Utility of Indium-111-Labeled Polyclonal Immunoglobulin G Scintigraphy in Fever of Unknown Origin

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We studied the role of $^{111}$In-labeled immunoglobulin ($^{111}$In-IgG) scintigraphy in different subgroups of patients with fever of unknown origin (FUO). Methods: During a 2-yr period (January 1992 through January 1994), the internal medicine wards of eight university hospitals in The Netherlands participated in this study. A total of 167 patients with FUO were prospectively included to prevent unintended selection. Fifty-eight patients underwent $^{111}$In-IgG scintigraphy. For 23 patients without potentially diagnostic clues (PDCs) or only misleading PDCs, the technique was used as a screening procedure. In 35 patients with PDCs pointing at local inflammation, this technique was used when indicated. Results: After diagnostic work-up, infections were found in 17 patients (29%), neoplasms in 6 (10%), noninfectious inflammatory diseases in 14 (24%) miscellaneous disorders in 5 (5%) and no diagnosis in 18 (31%). Indium-111-IgG scintigraphy was helpful in the diagnostic process for patients with PDCs at local inflammation only. The diagnostic yield of this technique in this subgroup was 26%. Infection was found in only 10/41 patients with negative scans. All infections were nonfocal or located in the heart, liver region or urinary tract where physiological uptake obscures possible pathologic uptake. The overall sensitivity and specificity were 60% and 83%, respectively. Conclusion: In patients without PDCs for local inflammation, the diagnostic yield of scintigraphic techniques was quite low since no focal inflammation was observed. Therefore, $^{111}$In-IgG scintigraphy should not be used as a second-step procedure in the work-up of these subgroup of patients with FUO. In patients with PDCs at local inflammation, $^{111}$In-IgG is helpful in the diagnostic process in one-fourth of the patients. This diagnostic yield is comparable with that of the majority of other scintigraphic techniques used in the diagnostic process of patients with FUO.

Key Words: fever of unknown origin; indium-111-IgG scintigraphy

J Nucl Med 1997; 38:484-489

Patients

From January 1992 through 1994, a prospective study on FUO, approved by all local ethical committees, was performed in all eight Dutch university hospitals. All immunocompetent patients fulfilling the classic criteria of FUO formulated by Petersdorf and Beeson (1) were entered into the study. All participants gave informed consent and 167 patients were included in our FUO protocol, which consisted of a standardized multiple choice history, physical examination and certain obligatory investigations (Table 1). Indium-111-IgG scintigraphy was performed in 58 of these 167 patients (33 women, 25 men; age range 21-87 yr, mean 55 yr).

Much consideration was given to the presence or absence of potentially diagnostic clues (PDCs), defined as all localizing abnormalities potentially pointing towards a diagnosis and the use of these PDCs in the diagnostic process. Misleading PDCs were defined as PDCs not leading to the definite diagnosis. All data, including those on PDCs, were prospectively registered in a structured data collection form. In the presence of PDCs, appropriate investigations were performed. In the absence of PDCs or in the presence of only misleading PDCs, patients underwent a two-stage screening diagnostic protocol (Table 1) which included $^{111}$In-IgG scintigraphy in the first stage. This diagnostic protocol was discontinued when a definite diagnosis was made, PDCs appeared or fever subsided.

No PDCs or only misleading PDCs were present in 43 patients when prospectively studied. In these patients, the first stage of the diagnostic screening protocol was performed. Because this scintigraphic part of the study was not initiated until January 1993, only 23 of these 43 patients underwent $^{111}$In-IgG scintigraphy. In the remaining 124 patients with PDCs, $^{111}$In-IgG scintigraphy was performed in 35 patients because of suspected localized inflammation based on PDCs. Both groups are evaluated separately in this study.

