

# Rapid Differential Diagnosis of Cerebral Toxoplasmosis and Primary Central Nervous System Lymphoma by Thallium-201 SPECT

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This study sought to assess whether  $^{201}\text{Tl}$  brain SPECT can significantly reduce the time required for the differential diagnosis of primary central nervous system (CNS) lymphoma and cerebral toxoplasmosis in patients with AIDS. **Methods:** Eighteen patients who presented with focal lesions on CT or MRI, or both, underwent  $^{201}\text{Tl}$  brain SPECT shortly after admission and before a CT-guided stereotactic brain biopsy. Early and delayed  $^{201}\text{Tl}$  uptake ratios were obtained for patients with positive  $^{201}\text{Tl}$  study results, and the retention index of  $^{201}\text{Tl}$  was calculated. **Results:** Ten patients had 11 foci of significantly increased  $^{201}\text{Tl}$  uptake in regions of corresponding CT/MRI lesions. Five of these patients had biopsy-proven lymphomas, one of them in two separate foci. Another patient was found to have metastatic adenocarcinoma. Three patients had a clinical course and response to radiation therapy consistent with lymphoma, and study results in another patient were considered falsely positive. Of nine patients with no  $^{201}\text{Tl}$  uptake in regions of CT/MRI lesions, two had biopsy findings consistent with a benign etiology, and the other seven improved clinically on antitoxoplasmosis medications alone. The overall sensitivity of  $^{201}\text{Tl}$  brain SPECT was 100%, and specificity was 90%. The  $^{201}\text{Tl}$  retention index in patients with lymphomas was significantly higher than that in patients with adenocarcinomas and nonmalignant lesions ( $1.35 \pm 0.16$  versus 0.24 and 0.56, respectively). **Conclusion:** Thallium-201 brain SPECT is a sensitive and specific method for rapid differential diagnosis of CNS lymphoma and toxoplasmosis in patients with AIDS. The  $^{201}\text{Tl}$  retention index is useful in differentiating CNS lymphomas from other malignant and nonmalignant pathologies.

**Key Words:** acquired immunodeficiency syndrome; central nervous system lymphoma; toxoplasmosis; thallium-201; retention index

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Cerebral toxoplasmosis, the most common central nervous system (CNS) complication in patients with AIDS, affects 3%–40% of such patients in the United States (1) and is the cause of CNS mass lesions in 50%–70% of these patients (2,3). Although primary CNS lymphoma is rare in patients without AIDS, it occurs in 2%–6% of those with AIDS (4). Patients with cerebral toxoplasmosis and CNS lymphoma present clinically and neuroradiologically in a similar manner (2,5). Definitive diagnosis is made histologically. However, because of the reluctance to perform brain biopsies, empiric antitoxoplasmosis therapy is usually instituted for a period of 7–14 days, resulting in an unnecessary delay in diagnosis and treatment.

The present preliminary study sought to determine whether  $^{201}\text{Tl}$  brain SPECT can discriminate CNS toxoplasmosis from primary CNS lymphoma as a cause of mass lesions in the brain in less than 72 hr. The characteristic wash out pattern of  $^{201}\text{Tl}$

from primary brain lymphomas in patients with AIDS was also analyzed.

## MATERIALS AND METHODS

### Patients

We studied 18 patients (9 men, 9 women; 29–53 yr old, mean age 39 yr) requiring a differential diagnosis for cerebral toxoplasmosis and primary CNS lymphoma. All patients had focal intracranial mass lesions seen on CT or MRI, or both. The clinical presentation varied from nonfocal symptoms of confusion and agitation to focal seizures, hemiparesis and hemiplegia. The serum of all patients was tested for antitoxoplasmosis immunoglobulin (Ig) G antibodies, and results were reported as either positive or negative because measurement of the actual titers is unreliable in patients with AIDS (6).

