

veloping adriamycin cardiotoxicity. Since publication of that paper, we have continued studying an entire series of patients, including those described in our article. We have used several methods of diagnosis, including echoradiography, technetium pyrophosphate imaging, electrocardiography, enzyme studies, conventional chest radiographs, and clinical evaluation. We hope to be able to publish this work in the near future. We also hope at that time to have completed our experimental work in support of our clinical data.

In answer to Dr. Soin's contention that the majority of patients showing cardiac uptake of Tc-99m pyrophosphate had prior chest irradiation, we can only say that this abnormality was to be expected. Patients with prior irradiation do stand a higher chance of developing cardiac toxicity from adriamycin than patients without (2,3).

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#### Modification of a Gated Acquisition Test Device

It has been reported recently that a Tc-99m source mounted on a modified, 78-rpm, phonograph turntable can be used to evaluate and study gated-acquisition techniques (1). The suggested modification of the turntable includes a simple pulse-forming circuit that is triggered by a micro-switch mounted to the edge of the turntable platter.

We describe here a simple approach that has enabled us to evaluate gated-acquisition programs without the necessity of building a pulse-forming network. The device uses only an existing turntable and tone arm. We have found that the output of an inexpensive phonograph cartridge mimics a QRS complex and triggers a commercially available gating device, thereby obviating the need for a pulse-forming circuit. The arm of the phonograph is suspended over the turntable platter and a 21-gauge needle is fixed to the surface of the platter at an angle that minimally disturbs the phonograph needle once for each revolution. The gating device is connected to the output signal plug of the turntable. A Tc-99m source is placed on a turntable at the same radial as the 21-gauge needle, thus fixing in time the relationship between the "R wave" and the geometric position of the source.

Since we are continuously upgrading our existing programs for gated acquisition, this device has enabled us to perform simple tests of acquisition and processing without exposing patients to prolonged imaging time.

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#### Clinical Assessment of the Importance of the Quantity of Tin in Commercial Bone Imaging Kits

Technetium-99m-labeled phosphates, especially the pyrophosphate, have become the popular agent for skeletal and cardiac imaging (1,2). To achieve firm technetium-to-phosphate binding, the valence state of technetium (pertechnetate) is reduced from seven to four by a reducing agent. In the case of Tc-99m, tin in the form of stannous chloride accomplishes this. Too little tin in the reaction vial results in an excess of free pertechnetate, and too much tin may produce colloid. It is important to note that excess tin would, upon injection, coat the red blood cells and the choroid plexus, which would accumulate increased amounts of Tc-99m pertechnetate used subsequently for brain imaging. False-positive brain scans resulting from previous bone scans have been reported (3,4). Therefore, it is crucial that the quantity of tin in a bone-imaging reagent be restricted to the absolute minimum necessary for firm labeling. At present several commercial firms supply pyrophosphate kits for bone imaging, with varying quantities of tin as the reducing agent. In the two kits approved by the FDA for clinical use, different amounts of pyrophosphate and tin are present. In the kit made by Mallinckrodt Nuclear (Technescan-pyp kit), the pyrophosphate/Sn ratio (by weight) is 3.5 (a low-ratio agent); in the kit made by Squibb (Phosphotec), the ratio is 20 (high-ratio agent). The present study was undertaken to compare the clinical significance of the varying quantities of tin on the biologic behavior, in vivo and in vitro stability of the labeled agents.

Nine patients ranging in age from 30 to 75 yr (mean, 53), for whom a bone-imaging study was requested, were chosen. The purpose of the investigation and the procedure were