Exclusion criteria for $^{111}$In-IgG scintigraphy were agammaglobulinemia, selective IgA deficiency and a history of severe adverse reactions after intravenous or intramuscular administration of human IgG. Pregnant or lactating women were also excluded from this study. None of the patients had uremia, but this was not an exclusion criterion.
investigations Performed in all Patients after Study Inclusion
Sedimentation rate; hemoglobin; mean cellular volume; platelet count; leukocyte count and differential count; serum urea nitrogen; creatinine; sodium; potassium; protein; protein fractions; alkaline phosphatase; aminotransferase; lactate dehydrogenase; creatine phosphokinase; antinuclear antibodies; rheumatoid factors; urinary analysis; faeces for occult blood; blood cultures aerobic and anaerobic (three times); tuberculin test; urine-, feces-, and sputum culture when indicated; chest radiography; ultrasonography of upper abdomen

Phase 1: Diagnostic Protocol in Patients without PDCs
Pulse/temperature measurement with observer
Fundoscopy by an ophthalmologist
Calcium, phosphate, urate, amylase and TSH/T4
Immunoelectrophoresis of serum and urine
CRP, ACE, ANCA, anti-dsDNA, AST and cryoglobulin
C3, C4, CH50 and circulating immune complexes
Serology for Cytomegalovirus, Epstein-Barr virus, Mycoplasma, Brucella, Toxoplasma, Borrelia, Coxiella, Treponema and Yersinia
Blood cultures for more than a week, stools for worms, eggs, cysts
Blood, urine and gastric fluid cultures for tuberculosis
Bone marrow puncture and culture on Mycobacteria, Brucella, Yersinia
Indium-111-IgG scintigraphy
Radiography of teeth and sinus
Ultrasound of lower abdomen

Phase 2: Diagnostic Protocol in Patients without PDCs
Hepatitis B serology
Repeated PPD, when negative Merieux skin tests on anergy
Repeated chest radiography
IgG measurement
Liver biopsy and culture for Mycobacteria and other bacteria and fungi; IF on Yersinia
Crista biopsy and culture on Mycobacteria, Brucella, bacteria; IF on Yersinia
Ultrasound of the heart
CT abdomen and thorax
Colon radiography
Temporal artery biopsy if the patient is older than 55 yr

CRP = C-reactive protein; ACE = angiotensin converting enzyme; ANCA = antineutrophil cytoplasmatic antibody; AST = aspartate transaminase; C = complement; CMV = cytomegalovirus; EBV = Epstein-Barr virus; IF = immunofluorescence; PPD = purified protein derivative.

When possible, the scintigraphic findings were verified microbiologically but in some cases verification was made by clinical, radiographic and ultrasonographic methods. The final diagnosis and prospective analysis of diagnostic clues were made by one of the authors of this article and the attending physicians.

Radiopharmaceuticals
Human nonspecific polyclonal IgG conjugated to diethyleneetriaminepentaacetic bicyclic anhydride was prepared as a lyophilized kit for one step labeling with $^{111}$In according to the manufacturer’s instructions. A dose of 2 mg IgG labeled with 75 MBq of $^{111}$In was injected intravenously.

Imaging Procedures
Scintigraphic images were obtained with a gamma camera connected to an image processor. All images were collected in digital format in a 256 × 256 matrix. A medium-energy, parallel-hole collimator was attached to the camera. Both $^{111}$In peaks of 173 and 247 keV were used with 15% symmetric windows.

The $^{111}$In-IgG images were acquired 4, 24 and 48 hr after injection for a preset time of 5, 7.5 and 10 min, respectively. At least once, 24 hr after injection, spot views of the total body were obtained. All images were interpreted by two observers who were blinded to the results of the verification procedures. Disagreements were resolved by consensus.

An $^{111}$In-IgG scan was interpreted as positive only if consistent, focally increasing accumulation could be observed over time. An $^{111}$In-IgG scan was considered true-positive only when this imaging procedure was considered helpful in the diagnosis.

Statistical Analysis
Differences between groups were analyzed using Fischer’s exact test and Mann-Whitney U-test or Student’s t-test.

RESULTS
Of the 58 patients who underwent $^{111}$In-IgG scintigraphy, no diagnosis was established in 18 patients (31%), infection was found in 17 patients (29%), a neoplasm in 6 (10%), noninfectious inflammatory disease (NIID) in 14 patients (24%) and miscellaneous diseases in 3 (5%). For the following variables there were no significant differences between the group of patients with FUO who underwent $^{111}$In-IgG scintigraphy (n = 58) and those who did not (n = 109): percentage of patients with no diagnosis, duration of diagnostic process, period of follow-up, age, percentage of patients with periodic fever and duration of hospitalization.

Fourteen of 35 (40%) patients (Table 2) with PDCs had positive scans as compared to 3 of 23 (13%) patients (Table 3) who had undergone $^{111}$In-IgG scintigraphy as a screening procedure (p = 0.04).

