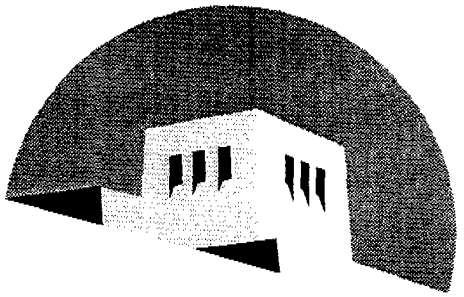

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A Review of Radiopharmaceutical Formulation Problems and Their Clinical Manifestations

by:

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A REVIEW OF RADIOPHARMACEUTICAL FORMULATION PROBLEMS AND THEIR CLINICAL MANIFESTATIONS

STATEMENT OF OBJECTIVES

The primary goal of this review is to increase the reader's knowledge and understanding of problems associated with the formulation of common radiopharmaceuticals and their subsequent effects in clinical use. To this end, problems are discussed in terms of factor categories, citing numerous literature-based examples as well as listing specific problems reported with common radiopharmaceuticals. Although this review is intended to be comprehensive, it cannot claim to be complete; therefore, the reader is encouraged to apply these factors to extrapolate potential problems likely to be encountered with other radiopharmaceuticals.

Upon successful completion of this course, the reader should be able to:

1. Describe the clinical manifestations (i.e., appearance upon imaging) of common radiochemical impurities such as pertechnetate, colloidal particles, large particles, and others.

2. Explain how each of the factors listed below can result in radiopharmaceutical formulation problems:

    a. carrier ^{99}Tc
    b. total radioactivity/specific concentration
    c. aluminum ion
    d. stannous ion
    e. pH
    f. mixing order
    g. reagent concentration
    h. heating
    i. incubation
    j. particulate size and number
    k. commercial source
    l. oxidation and/or radiolytic decomposition
    m. specific activity
    n. solubility
    o. preservatives/antiseptics
    p. anticoagulants
    q. stereoisomeric form
    r. encapsulation
    s. isotope exchange
    t. iodine volatility
    u. radionuclide contamination
    v. miscellaneous factors

3. Describe the effects of the factors listed above on common radiopharmaceuticals.

4. Differentiate between factors that affect radiopharmaceuticals before or during formulation and those that affect radiopharmaceuticals after formulation.

5. Differentiate between factors that are in the manufacturer's realm and those that can be controlled by the nuclear pharmacist.

COURSE OUTLINE

I. INTRODUCTION

II. PROBLEMATIC FACTORS IN FORMULATING RADIOPHARMACEUTICALS

- A. Carrier ^{99}Tc
- B. Total Radioactivity/Specific Concentration
- C. Aluminum Ion
- D. Stannous Ion
- E. pH
- F. Mixing Order
- G. Reagent Concentration
- H. Heating
- I. Incubation
- J. Particulate Size and Number
- K. Commercial Source
- L. Oxidation and/or Radiolytic Decomposition
- M. Specific Activity
- N. Solubility
- O. Preservatives/Antiseptics
- P. Anticoagulants
- Q. Stereoisomeric Form
- R. Encapsulation
- S. Isotope Exchange
- T. Iodine Volatility
- U. Radionuclide Contamination
- V. Miscellaneous Factors

III. LISTING OF FORMULATION PROBLEMS FOR COMMON RADIOPHAMACEUTICALS

A REVIEW OF RADIOPHARMACEUTICAL FORMULATION PROBLEMS AND THEIR CLINICAL MANIFESTATIONS

By

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Unexpected patterns of radiopharmaceutical biodistribution usually provoke a flurry of inquiries regarding the quality of the administered agent. Although this unexpected biodistribution may be related to nonradiopharmaceutical factors (1-4), past experience has shown that an improperly formulated radiopharmaceutical may be to blame.

The clinical manifestations of most ^{99m}Tc-radiopharmaceutical formulation problems are generally associated with increased amounts of ^{99m}Tc-pertechnetate, ^{99m}Tc-colloid, and/or ^{99m}Tc-particulate impurities in th desired ^{99m}Tc-agent. Free pertechnetate is distributed throughout the vasculature and interstitial fluid and is concentrated in the stomach, intestinal tract, thyroid gland, and salivary glands; the presence of ^{99m}Tc-pertechnetate impurities will, therefore, result in increased activity in these organs (Figure 1). Colloid particles are phagocytized by cells of the reticuloendothelial system (RES) which are located primarily in the liver and spleen; the presence of ^{99m}Tc-colloid impurities will, therefore, result in increased activity in the liver and spleen (Figure 2). Large (> 10 μ) particles administered intravenously become physically lodged in the pulmonary capillaries; the presence of large ^{99m}Tc-particulate impurities will, therefore, result in increased activity in the lungs (Figure 3).

In addition to the common radiochemical impurities described above, a variety of other ^{99m}Tc-impurities may be formed during radiolabeling and/or decomposition. If these impurities are hydrophilic, ionized, non-protein bound, and less than 5000 molecular weight, they will likely be excreted in the urine by glomerular filtration. One example of this type of impurity is the so-called secondary complex of ^{99m}Tc-exametazime (HMPAO) (5). On the other hand, if the impurities are lipophilic, possess both polar and nonpolar groups, and have a molecular weight of 300 - 1000, they will likely be

excreted by the hepatobiliary system. One example of this type of impurity is an unidentified complex in ^{99m}Tc-mertiatide (MAG_3) (6).

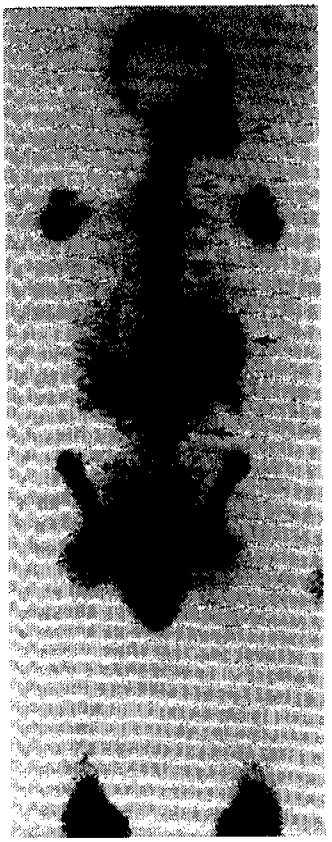

Figure 1. ^{99m}Tc-pyrophosphate bone scan demonstrating free pertechnetate distribution in the stomach, intestinal tract, thyroid, and salivary glands (arrows).

As a standard of practice, quality control testing should be performed on each preparation prior to use to assure that the radiopharmaceutical complies with USP specifications for radiochemical purity, etc. Unfortunately, many formulation problems are not detectable with routinely used quality control techniques (7), occur after dispensing (8), occur *in vivo* (9), or are otherwise unknown at the time of use. Furthermore, even a radiopharmaceutical that does meet USP specifications for radiochemical purity may, depending on its use, provide misleading information to the interpreting physician (10-12).

In this lesson, common formulation factors which affect the level of these various impurities in ^{99m}Tc-radiopharmaceuticals are discussed. In addition, formulation factors that may produce alternate effects on the biodistribution of ^{99m}Tc-labeled agents and other radiopharmaceuticals are presented.

CARRIER ^{99}Tc

^{99m}Tc undergoes isomeric transition to the very long lived isotope ^{99}Tc (half-life = 200,000 years) which can, for practical purposes, be considered stable in comparison to its metastable isomer. The decay of

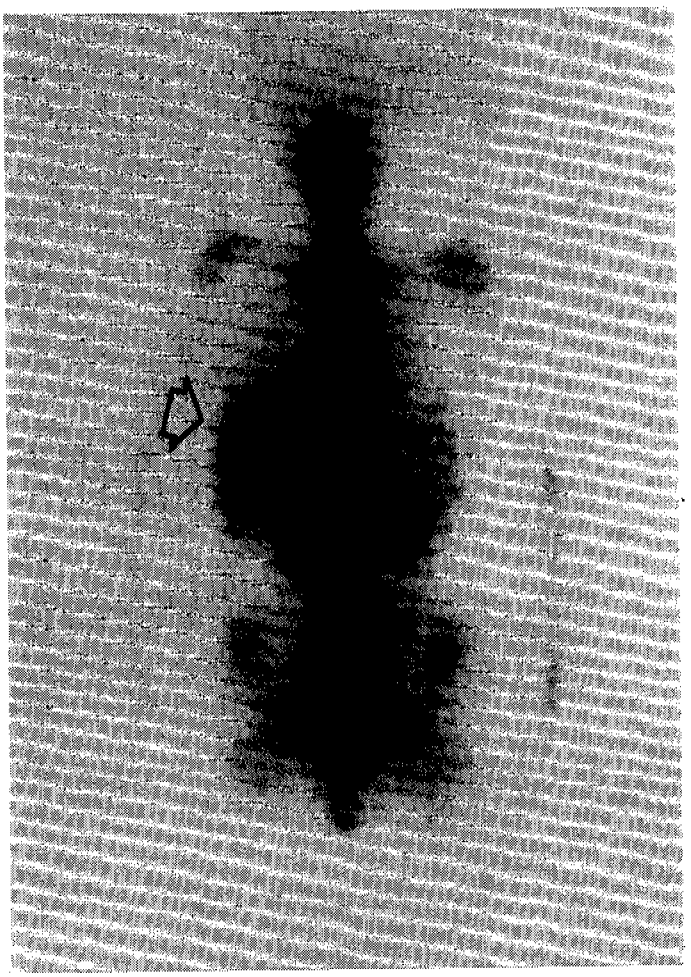

Figure 2. ^{99m}Tc-pyrophosphate bone scan demonstrating colloidal impurities taken up in the liver (arrow).

^{99m}Tc, therefore, results in a rapid buildup of carrier technetium with corresponding depression of ^{99m}Tc specific activity. Excessive carrier ^{99}Tc is commonly present in the eluate of a generator which has not been eluted for several days. Expressed as a percentage of

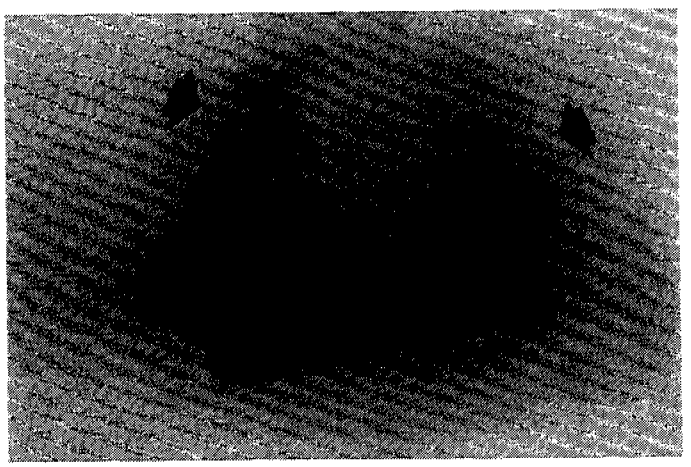

Figure 3. ^{99m}Tc-sulfur colloid liver scan demonstrating particulate impurities trapped in the lungs (arrows).

Total technetium atoms (^{99m}Tc plus ^{99}Tc) obtained in the generator eluate, ^{99m}Tc comprises 28% of the total at 24 hours, 13% at 48 hours, and only 8% at 72 hours after prior elution (13,14). Furthermore, the specific activity of a ^{99m}Tc eluate decreases over time as a direct consequence of its radioactive decay. Hence, a typical twelve hour old ^{99m}Tc eluate has a specific activity approximately equal to that of the first eluate of a new Monday generator.

^{99}Tc, which is chemically identical to all other technetium isotopes, can compete with ^{99m}Tc for the reductive capacity and the ligand-binding sites of fixed concentrations of stannous ion and chelating reagents, respectively. Hence, it is not surprising that an unacceptably high concentration of ^{99m}Tc-pertechnetate impurity is found in many ^{99m}Tc-radiopharmaceuticals prepared with use of low specific activity Monday morning generator eluates. This effect has been reported with the preparation of ^{99m}Tc-labeled sulfur colloid (15), gluconate (16), human serum albumin (HSA) (17,18), red blood cells (RBC) (19-25), HMPAO (5,26,27), and pentetate (DTPA) (28), and may occur with many other ^{99m}Tc preparations (14,19). Similarly, the use of "aged" ^{99m}Tc eluates (i.e., > 6-12 hours old) has been reported to decrease the labeling efficiency of ^{99m}Tc-MAG_3 (RG Wolfangel, Mallinckrodt, 1992), either because of the effect of carrier ^{99}Tc and/or the presence of peroxides (*vide infra*). The use of "aged" ^{99m}Tc eluates also results in decreased labeling efficiency and stability of ^{99m}Tc-HMPAO (5,29).

Even if the reductive capacity of the kit is not exceeded, high levels of ^{99}Tc or ^{99m}Tc may affect the biodistribution of the labeled product. For example, blood clearance rates of ^{99m}Tc-oxidronate (HDP) prepared with high levels of either ^{99}Tc or ^{99m}Tc are significantly slower than those prepared with less total technetium (30).

TOTAL RADIOACTIVITY/SPECIIFIC CONCENTRATION

Even taking into account the presence of carrier ^{99}Tc and reagent concentrations (*vide infra*), the total radioactivity of ^{99m}Tc used in the preparation of, and thus the final specific concentration of, several radiopharmaceuticals can affect the quality of the final product. For example, use of excessive ^{99m}Tc activity (e.g., > 3.7 GBq [100 mCi]) in the preparation of an UltraTag® RBC kit can decrease both the rate and extent of the labeling reaction (31). MAG_3 kits labeled with excessive ^{99m}Tc activity (e.g., > 3.7 GBq [100 mCi]) demonstrate poor labeling efficiency and stability with formation of impurities that are excreted via the hepatobiliary system (32,33). HMPAO kits prepared with excessive ^{99m}Tc activity (high specific concentration) demonstrate decreased labeling efficiency and stability resulting in a lower brain/parotid ratio due to increased free pertechnetate (5,27,34-37).

On the other hand, too little ^{99m}Tc activity (or mass) may result in poor labeling efficiency for some radiopharmaceuticals. For example, acceptable yields of ^{99m}Tc-sulfur colloid preparations require the use of at least a minimum amount of technetium (38).

The specific concentration of the radiopharmaceutical also determines the mass amount that is administered to the patient. In some cases, the administered mass can influence the biodistribution of the radiopharmaceutical. For example, liver uptake of ^{99m}Tc-HDP increases substantially with administered dosages of greater than 0.05 mg/kg (39); this is not a practical concern, however, as this dosage for a standard adult would exceed the entire contents of an Osteoscan®-HDP vial.

ALUMINUM ION

The distribution of a number of ^{99m}Tc-radiopharmaceuticals may be altered by the presence of aluminum ion (Al^{+3}). The most common source of excessive Al^{+3} is breakthrough from the aluminum oxide anion exchange column in the ^{99}Mo/^{99m}Tc generator. If present, Al^{+3} breakthrough is generally the highest with the first generator elution and decreases with subsequent elutions (40-42), although it may vary from day to day and from manufacturer to manufacturer (42-45). Al^{+3} breakthrough was much more of a problem with the older, large-column, neutron-activated ^{99}Mo generators than it is with the present, small-column, fission ^{99}Mo generators (46-48). Limits for the amount of permissible Al^{+3} breakthrough have been established in the *United States Pharmacopeia* (USP), whereby Al^{+3} concentrations cannot exceed 10 μg/ml generator eluate (49). Another source of Al^{+3} is leaching from aluminum-hub needles (50). Although Al^{+3} concentrations in solutions passed through these needles vary depending on pH, etc., they may exceed the USP limit stated above in some situations (50).

As early as the 1960s, it had been reported that Al^{+3} interacts with ^{99m}Tc-sulfur colloid to form a flocculant precipitate (41,46). In later studies, it was shown that this flocculation could result with Al^{+3} concentrations as low as 1 μg/ml (51). Although the precipitate was originally thought to be aluminum hydroxide (43), it was later determined that Al^{+3} combines with the phosphate buffer to form insoluble aluminum phosphate (52,53). A flocculant aluminum phosphate precipitate may also be formed *in vivo* when ^{99m}Tc-sulfur colloid is

administered to patients in whom plasma levels of Al^{+3} are elevated (54). In both cases, the ^{99m}Tc-sulfur colloid is coprecipitated with the aluminum phosphate precipitate and results in lung localization, since these flocculated particles become lodged in the pulmonary capillaries (43,50,51,54,55). Alleviation of this problem may be achieved with the addition of ethylenediaminetetraacetic acid (EDTA), a chelating agent for Al^{+3}, to the sulfur colloid formulation (51,53). Additionally, it has been shown that sulfur colloid preparations formulated with an acetate buffer instead of a phosphate buffer do not flocculate in the presence of Al^{+3} (52,53).

Similarly, ^{99m}Tc-albumin colloid is affected by excessive amounts of Al^{+3} to result in large particles that are trapped in pulmonary capillaries (56). This effect is likely caused by Al^{+3} neutralization of stabilizing factors that protect the original colloid (56).

Another group of radiopharmaceuticals affected by Al^{+3} is ^{99m}Tc-diphosphonates. Visualization of liver and spleen activity results from phagocytosis of a radiocolloid formed by the interaction of ^{99m}Tc-diphosphonate with Al^{+3} present in elevated concentrations (57-60). This effect is not seen with Al^{+3} concentrations of < 10 μg/ml, but liver localization and degradation of bone images progress with increasing Al^{+3} concentrations above this level (57).

The biodistribution of pertechnetate may also be altered by excessive Al^{+3}. Failure of ^{99m}Tc-pertechnetate to leave the vascular space was observed in a patient with a plasma aluminum level of 65 μg/l (61). Moreover, ^{99m}Tc-pertechnetate injections containing Al^{+3} in concentrations of 4 μg/ml or more may result in reduced thyroidal uptake of pertechnetate (62). Al^{+3} in these higher concentrations apparently interacts with pertechnetate to form neutral and ionic pertechnetate-aluminum complexes that remain in soft tissues. These complexes are relatively unstable and slowly release pertechnetate over a period of hours, as aluminum ion is hydrolyzed (62).

Al^{+3} also acts as an erythrocyte-agglutinating agent. Results of *in vitro* studies indicate that the critical concentration for this effect is about 5 μg Al^{+3}/ml at a pH of 4 - 5 (63). Since necessary conditions for red cell agglutination by Al^{+3} do not occur *in vivo*, intravascular agglutination with administration of generator eluates containing Al^{+3} appears highly improbable.

Additionally, Al^{+3} contamination from aluminum-hub needles can interact with In-111 tropolone (for neutrophil labeling) to produce a flocculant precipitate that localizes in the lungs (50).

STANNOUS ION

The importance of an optimal amount of stannous ion (Sn^{+2}) as a reducing agent in the preparation of ^{99m}Tc-radiopharmaceuticals is widely recognized. Too little Sn^{+2} limits reductive capacity, which leads to decreased labeling efficiency and increased ^{99m}Tc-pertechnetate impurity; too much Sn^{+2} may result in the formation of ^{99m}Tc-colloid impurities and/or decreased labeling efficiency (64). This phenomenon is aptly illustrated by the marked effects produced by relatively small variations in Sn^{+2} quantities used in the labeling of ^{99m}Tc-RBC (20,65-70).

Most ^{99m}Tc kits start with sufficient, and usually excess, amounts of Sn^{+2}. This reducing capacity may be drastically decreased, however, by a variety of factors including loss of Sn^{+2} during manufacture, deterioration and/or oxidation during storage (especially following reconstitution and fractionation), and oxidation during kit preparation (71-77). Furthermore, excessive amounts of carrier ^{99}Tc decrease the apparent reducing capacity by competing with ^{99m}Tc (*vide supra*).

Addition of excessive amounts of Sn^{+2} to ^{99m}Tc kits is a common practice for counteracting the effects of oxidants and inhibiting radiation-induced decomposition (72,77,78). Although this practice does effectively inhibit the formation of ^{99m}Tc-pertechnetate impurities, hydrolysis of the excess Sn^{+2} can result in the formation of ^{99m}Tc-stannous colloids with resultant RES and other soft-tissue localization (75,79). On the other hand, some ^{99m}Tc-radiopharmaceuticals may display decreased labeling in the presence of excess Sn^{+2} (65-68). In the case of ^{99m}Tc-HMPAO, excess Sn^{+2} increases the rate of decomposition with conversion to reduced/hydrolyzed ^{99m}Tc (37,80).

The molar ratio of ligand to Sn^{+2} may also influence the formation of the ^{99m}Tc-labeled complex(es), and thus the ultimate biodistribution. For example, several complexes of ^{99m}Tc-HDP have been observed, depending on the ligand/Sn^{+2} ratio (39,81). Moreover, biodistribution studies in animals show that the more negatively-charged complexes are associated with superior bone uptake (39). Similarly, variations in medronate (MDP)/Sn^{+2} and etidronate (HEDP)/Sn^{+2} ratios result in small but definite changes in tissue distribution (82,83). Furthermore, a low HDP/Sn^{+2} ratio with subsequent aggregation *in vivo* has been suggested as the cause of lung uptake observed in a group of patients undergoing routine bone imaging (9).

pH

Alterations in pH can have marked effects on the

radiochemical purity and/or the final chemical form of many ^{99m}Tc-radiopharmaceuticals. For example, decreased labeling efficiencies of ^{99m}Tc(Sn)-HSA and electrolytically prepared ^{99m}Tc-gluceptate occur above or below the optimal pH ranges of 2 - 3 and 6.7 - 7.2, respectively (84,85). Decreased labeling rates of ^{99m}Tc-iminodiacetic acid (IDA) derivatives are observed at pH values higher than the optimal pH of 5.5 (86). Maximal labeling of leukocytes with ^{99m}Tc-HMPAO requires that the pH be maintained near neutrality (87-89). Also, ^{99m}Tc-sulfur colloid breaks down and liberates ^{99m}Tc-pertechnetate at a neutral or alkaline pH (90-91). Stannous ion solutions become insoluble and form colloidal precipitates at neutral and alkaline pH. If ^{99m}Tc-pertechnetate is present, the ^{99m}Tc can coprecipitate and/or complex with the tin colloid, which results in a radiocolloid impurity that localizes in the RES (75,92).

