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Review article

The contribution of nuclear medicine to the patient with infection

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Abstract. Nuclear medicine imaging of infection has two major indications: (a) the localization of a focus of infection in patients with fever of unknown origin; in this context the radio-pharmaceutical should be highly sensitive whereas specificity is not so important because subsequent biopsy or morphologically based imaging can be performed; (b) the diagnosis of an infection in patients with localized symptoms, for example after surgery, when normal anatomy is absent or when metal implants prevent computed tomography or magnetic resonance imaging. In these latter cases high sensitivity and to an even greater extent high specificity are mandatory to guide further clinical management (conservative or surgical). All radiopharmaceuticals available to date, such as technetium-99m nanocolloids, gallium-67 citrate, indium-111- and ^{99m}Tc-labelled white blood cells, ^{99m}Tc-antigranulocyte antibodies, and ^{99m}Tc-or ^{111}In-labelled unspecific human immunoglobulin, have different biodistributions and different physical characteristics. The absence of physiological uptake in an organ and the radiation exposure of a patient are reasons to use different radiopharmaceuticals in different clinical situations, adapted to the inidividual carcumstances of the patient.

Key words: Infection – Gallium-67 citrate – Technetium-99m nanocolloids – Labelled white blood cells – Technetium-99m antigranulocyte antibodies – Labelled unspecific human immunoglobulin

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Introduction

Nuclear medicine imaging provides information on changes in *pathophysiological* and *pathobiochemical* processes in the patient, whereas morphologically based imaging provides information with high resolution on the morphological changes occurring in a specific process. Nuclear medicine imaging is available as whole-body imaging in routine clinical practice, whereas computed tomography (CT), magnetic resonance imaging (MRI) and other techniques provide information on one part of the body.

For the *localization* of an infectious process a nuclear medicine procedure needs high sensitivity in all areas of the body. A typical example is fever of unknown origin. After the localization of an infection or inflammation, further investigations such as CT, MRI, biopsy and culture are necessary. For the differential diagnosis of inflammation or infection, e.g. after a surgical procedure, when the surgeon needs information on whether to reoperate or to administer conservative treatment, *infection-specific methods* are necessary.

Pathophysiological aspects of imaging infection

All nuclear medicine procedures use one single step of the infection cascade as a part of the host defence mechanism to demonstrate all the typical phenomena in infectious diseases. Host defence mechanisms may be categorized as non-specific or specific. *Non-specific* responses protect against a wide range of infectious agents, whereas *specific* responses are directed against one particular microorganism [1].

Specific infection imaging directed against one particular microorganism has been described with a radiolabelled monoclonal antibody against *Pneumocystis carinii*, with a reported sensitivity of 85.7% and a specificity of 86.7% [2]. However, this approach can only be used in a patient population with a high likelihood of having just one typical infectious agent.

Non-specific defence mechanisms include physical barriers to invasion, secretions at potential portals of entry, complement and phagocytic cells (granulocytes and monocytes). Monocytes are also an essential component of the specific cell-mediated immune response. Polymorphonuclear neutrophils (PMNs) are essential in host defence against infections with bacteria and some viruses and fungi, but they also mediate tissue damage in certain non-infectious diseases [1]. Their primary function

This paper is dedicated to Professor Dr. Friedrich Wolf, Head of the Department of Nuclear Medicine of the University of Erlangen-Nuremberg, on the occasion of his 65th birthday

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is ingestion and destruction of invading pathogens, a process that involves several steps. One of the first steps in the neutrophil's response to inflammatory stimuli is adherence to endothelial surfaces, an event mediated by the cell surface glycoproteins (non-specific cross-reacting antigens) and on the epithelial side by the adhesion molecules expressed there. Neutrophils then migrate to sites of infection or inflammation in response to chemotactic substances generated by invading bacteria, by phagocytic cells at the involved site or by activation of the classical complement pathway. Neutrophils sense these substances in nanomolar concentrations and migrate towards them with directed movement. This migration of granulocytes out of the circulation is preceded shortly beforehand by increased blood flow and capillary permeability, leading to the well-known signs of infection, i.e. calor, rubor, tumor and dolor (Celsus, 30 B.C.–50 A.D.) accompanied by reduced function of the infected part of the body (*functio laesa*; Galen, 131–200 A.D.). The aim of an inflammatory reaction of the organism is to eliminate the inducing agents.

An acute inflammation is characterized by hyperaemia, increased vascular permeability with exudation of proteins and leucocyte migration. In a chronic inflammation, macrophages, lymphocytes and plasma cells dominate, while hyperaemia and vascular permeability are less severe. These pathophysiological processes occur in both infectious and inflammatory diseases (Fig. 1). Currently no routinely available procedure is able to answer the surgeon's most important question, namely whether there is only inflammation in a wound after surgery, which allows conservative treatment, or whether bacterial contamination is present, which necessitates immediate surgical intervention. Although this question cannot be resolved using routinely available radiopharmaceuticals, first reported investigations with technetium-99m-labelled chinolons (infecton) have demonstrated infections before labelled granulocytes migrate to the foci [3].

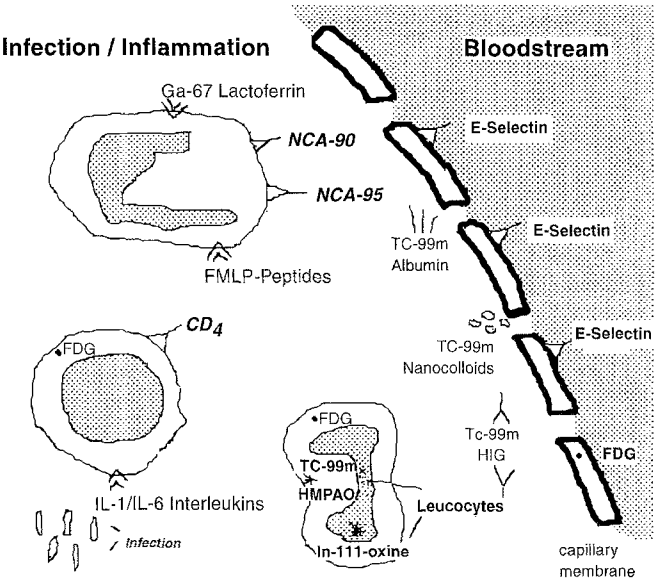

Fig. 1. Possible targeting with nuclear medicine procedures in patients with infectious and inflammatory diseases

Radiopharmaceuticals for imaging infection

Of all the radiopharmaceuticals that have been described in the literature for the localization of infectious diseases, here I shall discuss only those which are routinely available (Table 1). Gallium-67 displays receptor binding to lactoferrin, but probably first has to be taken up unspecifically in the focus. The same uptake mechanisms are discussed for ^{99m}Tc-labelled nanocolloids and for ^{99m}Tc- and indium-111-labelled human immunoglobulin (HIG), the last-mentioned of which is not commercially available. The major mechanism of uptake of these radiopharmaceuticals is increased capillary permeability, which immediately precedes leucocytic migration and is a characteristic of infection but also inflammation (Table 2).

Table 1. Routinely available radiopharmaceuticals for imaging infectious diseases

Radiopharmaceutical	Physical characteristics		Uptake mechanism
	Half-life	Energy	
^{67}Ga citrate	78 h	93, 185, 300 and 394 keV	Transferrin receptor binding/ lactoferrin receptor binding
^{99m}Tc-nanocolloids	6 h	140 keV	Non-specific via capillary permeability/active uptake in activated endothelial cells
^{99m}Tc/^{111}In-labelled human immunoglobulin (HIG)	6 h/ 67 h	140 keV/ 173 and 247 keV	Non-specific via increased capillary permeability
^{111}In oxine/^{99m}Tc-HMPAO-labelled leucocytes	67 h/6 h	173 and 247 keV/140 keV	Specific chemotactic activation
^{99m}Tc-labelled granulocyte anti-bodies	6 h	140 keV	Increased capillary permeability and specific binding or uptake as antibody labelled granulocytes

Table 2. Estimated radiation dose after injection of various routinely available radiopharmaceuticals to detect infection and inflammation

Radiopharmaceutical	Dose (MBq)	Effective dose equivalent (mSv/dose)	Reference
^{67}Ga citrate	220	27	[6]
^{99m}Tc-nanocolloids	370	–	–
^{99m}Tc-HIG	370	3	[7]
^{111}In-HIG	75	15	[8]
^{111}In-labelled leucocytes	25	15	[9]
^{99m}Tc-HMPAO leucocytes	370	6	[10]
^{99m}Tc-labelled granulocyte antibodies	370	3.9	[11]

