

Pulmonary nuclear medicine

R.F. Miller¹ and M.J. O'Doherty²

¹ Department of Medicine, University College and Middlesex School of Medicine, E1 Cross Piece, The Middlesex Hospital, London W1N 8AA, UK

² Departments of Medicine and Nuclear Medicine, St. Thomas Hospital, London SE1, UK

Abstract. This article reviews the contribution made by nuclear imaging to the assessment, diagnosis and monitoring of patients with respiratory disease. It focuses on several specific areas including the diagnosis of pulmonary embolism, the investigation of intrapulmonary infection and neoplasm and the role of positron emission tomography (PET) scanning.

Key words: Infection – Neoplasm – Acquired immunodeficiency syndrome (AIDS) – Positron emission tomography (PET) scanning – Pulmonary embolism – Mucociliary clearance – Lung permeability

Eur J Nucl Med (1992) 19:355–368

Introduction

Respiratory disease is an increasingly significant contributor to morbidity and mortality in the Western world. Lung cancer and chronic bronchitis continue to be major clinical problems. As the population lives longer, there are many older patients with pulmonary disease. These elderly patients are increasingly likely to undergo both emergency and elective surgery, with the attendant risks of pulmonary embolism and postoperative infection.

The acquired immunodeficiency syndrome (AIDS) pandemic continues unabated. This disease has already had a significant impact on the practice of medicine throughout Europe. Initially a disease of homosexual men, there are now increasing numbers of bisexual and heterosexual intravenous drug users presenting with human immunodeficiency virus (HIV) infection. By the end of 1993 it is likely that over half of the new cases of AIDS throughout Europe will be in the intravenous drug-using population. This disease has particular importance in the context of respiratory problems as over 60% of all HIV-positive patients will have a respiratory illness during their disease course. In this patient group

Table 1. Pulmonary nuclear medicine

Ventilation and perfusion scanning
Investigation of intrathoracic infection
Investigation of intrathoracic malignancy
Assessment of lung permeability
Assessment of mucociliary clearance
Positron emission tomography (PET) scanning

localising signs and symptoms may be absent, and the diagnosis of infection may be limited by the utility of conventional radiological imaging techniques such as computed tomography (CT) scanning, magnetic resonance imaging (MRI) or ultrasound examination.

Positron emission tomography (PET) scanning, which has already been shown to provide detailed information about the metabolic functions of the organ under study, is now being applied to the lung in both health and disease. PET appears to have a particularly useful role in the assessment of pulmonary neoplasia.

This article reviews the contribution made by nuclear medicine to the assessment, diagnosis and monitoring of respiratory disease. Table 1 outlines the main areas covered. The emphasis is on the application of nuclear medicine techniques to the practice of clinical respiratory medicine.

Ventilation and perfusion imaging

For most clinicians the main use of pulmonary nuclear medicine is for the diagnosis or exclusion of pulmonary embolism using both ventilation and perfusion imaging. Ventilation (V) and perfusion (P) images have, however, been used separately to assess a number of different aspects of lung function or pathology (Table 2).

Perfusion imaging

This is most frequently performed using either microspheres or macroaggregates labelled with technetium-

Table 2. Uses of perfusion and ventilation scanning*Perfusion scanning*

Assessment of arteriovenous malformations
 Assessment of surgical operability of lung cancer
 Differentiation of primary and secondary pulmonary hypertension

Ventilation scanning

Assessment of regional ventilation
 Assessment of small airways function

Ventilation/perfusion scanning

Monitoring of response to radiotherapy
 Assessment of resectability of bullae
 Diagnosis of suspected pulmonary embolism

^{99m}Tc. Krypton-81m and xenon-133 have also been used as research tools, the radiotracers being infused intravenously and carried to the pulmonary circulation prior to exhalation. Recently, PET compounds such as red blood cells labelled with C¹⁵O or H₂¹⁵O have been used to measure pulmonary perfusion.

Perfusion imaging has also been used to:

1. Quantitate the size of shunts associated with intrapulmonary arteriovenous malformations (Chilvers et al. 1988).
2. Assess the operability of bronchial carcinomas by predicting postoperative lung function (Konietzko 1987). In peripheral carcinomas of the lung, ventilation and perfusion are reasonably well matched and correspond to the extent of the lesion seen on the chest radiograph. In central tumours both perfusion and ventilation defects may be unexpectedly large with the occasional absence of function occurring on the infected side even though the lung is not collapsed (Ellis et al. 1983). In this situation, it is likely that mediastinal structures are involved with tumour spread.

The major indication for perfusion scanning in the assessment of bronchial carcinoma is in the prediction of postoperative function following pneumonectomy. Prospective studies comparing the estimates with forced expiratory volume in 1 s (FEV₁) and exercise performance (in terms of VO₂ max) may be predicted with considerable accuracy (Corris et al. 1987). The best correlation is obtained with perfusion scanning carried out in the upright position.

Postsurgical function =

$$\text{Preoperative function} \times \frac{\text{Perfusion to contralateral lung}}{\text{Total perfusion to both lungs}}$$

If the predicted postoperative FEV₁ ≥ 800 ml, the majority of surgeons will operate and perform a pneumonectomy.

3. Distinguish between primary pulmonary hypertension and secondary causes. Patients with primary pulmonary hypertension tend to have normal or low probability

ventilation perfusion scans, whilst those with secondary pulmonary hypertension tend to have multiple segmental perfusion defects caused by multiple pulmonary emboli; there is some overlap, however (Powe et al. 1987; Moser et al. 1988), and it is possible that pulmonary angiography will permit distinction (Gray et al. 1990a).

Ventilation imaging

Ventilation studies are performed with gases such as ¹³³Xe, ¹²⁷Xe, ^{81m}Kr or by using aerosols of ^{99m}Tc-labelled diethylene triamine penta-acetic acid (DTPA) or colloids. Although aerosols and particles are perfectly adequate for performing ventilation imaging and the images obtained with these techniques look similar to those performed with gases, aerosols and particles behave differently to gases and so cannot be used to assess regional ventilation.

In patients with chronic airflow limitation (CAFL) ^{99m}Tc-DTPA aerosols penetrate the peripheral lung poorly. ^{99m}Tc-DTPA particles of mass median aerodynamic diameter (MMAD) ≤ 1 μm will penetrate the periphery adequately in patients with normal lung function. Proximal impaction in the major bronchi occurs in patients with CAFL, with a reduced and uneven peripheral deposition. Because of these limitations arising from the use of conventional ^{99m}Tc-DTPA aerosols in patients with CAFL, newer, smaller particle aerosols have been developed.

1. Technegas. This consists of ^{99m}Tc-labelled carbon particles measuring 0.02–0.2 μm, approximately one-tenth the size of a conventional nebulised aerosol. Its use in ventilation imaging has been evaluated in several studies. Technegas ventilation images are comparable with ¹³³Xe images in normal subjects (Amis et al. 1990) and in patients with CAFL (Crawford et al. 1990). No central airways deposition of Technegas was seen in patients in either study, and a static distribution of radiotracer was seen for 20 min post inhalation, thus providing adequate time for single photon emission tomography (SPET) acquisition or multiple planar views. In a study of patients with suspected pulmonary embolism, the accuracy of Technegas ventilation scans was compared with ¹³³Xe images and also the accuracy of ventilation/perfusion scanning using Technegas and ^{99m}Tc-macroaggregates of albumin (MM) MAA was compared with pulmonary angiography. Technegas had a comparable accuracy to ¹³³Xe imaging. There was also an excellent correlation between ventilation perfusion images using Technegas and ^{99m}Tc-MAA and the results of pulmonary angiography (Rimkus and Ashburn 1990). Other studies report some reservations with the use of Technegas for ventilation imaging as deposition of particles has been demonstrated in the central airways (DeGeeber et al. 1989; Hilson et al. 1989).

2. Particulate aerosol. This is produced by a new type of aerosol delivery system called the APE (from the acro-

nym aerosol production equipment) nebuliser. By generating pressurised dry air and mixing this with ^{99m}Tc -DTPA suspended in alcohol and allowing the mixture to return to room pressure in a collecting bag, a dry particulate aerosol is created with a MMAD of 0.3 μm . Evaluation of the APE nebuliser to deliver particulate ^{99m}Tc -DTPA was carried out in both normal subjects and in patients with very mild airways disease (mean $\text{FEV}_1 = 80\%$ of predicted). Results showed that ventilation images with this technique were similar to those obtained with ^{133}Xe (Miller et al. 1991).

Other uses of ventilation imaging include:

1. Assessment of regional ventilation within the lung. Studies of regional ventilation provide a sensitive indication of early air flow obstruction. A delay in the washout of ^{133}Xe is more sensitive than abnormalities in the tidal breathing of ^{81m}Kr . Abnormalities of regional ventilation become more marked in those patients with severe CAFL and in this situation become associated with abnormalities of perfusion imaging. The overall clearance of ^{133}Xe from the lung measured as a function of exchange of air per second has been shown to correlate well with the FEV_1 (Secker-Walker et al. 1974).

