies, medication or by a history of immunosuppression related to the human immunodeficiency virus (HIV) or drug therapy. Investigations often do not involve nuclear medicine although the tests that can be offered may be used in monitoring disease or at least indicating the most affected areas of the lung for biopsy.

Extrinsic allergic alveolitis.

There are a number of possible causes of this condition but the histological change in the subacute phase is that of non-caseating granulomata with oedema and thickening of the alveolar walls. This disruption of the alveolar membrane by cell infiltrates has been monitored using the technique of lung ^{99m}Tc DTPA clearance/transfer and has been shown to be abnormal in at least one cause of the condition "pigeon fanciers" lung [20]. The clearance rate is increased in this condition, and appears to be related to the amount of antibody in the blood since those patients with high levels of antibody had

increased clearance and those patients with antigen exposure but without an antibody response had faster times than normal controls but not as fast as those with antibody. The clearance rates were increased when conventional pulmonary function test were normal.

Cryptogenic fibrosing alveolitis

There are a variety of disease processes that affect the alveolar regions of the lung which include cryptogenic fibrosing alveolitis, connective tissue diseases [21], radiation pneumonitis and drug induced alveolitis [22] as well as infection. All of these conditions affect the transfer of ^{99m}Tc DTPA as a marker of the inflammatory damage to the lung (figs.4,5). Serial measurements of ^{99m}Tc DTPA clearance have been made to follow response to therapy in cryptogenic fibrosing alveolitis [23,24].

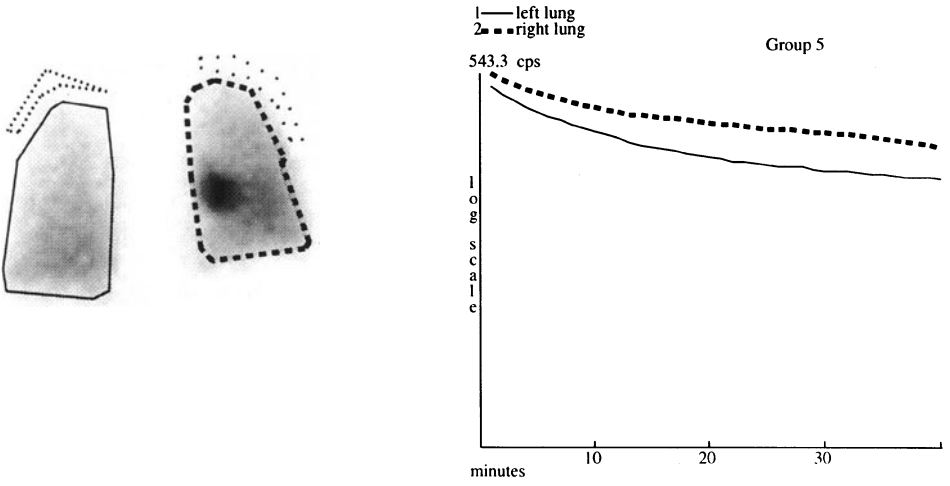

Figure 4. *^{99m} Tc DTPA transfer curves in bleomycin induced alveolitis in a patient with lymphoma. The transfer times are biphasic (at least biexponential); the first component half times for the left lung were 3 min and for the right lung 3.5 min.*

Fibrosing alveolitis is characterised by the infiltration of the lung parenchyma with inflammatory cells that may lead to progressive fibrosis. The degree and distribution of the inflammation and fibrosis can be assessed by open lung biopsy; bronchoalveolar

lavage can assess the amount of inflammation but not the relative amounts of fibrosis and inflammation, similarly pulmonary function tests cannot discriminate. Labrune et al [23] demonstrated a positive correlation between the rate of DTPA clearance and alveolar lymphocytosis which negatively correlated with vital capacity. They also demonstrated that the DTPA clearance rate decreased when patients responded to corticosteroids but the rate did not return to normal.

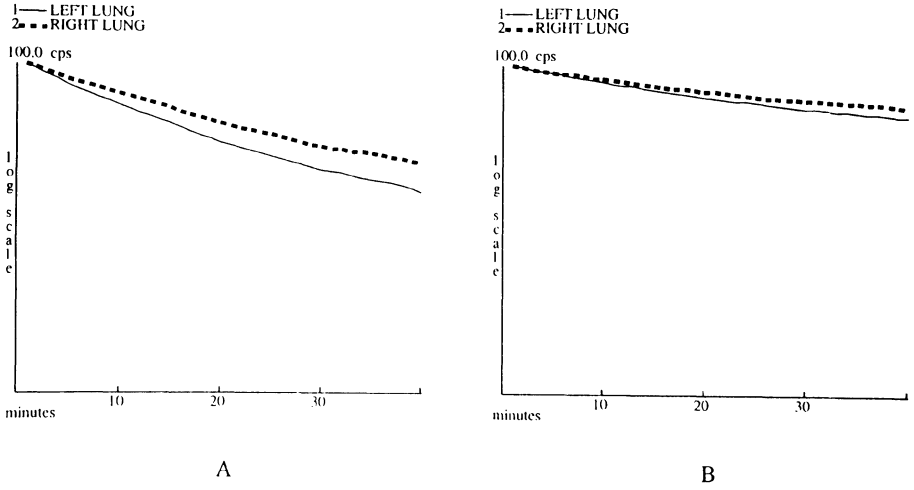

Figure 5. ^{99m} *Tc DTPA transfer curves in fibrosing aveolitis A) pre and B) post treatment with steroids. The curves are presented as a plot of lung activity against time. There is an improvement in the transfer times as seen by a decrease in the slope of the time activity curves*

The persistent increase in the clearance of DTPA may be a result of the stretching of lung units by fibrosis. The test represents a potential method for documenting response to steroids allowing follow up as they are reduced. Uh et al [25] examined the clearance of ^{99m}Tc DTPA in patients with diffuse infiltrative lung disease (DILD) and found that for patients with DILD the T½ was significantly shorter in all lobes than normal

controls, but that patients with early stage disease had longer times than those with late disease in the upper and middle lobes. There was however overlap between the normal range and those patients with disease, such that it was difficult to use the test to identify those patients with disease and normal carbon monoxide transfer values. Thus it is unlikely to be a diagnostic test but may be used to monitor therapy and relapse.