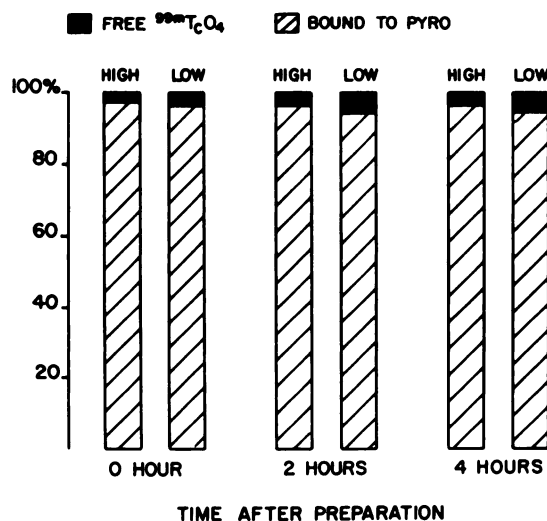
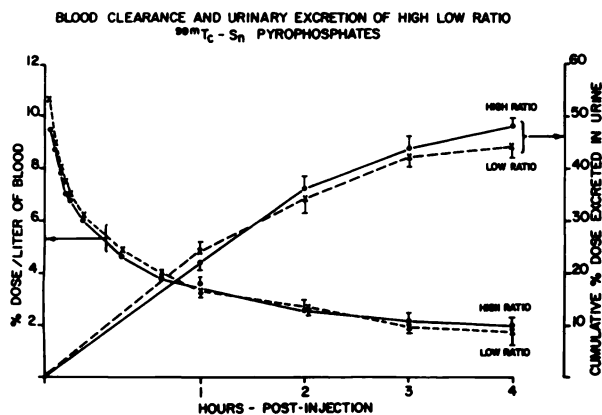
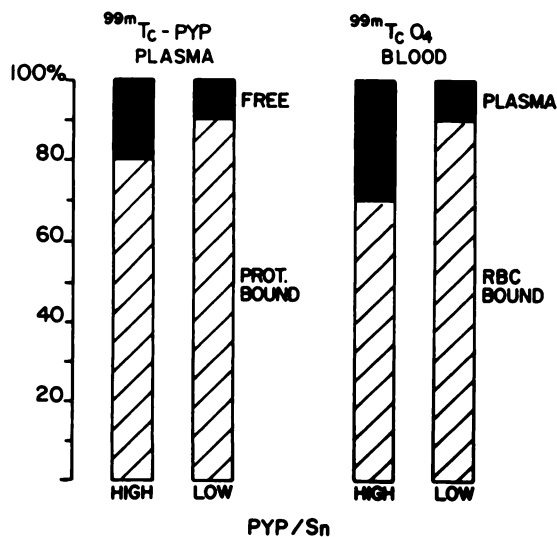


FIG. 1. Results of thin-layer radiochromatographic analysis of high- and low-ratio pyrophosphate/Sn imaging agents labeled with Tc-99m, showing identical binding efficiency and 4-hr in vitro stability.



**FIG. 2.** Blood clearance (left scale) and urinary excretion (right scale) of high- and low-ratio pyrophosphate/Sn imaging agents labeled with Tc-99m, showing identical patterns.

explained to the patients and their informed consent obtained. The study was performed with 20 mCi of one agent and repeated 1 wk later with an identical quantity of the other agent. In five patients, high-ratio pyrophosphate/Sn agent was used first, followed 1 wk later by the low-ratio agent; the order was reversed in the other four patients. The entire contents of a vial were used for each patient. Periodic blood and urine samples were collected and counted simultaneously with an aliquot of the standard, and the result was expressed as dose percentage per liter of blood and dose percentage excreted in urine. The radioactivity free in plasma and that bound to protein were determined after precipitating proteins with zinc sulfate and sodium hydroxide. A 2-hr blood sample was stored for 48 hr, and 20  $\mu$ Ci of [ $^{99m}$ Tc] sodium pertechnetate were added to 1 cc of blood.



**FIG. 3.** Tc-99m (Sn) pyrophosphate present in free form and bound to proteins in plasma. Difference is not statistically significant (left two columns). Right two columns show pertechnetate binding by red blood cells of 2-hr blood sample tested after 48 hr storage. Tc-99m radioactivity bound to red blood cells with low-ratio agent (high-tin) was significantly greater than that with high-ratio agent ( $p < 0.1$ ).