In patients with PDCs, $^{111}$In-IgG scintigraphy helped establish the final diagnosis in 9 of 35 (26%) patients (Table 2, Figs. 1, 2 and 3), whereas it was not helpful diagnostically in 23 patients (Table 3) who had the test as a screening procedure (p = 0.03).

In nine patients (16%), all patients with PDCs at local inflammation, $^{111}$In-IgG scintigraphy was helpful in establishing a diagnosis. In eight patients (14%), a positive $^{111}$In-IgG scintigram did not lead to the final diagnosis. In two of these patients, clinically suspected arthritis was confirmed by the $^{111}$In-IgG scintigraphy, and in one patient, activity in the maxillary sinus was confirmed radiographically. However, a malignant lymphoma proved to be the cause of the fever. In the five remaining patients, $^{111}$In-IgG scintigraphy was false-positive and resulted in several unnecessary tests. In one of the latter patients, focal activity was observed in the right iliosacral joint. Pathological abdominal activity was observed in two patients, in the right ankle in one patient and abnormal activity was observed in both lungs in the fifth patient. In four of these five patients, no definite diagnosis could be established.

The data on the 41 patients with negative $^{111}$In-IgG scans are shown in Tables 2 and 3. In 14 of these patients, no diagnosis was established after extensive work-up. Overall follow-up after inclusion in the study varied from 33 to 1421 days (median 834 days). For patients without diagnosis, follow-up after study inclusion ranged from 362-1400 days (median 1053 days). In 10 patients, an infection was diagnosed. Urinary tract infections (n = 3), viral infections (n = 3), endocarditis, secondary syphilis, cholangitis due to sludge and chronic yersiniosis.

Calculated overall sensitivity of $^{111}$In-IgG scintigraphy in this study was 60% with a specificity of 83%.

DISCUSSION
In this study, we prospectively studied the utility of $^{111}$In-IgG scintigraphy in patients with FUO. Sixteen percent of the
Percentage of scans helpful in the diagnostic process, as reported in literature, varied from 18% to 75% (Table 4), but in our study, only a small percentage of scans were helpful in the diagnostic process. This is probably legitimate to presume that local inflammation is not the cause of fever in these patients. In 30% of patients in our study, no diagnosis could be made after a median follow-up of 2.5 yr. Second, in the subgroup of patients without PDC, no local inflammatory processes were found causing FUO. Thus, neither true-positive scans nor false-negative scans were found, making calculation of sensitivity and specificity impossible in this subgroup. Third, in patients with a negative scintigram, a large percentage of postoperative patients were included. No diagnosis could be made in 18/58 (31%) patients in our study. Our findings were similar to data presented in recent studies (9,10).

111In-IgG scans were helpful in the diagnostic process. The percentage of scans helpful in the diagnostic process, as reported in literature, varied from 18% to 75% (Table 4), but in most studies, the scintigraphic method was helpful in the diagnostic work-up in about one-quarter of the patients. This was also observed in our study, since a final diagnosis is not established in all patients undergoing scintigraphy, the interpretation of the results of this procedure is hampered due to a lack of a golden standard. When additional investigations are negative and long-term follow-up does not reveal an infection in these patients, it is probably legitimate to presume that local inflammation is not the cause of fever in these patients. In 30% of patients in our study, no diagnosis could be made after a median follow-up of 2.5 yr. Second, in the subgroup of patients without PDC, no local inflammatory processes were found causing FUO. Thus, neither true-positive scans nor false-negative scans were found, making calculation of sensitivity and specificity impossible in this subgroup. Third, in patients with a negative scintigram, a variety of diseases were found that could not be diagnosed with