Gallium-67 scanning has been performed in a variety of diffuse infiltrative lung conditions. These include sarcoidosis (described below), idiopathic fibrosing alveolitis [26,27,28], drug toxicity [29,30], pneumoconiosis [31], pneumocystis carinii pneumonia (see below) and a variety of other conditions including diffuse acute bacterial and viral pneumonitis, carcinomatosis and post irradiation [32]. Usually the diffuse abnormality on the gallium scan suggests the need for further investigation or depending on the clinical situation the likely disease process. In fibrosing alveolitis gallium scanning has been used to stage the disease. A good correlation has been reported between disease activity on transbronchial biopsy and gallium uptake [26]. The closest correlation however was found with the neutrophil content of bronchoalveolar lavage fluid and not the lymphocyte count which is surprising in view of the cellular response in the interstitium.

Drug and radiation induced pneumonitis.

A variety of drugs can cause a pneumonitis, the most common is bleomycin induced toxicity. Other drug causes are far less common but amiodarone toxicity can present a problem in distinguishing an alveolitis from interstitial pulmonary oedema due to heart failure, since the drug is used in patients with cardiac disease. The differential diagnosis is therefore between congestive cardiac failure and amiodarone pneumonitis. Since cardiac failure does not alter the alveolar-capillary interface the transfer of DTPA in these conditions is normal [33] then this test should be able to separate cardiogenic from an alveolitic cause of breathlessness. Terra-Filho et al [34] demonstrated that the clearance half times were faster than normal non-smokers and patients on amiodarone but with no respiratory problems. The technique of DTPA clearance was more sensitive than spirometry in detecting this condition. It would however not have distinguished smokers who had pneumonitis. Further abnormalities have been reported

in the inflammatory response due to "crack" use with increased clearance detected [22]. O'Doherty et al [35] reported a differential effect on pulmonary clearance throughout the lungs of patients with haematological malignancy trated with a variety of cytotoxic drugs with the effect greater at the base of the lung than the apex. The postulate was that this effect was distributed according to the blood flow and thus the concentration of the drug delivery to the lung, but no biopsy proof for this was available.

Gallium scans are also abnormal in acute inflammation associated with drug induce pneumonitis or radiation induced pneumonitis [29,30]. These changes present problems in distinguishing drug induced damage from diffuse uptake due to infection.

Connective tissue disorders affecting the lung.

All connective tissue diseases can potentially affect the lung. Usually the inflammatory process affects the bases more than the apices of the lung. This has been demonstrated in early publications on ^{99m}Tc DTPA clearance [21]. Chopra et al [36] studied a group of patients with systemic sclerosis and found that the ^{99m}Tc DTPA clearance from the lung was much faster in the affected lower zones. Gallium-67 has been reported to have increased uptake in the lungs of patients with pulmonary involvement with systemic lupus erythematosis [37] and one would expect similar increased uptake to be observed with acute changes associated with rheumatoid arthritis and polyarteritis nodosa. However no uptake was seen in patients with scleroderma or chronic rheumatoid lung [37]. This would be consistent with fibrosis without inflammation in these lesions.

Adult respiratory distress syndrome.

Widespread severe inflammation associated with the adult respiratory distress syndrome has been evaluated with lung permeability measurements both of the vascular and the epithelial surfaces. These techniques reflect the structural damage that can be done to the membranes of the lung. Lung ^{99m}Tc DTPA transfer has been shown to have fast transfer rates [33], the amount of damage to the endothelium has also been shown to be severe using ^{113m}In transferrin accumulation within the lung [38]. Braude S. et al [39] demonstrated a correlation between ^{99m}Tc DTPA transfer and the ^{113m}In transferrin

measurement in patients with adult respiratory distress syndrome. This illustrates that the movement of molecules from the vascular space to the airspace can give comparable results to the movement from the airspace to the vascular space. This degree of structural damage has also been shown using PET techniques in humans [40,41] and dogs [42,43] by showing the changes in blood flow using ^{15}O H_2O, protein flux ^{68}Ga transferrin and blood volume ^{15}O CO measurements. The degree of inflammation and damage can be shown in infants with respiratory distress syndrome using ^{99m}Tc DTPA [44]. The question perhaps is why bother since the damage is known from the blood gases and the CXR. The measurements used with PET are the transcapillary escape rate and the normalised slope index. These measurements potentially provide a marker of acute lung injury and a means of separating cardiogenic pulmonary oedema from noncardiogenic causes. The marker may also provide an insight into the mechanism and a means of predicting patients who will respond and recover or at least enable an evaluation of therapy options.

Granulomatous diseases of the Lung.

There are a variety of granulomatous disease that affect the lung including miliary tuberculosis, sarcoidosis and talc granulomatosis in intravenous drug use [32]. Gallium-67 scanning has been demonstrated to have increased uptake in these. The use of scanning is to define the extent of disease and the disease activity. The most studied disease process is pulmonary sarcoidosis.

Sarcoid.

Sarcoidosis is a multisystem inflammatory granulomatous disease which predominantly presents as pulmonary disease but can affect almost any organ. The presenting features in the lung are either pulmonary infiltrates or hilar and mediastinal lymphadenopathy, the chest radiograph however is highly insensitive and up to 60% of patients with granulomas in the parenchyma may have a normal chest radiograph. The differential diagnosis with the predominant hilar and mediastinal adenopathy is between lymphoma and sarcoidosis. The scales are tipped in favour of sarcoid by the ethnic origin of the patient. The predominant radionuclide is the assessment of sarcoidosis is Gallium-67

which shows a diffuse uptake in the lung in parenchymal sarcoid and intense uptake in the mediastinum and the hilum when these nodes are involved (fig.6,7).