**TABLE 1. BLOOD CLEARANCE OF Tc-99m-LABELED HIGH- AND LOW-RATIO PYROPHOSPHATE/Sn AGENTS (DOSE PERCENTAGE PER LITER OF BLOOD: MEAN  $\pm$  s.e., N = 9)**

Time post-injection	High ratio	Low ratio
2 min	9.5 $\pm$ 1.2	10.7 $\pm$ 1.7
4 min	8.8 $\pm$ 0.6	8.9 $\pm$ 0.9
6 min	7.8 $\pm$ 0.5	7.9 $\pm$ 0.8
8 min	7.1 $\pm$ 0.5	7.5 $\pm$ 0.6
10 min	6.8 $\pm$ 0.6	7.0 $\pm$ 0.6
15 min	6.0 $\pm$ 0.5	6.2 $\pm$ 0.6
30 min	4.7 $\pm$ 0.3	4.9 $\pm$ 0.4
45 min	3.8 $\pm$ 0.2	4.0 $\pm$ 0.5
1 hr	3.4 $\pm$ 0.3	3.4 $\pm$ 0.3
2 hr	2.6 $\pm$ 0.2	2.6 $\pm$ 0.3
3 hr	2.2 $\pm$ 0.2	2.0 $\pm$ 0.2
4 hr	2.0 $\pm$ 0.1	1.9 $\pm$ 0.9

Percentage of radioactivity bound to red blood cells, washed thrice with saline, was calculated.

Both agents were labeled with a single commercial source of instant [ $^{99m}$ Tc] sodium pertechnetate. To calculate binding efficiency and in vitro stability, thin-layer radiochromatography, with acetone as solvent, was performed immediately and at 2 and 4 hr after preparation.

Bone images were obtained 3–4 hr after injection, using the same technique and equipment for both agents. The bone-image quality was subjectively graded by two nuclear medicine physicians. Particular attention was given to clarity of bone structure and the background radioactivity. The quality of the kidney image and the uptake by the liver were also observed.

For both high- and low-ratio pyrophosphate/Sn agents, the binding efficiency and in vitro stability up to 4 hr were identical (Fig. 1;  $p > 0.1$ ). Blood clearance and urinary excretion were similar (Fig. 2;  $p > 0.1$ ). With high- and low-ratio agents, 80.4 and 85.0%, respectively, of plasma radioactivity was protein-bound (statistically not significant) (Fig. 3). After 48 hr of storage, the red-cell binding of pertechnetate was 87.9% for low- and 69.6% for high-ratio agents ( $p < 0.1$ ). Bone-image quality and kidney uptakes were similar. There was no uptake by the liver.

Technetium-99m in the pertechnetate form is still being used for brain scanning in many institutions in this country and most countries around the world. Therefore, factors that would alter the normal pattern of distribution of pertechnetate should be avoided or minimized. The result of the present study shows that both low- and high-ratio (by weight) pyrophosphate/Sn agents exhibit identical blood clearance and urinary excretion, and give bone images of equal quality. The major difference was observed in the red-blood-cell binding of pertechnetate, where the low-ratio agent (more tin) showed significantly ( $p < 0.1$ ) greater bound  $^{99m}$ TcO $_4^-$ . The amount of tin (stannous chloride) in a reaction vial of Technescan-pyp kit is 3.4 mg, and in a Phosphotec kit 0.76 mg. The quantity of pyrophosphate in these reaction vials is 12.0 and 15.6 mg, respectively, giving pyrophosphate/Sn ratios of 3.5 (low-ratio agent) and 20.5 (high-ratio agent). The higher red-blood-cell binding of  $^{99m}$ TcO $_4^-$  with the low-ratio can be attributed to its greater tin content.

Many factors play a role in determining the quality of

bone images, notably the amount of labeled pyrophosphate entering the bone. The tin, which functions primarily as a reducing agent (5) in a bone-imaging kit, will, if present in excess, coat the red blood cell (6). Note that even with the high-ratio kit (less tin) there was a red-blood-cell binding of 69.9%, large enough for concern. Clinically false-positive brain images obtained with pertechnetate were attributed to prior injection of tin-containing radiopharmaceuticals (7,8). The tin effect lasts up to 6 days following administration. It is necessary therefore, either that brain imaging precede bone imaging, or that Tc-99m DTPA be used for subsequent brain imaging. Technetium-99m DTPA has been shown to be unaffected by prior injection of a tin-containing radiopharmaceutical.