In most patients, a  $^{201}\text{Tl}$  scan was obtained within 48–72 hr of initial diagnosis of a focal lesion on the CT/MRI studies. The final diagnosis was based on biopsy results or clinical improvement after therapy. All patients were receiving steroid therapy at the time of the  $^{201}\text{Tl}$  scan (range 2–6 days).

Brain SPECT was performed 10 min after intravenous injection of 4 mCi (148 MBq) of  $^{201}\text{Tl}$ . In seven patients, delayed  $^{201}\text{Tl}$  SPECT was also performed at 3 hr after injection. Sixty-four projections of 40 sec each were acquired using a low-energy, high-resolution, parallel-hole collimator in a dual-head gamma camera. The images were prefiltered using a Butterworth filter (cutoff frequency 0.15 cycles/cm; power factor 5). Transaxial, coronal and sagittal slices 1 pixel thick (3.5 mm) were reconstructed and displayed on a  $128 \times 128$  matrix.

All SPECT studies were interpreted by a consensus of two experienced nuclear medicine physicians (ML, JM) using the CT/MRI images for anatomic correlation. Study results were interpreted as consistent with a viable tumor if the uptake in the region of the CT/MRI abnormalities was clearly greater than that in the corresponding region of the unaffected hemisphere.

For quantitative analysis, the transaxial image in which the lesion showed the greatest activity was selected, and a region of interest (ROI) was drawn around the lesion. A similar ROI was drawn in the contralateral brain. The average number of counts per pixel was determined for each ROI. The ratio of the average number of counts per pixel in the lesion to the average number of counts per pixel in the normal brain (uptake ratio) was obtained for all patients with positive study results. Special care was taken to avoid the normally high  $^{201}\text{Tl}$  activity in the scalp and at the base of the brain. In the seven patients with delayed  $^{201}\text{Tl}$  SPECT, the retention index was calculated as the delayed uptake ratio over the early uptake ratio (7).

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**TABLE 1**  
Summary of Patients with AIDS with Thallium-201 Brain SPECT Studies

Patient no.	Age (yr)	Sex	No. of lesions	Location* Lesion	Enhancement	Toxo AB	Uptake			Histopathologic findings	Clinical follow-up
							EUR	DUR	RI		
1	38	F	1	R thalamus	Solid	+	1.94	2.96	1.52	Lymphoma	Refused further RT, expired
2	36	M	2	L frontal L parietal	Thick Ring	+	30.6 5.2	38.4 6.7	1.25 1.29	Lymphoma, lymphoma	Improved with RT
3	48	F	2	R frontal R occipital	Ring	-	5.28 na	6.21 na	1.18 na	Lymphoma, gliosis	Improved with RT
4	46	M	2	R temporal	Solid	+	2.07	3.06	1.48	None	No RT, expired
5	45	F	1	L basal ganglia	Semisolid	+	4.46	2.50	0.56	None	Improved with antitoxoplasmosis therapy
6	51	M	1	L parietal	Irregular	+	11.95	2.93	0.24	Adenocarcinoma	Steroids and RT
7	38	M	1	R cerebellum	Ring	-	2.00	2.52	1.26	Lymphoma	Improved with RT
8	43	F	1	L corpus callosum	Thick, ring	-	4.27	∅	∅	None	Improved with RT
9	36	F	2	L basal ganglia	Irregular	-	8.27	∅	∅	Lymphoma	Expired
10	53	M	3	L thalamus, corpus callosum	Ring	+	2.16	∅	∅	Peripheral lymphoma	Improved with RT and antitoxoplasmosis therapy
11	33	F	1	L frontal	Ring	+	na	na	na	None	Improved with antitoxoplasmosis therapy
12	31	M	3	L temporoparietal, thalamus	Ring	+	na	na	na	Toxoplasmosis	Improved with antitoxoplasmosis therapy
13	41	F	1	R parietal	None	-	na	na	na	Cryptococcus	Responded to amphotericin therapy
14	31	F	6	L frontal, R parietal, occipital	Ring	-	na	na	na	None	Improved with antitoxoplasmosis therapy
15	36	M	3	Basal ganglia, R temporal	Ring	+	na	na	na	None	Improved with antitoxoplasmosis therapy
16	29	F	8	L frontoparietal, cerebellum	Ring	+	na	na	na	None	Improved with antitoxoplasmosis therapy
17	41	M	1	L frontal	Ring	-	na	na	na	None	Improved with antitoxoplasmosis therapy
18	34	M	5	Cerebellum, basal ganglia	Ring	+	na	na	na	None	Improved with antitoxoplasmosis therapy