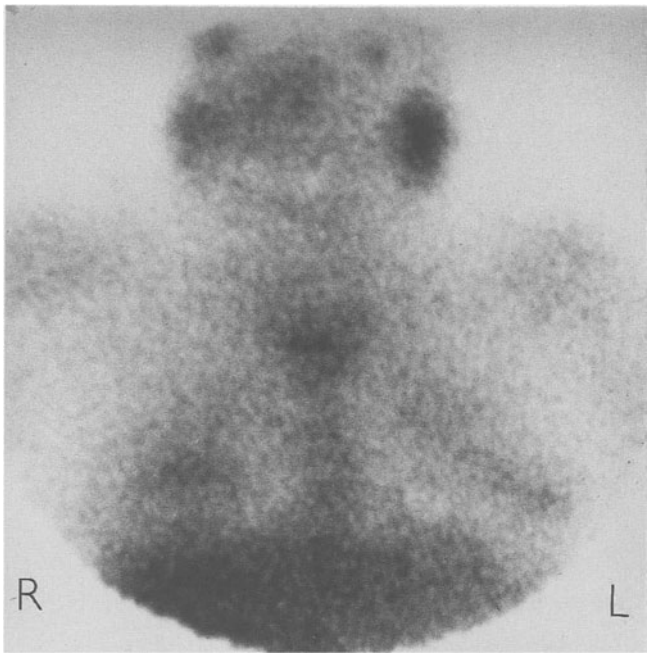

Figure 6. *An anterior thoracic gallium scan, the appearances show increased uptake in the parotid glands and low grade diffuse increased uptake in the lungs of a patient with predominant parenchymal sarcoid.*

The degree of lung uptake relates to disease activity [27]. The uptake has been described as the "lambda" distribution which has been found to be helpful particularly when associated with lachrymal, parotid and nasal uptake ("panda" pattern) in determining that the uptake is due to sarcoidosis [45,46]. Gallium-67 imaging is seen as a method of following the activity of disease in response to therapy [47,48]. Quantitation has been attempted using Gallium-67 to assess response of diffuse parenchymal uptake to therapy [49]. The other technique used to assess active sarcoid is the ^{99m}Tc DTPA transfer as a non-specific indicator of disease activity (see above).

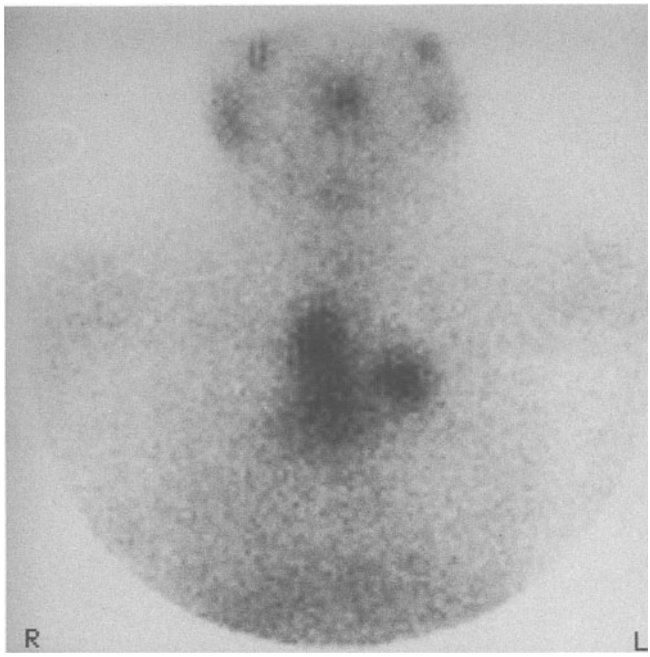

Figure 7. *An anterior thoracic gallium scan, the appearances show increased uptake in the hila and mediastinal lymph nodes in a patient with sarcoidosis*

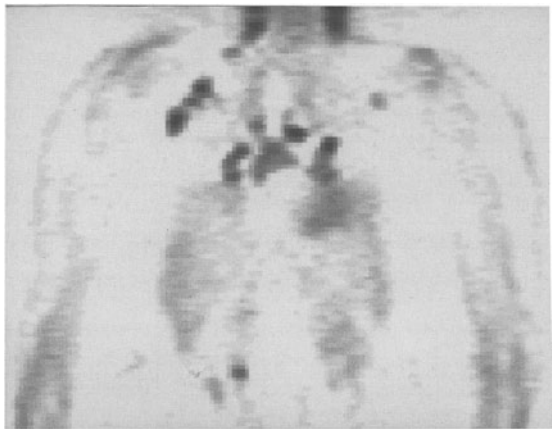

Figure 8. *A ^{18}F FDG PET study in a patient with pulmonary sarcoidosis. The coronal cut shows uptake in the mediastinum, hilae, axillary and supraclavicular lymph nodes.*

^{18}F-FDG uptake has been documented in sarcoidosis (fig.8) due to the non-specific nature of FDG uptake in inflammation [50]. This uptake was demonstrated in lymph nodes [50] and has been demonstrated in the lung parenchyma [51]. Brudin et al [52] measured the regional glucose metabolism per gram of lung tissue using PET and found that the abnormal levels returned to normal during treatment with steroids. This improvement was similar to the change in angiotensin converting enzyme levels and was thought to reflect "disease activity". In vitro, FDG has been shown to be taken up by leucocytes, lymphocytes and macrophages [53] and therefore it is a non-specific tracer.

Lung permeability is also increased in pulmonary sarcoidosis. The increase in ^{99m}Tc DTPA flux across the epithelial membrane of the lung has been observed in Type I, II and III pulmonary sarcoidosis [54,55,56]. The transfer increases with deterioration in pulmonary function as well as decreasing with response to treatment with steroids [54]. The transfer is thought to be related to the degree of inflammation associated with the sarcoidosis, but the rate of transfer has no definite relationship to the serum angiotensin converting enzyme levels or to the lymphocyte amounts in bronchoalveolar lavage fluid.

Other imaging in granulomatous diseases in addition to sarcoidosis has been demonstrated with ^{111}In octreotide [57]. The abnormal uptake occurred in lung parenchyma as well as lymph nodes. This was more sensitive than radiological imaging but no comparison was made with Gallium-67 which would have been of greater interest. The method does appear to document response to treatment, although in this study only five patients were followed, in two the scans became negative and three remained positive with apparent failure of response to therapy by other parameters. Other approaches to the imaging of sarcoidosis are being developed with the use of macrophage targeted glycolipeptide JOO1 [58], their usefulness remains to be seen.

Wegeners granulomatosis.