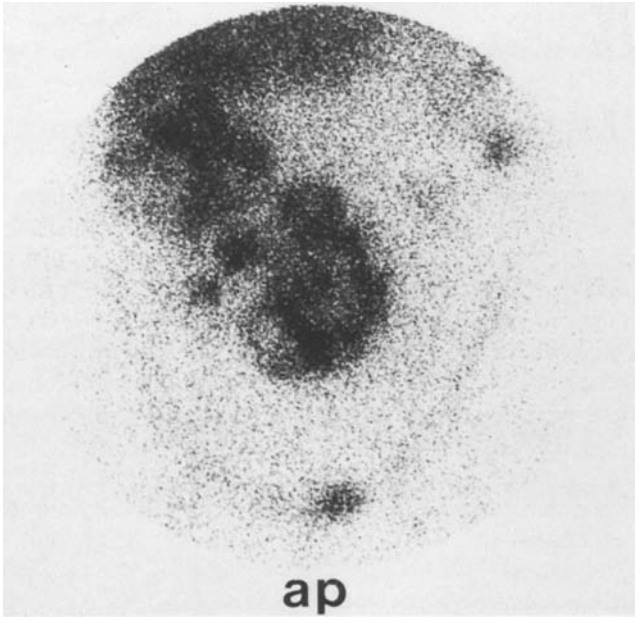

Fig. 2. ^{111}In-labelled leucocyte scan in a patient with polycystic kidney disease who underwent regular dialysis treatment. Nearly total leucocytic infiltration of the right kidney, circumscribed infiltration of one cystic lesion in the left kidney and bladder infection as the possible portal of infection can be diagnosed and (and were surgically proven)

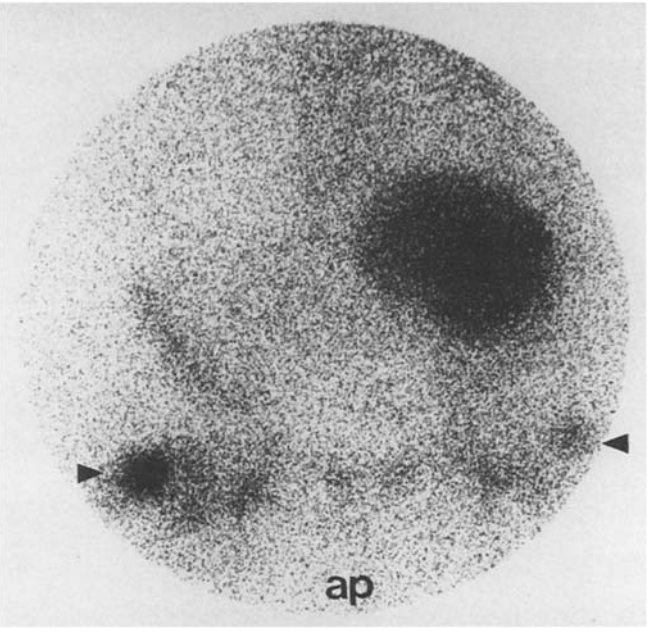

Fig. 3. ^{111}In-labelled granulocyte scan in a patient with kidney graft, septic temperature and decreasing kidney function. The scan shows complete leucocytic kidney infiltration and two cutaneous ulcerations on the patient's back (proven by kidney explanation)

In vitro labelling demonstrates specifically the chemotactically triggered migration of leucocytes [4]. Monoclonal antigranulocyte antibodies partly bind to circulating granulocytes and partly circulate as free antibodies which are available to target granulocytes at the focus after having unspecifically passed the capillary wall [5].

The dicision to perform a specific infection scan always has to be based on the clinical situation; however, biodistribution of the radiopharmaceutical and radiation exposure also influence the decision. The high radiation exposure (Table 2) resulting from an examination with ^{67}Ga citrate or ^{111}In-labelled leucocytes limits their use to specific, clinically important situations. Thus ^{67}Ga citrate is employed in cases of suspected cytomegalovirus pneumonia in AIDS-compromised patients or in cases of chronic vertebral osteomyelitis, and ^{111}In-labelled leucocytes are used if renal infection has to be excluded or proven (Figs. 2, 3). Table 3 demonstrates that the local-

Table 3. Whole-body distribution of radiopharmaceuticals for imaging infectious lesions (qualitative overview)

Radiopharmaceutical	Liver	Spleen	Kidneys	Bladder	Bowel	Bone marrow	Blood
^{67}Ga citrate	Yes	Yes	Yes	Yes	Yes	Yes	No
^{99m}Tc-nanocolloids	Yes	Yes	Yes	Yes	No	Yes	No
^{99m}Tc-HIG	Yes	Yes	Yes	Yes	Yes/no	No	Yes
^{111}In-HIG	Yes	Yes	Yes	Yes	Yes/no	Yes	Yes
^{111}In-labelled leucocytes (24 h)	Yes	Yes	No	No	No	Yes	No
^{99m}Tc-HMPAO-labelled leucocytes	Yes	Yes	Yes	Yes	Yes	Yes	No
^{99m}Tc-labelled granulocyte antibodies (24 h)	Yes	Yes	Yes	Yes	No	Yes	No

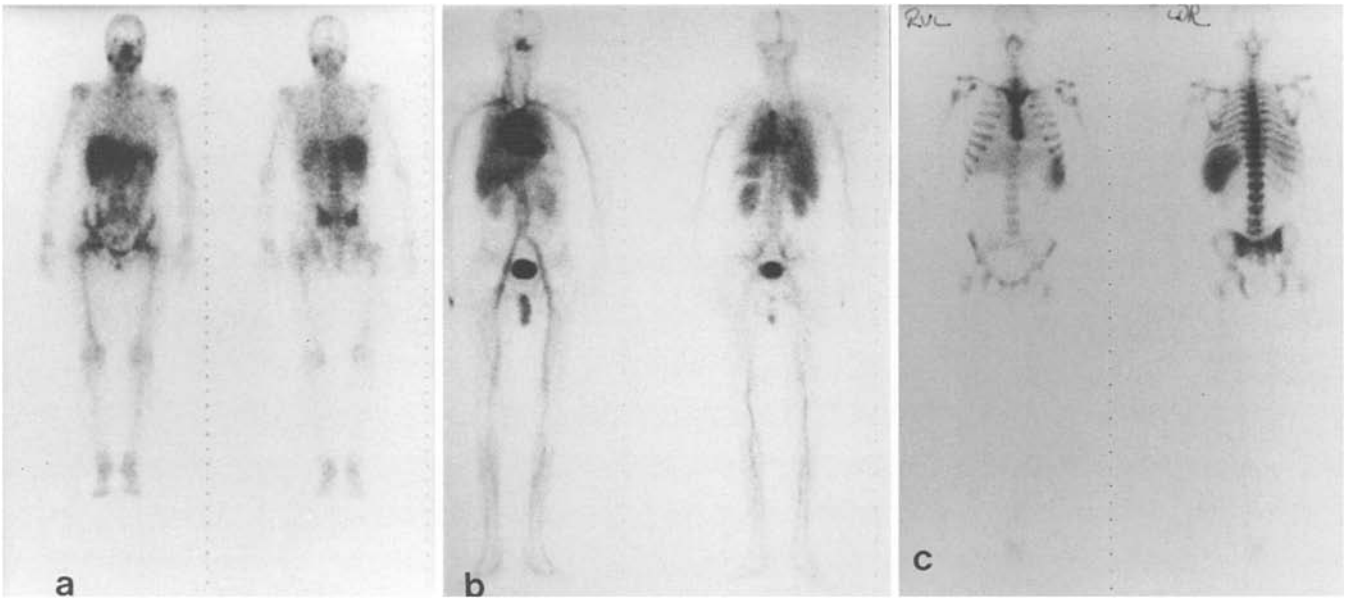

Fig. 4. Whole-body scan with ^{67}Ga citrate (**a**), ^{99m}Tc-labelled non-specific HIG (**b**) and ^{99m}Tc-labelled antigranulocyte antibodies (**c**). ^{67}Ga nicely shows low chest uptake but physiological intestinal excretion of the tracer. ^{99m}Tc-HIG shows high blood pool and chest activity whereas the antibody demonstrates an "empty" abdomen and "empty" extremities

ization of liver, bone marrow and splenic infection is hindered by the physiological uptake of the tracers. Kidney infections are best examined with ^{111}In-labelled leucocytes; this is also true of intestinal infections and their differentiation from abscesses and enteric communications because 24-h scans are possible. By contrast the intestinal excretion of ^{99m}Tc-hexamethylpropylene amine oxime (HMPAO) labelled leucocytes means that the bowel is clean of activity within 3 h p.i.. If the aim of a study is to prove vascular prosthetic or heart valve infection, only tracers with very low activity in the circulation should be injected, such as in vitro labelled leucocytes (^{111}In or ^{99m}Tc) or antigranulocyte antibodies; tracers with a very high activity in the circulation such as ^{99m}Tc-HIG, display only limited tracer uptake in cases of moderate infection (Fig. 4).