2. Assessment of small airways function. By deriving the ratio of peripheral to central deposition of inhaled aerosols and comparing this ratio with the peripheral and central deposition of ^{133}Xe or ^{81m}Kr , an assessment of small airways disease (of bronchi or bronchioles) may be made (Agnew et al. 1981). Comparison of the penetration index (obtained by dividing the ratio of peripheral to central deposition of Technegas to the peripheral/central distribution of ^{133}Xe or ^{81m}Kr) with the predicted FEV_1 shows a linear relationship in patients with mild obstructive airways disease. Theoretically, it would be possible to estimate the FEV_1 in a patient from the penetration index obtained by ventilation studies with Technegas and ^{81m}Kr (Arnott et al. 1986).

Ventilation/perfusion scanning

The use of radionuclide imaging for the diagnosis of emboli has always been fraught with controversy (Gray 1990; Windebank 1990). The introduction of a classification by McNeil (McNeil et al. 1974) and Biello (Biello et al. 1979) has provided a basis for reporting and discussion. More recent publications have reopened the old wounds; the large Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study (PIOPED Investigators 1990) and a smaller study from Glasgow (Gray et al. 1990b) used modifications of the original Biello classification (Table 3). Both studies used ^{133}Xe as the ventilation agent and employed the presence or absence of chest radiograph abnormalities to place patients into differing categories.

Table 3. PIOPED criteria used to assess radionuclide scans for the probability of pulmonary embolism (PE) on angiograms

Likelihood of PE	Imaging results
Normal	Normal perfusion scan
Very low probability	One of three small ^a perfusion defects; normal chest radiograph
Low probability	Non-segmental perfusion defects ^b Single moderate ^c perfusion defect; chest radiograph normal Any perfusion defect substantially smaller than chest radiographic defect Ventilation-perfusion match $\leq 50\%$ of lung including $\leq 75\%$ of one lung zone ^d with normal or almost normal chest radiograph More than three small ^a perfusion defects; chest radiographic and ventilation scan irrelevant Three or fewer small perfusion/chest radiograph-matched defects; ventilation irrelevant
Indeterminate or intermediate	Any abnormality that is not defined clearly by other criteria
High probability	Two or more large ^e perfusion defects; ventilation and chest radiograph normal Two or more large ^e perfusion defects in which the perfusion defect is substantially larger than either matching ventilation scan or chest radiograph defect Two or more moderate ^c perfusion defects and one large ^e perfusion defect; ventilation scan and chest radiograph normal Four or more moderate ^c perfusion defects; ventilation scan and chest radiograph normal

^a 25% or less of an anatomic segment

^b Very small effusion, cardiomegaly, hila, etc.

^c $> 25\%$ and $< 75\%$ of a segment

^d Upper, middle or lower third of the lung

^e $> 75\%$ of a segment

PIOPED study

This multi-centre study attempted to evaluate the utility of ventilation/perfusion imaging in the diagnosis of acute pulmonary embolism. Patients referred for ventilation/perfusion scanning or pulmonary angiography within 24 h of a suspected pulmonary embolism were included. Of 5587 possible patients considered in the study period from January 1985 to September 1986, 933 patients were included. Posterior view ventilation scans were performed with ^{133}Xe . Left posterior oblique and right posterior oblique views were also obtained during the washout. Eight view perfusion studies were performed using ^{99m}Tc -MAA.

Ventilation/perfusion scans were interpreted according to predetermined criteria by two readers from out-

side the centre, and a third party adjudication was used for disagreements between observers. Pulmonary angiography was interpreted similarly. The intent of the study was to carry out pulmonary angiography in all patients following ventilation/perfusion scanning, but in fact this was carried out in only 755 patients. The follow-up was by telephone for up to 12 months after the investigation, and an outcome classification was obtained for 902 (97%) of the participants. The greatest agreement between scan readers was seen in the high probability, very low probability and normal categories ($\geq 92\%$). Lower agreement was obtained for patients with intermediate or indeterminate probability scans (75%) and low probability categories. Pulmonary angiography agreement was 92% for the presence of pulmonary embolism, 83% for the absence of pulmonary embolism and 89% for those in the uncertain category. The sensitivity of a high probability scan for the diagnosis of pulmonary embolism was 41%, with a specificity of 97%. Combining the high and intermediate probability scans, the sensitivity was increased to 82%, but this was associated with a fall in specificity for the diagnosis to 52%.

The important results from this study were:

1. Most patients with documented pulmonary emboli did not have high probability scans, 102 of 251 scans (sensitivity 41%).
2. A high probability study strongly correlated with a positive pulmonary angiogram result, 102 of 116 patients, positive predictive value = 88%.
3. A past history of pulmonary embolism reduced the positive predictive value of a high probability scan from 88 of 97 patients (91%) with no prior history to 14 of 19 patients (74%) with a prior history.
4. The likelihood of pulmonary embolism in cases of near normal or normal perfusion scans – is very low, 5 of 128 patients (4%).
5. An intermediate or indeterminate probability scan (the largest single category) was not diagnostic; it had a positive predictive value of 33% (104 of 345 patients). If combined with a high pretest clinical probability assessment, its diagnostic value was increased.
6. The presence of emboli in the low probability group was demonstrated in 39/238 of those who had undergone angiography (a further 74 patients did not have angiograms) and in 5/55 with near normal/normal scans (a further 76 patients in this group did not undergo angiography).

The main concern arising from the PIOPED study was the low degree of interobserver agreement in the intermediate/indeterminate and low probability groups (75% and 70%, respectively). Because of the dangers implicit in clinicians equating low probability with “no probability” of pulmonary embolism, some centres now advocate that scans should only be interpreted as being high probability, normal, or non-diagnostic (Moser 1990). On the other hand, of the 170 patients in the PIOPED study who had low probability, normal or near

normal scans, approximately 10% would have been predicted to have emboli. None of these patients received anticoagulant therapy, and none had clinical events. The question is then raised: in this group is there a need to anticoagulate and are the “emboli” detected on angiography clinically relevant? The conclusions that can be drawn from the studies are that the probability of a correct diagnosis is high for the high probability, normal and low probability scans. However, as in most studies 30%–40% of patients have indeterminate scans and since there are risks associated with anticoagulation, this group should be targeted for a further test, either angiography or impedance plethysmography (Hull et al. 1989). The size of the group may be reduced by treating those patients with a high pretest clinical suspicion of disease.

Other uses of ventilation/perfusion scanning include:

1. Assessment of response to radiotherapy for bronchial carcinoma. With a successful response to radiotherapy, a regional improvement in ventilation and perfusion may be seen in patients with an unresectable lung cancer.
2. Assessment of the resectability of bullae. Patients with large bullae and co-existing CAFL may derive functional benefit from plication or excision of the bullae. The prediction of the likelihood of benefit is difficult if ventilation/perfusion imaging shows that the bullae are ventilated but not perfused (i.e. dead space). This is an indication for surgery. In reality, bullae are rarely significantly ventilated or perfused. Nevertheless, ventilation/perfusion imaging is useful since it provides an estimate of the regional ventilation/perfusion relationships within the lung as a whole, and also if the lung around the bullae is well ventilated and perfused, then removal of the tense bullae may allow any compressed healthy tissue to regain its physiological function.
3. The assessment of foreign body inhalation in children, if the foreign body is radiolucent.

Diagnosis of intrathoracic infection

The localisation of infection presents a major challenge to the clinician. Early and accurate detection of infection permits earlier therapy with antibiotics (with potentially a better outcome). In immunosuppressed patients, for example those with HIV infection or those receiving steroids or immunosuppressive drugs, there may be few localising signs, if any, and fever may be absent despite the presence of focal infection.

Radionuclide imaging techniques play an important role in the detection of infection before the occurrence of the extensive damage which is detected by conventional radiography, CT, MRI and ultrasonography. Radionuclide scanning is particularly useful in localising the site of infection (a) when the disease location is unknown, as in those patients with pyrexia of undetermined origin (PUO), as whole body imaging may be undertaken without an additional radiation burden to

Table 4. Imaging techniques to localise intrathoracic infection

Gallium-67 citrate
Indium-111-oxine white blood cells (WBC)
Technetium-99m-hexamethyl propylene amine oxime (HMPAO) WBC
^{99m} Tc granulocyte-specific antibodies
¹¹¹ In human polyclonal immunoglobulin
^{99m} Tc human polyclonal immunoglobulin
¹¹¹ In chemotactic peptide analogues

the patient, or (b) when distorted anatomy is present, for example following previous thoracic surgery, pulmonary fibrosis or pleural thickening. Radionuclide imaging techniques that have been employed to identify and localise intrathoracic infection are shown in Table 4.

