

# Indium-111 labelled granulocyte scanning to detect inflammation in the lungs of patients with chronic sputum expectoration

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## Abstract

**Thirty eight patients with chronic sputum expectoration underwent indium-111 labelled granulocyte lung scanning and measurement of whole body loss of indium-111 labelled granulocytes. Twenty four patients had radiologically proved bronchiectasis and 14 had mucus hypersecretion without radiological evidence of bronchiectasis. None was having an acute exacerbation at the time of the scan. The median 24 hour volume of sputum expectorated was 17 (range 2-175) ml. The 24 hour volume of purulent sputum was 5 (0-142) ml; six patients expectorated mucoid sputum only. Twenty one of the 38 patients had a positive granulocyte lung scan. All nine patients expectorating more than 20 ml purulent sputum in 24 hours had positive lung scans and all had lost more than 19% of the indium-111 from the body after five to seven days. Of the six patients with mucoid sputum, only one had a positive scan and these subjects lost only 6-11% of the indium-111 in five to seven days. The percentage loss of indium-111 from the body correlated with 24 hour purulent sputum volume ( $r = 0.41$ ,  $n = 38$ ,  $p < 0.001$ ) and total elastolytic activity in 24 hour sputum ( $r = 0.54$ ,  $n = 14$ ,  $p < 0.01$ ). The loss of indium-111 was not related to the extent of bronchiectasis when purulent sputum volume was allowed for. Indium-111 labelled granulocyte scanning provides a sensitive and objective method for detecting inflammation in the lungs and should help to improve understanding of chronic bronchial sepsis and possibly treatment in selected cases.**

No established method exists for the direct quantification of inflammation in the lungs of patients with chronic bronchial sepsis. Indirect methods depend on the analysis of expectorated sputum samples or blood samples. Inflammation may be assessed in sputum on the basis of its macroscopic appearance (purulent, mucopurulent, mucoid), the number of neutrophils, the level of elastolytic activity, and the ratio of sputum to serum albumin concentrations.<sup>1</sup> A variable proportion of sputum is swallowed<sup>2</sup> and sputum is heterogeneous. Blood is easier to handle for monitoring inflammation but the tests, such

as erythrocyte sedimentation rate, white cell count, and concentration of immunoglobulins and acute phase proteins, are insensitive and non-specific.

We have shown that indium-111 labelled autologous granulocyte scanning will detect inflammation directly in the lungs of patients with bronchiectasis and suggested that it should prove useful in the objective assessment of inflammation in such patients.<sup>3</sup> In the present study we have compared the results of indium-111 labelled granulocyte scanning and measurement of granulocyte loss with indirect methods for assessing lung inflammation in a group of patients with purulent and non-purulent sputum of varying volume.

## Methods

### PATIENTS

Thirty eight patients (28 female; median age 42 (range 22-70) years) with chronic sputum expectoration (fig 1) received indium-111 labelled autologous granulocytes. Twenty four patients had bronchiectasis, which was diagnosed by bronchography in 19, by pathological examination of a pneumonectomy specimen and computed tomography of the remaining lung in one, by plain chest radiography in three, and by computed tomography alone in one. Of the other 14 patients, one had severe emphysema due to  $\alpha_1$  antitrypsin deficiency and two had asthma. All patients had expectorated sputum daily for a median of 18 (0.25-67) years. Thirty two had purulent sputum. Seven had undergone lung resection for bronchiectasis. The median forced expiratory volume in one second (FEV<sub>1</sub>) was 70% (33-117%) predicted.<sup>4</sup> Chest symptoms followed severe whooping cough in five patients and pneumonia in six. Three patients had allergic bronchopulmonary aspergillosis, two had concomitant inflammatory bowel disease, one had bilateral lymphoedema of the lower legs, and one obstructive azoospermia and sinusitis (Young's syndrome)<sup>5</sup>; one woman reported infertility. None of the patients had cystic fibrosis or primary ciliary dyskinesia.

Cigarette smoking may have been an important causative factor for chronic sputum production in seven patients (15-60 pack years): three (two with bronchiectasis) were current smokers and four (one with bronchiectasis) ex-smokers. Twenty four patients also had chronic rhinosinusitis.