Patients with systemic vasculitis have been shown to have increased margination of leucocytes within the lung [59] and in the case of Wegeners granulomatosis have been shown to have focal nasal uptake [59] in addition to focal uptake within the lung parenchyma [60].

Two patients with Wegeners granulomatosis have had positive uptake with ^{111}In octreotide visualised in the lung [57].

Mycobacterial infections.

Mycobacterial infections have had a resurgence with the onset of HIV infection. The use of Gallium-67 imaging in mycobacterium tuberculosis identifies the sites of infection (Fig.9) and has been shown to have a diffuse uptake in miliary tuberculosis [61].

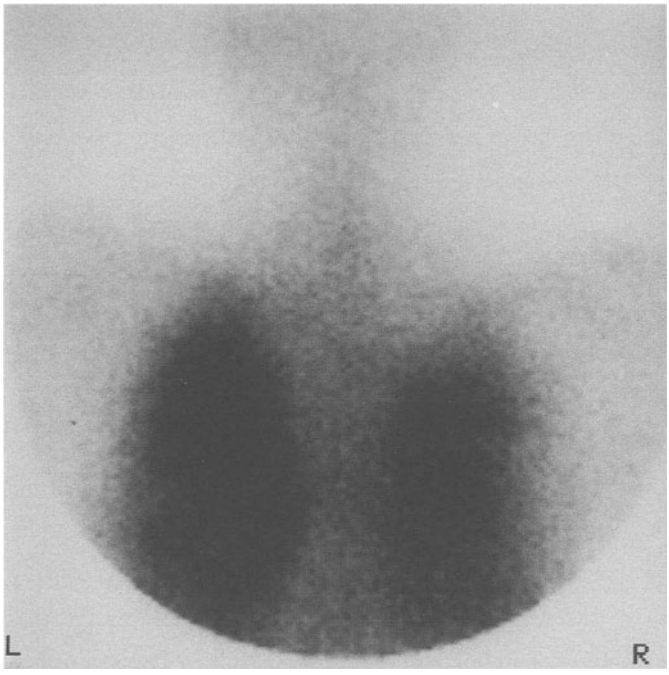

Figure 9. *The posterior thoracic gallium scan appearances in a patient with miliary mycobacterium tuberculosis. Diffuse uptake is demonstrated throughout both of the lungs*

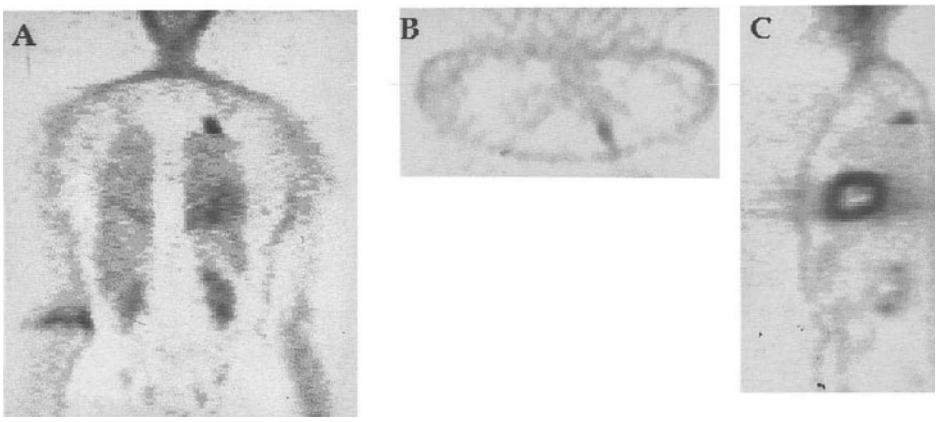

Figure 10. *A ^{18}F FDG scan in a patient with left upper lobe opacity and suspicious cells on needle aspiration. The lesion has a high uptake on FDG uptake seen on the coronal (A), transaxial (B) and the sagittal (C) cuts, despite the high uptake this was not a carcinoma but was shown to be mycobacterium tuberculosis.*

In the population of patients that tend to have tuberculosis, consideration has to be given to the fact that talc granulomatosis will also lead to a diffuse increased uptake [32]. Increased uptake of gallium in the chest may localise the atypical mycobacterial infections, which may also be found in lymph nodes as well as soft tissue (see below in the section on immunosuppression). Abnormal uptake may also be seen with ^{111}In octreotide imaging [57].

PET imaging has also been shown to be abnormal with tuberculosis and may lead to confusion in peripheral lesions within the lung (Fig.10). These lesions may have high standardised uptake values. Patz et al [62] reported high FDG uptake in tuberculosis and fungal infections in the lung. The identification of such abnormalities may direct the clinician to the correct area to biopsy. The advantage over gallium imaging is the capability of same day imaging with higher resolution and in the future the opportunity to register the PET image to the CT to allow precise anatomical definition of the abnormality.

Pneumoniaand Bronchiectasis.

The role of leucocyte imaging in the thorax is limited. It may be used to assess whether bronchiectatic areas are active or inactive [63]. The role in straight forward lobar pneumonia or other abnormalities seen on CXR is severely limited since lobar pneumonia often has a negative leucocyte scan, presumably because once the consolidation has developed there is little turnover of leucocytes in the abnormal area [64]. The potential is in a abnormal chest with chronic abnormalities on CT or CXR where a suspicion of disease activity is raised and needle aspiration or surgical drainage is required then the focus of infection may be localised using leucocytes.

Detection of Inflammation/Infection in the lung of immunosuppressed Patients.

The lung is the most commonly affected organ in the immunocompromised host and mortality is often high. Therefore a fever and a new lung symptom or sign presents an urgent clinical problem. There are a wide variety of possible causes of fever in the immunocompromised patient which tends to confound the choice of empirical therapy. The patients are often debilitated from the underlyeing disease and therefore invasive investigations are hazardous. The question is therefore does nuclear medicine have anything to offer in this patient population? There are differences which depend on he cause of the immunosuppressed state. For example if the patient is suppressed by chemotherapy compared with HIV disease then the underlying infection causing the pyrexia will be different and also is likely to have a different urgency with regards to investigation. Often the HIV patient with a fever and respiratory symptoms can be investigated in a little more slowly than the former group who may become unwell very quickly. The frequency of certain infections vary between the HIV positive patients and the iatrogenic group, transplanted patients have a higher incidence of cytomegalovirus (CMV) infection [65], whereas HIV positive patients have a higher incidence of PCP and bacterial infections such as streptococcus pneumoniae, pseudomonas aerogenosa and mycobacteria. Fungal infections may occur in either group.