Gallium-67 citrate

Gallium was first noted to localise in inflammatory lesions over 20 years ago (Lavender et al. 1971). The major problem with ⁶⁷Ga imaging of the thorax is that at least 48–72 h are required between the injection and imaging, and despite its high sensitivity for identifying infection, its specificity is poor. Diffuse or focal intrathoracic accumulation of this tracer is seen in a variety of other conditions including sarcoidosis, amiodarone use and following cytotoxic therapy with bleomycin and probably any other cause of interstitial pneumonitis, i.e. in “rheumatoid lung”, an immunologically mediated process. ⁶⁷Ga appears to be taken up by activated lymphocytes (Specht et al. 1991), rather than neutrophils.

In HIV-positive patients with suspected *Pneumocystis carinii* pneumonia (PCP) diffuse intrapulmonary accumulation of ⁶⁷Ga has been shown to be a very sensitive method of confirming the diagnosis (Bitran et al. 1987). Unfortunately, a number of other infective causes (including bacterial pneumonia, mycobacterial infection and lymphoid interstitial pneumonitis) and non-infective conditions such as pulmonary talc granulomatosis, other granulomatous conditions and lymphoma may produce similar appearances (Kramer et al. 1989; Miller 1990). Focal accumulation within the thorax may also be seen with PCP, bacterial and mycobacterial infection, including lung abscess, as well as lymphoma (Lavender et al. 1971; Miller 1990). The use of “high” dose ⁶⁷Ga permits SPET acquisition and also allows a longer delay between injection and imaging in order for bowel activity to subside.

Indium-111 oxine white blood cells

Indium-111 oxine autologous white cells (WBC) were used to image 38 patients with chronic sputum expectoration. Some 24 patients had radiologically proven bron-

chiectasis, and 14 had mucus hypersecretion without bronchiectasis. Twenty-one of the 38 patients had a positive scan showing intrapulmonary accumulation of ¹¹¹In-oxine WBC. This accumulation was not seen in 5 patients who were producing small quantities (<20 ml) of mucoid sputum. ¹¹¹In-WBC scanning appeared to be useful in assessing the level of intrapulmonary inflammation in patients with bronchiectasis (Currie et al. 1990). ¹¹¹In-WBC imaging has also been shown to demonstrate focal accumulation in patients with lung abscess but can be negative in patients with acute pneumonia (Savery-muttu et al. 1985).

Imaging with ¹¹¹In-oxine WBC has been shown to be superior to ⁶⁷Ga in the detection of extrapulmonary infective foci in HIV-positive patients with PUO (Fine-man et al. 1989). However, within the thorax ⁶⁷Ga scanning appeared superior. ¹¹¹In-oxine-WBC scanning detected only 12 of 16 intrathoracic abnormalities detected by ⁶⁷Ga scans. Ten patients had diffuse intrapulmonary accumulation of ⁶⁷Ga; 9 of these patients had PCP. In only 5 was the ¹¹¹In-oxine-WBC scan positive. Of 6 other patients who had focal intrapulmonary uptake of ⁶⁷Ga (due to bacterial infection), only 3 were positive with ¹¹¹In-oxine-WBC scanning.

A major drawback of using labelled WBC techniques in HIV-positive patients is the perceived risk to the nuclear medicine department personnel carrying out the test. The risk of needle stick injury is present during venesection of the HIV-positive patient's blood, handling of the blood sample, carrying out leucocyte separation prior to labelling and during reinjection of the labelled white cells into the patient. As an alternative, donor leucocytes have been used successfully (O'Doherty et al. 1990a).

Technetium-99m hexamethyl propylene amine oxime WBC

The use of technetium-99m hexamethyl propylene amine oxime (HMPAO) WBC is well established for imaging intra-abdominal inflammation. A small study of 9 patients with clinical and radiographic evidence of acute chest infection or bronchiectasis were studied using both ¹¹¹In-oxine-WBC and ^{99m}Tc-HMPAO-WBC. There was complete concordance between the two techniques for imaging infection. False-negative results were seen in 3 patients, 1 with tuberculosis, 1 with bronchiectasis and 1 with acute bronchitis (Buscombe et al. 1991a).

Technetium-99m-labelled monoclonal antibodies to granulocytes

^{99m}Tc-labelled monoclonal antibodies (MoAb) to granulocytes (WBC) bind directly to leucocytes. There are few data on the use of this radiotracer to image intrathoracic infection, and there are no studies comparing its use with other radionuclides in this clinical situation. Murine

monoclonal antibody (MoAb BW 250/183), which reacts with an epitope of non-cross-reacting antigen 95 on the surface of neutrophil granulocytes (but which does not induce antibody- or complement-dependent lysis of cells), has been used to image possible sites of infection in a mixed group of surgical and medical patients. The technique correctly identified 20 cases of infection including sites of osteomyelitis, soft-tissue infections and internal sepsis. There were 2 false-positive results in the 11 patients without infection. In addition, of 2 patients with intrapulmonary foci, infection imaging with MoAb failed to detect an encapsulated lung abscess in 1 patient (Lind et al. 1990).

Indium-111-labelled polyclonal immunoglobulin

^{111}In -labelled polyclonal human immunoglobulin (HIG) localises in areas of infection and inflammation. In a study of 128 patients with suspected focal infection, localisation of ^{111}In -HIG correlated with the clinical findings in 51 patients with proven infection, and in 63 patients shown ultimately not to have infection, no accumulation of radiotracer occurred (Rubin et al. 1989). Of note, a diffuse intrapulmonary accumulation of ^{111}In -HIG was seen in 5 patients with PCP. *Candida* septic pulmonary emboli and *Mycoplasma pneumoniae* were also identified, shown by focal intrapulmonary accumulation of tracer. There was 1 false-negative as imaging failed to detect a pulmonary cryptococcoma. ^{111}In -HIG has been compared with ^{111}In -WBC to image 35 patients with subacute infections. Four patients had a pulmonary focus of infection due to *Mycobacterium tuberculosis*, in 2 patients both techniques were positive, in 1 both were negative and in another the labelled WBC scan was positive and the HIG scan negative (Oyen et al. 1991).

^{111}In -HIG has been compared with ^{67}Ga in steroid-immunosuppressed rats with PCP (Fischman et al. 1991). In rats with early PCP, ^{111}In -HIG scans showed diffuse intrapulmonary uptake, and ^{67}Ga scans were negative. In advanced PCP both scanning modalities were positive, but greater intrapulmonary accumulation occurred with ^{111}In -HIG compared with ^{67}Ga . In rats successfully treated for PCP, clinical recovery was mirrored by a reduction in the intensity of the pulmonary accumulation of ^{111}In -HIG on follow-up scanning. In some rats, bacterial or fungal superinfection occurred, and here ^{111}In -HIG scanning showed patchy, focal, intrapulmonary accumulation in addition to a diffuse uptake. ^{67}Ga images did not demonstrate these abnormalities.

In a small prospective study, 13 HIV-positive patients with respiratory symptoms were imaged with ^{111}In -HIG and the results correlated with bronchoscopic, radiographic and laboratory data. A diffuse accumulation of tracer was seen in PCP; focal accumulation was also seen in PCP and in bacterial pneumonia. No accumulation was seen in patients with pulmonary Kaposi's sarco-

ma (Miller et al. 1992). The major advantage of ^{111}In -HIG scanning compared with ^{67}Ga scanning is that it results in a lower radiation dose to the patient and the imaging protocol is faster (24–48 h with ^{111}In -HIG and 48–72 h with ^{67}Ga). In HIV-positive patients with suspected PCP, it may not be possible to defer decisions regarding treatment for 72 h pending the results of gallium scanning, and in this context ^{111}In -HIG scanning has a major advantage.

Technetium-99m-labelled polyclonal immunoglobulin

$^{99\text{m}}\text{Tc}$ -HIG has been compared with ^{67}Ga in 25 HIV-positive patients presenting with fever; 14 of these patients had 29 microbiologically confirmed sites of infection. ^{67}Ga identified 27 sites and $^{99\text{m}}\text{Tc}$ -HIG identified 16 sites. Of those identified by ^{67}Ga and not by $^{99\text{m}}\text{Tc}$ -HIG 7 were intrathoracic (Buscombe et al. 1996). An accumulation of ^{67}Ga not due to infection occurred in 8 sites (including 5 patients with lymphoma). $^{99\text{m}}\text{Tc}$ -HIG showed accumulation in only 1 of these patients with lymphoma. Outside of the chest, both agents had equal sensitivity for identifying infection, but a better specificity was seen with $^{99\text{m}}\text{Tc}$ -HIG. Within the thorax, the reduced sensitivity was attributed to the short physical half-life of the radiolabel, resulting in images of impaired quality if they were obtained more than 6 post injection. Images obtained at 4 h post injection were obscured by persistent cardiac and pulmonary blood pool effects.

Indium-111-labelled chemotactic peptide analogues

Leucocyte chemotactic peptides derived from bacteria have three potential advantages over monoclonal and polyclonal antibody nuclear medicine studies. Firstly, their smaller size facilitates better diffusibility to the extravascular space. Secondly, faster blood clearance results in a low background activity (an important consideration in imaging infection in the highly vascular lungs and mediastinum). Thirdly, well-defined receptor systems exist on known populations of tissue cells. Evidence from animal studies suggests that infection may be imaged within a few minutes of injection of this tracer (Fischman et al. 1991). Exciting possibilities exist for the future. Analogues of these peptides may be synthesised and by varying the size, charge and other properties of the molecule could theoretically produce the ideal radiotracer for imaging infection. Further work in humans is required.