Toxo AB = antitoxoplasmosis antibodies; EUR = early uptake ratio; DUR = delayed uptake ratio; RI = retention index of <sup>201</sup>Tl; R = right; + = present; RT = radiotherapy; L = left; - = not present; na = not applicable.

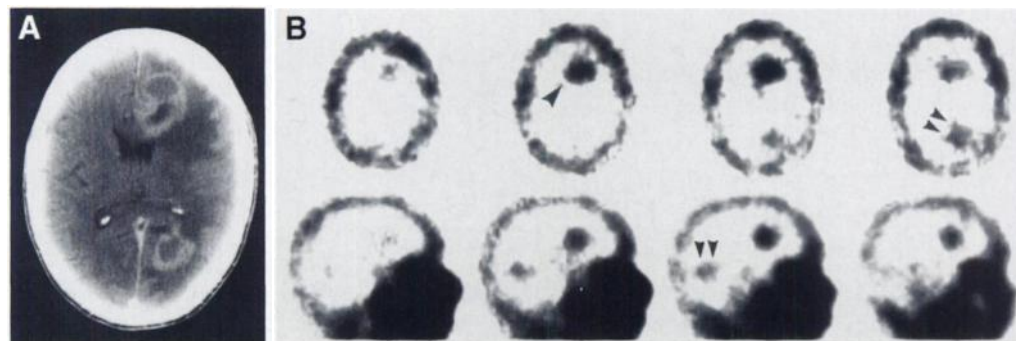
### Statistics

For statistical analysis, a one-tailed Mann-Whitney U-test was used.