^{67}Ga citrate

Physics. ^{67}Ga citrate is a cyclotron-generated radiopharmaceutical with emission of gamma rays over a broad range of 93–880 keV, with dominant energies of 93, 184, 296 and 388 keV. The physical half-life is 78 h.

Biodistribution. Physiologically 10%–25% of the nuclide is excreted via the kidneys over the first 24 h, but thereafter the principal route of excretion is the colon. At 48 h after injection about 75% of the injected dose remains in the body and is equally distributed among the liver, bone and bone marrow and soft tissues [12]. This equal distribution in a lot of organs predefines the indications for imaging. Organs with physiological uptake of ^{67}Ga citrate may be better examined with other radiopharmaceuticals.

Uptake mechanism. Leucocytes at the site of inflammation or infection excrete some of their intracellular lactoferrin, which remains localized and bound to macrophages. ^{67}Ga citrate is transported either in ionic form or bound to transferrin, and may leak through the vascular epithelium at the site of infection, where it is then bound to lactoferrin. Another mechanism might be the production, by microorganisms grown in a low iron environment, of siderophores that have a binding affinity for iron as well as for gallium: because of a lack of freely available iron, ^{67}Ga may be transported directly into the cell in its place.

Clinical indications. ^{67}Ga entails high radiation exposure, is not routinely available and has unfavourable physical characteristics for gamma camera imaging; these features, combined with the availability of ^{99m}Tc-labelled radiopharmaceuticals for imaging infections, limit the use of ^{67}Ga to certain indications such as fever of unknown origin, chronic osteomyelitis of the spine and lung infections, especially in immunocompromised patients.

The diagnosis "fever of unknown origin" (FUO) is restricted to patients who have an elevated temperature (38.8° C) for 2–3 weeks and in whom the cause of fever cannot be ascertained despite intensive investigations [13].These rigid criteria eliminate obvious bacterial and viral infections, those in whom the diagnosis becomes more obvious with the passage of time and those whose fever is due to a non-infectious cause. However, it does not exclude all patients suffering from an infectious disease who have prolonged fever. In different studies which together examined a total of 647 patients with FUO, the mean percentage with an infectious origin was

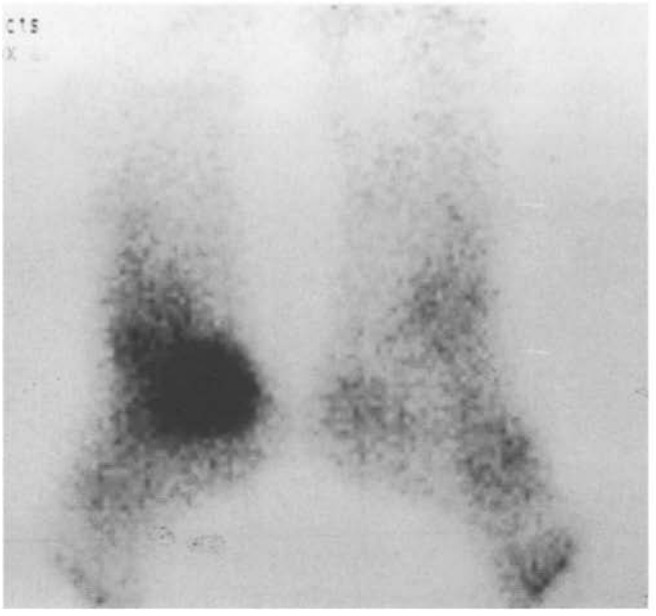

Fig. 5. ^{67}Ga scan in a patient with FUO of 5 weeks' duration. ^{67}Ga uptake is seen in the calcaneus, which was proven by biopsy to be a localized B-cell non-Hodgkin's lymphoma

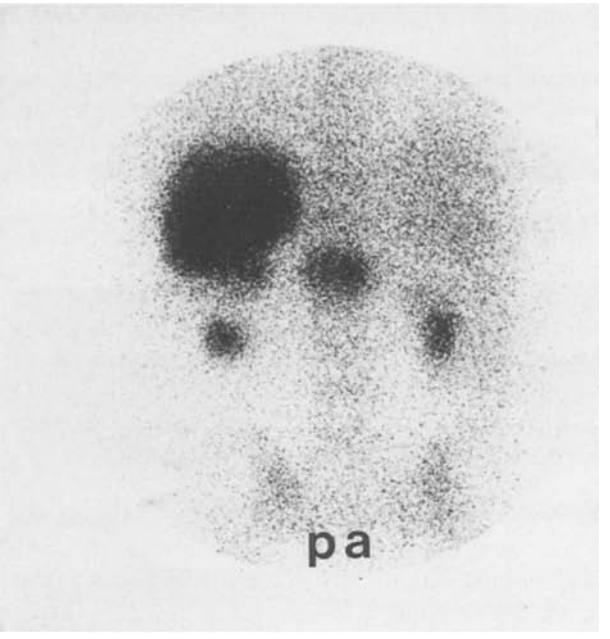

Fig. 6. ^{111}In-labelled leucocyte scan in a patient undergoing regular dialysis treatment and with a 2-day history of leucocytosis, fever and back pain. The scan demonstrates infection of both kidneys and osteomyelitis of the spine. Ultrasonography of the kidneys and X-ray of the spine were not suspicious but became positive 15 days after the first clinical symptoms

found to be 32.7% [13–18]. Other important causes of FUO include collagen vascular diseases and neoplasms [13–18] (Fig. 5). It is well known that ^{67}Ga has a high sensitivity but a low specificity in the diagnosis of infections. This is necessary in FUO patients, because a lesion first needs to be detected and then can be diagnosed by further methods such as biopsy. The low specificity also allows the detection of neoplasms or, sometimes, collagen vascular diseases, which subsequently may be further examined using more specific methods.

The results of white blood cell imaging [19], immunoscintigraphy [20–22] and ^{99m}Tc-HIG imaging of infections are not very satisfactory in patients with suspected vertebral osteomyelitis. This is difficult to explain, but it may be that a very high pressure in one disk with chronic infection prevents proteins and granulocytes from migrating in the focus during the available imaging time. The data are limited, but ^{67}Ga citrate may be superior to labelled leucocyte, antibody and immunoglobulin imaging for vertebral osteomyelitis, although it is less specific and shows tumours as well (Fig. 6).

In general chest X-ray and sputum cultures are easily obtainable and verify most suspected respiratory infections. Radionuclide studies are not of wide importance in this area, because white blood cells, antibodies and immunoglobulins fail to demonstrate pneumonia with high accuracy. It is within this context that ^{67}Ga has come to play a role in the diagnosis of AIDS-related respiratory disease (Fig. 7).

Lymph node uptake of ^{67}Ga is a frequent finding in the HIV-positive patient and may be identified virtually anywhere in the body [23]. This is a characteristic finding in patients with *Mycobacterium tuberculosis* and

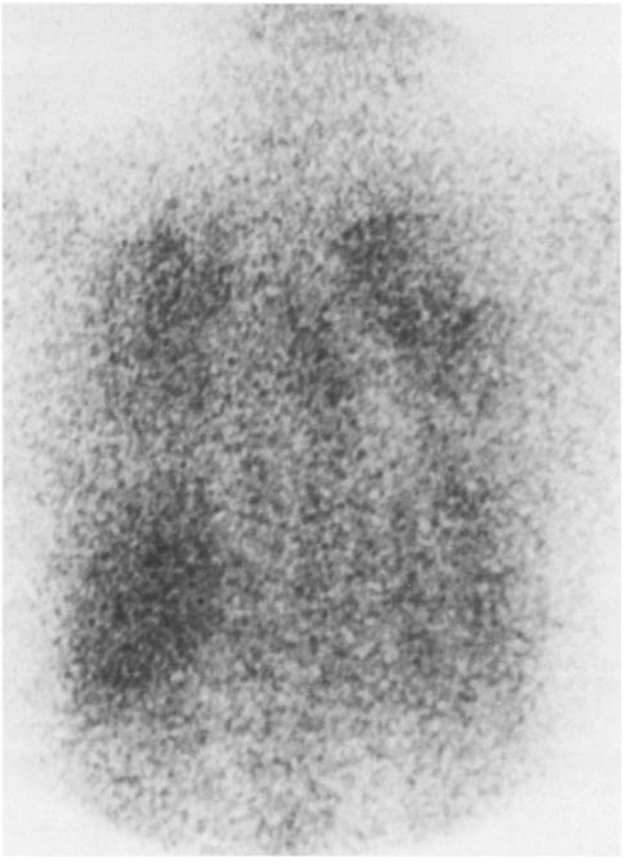

Fig. 7. Diffuse ^{67}Ga chest uptake in a patient with *Pneumocystis carinii* pneumonia

lymphoma. Localized pulmonary uptake is more typical in the setting of bacterial pneumonia, whereas diffuse pulmonary uptake may be caused by *Pneumocystis carinii* pneumonia, cytomegalovirus pneumonia, interstitial pneumonia and pneumonitis [23]. A negative scan represents strong evidence against an infectious process.