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Clinical data</th>
<th>Localization uptake 111In-IgG scan</th>
<th>Final diagnosis (follow-up from inclusion, d)</th>
<th>Additional investigations (plus obligatory investigations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>Abdominal pain, diarrhea</td>
<td>Colon area</td>
<td>Diverticulitis</td>
<td>Coloscopy, abdominal CT</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>Rattling with normal x-ray</td>
<td>Right lung (Fig. 1)</td>
<td>Pleural empyema</td>
<td>CT, pleura puncture, course</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>Diffuse abdominal pain</td>
<td>Right lower abdomen</td>
<td>Right adnexitis</td>
<td>Laparoscopy, culture, course</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>Diffuse abdominal pain</td>
<td>Ascending colon</td>
<td>Diverticulitis</td>
<td>Colon radiography, abdominal US</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>Cervix cancer, tumor US</td>
<td>Low abdomen (Fig. 2)</td>
<td>Pelvic abscess</td>
<td>Laparotomy and culture</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>Pain wrist, sicca syndrome</td>
<td>Left arm</td>
<td>Granulomatous myositis</td>
<td>Muscle biopsy</td>
</tr>
<tr>
<td>7</td>
<td>33</td>
<td>Gartner’s syndrome, abdominal pain</td>
<td>Desmoid tumor</td>
<td>Necrosis desmoid tumor</td>
<td>Abdominal CT, negative culture</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>Anemia, vascular graft</td>
<td>Colon</td>
<td>Ischemic colitis</td>
<td>Laparotomy</td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>Heart murmur/S. aureus</td>
<td>Hip (Fig. 3)</td>
<td>Endocarditis, abscesses</td>
<td>Echocardiography</td>
</tr>
</tbody>
</table>

Positive, Not Helpful Scans

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Clinical data</th>
<th>Localization uptake 111In-IgG scan</th>
<th>Final diagnosis (follow-up from inclusion, d)</th>
<th>Additional investigations (plus obligatory investigations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>48</td>
<td>Vasculitis, breast cancer, arthritis</td>
<td>Many joints</td>
<td>Small metastasis</td>
<td>Protocol 1 plus 2*, lymph node biopsy</td>
</tr>
<tr>
<td>11</td>
<td>27</td>
<td>Abnormal liver biopsy, arthritis knee</td>
<td>Knee</td>
<td>Hepatitis C</td>
<td>Serology, puncture knee</td>
</tr>
<tr>
<td>12</td>
<td>52</td>
<td>IBD in past, abscess thoracic wall</td>
<td>Right iliosacral joint</td>
<td>Relapse IBD</td>
<td>MRI bony pelvis/2* coloscopy</td>
</tr>
<tr>
<td>13</td>
<td>69</td>
<td>Abdominal pain, diarrhea</td>
<td>Ascending colon</td>
<td>No diagnosis (362)</td>
<td>Coloscopy, colon radiography cultures</td>
</tr>
<tr>
<td>14</td>
<td>46</td>
<td>Lymphoma neck, abscess liver biopsy</td>
<td>Terminal ileum</td>
<td>No diagnosis (1067)</td>
<td>Protocol 1 plus 2*, no coloscopy</td>
</tr>
</tbody>
</table>