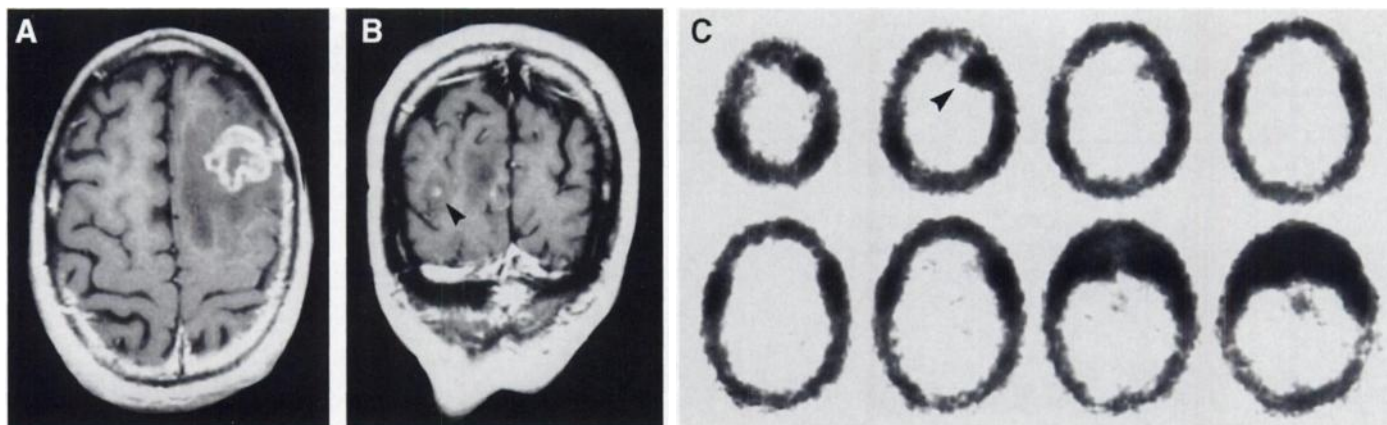
### RESULTS

The number of CT/MRI lesions in each patient varied from one to eight, although the majority (eight patients) had a single lesion (mean lesion size, 1.8 cm, range 2 mm to 4.8 cm). Most patients had ring enhancing lesions with brain edema and, sometimes, mass effect, but some lesions showed dense homogeneous or irregular enhancement. One patient with *Cryptococcus meningitis* had a large, nonenhancing hypodense lesion.

Ten patients had 11 foci of significantly increased <sup>201</sup>Tl uptake in regions of corresponding CT lesions (Table 1). Five of these patients had biopsy-proven diffuse large-cell lymphoma, which was present in two separate foci in one patient (Fig. 1). Another patient was found to have metastatic adenocarcinoma. Two patients had radiation therapy without a biopsy on the basis of the <sup>201</sup>Tl results and CT/MRI images and improved clinically. One of these two patients also received antitoxoplasmosis therapy at the same time. He had a previously diagnosed peripheral, non-Hodgkin's lymphoma in a cervical lymph node. He was taking trimethoprim-sulfamethoxazole for *Pneumocystis carinii* prophylaxis, which also greatly decreases the risk of developing CNS toxoplasmosis (8). One patient did not respond



**FIGURE 1.** Transaxial contrast CT scan shows two ring-enhancing lesions in the left frontal and left occipital lobes (A). Transaxial and sagittal slices from the SPECT scan, 1 pixel thick (B), show abnormal uptake of <sup>201</sup>Tl in both lesions (single arrowheads, left frontal; double arrowheads, left occipital), confirmed to be lymphoma.



**FIGURE 2.** Transaxial (A) and coronal (B) contrast T1-weighted MRI scans show an irregular enhancing lesion in the left frontal lobe with surrounding edema and a smaller enhancing lesion in the right occipital lobe (arrowhead). The  $^{201}\text{Tl}$  scan (C) shows abnormal uptake only in the left frontal lesion (arrowhead), proven to be lymphoma, and no uptake in the right occipital lesion, histologically confirmed brain gliosis.

to antitoxoplasmosis medications and died shortly after diagnosis. Another patient improved with antitoxoplasmosis medications and steroids alone and remains neurologically stable at 6 mo; results were considered falsely positive in this patient. Four patients with lymphoma and the patient with adenocarcinoma had positive antitoxoplasmosis antibodies. Figure 2 shows a patient with two separate lesions on the CT scan, one showing positive  $^{201}\text{Tl}$  uptake and biopsy-proven lymphoma and another, not evident on the  $^{201}\text{Tl}$  study, that proved to be brain gliosis.

In the two patients with positive  $^{201}\text{Tl}$  SPECT scan results and a high clinical suspicion of CNS lymphoma (Patients 8 and 10), radiation therapy was started at 6 and 11 days, respectively (mean 8.5 days), after admission.

Nine patients showed no  $^{201}\text{Tl}$  uptake in the corresponding regions of CT abnormalities. Two of them underwent biopsy: One showed toxoplasmosis, and the other had brain gliosis. Six other patients improved clinically on antitoxoplasmosis medications alone. One patient had *Cryptococcus meningitis* with a follow-up contrast CT findings consistent with evolving vascular infarction. The overall lesion detectability was 100% (10 of 10), with a sensitivity of 100% and a specificity of 90% (9 of 10).

### Quantitative Analysis

The early uptake ratios in patients with lymphoma ranged from 1.94 to 5.28 ( $4.07 \pm 2.12$  [mean  $\pm$  s.d.]), and delayed uptake ratios ranged from 1.90 to 6.21 ( $3.47 \pm 1.54$ ) (Fig. 3). The retention index for lymphomas was  $1.35 \pm 0.16$  (range 1.18–1.52). The patient with adenocarcinoma had a retention index of 0.24, and the patient with false-positive  $^{201}\text{Tl}$  uptake results had a retention index of 0.56, both statistically lower than the retention index for lymphoma ( $p < 0.036$ ).