In the patient who is neutropenic due to chemotherapy the investigation clinician is likely to want an instant test to demonstrate the type of abnormality and the

distribution of the abnormality to direct further investigation. The use of ^{99m}Tc DTPA clearance can demonstrate the location of the main ventilatory abnormality if there is a focal problem before the chest radiograph changes or the clearance/transfer times may indicate the presence of a pneumonitis. Thus in renal transplant patients PCP has a rapid transfer time for DTPA [66] but these changes would also occur with CMV infection which is common in transplant patients, therefore the test is used to direct investigation away from a possible cause of fluid overload or a bacterial pneumonia towards a definitive invasive test, transbronchial biopsy, or an urgent induced sputum examination. The alternative tests would be Gallium-67 scanning which has a variable uptake in CMV and therefore a variable sensitivity [67,68]. ^{111}In leucocyte scans have also been shown to be positive in CMV pneumonitis [69]. Although it may be stated that gallium has a lower uptake in CMV than PCP, the unfortunate truth is that this fact is unhelpful in the individual since the uptake of gallium in PCP is so variable. The most discriminatory role for gallium and ^{99m}Tc DTPA is in the patient with a normal chest radiograph. The DTPA scan in patients on chemotherapy is of less diagnostic value since agents such as bleomycin will also produce a pneumonitis and therefore although the cause of the breathlessness is identified as a pneumonitis the differential is far greater than in HIV positive patients.

With the increasing use of immunosuppressants in a variety of diseases the clinician has to be aware of the potential disease processes affecting the lungs and the effect of the various immunosuppressants on the lungs. Patients are more susceptible to a range of bacterial, fungal and viral illnesses. The use of leucocytes labelled with either ^{99m}Tc exametazime or ^{111}In oxine or tropolone can be effected using donor leucocytes (Fig.11) rather than autologous cells in patients who are HIV positive [70], or by using agents that can be labelled from manufacturers kits e.g. antigranulocyte antibodies, polyclonal antibodies or human immunoglobulin IgG. Usually leucocyte imaging is best applied to infections which are outside the chest [71] although disease may be localised coincidentally while looking elsewhere. The use of an antigranulocyte antibody to try and detect a variety of lung infections in HIV positive patients has proven to be unsuccessful, confirming the fact that this method should not be used for respiratory infections [72]. The technique may be unsuccessful for a number of reasons and may be

related to few neutrophils present or the fact that the patients own neutrophils were not functioning adequately. An alternative non-specific method of examining inflammation in the lung is to use aerosolised ^{99m}Tc DTPA as a reflection of lung permeability.

Often the clinician wants to know whether the source of the temperature is in the chest or elsewhere and then decide on a course of investigation as rapidly as possible or institute empirical therapy. The nuclear physician has to be aware of the differential diagnosis of various tests when they show abnormalities within the lung especially in this era of HIV diseases when the range of infections, tumours etc. affecting young men and women are increased.

Gallium has been the preferred agent to assess the thorax since it allows visualisation of the lung parenchyma, soft tissues, heart and lymph nodes. Scans can be performed as early as 4 hours and as late as 7 days after the injection of 150 - 400 MBq of Gallium-67. Late imaging may be useful in detecting mediastinal disease with tomography after injection of 400 MBq of Gallium-67. Unless a department has gallium in stock the imaging procedure may be delayed by several days, therefore to improve the efficiency in giving the clinician a diagnosis, protocols for early imaging and quantifying lung/liver count rate ratios at 4 hours following injection have been suggested [73]. These ratios were similar at 4,24, 48 en 72 hours in patients with PCP however it is likely this technique could be unreliable in those patients with disease of the liver where the uptake may be very low, for example in patients with hepatitis B or C disease, a common problem in this patient group (Fig.11).

The most common infection in patients with HIV infection is PCP although this is slowly changing. The classical appearance of a Gallium-67 scan in PCP is diffuse uptake in both lungs with a negative cardiac silhouette [74,75] but a variety of scan appearances can be seen [76,77]. Uptake in the lung can be graded between 0 (normal) and 4, by comparing the uptake in the lung to that in the liver and bone marrow, if this accumulation is less than (grade 2), equal to (grade 3) or higher (grade 4) than that

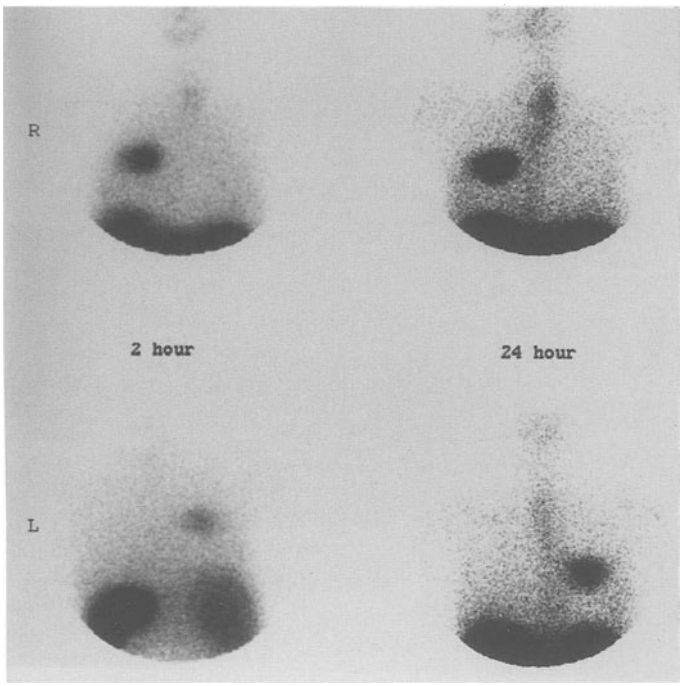

Figure 11. *A donor ^{111}In leucocyte scan in a HIV positive patient with a pseudomonas aerogenosa chest infection. The high accumulation of leucocytes is clearly seen on the 2 and 24 hour images*

in the liver and is diffuse, a confident diagnosis of diffuse lung disease can be made and the probability of this being due to PCP is high in HIV positive patients (Fig.12). If it is higher than normal but just less than the rib uptake (grade 1) this is equivocal uptake. However, in other immunosuppressed patients this will not be the case since cytomegalovirus infection or drug toxicity may be more prevalent. Low uptake in the context of an abnormal chest radiograph often carries a worse prognosis [74]. The sensivity and specificity of ^{67}Ga in PCP are 80 - 90% and 50 - 74% respectively [78], rising to 100% in those HIV positive patients with a normal chest X-ray [79]. An important point is that the negative predictive value for pulmonary pathology is high