Investigation of intrathoracic malignancy

The clinical evaluation of patients with unclassified intrathoracic masses or known lung malignancy (lymphoma or carcinoma) includes 4 clearly defined situations: firstly, the discrimination of infection from malignancy

Table 5. Imaging tracers to localise intrathoracic malignancy

⁶⁷ Ga-citrate
²⁰¹ Tl
^{99m} Tc-glucoheptonate
¹³¹ I-labelled antibodies to vasopressin-associated human neurophysin
¹¹¹ In-labelled carcinoembryonic antigen-specific monoclonal antibodies
¹²³ I-labelled somatostatin analogue

in patients with a solitary pulmonary nodule or focal consolidation seen on a chest radiograph or CT scan; secondly, the delineation of the extent of tumour involvement in patients with a known lung malignancy; thirdly, the assessment of the response to treatment; and fourthly, the early diagnosis of tumour recurrence in patients with previously treated lung cancer. Several radiotracers have been used in the assessment of intrathoracic malignancy; these are shown in Table 5.

Gallium-67 citrate

Lavender first demonstrated that this radiotracer accumulates in tumour tissue, as well as at sites of infection (Lavender et al. 1971). This lack of specificity limits its use in the assessment of the undiagnosed pulmonary nodule but does not reduce its utility in delineating the tumour's extent or the assessment of the response to therapy in patients with pathologically confirmed tumours.

Thallium-201 chloride

This radiotracer also accumulates in lung neoplasms (Tonami et al. 1976). Imaging with thallium-201 chloride was compared with ⁶⁷Ga in 38 patients with lymphoma of diffuse grades (26 had non-Hodgkin's lymphoma, and 12 had Hodgkin's disease). ²⁰¹Tl accumulation occurred more avidly in low-grade lymphomas compared with intermediate and high-grade ones. Also, in patients with low-grade lymphoma, ²⁰¹Tl accumulation was more clearly defined than that of ⁶⁷Ga (Waxman et al. 1991).

²⁰¹Tl with delayed SPET imaging at 3 h post injection was used to detect mediastinal lymph node metastases in 80 patients with lung cancer (all of whom proceeded to thoracotomy within 1 week of scintigraphic imaging). Some 51 patients did not have metastatic mediastinal lymph nodes at thoracotomy; 6 patients had received a false-positive result. Of 29 patients with mediastinal lymph node involvement, 22 were imaged by ²⁰¹Tl-SPET. All had multiple lymph node involvement, and the nodes were ≥ 14 mm in size; accumulation of ²⁰¹Tl was not seen in 7 (false-negative) patients with metastatic lymph node disease. These patients had single lymph

nodes <12 mm size involved with tumour (Tonami et al. 1991).

Technetium-99m glucoheptonate

^{99m}Tc-glucoheptonate (GH) accumulates in lesions and reflects the blood pool activity. In one study, 108 patients with focal chest radiographic abnormalities (85 with carcinoma and 23 with other pathology) were imaged with ^{99m}Tc-GH. Accumulation of tracer within the lesions was seen in 71 of the 85 patients with cancer but also in 16 of 23 patients with other diagnoses. Of note, in this latter group, 11 of 12 patients with *M. tuberculosis* showed focal uptake of the radiotracer. Thus, although the sensitivity of ^{99m}Tc-GH was 84%, the specificity for the diagnosis of lung cancer was only 30%. The intensity of uptake with this tracer did not vary significantly with the different histology results (Langford et al. 1986b).

Indium-111-labelled carcinoembryonic antigen-specific monoclonal antibodies

The clinical use of MoAb directed against tumour-associated antigens has developed rapidly over the past few years. Immunoscintigraphy with labelled MoAb exploits a quantitative difference between the tumour and adjacent normal tissues with respect to tumour-associated antigen.

Carcinoembryonic antigen (CEA), a tumour-associated glycoprotein first described in patients with colorectal cancer, has been shown also to be present in primary lung cancers. Immunoscintigraphy with ¹¹¹In-CEA-specific MoAb (type F023C5) F(ab')₂ fragments was carried out in 66 patients who had a high index of suspicion of primary lung cancer and also in 8 control patients with different chest diseases (including lung abscess, *M. tuberculosis* infection and pulmonary fibrosis; Biggi et al. 1991). Positive scans showing a focal accumulation of indium-labelled MoAb occurred in 60 of 66 cancers, including 32 of 35 patients with squamous cell carcinoma, all 6 patients with small cell carcinoma, 9 of 10 with adenocarcinoma, 4 of 6 with large cell and all 6 with undefined histology. Focal accumulation was also seen in the patients with other diagnoses including those with lung abscess, active tuberculosis and bacterial pneumonia but was not seen in those with fibrosis. False-negative results were noted in those with central tumours or with a tumour <2 cm in diameter. Overall, the scans had a sensitivity of 90%, a specificity of 45% and an accuracy of 85% for the diagnosis of cancer.

A second study using the same MoAb (FO23C5) F(ab')₂ was carried out in 41 patients with known or suspected primary lung cancer (Torres et al. 1991). Patients were divided into 3 groups. In group 1 were 10 patients with undiagnosed pulmonary masses (3 patients

eventually were found to have abscesses and 1 a neurofibroma; the other 6 had cancer). In group 2 were 22 patients with bronchoscopically confirmed lung cancer, and in group 3 were 9 patients undergoing follow-up after surgical resection of their lung cancer. Of the patients with malignancy, 23 had squamous carcinoma, 4 adenocarcinoma, 4 small cell carcinoma and 3 large cell carcinoma, MoAb scanning identified 5 of 6 cancers in group 1 but was also positive in 1 patient with an abscess. Fifteen of the 22 patients (68%) in group 2 who had known carcinoma were identified by MoAb imaging, and in group 3 5 of the 6 patients with intrathoracic recurrence following surgery were correctly identified.

Iodine-131-labelled antibodies to vasopressin-associated human neurophysin

Human neurophysins (HNP) appear to be produced and secreted by the tumours of approximately two-thirds of patients with small cell carcinoma. Vasopressin-associated HNP (VP-HNP) occurs as a tumour-associated product in approximately 44% of small cell carcinomas. In one study, highly specific rabbit polyclonal ^{131}I -labelled antibodies to VP-HNP were used in the immunoscintigraphy of neurophysin-secreting tumours (North et al. 1989). Six patients with suspected small cell carcinoma who had been previously screened and found to have evidence of raised serum levels of HNP were imaged with ^{131}I -VP-HNP. Five patients had active tumour, and one patient was in remission as judged by clinical, chest radiographic and CT criteria. All 5 patients with tumour had positive scans; in 1 of these patients, in addition to intrathoracic accumulation of radiotracer, confirmation of an adrenal metastasis previously detected by ultrasound was seen with this technique. The single patient in remission demonstrated no accumulation of radiotracer.

Iodine-123-labelled somatostatin analogue

Somatostatin receptors have been characterised on biopsies from patients with small cell carcinoma of the lung and also on small cell tumours grown in athymic nude mice. ^{123}I -Tyr-3-octreotide, a radiolabelled somatostatin analogue, was used to image 11 patients with lung cancer: 8 had small cell tumours, 2 had "Askin" tumours with small cells (these tumours are like small cell carcinomas and are thought to arise from neuroendocrine tissue), and 1 patient had a squamous cell carcinoma and a co-existent bronchial adenoma (Kwekkeboom et al. 1991). Of 8 patients with small cell carcinoma, the tumour was identified in 5 using ^{123}I -Tyr-3-octreotide, and in 2, unexpected metastases were also seen. Three patients with small cell carcinoma had negative scans; in 1 extensive tumour necrosis was found following radiotherapy. Accumulation was seen in only 1 of the 2 Askin

small cell tumours and not in the patient with squamous cell carcinoma and adenoma.

Although only a preliminary study with small numbers of patients, these data suggest that this is a promising technique for the identification of small cell carcinoma in the lung and even its metastases. By labelling Tyr-3-octreotide with a β -emitter, tumour sites may theoretically be targeted with tumour-specific radiotherapy.

Mucociliary clearance

The investigation of mucociliary clearance by the lungs may be achieved by the use of radiolabelled aerosols. Monodisperse, non-hydroscopic aerosols of MMAD $\geq 5 \mu\text{m}$ are used. This size of aerosol particle means that deposition occurs mainly in the ciliated tracheobronchial tree. Conventionally, $^{99\text{m}}\text{Tc}$ -labelled microspheres of albumin, polystyrene or Teflon particles are used. Following inhalation, the tracheobronchial clearance in normal subjects is largely complete within 4–6 h, but there is considerable intersubject variation. The measurements of clearance may be improved by "normalising" data using a penetration index derived from a $^{81\text{m}}\text{Kr}$ ventilation scan (Agnew et al. 1986).