Negative Scans

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Clinical data</th>
<th>Localization uptake 111In-IgG scan</th>
<th>Final diagnosis (follow-up from inclusion, d)</th>
<th>Additional investigations (plus obligatory investigations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>78</td>
<td>Cystitis, cryoglobulinemia, dizziness</td>
<td>No activity</td>
<td>Mixed cryoglobulinemia</td>
<td>No infections, cryoglobulines</td>
</tr>
<tr>
<td>16</td>
<td>65</td>
<td>Erythrocyturia, heart murmur</td>
<td>No activity</td>
<td>Mixed cryoglobulinemia, glomerulonephritis</td>
<td>Biopsy kidney, cryoglobulines</td>
</tr>
<tr>
<td>17</td>
<td>77</td>
<td>Abnormal urinary analysis</td>
<td>No activity</td>
<td>Urinary tract infections</td>
<td>Third urine culture during antibiotics</td>
</tr>
<tr>
<td>18</td>
<td>87</td>
<td>Heart murmur, anemia, splenomegaly</td>
<td>No activity</td>
<td>Culture negative endocarditis</td>
<td>Echocardiography positive</td>
</tr>
<tr>
<td>19</td>
<td>67</td>
<td>Raynaud phenomena, valve disease</td>
<td>No activity</td>
<td>Drug fever</td>
<td>Clinical course</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
<td>Tropical travels, gonorrhea paste</td>
<td>No activity</td>
<td>Secondary syphilis</td>
<td>Serology, abdominal US/CT</td>
</tr>
<tr>
<td>21</td>
<td>42</td>
<td>Hematoperomia, gonorrhea paste</td>
<td>No activity</td>
<td>Recurrent prostatitis</td>
<td>Clinical course, response therapy</td>
</tr>
<tr>
<td>22</td>
<td>68</td>
<td>Mexican travel/divaric, dysuria</td>
<td>No activity</td>
<td>Urinary tract infection</td>
<td>Second urine culture/therapy typhus</td>
</tr>
<tr>
<td>23</td>
<td>70</td>
<td>Erythema nodosum, abdominal pain</td>
<td>No activity</td>
<td>Polymyalgia rheumatica</td>
<td>Abdominal US/CT, course</td>
</tr>
<tr>
<td>24</td>
<td>64</td>
<td>Heart murmur, lung atelectasis</td>
<td>No activity</td>
<td>Endocarditis S. bovis</td>
<td>Echocardiography/culture</td>
</tr>
<tr>
<td>25</td>
<td>65</td>
<td>Pain back, caries, breast cancer past</td>
<td>No activity</td>
<td>Temporal arteritis</td>
<td>Protocol 1 plus 2* (temporal biopsy)</td>
</tr>
<tr>
<td>26</td>
<td>55</td>
<td>Tropical travel, pain, smelly urine</td>
<td>No activity</td>
<td>Chronic yersiniosis</td>
<td>Protocol 1*, clinical course</td>
</tr>
<tr>
<td>27</td>
<td>31</td>
<td>Epididymitis, lesion spine MRI, rash</td>
<td>No activity</td>
<td>Nonclassifiable vasculitis</td>
<td>Protocol 1 plus 2*, spine biopsy</td>
</tr>
<tr>
<td>28</td>
<td>21</td>
<td>Wound contact mud, heart murmur</td>
<td>No activity</td>
<td>Reiter’s syndrome</td>
<td>Exclusion endocarditis, course</td>
</tr>
<tr>
<td>29</td>
<td>21</td>
<td>Yersinia abscess spleen, aneurysms</td>
<td>No activity</td>
<td>Polyangiitis syndrome</td>
<td>Skin biopsy, thoracic DSA</td>
</tr>
<tr>
<td>30</td>
<td>39</td>
<td>Arthritis, heart murmur, urtica</td>
<td>No activity</td>
<td>No diagnosis (1365)</td>
<td>Protocol 1*, joint radiography, US heart</td>
</tr>
<tr>
<td>31</td>
<td>31</td>
<td>Spitz-Holter drain, cough, blood stools</td>
<td>No activity</td>
<td>No diagnosis (1113)</td>
<td>Colon radiography, negative cultures</td>
</tr>
<tr>
<td>32</td>
<td>65</td>
<td>Heart murmur, hip prothesis</td>
<td>No activity</td>
<td>No diagnosis (1107)</td>
<td>Echocardiography, course</td>
</tr>
<tr>
<td>33</td>
<td>57</td>
<td>Lung infiltrate, paraprotein, osteolysis</td>
<td>No activity</td>
<td>No diagnosis (1142)</td>
<td>Protocol 1 plus 2*, bronchoscopy</td>
</tr>
<tr>
<td>34</td>
<td>32</td>
<td>Abdominal pain, polycystic ovarian disease</td>
<td>No activity</td>
<td>No diagnosis (654)</td>
<td>US, coloscopy, laparoscopy</td>
</tr>
<tr>
<td>35</td>
<td>18</td>
<td>Abdominal pain, cough</td>
<td>No activity</td>
<td>No diagnosis (627)</td>
<td>Protocol 1*, abdominal CT</td>
</tr>
</tbody>
</table>

See Table 1.

111In-IgG scan = inflammatory bowel disease; ANA = antinuclear antibody; RA = rheumatoid arthritis; T4 = thyroxine; TSH = thyroid-stimulating hormone.

There are definitely some problems with the calculation of sensitivity and specificity of scintigraphic techniques in patients with FUO. First, since a final diagnosis is not established in all patients undergoing scintigraphy, the interpretation of the results of this procedure is hampered due to a lack of a golden standard. When additional investigations are negative and long-term follow-up does not reveal an infection in these patients, it is probably legitimate to presume that local inflammation is not the cause of fever in these patients. In 30% of patients in our study, no diagnosis could be made after a median follow-up of 2.5 yr. Second, in the subgroup of patients without PDC, no local inflammatory processes were found causing FUO. Thus, neither true-positive scans nor false-negative scans were found, making calculation of sensitivity and specificity impossible in this subgroup. Third, in patients with a negative scintigram, a variety of diseases were found that could not be diagnosed with
TABLE 3
Patients Characteristics of Indium-111-lgG Scans Performed as Screening (n = 23)