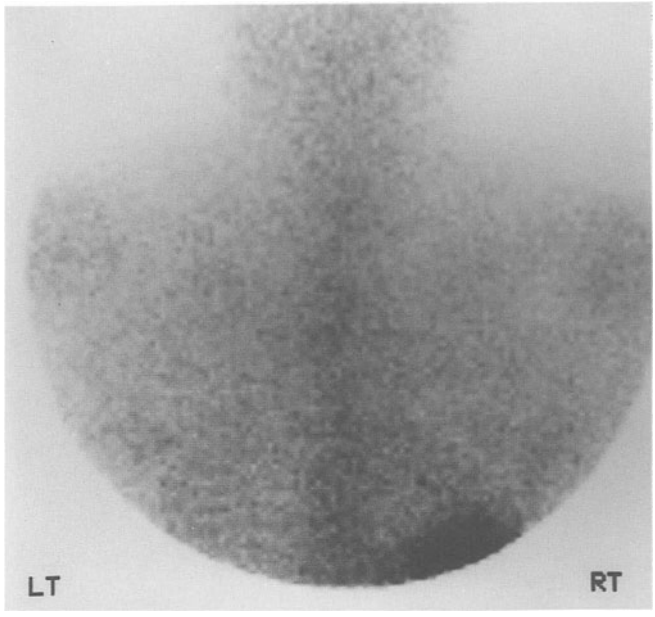

Figure 12 (a)

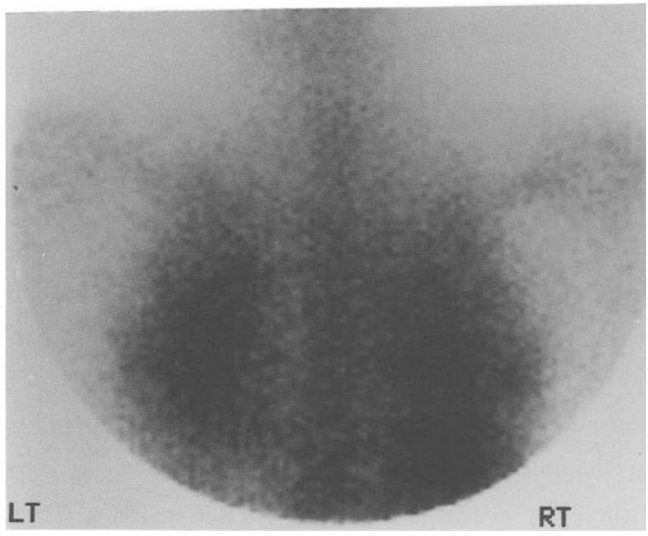

Figure 12 (b)

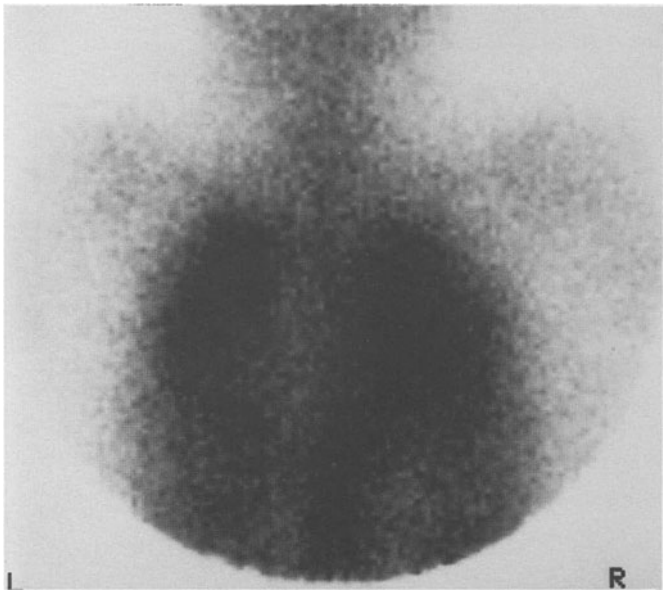

Figure 12.(c) *Various grades of uptake of gallium in patients with pneumocystis carinii pneumonia. Posterior scans are shown, the first A) has normal gallium distribution, the second B) has uptake which is slightly lower than liver uptake, the third C) has higher uptake in the lung than the liver.*

91%) [80] when both the CXR and the gallium scans are normal. The distribution of Gallium-67 within the chest in HIV positive patients may point to the pathology present. Bilateral upper lobe uptake can occur with PCP in patients treated with nebulised pentamidine [81], but this may also be seen in patients with mycobacterial infection. Similarly diffuse uptake may be seen with lymphocytic pneumonitis [82], non-specific pneumonitis [83] or miliary mycobacterial infection or probably cryptococcal infections.

Bacterial pneumonias tend to show focal accumulation in either a lobar or multilobar distribution with gallium imaging (Fig.13). If accumulation is focal in the lung and/or is associated with bone involvement, then atypical fungal infection or lymphoma should be considered in the differential diagnosis. Accumulation of gallium in regional lymph

nodes in HIV positive patients within the chest is consistent with lymphoma, mycobacterium avium intracellulare, persistent generalised lymphadenopathy, pneumocystis carinii infection or other infective processes.