^{99m}Tc-nanocolloids

Physics. The physics of ^{99m}Tc as a generator product is well known, with its physical half-life of 6 h and its 40-keV gamma energy. Moreover it is always available in every nuclear medicine unit and results in a reasonable radiation exposure of the patient.

Biodistribution. The biodistribution of^{99m}Tc-nanocolloids has been extensively measured in the rat model [24]. The blood activity within the time relevant for imaging decreases from 3.4% (30 min) to 1.8% (1 h) to 0.5% (3 h) of the injected dose; in the liver over the same period it decreases from 72.4% to 68.7% to 52.5%, but for the bone marrow the figures are 14.5%, 12.5% and 12.4%, respectively – consequently this radiopharmaceutical also can be used for bone marrow imaging. After the active uptake in the reticuloendothelial system the nanocolloids are lysosomally degraded, so 54.5% are renally excreted after 24 h.

Uptake mechanism. Approximately 86% of these particles are 30 nm in diameter or smaller and the remainder are between 30 and 80 nm [25]. The passage of these inert particles into the pericapillary spaces and their subsequent accumulation is due to the increased permeability of the capillary basal layer induced by cytokines. Unlike macromolecules, however, the blood clearance is rapid, so that imaging may be completed within 2–4 h. Thereafter the activity may appear in the gastrointestinal tract, probably from spontaneous oxidation to pertechnetate. The absolute concentration of ^{99m}Tc-nanocolloids has been found to be about 100 times lower than that of ^{111}In-labelled leucocytes, and the abscess/blood concentration ratios were also lower for ^{99m}Tc-nanocolloids than for other radiopharmaceuticals [26]. However, in these experimental studies measurements were performed 24 h after injection of the radiopharmaceuticals, which is an improper time for nanocolloids; clinically relevant times are between 1 and 4 h following injection.

Clinical indications. The main indications for nanocolloids are skeletal and joint infections and inflammations. Soft tissue and especially gastrointestinal infections cannot be reliably diagnosed [27], which is perhaps due to a slower uptake mechanism in soft tissues and also to a physiological excretion of ^{99m}Tc degraded particles after 4-h p.i..

To date only a few studies have evaluated ^{99m}Tc-nanocolloids clinically in patients with osteomyelitis [28–31]. The results indicate values similar to those of ^{111}In-labelled leucocytes, with sensitivity ranging from 87% to 95% and specificity between 77% and 100%. Consequently some authors have concluded that ^{111}In- and ^{99m}Tc-labelled leucocytes are equivalent [28]. Another study [32] calculated a sensitivity of 75% with ^{111}In-labelled leucocytes and 94% with ^{99m}Tc-nanocolloids and a specificity of 90% and 84%, respectively. Thus their diagnostic accuracy was 85% and 87%, respectively. In this study the authors also calculated the sensitivity and specificity when patients with "slightly increased activity" were regarded as being negative. This resulted in a specificity of almost 100%. This "manipulation" seems necessary because ^{99m}Tc-nanocolloids are able to leave the circulation wherever the permeability is increased, independendent of an infection or non-specific inflammation. The two subtypes of lesion cannot be separated, a fact that is true for most of the other imaging agents as well. However, the great advantage of these nanocolloids is rapid localization of an infectious process within 30–60 min, after which the study can be terminated.

^{99m}Tc-nanocolloids also work well in rheumatoid arthritis. In a recently published study [33] Liberatore et al. found that 79% of all actively inflamed joints had a positive scan with ^{99m}Tc-nanocolloids while 95% of all clinically negative joints had a negative scintigram. In their comparison of the ^{99m}Tc-nanocolloids with ^{99m}Tc-HIG they found that the results with both radiopharmaceuticals were in agreement with clinical examinations; only in the initial phase of the disease did ^{99m}Tc-HIG seem to have some advantages.

^{111}In-labelled autologous leucocytes

Physics. ^{67}Ga citrate, one of the oldest radiopharmaceuticals for imaging infection, has a poor target-to-background ratio, needs 48- or 72-h images, has bowel excretion and shows both infection and tumours. A much higher specificity has been demonstrated for ^{111}In-labelled autologous leucocytes [34, 35]. ^{111}In, with its physical half-life of 67 h and 173- and 247-keV photopeaks, allows delayed imaging within 24 h and relatively efficient imaging with conventional gamma cameras.

Biodistribution. The numbers of neutrophils that accumulate at sites of inflammation are extremely high: as many as 10% of the circulating neutrophils will accumulate in such sites each day [36].

Twenty-four hours after re-injection of ^{111}In oxine-labelled cells in dogs, 48.5% of the activity was found to be in the liver, 11% in the spleen, 7.9% in the lungs and 8.5% in the blood [37]. This biodistribution, which is quite similar to that in humans, suggests that the detection of splenic and liver but also lung abscesses may be difficult. However, there is no kidney, bladder or bowel excretion, so the whole abdomen is an excellent field for

localizing infectious or inflammatory diseases. Also, soft tissue infection in muscles can be easily seen.

Cell isolation and labelling. ^{111}In oxine, ^{111}In-tropolonate and ^{99m}Tc-HMPAO have one common property, their lipophilicity. Thus ^{111}In labels all cell types indiscriminately. For this reason, the leucocytes first must be separated from other blood cells before labelling. In addition subtypes of cells, such as lymphocytes and monocytes, can be separated and labelled. The labelling technique itself was first described by Thakur et al. [38] and later, with many modifications, by other authors [39, 40]. Instead of oxine, other lipophilic agents such as tropolonate [41] and acetylacetone [42] may be used. Especially tropolonate-labelled cells performed better at early imaging times than oxine-labelled cells, although the difference between the cell kinetics is not uniformly accepted [43].

Uptake mechanism and physiology. Neutrophils have a life cycle of 2 weeks [44]. Originating from stem cells in the bone marrow, mature neutrophils are released into the peripheral blood after 6–12 days. There they are distributed into two pools; about half of the cells are in the circulating pool and can be removed, while the other half are in the marginating pool, being temporarily sequestered in capillaries or adhering to the endothelium of larger vessels. The cells can move between the two pools after physical exercise, epinephrine administration and exposure to bacterial endotoxin. In all conditions the cells migrate from the marginating into the circulating pool [45, 46]. In inflammatory or infectious diseases the emigration of leucocytes via chemotactic stimulus occurs as early as 30–40 min after stimulation of the neutrophils.

Radiation effects. There are two primary sources of radiation to the leucocytes after ^{111}In-leucocyte labelling.The first is external radiation absorbed by the leucocytes during the labelling process itself when the cells are incubated. The second and more important source of radiation is internal, deriving from the ^{111}In that is incorporated in the cells. Most of the internally derived dose comes from low-energy Auger electrons (0.6–25.4 keV); these have a range much less than the cell diameter, so that the radiation burden is extremely high, up to 14.8 Gy [47]. Nonetheless, there is significant evidence that even in mixed-cell populations of leucocytes, labelled with 500 μCi of ^{111}In, the oncogenic risk to the patient is extremely low [48].

Clinical indications. First it has to be mentioned that while leucocyte scintigraphy is highly specific for leucocytic infiltration, which can be seen in many different disease entities [49], from infection to tumours, it is not specific for bacterial contamination. Despite the latter fact, ^{111}In-labelled leucocytes have a variety of potential indications due to the high specificity for leucocytic infiltration. Their accuracy has been tested in detail in patients with chronic inflammatory bowel disease [50–53] (Fig. 8) or other intestinal infections [54], osteomyelitis [55–57], prosthetic valvular heart disease [59–61], prosthetic vascular prostheses [58, 59], kidney diseases [62], lung infections [63, 64] and fever of unknown origin [65, 66].