No patient had peripheral blood eosino-

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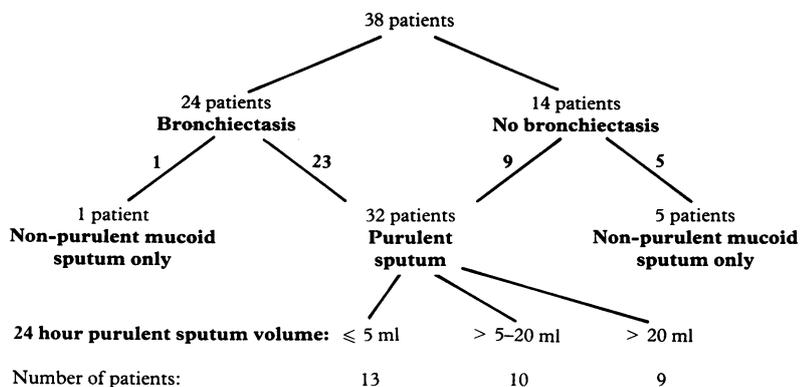


Figure 1 Distribution of patients by disease and character of sputum.

philia or basophilia. No patient had an acute exacerbation of symptoms at the time of  $^{111}\text{In}$  scanning or computed tomography. The studies were approved by the ethical committee of both the Brompton and the Hammer-smith Hospital and each patient gave informed consent.

#### INVESTIGATIONS

Sputum was collected from all patients at the time of scanning to determine the volume expectorated in 24 hours. A four hour sputum collection was also made to determine the proportion of sputum that was purulent and the colour and the degree of colour (graded +, ++, or +++ ) of the purulent portion. The 24 hour purulent sputum volume was estimated by multiplying the 24 hour sputum volume by the proportion of the four hour sample that was purulent. In 14 patients with bronchiectasis and purulent sputum, sputum "sol" elastolytic activity was measured at the time of the scan by the fluorescein-elastin method.<sup>6</sup> The elastolytic activity in the sputum sol was multiplied by the 24 hour sputum volume to derive an estimate of the total elastolytic activity. The concentrations of serum immunoglobulins (Ig), white cell count, and erythrocyte sedimentation rate were also determined.

Computed tomography of the chest was performed in all but two patients (both with bronchiectasis) on an Elscint 2002 scanner with the patient lying supine in suspended full inspiration for each film. A series of films were taken of contiguous 10 mm width slices from lung apex to base with selected 3 mm width slices in areas of abnormality.<sup>7</sup> All films were taken at a wide window setting with a scanning time of 5.5 seconds. Bronchiectasis was defined as the presence of bronchi of greater diameter than the accompanying pulmonary arteries as judged by a pulmonary radiologist.

#### GRANULOCYTE SCANNING

A population of pure granulocytes was isolated from the blood of each patient and labelled with  $^{111}\text{In}$  tropolonate without being separated at any stage from plasma.<sup>3,8</sup> The injected dose of radioactivity was 250–300  $\mu\text{C}$  (9–11 MBq). Large field of view gamma

camera imaging (IGE 400A or 400T, interfaced to an MDSA2 computer) was performed two to five hours after injection and again after 20–24 hours and five to seven days. Anterior, posterior, and often lateral oblique views of the chest and views of the abdomen were obtained on each occasion. The lung uptake of  $^{111}\text{In}$  and the lobar distribution were recorded from the 20–24 hour images. The lung uptake of  $^{111}\text{In}$  was assessed visually by two nuclear medicine physicians and graded as negative or mildly, moderately, or strongly positive. The amount of  $^{111}\text{In}$  in the whole body was measured with an uncollimated gamma camera two to five hours after the injection and after five to seven days. The percentage  $^{111}\text{In}$  retention after five to seven days was calculated for each patient after correction for isotope decay. The whole body loss of granulocytes was defined as 100 minus the percentage whole body  $^{111}\text{In}$  retention at this time. The whole body loss from eight control subjects with no evidence of respiratory disease was on average 5% at five to seven days<sup>3</sup> and did not exceed 11%. In patients with a positive  $^{111}\text{In}$  granulocyte lung scan and no evidence of inflammatory bowel disease the additional loss of  $^{111}\text{In}$  (by comparison with control values) is assumed to be from sputum. The computed tomography and other clinical results were not available at the time the  $^{111}\text{In}$  scan was reported.

