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## REPLY

We are very happy that our paper stimulated the interesting discussion by Dr. Turner. Our third study of liver scanning at Johns Hopkins differed from the previous two, referred to by Dr. Turner, in that the basic populations under study differed. In the studies by Poulouse et al and by Fee et al, the basic populations were patients coming to abdominal surgery because of suspected abdominal malignancy; thus a relatively great number of patients had liver metastases at the time of surgery.

The present study population consisted of patients who had needle biopsy of the liver for various indications. The criterion for including a patient in this study was that the patient should have had a liver scan and a liver biopsy within 1 week. We can postulate some possible explanations for the low number of normal biopsies: either the clinicians have a very good index of suspicion in selecting patients for this

procedure or the pathologists have a low threshold in diagnosing liver disease from needle biopsy preparations. We agree that the problem of liver imaging must take into consideration both the false positives and false negatives.

The high rate of false negatives in the study by Poulouse et al using the rectilinear scanner was explained by the fact that numerous small metastases, as well as larger ones, on the liver surface could not be detected. It was hoped that the scintillation camera with its higher resolution and parallel-hole collimator and multiple views would decrease the number. Unfortunately, it did not. Despite the use of multiple views, we did not get rid of the problem of missing 20% of the lesions within the liver.

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## CHEMICAL STATE OF TECHNETIUM IN VIVO (LETTER NO. 1)

In a recent article (1), Hambright et al state that Tc(IV) should be inert, that is, kinetically slow to substitution reactions. They invoke an inert Tc(IV) gluconate on theoretical grounds and on the basis of a competitive binding experiment between  $^{99m}\text{Tc}$ -HEDP and 0.1 M gluconate. However, in a previous article (Ref. 2 of their paper) they point out that  $^{99m}\text{Tc}$ -gluconate is dissociated by the competitive binding of  $^{99m}\text{Tc}$  by Sephadex during a quick chromatographic analysis. The discussion of the mechanism of the inorganic reaction thus seems to contradict their previous statements about chromatographic artifacts.

They further state that the conclusion of earlier work on  $^{99m}\text{Tc}$  chelates, including several papers by myself and others, is that "the chemistry at macro  $^{99}\text{Tc}$  levels may be different than that shown by

micro  $^{99m}\text{Tc}$ ." In fact, we had tried to show that  $^{99}\text{Tc}$  and  $^{99m}\text{Tc}$  reduced with stannous ion, for example, show similar reactivities with DTPA and, therefore, that the same reduced state present in  $^{99}\text{Tc}$ -DTPA is probably present in the  $^{99m}\text{Tc}$  radiopharmaceutical. This is similar to the authors' conclusion that  $^{99}\text{Tc}$  and  $^{99m}\text{Tc}$  reduced with stannous ion show similar biologic behaviors when chelated with HEDP and, therefore, that the Tc(IV) state can be assigned to the carrier-free  $^{99m}\text{Tc}$  radiopharmaceutical. Both experiments are based on the assumption that the only variable is the concentration of technetium. However, the concentration of other species, such as stannous and stannic ion, which can affect the oxidation potential may not be held constant. Also, it has not been proved that only one oxidation state of technetium can bind to the chelating agent or give the

same distribution *in vivo*. Therefore, the question of the chemical state of  $^{99m}\text{Tc}$  in radiopharmaceuticals remains open.

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## REPLY

We apologize to Prof. Eckelman for citing his work (Refs. 11,12) as examples of the belief that the chemistry of macro  $^{99}\text{Tc}$  may be different from that shown by micro  $^{99m}\text{Tc}$ . As is true in any scientific field, we also agree that much remains to be known about the chemical state, both *in vivo* and *in vitro*, of  $^{99m}\text{Tc}$  radiopharmaceuticals.

In our work, we used a direct redox titration technique to show that the final *in vitro* oxidation state of  $^{99}\text{Tc}$  in the kidney agent Tc-Sn-gluconate and the bone agent Tc-Sn-HEDP is Tc(IV). Such results agree with low-temperature electron spin resonance data. The biologic distribution of  $^{99m}\text{Tc}$ -Sn-DTPA, prepared in a manner similar to that for  $^{99m}\text{Tc}$ -Sn-HEDP, depends markedly on the time that the reagent has stood, as does the color of this  $^{99}\text{Tc}$ -DTPA adduct. Accordingly, an analysis of its properties, which may involve a mixture of oxidation states, is more difficult than for gluconate or HEDP. For the latter reagents, we showed that the tissue distributions were similar for  $^{99m}\text{Tc}$  and carrier  $^{99}\text{Tc}$ . Our unpublished experiments have shown the same for  $\text{TCO}_4^-$  at  $^{99}\text{Tc}$  concentrations below saturation.

Both  $^{99m}\text{Tc}$ -Sn-HEDP and pyrophosphate are substitution-inert with respect to sodium gluconate under stated conditions, according to the accepted definition of chemical inertness (1). Pyrophosphate is an order of magnitude more labile than HEDP. There is no contradiction between the observation that certain adducts are substitution-inert and the observation that some chromatographic procedures produce artifacts. The classification of a metal complex as "inert" is based solely on experimental measurements and does not depend on any assumed reaction mechanism. We might also note that the thermodynamic stability of a complex and the direction of a reaction in terms of its oxidation potential have no relationship to the kinetically determined rate of ligand exchange or the rate of the reaction's approach to equilibrium.

By assuming that the substitution-inertness of Tc(IV) could explain aspects of radiopharmaceu-

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tical behavior, we suggested a number of ligand-binding mechanisms for various oxidation states of technetium which can be tested by future work. One of our current related hypotheses is that *in vivo* ligand exchange (translocation) is also an important factor. This derives from experiments at high pH where  $^{99m}\text{Tc}$ -Sn,  $^{99m}\text{Tc}$ - $\text{S}_2\text{O}_4^{2-}$ , and a variety of cis-dihydroxyglycols all show tissue distributions similar to those found for  $^{99m}\text{Tc}$ -Sn-gluconate and  $^{99m}\text{Tc}$ -Sn-glucoheptonate. Many of these *in vivo* translocations and *in vitro* transformations are catalyzed by physiologic metal ions.

Our work provides a rational justification for the serious study of the kinetic and thermodynamic properties of  $^{99}\text{Tc}$  adducts; such studies will produce important and otherwise unobtainable data for use in the  $^{99m}\text{Tc}$  radiopharmaceutical field.

We would like to warn investigators that  $^{99}\text{Tc}$  is a potentially dangerous substance. Its relatively low beta energy makes laboratory and human contamination more difficult to detect than is the case for the familiar gamma-emitting  $^{99m}\text{Tc}$ . Strict methods of confinement should be exercised when contemplating use of the long-lived  $^{99}\text{Tc}$  isotope. A concentration of 1 mg/kg of tissue would result in a radiation dose of roughly 30 rads per year.

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