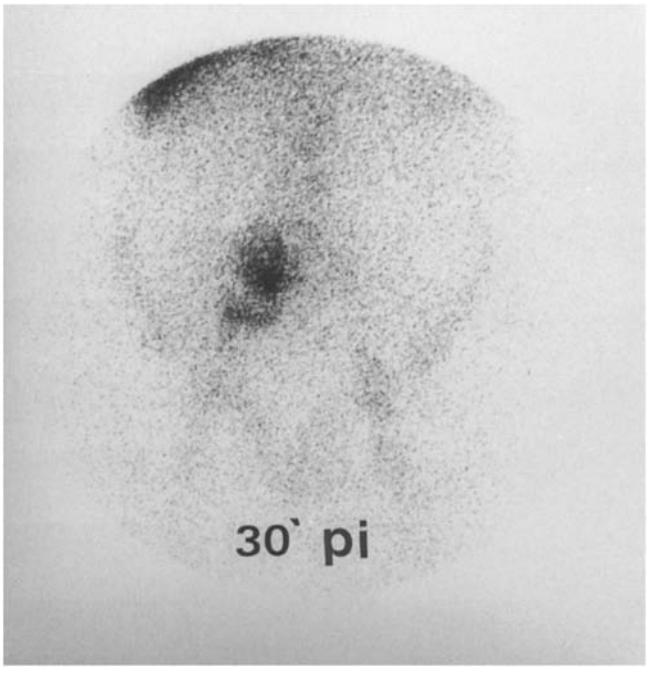

Fig. 8. ^{111}In-labelled granulocyte migration to a small abdominal abscess in a patient with Crohn's disease. As early as 30 min p.i. the leucocyte migration shows the focus

The physical characteristics of ^{111}In, with its medium energy, long physical half-life and high radiation burden to the patient, combined with its production in a cyclotron, causing limited availability, mean that the resolution achieved with gamma camera imaging is suboptimal and that ^{111}In is not favoured in clinical practice. Given that the possibility exists of labelling leucocytes with ^{99m}Tc-HMPAO, there are only a few indications for which the use of ^{111}In is mandatory. These indications derive from the physical biodistribution and excretion of ^{99m}Tc-HMPAO leucocytes, which prevent the diagnosis of infection in the kidneys, the bladder or small pelvis and the gallbladder and gut, where 4-h and 24-h images are necessary for the differentiation of segmental inflammation or abscess [38] due to the physical ^{99m}Tc excretion via these organs. In all the other indications mentioned above, ^{111}In-labelled granulocytes may be replaced by ^{99m}Tc-HMPAO leucocytes.

^{99m}Tc-HMPAO labelled leucocytes

Because of the cost, convenience, image resolution and dosimetry there has been a clear need for a ^{99m}Tc labelling procedure for leucocytes.

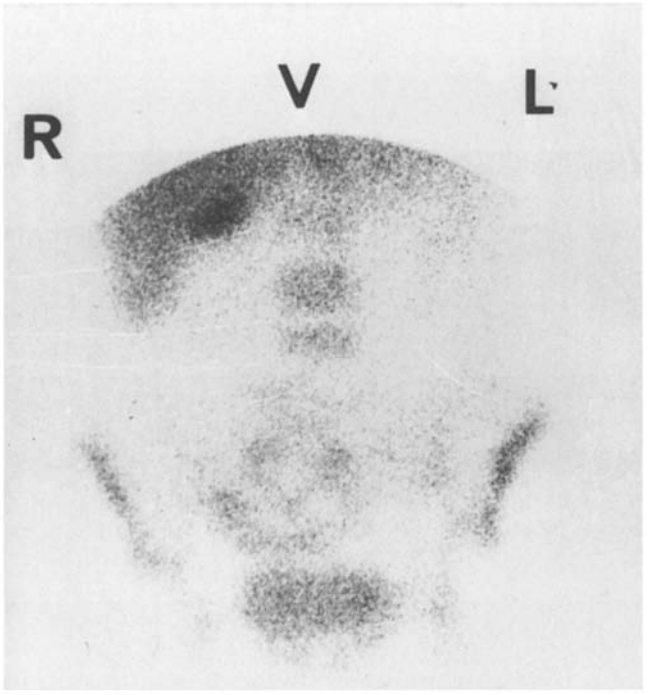

Fig. 9. ^{99m}Tc-HMPAO labelled granulocyte scan 4 h p.i. demonstrating physiological excretion of the tracer via the gallbladder into the small intestine. Diagnostic scans therefore must be performed between 2 and 3 h after re-injection of the labelled cells

Physics. The physics of ^{99m}Tc are well known. Its advantages are the energy of 140 keV, the physical half-life of 6 h, the availability in each nuclear medicine facility and the cost. The only reliable and reproducible method is the ^{99m}Tc-HMPAO labelling of leucocytes. The baseline mechanism of ^{99m}Tc-HMPAO labelling is the lipophilicity of HMPAO, which allows the ^{99m}Tc to enter the cells, which also have to be isolated before labelling.

Biodistribution and clinical indications. Whereas ^{111}In is highly stable in all labelled cell types, ^{99m}Tc-HMPAO is not. In vitro we measured an elution out of labelled leucocytes of up 7% of the label per hour [67]. As a consequence of this instability of ^{99m}Tc, bound secondary hydrophilic complexes of HMPAO are excreted via kidney and bladder starting several minutes after re-injection of the labelled cells. Gallbladder visualization starts between 2 and 3 h after re-injection and small bowel routinely can be seen 3 h after re-injection of the cells (Fig. 9). These excretion pathways define the indications for ^{99m}Tc-HMPAO, which are all kinds of infectious disease other than kidney, bladder and gallbladder infections, inflammatory bowel disease or abscesses with enteric communications, and the differential diagnosis between abscesses and segmental inflammation [67, 68]. Chronic inflammatory bowel disease can already be seen 30 min after re-injection of the cells. Thus the localization of diseased segments can be performed before physiological excretion starts [67].

Several reports document the superiority of ^{99m}Tc over ^{111}In in the management of inflammatory bowel disease [69, 70]. This is because of its superior ability to localize disease to specific bowel segments and its ability to identify small bowel disease reliably. The role of labelled white blood cells in chronic inflammatory bowel disease is the localization of diseased bowel segments in highly acute disease with the danger of perforation during endoscopy and in chronic disease with stenosis where endoscopy cannot pass the stenosis to localize the total number of diseased segments.

The use of ^{99m}Tc-HMPAO labelled cells is also indicated today for the diagnosis of complications such as fistulas and of abscesses, but only ^{111}In-labelled cells are useful for the quantification of disease activity [71]. In the author's experience the sensitivity of^{99m}Tc-HMPAO labelled leucocytes in patients with osteomyelitis is comparable to that of ^{111}In-labelled leucocytes. Despite its higher resolution, ^{99m}Tc-HMPAO seems not to be more accurate because more often imaging of chronic osteomyelitis is necessary, where late scans are required due to the limited granulocyte turnover. In addition the problem of vertebral osteomyelitis with its usually reduced uptake of cells cannot be solved with ^{99m}Tc-HMPAO labelled leucocytes. Why infection in the vertebrae should be more difficult to confirm with labelled leucocytes and antibodies than infection in other areas of the axial skeleton with comparable bone marrow has not been satisfactorily explained. One may hypothesize that the high pressure in one infected vertebra prevents the granulocyte uptake or that the "coldness" of a vertebra is only relative due to the physiological bone marrow in the neighbouring vertebral bodies.

Labelled leucocyte scanning has a relatively minor role in the management of patients with intrathoracic disease. Some reports indicate labelled leucocytes to be of use in patients with bronchiectatic lobes before surgery [72, 73] and in patients with vasculitis [74].

In patients with fever of unknown origin examination with ^{111}In-labelled leucocytes is probably preferable because of the greater stability in both circulating cells and targeted disease and because of the longer physical half-life. However, this remains to be proven clinically.

^{99m}Tc-labelled antigranulocyte antibodies

The advantage of immunoscintigraphy over autologous leucocyte techniques in the imaging of infection is the simplicity of its use compared with techniques that require the isolation of autologous white blood cells.

Biodistribution and uptake mechanism. The widely available ^{99m}Tc-labelled antigranulocyte antibodies are directed against the non-specific cross-reacting antigen 95 (NCA-95). The use of such an antibody against granulocytes was first reported by Locher et al. [75] with a ^{123}I-NCA-95 immunoglobulin (IgG1); shortly thereaf-

ter, Joseph et al. [76] reported use of a ^{99m}Tc-labelled anti-NCA-95 antibody, which is now the most widely used antibody. Recently, the use of a ^{99m}Tc-labelled anti-NCA-90 Fab′ fragment was reported by Becker et al. [77], but this promising fragment is not yet routinely available. The antibody targeted epitope is expressed in humans only on granulocytes, promyelocytes and myelocytes. The affinity constant of the ^{99m}Tc-antigranulocyte antibody (IgG1) BW 250/183 was calculated to be 2×10^9 *M*. Despite this strong binding capacity, BW 250/183 does not significantly influence granulocyte-mediated functions [78]. Approximately 10%–20% of the radiolabelled injected whole antibody is bound to circulating granulocytes that are functionally normal and may target an infectious area. About 19% of the injected antibody circulates as free immunoglobulin and has the same potential as labelled non-specific human IgG [78]. This often gives rise to problems in routine clinical practice, when inflammatory lesions, due to their increased capillary permeability, are imaged as well, and reliable differentiation of inflammatory non-specific and granulocyte-associated specific uptake in a lesion is not possible.