Several disease processes reduce the rate of mucociliary clearance, including chronic bronchitis, asthma, cystic fibrosis and influenza (Camner 1980; Pavia 1984). Physiological factors such as sleep and increasing age also reduce the rate of clearance. Using inhaled radiolabelled aerosols, improved mucociliary clearance by drugs including β_2 -agonists such as salbutamol and theophyllines has been demonstrated (Pavia 1984); no effect on clearance was demonstrated by inhaling 15-(S)-hydroxyeicosatetraenoic acid, and therefore the reduction in clearance in asthma is thought not to be by this mechanism (Lai et al. 1991). The effects of deep coughing and physiotherapy may also be assessed (Rossman et al. 1982; Sutton 1984).

Other methods, which are more generally available, involve the inhalation of labelled colloids. These techniques have assessed the kinetics of mucociliary clearance over a 24-h time period with both quantitative (Merrina et al. 1991) and qualitative analysis using cine-scintigraphic analysis (Isawa et al. 1990).

Lung permeability

The alveolar-capillary interface provides a huge surface area susceptible to damage by microbiological, chemical or physical agents. Two main approaches are available to assess this interface:

1. The epithelial component (which represents the main barrier to the transfer of molecules) may be assessed by studying the flux of solute from the airspace into the blood.

2. The endothelial component which may be assessed by measuring the flux of solute from the blood into the interstitium, lymphatics and airspace.

It is possible to measure the integrity of the epithelial membrane by the administration into the airspaces of radiolabelled solutes; the rate of removal is measured either with scintillation probes or a gamma-camera. These data may then be expressed either as a half-time of clearance or as a rate constant (the gradient of the transfer/clearance curve). Disagreement continues over whether or not a background correction is necessary and the exact method of this correction (Coates and O'Brodovich 1986; Langford et al. 1986a; Oberdorster et al. 1986; Jones and McAteer 1990).

All these methods rely on the generation of an aerosol containing small particles (with MMAD of approximately 1 μm). This is used to deliver the molecule under consideration to the respiratory bronchiole/alveolar region. Increasing the size of the inhaled molecule, for example by using $^{113\text{m}}\text{In}$ transferrin instead of $^{99\text{m}}\text{Tc}$ -DTPA, slows the half-time of transfer (Huchon et al. 1987). Changing the charge on the molecule alters the transfer and permits the assessment of the degree of damage due to different lung pathologies (Barrowcliffe et al. 1990). Most of the studies that examined lung permeability have used $^{99\text{m}}\text{Tc}$ -DTPA, which has a monoexponential removal pattern from the airspace. This rate of clearance is faster in smokers than non-smokers, indicating an increased lung permeability (Minty et al. 1987).

Many factors affect the rate of removal. Removal may be increased by increasing the lung volume (Egan 1980; Marks et al. 1985; Woolman et al. 1987), exercise (Lorino et al. 1989), high oxygen concentration (Griffith et al. 1986) and positive end expiratory pressure (Nolop et al. 1987a; Barrowcliffe et al. 1989). This variability therefore leads to difficulties in applying the test in the study of certain clinical disorders. There are, however, a wide variety of conditions that result in fast transfer either affecting the whole lung or regional changes. The upper lobes normally have a faster transfer than the lower (O'Doherty et al. 1985), which has been illustrated using functional imaging (O'Doherty et al. 1986).

In a number of pathological conditions, this apical basal gradient is, however, affected such that in patients with systemic sclerosis (Chopra et al. 1979), haemophiliacs with HIV (O'Doherty et al. 1990) and patients with chronic lymphatic leukaemia (O'Doherty et al. 1986) the basal transfer is faster than the apical transfer. Various toxic substances including fumes inhaled by firemen (Minty et al. 1987), oral amiodarone (Terra-Filho et al. 1990) and cytotoxic agents (O'Doherty et al. 1986; Minty et al. 1987) cause a diffuse increase in transfer. There is, therefore, a possible role in the assessment of damage and response to treatment in drug-related disorders and the inhalation of toxic substances with this method.

While the transfer curve is normally monoexponen-

tial, even in a number of diffuse lung disorders, i.e. sarcoid (Dusser et al. 1986) and cardiogenic pulmonary oedema (Mason et al. 1985), in certain other clinical conditions it has been found to be multiexponential, i.e. adult respiratory distress syndrome (Barrowcliffe et al. 1989), infant respiratory distress syndrome (Jefferies et al. 1984), fibrosing alveolitis (Pantin et al. 1984), PCP and *Legionella pneumophila* infection (O'Doherty et al. 1989; Robinson et al. 1991; Van der Wall et al. 1991). This multiexponential appearance is assumed to represent multiple areas throughout the lung with varying degrees of damage. The measurement of $^{99\text{m}}\text{Tc}$ -DTPA transfer has proved to be useful in the assessment of breathless HIV-antibody-positive patients with suspected PCP (O'Doherty et al. 1987, Leach et al. 1991; Robinson et al. 1991; Van der Wall et al. 1991) and may be more sensitive than ^{67}Ga scanning for diagnosing this condition (Picard et al. 1987). It may also be of use in the evaluation of the breathless renal transplant patient (O'Doherty et al. 1991), although more work is necessary to evaluate this.

Although there are a large number of conditions which result in an abnormal transfer of $^{99\text{m}}\text{Tc}$ -DTPA, a well-defined clinical role (other than the assessment of the HIV-positive patient) has yet to be established. There is no doubt that the studies of permeability are advancing the understanding of the alveolar capillary interface in lung injury and will play a role in the monitoring of therapies used to treat alterations in the function of this interface.

The assessment of the endothelium has until recently been performed using scintillation probe systems and the monitoring of ^{113}In -transferrin efflux from the vascular compartment. Keegan et al. (1989) demonstrated that the measurement can be performed using a gamma-camera and that regional information is available with this method. This group also demonstrated that one of the problems with using single probes for this measurement is to make the repositioning of the probe over the lung field of interest and over the heart reproducible, which is necessary for the measurement. The method generally in use is adapted from that of Gorin (Gorin et al. 1978, 1980) and measures the accumulation of $^{113\text{m}}\text{In}$ -transferrin in a lung region and compares this with the $^{99\text{m}}\text{Tc}$ blood pool marker in the same region and over the heart (acting as the blood pool marker). The studies have mainly been confined to conditions associated with dramatic endothelial leak, i.e. adult respiratory distress syndrome (ARDS) (Basran et al. 1985; Braude et al. 1985), but more recently have included patients with less clear-cut endothelial problems including those on haemodialysis (Rocker et al. 1987) and those who have received radiotherapy to the lungs (Campbell et al. 1991). The problem with the method arises from the use of two differing radionuclides of widely discrepant energies with variable cross-talk and the possible varying attenuation in the highly abnormal lung studies (which with increasing oedema will undoubtedly be

changing). It is also possible that the accumulation of transferrin is a result of direct uptake into migrating neutrophils; these difficulties have yet to be resolved.

Despite these problems, the conventional use of the $^{113\text{m}}\text{In}$ -transferrin measurement in patients on the intensive care unit and its response to treatment (Basran et al. 1985) may provide a means to observe the early effect of various therapies. More recently, pulmonary vascular permeability has been assessed using ^{68}Ga -transferrin, showing that changes exist in patients with ARDS up to 2 weeks after onset and during recovery (Calandrino et al. 1988). The use of PET in this context is of interest and should allow the evaluation of possible regional changes occurring in other disease processes, with accurate corrections for the extravascular tissue and water accumulation of tracer.

Positron emission tomography

Application of PET to the study of pulmonary disease has recently been reviewed (Schuster 1989). The major advantage of PET studies is that the biological process under review is imaged using a true tracer, that is a molecule or compound that is itself biologically active. The most common radionuclides used for PET images are carbon-11, nitrogen-13, oxygen-15, fluorine-18, neon-19 and gallium-68. Carbon, oxygen and nitrogen are the constituents of most organic compounds and as such can be incorporated into the active product, and the other agents may be attached to compounds already in use in nuclear medicine, for example, ^{68}Ga attached to microspheres or to transferrin. Use of PET scanning permits the investigation of several physiological processes (Table 6).

Despite the lung appearing to be the ideal organ for PET imaging, the range and variety of pulmonary studies using PET are limited. The potential advantages of PET imaging which make it particularly attractive for the lung include:

1. Radioactive gases used to image ventilation are those of normal air, i.e. $^{15}\text{O}_2$, $^{11}\text{CO}_2$, ^{19}Ne , and the agents used to image perfusion are either water or labelled haemoglobin.

Table 6. Physiological processes that may be studied by PET

Pulmonary blood flow
Ventilation
Ventilation/perfusion relationships
Vascular permeability
Metabolic functions — Glucose metabolism
— Drug metabolism
— Drug and hormone receptor physiology
— Tumour imaging (receptor/blood flow)
Lung density
Extravascular lung water
Intrathoracic blood volume

2. Tissue concentration and localisation of tracers may be determined accurately and quantitatively.

3. Use of agents with short half-lives permits repeat studies to be performed with moderate radiation dosimetry to the patient.