Good bone uptake and urinary excretion result from use of acidic formulations of ^{99m}Tc-pyrophosphate, whereas negligible bone affinity and concentration in the kidney result from use of neutral and alkaline formulations (93,94). Imaging with alkaline ^{99m}Tc-pyrophosphate formulations rather than with slightly acidic formulations demonstrates significantly inferior bone scan quality (95). High liver, kidney, and/or stomach uptake have been demonstrated when ^{99m}Tc-HEDP or ^{99m}Tc-MDP is prepared at alkaline pH (59,83); at excessively acid pH, on the other hand, higher uptake occurs in the urine and stomach (82). It is not clear, however, whether these pH effects on ^{99m}Tc-bone agents are solely associated with the formation of radiocolloid or ^{99m}Tc-pertechnetate impurities, since there is evidence which suggests that the alteration in biodistribution may be a result of differing chemical complexes formed at different pH values (81). For example, Tc(IV)-HEDP is formed in acidic solution, whereas Tc(V)-HEDP is formed in neutral or alkaline solutions (96). Similarly, several components showing markedly different degrees of bone uptake and soft-tissue localization have been separated from ^{99m}Tc-MDP mixtures prepared at different pH ranges (97,98).

A number of different complexes of ^{99m}Tc-succimer (DMSA) have been observed at different pH values. The complex formed under acidic conditions with relatively high Sn^{+2} concentrations is retained in the renal cortex, while another distinct complex formed at an alkaline pH with standard to low Sn^{+2} concentrations exhibits rapid urinary excretion and moderate uptake in tumor and bone (99-103). Several factors may be involved in the formation of these different complexes. For example, the ratio of DMSA to Sn^{+2} at pH 4 is 2:1, while the ratio at pH 8 is 1:1 (99,100). Furthermore, the kidney localizing complex formed at acidic pH is probably Tc(III)-DMSA, whereas that formed at alkaline pH is probably Tc(V)-DMSA (102). Tc(V) may then dissociate from the DMSA complex as TcO_4^{-3} and, as a structural analog to PO_4^{-3}, may localize in some tumors and bones (102).

Different complexes of ^{99m}Tc-IDA compounds have also been observed at different pH values (104). Rapid conversion *in vivo* to a common form probably occurs, however, since the biodistribution patterns are essentially the same (104).

The equilibrium between thallous (I) and thallic (III) ions is strongly influenced by pH. An alkaline pH favors the formation of thallous ions and myocardial uptake, whereas an acidic pH favors the formation of thallic ions (105). Thallic ions, which are not readily localized in myocardial cells, may form hydrated colloids (liver uptake), and/or may form complex ions (thyroid, red blood cell uptake) (105).

The stability of some radiopharmaceuticals is also affected by pH. For example, ^{99m}Tc-HMPAO is most stable at near-neutral pH, but demonstrates increasing rates of decomposition with increasing alkalinity (80), even when stabilized with gentisic acid (106). Maintenance of optimal pH may be problematic, however, as phosphate buffers increase the rate of decomposition of ^{99m}Tc-HMPAO with a corresponding increase in the production of ^{99m}Tc-pertechnetate (80). Similarly, ^{18}F-fluoro-DOPA exhibits rapid decomposition at pH 7 but remains chemically unchanged at pH 3.5 (107). Also, alkaline conditions during the preparation of ^{99m}Tc-MAG_3 can promote hydrolysis of the ligand to form lipophilic impurities that are excreted in the hepatobiliary system (6).

The pH of the suspending medium is critical during the labeling of platelets with ^{111}In-oxyquinoline (oxine). When outside of their natural plasma environment, platelets must be maintained at a pH of $\leq$ 6.5 in order to prevent aggregation and clumping (108-110).

MIXING ORDER

The order of mixing components in the formulation of ^{99m}Tc-radiopharmaceuticals can have dramatic effects on the resulting biodistribution. In general, the reducing agent and the chelating agent should be mixed prior to the addition of ^{99m}Tc-pertechnetate in order to obtain high labeling efficiencies. If Sn^{+2} and ^{99m}Tc-pertechnetate are combined first, an insoluble ^{99m}Tc-tin colloid may be formed, with resultant increased liver uptake (16,20,82,111). Similarly, if gentisic acid is added to HMPAO prior to its labeling with ^{99m}Tc,

excessive production of reduced/hydrolyzed Tc results (106).

Improved labeling efficiency of several ^{99m}Tc-radiopharmaceuticals can be achieved with a simple alteration in the mixing order during preparation. Instead of reconstituting the kit with the required volume of ^{99m}Tc-pertechnetate diluted previously with normal saline, the modified procedure calls for reconstitution with concentrated ^{99m}Tc-pertechnetate, incubation for 3-10 minutes, and then dilution with an appropriate volume of normal saline (112,113).

The radiopharmaceutical most affected by the mixing order is ^{99m}Tc-sulfur colloid. ^{99m}Tc-pertechnetate, hydrochloric acid, and thiosulfate solutions must be combined before being heated in order to ensure a high yield. Addition of ^{99m}Tc-pertechnetate or the acid solution after heating and/or addition of the buffer solution before heating results in negligible labeling and alterations in biodistribution reflecting ^{99m}Tc-pertechnetate (51,114). A similar effect occurs with the UltraTag® RBC kit: if Syringe I (sodium hypochlorite) is added to the reaction vial prior to the addition of anticoagulated whole blood, it will oxidize the Sn^{+2} and thus preclude subsequent ^{99m}Tc-pertechnetate reduction and labeling to RBCs (RG Wolfangel, Mallinckrodt, 1992).

REAGENT CONCENTRATION

Reagent concentrations are inversely proportional to the final preparation volumes. Low reagent concentrations may necessitate longer incubation times and/or result in complexes having different biodistribution patterns. Therefore, preparation volumes should not be unnecessarily large.

Use of a DMSA kit prepared with 2 ml of ^{99m}Tc-pertechnetate yields about 90% of the kidney-localizing complex in 15 minutes, whereas a preparation volume of 10 ml yields only about 70% in 15 minutes (101). In both cases, the remainder of the preparation consists of a different complex which is moderately localized in the bone and rapidly excreted in the urine (101). Similarly, ^{99m}Tc-IDA derivatives prepared in a volume of 10 ml compared with those prepared in a volume of 2 ml show a decreased rate of labeling (86).

The rate and extent of labeling of RBCs with ^{99m}Tc are affected by cell concentration. The incorporation of ^{99m}Tc into RBCs is directly related to hematocrit (or red cell concentration), not to cell number (67,115). With the Ultra-Tag® RBC kit, the rate and extent of labeling are decreased with the use of smaller than recommended volumes of blood and/or larger than recommended volumes of ^{99m}Tc-pertechnetate (31). Similarly, suboptimal labeling of RBCs with ^{99m}Tc using the modified *in vivo* technique occurs when inadequate blood volume is used (25).

The labeling of leukocytes or platelets with ^{111}In-oxine is also related to the number of isolated cells as well as to the concentration of oxine. Poor labeling efficiencies may result from labeling an inadequate number of cells (108,110,116-121) or from using an inadequate amount of oxine (108,117). Similarly, optimal labeling of leukocytes with ^{99m}Tc-HMPAO requires a sufficient number of cells and an adequate concentration of HMPAO (87-89,122,123).

On the other hand, excessive concentration of reagents may be detrimental to the labeling reaction. For example, use of less than 4 ml of ^{99m}Tc eluate results in decreased labeling efficiency of TechneScan MAG3™ (32); if a smaller volume of ^{99m}Tc eluate is used, dilution with normal saline to a total of at least 4 ml, either before or after addition to the reaction vial, produces acceptable labeling efficiencies (124). In the case of ^{111}In-leukocytes or -platelets, excessive concentrations of oxine can result in decreased labeling efficiency and/or decreased cell viability (108,117,119,125).

The concentration of MDP that is labeled with ^{99m}Tc may affect its subsequent biodistribution. For example, studies in rats have shown that changes in MDP concentration can result in alterations in bone, kidney, and liver uptake (83).

Following completion of the labeling procedure for some radiopharmaceuticals, the concentration of final product may also affect its stability. For example, several brands of ^{99m}Tc-DTPA are stable in stock concentrations but exhibit decreased stability with liberation of free pertechnetate when diluted (126). Solutions of ^{99m}Tc-pyrophosphate diluted *in vitro* and, to a lesser extent, *in vivo* demonstrate decreased bone uptake and increased soft-tissue and kidney localization (94). Similarly, ^{99m}Tc-HEDP and ^{99m}Tc-MDP diluted *in vitro* demonstrate decreased bone uptake and increased soft-tissue localization (127,128). The altered biodistribution of these latter radiopharmaceuticals following dilution has been ascribed to the formation of different molecular weight complexes and/or liberation of free pertechnetate (94,127,128).

HEATING

The distribution of radiopharmaceuticals that require heating as part of their preparation may be influenced by a number of factors involved in the heating process. These factors include temperature, duration of heating, and volume heated.

Temperature plays an important role in the

formation and labeling of ^{99m}Tc-sulfur colloid. Because the reaction between thiosulfate and acid is slow at room temperature, the sulfur colloid reagents are heated in a boiling water bath. For consistently high labeling yields, the temperature of this water bath should be 95-100° C. Heating at temperatures of less than 95° C may result in poor labeling of the colloid with increased remaining ^{99m}Tc- pertechnetate (38). Similarly, inadequate heating temperatures result in suboptimal ^{99m}Tc labeling of sestamibi (129,130).

The temperature used to damage ^{99m}Tc- or ^{51}Cr-RBCs for splenic sequestration studies is critical. Too low of a temperature results in insufficient RBC damage with significant activity remaining in the blood pool; too high of a temperature results in excessive RBC damage and decreased spleen uptake with increased liver uptake (131). The recommended temperature for optimal RBC damage is 49-50° C (20,131-133).

A second important factor is the duration of heating. When ^{99m}Tc-sulfur colloid is heated at 90-100° C, its labeling efficiency initially increases rapidly and then plateaus at 3-10 minutes (38,46,51,134). Thus, heating for an insufficient length of time may result in a poor labeling efficiency and increased ^{99m}Tc-pertechnetate impurity (135). The length of heating also affects the colloid particle size, with the mean colloid particle diameter increasing as a function of heating time (46,90,135). If the ^{99m}Tc-sulfur colloid is heated for an insufficient period of time, poor splenic uptake can result, whereas if it is heated for an extended period of time, lung uptake of large "colloidal" particles may result.

The degree of radiolabeled RBC damage varies directly with the length of heating time. Inadequate or extended heating of RBCs results in insufficient or excessive damage, respectively, with resultant alteration in the expected biodistribution. Optimal duration of heating is variable, depending on the type of apparatus, volume, and suspending media (131,136-140). The optimal length of heating time with use of the Brookhaven National Laboratory procedure appears to be 10-15 minutes (132,136).

Also demonstrating inferior labeling efficiencies from inadequate boiling times are ^{99m}Tc-MAG_3 (32,141), ^{99m}Tc-sestamibi (142), and ^{186}Re-HEDP (143).

The third heating-related factor is the volume to be heated. Heating of small volumes is more uniform than is heating of large volumes. Sulfur colloid preparations containing > 10 ml show inconsistent labeling efficiencies as compared with smaller volume preparations boiled for the same length of time (51). Similarly, large volumes of RBCs may demonstrate insufficient damage for splenic sequestration as compared with small volumes heated for the same length of time (138).

Even with comparable labeling efficiencies, different heating profiles may affect the subsequent biodistribution of the radiopharmaceutical product. For example, insufficient heating in the formulation of ^{186}Re-HEDP results in lower bone uptake and higher soft tissue localization, presumably because more heating is needed to drive the equilibrium to the optimal polymeric complex (143).

A related matter is that of reheating. In the case of ^{99m}Tc-sulfur colloid, reheating after buffering, especially if the final product is slightly alkaline, causes dissolution of sulfur particles which react with sulfite to reform thiosulfate; the remaining technetium sulfide is associated with extremely small colloidial particles (144).

With any heating process, expansion of gases results in increased pressure. In some cases, especially with heating in a microwave oven, the pressure generated may be high enough to cause rupture of the septum, ejection of the rubber stopper, or breakage of the vial (130,135,145,146). Therefore, an important step in the preparation of these radiopharmaceuticals is the creation of negative pressure within the vial by partial removal of its headspace atmosphere prior to heating (129,130,141).

INCUBATION

Although most ^{99m}Tc chelates are formed very rapidly, some complexation reactions require a substantial incubation time. In these latter reactions, labeling usually follows an exponential curve, with plateaus achieved after several minutes. Incubation times of approximately 10- 20 minutes are required to reach labeling plateaus for ^{99m}Tc-DMSA (101), ^{99m}Tc-IDA derivatives (86,147), ^{99m}Tc-DTPA (148,149), and both *in vitro* and *in vivo* labeled ^{99m}Tc-RBCs (25,31,66,150-152). In some of these cases, initial mononuclear complexes may form rapidly, but progression to the final dinuclear complex (dimer) proceeds more slowly (148,153). In the case of ^{99m}Tc-RBC, the rate-limiting step appears to be the transport of pertechnetate ions across the red cell membrane (151,154). Use of the agents before maximal labeling may result in increased levels of ^{99m}Tc-pertechnetate and/or other radiochemical impurities.

Similarly, incubation times of at least 10-20 minutes are required to achieve maximal labeling of leukocytes or platelets with ^{111}In-oxine (108,116-119,125,155-158) or ^{99m}Tc-HMPAO (87,89).

On the other hand, excessive incubation times or

excessive time delays between preparation steps for some radiopharmaceuticals can produce undesirable effects. For example, unacceptable labeling efficiency of ^{99m}Tc-MAG_3 occurs if there is an excessive time delay (e.g., > 5 minutes) before air is added or if there is an excessive time delay (e.g., > 3 minutes) between the addition of air and boiling (32).

The temperature at which the reactants are incubated may significantly affect the rate of labeling. In general, refrigerated reagents should be allowed to warm to room temperature prior to use. For example, preparation of cold [temperature] reagent vials can decrease the rate of radiolabeling of ^{99m}Tc-HMPAO (159). Furthermore, both the rate and extent of ^{99m}Tc-RBC labeling are related to incubation temperature with moderate and marked decreases occurring at 22° and 4°, respectively, as compared to that at 37° (67). Incubation at 37° increases the rate of ^{111}In-oxine labeling of platelets, although adequate labeling efficiencies can still be achieved at room temperature (108,118,119). In contrast, incubation at 37° does not significantly affect the rate of leukocyte labeling with ^{111}In-oxine or ^{99m}Tc-HMPAO as compared to that at room temperature (87,116,117,157,160).

The presence of other substances in the incubating medium may compete for the labeling reaction and result in radiolabeled contaminants. For example, the presence of plasma transferrin interferes with the labeling of ^{111}In-oxine to leukocytes and platelets because it strongely chelates the indium (108,110,116-118,121,125,157,158,160-163). Any ^{111}In-transferrin contamination present in the final product will then demonstrate prolonged blood pool retention and bone marrow localization (116,164). The effect of plasma on the labeling of leukocytes with ^{99m}Tc-HMPAO, however, is much less pronounced (87,123,165). Furthermore, the presence of excessive amounts of erythrocytes and/or platelets during leukocyte radiolabeling will result in radiolabeled RBCs or platelets (87,116,155,156,159,160,166-171). These contaminants then demonstrate prolonged blood pool retention and spleen uptake (156,167,168,170-172). Similarly, the presence of excessive amounts of erythrocytes during platelet radiolabeling will result in radiolabeled RBCs (118).

The *in vitro* particle size of ^{99m}Tc-tin colloid preparations increases with the length of incubation time after reconstitution and affects the relative organ uptakes (173).

The chemical form and/or nature of a radiopharmaceutical may change during the incubation period, with resultant alteration in biodistribution. For example, bone-to-soft tissue ratios for ^{99m}Tc-MDP are reportedly higher after a 30-60 minute incubation period than after shorter incubation times, even though the percent labeling efficiency remains unchanged (174,175). Apparently, a chemical form of ^{99m}Tc-MDP with a different renal clearance is slowly formed from the initial labeled product. Gel column chromatography, interestingly, shows that one hour is required to achieve maximum labeling of ^{99m}Tc-MDP (176). On the other hand, measurable deterioration in bone scan quality (with and without gastric visualization) has been reported to occur sporadically with use of incubated ^{99m}Tc-MDP (128,177). In these cases, polymeric complexes of ^{99m}Tc-MDP apparently dissociate over time to form low molecular weight complexes that have a lower affinity for bone (128). Similarly, abnormal soft-tissue localization of ^{99m}Tc-HDP and ^{99m}Tc-MDP have been associated with long makeup-to-injection times (178,179). Another example of chemical change over time involves ^{99m}Tc-DTPA for determination of glomerular filtration rate. Because of concern for radiolytic decomposition, manufacturers recommend that ^{99m}Tc-DTPA be used within one hour of preparation; protein binding to human serum albumin, however, actually decreases over time, suggestive of a radiochemical impurity that is minimized after 60-90 minutes of incubation (11).

In the case of radiolabeled blood cells, prolonged handling/storage outside of the natural plasma environment may lead to decreased viability. For example, a somewhat lower sensitivity for abscess detection has been reported for ^{111}In-leukocytes suspended in normal saline for more than one hour as compared to those suspended in normal saline for less than one hour (180).

PARTICULATE SIZE AND NUMBER

The biodistribution of particulate radiopharmaceuticals occurs as a function of their size. Particles so small as to be considered soluble (e.g., ^{99m}Tc-HSA and some other proteins) remain in the blood pool and soft tissue and may degrade image quality (181,182). Particles in the colloid size range demonstrate RES localization; maximal bone marrow uptake is correlated with smaller colloid size (183-187), with progressive splenic localization occurring as the colloid size increases (188-190). Particles of even larger size (> 5-10 μ) become physically trapped in capillaries and precapillary arterioles (191).

The particle size of ^{99m}Tc-sulfur colloid can be influenced by a number of factors (discussed here and elsewhere in this lesson) including aluminum ion concentration, heating time and temperature, and storage time. After preparation and during storage,

^{99m}Tc- sulfur colloid particles may aggregate over time to form clumps large enough to lodge in the pulmonary capillaries and produce lung visualization (90,192). The use of stabilizing or protecting agents, such as gelatin, in the sulfur colloid formulation markedly improves particle size stability (192,193).

^{99m}Tc-tin colloid is another radiopharmaceutical in which particle size increases over time resulting in increasing spleen/liver ratios (173,194). Stabilization with a surfactant (Poloxamer 188) effectively maintains initial particle size when the preparation is left undisturbed (194,195); when the preparation is subjected to continuous agitation (e.g., during transportation), however, particle size increases significantly to the extent that lung uptake occasionally occurs (194,195).

On the other hand, small radiocolloids may underestimate splenic function and possibly result in a misdiagnosis of functional hyposplenia. This problem has been observed with ^{99m}Tc-phytate colloid, which frequently demonstrates insufficient splenic uptake to provide images of diagnostic quality (188,190). The splenic uptake of ^{99m}Tc-phytate can be improved by the addition of ionic calcium to induce colloid aggregation (190).

The particle size of perfusion lung imaging agents may have undesirable effects on pulmonary localization. High blood pool activity has been reported following the administration of ^{99m}Tc-macroaggregated albumin (MAA) preparations containing significant amounts of soluble protein (181,182). Small particles and particle fragments < 10 μ may pass through the pulmonary capillaries and be phagocytized by the liver and spleen (181,191). MAA and albumin microsphere preparations may also demonstrate clumping of the particles during storage. Injected intravenously, particulate clumps > 100 μ lodge in pulmonary arteries and result in focal hot spots on the lung image (191-196).

The particle size of perfusion lung imaging agents may also affect their late biodistribution. For example, MAA products with a larger mean particle size demonstrate longer biologic half-lives in the lungs (197).

Clumping of blood cell preparations will also result in pulmonary embolization. For example, clumping of leukocytes can occur during the radiolabeling procedure and result in lung localization (116,120).

The number of injected particles in MAA and microsphere preparations is important in terms of both image quality and toxicity. Too few injected particles may result in degradation of lung images with demonstration of definite perfusion abnormalities, especially peripheral patchiness (198,199). The minimum number of particles that should be administered for lung imaging in an adult patient is 60 particles/gm of lung tissue or 60,000 particles (198,199). Injection of > 250,000 particles offers little improvement in image quality while increasing the risk of toxicity (199).

