reflect the distribution of functioning Kupffer cells and we must therefore discard the concept that focal scan defects represent "space-occupying lesions." The point to be stressed is that abscesses have more than one phase (as do necrotic tumors) and the actual size of the cavities (necrotic centra) can probably be more accurately assessed with $^{67}$Ga-citrate than with $^{99m}$Tc-sulfur colloid. This was demonstrated in both our cases by the discrepancy in size of the abscesses as seen on the $^{99m}$Tc-sulfur colloid scans (larger) compared with the $^{67}$Ga-citrate scans (smaller). Moreover, the rim of increased activity on the $^{67}$Ga-citrate liver scans was essentially contained within the area of the $^{99m}$Tc-sulfur colloid scan defects. The rationale for the larger scan defect with $^{99m}$Tc-sulfur colloid is that the peripheral area of hyperemia about the acute abscess cavity inactivates the Kupffer cells in this region and, thus, the radiocolloid scan defect not only represents the abscess cavity but the inflammatory hyperemic zone. Delineation of the cavity is best done with $^{67}$Ga-citrate since it localizes in the hyperemic zone and to only a lesser extent in the necrotic center. Secondly, as the abscess becomes older, the zone of hyperemia disappears and the phagocytic activity in this zone returns. This results in a defect on the $^{99m}$Tc-sulfur colloid scan which is smaller and represents the negative defect of the pus cavity. This rapid return of phagocytic activity when the zone of hyperemia disappears may account for the discrepancy in the literature on the rate of healing of amebic abscesses.

We thank Maze and Wood for allowing us to reaffirm our observations.

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## TOXICITY OF $^{99m}$Tc-Sn-EHDP

Tofe and Francis (*1*) representing Procter and Gamble state that the appropriate amount of $^{99m}$Tc-Sn-EHDP for human administration (1–2 mg EHDP) for the purpose of skeletal scintigraphy is very low. The same authors state that 10–20 mg/kg/day EHDP has been therapeutically administered orally to patients with disordered mineral metabolism with no adverse effect. These statements are misleading.

An oral dose of 10–20 mg/kg/day of EHDP of which an average of 2–3% is absorbed (range, 0.1–15%) represents an average total absorbed dose of 14–42 mg (range, 0.7–210 mg) in a man weighing 70 kg (*2*). This dosage produces therapeutic effects in certain bone diseases (*2*), and reproducibly causes hyperphosphatemia(*2*) and decreased ionized serum calcium associated with elevation of plasma PTH (*3*). I would hesitate to claim that these effects may not be "adverse."

Obviously all EHDP injected intravenously is absorbed and the dose recommended by Tofe and Francis for bone scans, 1–2 mg, is definitely in the range of absorbed dose ($> 0.7$ mg) associated with the previously mentioned effects, at least in chronic administration of the drug to some patients.

Although the safety margin of the recommended bone scan dose of EHDP is acceptable, it most certainly is not a tracer dose and its having some pharmacologic action in at least a fraction of patients to whom it is administered can be predicted.

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## THE AUTHORS' REPLY

We believe that the concern expressed about the possibility of a pharmacologic action related to the intravenous administration of $^{99}$Tc-Sn-EHDP (1–2 mg EHDP) can be satisfied by the results of more extensive urinary excretion studies (unpublished) and a review of the recent literature.

Urinary excretion data collected on both normal patients and those with Paget's disease show that the

percent of absorption of orally administered EHDP is dose-related (*4*). In normal subjects, a dose of 20 mg/kg body weight per day results in 6.4 ± 2.4% (s.e.) absorption whereas only 0.8 ± 0.3% of a 2.5 mg/kg/day dose will be absorbed. The absorption values are about the same for patients with Paget's disease. Approximately half of the absorbed EHDP is chemisorbed to bone while the other half is eliminated in the urine (*2*). Consequently, after a single oral dose of 20 mg/kg (1,400 mg for a 70-kg man), approximately 45 mg of the absorbed EHDP is distributed throughout the skeleton. Following a single oral dose of 2.5 mg/kg (175 mg for 70-kg person), 0.7 mg of EHDP is delivered to the skeleton. The Procter and Gamble skeletal-imaging agent, Osteoscan, is also approximately 50% chemisorbed to bone, i.e., 0.5–1.0 mg of a 1–2-mg dose is distributed over the complete skeleton. This is systemically equivalent to the dose absorbed on skeleton following one oral dose of 2.5 mg/kg.

Hyperphosphatemia has not been seen in patients given a 2.5 mg/kg/day dosage for 6 months nor in fact at the 5 mg/kg/day level but only at the 10 and 20 mg/kg/day level (*5,6*). The increased serum phosphorus is significant only after 1 month at the 10 mg/kg/day dosage while at the 20 mg/kg/day dose, increased serum phosphorus has been reported as soon as 2 days after start of therapeutic treatment (*6*). Even at the 20 mg/kg dose, the onset of hyperphosphatemia corresponds to the systemic chemisorption of 90 mg of EHDP which is approximately two orders of magnitude greater than the skeletal load of EHDP from a single intravenous dose of $^{99m}$Tc-Sn-EHDP.

The study cited in which decreased ionized serum calcium and elevated plasma parathyroid hormone levels were observed was conducted in only four patients who received varying dose levels of the drug (*3,7*). The small number of subjects and lack of any control patients make the conclusions drawn by the authors difficult to interpret. Recent clinical studies involving about 50 patients have shown that both total serum calcium (*5,8*) and ionized serum calcium (*5*) have remained unchanged at dosages up to 20 mg EHDP/kg/day for periods up to 8 months. Neither Kolb (*9*) nor Russell (*6*) has found any change in PTH values measured in patients with Paget's disease treated with 20 mg EHDP/kg/day for 6 months.

The extensive clinical studies cited and other clinical studies in progress at a chronic dose of 20 mg/kg/day of EHDP clearly support a very high margin of safety for the single diagnostic dose of $^{99m}$Tc-Sn-EHDP. Considering the total dose being chemisorbed onto bone in the 8-month chronic study, the diagnostic level (0.5–1.0 mg) can be considered a trace amount. In our own clinical trials with the $^{99m}$Tc-Sn-EHDP diagnostic skeletal-imaging agent, no pharmacologic action was noted in administering it to over 2,000 patients.

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