<table>
<thead>
<tr>
<th>Patient Age no. (yr)</th>
<th>Clinical data</th>
<th>Localization uptake 111In-IgG scan</th>
<th>Final diagnosis (follow-up from inclusion, d)</th>
<th>Additional investigations (plus obligatory investigations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 70 None</td>
<td></td>
<td>Positive, Not Helpful Scans</td>
<td></td>
<td>Ankle radiography, bone biopsy negative</td>
</tr>
<tr>
<td>37 57 Heart murmur/negative echocardiography, dyspnea with negative chest x-ray, RA</td>
<td></td>
<td>Malleolus lateralis No diagnosis (1169)</td>
<td></td>
<td>Ventilation/perfusion scan</td>
</tr>
<tr>
<td>38 52 Abdominal lymphadenopathy</td>
<td></td>
<td>Paranasal sinuses Malignant lymphoma</td>
<td>Sinus radiography, mucosal swelling</td>
<td></td>
</tr>
<tr>
<td>39 37 Lymphadenopathy, erythema nodosa</td>
<td></td>
<td>No activity No diagnosis (1400)</td>
<td>Protocol 1*</td>
<td></td>
</tr>
<tr>
<td>40 38 Changed defecation/normal coloscopy</td>
<td></td>
<td>No activity No diagnosis (1269)</td>
<td>Protocol 1*</td>
<td></td>
</tr>
<tr>
<td>41 36 Cough, lymphadenopathy, splenomegaly</td>
<td></td>
<td>No activity No diagnosis (1039)</td>
<td>Protocol 1*</td>
<td></td>
</tr>
<tr>
<td>42 46 Arthralgia, redness skin joint</td>
<td></td>
<td>No activity No diagnosis (999)</td>
<td>Protocol 1 plus 2*</td>
<td></td>
</tr>
<tr>
<td>43 67 Empysema, liver function disturbance</td>
<td></td>
<td>No activity No diagnosis (976)</td>
<td>Culture, US, liver biopsy</td>
<td></td>
</tr>
<tr>
<td>44 62 Prosthetic valves, right heart failure</td>
<td></td>
<td>No activity No diagnosis (948)</td>
<td>Protocol 1 plus 2*</td>
<td></td>
</tr>
<tr>
<td>45 71 Lung lesion for 1 yr, thrombocytopenia</td>
<td></td>
<td>No activity No diagnosis (868)</td>
<td>Chest radiography, bone marrow biopsy</td>
<td></td>
</tr>
<tr>
<td>46 21 Lymphadenopathy, splenomegaly, hemolysis</td>
<td></td>
<td>No activity No diagnosis (904)</td>
<td>Protocol 1 plus 2*, hemolysis analysis</td>
<td></td>
</tr>
<tr>
<td>47 66 None</td>
<td></td>
<td>No activity Mixed cryoglobulinemia</td>
<td>Protocol 1*</td>
<td></td>
</tr>
<tr>
<td>48 64 Generalized lymphadenopathy</td>
<td></td>
<td>No activity</td>
<td>AILD Fourth lymph-node biopsy</td>
<td></td>
</tr>
<tr>
<td>49 25 Lymphadenopathy, abdominal pain</td>
<td></td>
<td>No activity Takayasu's disease</td>
<td>Protocol 1 plus 2*, laparoscopy</td>
<td></td>
</tr>
<tr>
<td>50 33 Unexplained abundant diarrhea</td>
<td></td>
<td>No activity Factitious fever</td>
<td>Prolaven laxative disuse</td>
<td></td>
</tr>
<tr>
<td>51 43 Urticaria, lymphadenopathy</td>
<td></td>
<td>No activity Urticarial vasculitis</td>
<td>Protocol 1 plus 2*, skin biopsy</td>
<td></td>
</tr>
<tr>
<td>52 58 Liver function disorder, skin lesions</td>
<td></td>
<td>No activity Cholangitis/sludge</td>
<td>Abdominal CT and US</td>
<td></td>
</tr>
<tr>
<td>53 29 Low back pain, diarrhea, iridocyclitis</td>
<td></td>
<td>No activity Still's disease</td>
<td>Protocol 1*, clinical course</td>
<td></td>
</tr>
<tr>
<td>54 55 Sarcoïdosis past, rash, lymphocytosis</td>
<td></td>
<td>No activity Cytomegalovirus infection</td>
<td>Serology, ACE/chest x-ray</td>
<td></td>
</tr>
<tr>
<td>55 71 Urticarial vasculitis, monoclonal IgM</td>
<td></td>
<td>No activity Schnitzler's disease</td>
<td>Protocol 1*, skin biopsy, course</td>
<td></td>
</tr>
<tr>
<td>56 42 Cardiac valve disease/negative US of heart, abdominal lymphadenopathy</td>
<td></td>
<td>No activity Hodgkin's disease</td>
<td>Bone biopsy, histology spleen</td>
<td></td>
</tr>
<tr>
<td>57 44 Hepatosplenomegaly, lymphocytosis</td>
<td></td>
<td>No activity Cytomegalovirus infection</td>
<td>Serology</td>
<td></td>
</tr>
<tr>
<td>58 65 Weight loss, dyspnea, heart failure, irregular heartbeat</td>
<td></td>
<td>No activity Hyperthyroidism</td>
<td>T4 and TSH</td>
<td></td>
</tr>
</tbody>
</table>