The identical quality of the bone images and the similar in vitro binding and stability obtained with both high- and low-ratio agents suggest that the amount of tin in the high-ratio agent (0.76 mg/vial) is sufficient to accomplish this goal. It appears reasonable to reduce the amount of tin in reaction vials, especially in the low-ratio (by weight) pyrophosphate/tin bone-imaging kit.

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#### Imaging Experimental Pulmonary Ischemic Lesions after Inhalation of a Diffusible Radioaerosol—Recent Experience and Further Developments

A concise communication on this subject by Taplin, Cho-

pra, and Elam was published in the *Journal* (1). It was stated that inhalation lung imaging with the rapidly diffusible pertechnetate aerosol might suffice to localize regional pulmonary ischemia from emboli without the need for a separate perfusion imaging procedure, and that clinical studies were underway to determine the validity, sensitivity, clinical applicability, and limitations of this new method.

This letter is submitted to review our clinical experience with the  $\text{TcO}_4^-$  aerosol inhalation lung imaging procedure for detecting emboli as "hot spots" in surrounding areas of lower activity. First of all, the 10-min half-time removal rate from the lungs plus rapid appearance of radioactivity in the stomach posed technical problems. It was difficult to obtain satisfactory lung images in more than two projections during the first 10 min. Secondly, the oxygen driven Blount nebulizer delivered aerosol droplets larger than 5 micrometers in diameter, which caused excessive deposition in the posterior pharynx and major airways, especially in patients who were unable to breathe naturally and with normal tidal volume respiration. Although the first patient with angiographically proved pulmonary embolism showed promising results, one embolized region showed persistently prolonged retention of the aerosol, while other embolized regions cleared normally. More importantly, in two other well-documented pulmonary embolism patients, and another young man with congenital right pulmonary artery atresia, the pertechnetate aerosol was removed from the ischemic and normal areas of lung at the same rates ( $T_{1/2}$  values of 8-10 min). These findings, made by one of our colleagues, provided the impetus to learn more of the mechanisms involved in liquid in contrast to gaseous alveolar-capillary membrane diffusion.

It was known from previous radioactive carbon monoxide inhalation studies (2), that  $^{14}\text{CO}$  gas diffusion was definitely pulmonary arterial blood flow dependent in that its removal rates from better perfused lower lung fields were faster than from the more poorly perfused apical regions in subjects examined in the upright position. It was found, however, that the diffusion of pertechnetate was probably not blood flow dependent because its diffusion rates were faster from the poorly perfused apical regions than from the better perfused basal regions in normal volunteers. These differences between gaseous and liquid diffusion rates led us to study other soluble radioactive materials, with the findings that the molecular weight of the aerosolized agent was important in its rate of diffusion. For example, sodium pertechnetate with a molecular weight of 163 diffuses across the membrane with a half-time of  $10 \pm 2$  min, whereas technetium DTPA with a molecular weight of 492, has a halftime of  $45 \pm 10$  min, and normal human serum albumin (molecular weight 67,000) is much more slowly absorbed with a half-time of approximately 12 hr.

Regarding the search for a "hot spot" imaging procedure for pulmonary embolism detection, these findings were disappointing but they led to the use of Tc-99m DTPA as an improved test agent for routine aerosol inhalation lung imaging. When administered as a high specific activity (10-15 mCi/ml) aerosol in a dose three times that required for the perfusion examination, the airway-ventilation examination can be performed immediately after perfusion imaging using the same radionuclide. By this combined perfusion-aerosol-ventilation procedure, pairs of images may be obtained in as many projections as indicated during a single visit to the nuclear medicine clinic. Furthermore, the aerosol images provide evidence of large and medium size airway obstruc-