The current hypothesis on the uptake mechanism of radiolabelled monoclonal antigranulocyte whole antibody can be summarized as follows: (a) migration of antibody-labelled circulating granulocytes to the focus due to their undisturbed chemotactic behaviour and (b) non-specific, non-antigen-related uptake of free antibody due to an increased capillary permeability at the focus, with subsequent binding to granulocytes. The resulting image quality with high target-to-background ratios is due to the specific binding of high amounts of the injected antibodies to epitopes in bone marrow and spleen and the consequent low background activity. This rapid endogenous background subtraction allows the detection of small lesions with excellent image quality [78]. This low background activity is due to the very rapid binding of the antibody to the bone marrow 55% (4 h), the liver 10% (4 h) and the spleen (6%) [78].

Clinical indications. In bone infection the sensitivity of antigranulocyte antibody scintigraphy in 106 patients was calculated to be 69% for the hips, 79% for the thigh, 85% for the knees and 100% for the lower leg and ankle [20] (Fig. 10). The sensitivity decreased from the periphery of the bone to the central parts. This may be due to the physiological uptake of the antibody in the bone marrow-containing parts of the bone, where the normal uptake of the antibody does not allow normal bone marrow to be distinguished from small infectious foci. Other hypotheses discuss increased pressure in the vertebral bodies in cases of infection, which prevents labelled white cells or antibodies from penetrating.

False-positive uptake can be seen in haematomas, contusions and aseptic inflammation. Using ^{99m}Tc-BW250/183 scintigraphy in chronic inflammatory bowel disease, 49% of segments could be detected at 2 h p.i.,

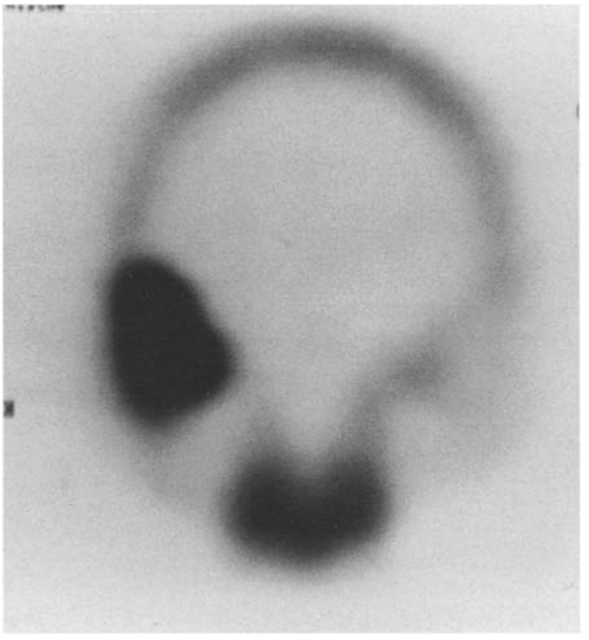

Fig. 10. SPET of the head after injection of ^{99m}Tc-labelled antigranulocyte antibodies in a patient with osteomyelitis of the skull after tumour surgery and external beam radiation

55% at 5 h p.i. and 91% at 20 h p.i. [79]. In another prospective study of CIBD, Segarra et al. [80] found sensitivity, specificity and accuracy to be 61%, 100% and 78% respectively at 4 h and 79%, 92% and 78% respectively at 24 h p.i.. It should be mentioned that there is no transport of the activity through the bowel wall, as is known from the use of ^{111}In-labelled white blood cells. The activity increases in the bowel wall over the 24 h following injection. This may be due to an antibody Fc-part interaction with Fc receptors on granulocytes within the bowel wall [78] (Figs. 11, 12).

In vascular graft infection, nuclear medicine procedures are used to determine the complete extent of the infection following its clinical diagnosis. Immunoscintigraphy with specific antigranulocyte antibodies offers the best means for the localization of vascular graft infections due to the rapid endogenous background subtraction and low vascular activity. The sensitivity is reported to be 94% and the specificity 85% [81]. False-positive results have been observed in perivascular haematoma, especially in late 24-h images; such findings have to be excluded by ultrasonography and computed tomography.

In prosthetic vascular heart disease the combination of immunoscintigraphy with SPET and echocardiography localizes subacute infective endocarditis with a high sensitivity [82].

Use of immunoscintigraphy with antigranulocyte antibodies has not yet been examined systematically in patients with pneumonia or other infective lung diseases. We found that lung abscesses can be detected well; however, we were not able to detect pneumonia. Our findings concur well with another report on false-negative

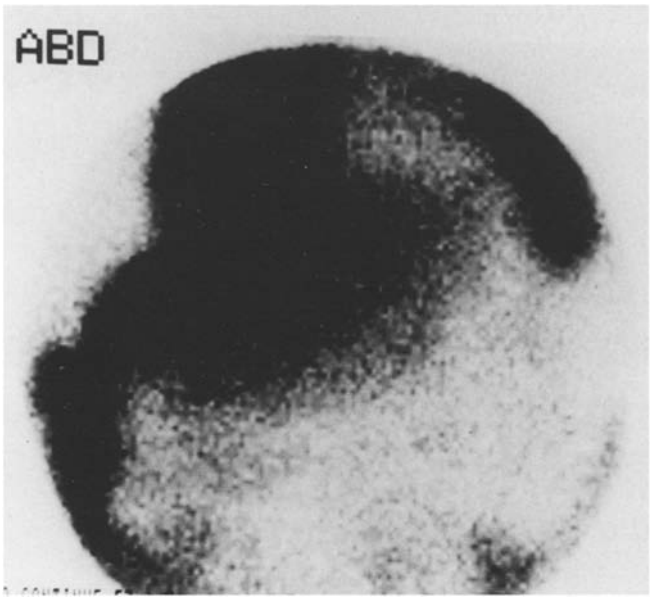

Fig. 11. ^{99m}Tc-labelled antigranulocyte antibody scan (1 h p.i.) in a patient after colorectal cancer surgery and left hemihepatectomy with septic peritonitis (*left upper quadrant of the image*: right lobe of the liver; *right upper quadrant of the image*: spleen)

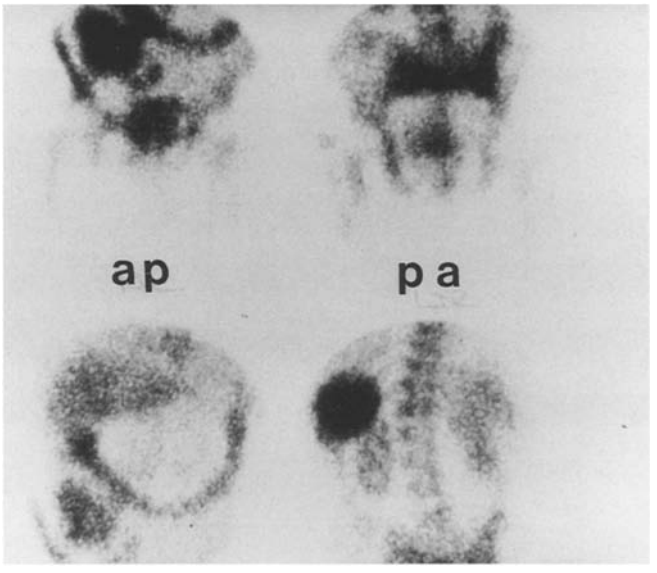

Fig. 12. ^{99m}Tc-labelled antigranulocyte antibody scan 24 h p.i. in a patient with pseudomembranous colitis

scans in lung abscesses [83]. Similar findings in AIDS patients demonstrate that extra-abdominal infections can be excluded or shown, whereas opportunistic pneumonia is never shown [84].

In general ^{99m}Tc-labelled antibodies are well accepted due to their easy handling and high sensitivity in identifying a focus in the body. However, the scans need careful interpretation in patients in whom the surgeon requires differentiation between postsurgical inflammation and infection, because both situations yield a signal (Fig. 13). Although the antibodies are widely accepted in routine clinical diagnosis (Fig. 14), they produce human antimouse antibodies (HAMAs). The production of such antibodies seems to be dose dependent, the frequency ranging from more than 30% in patients receiving repeated injections down to 4.5% in patients with a fixed dose of 125 µg of the antibody. Consequently we recommend that not more than 250 µg of the antibody be used in order to ensure a low HAMA response rate [78].

^{111}In-labelled human non-specific immunoglobulin

In comparison to the before mentioned murine antibodies HIG preparations have the advantage of absence of a HAMA response. As a spin-off of research on monoclonal antibodies specific for unique antigens on *Pseudomonas aeruginosa* bacteria, Rubin et al. [85] discovered serendipitously that human non-specific polyclonal immunoglobulin G (IgG) in their rat model of infection provided results similar to those for a specific monoclonal antibody. Although there are differences between radiolabelled monoclonal antibodies and polyclonal IgG in terms of origin (murine or human), specificity, dynamic biodistribution, mechanism of action etc., there are also many similarities between these radioimmunoconjugates as agents for detecting infection and inflammation [86].