Particulate radiopharmaceuticals for perfusion lung imaging tend to settle or sediment with time (200). The rate of sedimentation is variable depending on the manufacturer (200). Therefore, before a dosage is withdrawn, the vial should be gently inverted several times to resuspend the particles. Failure to resuspend particles may result in withdrawal of a larger-than-expected volume, a somewhat higher percentage of ^{99m}Tc-pertechnetate in the withdrawn dose, and/or an inadequate number of particles for lung imaging. These same results can also be caused by adsorption of ^{99m}Tc-MAA particles onto the walls of vials or syringes; in some combinations of MAA product/container/storage condition, up to 75% of the particles are adsorbed (201). Similarly, ^{99m}Tc-sulfur colloid has a tendency to adsorb over time onto the surfaces of glass vials, which thus necessitates withdrawal of a larger-than-expected volume for the required radioactivity dosage (90,192,194,202,203). An even greater degree of adherence to glass vials occurs with ^{99m}Tc-tin colloids, which further increases over time and with agitation (194).

Droplet size of radioaerosols for inhalation lung imaging is also extremely important. Droplets too large tend to deposit in the mouth and central airways while droplets too small tend to be exhaled (204,205). Thus, the different mean droplet sizes produced by different radioaerosol delivery systems may result in variations in the rate of deposition and/or the distribution of deposited radioaerosol (204). Other factors than can affect the size and abundance of radioaerosol droplets include relative humidity (204), air (or oxygen) flow rate (205), and addition of ethanol (205-207).

COMMERCIAL SOURCE

The commercial source of reagent kits and the compatibility of generator eluates with these kits may affect the final radiochemical purity of many ^{99m}Tc-radiopharmaceuticals. A specific kit that yields a highly labeled product when it is prepared with ^{99m}Tc from one generator supplier may demonstrate decreased labeling and increased ^{99m}Tc-pertechnetate impurity when it is prepared with ^{99m}Tc from an alternate supplier. This phenomenon has been reported in the preparation of various ^{99m}Tc-sulfur colloid (15,208), ^{99m}Tc-HSA (208), ^{99m}Tc-DTPA (126), and ^{99m}Tc-HDP products (209). The radiochemical purity of

^{99m}Tc-HMPAO has a tendency to be lower when prepared with eluates from one company's generators, although this decrease is not statistically significant (211). In the case of ^{99m}Tc-MAG_3, the poor labeling efficiency reported with the use of one company's generators (32) has been traced to the presence of chemical contaminants leached from the vial stoppers (RG Wolfangel, Mallinckrodt, 1992). Similarly, the poor radiochemical purity of some ^{99m}Tc-antibody conjugates prepared with pertechnetate from certain generators has been shown to coincide with the presence of 2-mercaptobenzothiazole, a chemical used in manufacturing the non-halogenated butyl stoppers of the collection vials (210); this problem is not apparent if the pertechnetate is collected in vials fitted with chlorobutyl stoppers (210).

The biodistribution of labeled kits may also be affected by the source of ^{99m}Tc. For example, abnormal soft-tissue localization is seen much more frequently when ^{99m}Tc-MDP and ^{99m}Tc-HDP are prepared with instant (methyl ethyl ketone extraction) technetium than with technetium from generators (179,212). Also, differences in Al^{+3} contamination in different generator eluates (42,43,45) may affect several radiopharmaceuticals as described above.

Even with comparable labeling, reagent kits from different commercial sources may result in significant differences in biodistribution and elimination kinetics. Various ^{99m}Tc-HSA kits contain differing amounts of α-colloids which localize in the liver (213). The various ^{99m}Tc-HSA kits also exhibit substantial differences in plasma clearance rates and urinary excretion (214,215). Similarly, various preparations of ^{99m}Tc-DTPA exhibit significantly different glomerular filtration rates (11,216-218). Although the renal concentrations of two ^{99m}Tc-DMSA preparations are equivalent, values for liver uptakes are markedly different (219). Gastric, hepatic, gallbladder, and/or intestinal localization is reportedly more frequent with unstabilized ^{99m}Tc-MDP products than with ^{99m}Tc-MDP products containing antioxidants (220,221). Also, variations in lung-to-background ratios for ^{99m}Tc-MAA may be related to differences in particle size distribution and/or soluble radiochemical impurities (222).

At least four different complexes of ^{99m}Tc-MDP have been demonstrated by electrophoretic analysis of MDP kits from different manufacturers (223). One of these complexes results in accumulation of activity in the liver. Results of *in vitro* and *in vivo* studies have suggested that this liver localization is associated with methylphosphate, a degradation product formed from the hydrolysis of MDP (223). The results of further studies have suggested that variations in image quality obtained with different preparations of MDP may be associated with differences in kit formulation such as the MDP salt form, the ratio of stannous to MDP, and the presence of an antioxidant (224). Similarly, ^{99m}Tc-HDP and ^{99m}Tc-HEDP have been shown to exist as various complexes that exhibit various biodistributions (39,225).

In some instances, poor labeling efficiencies may simply be attributed to substantial intra- and inter-lot variability of the reagent kits. Examples of this type of variability include HSA (18) and Ceretec™ (29,211).

Poor labeling of some kits with ^{99m}Tc may also be related the source of normal saline used in their preparation. For example, certain sources of normal saline have been implicated in poor radiolabeling of HMPAO (26) and of RBCs (226).

Radiochemical impurities can also arise from chemical contaminants leached from disposable syringes. For example, chemical impurites leached from the rubber tips of some syringe plungers can be labeled with ^{99m}Tc and show kidney and hepatobiliary excretion (227).

Alterations in biodistribution can also occur with non-^{99m}Tc-labeled radiopharmaceuticals obtained from different sources. ^{67}Ga-citrate obtained from one manufacturer readily localizes in cerebral infarctions but that obtained from another manufacturer does not (228). This phenomenon may be related to differing citrate concentrations in the preparations (229). Considerable differences in the percentage of radioactive impurities (e.g., free iodide) in commercially available ^{131}I-iodohippurate products can result in important differences in the patient's thyroid dose (230). Also, ^{131}I sodium iodide capsules from different vendors exhibit different dissolution profiles which may result in differences in bioavailability (231,232).

Radioiodination yields may also be associated with the source of the radioiodide. For example, some radioiodide solutions contain a mixture of radiochemicals that, albeit unidentified, are separatable by high performance liquid chromotography (HPLC), and that do not significantly contribute to radioiodination reactions (233).

Incompatibilities between radiopharmaceutical solutions and rubber-stoppered glass vials have also been reported. For example, significant differences in the stability of stannous chloride solutions have been observed in vials stoppered with different types of elastomeric closures (234). Similarly, significant differences in the adsorption of ^{99m}Tc-DMSA on the walls and stoppers of glass vials from different manufacturers have been observed with storage (235).

OXIDATION AND/OR RADIOLYTIC DECOMPOSITION

In the formulation of ^{99m}Tc-radiopharmaceuticals, a variety of factors may produce detrimental effects on the initial labeling process and subsequent stability. Many of these factors are related to oxidation and radiolytic decomposition which lead to increased levels of ^{99m}Tc- pertechnetate and/or ^{99m}Tc-colloid impurities.

In order for ^{99m}Tc to be chelated by most reagents, it must be reduced from the + 7 valence state of pertechnetate to a lower valence state. This reduction usually is accomplished by stannous ion (Sn^{+2}) in the reagent kit. Sn^{+2} is readily oxidized by atmospheric oxygen to stannic ion (Sn^{+4}) which is no longer capable of reducing pertechnetate. Therefore, reagent solutions and lyophilized kits usually are purged with nitrogen (or argon) and/or have nitrogen (or argon) atmospheres in order to remove the atmospheric oxygen responsible for this oxidation (20,29,71,72,75,76,236). Furthermore, storage at refrigerator or freezer temperatures has been shown to inhibit the rate of oxidation (71). Trace amounts of oxygen may continue to produce this oxidation during manufacture and/or storage of reagent kits, especially if faulty vial seals allow the entrance of air (237). Formulation of such a product usually results in decreased labeling efficiency with increased ^{99m}Tc-pertechnetate impurity.

Oxidizing agents present in ^{99}Mo/^{99m}Tc generator eluates also may interfere with the technetium labeling process. Ionization of water in the generator column produces hydrogen peroxide (H_2O_2) and, in the presence of oxygen, hydroperoxy free radicals ($\bullet HO_2$) (28,48,238). Both of these compounds are strong oxidizing agents and react with Sn^{+2} to produce Sn^{+4}. In some cases, the number of peroxide molecules added to a reagent kit may be of the same order of magnitude as the number of Sn^{+2} ions (28). Reports of decreased labeling efficiencies and increased ^{99m}Tc-pertechnetate impurities are commonly associated with these larger-than-expected concentrations of peroxides and hydroperoxy radicals (26,28,84,239). Similarly, the presence of sodium nitrate, another oxidizing agent in some ^{99m}Tc generator eluates, can interfere with labeling reactions (126). Dissolved oxygen present in ^{99m}Tc generator eluates is another potential oxidizing agent. For example, nitrogen-purging of eluates has shown beneficial, albeit small, effects on ^{99m}Tc-HMPAO labeling efficiency and stability (240). The actual amounts of oxidizing agents in eluates are variable depending on the manufacturer of the generator, but appear to be the greatest in the first eluate (45).

Free radicals and peroxide may also be produced over time in ^{99m}Tc-pertechnetate solutions, especially those of high specific concentrations. Peroxide production has been shown to be a function of Tc-99m radioactivity (relatively constant at about 33 X 10^{-5} μg/mCi/hr) and of dissolved oxygen (48). For example, the poor labeling efficiency of ^{99m}Tc-MAG_3 observed when prepared with ^{99m}Tc-pertechnetate greater than six hours old has been attributed to this effect (RG Wolfangel, Mallinckrodt, 1992). Similarly, radiolytic production of oxidizing agents in ^{99m}Tc-pertechnetate solutions is a contributing factor in the poor labeling efficiency and stability of ^{99m}Tc-HMPAO prepared with aged eluates (240). This effect may be attenuated by the addition of sodium iodide, a reducing agent, to the eluate (240).

Oxidation of reduced and chelated ^{99m}Tc may also be associated with physical factors. For example, aerosolization of ^{99m}Tc-DTPA for inhalation lung studies using either ultrasonic or jet nebulizers reportedly results in significant oxidation of the ^{99m}Tc with liberation as free pertechnetate (241-243). However, this phenomenon has not always been reproduced by others (149). In any case, since ^{99m}Tc-pertechnetate and ^{99m}Tc-DTPA have different clearance rates from the lung, liberation of activity as free pertechnetate by any mechanism may result in variable, inconsistent lung studies.

On the other hand, purposeful addition of oxidizing agents may, in limited instances, be required to produce a high labeling yield. For example, at least 2 ml of air must be added during the preparation of ^{99m}Tc-MAG_3 to prevent the progressive formation of radiochemical impurities (32). A second example is that involving ^{99m}Tc-labeling of RBCs *in vitro* wherein dilute sodium hypochlorite is used to oxidize excess extracellular stannous ion; high labeling efficiencies are thus achieved without the need for centrifugation (244-246). Since optimum labeling efficiencies of ^{99m}Tc-RBC preparations are achieved in the absence of extracellular Sn^{+2}, chelating agents such as EDTA or acid-citrate-dextrose (ACD) are used to sequester remaining extracellular Sn^{+2} and make it available to the hypochlorite. Of these two sequestering agents, ACD is preferred since EDTA may cause RBC damage resulting in a shortened biologic half-life in the blood and splenic accumulation (244,245,247).

Decomposition of radiopharmaceuticals is characterized by four mechanisms: internal radiation effects, direct radiation effects, indirect radiation effects, and nonradiolytic chemical effects (52). Of significance in radiopharmaceutical solutions are the indirect radiation effects resulting from the ionization of

water which produces the strong oxidants, hydrogen peroxide and, in the presence of dissolved oxygen, hydroperoxy free radicals (48,238,248). Radiolytic decomposition is a function of total radioactivity content, since it is dose rate dependent rather than total dose dependent (78,249). Decomposition of virtually all radiopharmaceuticals will occur if sufficient time is allowed; however, the rate of decomposition varies widely from one radiopharmaceutical to another and from one formulation and/or storage factor to another (10,126,230,250,251). All radiopharmaceuticals should, therefore, be used as soon after preparation as possible to avoid radiolytic decomposition problems.

The stability of radiopharmaceuticals can be prolonged by a number of tactics that inhibit oxidation and/or radiolytic decomposition. Since dissolved oxygen promotes formation of peroxide and hydroperoxy radicals, various approaches such as minimizing the exposure of a radiopharmaceutical to the atmosphere, purging the solution with nitrogen, limiting introduction of air (especially bubbling) into the vial, avoiding vigorous shaking, avoiding or mininizing addition of standard sodium chloride injection for dilution, and storing the product in a glass vial instead of in a plastic syringe can be applied to help minimize oxidation and/or decomposition (10,37,74,78,79,99,111,126,159, 252-256). Oxygen-free saline and commercially available low dissolved oxygen (LDO) saline have been recommended as offering beneficial effects on radiopharmaceutical labeling and stability (48,76). For example, the use of low dissolved oxygen in the preparation of ^{99m}Tc-HDP apparently prevents of the formation of an unidentified radiochemical impurity that localizes in liver and gallbladder (209). Routine use of low dissolved oxygen saline remains controversial, however, in light of data showing that the labeling efficiency and stability of ^{99m}Tc-gluceptate and the clinical performance of ^{99m}Tc-MDP are only minimally affected by the oxygen content of the saline used (257,258).

Excess stannous ion is effective for prolonging stability but may result in colloid formation if there is an overabundance of this ion (74,75,78,79). Perhaps more effective is the use of antioxidants (e.g., ascorbic acid), which have been shown to remove peroxide already present as well as to prevent subsequent peroxide buildup (48). For example, the use of ascorbic acid or gentisic acid in ^{99m}Tc- bone imaging agents has been shown to dramatically improve stability and image quality with storage over several hours (75,79,255,259-263). Gentisic acid has also been investigated as a stabilizing agent for ^{99m}Tc-HMPAO (106). It should be noted, however, that preparations stabilized with these antioxidants often demonstrate higher levels of reduced-hydrolyzed technetium than do non-stabilized preparations (264). Ammonium formate may also be useful to retard radiolytic decomposition (265).

Oxidation and/or radiolytic decomposition proceeds at faster rates with increased temperatures; therefore, reducing the temperature by refrigeration may noticeably prolong the stability of most radiopharmaceuticals (101,249,266,267). The addition of carrier, although seldom desired, may also improve the stability of many radiopharmaceuticals (85,249). Closely paralleling the effect of carrier, the addition of HSA may improve the stability of labeled antibodies (268). Finally, because radiolytic decomposition is a function of total radioactivity content/specific concentration, greater stability is achieved from formulation with the minimum desired radioactivity than is achieved from formulation with larger amounts of radioactivity (29,35,36,78,248,255,267,268).

Radiolytic generation of free radicals may be problematic in the development and utilization of alpha- and/or beta-emitting therapeutic radiopharmaceuticals as well as positron-emitting radiopharmaceuticals. High specific concentrations, coupled with large equilibrium dose constants, produce an environment conducive to the production of free radicals. For example, high specific activity ^{18}F-N-methylspiroperidol undergoes significant radiolytic decomposition resulting in the production of ^{18}F-fluoride (265). Half of the original stannous and gentisic acid in commercially-produced ^{186}Re-HEDP is lost within 14 days as a consequence of free radical production (269). Furthermore, high levels of radioactivity can degrade proteins such as monoclonal antibodies (270).

SPECIFIC ACTIVITY

The specific activity of radiopharmaceuticals may have important effects on their biodistribution. The effects of lowered specific activity on radiopharmaceutical biodistribution are most pronounced when the mechanism for localization of the agent demonstrates saturation pharmacokinetics. Saturation may occur whenever there are only a limited number of receptor sites, carriers, enzymes, or other interactive biological substances responsible for the localization (271). In these circumstances, carrier will compete with the specific radiopharmaceutical for these limited sites, and if saturation occurs, target-to-background radioactivity ratios will decrease.

A classic example of this phenomenon is the thyroid uptake of radioiodide. As little as 1 mg of carrier

iodide may produce notable decreases in the 24-hour ^{131}I uptake (272), and dosages of sodium iodide > 10 mg suppress the 24-hour radioiodine uptake by 98% (273).

For the Schilling test, the amount of nonradioactive cyanocobalamin in the ^{57}Co-cyanocobalamin capsules has been shown to be critical. Amounts > 2 μg appear to exceed the saturation level for intrinsic factor and may result in falsely low values for absorption and urinary excretion (274,275). Increasing amounts of ^{99m}Tc-sulfur colloid particles affect phagocytic localization, which results in a gradual decrease in liver uptake and an increase in bone marrow uptake (183). Likewise, the number of damaged radiolabeled RBCs administered for a splenic sequestration study may be important in certain clinical situations in which overloading the sequestering ability of the spleen is possible (138). The presence of carrier markedly affects the biodistribution of ^{67}Ga-citrate by inhibiting localization in all usual (expected) organs except bone (276,277).

Many of the newer and investigational radiopharmaceuticals are localized by mechanisms with limited capacities. Examples include carrier-mediated uptake of hepatobiliary agents (271), antibody-antigen interactions involving radiolabeled specific antibodies (278,279), and hormone-receptor localization of radiolabeled hormone analogs (280,281). In each of these cases, lowered specific activity results in decreased target-to-background radioactivity ratios and inferior image quality. It should be noted, however, that in the presence of circulating antigen, a lower specific activity of radiolabeled antibodies is desired. If high specific activity and small amounts of total antibody are administered in this latter case, most of the radioactivity will be complexed to circulating antigen and cleared into the liver (282).

The distribution of some radiopharmaceuticals is relatively unaffected by specific activity. Carrier MAA does not affect the quality of lung perfusion images (199) and a 10^6-fold excess of carrier gluconate does not influence distribution of ^{99m}Tc-gluconate (16).

SOLUBILITY

The solubility of ^{99m}Tc-radiopharmaceuticals in a suitable medium for intravenous administration usually does not present a significant problem since the polar hydrophilic nature of these agents allows formulation in normal saline. Some of the more lipophilic agents, however, may require a certain volume of normal saline to effect and maintain dissolution. For example, ^{99m}Tc-disofenin reconstituted in a total volume of 2-3 ml becomes cloudy over time, whereas it remains in solution when reconstituted in a total of 4-5 ml (RM Sullivan, Du Pont, 1988).

A few radiopharmaceuticals (e.g., radiolabeled cholesterols, amino acids, fatty acids) are essentially insoluble in water at physiological pH values, and their formulation is problematic. A common problem encountered with use of these latter agents is incomplete or unstable solubilization leading to increased RES and/or lung localization as a result of colloid and/or particulate formation (283). Based on toxicity considerations, the requirement for intravenous administration of most radiopharmaceuticals limits the choice of surfactants available for solubilization of agents (284,285). Recent evidence supports the use of hydroalcohol HSA (286) and the relatively nontoxic poly(oxypropylene)poly(oxyethylene) condensates (Pluronics) for this purpose (287).

PRESERVATIVES/ANTISEPTICS

Since sterility of products for parenteral administration is essential, it might be surmised that bacteriostatic saline should be used in the preparation of injectable radiopharmaceuticals. Unfortunately, bacteriostatic saline may have serious deleterious effects on many ^{99m}Tc- radiopharmaceuticals. Most of these effects can be traced to reactions with benzyl alcohol, the most commonly used active agent in bacteriostatic saline.

When bacteriostatic saline is used to elute a $^{99}Mo/^{99m}Tc$ generator, up to 99% of the ^{99m}Tc activity may be retained on the generator column (288). It is theorized that the benzyl alcohol in the bacteriostatic saline may be transformed by radiolytic oxidation to benzaldehyde, a weak reducing agent. One or both of these species may then reduce the ^{99m}Tc-pertechnetate *in situ* to an insoluble form which is retained on the column.

Bacteriostatic saline used in the preparation of ^{99m}Tc-radiopharmaceuticals may adversely affect the radiochemical purity, stability, and biodistribution. ^{99m}Tc-pertechnetate dissolved in bacteriostatic saline demonstrates a significant increase in the percentage of ^{99m}Tc-colloid impurities (288). ^{99m}Tc-MDP prepared with bacteriostatic saline exhibits significantly more ^{99m}Tc-pertechnetate impurity, a faster rate of decomposition, and higher blood, muscle, and liver background activity than does ^{99m}Tc-MDP prepared with preservative-free saline (288). Because of these potential deleterious effects, only preservative-free saline should be used in the preparation of ^{99m}Tc-radiopharmaceuticals.

Additionally, benzyl alcohol (and sodium bisulfite) has been shown to increase the rate of radiolytic decomposition of ^{18}F-N-methylspiroperidol (265).

Benzyl alcohol is of limited applicability for two additional reasons. First, it is a vasodilator and, therefore, cannot be used with a radiotracer such as ^{133}Xe in saline solution intended for regional blood flow measurements (289). Second, it undergoes radiation decomposition with the production of a precipitate (presumably benzoic acid) in certain solutions of high radioactive concentrations (289).

Another source of potentially interfering chemicals is the inadvertent entry of antiseptic solutions during puncture of vial diaphragms. For example, iodinated antiseptics, which are good oxidizing agents, can inhibit ^{99m}Tc-labeling reactions and cause rapid release of previously bound ^{99m}Tc as free pertechnetate (290); it has been suggested that this effect can be avoided by using alcohol instead of iodinated antiseptics (290). A more recent report, however, has shown that isopropyl alcohol contamination can also cause a time-related breakdown of ^{99m}Tc-HDP with gastric localization of the resulting ^{99m}Tc-pertechnetate (291). In another example, entry of trace amounts of cetrimide/chlorhexidine solution in ^{99m}Tc-DMSA preparations was shown to result in a labeled colloid that is taken up in the liver and spleen (292).