#### ANALYSIS

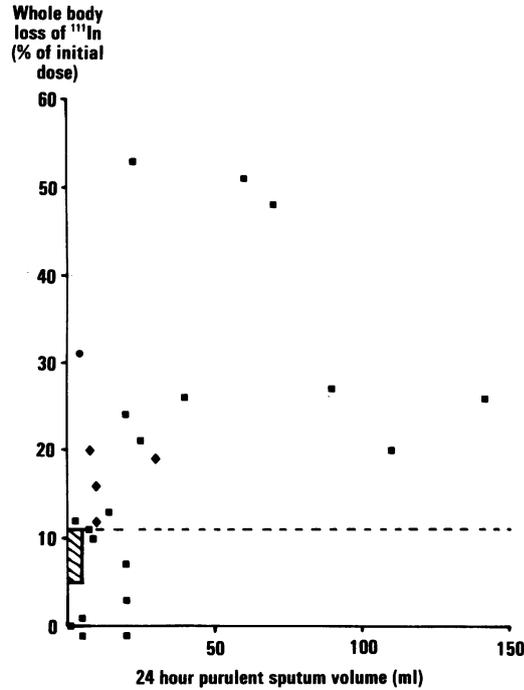
The whole body loss of granulocytes was correlated with other markers of inflammation and the extent of bronchiectasis by means of the non-parametric Kendall's rank correlation.<sup>9</sup> Multiple regression analysis was performed with the SPSSX statistics package (Statistical Packages for the Social Sciences, Chicago) to determine the correlation of the 24 hour purulent sputum volume and the number of lobes containing bronchiectasis with the loss of indium labelled granulocytes.

#### Results

##### SPUTUM AND HAEMATOLOGICAL MARKERS OF INFLAMMATION

The median 24 hour sputum volume was 17 (range 2–175) ml and the 24 hour purulent sputum volume was 5 (0–142) ml; six of the 38 subjects produced mucoid sputum only. The colour of the purulent portion was green in all cases with an average grade ++ (range + to +++). The total elastolytic activity in 14 patients with purulent sputum and bronchiectasis ranged from 2 to 513  $\mu\text{g}$ . Serum IgA was raised in 10 of the 14 patients (range 1.2–9.6 (normal 0.7–3.2) g/l) and IgG was raised in four (range 8.9–33.1 (normal 6.4–16) g/l); none had a raised IgM concentration. The erythrocyte sedimentation rate was raised in nine of the 14 cases with a range of 3–51 mm in the first hour. The leucocyte count was raised in only one patient.

Figure 2 Relation of whole body loss of indium-111 to 24 hour purulent sputum volume in the 38 patients ( $r = 0.41$ ,  $p < 0.01$ ).  $\blacklozenge$   $^{111}\text{In}$  scan still positive at 5–7 days;  $\bullet$  negative  $^{111}\text{In}$  scan (inflammatory bowel disease accounts for whole body loss of  $^{111}\text{In}$ );  $\blacksquare$   $\square$  all other chronic sputum producers. The cross hatched square represents the 14 patients who expectorated 0–5 ml of purulent sputum and whose whole body loss was 5–11%. - - - upper limit for  $^{111}\text{In}$  loss in control subjects.



GRANULOCYTE LUNG SCANS

Twenty one of the 38 patients had a positive lung granulocyte scan at 21–24 hours. All nine patients who expectorated more than 20 ml purulent sputum in 24 hours had a positive granulocyte scan at 21–24 hours (grade +++: 2, ++: 6, +: 1); all had lost over 19% of the indium-111 from the body after five to seven days. Five of the 19 patients with a purulent sputum volume of less than 5 ml had a positive scan. The six patients producing mucoid sputum had lost 6–11% of the  $^{111}\text{In}$  by five to seven days; only one of these patients had a positive scan (grade +).

The percentage loss of indium-111 from the body correlated with the 24 hour volume of purulent sputum ( $r = 0.41$ ,  $n = 38$ ,  $p < 0.001$ ; fig 2). The granulocyte scan grade also correlated with 24 hour purulent sputum volume (table 1). Four patients still had a positive granulocyte scan after five to seven days and they had lost less indium (12–20%) than the patients whose scans were positive to a similar extent at 21–24 hours (++ or +++ grade,  $^{111}\text{In}$  loss 21–53%) but had become negative. Of the 17 patients with a negative granulocyte scan, two lost more  $^{111}\text{In}$  than the six subjects producing non-purulent sputum; one of these two patients lost 31% of the  $^{111}\text{In}$

Table 1 Association between the grade of the indium-111 labelled granulocyte scan and the volume of purulent sputum expectorated in 24 hours by the 38 patients

24 h purulent sputum volume (ml)	No of patients* with $^{111}\text{In}$ labelled granulocyte scan of grade:		
	0	+	++ or +++
≤ 5	14 (4)	5 (4)	0
> 5–20	3 (1)	4 (4)	3 (3)
> 20	0	1 (1)	8 (7)

\*Numbers of patients with bronchiectasis in parentheses.