Problems associated with PET scanning include logistical ones: coordinating the timing of the scan, the production of short-lived compounds and also keeping breathless patients immobile for sufficient periods to facilitate data acquisition. More serious problems arise from quantitation, in particular: repeat studies comparing "like" regions, the models used for obtaining quantitated results and the resolution of the equipment.

Positron-emitting compounds may simply be used to provide (a) an image to be interpreted, (b) semi-quantitative data, for example using pulmonary lesion to muscle ratios in tumours (Kubota et al. 1990), or (c) kinetic data, which often requires invasive blood sampling. It is the last aspect which is currently providing the most interest, but it is important to remember that the results are determined by the accuracy of the model employed.

PET has been applied to the study of a variety of lung diseases and also to normal physiology. In the normal lung, applications have included the measurement of lung density, lung water and blood volume (Rhodes et al. 1981; Schuster and Marklin 1986a) and also extravascular lung density in smokers and non-smokers (Burdin et al. 1987).

Acute lung injury

This has been studied by measuring the vascular permeability, extravascular lung water and regional blood flow (Wollmer et al. 1984; Schuster and Marklin 1986b; Calandrino et al. 1988). Kaplan et al. studied the pulmonary vascular permeability and extravascular density using PET and ^{67}Ga -transferrin. They found that although the extravascular density and pulmonary vascular permeability were increased in both ARDS and pneumonia, in congestive cardiac failure the pulmonary vascular permeability was normal, and so it could be used to discriminate this condition from non-cardiac pulmonary oedema (Kaplan et al. 1991).

Chronic lung disease

Chronic lung disease and its effects on blood volume (Wollmer et al. 1984) and ventilation/perfusion relationships (Burdin et al. 1987; Valind et al. 1987) have also been studied. There are problems with using these short half-life gases for quantifying the regional ventilation in abnormal lungs. A non-uniform distribution of gas flow will result in an underestimation of the regional ventilation.

Lung metabolism

Assessment of the lung as a metabolic organ in both health and disease has been studied using ^{18}F -deoxyglucose (FDG) (Nolop et al. 1987b) and ^{11}C -L-methionine (Kubota et al. 1988). The use of labelled drugs to investigate their binding in the lung is now possible. ^{18}F -captopril has been studied in rats (Hwang 1991). This may provide a way of probing the angiotensin converting enzyme activity in the human lung in various disease states.

PET scanning to image lung cancers

The role of CT scanning for the diagnosis of lung tumours in the thorax is well established, and as an imaging modality it permits mainly morphological assessment; the addition of contrast media enables a limited evaluation of the lesion's vascularity. ^{18}F -FDG has been shown to accumulate in malignant tumours (Som et al. 1980). A degree of contrast is observed because the FDG uptake in the lung parenchyma and mediastinal structures is fairly low compared with tumours. PET allows metabolic-dependent imaging, and a quantitative analysis of the tracer uptake can be used to classify the metabolic activity of a tumour. This information may be used in direct correlation with morphological information from CT scanning. Knop has shown (Knop et al. 1989) an intense uptake of FDG in a tumour 60 min post injection. This may permit the reliable differentiation of malignant from benign lesions. In a study comparing FDG PET and CT, PET correctly identified 53 of 54 malignant lesions and 10 of 11 benign lesions. In addition, it correctly discriminated between the malignant and benign conditions (Knop et al. 1989). Similar results were obtained by Kubota et al. (1990) who obtained a greater than 83% sensitivity for the diagnosis of malignant intrathoracic lesions.

Conclusions

Nuclear medicine potentially has a major role in the future for respiratory medicine.

1. The lung provides a large surface area directly exposed to the atmosphere and contains an ample blood supply; both may theoretically be utilized to deliver drugs directly to the systemic circulation.

2. Agents that accumulate specifically in tumour cells are being developed for both imaging and therapy (either tumour-specific local chemotherapy or radiotherapy).

3. The use of molecules with different sizes and charges will provide additional information about the alveolar-capillary interface and the effects of disease and therapy on this interface.

4. PET imaging used to study lung metabolism, pul-

monary blood flow, ventilation and epithelial permeability provides perhaps the most exciting challenge for nuclear medicine.

References

- Agnew JE, Pavia D, Clarke SW (1981) Airways penetration of inhaled radioaerosol: an index to small airways function? *Eur J Respir Dis* 62:239–255
- Agnew JE, Sutton PP, Pavia D, Clarke SW (1986) Radioaerosol assessment of mucociliary clearance: towards definition of a normal range. *Br J Radiol* 59:147–151
- Amis TC, Crawford ABH, Davison CA, Engel LA (1990) Distribution of inhaled $^{99\text{m}}\text{Tc}$ -labelled ultrafine carbon particle aerosol (Technegas) in human lungs. *Eur Respir J* 3:679–685
- Arnott RN, Burch WM, Orfanidou DG, Gwilliam ME, Aber VR, Hughes JMB (1986) Distributions of an ultra-fine $^{99\text{m}}\text{Tc}$ aerosol and ^{81}Kr gas in human lungs compared using a gamma camera. *Clin Phys Physiol Meas* 7:345–349
- Barrowcliffe MP, Jones JG (1989) Pulmonary clearance of $^{99\text{m}}\text{Tc}$ -DTPA in the diagnosis and evolution of increased permeability pulmonary oedema. *Anaesth Intensive Care* 17:422–432
- Barrowcliffe MP, Zanelli GD, Jones JG (1989) Pulmonary clearance of radiotracers after positive end expiratory pressure or acute lung injury. *J Appl Physiol* 66:288–294
- Barrowcliffe MP, Zanelli GD, Ellison D, Jones JG (1990) Clearance of charged and uncharged dextrans from normal and injured lungs. *J Appl Physiol* 68:341–347
- Basran GS, Byrne AJ, Hardy JG (1985) A noninvasive technique for monitoring lung vascular permeability in man. *Nucl Med Commun* 3:3–10
- Biello DR, Mattar A, McNight RC, Siegal BA (1979) Ventilation perfusion studies in suspected pulmonary embolism. *Am J Radiol* 133:1033–1037
- Biggi A, Buccheri G, Ferrigno D, et al. (1991) Detection of suspected primary lung cancer by scintigraphy with indium-111-anti-carcinoembryonic antigen monoclonal antibodies (type-FO23C5). *J Nucl Med* 32:2064–2068
- Bitran J, Beckerman C, Weinstein R, Bennett C, Ryo U, Pinsky S (1987) Patterns of gallium-67 scintigraphy in patients with acquired immunodeficiency syndrome and the AIDS related complex. *J Nucl Med* 28:1103–1106
- Braude S, Apperley J, Krausz T, Goldman JM, Royston D (1985) Adult respiratory distress syndrome after allogenic bone marrow transplantation: evidence for a neutrophil independent mechanism. *Lancet* I:1239–1242
- Brudin LH, Rhodes CG, Valind SO, Wollmer P, Hughes JMB (1987) Regional lung density and blood volume in non-smoking and smoking subjects measured by PET. *J Appl Physiol* 63:1324–1334
- Buscombe JR, Miller RF, Hounslow N, Compos-Costa D, Ell PJ (1991a) $^{99\text{m}}\text{Tc}$ -HMPAO and ^{111}In -oxine-labelled white blood cells (WBC) in the investigation of infective chest disease (abstract). *Nucl Med Commun* 12:318–319
- Buscombe JR, Miller RF, Lui D, Ell PJ (1991b) Combined ^{67}Ga citrate and $^{99\text{m}}\text{Tc}$ -human immunoglobulin imaging in human immunodeficiency virus-positive patients with fever of undetermined origin. *Nucl Med Commun* 12:583–592
- Calandrino FS, Haller JW, Anderson DJ, Schuster DP (1988) Pulmonary vascular permeability one week after the onset of the adult respiratory distress syndrome: a positron emission tomography study. *Am Rev Dis* 138:142–428