ANTICOAGULANTS

The *in vitro* labeling of RBCs for subsequent reinjection requires that the blood sample be fully anticoagulated. Unfortunately, the presence of an anticoagulant, usually heparin or ACD, may affect the labeling and/or biodistribution of the labeled RBCs. For example, using the *in vivo - in vitro* technique, RBCs labeled with ^{99m}Tc in the presence of heparin show a lower labeling efficiency, more extravascular activity, and more urinary excretion than do those labeled in ACD (21). Conversely, *in vitro* labeling using the UltraTag® RBC kit produces excellent labeling efficiencies using heparin in concentrations ranging from 10 units/ml blood through 10,000 units/ml blood, whereas labeling efficiencies using ACD, although excellent at a concentration of 0.15 ml/ml blood, rapidly decrease with excessive ACD concentrations (31). This effect is apparently caused by the ability of excessive ACD to sequester stannous ions and thereby effectively inhibit the rate and extent of the RBC "tinning" process (31). This effect also occurs if EDTA is used as the anticoagulant (115). Furthermore, with the UltraTag® RBC kit, the presence of clinically-encountered amounts of carrier ^{99}Tc has no appreciable effects on RBC labeling efficiency when heparin is used as the anticoagulant, whereas the RBC labeling efficiency is markedly decreased when ACD is used (22-24,31). These deleterious effects of ACD may be overcome, however, by employing an ACD concentration of only 0.125 ml/3 ml blood (293).

Even with comparable labeling efficiencies, the particular anticoagulant used may affect the subsequent biodistribution of the labeled cell product. For example, ACD, in contrast to heparin, results in less ^{99m}Tc labeling to hemoglobin and more to RBC membranes where it can more easily elute from the cell (294). In a clinical setting, ACD used for *in vitro* ^{99m}Tc RBC-labeling demonstrates a lower cardiac blood pool-to-background ratio than does use of heparin (295).

A marked excess of ACD may also cause damage to RBCs, with resultant sequestration in the spleen (296).

In the preparation of radiolabeled leukocytes, ACD is preferred over heparin as the anticoagulant because ACD decreases the tendency of neutrophils to adhere to plasticware (i.e., tubes, pipets) (164). Also, if leukocytes are labeled with ^{111}In-tropolone or ^{111}In-mercaptopyridine-N-oxide, anticoagulation with ACD results in substantially higher labeling efficiencies than those using heparin (297).

In the preparation of radiolabeled platelets, ACD is preferred over heparin as the anticoagulant because of its pH and buffering properties (*vide supra*). However, the presence of ACD in the final labeling medium reduces the labeling efficiency (108).

STEREOISOMERIC FORM

Molecules that have one or more chiral centers have the potential to exist in more than one three-dimensional configuration. Stereoisomers that are mirror-images of each other are termed enantiomers, while those that are not mirror-images are termed diastereoisomers. Although stereoisomers can have the same molecular weight, size, lipophilicity, charge, and general shape, the different spacial orientation of substituents can cause differences in biodistribution (298).

This phenomenon may be especially pronounced for substances that bind to specific receptors for transport, retention, or metabolism. For example, the *d,l* form of ^{99m}Tc-HMPAO exhibits greater uptake and longer retention in the brain than does the meso form (299). This difference may be reflective of differences in interaction with glutathione, since the *d,l* form shows a sevenfold greater rate of interaction with glutathione *in vitro* (300). Differences in the rate and extent of leukocyte labeling are also exhibited by the *d* and *l* forms of ^{99m}Tc-HMPAO (301). Similarly, in the case

of ^{99m}Tc-ethyl cysteinate dimer (ECD), both the "L,L-" and "D,D-" forms accumulate in the brain, but only the "L,L-" form is well retained (302). This difference reflects differences in metabolism involving enzymatic cleavage of the ester (302). Different biodistribution patterns are also apparent for the *d,l* and meso forms of ^{99m}Tc-DMSA (303).

The effects of stereoisomeric form are perhaps no more apparent for radiopharmaceuticals than for many of the positron-emission tomography (PET) radiopharmaceuticals. For example, the presence of ^{18}F-2-fluoro-2-deoxymannose, a stereoisomer of ^{18}F-2-fluoro-2-deoxyglucose (FDG), can affect the quantitative estimation of cerebral glucose metabolism due to differences in rates of phosphorylation and back-diffusion (304). Other examples of stereoisomers showing differences in localization due to differences in metabolism and/or receptor-binding include ^{11}C-raclopride, ^{11}C-nicotine, and ^{11}C-cocaine (305). A complete list of radiopharmaceuticals for which stereoisomeric effects are known or can be anticipated is almost endless.

ENCAPSULATION

Encapsulation of radiopharmaceutical dosages for oral administration has gained widespread acceptance as a convenient method for the handling, dispensing, and administering of certain radioactive compounds. The use of encapsulated radiopharmaceuticals presupposes that the capsule will rapidly disintegrate and its contents dissolve in the stomach fluids and that the radiopharmaceutical will not interact with the capsular materials. Some evidence has suggested that the aforementioned assumptions are not valid and that this oral dosage form may alter the biodistribution of the radiopharmaceutical.

The possibility of residual ^{131}I contained in some undissolved capsule was suggested as the cause of right-lower-quadrant activity reported in a patient administered encapsulated ^{131}I sodium iodide (306). Subsequent studies of the effect of encapsulation on the thyroid uptake of ^{131}I sodium iodide demonstrated substantially lower uptakes with capsules than with oral solution (306). Proposed mechanisms for this effect include delayed dissolution and absorption of the radioiodide, formation of a nonabsorbable iodine complex with capsular material, and/or formation of radioiodinated gelatin. A situation has also been reported in which the presence of β-naphthol, a bacteriostatic agent in the ^{131}I sodium iodide capsule, resulted in the formation of iodinated β-naphthol (307). This effect is most serious when it may alter the interpretation of a radioactive iodine uptake study or produce visualization of abdominal activity. With the recent development of a new ^{131}I sodium iodide capsule formulation, however, it is reported that the aqueous radioiodination of gelatin can be prevented by suspending the radioiodide within a polyethylene glycol base (308). Furthermore, rapid dissolution of the polyethylene glycol base in gastric fluid allows bioavailability equal to that from oral solutions (308). In spite of these advances in ^{131}I sodium iodide capsule formulations, currently marketed ^{131}I sodium iodide capsules exhibit different dissolution profiles which may result in differences in bioavailability (231). The dissolution profile of one vendor's product resembles that of a sustained release capsule, possibly due to the formation of an ^{131}I-magnesium stearate complex (231,232). Furthermore, some therapeutic ^{131}I sodium iodide capsules exhibit a decrease in radiochemical purity over time with a corresponding increase in radiolytically-produced iodinated capsule components (e.g., ^{131}I-gelatin), and may thus result in under-dosing the patient (309).

Encapsulated ^{57}Co-cyanocobalamin, compared with ^{57}Co-cyanocobalamin solution, has been shown to result in significantly decreased absorption and urinary excretion when administered for Schilling tests (310). The difference in drug availability between the capsule and the solution is probably due to both the speed of capsule dissolution and the passage of the capsule mass from the stomach to the duodenum. Since falsely low urinary excretion values obtained with the encapsulated material may result in a false interpretation of pernicious anemia, a liquid dosage form has been recommended (310).

The interpretation of second-stage Schilling tests may also be altered by the administration of encapsulated doses. The coadministration of encapsulated intrinsic factor, compared with the administration of a solution of intrinsic factor premixed with ^{57}Co-cyanocobalamin, has been shown to result in significantly decreased urinary excretion (311). The difference in urinary excretion between the two forms of administration may be due to prolonged capsule dissolution, biological inactivity of some commercial intrinsic-factor preparations, and/or the binding of intrinsic factor to blocking antibodies in the gastric juice (311-313). Since falsely low urinary excretion values obtained with encapsulated intrinsic factor may result in a false interpretation of intestinal malabsorption, it has been recommended that intrinsic factor and ^{57}Co-cyanocobalamin should be mixed together in water prior to administration (311-313).

ISOTOPE EXCHANGE

The dual isotope (Dicopac™) Schilling test allows simultaneous performance of first- and second-stage Schilling tests for the diagnosis of pernicious anemia or intestinal malabsorption syndrome. Unlike the traditional Schilling test, the dual-isotope procedure employs the co-administration of ^{58}Co-cyanocobalamin and ^{57}Co-cyanocobalamin bound to human intrinsic factor. Experience, however, has indicated a disturbingly high frequency (17-46%) of spurious results with use of the dual-isotope method (314-317). These misleading results are probably due to rapid or variable rates of exchange of bound and free cyanocobalamin on the intrinsic factor molecule (316-318). This exchange is especially striking at an acidic pH, at which equimolar equilibrium may be achieved within 10 minutes in simulated gastric juice (316). In order to obviate the effect of exchange reactions, it may be desirable to separate administration of the two dosages by two hours or to perform the traditional Schilling test (316,317). The significance of this effect in a clinical setting remains controversial, however, as the manufacturer continues to recommend that the two dosages be administered simultaneously (319).

IODINE VOLATILITY

Inhalation of volatilized radioiodine is a potential problem associated with the handling and administration of ^{131}I sodium iodide oral solutions. Airborne ^{131}I activity in excess of maximum permissible concentrations has been reported with the handling of therapeutic amounts of ^{131}I and the administration of such dosages (320,321). Furthermore, the thyroid glands of the personnel handling these dosages may be exposed to substantial radiation by the accumulation of ^{131}I (320-325).

The iodide ion in ^{131}I sodium iodide solution is easily oxidized to iodine by dissolved oxygen in an acidic solution (326,327). The presence of oxygen can occur from exposure to air (327) and/or oxygen generation by the radiolysis of water (324). Hydrogen ions can be present from acid formulation of the solution (321) and/or from reactions accompanying the dissolution of carbon dioxide in water (327). The iodine thus formed is not very soluble in water and rapidly volatilizes out of solution (327).

The rate of volatility is influenced by a variety of factors, and a number of methods that diminish this rate have been developed. The most important factor is that of pH. The use of buffers to maintain an alkaline pH has resulted in significantly lowered volatility rates and decreased thyroid accumulation, as compared with acidic formulations (321-323,325,328).

Several other formulation methods also focus on the oxidation reaction. Addition of an antioxidant such as sodium bisulfite or thiosulfate to the formulation helps to inhibit the oxidation of iodide to volatile forms of iodine (308,321,327,328). Inclusion of a chelating agent such as disodium edetate prevents catalytic oxidative reactions by metal ions (321,328), and the use of distilled water as a diluent circumvents the problem of iodide oxidation by chlorine in tap water (324). Storing and handling the solution at room temperature or below helps inhibit the heat catalysis of the oxidation reaction (327) and reduces the vapor pressure of volatile iodine (329).

One last formulation method for reducing volatility of ^{131}I sodium iodide is encapsulation. ^{131}I sodium iodide diagnostic and therapeutic capsules have been shown to produce negligible airborne radioactivity, probably because many oxidation factors are eliminated and/or the iodine may be absorbed by the capsular material (308,320). The major limitation with capsules from a clinical point of view is that patient dosages are restricted to combinations of available capsule sizes. In response to the inadequacies of conventional dosages forms (liquid and capsules), a new coated-bead formulation of ^{131}I sodium iodide has recently been developed that appears to provide a high degree of radiation safety while maintaining bioavailability and allowing flexibility in dosage selection (330).

Although formulation approaches have been designed to minimize the volatility of therapeutic ^{131}I sodium iodide products, significant differences exist between various commercial products for both oral solution and capsule dosage forms (331,332).

An additional source of inhaled radioactivity from ^{131}I sodium iodide capsules and solutions is ^{131m}Xe, a 1% abundant daughter of ^{131}I (333). Thus all ^{131}I containers, regardless of whether the contents are capsules or solution, should be opened in a suitable hood.

RADIONUCLIDIC CONTAMINATION

Several radiopharmaceuticals contain radionuclidic impurities in large enough quantities to be of concern. Especially susceptible to the production of radionuclidic contaminants are those radioisotopes produced in a cyclotron (334). Another possible cause of significant radionuclidic contamination is parent breakthrough in a generator eluate (335,336).

One of the most important concerns is the increase in radiation absorbed dose from radionuclidic impurities. For example, the radiation absorbed doses

to the thyroid and the whole body from radioiodide impurities (e.g., ^{124}I in some ^{123}I products) approach, and may even exceed, the absorbed doses from the principal radioisotope (337). Furthermore, in rare cases of excessive ^{99}Mo contamination in ^{99m}Tc generator eluates, radiation absorbed doses to the liver can be increased by up to three orders of magnitude (335). In routine practice, however, this is not a significant concern since quality control procedures are used to assure that ^{99}Mo contamination remains less than 0.015 % at the time of administration (338).

Another concern is the potential errors in dose calibration. Since an ionization chamber does not have intrinsic energy discrimination capability, the presence of radionuclidic impurities will affect the reading of the instrument (339). For example, the presence of radioiodide impurities in some ^{123}I products has been shown to significantly increase dose calibrator readings (340-342,367). Similarly, the presence of radioiodide impurities in some ^{123}I products can introduce substantial errors in radioactive iodine uptake measurements, especially if the probe counter is used in the integral mode (341-343).

Of paramount concern for clinical interpretation is image degradation caused by Compton scatter and septal penetration of high-energy photons emitted by radionuclidic impurities. Significant image degradation has been observed with the use of ^{123}I products containing ^{124}I and other radioiodide contaminants (337,344-346) and with the use of ^{201}Tl products containing ^{200}Tl and/or ^{202}Tl contaminants (347-349).

Radionuclidic impurities often have longer half-lives than do the principal radionuclides (e.g., ^{124}I , ^{202}Tl). Thus, the percentage of radionuclidic contamination continuously increases with time. Increases in radiation dose, errors in dose calibration and activity measurement, and image degradation, therefore, become more pronounced as the time of use approaches the expiration time.

MISCELLANEOUS FACTORS

The efficiency of delivery of radioaerosol droplets for inhalation lung imaging depends, in part, on the surface tension of the solution being nebulized. The addition of 10% ethanol to ^{99m}Tc-DTPA solution has been shown to substantially increase the delivery efficiency of the aerosolized droplets in both *in vitro* studies and in human volunteers (205,206). This effect is less pronounced, however, in patients with lung disease (207). Furthermore, beneficial effects of ethanol may be limited to use with only certain types of nebulizers (350-351).

During the process of freezing, a solute concentration gradient typically develops, which may persist even upon thawing. Volumetric withdrawal of an aliquot from such a stock solution may provide an amount of radioactivity that substantially differs from that calculated. For example, this phenomenon has been observed with ^{131}I sodium iodide therapy solution (352).

In the area of labeled monoclonal antibodies, a variety of chelate conjugate linkages have been used for labeling with radiometals. These different linkages may produce differences in biodistribution, metabolism, and excretion (353).

Many factors (e.g., removal from protective plasma environment, centrifugation, or exposure to trace metals) during the preparation of radiolabeled leukocytes can cause cell damage (116,117,156,164,169,170). Damaged leukocytes demonstrate decreased chemotaxis and may localize in liver, spleen, and lungs (116,117,156,164,172). Similarly, many factors (e.g., centrifugation, passage through small needles, exposure to ADP released from erythrocyte hemolysis) during the preparation of radiolabeled platelets can cause platelet aggregation or cell damage (109,125,169). Damaged platelets exhibit poor survival *in vivo* with localization in liver and spleen (110,121,162,354,355). Removal of platelets from their natural plasma environment for the radiolabeling procedure can also cause cell damage (121,125,355); this damage, however, is apparently reversible in many cases since *in vivo* survival following reinjection remains relatively unaffected (118,121,335,356).

Plastic materials and containers should be used in the preparation of radiolabeled platelets since platelets tend to adhere to glass (109,169,354).

Absorption of ^{99m}Tc-sestamibi to glass vials increases significantly with agitation (e.g., transportation) (357). If ^{99m}Tc-sestamibi is dispensed and transported in glass vials, larger activities may be needed in order to permit the withdrawal of the desired dosage.

SUMMARY

Many factors are known to have deleterious effects on radiopharmaceutical formulations. These effects often result in a product that, if administered, will demonstrate an altered biodistribution or will be otherwise problematic. Reported formulation problems for common radiopharmaceuticals are summarized in Table 1 at the end of this lesson. Since many of these problems can be detected prior to patient administration, a routine quality control program should be an integral part of each nuclear pharmacy service.

Table 1. Formulation Problems for Common Radiopharmaceuticals

Radiopharma-ceutical	Formulation Problem	Clinical Manifestation	Reference
Pertechnetate	Al^{+3}	Sustained blood pool localization	61,62
	Stannous ion	↑ liver and spleen uptake	75,92
	Preparation with bacteriostatic saline	↑ blood pool, liver, and spleen activity	288
^{99m}Tc- sulfur colloid	Carrier ^{99}Tc	↑ free pertechnetate	15
	Inadequate Tc activity/mass	↓ labeling efficiency	38
	Al^{+3}	Lung uptake	41,43,46,50-55
	Alkaline pH	↑ free pertechnetate	90,91
	Reheating after buffering	↓ particle size	144
	Incorrect order of mixing	↑ free pertechnetate	51,114
	Radiolytic decomposition and/or oxidation	↑ free pertechnetate	90
	Sterilization with iodinated antiseptics	↑ free pertechnetate	290
	Particle clumping	Lung uptake	90,358
	Particle settling and/or absorption to vial	↓ activity per volume withdrawn	90,194,202,203
	Low heating temperature	↑ free pertechnetate	38
	Inadequate boiling time	↑ free pertechnetate; ↓ spleen uptake	38,46,51,90,134, 135; 46,90

Table 1. (*Continued*)

Radiopharma-ceutical	Formulation Problem	Clinical Manifestation	Reference
^{99m}Tc- sulfur colloid (cont'd)	Heating large volume	↑ free pertechnetate	51
	Excessive boiling time	↑ particle size, lung uptake	46,90,135
	Excessive pressure in vial	Rupture rubber septum	135,145
	Commercial source	↑ free pertechnetate	15,208
	Low specific activity	↓ liver uptake; ↑ bone marrow uptake	183
	Variable incubation time	Variable particle size	173
^{99m}Tc-albumin colloid	Al^{+3}	Lung uptake	56
^{99m}Tc-phosphates and diphosphonates	Carrier ^{99}Tc	Slower blood pool clearance	30
	Al^{+3}	↑ liver and kidney uptake	57-60
	Alkaline pH	↑ liver, kidney, and/or stomach uptake	57,75,83,93-95
	Excessive acid pH	↑ free pertechnetate	82
	Inadequate stannous	↓ labeling efficiency, ↑ free pertechnetate	74,79,81,111,359
	Excess stannous	↑ liver and soft tissue uptake	57,79,259
	Preparation with bacterio-static saline/antiseptic contamination	↑ free pertechnetate (stomach)	288,291
	Improper mixing order	↑ blood pool activity; ↑ liver uptake	82,111
	Inadequate or prolonged incubation time	↓ bone, ↑ soft tissue uptake	128,152,175-179

Table 1. *(Continued)*

Radiopharmaceutical	Formulation Problem	Clinical Manifestation	Reference
^{99m}Tc-phosphates and diphosphonates (cont'd)	Radiolytic decomposition and/or oxidation	↑ free pertechnetate	74,75,78,79,111, 248,252,255,257, 259-262
	Low ligand concentration	↓ labeling efficiency, ↓ bone uptake; ↑ soft tissue and kidney uptake	81-83,94,127
	Excessive dilution	↓ bone, ↑ soft tissue uptake	128
	Storage temperature	↓ bone, ↑ soft tissue uptake	128
	Commercial source	↑ soft tissue uptake; stomach, liver, gallbladder, and/or intestinal localization	179,209,212,220, 221,223,224
	Improper Sn/ligand ratio	↓ bone uptake; ↑ lung uptake ?	9,39,81-83
^{99m}Tc-HSA	Carrier ^{99}Tc	↑ free pertechnetate	17,18
	Improper pH	↑ free pertechnetate; ↑ liver uptake	84
	Improper mixing order	↑ liver uptake	84
	Radiolytic decomposition and/or oxidation	↑ free pertechnetate	78
	Commercial source	↑ free pertechnetate; differences in blood clearance rates and liver uptake	208,213-215,360
	Inter- and intra-lot variability	↑ free pertechnetate	18
^{99m}Tc-MAA and albumin microspheres	Soluble protein	↑ blood pool activity	181,182

Table 1. *(Continued)*

Radiopharma-ceutical	Formulation Problem	Clinical Manifestation	Reference
^{99m}Tc-MAA and albumin microspheres (cont'd)	Mean particle size	Differences in biologic half-life in lung	197
	Small particles	↑ liver uptake	181,191
	Clumping of particles	Focal hot spots in lungs	181,196
	Inadequate number of particles	Perfusion defects, especially peripheral patchiness	198,199
	Excessive number of particles	↑ risk of toxicity	198,199
	Mixing order	↑ free pertechnetate	113
	Radiolytic decomposition and/or oxidation	↑ free pertechnetate	181
	Settling of particles and/or absorption to vial	Inadequate number of particles in suspension	200,201
	Commercial source	↓ radiochemical purity	222
^{99m}Tc-RBC	Carrier ^{99}Tc (especially with ACD)	↓ labeling efficiency, ↑ free pertechnetate	19-25,31,293
	Al^{+3}	RBC agglutination	63
	Very acidic pH	RBC hemolysis	63
	Inadequate stannous	↑ free pertechnetate	20,66,69,70
	Excessive stannous	↑ plasma activity; ↑ spleen uptake	20,65-69,361
	Excessive Tc-99m activity added	↓ rate and extent of labeling	31
	Improper mixing order	↑ liver uptake; ↓ labeling efficiency	20; RG Wolfangel
	Low cell concentration	↓ rate and extent of labeling	67,115