Table 2 Association between indium-111 labelled granulocyte scans and the presence of bronchiectasis on computed tomograms in 211 lobes of 36 patients

Bronchiectasis on computed tomogram	$^{111}\text{In}$ labelled granulocyte scan	
	Positive	Negative
Present	45	40
Absent	7	119

from the body as a result of early bowel activity due to inflammatory bowel disease; the other patient lost 12% of the  $^{111}\text{In}$ . These two were also the only patients from the 19 with a low 24 hour purulent sputum volume (up to 5 ml) to lose more  $^{111}\text{In}$  than the non-purulent sputum producers.

Whole body loss of  $^{111}\text{In}$  correlated with total elastolytic activity ( $r = 0.54$ ,  $n = 14$ ,  $p < 0.01$ ) and with serum IgG concentrations ( $r = 0.41$ ,  $n = 14$ ,  $p < 0.05$ ).  $^{111}\text{In}$  loss was not significantly correlated with serum immunoglobulin A or M, erythrocyte sedimentation rate, or white blood count.

The number of bronchiectatic lobes was correlated with  $^{111}\text{In}$  loss ( $r = 0.32$ ,  $n = 36$ ,  $p < 0.01$ ), though the correlation did not persist after volume of purulent sputum had been entered into the regression analysis. The relation between  $^{111}\text{In}$  labelled granulocyte scans and the presence or absence of bronchiectasis on computed tomograms is shown in table 2.

Discussion

The positive correlation between volume of purulent sputum and whole body loss of  $^{111}\text{In}$  labelled granulocytes found in our original study<sup>3</sup> was confirmed in this study, in which the patient population was extended to include patients with no evidence of bronchiectasis and patients with smaller volumes of purulent sputum or mucoid sputum expectoration. The gamma camera lung scan at 21–24 hours is more sensitive than whole body counting for the detection of lung granulocyte migration. Five of 19 patients with a 24 hour purulent sputum volume of less than 5 ml had a positive lung scan, but whole body granulocyte loss from the lungs was detected in only one. From a practical point of view, a negative indium-111 scan at 21–24 hours was not associated with significant whole body granulocyte loss and recall of patients four to seven days after scanning is therefore unnecessary.

The volume of sputum expectorated is a poor predictor of the volume of mucus being cleared from the lungs<sup>2</sup> and this is likely to have reduced the correlation between loss of  $^{111}\text{In}$  labelled granulocytes and sputum markers of inflammation (purulent sputum volume and total elastolytic activity) in this study.

The delayed clearance of indium-111 from the lungs of four patients is interesting and suggests that the time course of the movement of neutrophils through the lungs of these patients was different from that of the other patients. The whole body granulocyte loss in

these patients was low in relation to the positivity grade of their 21–24 hour lung scans and highlights the importance of the image at 21–24 hours, even though it is not quantitative. Further control populations are required to determine the specificity of the granulocyte lung scan; granulocyte scans are known to be positive in patients with lung abscess, but negative in patients two days or more after the onset of acute pneumonia.<sup>11</sup>

Knowledge of whether inflammation is present in the lungs of patients with bronchiectasis is important for several reasons. Firstly, systemic symptoms (for example, tiredness and malaise) in bronchiectasis are frequently a major cause of morbidity but are poorly recognised as such, attention being paid mainly to sputum production. Objective evidence of inflammation in such patients would strengthen the case for more intensive treatment of the bronchiectasis to relieve such symptoms. Secondly, the efficacy of medical treatments of bronchiectasis can be assessed objectively by performing a granulocyte scan before and during (or after) such treatment. Thirdly, when surgical resection is being considered for patients with limited bronchiectasis bronchography and computed tomography identify areas of bronchial damage whereas <sup>111</sup>In labelled granulocyte scanning identifies sites of inflammatory activity. Evidence of inflammation may indicate in a radiologically non-bronchiectatic area a reduced chance of surgical cure. The risk of progression of bronchiectasis may be related to the level of inflammatory activity on the basis of the “vicious circle” hypothesis.<sup>10</sup>

We conclude that assessment of the migra-

tion of <sup>111</sup>In labelled granulocytes into the lungs is a useful method of objectively monitoring the level of local inflammation in patients expectorating purulent sputum.

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