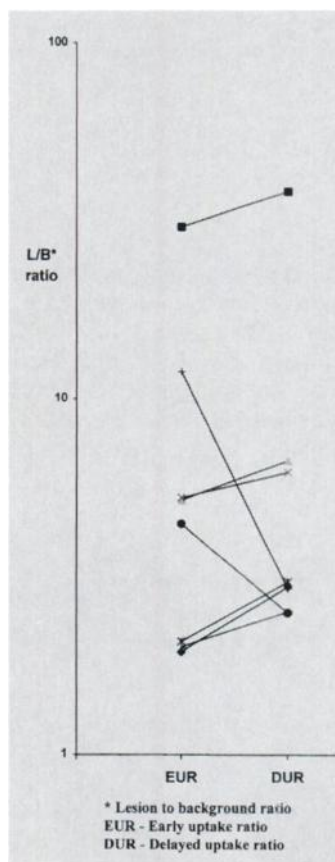
### DISCUSSION

The most common causes of focal brain lesions in patients with AIDS are toxoplasmosis (50%), primary CNS lymphoma (30%) and progressive multifocal leukoencephalopathy (20%) (2). Less common causes include Kaposi's sarcoma, herpes simplex, cryptococcoma, bacterial abscesses, *Candida albicans* and aspergillosis (3). It is often difficult to differentiate between these lesions, especially between toxoplasmosis and lymphoma. Both processes often appear as ring-enhancing lesions on CT and MRI, with mild to moderate edema and mass effect (2,5). Toxoplasmosis and CNS lymphoma can present as singular or multiple lesions and may occur anywhere in the brain. The two entities may coexist in some patients and may not be differen-

tiated at clinical presentation. Laboratory studies are also not conclusive: A positive serum toxoplasmosis antibody titer merely indicates exposure to the agent and cannot exclude a coexistent malignant lesion.

Given the greater likelihood that a characteristic CNS mass lesion is due to toxoplasmosis, empiric therapy is typically begun for a presumptive diagnosis of CNS toxoplasmosis. A brain biopsy is strongly considered only if the patient's condition deteriorates clinically in the first week of therapy or does not improve clinically or radiographically in 2–3 wk. The need to add steroids in some cases for treatment of marked brain edema further complicates the ability to make an accurate diagnosis because patients with CNS lymphoma or toxoplasmosis can improve initially with steroids.

Awaiting this 7–14-day course of empiric therapy creates a delay in the diagnosis and treatment of diseases other than



**FIGURE 3.** Comparison of early (EUR) and delayed (DUR)  $^{201}\text{Tl}$  uptake ratios in patients with positive SPECT study results.

toxoplasmosis and also exposes the patient to medications with a high incidence of adverse reactions.

Although image-guided stereotactic brain biopsy is usually safe and effective when performed appropriately (9), it has been reported to be nondiagnostic in up to 50% of patients with AIDS (10,11) and carries a risk of hemorrhage (9). Targeting only the center of an enhancing lesion may lead to a biopsy of nondiagnostic necrotic tissue.

PET using the glucose analog [ $^{18}\text{F}$ ] has also been used to differentiate toxoplasmosis from lymphoma (12). It is superior to SPECT imaging in resolution and quantification of brain uptake. However, PET is more expensive and not readily available. PET cannot be performed on an emergency basis and could create an unnecessary delay in the treatment of lymphoma. In addition, FDG is taken up by both normal tissues as well as viable tumor, which may lower the target/background ratio in PET compared with  $^{201}\text{Tl}$  SPECT.