Table 1. *(Continued)*

Radiopharma-ceutical	Formulation Problem	Clinical Manifestation	Reference
^{99m}Tc-RBC (cont'd)	Radiolytic decomposition and/or oxidation	↑ free pertechnetate	66,69
	Inadequate incubation time	↑ free pertechnetate	25,66,67,69,150, 151
	Incubation at lower than 37°C	↓ rate of labeling; ↑ free pertechnetate	67,151
	Heparin versus ACD	↓ labeling efficiency; ↑ extravascular activity; ↑ urinary excretion	21
	ACD versus heparin	↓ stability, ↓ blood/ background ratio	294,295
	EDTA as the anticoagulant	↓ labeling efficiency	115
	Excess ACD	Sequestration in spleen; ↓ labeling efficiency	296; 31,293
	Large volume of added pertechnetate solution	↓ rate and extent of labeling	31
	Inadequate volume of blood	↓ labeling efficiency	25,31
	EDTA as a sequesterant	↓ blood pool retention, ↑ splenic accumulation	244,245,247
	Commercial source	↓ labeling effiency; ↑ free pertechnetate	226
^{99m}Tc-damaged RBC	Low heating temperature	↓ spleen uptake; ↑ blood pool activity	131,133
	High heating temperature	↓ spleen uptake; ↑ liver uptake	131,133
	Inadequate heating time	↓ spleen uptake; ↑ blood pool activity	131-133,139,140
	Excessive heating time	↓ spleen uptake; ↑ liver uptake	131-133

Table 1. *(Continued)*

Radiopharma-ceutical	Formulation Problem	Clinical Manifestation	Reference
^{99m}Tc-damaged RBC (cont'd)	Heating large volume	↓ spleen uptake; ↑ blood pool activity	138
	Low specific activity	↓ spleen uptake; ↑ blood pool activity	138
^{99m}Tc-IDA derivatives	pH > 5.5	↓ rate of labeling	86
	Radiolytic decomposition and/or oxidation	↑ free pertechnetate	7,86,254,362
	Inadequate incubation time	↑ free pertechnetate; ↑ blood pool activity	86,147
	Low ligand concentration	↓ rate of labeling	86
	Inadequate volume	cloudiness (precipitation?)	RM Sullivan
^{99m}Tc-HMPAO	Intra- and inter-lot variability	↓ labeling efficiency	29,211
	Excessive ^{99m}Tc activity/ concentration	↓ labeling efficiency, ↓ stability, ↑ free pertechnetate; ↓ brain/parotid ratio	5,27,29,35,37; 36
	Use of "aged" ^{99m}Tc eluate	↓ stability, ↑ free pertechnetate	5,29,240
	Carrier ^{99}Tc/first eluate of new generator	↓ labeling efficiency, ↓ stability, ↑ free pertechnetate	5,26,27
	Dissolved oxygen (shaking)	↓ labeling efficiency, ↓ stability	37,159,240
	Decomposition	↓ brain/parotid ratio	29,35
	Mixing with blood	↓ stability, ↓ brain/parotid ratio	29
	Excess stannous	↓ stability, ↑ reduced/ hydrolyzed Tc	37-80

Table 1. (*Continued*)

Radiopharma-ceutical	Formulation Problem	Clinical Manifestation	Reference
^{99m}Tc-HMPAO (cont'd)	Commercial source of normal saline	↓ labeling efficiency, ↑ free pertechnetate, ↓ brain/parotid ratio	26
	Alkaline pH	↓ stability, ↑ free pertechnetate	80
	Phosphate buffer	↓ stability, ↑ free pertechnetate	80
	Mixing order (with gentisic acid)	↓ labeling, ↑ reduced/ hydrolyzed Tc	106
	Stereoisomeric form	↓ brain uptake and retention	29
	Refrigerated vial not at room temperature	↓ rate of labeling	159
^{99m}Tc-(HMPAO)-leukocytes	Inadequate HMPAO concentration	↓ labeling efficiency	87-89
	Inadequate number of leukocytes	↓ labeling efficiency	87,89,122,123
	Improper pH	↓ labeling efficiency	87-89
	Inadequate incubation time	↓ labeling efficiency	87,89
	Excessive amount of red cells and/or platelets	Labeled RBCs or platelets	87
	Excessive plasma	↓ labeling efficiency	123
	Stereoisomeric form	Differences in labeling rates and efficiencies	301
^{99m}Tc-DTPA	Carrier ^{99}Tc	↑ free pertechnetate;	28
	Inadequate stannous	↑ free pertechnetate	28,237,239
	Improper mixing order	↑ free pertechnetate	112
	Inadequate incubation time	↑ protein binding, blood pool retention	11,148

Table 1. (*Continued*)

Radiopharma-ceutical	Formulation Problem	Clinical Manifestation	Reference
^{99m}Tc-DTPA (cont'd)	Radiolytic decomposition and/or oxidation	↑ free pertechnetate	10,112,239,241, 251,363
	Dilution with normal saline	↓ stability, ↑ free pertechnetate	112
	Commercial source	↓ stability, ↑ free pertechnetate; differences in renal excretion rates	112; 11,216-218
^{99m}Tc-DTPA aerosol	Addition of 10% ethanol	↑ efficiency of radioaerosol delivery	205-207,350
	Commercial source	Variation in deposition rate and/or distribution	204
	Relative humidity	Variation in deposition rate and/or distribution	204
	Flow rate	Variation in deposition rate and/or distribution	205
	Radiolytic decomposition and/or oxidation	↑ free pertechnetate	241-243
^{99m}Tc-gluceptate	Improper pH	↑ free pertechnetate	85
	Improper mixing order	↑ free pertechnetate or ↑ liver uptake	85
	Radiolytic decomposition and/or oxidation	↑ free pertechnetate	85,258,264,267
^{99m}Tc-DMSA	Alkaline pH	Rapid urinary excretion	99-103
	Radiolytic decomposition and/or oxidation	↑ free pertechnetate, ↓ kidney uptake, ↑ liver uptake	101,219,253,363
	Low ligand concentration	↓ kidney uptake; ↑ bone uptake	101

Table 1. (*Continued*)

Radiopharma-ceutical	Formulation Problem	Clinical Manifestation	Reference
^{99m}Tc-DMSA (cont'd)	Inadequate incubation time	↓ kidney uptake; ↑ bone uptake	101
	Contamination with antiseptic	↑ liver/spleen uptake	292
	Commercial source	Differences in adsorption onto walls and stoppers of glass vials	235
	Stereoisomeric form	Differences in biodistribution	303
^{99m}Tc -MAG3	Excessive ^{99m}Tc activity	↓ labeling efficiency and stability, ↑ hepato-biliary activity	32,33
	Use of "aged" ^{99m}Tc eluate	↓ labeling efficiency	RG Wolfangel
	Inadequate ^{99m}Tc volume added to vial	↓ labeling efficiency	32
	Inadequate air added	↓ labeling efficiency	32
	Excessive time delay before adding air	↓ labeling efficiency	32
	Excessive time delay between adding air and boiling	↓ labeling efficiency	32
	Inadequate boiling time	↓ labeling efficiency	32,141
	Commercial source of ^{99m}Tc-pertechnetate	↓ labeling efficiency	32
	Excessive pressure in vial	Breakage of vial	141
	Loss of argon atmosphere in vial	↓ labeling efficiency	76
	Alkaline pH	↑ impurities, ↑ hepato-biliary activity	6

Table 1. (*Continued*)

Radiopharmaceutical	Formulation Problem	Clinical Manifestation	Reference
^{99m}Tc-sestamibi	Inadequate heating	↓ labeling efficiency	129,130,142
	Excessive pressure inside vial	ejection of stopper or breakage of vial	129,130,146
	Exposure to air	↓ labeling efficiency	256
	Agitation	↑ adsorption to vial	357
^{99m}Tc-teboroxime	Exposure to air	↓ labeling efficiency	256
^{99m}Tc -misc.	Commercial source of ^{99m}Tc-pertechnetate	↓ labeling efficiency	210
^{131}I sodium iodide	Acidic pH	↑ thyroid uptake in personnel	321-323,325,327, 328
	Radiolytic decomposition and/or oxidation	↑ thyroid uptake in personnel	324,326,327
	Metal ions	↑ thyroid uptake in personnel	321,328
	Chlorinated tap water for dilution	↑ thyroid uptake in personnel	324
	Storage above room temperature	↑ thyroid uptake in personnel	327,329
	Carrier iodide	↓ thyroid uptake	272,273
	Encapsulation	↓ thyroid uptake; retention of abdominal activity	306,307
	Commercial source	↓ dissolution and bioavailability; ↑ volatility; ↑ radiochemical impurities	231-232; 331,332; 309
	Freezing/thawing	Activity differing from that calculated	352

Table 1. *(Continued)*

Radiopharma-ceutical	Formulation Problem	Clinical Manifestation	Reference
^{123}I sodium iodide	Radionuclidic contamination	↑ radiation dose; errors in dose calibration; image degradation	337,340-346
^{131}I iodo-hippurate	Commercial source	↑ free iodide, ↑ dose to thyroid	230
	Radiolytic decomposition and/or oxidation	↑ free iodide, ↑ dose to thyroid, ↓ urinary excretion rate	230,249,266,365
Iodinated cholesterol derivatives	Unknown	↑ liver, spleen, and bone marrow uptake	366
	Limited solubility in vehicle	Lung uptake	283
^{201}Tl chloride	Radionuclidic contamination	Image degradation	347-349
	Acid pH	↓ myocardial uptake; ↑ uptake in blood pool, liver, and/or thyroid	105
^{67}Ga-citrate	Commercial source	Uptake vs. no uptake in cerebral infarct	228
	Carrier gallium	↑ bone uptake ; ↓ uptake in usual organs	276,277
^{57}Co-cyano-cobalamin and intrinsic factor	Carrier cyanocobalamin	↓ absorption and urinary excretion	275
	Encapsulation	↓ absorption and urinary excretion	310-312
	Isotope exchange	Spurious results	314-317

Table 1. (*Continued*)

Radiopharma-ceutical	Formulation Problem	Clinical Manifestation	Reference
^{111}In-leukocytes	Inadequate number of WBC	↓ labeling efficiency	116,117,120
	Excessive number of RBC and/or platelets	↓ target/background ratio,↑ blood pool, ↑ spleen uptake	116,120,155,156, 160,166-172
	Presence of plasma transferrin	↓ labeling efficiency, ↑ blood pool, ↑ bone marrow uptake	116,117,157,160, 161,164
	Prolonged incubation/ storage out of plasma	↓ cell viability	172,180
	Inadequate incubation time	↓ labeling efficiency	116,117,155-157
	Cell damage	↓ cell viability, ↑ uptake in liver, spleen, lungs	116,117,156,164, 172
	Cell clumping	↑ lung uptake	116,120
	Heparin versus ACD	↑ adherence of WBC to tubes, pipets, etc.	164
	Inadequate oxine	↓ labeling efficiency	117
	Excessive oxine	↓ cell viability	117
^{111}In-platelets	Presence of plasma transferrin	↓ labeling efficiency, ↑ blood pool, ↑ bone marrow uptake	108,110,118,125, 158,161-164
	Cell damage	Aggregation and clumping; ↓ survival, ↑ uptake in liver and spleen	109,169; 110,121,162,354, 355
	Glassware instead of plasticware	Adherence to glass	169,354
	Inadequate incubation time	↓ labeling efficiency	108,118,119,125, 158
	Inadequate number of platelets	↓ labeling efficiency	108,110,118,121

Table 1. (*Continued*)

Radiopharma-ceutical	Formulation Problem	Clinical Manifestation	Reference
^{111}In-platelets (cont'd)	Presence of citrate ions during labeling reaction	↓ labeling efficiency	108
	Inadequate oxine	↓ labeling efficiency	108
	Excessive oxine	↓ labeling efficiency, ↓ function	108,119,125
	pH above 6.5	Aggregation and clumping	108-110
	Excessive number of RBC	↓ labeled platelets, ↑ labeled RBC	118
	Contact with metal	Aggregation and clumping	109

REFERENCES

1. Hladik WB, Ponto JA, Lentle BC, Laven DL. Iatrogenic alterations in the biodistribution of radiotracers as a result of drug therapy: reported instances. In: Hladik WB, Saha GB, Study KT, editors. *Essentials of Nuclear Medicine Science*. Baltimore: Williams & Wilkins. 1987:189-219.

2. Lentle BC, Styles CB. Iatrogenic alterations in the biodistribution of radiotracers as a result of radiation therapy, surgery, and other invasive medical procedures. In: Hladik WB, Saha GB, Study KT, editors. *Essentials of Nuclear Medicine Science*. Baltimore: Williams & Wilkins. 1987:220-33.

3. Coupal JJ, Kim EE. Normal clinical variation in anatomic structure and physiologic function and its effect on radiopharmaceutical biodistribution. In: Hladik WB, Saha GB, Study KT, editors. *Essentials of Nuclear Medicine Science*. Baltimore: Williams & Wilkins. 1987:234-47.

4. Kim EE, Coupal JJ. Unusual or unanticipated alterations in the biodistribution of radiopharmaceuticals as a result of pathologic mechanisms. In: Hladik WB, Saha GB, Study KT, editors. *Essentials of Nuclear Medicine Science*. Baltimore: Williams & Wilkins. 1987:248-67.

5. Neirinckx RD, Canning LR, Piper IM, Nowotnik DP, Pickett RD, Holmes RA, et al. Technetium-99m d,l-HM-PAO: a new radiopharmaceutical for SPECT imaging of regional cerebral blood perfusion. *J Nucl Med* 1987;28:191-202.

6. Bannister KM, Penglis S, Bellen JC, Baker RJ, Chatterton BE. Kit preparation of techentium-99m-mercaptoacetyltriglycine: analysis, biodistribution and comparison with technetium-99m-DTPA in patients with impaired renal function. *J Nucl Med* 1990;31:1568-73.

7. Lecklitner ML, Benedetto AR, Straw JD. Failure of quality control to detect errrors in the preparation of technetium-99m disofenin (DISIDA). *Clin Nucl Med* 1985;10:468-74.

8. Hupp BD, Nagel MV, Augustine S. Unit dose radiochemical stability of commonly used technetium-99m radiopharmaceuticals. *J Nucl Med Technol* 1986;14:202-5.

9. Tatum JL, Burke TS, Hirsch JI, Fratkin MJ. Artifactual focal accumulation of Tc-99m bone imaging tracer in the chest. *Clin Nucl Med* 1985;10:16-8.

10. Hammes RJ, Rowe BR, Decorah MA, Perlman SB, Wilson MA, Gutelius CA. Quality control of Tc-99m DTPA used for GFR studies [abstract]. *J Nucl Med* 1988;29:980.

11. Russell CD, Rowell K, Scott JW. Quality control of technetium-99m DTPA: correlation of analytic tests with in vivo protein binding in man. *J Nucl Med* 1986;27:560-2.

12. Shih WJ, Coupal JJ, Donstad PA, DeLand FH. Diffuse thoracoabdominal radioactivity seen in bone imaging. *Clin Nucl Med* 1986;11;254-8.

13. Lamson ML, Kirschner AS, Hotte C, Lipsitz EL, Ice RD. Generator-produced $^{99m}TcO_4^-$: carrier-free? *J Nucl Med* 1975;16:639-41.

14. Molter M: The current status of ^{99m}Tc generators. *Nuklearmedizin* 1981;20:7-10.

15. Albers JW, Jenkins D, Sandee RJ, Wahner HW. Free (unreacted) pertechnetate in technetium-sulfur colloid preparations. *J Nucl Med Technol* 1974;2:14-7.

16. Hambright P, McRae J, Valk PE, Bearden AJ, Shipley. 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 99Tc. *J Nucl Med* 1975;16:478-82.

17. Porter WC, Dworkin HJ, Gutkowski RF. The effect of carrier technetium in the preparation of ^{99m}Tc-human serum albumin. *J Nucl Med* 1976;17:704-6,.

18. Maughan J, Riley A, Parkin A. Poor binding efficiency using $^{99}Tc^m$-labeled HSA [letter]. *Nucl Med Commun* 1990;11:720-2.

19. Smith TD, Steimers JR, Richards P. Chemical effect of ^{99}Tc on ^{99m}Tc labeled radiopharmaceuticals [abstract]. *J Nucl Med* 1975;16:570-1.

20. Smith TD, Richards P. A simple kit for the preparation of ^{99m}Tc-labeled red blood cells. *J Nucl Med* 1976;17:126-1.

21. Porter WC, Dees SM, Freitas JE, Dworkin HJ. Acid citrate-dextrose compared with heparin in the preparation of in vivo/in vitro technetium-99m red blood cells. *J Nucl Med* 1983; 24:383-7.

22. Wilson ME, Hung JC. Evaluation of heparin and anticoagulant citrate dextrose in the preparation of technetium-99m-red blood cells with UltraTag® RBC kit [letter]. *J Nucl Med* 1992;33:306-7.

23. Srivastava SC, Straub RF. Evaluation of heparin and anticoagulant citrate dextrose in the preparation of technetium-99m-red blood cells with UltraTag® RBC kit -- reply [letter]. *J Nucl Med* 1992;33:307-8.

24. Wolfangel RG. Evaluation of heparin and anticoagulant citrate dextrose in the preparation of technetium-99m-red blood cells with UltraTag® RBC kit -- reply [letter]. *J Nucl Med* 1992;33:308.

25. Kelly MJ, Cowie A, Antonino A, Kalff V. An assessment of factors which influence the effectiveness of the modified in vivo erythrocyte labeling technique [abstract]. *J Nucl Med* 1991;32:1090.

26. Brandau W, Schober O, Knapp WH. Determination of brain death with technetium-99m-HMPAO [letter]. *J Nucl Med* 1990;31:2075-6.

27. Gagnon A, Leveille J, Bavaria G, Taillefer R. Labelling efficiency analysis of 99mTc-HMPAO: comparison between standard elution and multiple elution method [abstract]. *J Nucl Med* 1991;32:1103.

28. Colombetti LG, Barnes WE. Effect of chemical and radiochemical impurities from eluants on ^{99m}Tc-labeling efficiency. *Nuklearmedizin* 1977;16:271-4.

29. Ballinger JR, Gulenchyn KY, Reid RH. Radiopharmaceutical factors in the variable quality of [^{99m}Tc]HMPAO images. *J Nucl Med* 1990;31:118-22.

30. Van Duzee BF, Bugaj JE. The effect of total technetium concentration on the performance of a skeletal imaging agent [abstract]. *Clin Nucl Med* 1981;6 Suppl P148.

31. Wolfangel RG, Srivastava SC, Bushman MJ, Straub RF. UltraTag RBC kit -- relationship between anticoagulants and reagent volume on RBC labeling efficiency and kinetics [abstract]. *J Nucl Med* 1992;33:989.

32. Nosco D, Wolfangel RG, Bushman M, Grummon G, Marmion M. TechneScan MAG3 -- labeling conditions and QC [abstract]. *J Nucl Med* 1992;33:1033-4.

33. Szlaczky LA, Latino FA, Payne SE, Anderson TL, Eshima D. The hepatobiliary excretion of Tc-99m MAG3 [abstract]. *J Nucl Med* 1992;33:990.

34. Ballinger J. Preparation of technetium-99m-HMPAO [letter]. *J Nucl Med* 1990;31:1892.

35. Tubergen K, Corlija M, Volkert WA, Holmes RA. Sensitivity of technetium-99m-d,l-HMPAO to radiolysis in aqueous solutions. *J Nucl Med* 1991;32:111-5.

36. Corlija M, Tubergen K, Volkert WA, Holmes RA. Contribution of radiolytically induced dissociation of ^{99m}Tc-d,l-HMPAO in aqueous solutions [abstract]. *J Nucl Med* 1990;31:806.

37. Lang J, Barbarics E, Lazar J, Janoki GA, Papos M, Csernay L. Effects of labeling conditions and formulation of kit on in vitro stability of 99m-Tc-d,l-HM-PAO [abstract]. *Eur J Nucl Med* 1989;15:424.

38. Fortman DL, Sodd VJ: ^{99m}Tc-sulfur colloid--evaluation of preparation parameters for kits from four commercial manufacturers. In: Sorenson JA, coordinator. *Radiopharmaceuticals II: proceedings of the 2nd international symposium on radiopharmaceuticals*: 1979 Mar 19-22: Seattle. New York: Society of Nuclear Medicine. 1979: 15-23.

39. Gouaillardouu D, Conti ML. The influence of the charge and of the tin-ligand ratio on bone uptake of technetium 99m labelled osteotropic radiopharmaceuticals. *Appl Radiat Isot* 1987;38:103-6.

40. Bell EG, McAfee JG, Subramanian G. Radiopharmaceuticals in pediatrics. In: James AE, Wagner HN, Cooke RE, editors. *Pediatric Nuclear Medicine*. Philadelphia: WB Saunders. 1974: 84-94.

