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

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REFERENCE

1. HAMBRIGHT P, MCRAE J, VALK PE, et al: Chemistry of technetium radiopharmaceuticals. I. Exploration of the tissue distribution and oxidation state consequences of technetium(IV) in Tc-Sn-gluconate and Tc-Sn-EHDP using carrier ^{99}Tc. *J Nucl Med* 16: 478–482, 1975

REPLY

We apologize to Prof. Eckelman for citing his work (Refs. *11,12*) as examples of the belief that the chemistry of macro ^{99}Tc may be different from that shown by micro ^{99m}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}Tc radiopharmaceuticals.

In our work, we used a direct redox titration technique to show that the final in vitro oxidation state of ^{99}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}Tc-Sn-DTPA, prepared in a manner similar to that for ^{99m}Tc-Sn-HEDP, depends markedly on the time that the reagent has stood, as does the color of this ^{99}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}Tc and carrier ^{99}Tc. Our unpublished experiments have shown the same for TcO_4^- at ^{99}Tc concentrations below saturation.

Both ^{99m}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 radiopharmaceutical 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}Tc-Sn, ^{99m}Tc-$S_2O_4^{-2}$, and a variety of cis-dihydroxyglycols all show tissue distributions similar to those found for ^{99m}Tc-Sn-gluconate and ^{99m}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}Tc adducts; such studies will produce important and otherwise unobtainable data for use in the ^{99m}Tc radiopharmaceutical field.

We would like to warn investigators that ^{99}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}Tc. Strict methods of confinement should be exercised when contemplating use of the long-lived ^{99}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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REFERENCE

1. TAUBE H: Rates and mechanism of substitution in inorganic complexes in solution. *Chem Rev* 50: 69–126, 1952