SPECT imaging with  $^{201}\text{Tl}$  has been shown to localize in brain tumors, with a good target/background ratio and appears to be related to cell growth rates and blood flow (13–15). The extraction of  $^{201}\text{Tl}$  is primarily mediated through the  $\text{Na}^+/\text{K}^+$  ATPase pump system in tumor cells (16). Other contributing factors include an ion cotransport system (17), calcium ion channel exchange (17), vascular immaturity with leakage (18) and increased cell membrane permeability (19). In addition, increased  $^{201}\text{Tl}$  uptake is not related to permeability of the blood-brain barrier in lesions other than tumors, and tumor uptake is independent of steroid administration. In contrast,  $^{201}\text{Tl}$  does not appear to accumulate in non-neoplastic lesions such as hematomas, radiation necrosis and infectious processes such as toxoplasmosis (14). Potential false-negative results in cases of CNS lymphoma may occur when the size of the lesion is below the resolution limit of the SPECT gamma camera, in lesions obscured by high normal activity at the base of the skull, activity in the scalp (20) and theoretically by a low avidity of  $^{201}\text{Tl}$  to certain types of lymphoma.

We found in our preliminary study that the use of  $^{201}\text{Tl}$  SPECT can dramatically reduce the time to referral for a brain biopsy in patients with AIDS, from a 1–2-wk interval to less than 72 hr. Positive  $^{201}\text{Tl}$  uptake indicates earlier biopsy, and lack of  $^{201}\text{Tl}$  uptake makes it safer to initiate empiric treatment for toxoplasmosis. The SPECT findings can guide the neurosurgeons to specific sites for biopsy when both lesions coexist in the same patient and can more specifically identify the viable portion of the tumor. Early diagnosis of CNS lymphoma is essential for proper treatment with radiation therapy, which potentially improves patient survival and quality of life. It may also decrease medical costs by eliminating the hospital stay necessary to evaluate empirical treatment of cerebral toxoplasmosis.

Only a few reports are available on the utility of  $^{201}\text{Tl}$  for the differential diagnosis of CNS lymphoma from toxoplasmosis. Ruiz et al. (20) evaluated 37 patients with AIDS with mass lesions on CT or MRI by  $^{201}\text{Tl}$  brain SPECT and reported 100% specificity and sensitivity. However, no information is provided regarding the timing of the scan in most patients, and no information is available on steroid therapy. O'Malley et al. (21) studied 13 patients and found false-positive  $^{201}\text{Tl}$  uptake in one patient with a pathologic diagnosis of toxoplasmosis and cytomegalovirus. The uptake ratio of  $^{201}\text{Tl}$  in this patient was relatively low, suggesting that quantitation may minimize false-positive interpretations.

In our study, the early thallium uptake ratio varied widely among patients with lymphomas, probably reflecting different blood flow rates and background clearance. Nevertheless, the

retention index was consistently high, showing net wash-in of  $^{201}\text{Tl}$  in all patients (minimum retention 1.18), probably reflecting accelerated active transport of  $\text{K}^+$  carried out by the  $\text{Na}^+/\text{K}^+$  ATPase pump in these highly malignant tumors. The high retention index contrasted with the low retention in the incidental adenocarcinoma detected by the  $^{201}\text{Tl}$  study and the low retention in the patient with false-positive uptake. We have found in a majority of patients with primary and metastatic brain tumors other than lymphomas a net wash out of thallium from the lesions (e.g., retention index smaller than 1) (Lorberboym et al., unpublished data). Other reports suggest good correlation between the retention index of  $^{201}\text{Tl}$  and histological types of meningiomas (7), as well as brain tumor grade postoperatively (22), although others were unable to separate primary and metastatic brain tumors on the basis of retention indices (23). The retention index was also used to separate benign and malignant thoracic lesions (24).

## CONCLUSION

Our findings suggest that  $^{201}\text{Tl}$  brain SPECT is highly sensitive and specific in patients with AIDS for rapid differential diagnosis of focal brain lesions and increases the likelihood of a diagnostic brain biopsy. The sensitivity of the study is apparently not affected by prior administration of steroids. The retention index of  $^{201}\text{Tl}$  may be a useful measurable variable in distinguishing CNS lymphoma in patients with AIDS from other malignancies or nonmalignant, thallium-avid pathological entities.