- Camner P (1980) Clearance of particles from the human tracheo-bronchial tree. *Clin Sci* 59:79–84
- Campbell JH, McCurrach GM, McBeth F, Bessent RG, McKillop JH, Banham SW (1991) Pulmonary vascular permeability to transferrin following thoracic irradiation in man – preliminary results in patients with lung cancer (abstract). *Nucl Med Commun* 12:307
- Chilvers ER, Peters AM, George P, Hughes JMB, Allison DJ (1988) Quantification of right to left shunt through pulmonary arteriovenous malformations using ^{99m}Tc albumin microspheres. *Radiology* 39:611–614
- Chopra SK, Taplin GV, Tashkin DP, Elam D (1979) Lung clearance of soluble radioaerosols of different molecular weights in systemic sclerosis. *Thorax* 34:63–67
- Coates G, O’Brodivich H (1986) Measurement of pulmonary epithelial permeability with ^{99m}Tc DTPA aerosol. *Semin Nucl Med* XVI (4):275–284
- Corris PA, Ellis DA, Hawkins T, Gibson GJ (1987) Use of radionuclide scanning in preoperative estimation of pulmonary function after pneumonectomy. *Thorax* 42:285–293
- Crawford ABH, Davison CA, Amis TC, Engel LA (1990) Intrapulmonary distribution of ^{99m}Tc -labelled ultrafine carbon aerosol (Technegas) in severe airflow obstruction. *Eur Respir J* 3:686–692
- Currie DC, Peters AM, Garbett ND, George P, Strickland B, Lavender JP, Cole PJ (1990) Indium-111 labelled granulocyte scanning to detect inflammation in the lungs of patients with chronic sputum expectoration. *Thorax* 45:541–544
- DeGeeber F, Bossuyt A, Jonckheer M (1989) Comparison of Technegas to ^{81m}Kr as ventilation agent (abstract). *Eur J Nucl Med* 15:442
- Dusser DJ, Collignon MA, Stanislas-Leguern G, Barritault LG, Chretien J, Huchon GJ (1986) Respiratory clearance of ^{99m}Tc -DTPA and pulmonary involvement in sarcoidosis. *Am Rev Respir Dis* 134:493–497
- Egan EA (1980) Response of alveolar epithelial solute permeability to changes in lung inflation. *J Appl Physiol* 49:1032–1036
- Ellis DA, Hawkins T, Gibson GJ, Norman S (1983) The place of lung scanning in the assessment of resectability of bronchial carcinoma. *Thorax* 38:261–268
- Fineman DS, Palestro CJ, Kim CK, et al. (1989) Detection of abnormalities in febrile AIDS patient with In-111-labelled leukocyte and Ga-67 scintigraphy. *Radiology* 170:677–680
- Fischman AJ, Pike MC, Kroon D, et al. (1991) Imaging focal sites of bacterial infection in rats with indium-111-labelled chemotactic peptide analogs. *J Nucl Med* 32:483–491
- Fishman JA, Strauss HW, Fischman AJ, et al. (1991) Imaging of *Pneumocystis carinii* pneumonia with ^{111}In -labelled non-specific polyclonal IgG: an experimental study in rats. *Nucl Med Commun* 12:175–187
- Gorin AB, Weidner WJ, Demling RH, Staub NC (1978) Non-invasive measurement of pulmonary transvascular protein flux in sheep. *J Appl Physiol* 45:225–233
- Gorin AB, Kohler J, DeNardo G (1980) Non-invasive measurement of pulmonary transvascular protein flux in normal man. *J Clin Invest* 66:869–877
- Gray H (1990) Ventilation perfusion imaging for pulmonary embolism: match or mismatch? *Nucl Med Commun* 11:154–157
- Gray H, Morgan JM, Kerr IH, Miller GAH (1990a) Clinical correlates of angiographically diagnosed idiopathic pulmonary hypertension. *Thorax* 45:442–446
- Gray H, McKillop JH, Bessent RG, Fogelman I, Smith ML, Moran F (1990b) Lung scanning for pulmonary embolism: clinical and pulmonary angiographic correlations. *Q J Med* 77:1135–1150
- Griffith DE, Holden WE, Morris JF, Min LK, Krishnamurthy GT (1986) Effects of common therapeutic concentrations of oxygen on lung clearance of ^{99m}Tc -DTPA and bronchoalveolar lavage albumin concentration. *Am Rev Respir Dis* 134:233–237
- Hilson AJW, Pavia D, Diamond PD, et al. (1989) An ultrafine ^{99m}Tc aerosol (Technegas) for lung ventilation scintigraphy: a comparison with Kr-81m (abstract). *J Nucl Med* 30:744
- Huchon GJ, Montgomery AB, Hoeffel JM, Murray JF (1987) Respiratory clearance of aerosolised radioactive solute of varying molecular weight. *J Nucl Med* 28:894–902
- Hull RD, Raskob GE, Coates G, et al. (1989) A new non-invasive management strategy for patients with suspected pulmonary embolism. *Arch Intern Med* 149:2549–2555
- Hwang L (1991) Position labelled angiotensin-converting enzyme (ACE) inhibitor: fluorine-18-fluorocaptopril. Probing the ACE activity in vivo by positron emission tomography. *J Nucl Med* 32:1730–1737
- Isawa T, Teshima T, Tomio H, et al. (1990) Mucociliary clearance and transport in bronchiectasis: global and regional assessment. *J Nucl Med* 31:543–548
- Jefferies AL, Coates G, O’Brodivich H (1984) Pulmonary epithelial permeability in hyaline-membrane disease. *N Engl J Med* 311:1075–1080
- Jones JG, McAteer EM (1990) The quantitative evaluation of acute lung injury. *Clin Phys Physiol Meas* 11 [Suppl A]:127–131
- Kaplan JD, Calandrino FS, Schuster DPJ (1991) A positron emission tomographic comparison of pulmonary vascular permeability during the adult respiratory distress syndrome and pneumonia. *Am Rev Respir Dis* 143:150–154
- Keegan J, Bailey J, Wilkinson P, Davies S, Rudd R (1989) Regional lung microvascular permeability using dual isotope scintigraphy. *Nucl Med Commun* 10:871–878
- Konietzko N (1987) Nuclear medicine techniques in the management of bronchogenic carcinoma. *Eur J Nucl Med* 13:S16–S19
- Kramer EL, Sanger JH, Garay SM, Grossman RJ, Tui S, Banner H (1989) Diagnostic implications of Ga-67 chest scan patterns in human immunodeficiency virus seropositive patients. *Radiology* 170:671–676
- Kubota K, Matsuzawa T, Fujiwara T, et al. (1988) Differential diagnosis of solitary pulmonary nodules with positron emission tomography using [^{14}C] L methionine. *J Comput Assist Tomogr* 12:794–796
- Kubota K, Matsuzawa T, Fujiwara T, et al. (1990) Differential diagnosis of lung tumour with positron emission tomography: a prospective study. *J Nucl Med* 31:1927–1933
- Kwekkeboom DJ, Krenning EP, Bakker WH, et al. (1991) Radioiodinated somatostatin analog scintigraphy in small cell lung cancer. *J Nucl Med* 32:1845–1848
- Lai CKW, Polosa R, Pavia D, Hasani A, Agnew JE, Clarke SW, Holgate ST (1991) Effect of inhaled 15-(s)-hydroxyeicosatetraenoic acid on tracheobronchial clearance in normal human airways. *Thorax* 46:446–448
- Langford JA, Lewis CA, Gellert AR, Tolfree SEJ, Rudd RM (1986a) Pulmonary epithelial permeability: vascular background effects on whole lung and regional half-time values. *Nucl Med Commun* 7:183–190
- Langford JA, Miller RF, Pearson MC, Rudd RM (1986b) Technetium-99-glucoheptonate lung imaging; has it a role in the diagnosis of bronchial carcinoma? *Nucl Med Commun* 7:907–914
- Lavender JP, Lhowe J, Bakere JR, et al. (1971) Gallium citrate