*See Table 1.
AILD = angioimmunoblastic lymphoma; ANA = antinuclear antibody; IBD = inflammatory bowel disease; RA = rheumatoid arthritis; T4 = thyroxine; TSH = thyroid-stimulating hormone.

111In-IgG scintigraphy because lesions were present in organs with relatively high physiologic uptake, such as the liver, heart and urinary tract. Nonfocal infections such as viral infections could not be excluded by 111In-IgG scintigraphy. Despite these limitations of the technique, a negative scan did rule out focal infection or inflammation with a high degree of certainty.

Similar to 67Ga, 111In-WBCs and 99mTc-HMPAO-labeled WBCs, 111In-IgG can be excreted in the bowel under physiological conditions (5,12,13). However, such excretion was not significant and hardly interfered with adequate evaluation of possible abdominal infections or inflammation (14). We observed in two patients only abnormal bowel activity. In six other patients, however, pathological activity in the abdomen led to the final diagnosis.

In contrast to Knockaert et al. (2), in our study the duration of hospitalization and diagnostic process of patients who underwent scintigraphy was not significantly longer than in patients who did not undergo scintigraphy. We performed 111In-IgG scintigraphy as a secondary step in the diagnostic protocol for patients without PDCs, whereas Knockaert et al. (2) scheduled 67Ga scintigraphy as a third step or last resort procedure when the source of fever remained unknown. Naturally, in this latter category, the chance of reaching a diagnosis is lower.

By prospectively separating patients without PDCs from those with PDCs for local inflammation, we found a strikingly low diagnostic yield of this technique when using it as a screening procedure in patients with FUO. Therefore, scinti-
After surgery and antibiotic therapy, she recovered and her fever coccus spp. fever and abdominal pain developed. Abdominal US revealed a tumor consistent with abnormal uptake in the lower abdomen on 111In-IgG scintigraphy. Laparotomy and culture revealed a pelvic abscess caused by Peptococcus spp. After surgery and antibiotic therapy, she recovered and her fever resolved (Patient 5).

graphic imaging should not be a second step procedure in the diagnostic work-up of this subgroup of patients with FUO.

CONCLUSION
During a 2-yr period, we prospectively investigated 167 patients with FUO. Of these patients, 58 underwent 111In-IgG scintigraphy. These patients were prospectively separated in patients with or without PDCs. Overall sensitivity and specificity was 60% and 83%, respectively. In patients without PDCs for local inflammation, the diagnostic yield of scintigraphic techniques is quite low since no focal inflammation was observed. Therefore, 111In-IgG scintigraphy should not be used as a second-step procedure in the work-up of these subgroup of patients with FUO. In patients with PDCs at local inflammation, 111In-IgG is helpful in the diagnostic process in one-fourth of the patients. This diagnostic yield is comparable with that of the majority of other scintigraphic techniques used in the diagnostic process of patients with FUO.

ACKNOWLEDGMENTS
We thank the members of The Netherlands FUO Study Group for their contribution. This study was supported in part by The Netherlands Institute for internal medicine through a grant from Glaxo Inc. Zeist, The Netherlands and a grant from R.W. Johnson Pharmaceutical Research Institute, Spring House, PA. Members of the Netherlands FUO Imaging Group include: E.M.H.A. de Kleijn, J.W.M. van der Meer, W.J.G. Oyen, F.H.M. Corstens, University Hospital, St. Radboud, Nijmegen; H.G. Kreeftenberg and D.R. Piers, University Hospital, Groningen; P. Speelman and E.A. van Royen, University Hospital of the University of Amsterdam; S. de Marie and E.P. Krenning, University Hospital Rotterdam.