Biodistribution and uptake mechanism. Although the mechanism for accumulation of ^{111}In-IgG, the first labelled immunoglobulin, in inflammatory and infectious foci may not be completely understood, it is obviously related to increased vascular permeability into an expanded extracellular fluid space and to the chemical nature of the radiolabel [87]. It has been shown that ^{111}In dissociates from IgG in the focus and can be retained, whereas the IgG leaves the abscess [88]. This release of indium from ^{111}In-diethylene triamine penta-acetic acid provides an explanation for the high ratio between the concentrations of ^{111}In-HIG in the interstitial fluid space of normal muscle and in plasma [89] and for the high sensitivity of the method especially in the late 48-h scans, when the immunoglobulin in circulation has decreased but the focal ^{111}In uptake is still high.

Physiological uptake of ^{111}In-IgG is observed in liver (17%), spleen (2%) and kidney (6%). Bone marrow uptake is approximately 6% of the injected dose [8]. ^{111}In-IgG clears from the blood pool with a $T_{½}$ alpha of approximately 13 h and a $T_{½}$ beta of approximately 72 h.

Clinical indications. ^{111}In-IgG accumulates in various types of pulmonary infection [87]. Most data are available in immunocompromised patients, where ^{111}In-IgG scintigraphy has proved useful in delineating *Pneumocystis carinii* penumonia (PCP) [90–92]. High sensitivity has also been reported in abdominal infection and inflammation [85].

The majority of patients undergo ^{111}In-IgG scintigraphy for suspected bone an joint infection. The sensitivity and specificity of the method were found to be excellent

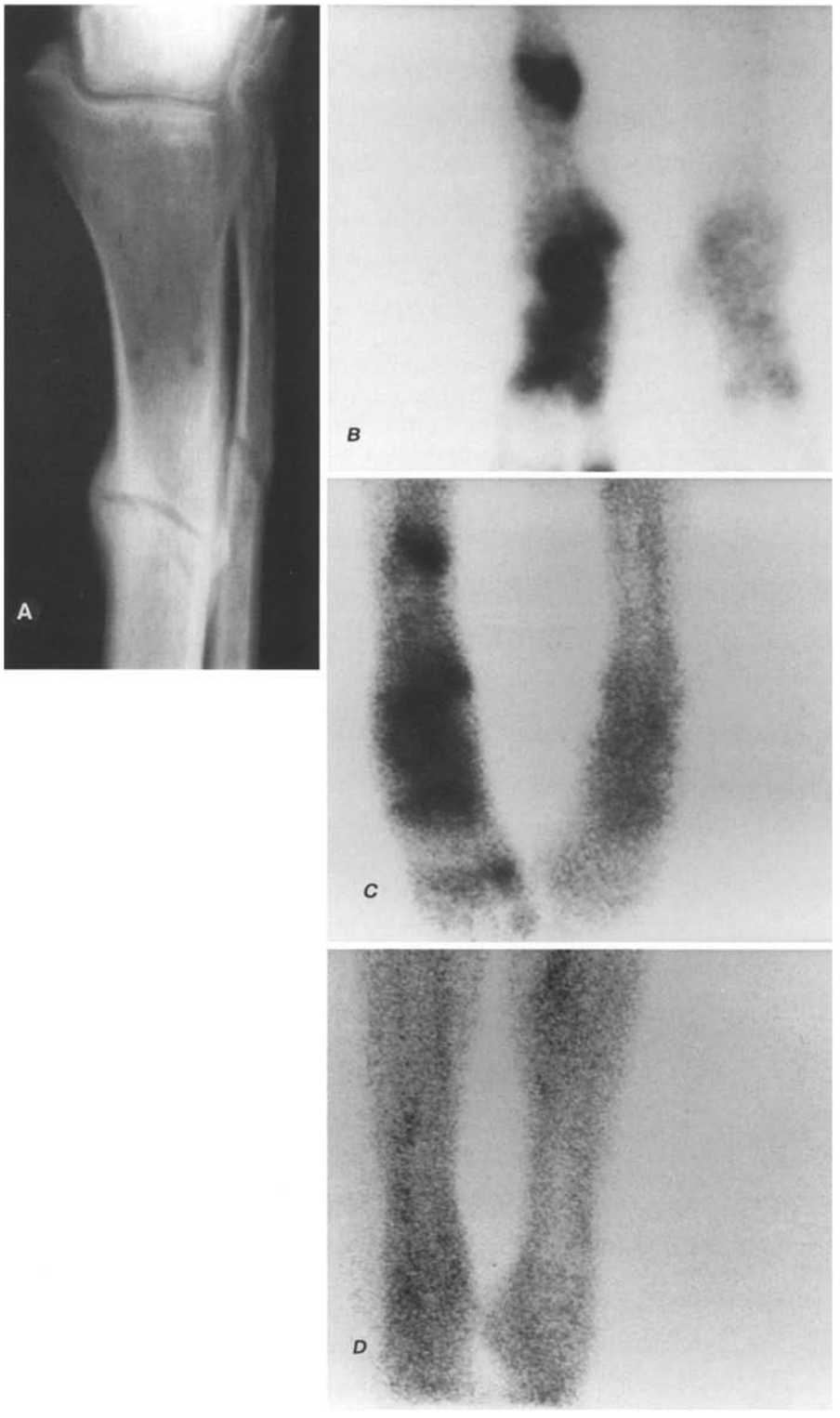

Fig. 13a–d. Twenty-three year old patient after tibial fracture. One year after primary surgery and metal removal he still suffered from pain and swelling. Planar X-ray shows the fracture with the diagnosis of pseudoarthrosis, but osteomyelitis could not be excluded (**a**). Bone scintigraphy demonstrated increased mineralization in the old fracture and the foot (**b**). ^{99m}Tc-antigranulocyte antibody scan demonstrated nearly comparable information with the suspicion of infection (**c**). ^{99m}Tc-HMPAO white blood cell scan was completely negative (**d**). Surgery excluded infection 5 days later

in a patient population of more than 100 [93]. Low-grade *Staphylococcus aureus* infection was missed in only two patients. However, ^{111}In-IgG accumulates both in infection and in sterile inflammatory processes such as haematomas, synovitis and recent fractures and is not able to distinguish the two situations. Of special interest are results in patients with suspected infected joint arthroplasty. The reported sensitivity and specificity for infection are 93% and 88% respectively, while for inflammation both are 100% [94, 95]. ^{111}In-HIG was also helpful in ruling out or confirming diabetic pedal osteomyelitis. In vascular graft infection studies showed a sensitivity of 92% and a specificity of 100% [85].

The major indication for scintigraphic delineation of infectious foci is fever of unknown origin. Although infection or inflammation is established as the cause of fe-

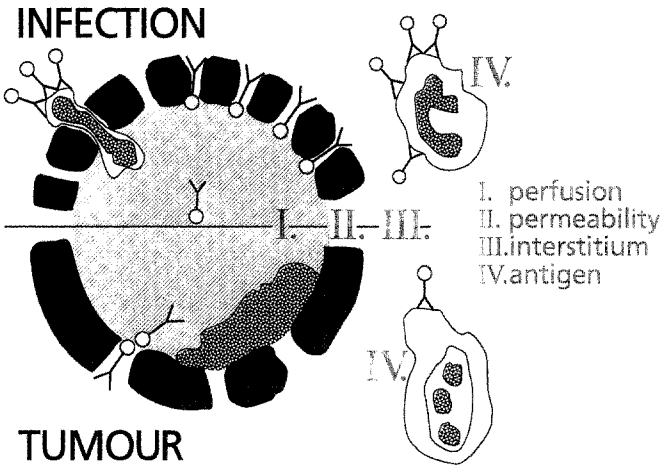

Fig. 14. Different antibody behaviour in tumour and in infection. In tumours the perfusion may be restricted: tumour thrombosis and high interstitial pressure may prevent antibody access to the target. In inflammation increased perfusion always occurs, capillary permeability is increased and the focus (granulocytes) may be easily targeted

ver in only a minority of patients, scintigraphic delineation of a possible infectious focus is considered for most of the patients. Proven inflammatory processes were missed in only one patient with endocarditis and infection of a renal cyst. This method is also helpful in febrile granulocytopenic patients, in whom it may be difficult to isolate enough leucocytes for labelling.

Currently the chief problem with ^{111}In-HIG is that it is not commercially available and cannot be used in every nuclear medicine unit.

^{99m}Tc-labelled human non-specific immunoglobulin

^{99m}Tc-HIG is widely available. Due to the 6-h half-life, images can be obtained at 24 h but not at 48 h.