- scanning in neoplastic and inflammatory lesions. *Br J Radiol* 44:361–366
- Leach R, Davidson AC, O'Doherty MJ, Nayagam M, Tang A, Bateman NT (1991) Non-invasive management of fever and breathlessness in HIV positive patients. *Eur Respir J* 4:19–25
- Lind P, Langster W, Költringer P, Dimai HP, Passl R, Eber O (1990) Immunoscintigraphy of inflammatory processes with a technetium-99m-labelled monoclonal antigranulocyte antibody (Mab BW 250/183). *J Nucl Med* 31:417–423
- Lorino AM, Meignan M, Bonisson P, Atlan G (1989) Effects of sustained exercise on pulmonary clearance of aerosolised 99mTc-DTPA. *J Appl Physiol* 67:2055–2059
- Marks JD, Luce JM, Lazar NM, Ngao-Sun Wu J, Lipavsky A, Murray JF (1985) Effect of increases in lung volume on clearance of aerosolised solute from human lungs. *J Appl Physiol* 59:1242–1248
- Mason GR, Effros RM, Uszler JM, Mena I (1985) Small solute clearance from the lungs of patients with cardiogenic and non-cardiogenic pulmonary oedema. *Chest* 88:327–334
- Merrina MS, O'Riordan TG, Smalldone GC (1991) Changes in mucociliary clearance during acute exacerbations of asthma. *Am Rev Respir Dis* 143:993–997
- Miller RF (1990) Nuclear medicine and AIDS. *Eur J Nucl Med* 16:103–118
- Miller RF, Jarritt PH, Lui D, Kidery J, Semple SJG, Ell PJ (1991) The APE nebuliser – a new delivery system for the alveolar targeting of particulate technetium 99m diethylene triamine penta-acetic acid. *Eur J Nucl Med* 18:164–170
- Miller R, Buscombe J, Grant A, et al. (1992) Investigation of acute respiratory illness in HIV positive patients using indium-labelled polyclonal immunoglobulin scans. *Thorax* 47: (in press)
- Minty BD, Scudder CM, Grantham CJ, Jones JG, Bakhle YS (1987) Sequential changes in lung metabolism permeability and oedema after ANTU. *J Appl Physiol* 62:491–496
- Moser KM (1990) Venous thromboembolism. *Am Rev Respir Dis* 141:235–249
- Moser KM, Page GT, Ashburn WL, Fedullo PF (1988) Perfusion lung scans provide a guide to which patients with apparent primary pulmonary hypertension merit angiography. *West J Med* 148:167–170
- Nolop KB, Braude S, Ryston D, Maxwell DL, Hughes JMB (1987a) Positive end-expiratory pressure increases pulmonary clearance of inhaled 99mTc-DTPA in non-smokers but not in healthy smokers. *Bull Eur Physiolpathol Respir* 23:57–60
- Nolop KB, Rhodes CG, Burdin LH, et al. (1987b) Glucose utilisation in vivo by human pulmonary neoplasms. *Cancer* 60:2682–2689
- North WG, Hirsch V, Lisbona R, Schulz J, Cooper B (1989) Imaging of small cell carcinoma using ¹³¹I-labelled antibodies to vasopressin associated human neurophysin (VP-HNP). *Nucl Med Commun* 10:643–651
- Oberdorster G, Utell MJ, Morrow PE, Hyde RW, Werer DA (1986) Bronchial and alveolar absorption of inhaled 99mTc DTPA. *Am Rev Resp Dis* 134:944–950
- O'Doherty MJ, Page CJ, Croft DN, Bateman NT (1985) Regional lung 'leakiness' in smokers and non-smokers. *Nucl Med Commun* 6:353–357
- O'Doherty MJ, Pette JEW Van de, Page CJ, Bateman NT, Singh AK, Croft DN (1986) Pulmonary permeability in haematological malignancies: effects of the disease and cytotoxic agents. *Cancer* 58:1286–1288
- O'Doherty MJ, Page CJ, Bradbeer CS, et al. (1987) Alveolar permeability in HIV patients with *Pneumocystis carinii* pneumonia. *Genitourin Med* 63:268–270
- O'Doherty MJ, Page CJ, Bradbeer CS, et al. (1989) The place of lung 99mTc-DTPA aerosol transfer in the investigation of lung infections in HIV positive patients. *Resp Med* 83:395–401
- O'Doherty MJ, Revell P, Page CJ, Lee S, Mountford PJ, Nunan TO (1990a) Donor leucocyte imaging in patients with AIDS: a preliminary report. *Eur J Nucl Med* 17:327–333
- O'Doherty MJ, Page CJ, Harrington C, Nunan TO, Savidge GF (1990b) Haemophilia, AIDS and lung epithelial permeability. *Eur J Haematol* 44:252–256
- O'Doherty MJ, Breen D, Page CJ, Barton I, Nunan TO (1991) Lung 99m-Tc DTPA transfer in renal disease and pulmonary infection. *Nephrol Dial Transplant* 6:582–587
- Oyen WJG, Claessens RAMJ, Meer JWM Van der, Corstens FHM (1991) Detection of subacute infectious foci with indium-111-labelled autologous leukocytes and indium-111-labelled human non-specific immunoglobulin G: a prospective comparative study. *J Nucl Med* 32:1854–1860
- Pantin CFA, Britton A, Lawrence R, Sweatman M, Turner-Warwick M (1984) Lung permeability in patients with interstitial lung disease. *Thorax* 39:701
- Pavia D (1984) Lung mucociliary clearance. In: Clarke SW, Pavia D (eds) *Aerosols and the lung: clinical and experimental aspects*. Butterworths, London, pp 127–155
- Picard C, Meignan M, Rosso J, Cinotti L, Mayaud C, Re Vuz J (1987) Technetium 99mDTPA aerosol and gallium scanning in acquired immune deficiency syndrome. *Clin Nucl Med* 12:501–506
- PIOPED Investigators (1990) Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA* 263:2753–2759
- Powe JE, Palevsky HI, McCarthy KE, Alavi A (1987) Pulmonary arterial hypertension: value of perfusion scintigraphy. *Radiology* 164:727–730
- Rhodes CG, Wollmer P, Fazio F, Jones T (1981) Quantitative measurement of regional extravascular lung density using positron emission and transmission tomography. *J Comput Assist Tomogr* 5:783–791
- Rimkus DS, Ashburn WL (1990) Lung ventilation scanning with a new carbon particle radioaerosol (Technegas): preliminary patient studies. *Clin Nucl Med* 15:222–226
- Robinson DS, Cunningham DA, Dave S, Fleming J, Mitchell DM (1991) Diagnostic value of lung clearance of 99mTc-DTPA compared with other non-invasive investigations in *Pneumocystis carinii* pneumonia in AIDS. *Thorax* 46:722–726
- Rocker GM, Morgan AG, Pearson D, Basran GS, Shale DJ (1987) Pulmonary vascular permeability to transferrin in the pulmonary oedema of renal failure. *Thorax* 42:620–623
- Rossmann CM, Waldes R, Sampson D, Newhouse MT (1982) Effect of chest physiotherapy on the removal of mucus in patients with cystic fibrosis. *Am Rev Resp Dis* 126:131–135
- Rubin RH, Fischman AJ, Callahan RJ, et al. (1989) ¹¹¹In-labelled nonspecific immunoglobulin scanning in the detection of focal infection. *N Engl J Med* 321:935–940
- Saverymuttu SH, Phillips G, Peters AM, Lavender JP (1985) ¹¹¹In-dium autologous leucocyte scanning in lobar pneumonia and lung abscesses. *Thorax* 40:925–930
- Schuster DP (1989) Positron emission tomography theory and its application to the study of lung disease. *Am Rev Resp Dis* 139:818–840
- Schuster DP, Marklin GF (1986a) Effect of changes in inflation

- and blood volume on regional lung density – a PET study: 2. *J Comput Assist Tomogr* 10:730–735
- Schuster DP, Marklin GF (1986b) Regional changes in extravascular lung water detected by positron emission tomography. *J Appl Physiol* 60:1170–1178
- Secker-Walker RH, Alderson PO, Forrest JV (1974) Detection of obstructive pulmonary disease. *Radiology* 112:643–649
- Som P, Atkins HK, Bandopadhyay D, et al. (1980) Fluorinated glucose analog 2-fluoro-2-deoxy-D-glucose (F18): non-toxic tracer for rapid tumour detection. *J Nucl Med* 21:670–675
- Specht HD, Bakke AC, Brazeil R, Miley A, Rashidi-Nezami S, Germain L (1991) Cellular basis for the elevated gallium-67 computed lung index in a rheumatoid lung patient. *J Nucl Med* 32:2288–2290
- Sutton PP (1984) Chest physiotherapy and cough. In: Clarke SW, Pavia D (eds) *Aerosols and the lung: clinical and experimental aspects*. Butterworths, London, pp 156–169
- Terra-Filho M, Vargas FS, Meneguetti JC, et al. (1990) Pulmonary clearance of technetium 99m diethylene triamine pentaacetic acid aerosol in patients with amiodarone pneumonitis. *Eur J Nucl Med* 17:334–337
- Tonami N, Michigishi T, Bunko H, et al. (1976) Clinical tumour scanning with ^{201}Tl chloride. *Radioisotopes* 25:892
- Tonami N, Yokoyama K, Taki J, et al. (1991) ^{201}Tl SPECT in the detection of mediastinal lymph node metastases from lung cancer. *Nucl Med Commun* 12:779–799
- Torres M, Jimenez-Heffernan A, Valverde A, et al. (1991) Immuno-scintigraphy of lung cancer using ^{111}In -labelled anti CEA FO23C5-F (ab')₂ fragment. *Nucl Med Commun* 12:937–950
- Wall H Van der, Murray IPC, Jones PD, MacKay DWJ, Walker BM, Monaghan P (1991) Optimizing technetium 99m diethylene triamine penta-acetate lung clearance in patients with the acquired immunodeficiency syndrome. *Eur J Nucl Med* 18:235–240
- Waxman AD, Ramanna L, Etter D (1991) Characterisation of lymphoma grading using thallium (Tl) and gallium (Ga) scintigraphy. *J Nucl Med* 32 [Suppl]:917, A36
- Windebank WJ (1990) The case for pulmonary angiography being the initial investigation in the management of patients suspected of having pulmonary embolism. *Nucl Med Commun* 11:151–153
- Wollmer P, Rhodes CG, Hughes JMB (1984) Regional extravascular density and fractional blood volume of the lung in interstitial disease. *Thorax* 39:286–293
- Woolman PS, Jones DK, Barber RW, Higenbottam TW (1987) The rapid reversibility of effects of changing lung volume on the clearance rate of inhaled $^{99}\text{Tc}^m$ DTPA in man. *Nucl Med Commun* 8:881–887