41. Dworkin HJ, Nelis A, Dowse L. Rectilinear liver scanning with technetium-99m sulfide colloid. *Am J Roentgenol Rad Ther* 1967;101:557-60.

42. Webber MM, Cragin MD, Victery WK. Aluminum content in eluents from commercial technetium generators [letter]. *J Nucl Med* 1971;12:700.

43. Weinstein MB, Smoak W. The author's reply [letter]. *J Nucl Med* 1970;11:767-8.

44. Craggin MD, Webber MM, Victery WK. Effect of aluminum concentration in technetium eluent on particle size [abstract]. *J Nucl Med* 1971;12:476.

45. Vinberg N, Kristensen K. Comparative evaluation of ^{99m}Tc-generators. *Eur J Nucl Med* 1976;1:219-33.

46. Larson SM, Nelp WB. Radiopharmacology of a simplified technetium-99m colloid preparation for photoscanning. *J Nucl Med* 1966; 7:817-26.

47. Rhodes BA, Croft BY. *Basics of Radiopharmacy*. St. Louis: CV Mosby, 1978.

48. Molinski VJ. A review of ^{99m}Tc generator technology. *Int J Appl Isot* 1982;33:811-9.

49. United States Pharmacopeial Convention. Sodium pertechnetate Tc 99m injection. In: The United States Pharmacopeia XXII. Rockville: United States Pharmacopeial Convention. 1989: 1016-.7.

50. Zabel PL, Chamberlain MJ, Stephenson JA, Leung FY. Aluminum from needles resulting in instability and altered biodistribution of radiopharmaceuticals [abstract]. *J Nucl Med* 1986;27:942.

51. Haney TA, Ascanio I, Gigliotti JA, Gusmano EA, Bruno GA. Physical and biological properties of a ^{99m}Tc-sulfur colloid preparation containing disodium edetate. *J Nucl Med* 1971;12:64-8.

52. Staum MM. Incompatibility of phosphate buffer in ^{99m}Tc-sulfur colloid containing aluminum ion. *J Nucl Med* 1972;13:386-7.

53. Study KT, Hladik WB, Saha GB. Effects of Al^{+3} ion on ^{99m}Tc sulfur colloid preparations with different buffers. *J Nucl Med Technol* 1984;12:16-8.

54. Bobinet DD, Sevrin R, Zurbriggen MT, Spolter L, Cohen MB. Lung uptake of ^{99m}Tc-sulfur colloid in patient exhibiting presence of Al^{+3} in plasma. *J Nucl Med* 1974;15:1220-2.

55. Miller W. Technetium-99m biorouting. In: Early PJ, Razzak MA, Sodee DB. *Textbook of Nuclear Medicine Technology*. 3rd ed. St. Louis: CV Mosby. 1979: 544-70.

56. Chia HL, De Schrijver M: Modified in vivo behavior of ^{99m}Tc-labeled liver-spleen preparations due to ^{99}Mo/^{99m}Tc-generator eluate impurities. *Eur J Nucl Med* 8:450-453, 1983.

57. Zimmer AM, Pavel DG. Experimental investigations of the possible cause of liver appearance during bone scanning. *Radiology* 1978;126:813-6.

58. Chaudhuri TK. Liver uptake of ^{99m}Tc-diphosphonate. *Radiology* 1976;119:485-6.

59. Chaudhuri TK. The effect of aluminum and pH on altered body distribution of ^{99m}Tc-EHDP. *Int J Nucl Med Biol* 1976;3:37-40.

60. Jaresko GS, Zimmer AM, Pavel DG, Spies SM. Effect of circulating aluminum on the biodistribution of Tc-99m-Sn-diphosphonate in rats. *J Nucl Med Technol* 1980;8:160-1.

61. Wang TST, Fawwaz RA, Esser PD, Johnson PM. Altered body distribution of [^{99m}Tc] pertechnetate in iatrogenic hyperaluminemia. *J Nucl Med* 1978;19:381-3.

62. Shukla SK, Manni GB, Cipriani C. Effect of aluminum impurities in the generator-produced pertechnetate-99m ion on thyroid scintigrams. *Eur J Nucl Med* 1977;2:137-41.

63. Lin MS, MacGregor RD, Yano Y. Ionic aluminum (III) in generator eluate as an erythrocyte-agglutinating agent. *J Nucl Med* 1971;12:297-9.

64. Krishnamurthy GT, Tubis M, Joe P, Blahd WH. Clinical assessment of the importance of the quantity of tin in commercial bone imaging kits [letter]. *J Nucl Med* 1978;19:565-7.

65. Bardy A, Fouye H, Gobin R, BeydonJ, de Tovac G, Panneciere C, et al. Technetium-99m labeling by means of stannous pyrophosphate: application to bleomycin and red blood cells. *J Nucl Med* 1975;16:435-7.

66. Zimmer AM. In vitro technetium-99m red blood cell labeling using commercial stannous pyrophosphate. *Am J Hosp Pharm* 1977;34:264-7.

67. Callahan RJ, Froelich JW, McKusick KA, Strauss HW. Factors affecting the rate and extent of incorporation of ^{99m}Tc into pre-tinned red blood cells (RBC) [abstract]. *J Nucl Med* 1982;23:P109.

68. Zanelli GD. Effect of certain drugs used in the treatment of cardiovascular disease on the "in vitro" labeling of red blood cells with ^{99m}Tc. *Nucl Med Commun* 1982;3:155-61.

69. Zimmer AM, Pavel DG, Karesh SM. Technical parameters of in vivo red blood cell labeling with technetium-99m. *Nuklearmedizin* 1979;18:241-6.

70. Feldkamp M, Spicer J. Problems with technetium-99m-red blood cell labeling [letter]. *J Nucl Med Technol* 1991;19:50.

71. McBride MHD, Shaw SM, Kessler WV. Deterioration of stannous ion in radiopharmaceutical kits during storage. *Am J Hosp Pharm* 1979;36:1370-2.

72. Owunwanne A, Church LB, Blau M. Effect of oxygen on the reduction of pertechnetate by stannous ion. *J Nucl Med* 1977;18:822-6.

73. Majewski W, Zimmer AM, Spies SM. Stannous-tin levels in commercial stannous pyrophosphate: effect of altering preparation methods [abstract]. *J Nucl Med Technol* 1981;9:116.

74. Kowalsky RJ, Dalton DR. Technical problems associated with the production of technetium ^{99m}Tc tin (II) pyrophosphate kits. *Am J Hosp Pharm* 1981;38:1722-6.

75. Francis MD, Tofe AJ, Hiles RA, Birch CG, Bevan JA, Grabenstetter RJ. Inorganic tin: chemistry, disposition and role in nuclear medicine diagnostic skeletal imaging agents. *Int J Nucl Med Biol* 1981;8:145- 52.

76. Fleming WK, Jay M, Ryo UY. Reconstitution and fractionation of radiopharmaceutical kits [letter]. *J Nucl Med* 1992;33:1915.

77. Chervu LR, Vallabhajosyula B, Mani J, Chun SB, Blaufox MD. Stannous ion quantitation in ^{99m}Tc-radiopharmaceutical kits. *Eur J Nucl Med* 1982;7:291-3.

78. Billinghurst MW, Rempel S, Westendorf BA. Radiation decomposition of ^{99m}Tc radiopharmaceuticals. *J Nucl Med* 1979;20:138-43.

79. Tofe AJ, Bevan JA, Fawzi MB, Whitehouse HS, Francis MD. Antioxidant stabilization of bone agents. In: Sorenson JA, coordinator. *Radiopharmaceuticals II: proceedings of the 2nd international symposium on radiopharmaceuticals*: 1979 Mar 19-22: Seattle. New York: Society of Nuclear Medicine. 1979: 637-4.

80. Hung JC, Corlija M, Volkert WA, Holmes RA. Kinetic analysis of technetium-99m d,l-HM-PAO decomposition in aqueous media. *J Nucl Med* 1988;29:1568-76.

81. Kroesbergen J, Wortelboer MR, Rijnsent A, Gelsema WJ, de Ligny CL. ^{99m}Tc bone scanning agents--V. Influence of experimental conditions on the labeling efficiency and gel chromatography of ^{99m}Tc(Sn)HMDP. *Nucl Med Biol* 1987;14:37-41.

82. van den Brand JAGM, Das HA, Dekker BG, van den Brand CJA. The influence of the method of preparation of the bone scanning agent ^{99m}Tc(Sn)EHDP on its tissue distribution in the rat. *Int J Appl Radiat Isot* 1982;33:917-28.

83. Vanlic-Razumenic N, Djokic D, Paunkovic N, Gorkic D. Studies of the chemical and biological properties of the skeletal imaging agent ^{99m}Tc-methylene diphosphonate. *Nuclearmedizin* 1982;21:150-6.

84. Lin MS, Winchell S, Shipley BA. Use of Fe(II) or Sn(II) alone for technetium labeling of albumin. *J Nucl Med* 1971;12:204-11.

85. Chi SL, Hoag SG, Yanchick VA. Electrolytic complexing of glucoheptonate and technetium-99m. *J Nucl Med* 1978;19:520-4.

86. Nunn AD, Schramm E. Analysis of Tc-HIDAs and factors affecting their labeling rate, purity, and stability [abstract]. *J Nucl Med* 1981;2:P52.

87. Danpure HJ, Osman S, Carroll MJ, Roddie ME, Peters AM, Lavender JP. In vitro studies to develop a clinical protocol for radiolabeling mixed leucocytes with Tc-99m HMPAO [abstract]. *J Nucl Med* 1987;28:694.

88. Solanki KK, Mather SJ, Janabi MAL, Britton KE. A rapid method for the preparation of ^{99}Tc^{m} hexametazime-labeled leucocytes. *Nucl Med Commun* 1988;9:753-61.

89. Vanlic-Razumenic N, Pujic N, Dedovic N, Kostic K, Nastic-Miric D. Labelling of leukocytes with ^{99m}Tc-HMPAO for scintigraphy of inflammatory lesions and abscesses. *Nucl Med Biol* 1992;19:251-56.

90. Kelly WN, Ice RD. Pharmaceutical quality of technetium-99m sulfur colloid. *Am J Hosp Pharm* 1973;30:817-20.

91. Harper PV, Lathrop KA, Gottschalk A. Pharmacodynamics of some technetium-99m preparations. In: Andrews GA, Kniseley RM, Wagner HN, editors. *Radioactive Pharmaceuticals*. Oak Ridge: US Atomic Energy Commission. 1966: 67-91.

92. Subramanian G, McAfee JG. Stannous oxide colloid labeled with ^{99m}Tc or ^{113m}In for bone marrow imaging. *J Nucl Med* 1970;11:365-6.

93. Schumichen C, Walden J, Hoffman G. Kinetics of various ^{99m}Tc-Sn-pyrophosphate compounds in the rat. I. In vivo studies. *Nuklearmedizin* 1977;16:100-3.

94. Schumichen C, Mackenbrock B, Hoffman G. Kinetics of various ^{99m}Tc-Sn-pyrophosphate compounds in the rat. II. In vitro studies. *Nuklearmedizin* 1977;16:157-62.

95. Hoogland DR, Forstrom LA, Mahdal AF, Lokwn MK. Effects of pH on tissue distribution of ^{99m}Tc-pyrophosphate (PYP) in bone imaging [abstract]. *Med Imaging* 1977;2:39.

96. Russell CD, Cash AG. Oxidation state of technetium in bone scanning agents. In: Sorenson JA, coordinator. *Radiopharmaceuticals II: proceedings of the 2nd international symposium on radiopharmaceuticals*: 1979 Mar 19-22: Seattle. New York: Society of Nuclear Medicine. 1979: 627-36.

97. Libson K, Deutsch E, Heineman WR, Tanabe S, Zodda JP. Preparative control, HPLC analysis, and in vivo evaluation of components of a technetium-MDP radiopharmaceutical mixture [abstract]. *J Nucl Med* 1983;24:P23.

98. Tanabe S, Zodda JP, Deutsch E, Libson K. Effect of pH on the formation of Tc($NaBH_4$)-MDP radiopharmaceutical analogues. *Int J Appl Radiat Isot* 1983;34:1577-84.

99. Krejcarek GE, Wicks JH, Heerwald PE, Tucker L, Kubik VM, Newmark RA, et al. The structure of stannous dimercaptosuccinic acid chelates [abstract]. *J Nucl Med* 1976;17:565.

100. Krejcarek GE, Heerwald PE, Tucker KL, Wicks JH. The chemistry of stannous dimercaptosuccinic acid chelates [abstract]. *J Labelled Compd Radiopharm* 1977;13:157.

101. Ikeda I, Inoue O, Kurata K. Preparation of various ^{99m}Tc dimercaptosuccinate complexes and their evaluation as radiotracers. *J Nucl Med* 1977;18:1222-9.

102. Hata N, Yokohama, Horiuchi K, Saji H, Morita R, Torizuka K. New ^{99m}Tc(V) DMSA tumor imaging radiopharmaceuticals, with distinctive behavior from renal ^{99m}Tc-DMSA [abstract]. *J Nucl Med* 1983;24:P126-7.

103. Jeghers O, Puttemans N, Urbain D, Lefebvre J, Ham HR. Comparison of two ^{99m}Tc(V)-dimercaptosuccinic acid preparations. *Appl Radiat Isot* 1987;38:13-8.

104. Fritzberg AR, Lewis D. HPLC analysis of ^{99m}Tc iminodiacetate hepatobiliary agents and a question of multiple peaks. *J Nucl Med* 1980;21:1180-4.

105. Hunter WW, Kulkarni MV, Price R. Thallous vrs thallic Tl-201: factors influencing biodistribution and myocardial turnover [abstract]. *J Nucl Med* 1981;22:P82.

106. Hung JC, Volkert WA, Holmes RA. Stabilization of technetium-99m-D,L-hexamethylpropylamine oxime (^{99m}Tc-D,L-HMPAO) using gentisic acid. *Nucl Med Biol* 1989;16:675-80.

107. DeJesus OT, Sunderland JJ, Nickles R. Synthesis of ^{18}F-6-FD [letter]. *J Nucl Med* 1990;31:2076-7.

108. Scheffel U, Tsan MF, McIntyre PA. Labeling of human platelets with [^{111}In] 8-hydroxyquinoline. *J Nucl Med* 1979;20:524-31.

109. Bauman JM, Landry AJ. Practical platelet labeling with indium-111-oxine. *J Nucl Med Technol* 1986;14:15-7.

110. Peters AM. Review of platelet labelling and kinetics. *Nucl Med Commun* 1988;9;803-8.

111. Yano Y, McRae J, Van Dyke DC, Anger HO. Technetium-99m-labeled stannous ethane-1-hydroxy-1, 1-diphosphonate: a new bone scanning agent. *J Nucl Med* 1973;14:73-8.

112. Levit N. Concentrated technetium and its effects on tagging efficiency. *Monthly Scan* 1979;Nov:1.

113. Bolstad DM, Valley TB, Wilson ME, Hung JC. An improved method for reducing particle number in a technetium-99m macroaggregated albumin injection [abstract]. *J Nucl Med Technol* 1992; 20:109.

114. Feezer B. Clinical manifestation of a radiopharmaceutical formulation problem. *Monthly Scan* 1979; Mar:1-2.

115. Gerson B, Ballinger JR, Gulenchyn KY. Improved modification for in vitro labeling of red blood cells with technetium-99m. *J Nucl Med Technol* 1988;16:9-11.

116. Thakur ML, Coleman RE, Welch MJ. Indium-111-labeled leukocytes for the localization of abscesses: preparation, analysis, tissue distribution, and comparison with gallium-67 citrate in dogs. *J Lab Clin Med* 1977;89:217-28.

117. Segal AW, Deteix P, Garcia R, Tooth P, Zanelli GD, Allison AC. Indium-111 labeling of leukocytes: a detrimental effect on neutrophil and lymphocyte function and an improved method of cell labeling. *J Nucl Med* 1978;19:1238-44.

118. Wistrow BW, Grossman ZD, McAfee JG, Subramanian G, Henderson RW, Roskopf ML. Labeling of platelets with oxine complexes of Tc-99m and In-111. Part 1. In vitro studies and survival in the rabbit. *J Nucl Med* 1978;19:483-7.

119. Thakur ML, Welch MJ, Joist JH, Coleman RE. Indium-111 labeled platelets: studies on preparation and evaluation of in vitro and in vivo functions. *Thromb Res* 1976;9:345-7.

120. Karesh SM, Henkin RE. Preparation of ^{111}In leukocytes after hemolytic removal of erythrocytes. *Nucl Med Biol* 1987;14:79-80.

121. Isaka Y, Kimura K, Matsumoto M, Kmada T, Imaizumi M. Functional alterations of human platelets following indium-111 labelling using different incubation media and labeling agents. *Eur J Nucl Med* 1991;18:326-31.

122. Ballinger JR, Proulx A, Gerson B, Gulenchyn KY. Effect of granulocyte concentration on leukocyte labelling efficiency with ^{99m}Tc-HMPAO. *Nucl Med Biol* 1990;17:443.

123. Ecclestone M, Proulx A, Balllinger JR, Berson B, Reid RH, Gulenchyn KY. In vitro comparison of HMPAO and gentisic acid for labelling leukocytes with ^{99m}Tc. *Eur J Nucl Med* 1990;16:299-302.

124. Millar AM, O'Brien. An investigation of factors that might influence the radiochemical purity and stability of ^{99m}Tc-MAG3. *Eur J Nucl Med* 1990;16:615-9.

125. Thakur ML, Walsh L, Malech HL, Gottschalk A. Indium-111-labeled human platelets: improved method, efficacy, and evaluation. *J Nucl Med* 1981;22:381-5.

126. Sampson CB, Keegan J. Stability of ^{99m}Tc-DTPA injection: effect of delay after preparation, dilution, generator oxidant, air and oxygen. *Nucl Med Commun* 1985;6:313-8.

127. Inoue O, Ikeda I, Kurata K. Evaluation of two different HEDP content kits: stability study against dilution both in vivo and in vitro. *Nuklearmedizin* 1982;21:121-5.

128. McCullough RW, Sheff MF, Tyson IB, Galasso F. The nature of Tc-MDP complexes and their localization *in vivo* [abstract]. *Nucl Med Commun* 1985;6:548-9.

129. Gagnon A, Taillefer R, Bavaria G, Leveille J. Fast labeling of technetium-99m-sestamibi with microwave oven heating. *J Nucl Med Technol* 1991;19:90-3.

130. Hung JC, Wilson ME, Brown ML, Gibbons RJ. Rapid preparation and quality control method for technetium-99m-2-methoxy isobutyl isonitrile (technetium-99m-sestamibi). *J Nucl Med* 1991;32:2162-8.

131. Early PJ, Razzak MA, Sodee DB. *Textbook of Nuclear Medicine Technology*. 3rd ed. St. Louis: CB Mosby. 1979:363-70.

132. Som P, Ansari AN, Oster ZH, Atkins HL, Sipe CR, Hosain F, et al. Effects of heating on the size-distribution and differential uptake of ^{99m}Tc-red blood cells (RBC) by spleen and liver [abstract]. *J Nucl Med* 1980;21:P44.

133. Som P, Oster ZH, Atkins HL, Golman AG, Sacker DF, Harold WH, et al. Detection of gastrointestinal blood loss with ^{99m}Tc-labeled, heat-treated red blood cells. *Radiology* 1981;138:207-9.

134. Frier M, Griffiths P, Ramsey A. The physical and chemical characteristics of sulphur colloids. *Eur J Nucl Med* 1981;6:255-60.

135. Morrissey GJ, Powe JE. Microwave preparation of technetium-99m sulfur colloid. *J Nucl Med Techno.* 1992;20:159-62.

136. Som P, Oster ZH. Spleen scanning with ^{99m}Tc-labeled red blood cells (RBC) [letter]. *J Nucl Med* 1980;21:1000.

137. Gottschalk A, Armas R, Thakur ML. Spleen scanning with ^{99m}Tc-labeled red blood cells (RBC). Reply [letter]. *J Nucl Med* 1980;21:1000-1.

138. Atkins HL, Goldman AG, Fairchild RG, Oster ZH, Som P, Richards P, et al. Splenic sequestration of ^{99m}Tc labeled, heat treated red blood cells. *Radiology* 1980;136:501-3.

139. Valk PE, Guille J. Measurement of splenic function with heat-damaged RBCs: effect of heating conditions: concise communication. *J Nucl Med* 1984; 25:965-8.

140. Armas RR, Thakur ML, Gottschalk A. A simplified method of selective spleen scintigraphy with Tc-99m-labeled erythrocytes: clinical applications. *J Nucl Med* 1980;21:413-6.

141. Hung JC, Wilson ME, Brown ML. Rapid preparation and quality control of technetium-99m MAG3™. *J Nucl Med Technol* 1991;19:176-9.

142. Taillefer R, Gagnon A, Lambert R, Leveille J. Labeling procedure and in-vitro stability of Tc-99m methoxy isobutyl isonitrile (MIBI): practical considerations [abstract]. *J Nuc Med* 1989;30:865.

143. Bushman M, Pipes D, Wolfangel R, MacDonald J, Harris J, Coveney J. Effects of heating on the composition and biodistribution in rats of rhenium Re-186 etidronate injection [abstract]. *J Nucl Med Technol* 1992;20:123.

144. Steigman J, Eckelman WC. The Chemistry of Technetium in Medicine. Washington D.C.: National Academy Press. 1992: 11-4.

145. Evdokimoff VN. Hot lab radiopharmaceutical accident: potential airborne release. *Health Physics* 1980;39:573-4.

146. Hung JC, Gibbons RJ. Breakage of technetium-99m-sestamibi vial with the use of a microwave oven [letter]. *J Nucl Med* 1992;33:176-8.