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## Decompression Illness in Sports Divers Detected with Technetium-99m-HMPAO SPECT and Texture Analysis

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Diving for sport and recreation has increased in recent years, resulting in more incidences of diving illness. Therefore, we studied potential use of regional cerebral blood flow SPECT imaging with <sup>99m</sup>Tc-HMPAO in the management of divers who have experienced decompression illness (DCI). **Methods:** A group of ten sports divers who had no experience of DCI were compared with ten sports divers who had experienced at least one episode of DCI. Transaxial SPECT images were first compared objectively using a first-order texture measure and then subjectively using a receiver operator characteristic (ROC) experiment. Experienced observers were asked to rate images subjectively in terms of the images' textural appearance. **Results:** Both these techniques showed that there is a statistically significant difference between the two groups and the images produced by the DCI divers were generally more coarsely patchy when compared to the non DCI divers. The quantitative texture technique proved significantly better in identifying divers with DCI than the visual analysis by observers using ROC curves. **Conclusion:** Differences between the cerebral blood flow patterns of sports divers who have experienced DCI and sports divers who have no experience of DCI can be detected using <sup>99m</sup>Tc-HMPAO SPECT and a texture analysis technique.

**Key Words:** diving illness; SPECT; technetium-99m-HMPAO; receiver operator characteristics

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With the popularity of diving for sport or recreation increasing in recent years, there have been more incidences of diving illness. The need for accurate and effective management of such patients is becoming increasingly important. The potential use of regional cerebral blood flow SPECT imaging with <sup>99m</sup>Tc-HMPAO in the management of divers who have experienced decompression illness (DCI) has been investigated by several groups (1-6). These investigations have produced conflicting results. For example, Wilmshurst et al. (2) found no evidence for or against the use of <sup>99m</sup>Tc-HMPAO SPECT in the management of DCI, whereas both Staff et al. (6) and Adkisson et

al. (3) found significant differences in image appearance between those who had experienced DCI and those who had not. Hodgson et al. (5), however, found the following: no difference between divers who had recently experienced DCI; divers who had experienced DCI some 3-5 yr earlier; control divers with no experience of DCI; and nondiving controls. The lack of correlation between the SPECT images and the clinical findings could be due to the <sup>99m</sup>Tc-HMPAO images being too sensitive for this diffuse disease (5). Adkisson et al. (3) also suggested that DCI should be recognized as diffuse and multifocal. The diffuse nature of DCI has also been identified by Calder (7) who, when considering the effects of DCI in terms of the histology, stated that "studies have shown definite evidence of damage to small cerebral vessels. The damage/change in the brain is diffuse, affecting both gray and white matter."

A popular assumption in decompression theory holds that DCI results from excess inert gas in the body which forms bubbles. After diving, insufficiently rapid washout of excess inert gases during ascent may form as a result of dive bubbles. Bubble growth can follow decompression when the pressure in the bubble reflects the pressure at greater depth and the ambient pressure has been reduced by decompression (8). This mechanism can result in symptoms and signs of DCI. The site and initial mechanism of bubble production within the body remains unclear. Gas bubbles may be intravascular, arising in either venous or arterial circulation, or extravascular, arising in situ within tissues. Intravascular and extravascular bubbles can disrupt tissue in a number of ways. They may exert a direct effect causing local mechanical damage and compression of the tissue. Additionally, intravascular bubbles may cause vessel occlusion with distal tissue ischaemia or disrupt the vascular endothelium. The bubbles may also cause secondary effects via activation of leucocytes, platelets and components of coagulation and complementary pathways (9).

With the exception of Staff et al. (6), the SPECT studies have attempted to analyze the images by detecting focal defects. Staff et al. (6) investigated the SPECT images in terms of the image texture and found significant differences between divers with DCI and a set of diving controls who had no experience of DCI.

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