REFERENCES
Optimization of Technetium-99m-Labeled PEG Liposomes to Image Focal Infection: Effects of Particle Size and Circulation Time

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In previous studies we have shown that liposomes sterically stabilized with polyethylene glycol (PEG), preferentially localize in infectious and inflammatory foci. In this study, we further optimized the formulation of PEG liposomes for infection imaging in a rat model. Methods: The biodistribution and imaging characteristics of different liposomal formulations labeled with 99mTc were determined in rats with S. aureus infection of the left calf muscle. The influence of liposomal size (mean diameter varying from 90 nm to 220 nm) as well as circulation time (modulated by inclusion of 0–10 mole% phosphatidylserine in the lipid bilayer of the PEG liposomes) were studied. Results: The smallest liposomes displayed improved characteristics for imaging infection: 90-nm liposomes revealed the highest abscess uptake (1.6% ± 0.4% ID/g, 24 hr postinjection) in combination with the lowest splenic accumulation (6.9% ± 0.7% ID/g, 24 hr postinjection) as compared to the larger sized preparations. Enhanced abscess-to-blood ratios (4.0 versus 1.3 at 24 hr postinjection) were obtained by including 1.0 mole% phosphatidylserine in the lipid bilayer of the PEG liposomes. However, enhanced blood clearance of these liposomes reduced their absolute abscess uptake. Conclusion: These results indicate that the in vivo behavior of PEG liposomes can be modulated to optimize their characteristics for infection imaging.

Key Words: PEGylated liposomes; sterically stabilized liposomes; S. aureus infection

J Nucl Med 1997; 38:489-493

Liposomes are microscopic lipid vesicles consisting of one or more concentric lipid bilayers enclosing discrete aqueous spaces. Liposomes have been investigated extensively as carriers for drugs in attempts to achieve selective deposition and/or controlled release of the encapsulated contents (1-5). In addition, liposomes have been tested as vehicles to image infection and inflammation (6,7). However, conventional liposomes are rapidly taken up by cells of the mononuclear phagocyte system (MPS), which are primarily located in the liver and spleen (8,9). A decade ago, one of the major goals in liposome research was to enhance their circulatory residence time to allow enhanced targeting to non-MPS tissues. It has been demonstrated that small, neutral, cholesterol-rich liposomes composed of rigid phospholipids of high-phase transition temperature show prolonged circulation times at relatively high lipid doses (10-12). More recently, it was demonstrated that inclusion of polyethylene glycol (PEG), conjugated to phosphatidylethanolamine in the bilayer increased the blood circulation time as well (13,14). This increment was at least as large as that observed with the rigid lipid composition but without the requirements of specific lipid composition, particle size and lipid dose (15-17). The prolonged circulation time of PEG liposomes, also referred to as sterically stabilized or Stealth® liposomes (Sequus Pharmaceuticals Inc., Menlo Park, CA), is caused by reduced recognition by the MPS, as reflected by delayed and diminished hepatic and splenic accumulation. The development of long-circulating liposomal formulations has offered several new applications for liposomes such as: (a) long-term controlled release of drugs in the circulation; (b) improved antibody-guided delivery of liposomes; and (c) enhanced targeting to non-MPS-related pathological sites such as tumors and inflammatory foci (18,19).

Our previous studies in rats have shown that PEG liposomes labeled with either 111In or 99mTc may be excellent radiopharmaceuticals for imaging infectious and inflammatory foci (1,2). The aim of this study was to tailor the PEG-liposomal formulation for scintigraphic application in rats with focal S. aureus infection. The PEG-liposomal formulation we used in our previous studies was originally developed for controlled delivery of chemotherapeutics (15,20,21). In this study, we modified the size and lipid composition of the liposomes to optimize their in vivo behavior for imaging infection. Different liposome dispersions with a narrow size distribution were produced (mean size: 90, 120, 160 and 220 nm) and evaluated in vivo. In addition, the effects of enhanced blood clearance were investigated by incorporating increasing amounts of phosphatidylserine (PS) (0, 1 and 10 mole%) in the lipid bilayer. It has been shown that PS exposure strongly increases the recognition of PEG liposomes by macrophages, thereby causing enhanced blood clearance (22,23).