147. Ponto JA, Ponto LLB. Time dependence of PIPIDA-labeling with ^{99m}Tc. *Am J Hosp Pharm* 1981;38:1939-41.

148. Blauenstein P, Iftimia M, Argentini M, Schubiger PA. The Tc-DTPA-complex: new aspects on an old but not yet solved problem [abstract]. *Eur J Nucl Med* 1983;8:A46.

149. Groth S, Mortensen J, Funch-Rosenberg H, Rossing N. Ultrasound nebulization does not cause chemical breakdown of 99m-Tc-DTPA [abstract]. *J Nucl Med* 1988;29:905.

150. Froelich JW, Callahan RJ, Leppo J, McKusick KA, Strauss HW. Time course of in vivo labelling of red blood cells [abstract]. *J Nucl Med* 1980;21:P44.

151. Callahan RJ, Froelich JW, McKusick KA, Strauss HW. Studies of red blood cell (RBC) labeling: rate of binding of ^{99m}Tc to hemoglobin (Hgb) in the intact cell and Hgb solution [abstract]. *J Nucl Med* 1981;22:P70.

152. Callahan RJ, Froelich JW, McKusick KA, Leppo J, Strauss HW. A modified method for in vivo labeling of red blood cells with ^{99m}Tc. *J Nucl Med* 1982;23:315-8.

153. Steigman J, Eckelman WC. The Chemistry of Technetium in Medicine. Washington, D.C.: National Academy Press. 1992.

154. Callahan RJ, Rabito CA. Radiolabeling of erythrocytes with technetium-99m: role of band-3 protein in the transport of pertechnetate across the cell membrane. *J Nucl Med* 1990;31:2004-10.

155. Weiblen BJ, Forstrom L, McCullough J. Studies of the kinetics of indium-111-labeled granulocytes. *J Lab Clin Med* 1979;94:246-55.

156. Thakur ML, Lavender JP, Arnot RN, Silvester DJ, Segal AW. Indium-111-labeled autologous leukocytes in man. *J Nucl Med* 1977;18:1012-9.

157. Ponto JA, Seabold JE. Time course of indium-111 oxine labeling of human leukocytes. *Nucl Med Commun* 1984;5:769-73.

158. Hill-Zobel RL, Gannon S, McCandless B, Tsan MF. Effects of chelates and incubation media on platelet labeling with indium-111. *J Nucl Med* 1987;28:223-8.

159. Karesh SM. Technetium-99m-exametazime: pitfalls in preparation and quality control. *J Nucl Med Technol* 1989;17:215-8.

160. McAfee JG, Thakur ML. Survey of radioactive agents for in vitro labeling of phagocytic leukocytes. I. soluble agents. *J Nucl Med* 1976;17:480-7.

161. Steffel FG, Rao S. Rapid and simple methods for labeling white blood cells and platelets with indium-111-oxine. *J Nucl Med Technol* 1987;15:61-5.

162. Goodwin DA, Bushberg JT, Doherty PW, Lipton MJ, Conley FK, Diamanti CI, et al. Indium-111-labeled autologous platelets for location of vascular thrombi in humans. *J Nucl Med* 1978;19:626-34.

163. Hawker RJ, Hawker LM, Wilkinson AR. Indium (^{111}In)-labelled human platelets: optimal method. *Clin Sci* 1980;58:243-8.

164. McAfee JG, Gagne GM, Subramanian G, Grossman ZD, Thomas FD, Roskopf ML, et al. Distribution of leukocytes labeled with In-111 oxine in dogs with acute inflammatory lesions. *J Nucl Med* 1980;21:1059-68.

165. Roddie ME, Peters AM, Danpure HJ, Osman S, Henderson BL, Lavender JP, et al. *Radiology* 1988;166:767-72.

166. Dewanjee MK, Chowdhury S, Brown ML, Warner HW. Distribution of In-111 in granulocyte and other cellular elements of blood (CEB) in human In-111-labeled mixed white cell (MWC) and platelet preparations [abstract]. *J Nucl Med* 1984;25:P98.

167. Goodgold HM, Gentilcore RC, Hendershott L, Fletcher JW, Samuels LD. Significance of diffuse cardiac activity on In-111 labeled leucocyte scans. *Eur J Nucl Med* 1986;12;271-3.

168. Gilbert BR, Cerqueira MD, Via HW, Nelp WB. Indium-111 labeled leukocyte uptake: false-positive results in noninfected pseudoaneurysms. *Radiology* 1986;158:761-3.

169. Loken MK, Clay ME, Carpenter RT, Boudreau RJ, McCullough JJ. Clinical use of indium-111 labeled blood products. *Clin Nucl Med* 1985;10:902-11.

170. Chowdhury S, Thorson L, Jenkins D, Herold T. Separation and labeling of human leukocytes by two methods for the detection of infectious, inflammatory disease and graft infection [abstract]. *J Nucl Med Technol* 1991;19:118.

171. Brown BM, Cheng KT, Gordon L, Patterson WA, Rogers T, Tou ZW. The sedimentation method for leukocyte labeling [abstract]. *J Nucl Med Technol* 1992;20:108.

172. Baker WJ, Datz FL. Preparation and clinical utility of In-111 labeled leukocytes. *J Nucl Med Technol* 1984;12:131-6.

173. Boudreau R, Rosenthall L, Tyler JL, Arzoumanian. Effect of ^{99m}Tc-Sn-colloid incubation time on in vivo distribution. *Eur J Nucl Med* 1983;8:335-7.

174. Henkin RE, Woodruff A, Chang W, Green AM. The effect of radiopharmaceutical incubation time on bone scan quality. *Radiology* 1980;135:463-6.

175. Buell U, Kleinhans E, Zorn-Bopp E, Reuschel W, Muenzing W, Moser EA, et al. A comparison of bone imaging with ^{99m}Tc DPD and ^{99m}Tc MDP. *J Nucl Med* 1982;23:214-7.

176. Darte L. A comparative investigation of the gel chromatography column scanning method for quality control of ^{99m}Tc-methylenediphosphonate. *Nuclearmedizin* 1981;20:51-63.

177. Wilson MA, Pollack MJ. Gastric visualization and image quality in radionuclide bone scanning. *J Nucl Med* 1981;22:518-21.

178. Van Duzee BF, DePrato DW, Cavanaugh DJ, Coburn T, Gelfand MJ, Harcke HT, et al. A multi-site clinical study of factors influencing soft-tissue localization of skeletal imaging agents in children [abstract]. *J Nucl Med* 1982;23:P99.

179. Van Duzee BF, Conway JJ, Cavanaugh DJ, Coburn T, Gelfand MJ, Harcke HT, et al. Radiopharmaceutical preparation conditions associated with abnormal soft-tissue localization of skeletal imaging agents [abstract]. *Pharm Pract* 1983;18:A-11.

180. Forstrom L. Clinical experience using In-111-leukocytes in 1001 cases. Presented at the Fourth Annual Midwestern Cell Labeling Conference: 1983: Iowa City.

181. McLean JR, Wise P. Impurities in a ^{99m}Tc lung imaging kit. *J Nucl Med Technol* 1977;5:28-31.

182. McLean JR, Welsh WJ, Rockwell LJ. Quality control procedures for ^{99m}Tc-MAA. *Int J Nucl Med Biol* 1979;6:142-3,

183. Atkins HL, Hauser W, Richards P. Factors affecting distribution of ^{99m}Tc-sulfur colloid. *J Nucl Med* 1969;10:319-20.

184. Davis MA, Jones AG, Trindade H. A rapid and accurate method for sizing radiocolloids. *J Nucl Med* 1974;15:923-8.

185. Heyman S, David MA, Shulkin PM, Treves S. Biologic evaluation of radiocolloids for bone marrow scintigraphy. In: Sorenson JA, coordinator. *Radiopharmaceuticals II: proceedings of the 2nd international symposium on radiopharmaceuticals*: 1979 Mar 19-22: Seattle. New York: Society of Nuclear Medicine. 1979: 593-601.

186. Martindale AA, Papadimitriou JM, Turner JH. Technetium-99m antimony colloid for bone marrow imaging. *J Nucl Med* 1980;21:1035-41.

187. Kloiber R, Damtew B, Rosenthall L. A crossover study comparing the effect of particle size on the distribution of radiocolloid in patients. *Clin Nucl Med* 1981;6:204-6.

188. Adams FG, Horton PW, Selim SM. Clinical comparison of three liver scanning agents. *Eur J Nucl Med* 1980;5:237-9.

189. Spencer RP. Role of radiolabeled erythrocyte in evaluation of splenic function. *J Nucl Med* 1980;21:489- 91.

190. Campbell J, Bellen JC, Baker RJ, Cook DJ. Technetium-99m calcium phytate--optimization of calcium content for liver and spleen scintigraphy. *J Nucl Med* 1981;22:157-60.

191. Davis MA. Particulate radiopharmaceuticals for pulmonary studies. In: Subramanian G, Rhodes BA, Cooper JF, Sodd VJ, editors. *Radiopharmaceuticals*. New York: Society of Nuclear Medicine. 1975: 267-81.

192. Rhodes BA, Croft BY. *Basics of Radiopharmacy*. St. Louis: CV Mosby. 1978: 142-4.

193. Pedersen B, Kristensen K. Evaluation of methods for sizing of colloidal radiopharmaceuticals. *Eur J Nucl Med* 1981;6:521-6.

194. Elliott AT, Murray T, Hilditch TE, Whateley TL. Investigation of factors affecting adhesion of ^{99}Tc^{m} labelled colloids to glass vials. *Nucl Med Commun* 1990;11:375-81.

195. Hilditch TE, Elliott AT, Murray T, Whateley TL. Formation of large particles in a ^{99}Tc^{m}- tin colloid preparation. *Nucl Med Commun* 1986;7:845-50.

196. Strout B, Hladik WB. Tc-MAA: focal hot spots. *Monthly Scan* 1978;Dec:1-2.

197. Vinberg N, Siboni J, Sorensen GM, Norbygaard E. Late biodistribution of ^{99}Tc^{m} macroaggregates for lung perfusion imaging [letter]. *Nucl Med Commun* 1990;11:719-20.

198. Heck LL, Duley JW. Statistical considerations in lung imaging with ^{99m}Tc albumin particles. *Radiology* 1974;113:675-9.

199. Dworkin HJ, Gutkowski RF, Porter W, Potter M. Effect of particle number on lung perfusion images. *J Nucl Med* 1977;18:260-2.

200. Coupal JJ, Hughes J, Ryo UY, Jay M. Sedimentatior characteristics of several Tc-99m aggregated albumi. radiopharmaceuticals [abstract]. *J Nucl Med* 1988;29:904.

201. Palmer AM. The absorption of ^{99}Tc^{m}-MAA onto vials and syringes [abstract]. *Nucl Med Commun* 1985;6:550.

202. Cohen MB, Spolter L. Effect of stabilizers and autoclaving in the preparation of ^{99m}Tc-sulfur colloid. *J Nucl Med* 1969;10:395-6,.

203. Porter WC, Dworkin HJ, Gutkowski RF. Vial retention of ^{99m}technetium sulfur colloid in commercial kits. *Am J Hosp Pharm* 1975;32:1141-3.

204. Phipps P, BorhamP, Gonda I, Bailey D, Bautovich G, Anderson S. A rapid method for the evaluation of diagnostic radioaerosol delivery systems. *Eur J Nucl Med* 1987;13:183-6.

205. Schuster K, Peterson J, Sirr S, Stuart D. Quality control in the production of radioaerosols [letter]. *J Nucl Med Technol* 1987;15, 97-8.

206. Sirr SA, Gramith F. Delivery efficiency of technetium-99m DTPA aerosol -- reply [letter]. *J Nucl Med* 1986;27:1500.

207. Porter WC, Juni JE, Dworkin HJ. Does ethanol improve aerosol ventilation scans? [abstract] *J Nucl Med* 1990;31:894.

208. Yano Y. Radionuclide generators: current and future applications in nuclear medicine. In: Subramanian G, Rhodes BA, Cooper JF, Sodd VJ, editors. *Radiopharmaceuticals*. New York: Society of Nuclear Medicine. 1975: 236-45.

209. Coupal JJ, Shih WJ. Degraded bone image quality from Tc-99m generator eluate contaminant(s) [abstract]. *J Nucl Med* 1986;27:1067.

210. Sanderson JA, Kasina S, Rao TN, Reno JM, Roser CA, Fritzberg AR. Characterization and resolution of Mo-99/Tc-99m generated eluate contaminants interfering with N_2S_2 and N_3S amide thiolate chelation [abstract]. *J Nucl Med* 1991;32:1102.

211. Ponto JA. Effect of pertechnetate source and age on the radiochemical purity of technetium Tc 99m exametazime. *Am J Hosp Pharm* 1990;47:2511-3.

212. Conway JJ, Weiss S, Van Duzee BF, DePrato DW. A comparative study of the effects of instant and generator produced technetium 99m on the nonosseous localization of skeletal imaging agents in children [abstract]. *J Nucl Med* 1982;23:P109.

213. Pettit WA, DeLand FH, Pepper GH, Blanton L. Characterization of tin-technetium colloid in technetium-labeled albumin preparations. *J Nucl Med* 1978;19:387-92.

214. Nusynowitz ML, Straw JD, Benedetto AR, Dixon RS. Blood clearance rates of technetium-99m albumin preparations. *J Nucl Med* 1978;19:1142-5.

215. Kristensen K. Biodistribution in rats of 99m-Tc-labelled human serum albumin. *Nucl Med Commun* 1986;7:617-24.

216. Atkins HL, Cardinale KG, Eckelman WC. Evaluation of ^{99m}Tc-DTPA prepared by three different methods. *Radiology* 1971;98:674-7.

217. Carlsen JE, Moller ML, Lund JO, Trap-Jensen J. Comparison of four commercial ^{99m}Tc(Sn)DTPA preparations used for the measurement of glomerular filtration rate. *J Nucl Med* 1980;21:126-9.

218. Russell CD, Bischoff PG, Rowell KL, Kontzen F, Lloyd LK, Tauxe WN, et al. Quality control of ^{99m}Tc-DTPA for measurement of glomerular filtration. *J Nucl Med* 1983;24:722-7.

219. Vanlic-Razumenic N. Comparative examinations of ^{99m}Tc-DMS preparations obtained by labelling dimercaptosuccinate kits with different formulations. II. Comparison of chemical and biological characteristics of TcP-5 and MPI kits. *Nuclearmedizin* 1981;20:46-9.

220. Fordham EW, Ali A, Turner DA, Charters JR. *Atlas of total body radionuclide imaging. Volume II.* Philadelphia: Harper & Row. 1982: 1587-667.

221. Simon TR, Carrasquillo JA, Fejka R, Der M. A clinical evaluation of bone imaging kits [abstract]. *J Nucl Med* 1990;31:829.

222. Callahan RJ, Swanson DP, Petry N, Beightol RW, Vaillancourt J, Dragotakes SC. A multi-institutional in vitro evaluation of commercial ^{99m}Tc macroaggregated albumin kits. *J Nucl Med Technol* 1986;14:206-9.

223. Najafi A, Hutchison N. Electrophoretic analysis of different technetium-99m($SnCl_2$) methylene diphosphonate complexes. *J Nucl Med* 1985;26:524-30.

224. Seevers RH, Apodaca DM, Ryo UY, Bekerman C, Pinsky S. Variations in quality of bone images obtained with four different preparations of MDP [abstract]. *J Nucl Med* 1985;26:P130.

225. Pinkerton TC, Ferguson DL, Deutsch E, Heineman WR, Libson K. *In vivo* distributions of some component fractions of Tc($NaBH_4$)-HEDP mixtures separated by anion exchange high performance liquid chromatography. Int *J Appl Radiat Isot* 1982;33:907-15.

226. Ponto JA, Preslar JS. Poor labeling of technetium-99m RBCs in vivo associated with source of normal saline used for Sn-PYP reconstitution [letter]. *J Nucl Med Technol* 1990;19:107-8.

227. Slater DM, Anderson M, Garvie NW. Syringe extractables: effects on radiopharmaceuticals [letter]. *Lancet* 1983;2(8364):1431-2.

228. Waxman AD, Siemsen JK, Lee GC, Wolfstein RS, Moser L. Reliability of gallium brain scanning in the detection and differentiation of central nervous system lesions. *Radiology* 1975;116:675-8.

229. Hnatowich DJ, Kulprathipanja S, Beh B. The effect of preparation quality on biodistribution of ^{67}Ga citrate [abstract]. *J Labelled Compd Radiopharm* 1977;13:180.

230. Hammermaier A, Reich E, Bogl W. Radiochemical purity and in vitro stability of commercial hippurans. *J Nucl Med* 1986;27:850-54.

231. Yu WKS, Peck GE, Shaw SM. A comparison of the dissolution profiles for several commercially available [^{131}I]sodium iodide capsules. *Nucl Med Biol* 1989;16:491-3.

232. Yu WKS, Shaw SM, Peck GE. Determination of dissolution profiles for several commercially available therapeutic [^{131}I]sodium iodide capsules. *Nucl Med Biol* 1990;17:465-7.

233. Spicer JA, Hannesen R, Baranczuk RJ. A comparison of radiochemical purity and reaction yields of iodine 123 sodium iodide solutions [abstract]. *J Nucl Med* 1990;31:947.

234. Petry NA, Shaw SM, Kessler WV, Born GS, Belcastro PF. Effect of rubber closures on the stability of stannous ion in reagent kits for radiopharmaceuticals. *J Parent Drug Assoc* 1979;33:283-6.

235. Millar AM. The absorption of ^{99m}Tc dimercaptosuccinic acid onto injection vials. *Nucl Med Commun* 1984;5:195-9.

236. Kowalsky RJ, Chilton HM. Re: stability of stannous ion in stannous pyrophosphate kits [letter]. *J Nucl Med* 1983;24:1080-1.

237. McKusick KA, Malmud LS, Kirchner PT, Wagner HN. An interesting artifact in radionuclide imaging of the kidneys. *J Nucl Med* 1973;14:113-4.

238. Thornton AK, Molinski VJ, Spencer JT. Radiolytic production of peroxides in technetium-99m solutions [abstract]. *J Nucl Med* 1979;20:653.

239. Robins PJ, Williams CC. An investigation of low tagging yields of ^{99m}Tc DTPA kits [abstract]. *J Nucl Med* 1979;20:653.

240. Bayne VJ, Forster AM, Tyrrell DA. Use of sodium iodide to overcome the eluate age restriction for Ceretec™ reconstitution. *Nucl Med Commun* 1989;10:29-33.

241. Waldman DL, Weber DA, Oberdorster G, Drago SR, Utell MS, Hyde RW, et al. Chemical breakdown of radioaerosols during nebulization [abstract]. *J Nucl Med* 1985;26:P131.

242. Waldman DL, Weber DA, Oberdorster G, Drago SR, Utell MJ, Hyde RW, et al. Chemical breakdown of technetium-99m DTPA during nebulization. *J Nucl Med* 1987;28:378-82.

243. Huchon GJ, Montgomery AB, Lipavsky A, Hoeffel JM, Murray JF. Respiratory clearance of aerosolized radioactive solutes of varying molecular weight. *J Nucl Med* 1987;28:894-902.

244. Kelbæk H, Bulow K, Aldershvile J, Mogelvang J, Nielsen SL. A new ^{99m}Tc-red blood cell labeling procedure for cardiac blood pool imaging: clinical results. *Eur J Nucl Med* 1989;15:333-5.

245. Srivastava SC, Straub RF. Blood cell labeling with ^{99m}Tc: progress and perspectives. *Semin Nucl Med* 1990;20:41-51.

246. Patrick ST, Glowniak JV, Turner FE, Robbins MS, Wolfangel RG. Comparison of in vitro RBC labeling with UltraTag® RBC kit versus in vivo labeling. *J Nucl Med* 1991;32:242-4.

247. Ryo UY, Mohammadzadeh AA, Siddiqui A, Colombetti LG, Pinsky S. Evaluation of labeling procedures and in vivo stability of ^{99m}Tc-red blood cells. *J Nucl Med* 1976;17:133-6.

248. Der M, Ballinger JR, Bowen BM. Decomposition of ^{99m}Tc pyrophosphate by peroxides in pertechnetate used in preparation. *J Nucl Med* 1981;22:645-6.

249. Hotte CE, Ice RD. The in vitro stability of [^{131}I]o-iodohippurate. *J Nucl Med* 1979;20:441-7.

250. Zimmer AM, Spies SM. Quality control of unidose dispensed radiopharmaceuticals: correlation to vial preparations [abstract]. *Pharm Pract* 1982;17:A-17.

251. Sampson CB. Instability of commercial ^{99m}Tc-DTPA kits--effect of dilution and delay before injection [abstract]. *Nucl Med Commun* 1984;5:239.

252. Dhawan V, Yeh DJ. Labeling efficiency and stomach concentration in methylene diphosphonate bone imaging. *J Nucl Med* 1979;20:791-3.

253. Taylor A, Lallone RL, Hagan PL. Optimal handling of dimercaptosuccinic acid for quantitative renal scanning. *J Nucl Med* 1980;21:1190-3.

254. Jovanovic V, Konstantinovska D, Memedovic T. Determination of radiochemical purity and stability of ^{99m}Tc-diethyl HIDA. *Eur J Nucl Med* 1981;6:375-8.