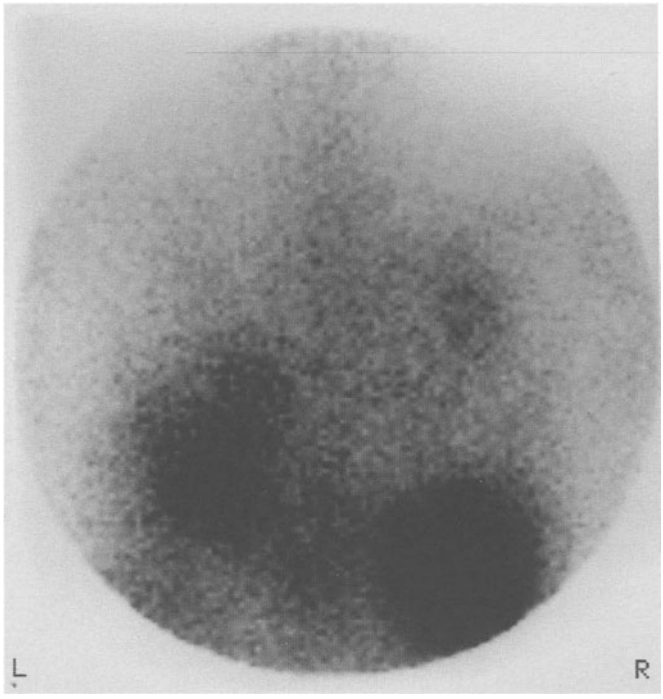

Figure 13. *A posterior gallium scan in a patient with a streptococcal pneumoniae infection. The scan shows the multiple foci of uptake of gallium in the left lower lobe and the right upper lobe*

The use of antibodies for the localisation of infection and inflammation has an advantage over leucocyte imaging because preparations are available in kit form and do not require handling of blood. This had a major advantage in HIV positive patients or those with neutropenia. The disadvantage of using Indium-111 as the radionuclide is that it is not produced on site and therefore has to be ordered especially for the labelling procedure. Animal and human studies have shown localisation of ^{111}In polyclonal antibodies (^{111}In HIgG) in lungs infected with PCP [84,85,86]. Imaging with ^{111}In and

^{99m}Tc HIgG has been studied [87,88]. It was found that HIgG had a superior sensitivity and specificity compared with ^{99m}Tc HIgG, which was thought to be due to the later imaging at 48 hours with ^{111}In HIgG. This allowed a greater clearance of HIgG from the blood pool. The pattern of uptake was diffuse with PCP and focal with bacterial infections. A recent study by Prvulovich et al [72] using antigranulocyte antibody imaging demonstrated the lack of localisation of infection within the chest, and poor localisation of infection elsewhere. This raises the question as to whether the neutropenic individual has sufficient labelling to localise or whether the neurophils are capable of functioning adequately in severe HIV disease. The technique may be suitable in immunosuppressed individuals from other causes.

Monoclonal antibody imaging, using a Fab' fragment raised in mice against pneumocystis carinii labelled with ^{99m}Tc, has been performed in HIV antibody positive patients and raises the possibility of a more specific test for PCP [89]. The 24 hour images provided the most reliable results. Only sixteen patients were studied with a presumptive or definite diagnosis of PCP, most had very abnormal chest radiographs. In this selected population the sensitivity and specificity were 85.7 and 86.7%. The technique raises the interesting possibility of its use in extrapulmonary disease detection but has not addressed the more relevant issues of whether uptake occurs in the lungs of patients with mild disease or normal chest radiographs. The study by Goldenberg et al [89] does indicate that therapy for PCP can be given without affecting the result since images were positive even when performed 28 days after the initiation of PCP treatment. This suggests that the test will be of little help in follow up studies.

Most of the above studies cannot be performed immediately on patients and therefore are unable to give a result on the same day. In patients with HIV infection who have a cough, breathlessness and a fever the question is normally: does the patient have PCP? Lung ^{99m}Tc DTPA transfer can give an answer to this question or at least indicate whether the patient has pulmonary pathology. The technique has been investigated in PCP and other lung infections by a number of groups [1,90-94], all have documented a rapid transfer or clearance time. Our own studies show that in an alveolitis the appearance of the curve is biphasic, with a rapid first component (half-time $<$ 4

minutes[12.5%/minute]) (Fig.14). The most likely cause of an alveolitis and hence the biphasic pattern (in HIV positive patients) is still PCP, but other causes of this pattern include CMV infection, lymphocytic interstitial pneumonitis and non-specific interstitial pneumonitis.

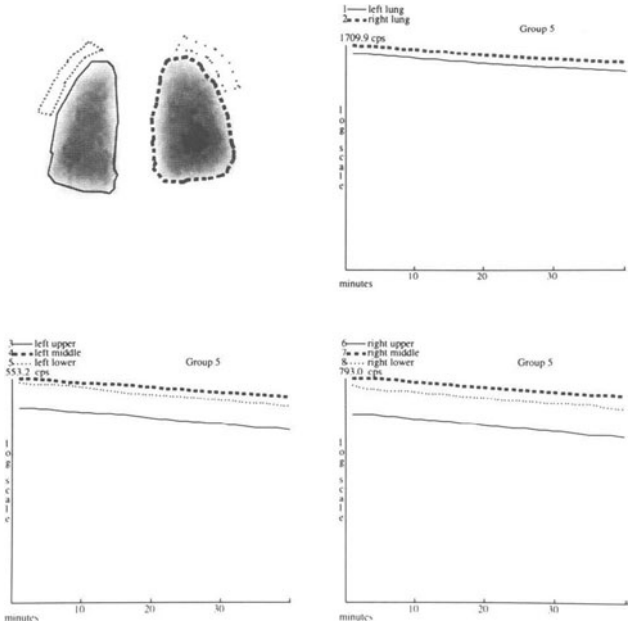

Figure 14 (a)

The test has a high sensitivity and specificity in this patient population for PCP, but false negative results may occur [92]. Occasionally a biphasic curve can be found in heavy smokers with HIV infection in the absence of an alveolitis and therefore it is suggested that baseline scans are performed in all smokers (authors experience). Transfer times are not biphasic in other bacterial infections (with the exception of Legionella pneumophila) [91]. Rosso et al [90] have demonstrated that the ^{99m}Tc DTPA technique has a higher sensitivity than gallium scanning (92%) compared with 72%) for infectious pulmonary complications [90]. This difference is more marked for patients with normal chest radiographs and normal blood gases. A normal chest radiograph and a normal DTPA clearance virtually exclude pulmonary infection/inflammation requiring therapy. A recent review of ^{99m}Tc DTPA transfer in HIV positive patients has outlined an