Biodistribution and uptake mechanism. In vitro and animal studies have provided some evidence for binding of ^{99m}Tc-IgG to bacteria as a mechanism for scintigraphic detection of infectious foci [97]. However, it is difficult to understand how this can play a significant role at sites of infection because ^{99m}Tc-IgG also accumulates in sterile inflammation. Consequently, the uptake mechanism is probably the same as for ^{111}In-HIG. However, there seems to be retention of ^{99m}Tc in the foci because in a rat model of acute infection there was initial good uptake in the infected area followed by a gradual decrease in ^{99m}Tc uptake after 6 h [97].

The whole-body distribution of ^{99m}Tc-HIG at 4 h p.i. shows 57.7% of the injected activity. The rest has been excreted via the kidneys. Lung uptake is still 7.3%, liver uptake 5.1%, splenic uptake 1.3%, kidney uptake 6.5%, estimated bone marrow uptake 22.1%, and gonadal uptake 1% [98]. At 24 h there is still 12.7% of the whole-body activity in the lungs, which is mainly due to the blood pool activity.

Clinical indications. Twenty-five patients with HIV were studied with both ^{67}Ga citrate and ^{99m}Tc-IgG; poor sensitivity of the latter agent was seen in the chest [99], which could be best explained by the high physiological blood pool activity in the lungs. However, the combination of ^{67}Ga citrate and ^{99m}Tc-HIG appeared helpful in differentiating between lymphoma and infection in HIV-positive patients with fever of unknown origin.

In the assessment of the presence or absence of inflammation, a sensitivity of 80% and a specificity of 87% were noted. However, when the extent of intestinal inflammation was evaluated, ^{99m}Tc-HIG appeared to perform poorly, indicating that the technique is of little value in the assessment of patients with proven chronic inflammatory bowel disease. This was intensively studied by Spinelli et al. [100].

In patients with suspected osteomyelitis the performance ^{99m}Tc-HIG and ^{99m}Tc-BW 250/183 was compared with the final diagnosis established by surgery, histology and bacteriology [101]. In peripherally located osteomyelitis, both agents showed similar and good results. However, in centrally localized osteomyelitis the performance of the two agents was very different because injection of the labelled polyclonal IgG resulted in "hot" lesions, whereas the administration of the monoclonal antibody showed "cold" lesions.

The use of ^{99m}Tc-HIG for imaging arthritis was first studied in an animal model, which showed that the localization and severity of inflammatory joint diseases can be detected with non-specific IgG [102–105]. A lot of clinical studies have demonstrated that ^{99m}Tc-HIG is able to distinguish between joints with and joints without active inflammation in chronic rheumatoid arthritis [106], to monitor therapeutic success, to demonstrate septic complications and to localize other joint infections and inflammation.

Summary and recommendation

Several radionuclides are available for imaging infection. They differ in terms of their physical characteristics, their biodistribution, their need for cell isolation and their radiation exposure. Based on all the data in the literature regarding all of the advantages and disadvantages of the commercially (i.e. widely) available radiopharmaceuticals, Table 4 shows the author's conclusions as to appropriate indications for the large variety of available radiopharmaceuticals.

Future prospects

Recently the results obtained using ^{99m}Tc-Fab′ fragments in patients with osteomyelitis have been published [107]. The authors compared the diagnostic accuracy with the accuracy of white blood cell imaging and found a sensitivity, specificity and diagnostic accuracy of 88%,

Table 4. Indications for the use of different radiopharmaceuticals in patients with infection and inflammation

Indication	Proposed radiopharmaceutical
Fever of unknown origin	^{67}Ga citrate
Osteomyelitis peripheral bone	^{99m}Tc-nanocolloids ^{99m}Tc-labelled granulocyte antibodies ^{99m}Tc-labelled white blood cells
Spine	^{67}Ga citrate ^{99m}Tc/^{111}In-HIG
Lung infection	^{67}Ga citrate
Heart valve endocarditis	^{99m}Tc-labelled white blood cells ^{99m}Tc-labelled granulocyte antibodies
Vascular prosthetic infection	^{99m}Tc-labelled white blood cells ^{99m}Tc-labelled granulocyte antibodies
Abdominal infection/ inflammation	^{99m}Tc-labelled white blood cells ^{99m}Tc-granulocyte antibodies
Assessment of disease activity in CIBD	^{111}In-labelled white blood cells
Differentiation of inflamed segments from complicating abscess in CIBD	^{111}In-labelled white blood cells
Kidney infection/transplant infection	^{111}In-labelled white blood cells

CIBD, Chronic inflammatory bowel disease

75% and 80% for the fragment and 86%, 78% and 81% for the white blood cell imaging. The new technique was much easier because it employs a one-vial labelling kit which is ready to use 5 min after techetium labelling. It showed the same diagnostic accuracy, but all the clinical information was already provided by the scans obtained 1 h p.i.. Another advantage over other antibodies was the negligible HAMA response rate. However, as yet this new technique is not routinely available.

None of the discussed methods is able to answer the surgeon's most important question in a patient who has clinical signs of inflammation or infection after surgery – namely whether such signs are indicative of infection or merely inflammation. While inflammation requires only conservative treatment, infection needs further surgical intervention. Nevertheless, the currently available methods do allow some opportunities for differentiation, e.g. if the uptake of a radiopharmaceutical around a knee prosthesis is intensive but homogeneous, it is probably indicative of inflammation while if it is more focal it is likely to represent infection. As a general rule, good interpretation of scans is feasible when they are considered in conjunction will all the available anamnestic and clinical data.

Certain specific steps that have been taken towards the detection of bacterial contamination are worthy of mention. Goldenberg et al. [2] injected ^{99m}Tc-Fab′ fragments directed against *Pneumocystis carinii* and were able to identify patients infected with the microorganism with a sensitivity of 85.7% and a specificity of 86.7%. It is therefore possible that rapid diagnosis and localization of other infectious lesions may be feasible using organism-specific, radiolabelled monoclonal antibodies. Another approach is the use of labelled antibiotics, which can be specifically metabolized by different microorganisms. The best method is the use of a broad-spectrum antibiotic, as has been achieved with the ^{99m}Tc labelling of a quinolone called "infection" by Bomanji et al. [3]. These authors found that imaging of infection was possible, but, more interestingly, scans turned positive before white cell scanning showed any uptake. This may represent a good approach for differential diagnosis of infection and inflammation.

Nuclear medicine, with its different approaches, images pathophysiology and pathobiochemistry. The available new techniques, especially within immunology and molecular biology, are yielding new insights into the cascade of infection and inflammation. We now understand that via cytokines, especially interleukins, endothelial cells become activated after a chemotactic signal and granulocytes are able to interfere with the expressed molecules, such as E-selectin, before they leave the circulation. The use of ^{111}In-labelled anti-E-selectin fragments is an exciting new method for imaging the expression of E-selectin and to have an epitope on the vascular surface, which allows specific images to be acquired without the need for an antibody to pass the vessel wall [111]. However, the labelling of interleukin-1 and interleukin-2 is also possible and provides specific signals from infectious and autoimmune diseases [108–110].

The value of these new techniques is the possibility of using peptides in infection. A major problem in the imaging of infection is the fact that nearly every radiopharmaceutical works, because the increased capillary permeability allows radiopharmaceuticals to emigrate from the circulation. For most techniques this yields a high sensitivity but no useful specificity. Small peptides also leave the circulation rapidly, but it they do not specifically bind to their receptor at the focus they may leave the focus within a given time. The rapid targeting together with rapid clearance from the focus promise to yield high sensitivity and, more importantly, high specificity in the detection of infection. Since the first report of the chemoattractant properties of small N-formyl peptides [112], these compounds have attracted increasing attention [113]. The results of Fischman et al. [114] demonstrate the localization of radiolabelled chemotactic peptide analogs at focal sites of infection in experimental models of deep-thigh infection at sufficient concentrations to permit external imaging soon after intravenous administration. Further improvements of such peptide analogs are, however, required before they can be administered to humans. Future aims for peptide imaging of infection are labelling of a small fraction of the available receptor with a high concentration of radioactivity labelling of the peptide with ^{99m}Tc and achieve-

ment of a reduced biological activity, e.g. with antagonists or partial agonists [114].

The localization and anatomical delineation of occult sites of infection are frequently important steps in the therapeutic management of critically ill patients. Current imaging procedures, such as x-ray computed tomography, ultrasonography, conventional radiography and magnetic resonance imaging rely primarily on focal changes in tissue density or composition to define lesions. When an inflammatory process has progressed to tissue necrosis and abscess formation, these modalities can localize the area of involvement. However, early in the course of this process, when the tissue changes associated with necrosis have not yet occurred, lesion localization may be extremely difficult. This is particularly true if normal anatomical landmarks have been obscured by previous surgery or disease. The implantation of prosthetic materials also sometimes prevents radiological access and thereby hinders diagnosis. Against this background, and given the available radiopharmaceuticals and future possibilities, one may conclude that nuclear medicine will indeed make an important contribution to the management of the patient with infection.

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