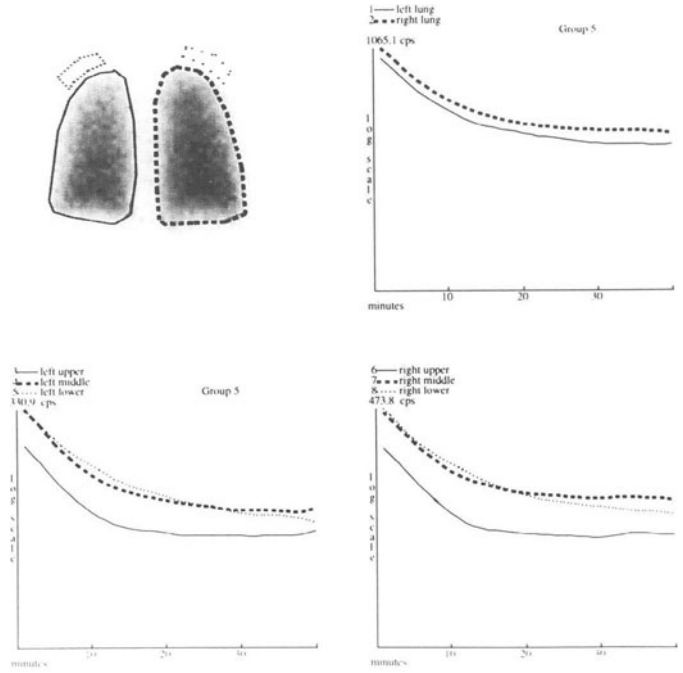

Figure 14 (a and b) *^{99m}Tc DTPA transfer study in an asymptomatic HIV positive patient and a patient with pneumocystis carinii pneumonia (PCP). The curves show A) a monoexponential pattern in the asymptomatic patient and B) a biphasic pattern when the patient developed PCP in all lung regions as well as the whole lung. The initial deposition of the aerosol is also shown.*

algorithm for its use in HIV infection [95]. This will cintinue to be of use only while PCP is the most common cause of an alveolitis in HIV positive patients.

A more recent development, Pertechnegas (which is generated from Technegas by the addition of oxygen) has been used to assess patients with HIV infection and respiratory

symptoms [96]. This imaging technique appears to convey little advantage over ^{99m}Tc DTPA.

FDG PET scanning has also been used in the evaluation of HIV positive patients [97]. It is apparent that although the scan is expensive there are a number of advantages. The ability to evaluate the whole patient from the brain to the toes is a valuable asset but in particular the scan can assess the mediastinal nodes for increased uptake to direct further investigation. The results of such a study are available the same day and it is possible that quantitative data will be able to discriminate inflammatory change from infection and malignancy.

This method of scanning saves patient visitis to the department, can hasten patient investigation as an inpatient and may therefore save costs. These latter statements are currently speculative and need to be explored further.

Heart-Lung transplants.

With heart lung transplantation the problems associated with inflammation are infection and rejection. Early reports suggested that conventional ventilation perfusion scans performed on a quantitative basis could detect early rejection [98]. An inhomogeneous perfusion scan develops with the onset of rejection and that there is gradual reduction in blood flow to the affected lung with time. Skeens et al [99] however found that the appearance of cytolytic lymphocytes in bronchoalveolar lavage fluid was more sensitive than the quantitative perfusion scan. A further method of investigating rejection has been the use of ^{99m}Tc DTPA clearance [100]. This is more rapid in patients with lung transplants ($2.62 \pm 0.25\%$/min) compared to nonsmoking controls ($1.2 \pm 0.12\%$/min) and during rejection this clearance is more rapid ($3.65 \pm 0.41\%$). The sensitivity and specificity of the measurement was 69 and 82% respectively whereas the use of FEV_1 had a sensitivity of 45% and specificity of 85%. These data suggest the technique may be a very simple method of monitoring this patient group, with biopsy if the clearance is increasing. Other pathology such as CMV and PCP would give similar changes to the clearance however.

Conclusion.

The thorax is an area of the body which is particularly suitable to assessment with nuclear imaging. The multifunctional roles of the lung in terms of gas exchange, drug metabolism present an area of interest for the delivery and absorption of drugs, the management of secretions and the maintenance of fluid balance across the vascular and epithelial surfaces. The increased use of cytotoxic drugs for cancer and for organ transplants increase the importance of noninvasive methods to localise sites of infection and inflammation. The areas of proven use are the investigation of mediastinal infection using ^{99m}Tc exametazime, mediastinal node inflammation with Gallium-67 and the assessment of parenchymal lung disease using Gallium-67 and ^{99m}Tc DTPA scanning. Both Gallium-67 and ^{99m}Tc DTPA can be used to monitor therapy and have been shown to predict improvement in the patients clinical condition e.g. sarcoidosis or response to PCP therapy in HIV positive patients. There is no clear role for imaging in endocarditis although it is possible that the use of antigranulocyte antibody imaging may have a selective role in assessing response to treatment in some patients. Myocardial imaging with antimyosin antibodies has a limited role in patients who are considered for endomyocardial biopsy since a negative scan in rejection and those suspected of having myocarditis makes the chance of obtaining a positive biopsy result very low.

The other areas of possible benefit in inflammation and infection are in the assessment of drug delivery to the lungs. This is achieved by direct labelling of drugs or indirect labelling of nebuliser solutions, thus assessing in semiquantitative terms delivery to areas of the lung. Other areas to be explored are the distribution of receptors within the lung e.g. β receptors and angiotensin converting enzyme and steroid sites using PET radionuclides. Further research on the capillary - alveolar interface may allow subgrouping of patients with ARDS into groups that require differing therapeutic strategies.

The number of days lost from work by adults due to respiratory and myocardial disease requires continued efforts to be made to evaluate investigative strategies within the thorax which will enable quick diagnosis and selection of the appropriate therapeutic intervention.

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