255. Beightol RW, Cochrane J. Radiochemical analysis of commercial MDP bone kits. *J Nucl Med Technol* 1983;11:173-6.

256. Hayes AC. Effects of multiple factors on the stability of new technetium-99m labeled radiopharmaceuticals: MAG_3, Cardiolite, and CardioTec. *J Nucl Med Technol* 1992;20:84-7.

257. Coupal JJ, Kim EE, DeLand FH. Effects of dissolved oxygen on ^{99m}Tc methylene diphosphonate. *J Nucl Med* 1981;22:153-6.

258. Zbrzeznj DJ, Khan RAA. Factors affecting the labeling efficiency and stability of technetium-99m-labeled glucoheptonate. *Am J Hosp Pharm* 1981;38:1499-502.

259. McCormick MV, Sinclair MD, Wahner HW. Chromatographic quality of three ^{99m}Tc bone-imaging agents. *J Nucl Med Technol* 1976;4:189-92.

260. Zimmer AM, Pavel DG. Radiochemical evaluation and image correlation of stabilized and non-stabilized ^{99m}Tc-Sn-diphosphonate kits [abstract]. *J Nucl Med Technol* 1977;5:54-5.

261. Tofe AJ, Bevan JA, Fawzi MD, Francis MD, Silberstein EB, Alexander GA. Gentisic acid: a new stabilizer for low tin skeletal imaging agents. *J Nucl Med* 1980;21:366- 70.

262. Hesslewood SR. Quality control procedures for ^{99m}Tc complexes. *Nuklearmedizin* 1981;20:3-6.

263. Ballinger J, Der M, Bowen B. Stabilization of ^{99m}Tc-pyrophosphate injection with gentisic acid. *Eur J Nucl Med* 1981;6:153-4.

264. Collins HR, Kavula M, Solomon AC: Stability of unit- dose technetium-99m radiopharmaceuticals: radiochemical purity of multidose syringe. *Pharm Pract* 18:A-12, 1983.

265. MacGregor, RR, Schlyer DJ, Fowler JS, Wolf AP, Shiue CY. Fluorine-18-*N*-methylspiroperidol: radiolytic decomposition as a consequence of high specific activity and high dose levels. *J Nucl Med* 1987;28:60-7.

266. Glenn HJ, Kidwell RE. Radioactive pharmaceuticals and the concept of stability. In: Andrews GA, Kniseley RM, Wagner HN, editors. *Radioactive Pharmaceuticals*. Oak Ridge: US Atomic Energy Commission. 1966: 165-75.

267. Porter WC, Grotenhuis I. ^{99m}Tc Sn glucoheptonate: a professional dialogue. *Monthly Scan* 1978; Sept:1.

268. Patel BA, Zimmer AM, Webber DI, Kazikiewicz JM, Spies SM, Spies WG, et al. Effects of activity and HSA concentration on the stability of radioiodinated monoclonal antibodies [abstract]. *J Nucl Med Technol* 1989; 17:117.

269. Pipes D, Wolfangel R, Bushman M, Roberts R, Helling D Radiolysis effects on the radiochemical and chemical stability of rhenium Re-186 etidronate injection [abstract]. *J Nucl Med* 1992;33:1024-5.

270. Frincke JM, Halpern SE, Hagan PL, Lollo CP, Bartholomew RM, Poggenburg JK, et al. The effect of radioautolysis on 90Y antibody (Ab) preparations [abstract]. *J Nucl Med* 1987;28:711.

271. Loberg M. The study of organ function using radiolabeled drugs. Presented at the 128th Annual Meeting of the American Pharmaceutical Association: 1981 Mar 30: St. Louis.

272. Grayson RR. Factors which influence the radioactive iodine thyroidal uptake test. *Am J Med* 1960;28:397-415.

273. Sternthal E, Lipworth L, Stanley B, Abreau C. Suppression of thyroid radioiodine uptake by various doses of stable iodine. *N Engl J Med* 1980;303:1083-8.

274. Herbert V. Detection of malabsorption of vitamin B_{12} due to gastric or intestinal dysfunction. *Semin Nucl Med* 1972;2:220-34.

275. Gobuty AH. Clinical radiopharmacy: troubleshooting the Schilling test. *ASHP Signal* 1979; Nov:5-6.

276. Halpern SE, Nagan PL, Chauncey D, McKegney M, Bernstein K. The effect of certain variables on the tumor and tissue distribution of tracers. Part 1: carrier. *Invest Radiol* 1979;14:482-92.

277. Hoffer P. Gallium: mechanisms. *J Nucl Med* 1980;21:282-5.

278. Goldenberg DM, DeLand F, Kim E, Bennett S, Primus FJ, van Nagell JR, et al. Use of radiolabeled antibodies to carcinoembryonic antigen for the detection and localization of diverse cancers by external photoscanning. *N Engl J Med* 1978;298:1384-8.

279. Goldenberg DM. Tumor imaging with monoclonal antibodies. *J Nucl Med* 1983;24:360-2.

280. Katzenellenbogen JA, Carlson KE, Heiman DF, Goswami R. Receptor-binding radiopharmaceuticals for imaging breast tumors: estrogen-receptor interactions and selectivity of tissue uptake of halogenated estrogen analogs. *J Nucl Med* 1980;21:550-8.

281. Feenstra A, Vaalburg W, Nolten GMJ, Reiffers S, Talma AG, Wiegman T, et al. Estrogen receptor binding radiopharmaceuticals: II. Tissue distribution of 17 α-methylestradiol in normal and tumor-bearing rats. *J Nucl Med* 1983;24:522-8.

282. Larson SM, Brown JP, Wright PW, Carrasquillo JA, Hellstrom I, Hellstrom KE. Imaging of melanoma with I-131 labeled monoclonal antibodies. *J Nucl Med* 1983;24:123-9.

283. Korn N, Nordblom GD, Counsell RE. The effect of vehicle on the tissue distribution profiles of radioiodinated cholesterol esters in the rat. *Int J Nucl Med Biol* 1981;8:27-32.

284. Swarbrick J. Solubilized systems in pharmacy. *J Pharm Sci* 1965;54:1229-37.

285. Burnell RH, Maxwell GM. General and coronary haemodynamic effects of Tween 20. *Aust J Exp Biol Med Sci* 1974;52:151-5.

286. Feinendegen LE: Cardiac imaging with labeled fatty acids for the diagnosis of coronary heart disease. Presented at the International Congress of Cardiac Ischemia and Arrhythmias--Diagnostic Methods and Associated Therapy: 1979 Apr 1-4: Montreaux, Switzerland.

287. BASF Wyandotte. Pluronic polyols--toxicity and irritation data [product information catalog]. Wyandotte (MI): BASF Wyandotte Corp.

288. Study KT, Schultz HW, Laven DL. The effect of acteriostatic saline on ^{99m}Tc-labeled radiopharmaceuticals. *J Nucl Med Technol* 1981;9:115-6.

289. Charlton JC. Problems characteristic of radioactive pharmaceuticals. In: Andrews GA, Kniseley RM, Wagner HN, editors. *Radioactive Pharmaceuticals*. Oak Ridge: US Atomic Energy Commission. 1966: 33-50.

290. Fisher SM, Brown RG, Greyson ND. Unbinding of ^{99m}Tc by iodinated antiseptics [letter]. *J Nucl Med* 1977;18:1139- 40.

291. Peterson EM, Ryan JW, Martin WB. Gastric activity on Tc-99m oxidronate bone scans can be caused by isopropyl alcohol [abstract]. *J Nucl Med* 1986; 27:1090.

292. Murray T, Hilditch TE, Whateley TL, Elliott AT. Formation of labelled colloid in ^{99}Tc^{m}-DMSA due to the presence of bactericidal fluid. *Nucl Med Commun* 1986;7:505-10.

293. Hung JC, Wilson ME. Optimum concentration of ACD in the preparation of technetium-99m red blood cells with the UltraTag® RBC kit [abstract]. *J Nucl Med Technol* 1992;20:107.

294. Chowdhury S, Dewanjee MK, Hung JC, Thorson L. Affect of anticoagulant, heparin vs. ACD, on the binding of Tc-99m to hemoglobin and red cell membrane-proteins [abstract]. *J Nucl Med Technol* 1991;19:118.

295. Bonacorrsi J, Russell JK, Rodriguez A, Snyder G, Abraham S, Murphy J. Heparin vs. ACD anticoagulant effect on Tc99m RBC in vitro labeling. A quantitative analysis [abstract]. *J Nucl Med Technol* 1992;20:107.

296. Mayer K, Dwyer A, Laughlin JS. Spleen scanning using ACD-damaged red cells tagged with ^{51}Cr. *J Nucl Med* 1971;11:455-8.

297. Danpure H. The importance of radiolabelling human granulocytes with ^{111}In-tropolonate or ^{111}In-mercaptopyridine-N-oxide in plasma containing acid-citrate-dextrose. *Brit J Rad* 1986;59:907-10.

298. Nowotnik DP, Jurisson SS. Structure and stereochemistry in technetium coordination complexes. In: Steigman J, Eckelman WC. *The Chemistry of Technetium in Medicine*. Washington, D.C.: National Academy Press. 1992: 111-30.

299. Sharp PF, Smith FW, Gemmell FG, Lyall D, Evans NTS, Gvozdanovic D, et al. Technetium-99m HM-PAO stereoisomers as potential agents for imaging regional cerebral blood flow: human volunteer studies. *J Nucl Med* 1986;27:171-7.

300. Ballinger JR, Reid RH, Gulenchyn KY. Technetium-99m HM-PAO stereoisomers: differences in interaction with glutathione. *J Nucl Med* 1988;29:1998-2000.

301. Hawker RJ, Tyrrell DA. Cell labeling with ^{99}Tc^{m} *d* and *l* HMPAO [abstract]. *Nucl Med Commun* 1989;10:374.

302. Walovitch RC, Makuch J, Knapik G, Watson AD, Williams SJ. Brain retention of Tc99m-ECD is related to in vivo metabolism [abstract]. *J Nucl Med* 1988;29:747.

303. Awh OD, Kim JR, Shim SC. ^{99}Tc^{m}-diastereomeric dimercaptosuccinic acid complexes: comparison of their biodistribution. *Nucl Med Commun* 1989;10;449-50.

304. Wienhard K, Pawlik G, Nebeling B, Rudolf J, Fink G, Hamacher K. Estimation of local cerebral glucose utilization by positron emission tomography: comparison between (^{18}F)-2-flouro-2-deoxy-D-glucose and (^{18}F)-2-flouro-2-deoxy-D-mannose [abstract]. *J Nucl Med* 1990;31:771.

305. Ponto LLB, Ponto JA. Uses and limitations of positron emission tomography in clinical pharmacokinetics/ dynamics (part II). *Clin Pharmacokinet* 1992;22:274-83.

306. Halpern S, Alazraki N, Littenberg R, Hurwitz S, Green J, Kunsa J. ^{131}I thyroid uptakes: capsule versus liquid. *J Nucl Med* 1973;14:507-10.

307. Cohen Y. Chemical and radiochemical purity of radioactive pharmaceuticals related to their biological behavior. In: Andrews GA, Kniseley RM, Wagner HN, editors. *Radioactive Pharmaceuticals*. Oak Ridge: US Atomic Energy Commission. 1966: 67-91.

308. Haney TA, Wedeking P, Morcos N, Loberg MD. A therapeutic and diagnostic ^{131}I capsule formulation with minimal volatility and maximum bioavailability [abstract]. *J Nucl Med* 1981;22:P74.

309. Bonnyman J, Van Every B. Radiolytic breakdown of sodium iodide (^{131}I) in sodium iodide (^{131}I) capsules. *Nucl Med Commun* 1986;7:839-43.

310. Baum DC, Bowen BM, Wood DE. Comparison of the bioavailability of cyanocobalamin from capsule and liquid dosage forms. *Am J Hosp Pharm* 1975;32:1047-9.

311. McDonald JWD, Barr RM, Barton WB. Spurious Schilling test results obtained with intrinsic factor enclosed in capsules. *Ann Intern Med* 1975;83:827-9.

312. Jacobson BE, Onstad GR. Misleading second-stage Schilling tests due to inactive intrinsic factor concentrate. *Ann Intern Med* 1979;91:579-80.

313. Ponto JA. Questionable bioactivity of intrinsic factor for second-stage Schilling test [letter]. *Am J Hosp Pharm* 1980;37:1294-6.

314. Pathy MS, Kirkman S, Molloy MJ. An evaluation of simultaneously administered free and intrinsic factor bound radioactive cyanocobalamin in the diagnosis of pernicious anemia in the elderly. *J Clin Pathol* 1979;32:244-50.

315. Choy YC, Kim EE, Domstad PA, DeLand FH. Reliability of dual isotope Schilling test for the diagnosis of pernicious anemia or malabsorption syndrome [abstract]. *J Nucl Med* 1980;21:P26.

316. Fairbanks VF, Wahner HW, Valley TB, Scheidt RM. Spurious results from dual-isotope (Dicopac) vitamin B_{12} absorption test due to rapid or variable rates of exchange of ^{58}Co-B_{12} for ^{57}Co-B_{12} bound to intrinsic factor. *Nucl Med Commun* 1983;4:17-23.

317. Briedis D, McIntyre PA, Judisch J, Wagner HN. An evaluation of a dual-isotope method for the measurement of vitamin B_{12} absorption. *J Nucl Med* 1973;14:135-41.

318. Donaldson RM, Katz JH. Exchange between free and gastric juice-bound cyanocobalamin. *J Clin Invest* 1963;42:534-45.

319. Medi-Physics, Inc. Dicopac® users guide. Arlington Heights (IL): Medi-Physics, Inc. 1990.

320. Browning EJ, Banerjee K, Reisinger WE. Airborne concentration of I-131 in a nuclear medicine laboratory. *J Nucl Med* 1978;19:1078-81.

321. Luckett LW, Stotler RE. Radioiodine volatilization from reformulated sodium iodide ^{131}I oral solution. *J Nucl Med* 1980;21:477-9.

322. Carey JE, Swanson DP. Thyroid contamination fror airborne ^{131}I [letter]. *J Nucl Med* 1979;20:362.

323. Jackson GL, MacIntyre F. Accumulation of radioiodine in staff members [letter]. *J Nucl Med* 1979;20:995.

324. Maguire WJ. A precaution for minimizing radiation exposure from iodine vaporization. *J Nucl Med Technol* 1980;8:90-3.

325. Nishiyama H, Lukes SJ, Mayfield G, Grossman LW. Internal contamination of laboratory personnel by ^{131}I. *Radiology* 1980;136:767-71.

326. Howard BY. Safe handling of radioiodinated solutions. *J Nucl Med Technol* 1976;4:28-30.

327. Croft BY. Safe handling of radioiodine [letter]. *J Nucl Med* 1979;20:362-3.

328. Wolfangel RG. Accumulation of radioiodine in staff members. Reply [letter]. *J Nucl Med* 1979;20:995.

329. Grossman LW, Williams CC. Chilling--an effective way of reducing volatility of therapeutic iodine solutions [abstract]. *J Nucl Med* 1980;21:P93.

330. Dansereau R, Dansereau R. A new coated-bead dosaged form of sodium iodide I-131 [abstract]. *J Nucl Me?* 1989;30:886.

331. Clanton JA, Chilton HM, Laven DL, Slater JB, Strane TR. Volatility of I-131 therapy solutions for oral administration: a multicenter study. Princeton (NJ): E. R. Squibb & Sons. 1989.

332. Clanton JA, Seibert J, Sneed D. Volatility of therapeutic I-131 sodium iodide solutions for oral administration [abstract]. *J Nucl Med* 1986; 27:1092.

333. Verbruggen AM, De Roo M. Contamination of the packing material of sodium iodide (^{131}I) therapy capsules with an unexpected radionuclide. *Eur J Nucl Med* 1983;8:406-7.

334. Saha GB. *Fundamentals of nuclear pharmacy*. 3rd ed. New York: Springer-Verlag. 1992.

335. Shearer DR, Pezzullo JC, Moore MM, Coleman P, Frater SI. Radiation dose from radiopharmaceuticals contaminated with molybdenum-99. *J Nucl Med* 1988;29:695-700.

336. Kowalsky RJ, Preslar J. Report of a positive Mo-99 breakthrough test [letter]. *J Nucl Med Technol* 1979;7:108.

337. Baker GA, Lum DJ, Smith EM, Winchell HS. Significance of radiocontaminants in ^{123}I for dosimetry and scintillation camera imaging. *J Nucl Med* 1976;17:740-3.

338. Ponto JA. Expiration times for ^{99m}Tc. *J Nucl Med Technol* 1981;9:40-1.

339. Suzuki A, Suzuki MN, Weis AM. Analysis of a radioisotope calibrator. *J Nucl Med Technol* 1976;4:193-8.

340. Johnson AS, Baker SI, Arnold JE, Colombetti LG, Pinsky S. Radionuclide impurities in commercial ^{123}I and their influence on the dose calibrator assay of ^{123}I [abstract]. *J Nucl Med* 1975;16:540.

341. Hughes JA, Williams CC, Thomas SR, Maxon HR, Basiewicz RH, Love WJ. Potential errors caused by variable radionuclidic purity of ^{123}I. *J Nucl Med Technol* 1979;7:167-70.

342. Chervu S, Chervu LR, Goodwin PN, Blaufox MD. Thyroid uptake measurements with ^{123}I: problems and pitfalls. *J Nucl Med* 1982;23:667-70,.

343. Grossman LW, Lukes SJ, Kruger JB, Nishiyama H. The influence of measurement technique and ^{124}I contamination on ^{123}I thyroid uptake determinations [abstract]. *J Nucl Med* 1983;24:P104.

344. Polak JF, English RJ, Holman BL. Performance of collimators used for tomographic imaging of ^{123}I contaminated with ^{124}I. *J Nucl Med* 1983;24:1065-9.

345. Madsen MT, Patel J, Thakur ML, Park CH. Collimator selection and ^{124}I contamination determination for ^{123}I imaging studies [abstract]. *J Nucl Med* 1984;25:P106.

346. Kasulis PW, Hill TC, Lee RG, Clouse ME. Comparison of gamma camera response to $^{123}I(p,5n)$ and $^{123}I(p,2n)$ [abstract]. *J Nucl Med Technol* 1984;12:90-1.

347. Groch MW, Lewis GK. Thallium-201: scintillation camera imaging considerations. *J Nucl Med* 1976;17:142-5.

348. Hines HH, Lagunassolar MC. The effect of different levels of ^{202}Tl and ^{200}Tl radiocontamination on ^{201}Tl imaging [abstract]. *J Nucl Med* 1980;21:P51.

349. Ricciardone M, Frey GD, Levine E. Imaging effects of the radiocontaminant ^{200}Tl from 4-day precalibrated lots of a commercially produced ^{201}Tl. Presented at the Twenty-fourth Annual Meeting of the Southeastern Chapter of the Society of Nuclear Medicine: 1983: Orlando.

350. Sirr SA, Juenemann PJ, Tom H, Boudreau J, Chandler RP, Loken MK. Effect of ethanol on droplet size, efficiency of delivery, and clearance characteristics of technetium-99m DTPA aerosol. *J Nucl Med* 1985;26:643-6.

351. Smart RC, Lyons NR, McLean RG. Delivery efficiency of technetium-99m DTPA aerosol [abstract]. *J Nucl Med* 1986;27:1500.

352. Billinghurst MW, Abrams DN, Coutts AD. Anomalous concentration gradient in NaI solutions inadvertently frozen in transit. *J Nucl Med Technol* 1990;18:54-5.

353. Deshpande SV, DeNardo SJ, Meares CF, McCall MJ, Adams GP, DeNardo GL. Effect of different linkages between chelates and monoclonal antibodies on levels of radioactivity in the liver. *Nucl Med Biol* 1989;16:587-97.

354. Mortelmans L, Verbruggen A, de Roo M, Vermylen J. Evaluation of three methods of platelet labeling. *Nucl Med Commun* 1986;7:519-29.

355. Chowdhury S, Pineda AA, Zylstra V, O'Conner MK, Forstrom LA, Dewanjee MK. Saline washing affects in-vivo recovery and platelet function [abstract]. *J Nucl Med Technol* 1989;17:113.

356. Robertson JS, Dewanjee MK, Dunn WL, Wahner HW. Biodistribution and survival of human platelets labeled in buffered media and plasma [abstract]. *J Nucl Med* 1983;24:P73-4.

357. Millar AM. The economical use of $^{99}Tc^{m}$-hexamibi kits [abstract]. *Nucl Med Commun* 1989;10:247.

358. Stadalnik RC. Diffuse lung uptake of ^{99m}Tc-sulfur colloid. *Semin Nucl Med* 1980;10:106-7.

359. Tofe AJ, Francis MD. Optimization of the ratio of stannous tin:ethane-1-hydroxy-1, 1-diphosphonate for bone scanning with ^{99m}Tc-pertechnetate. *J Nucl Med* 1974;15:69- 74.

360. Ford DR. Evaluation of commercially and electrolytically produced technetium ^{99m}Tc human serum albumin. *Am J Hosp Pharm* 1979;35:1081-3.

361. Eckelman W, Richards P, Atkins HL, Hauser W, Klopper JF. Visualization of the human spleen with ^{99m}Tc- labeled red blood cells. *J Nucl Med* 1971;12:310-1.

362. Majewski W, Zimmer AM, Spies SM. Radiochemical evaluation of commercial hepatobiliary IDA radiopharmaceuticals [abstract]. *J Nucl Med Technol* 1981;9:116.

363. Cooper PA, Zimmer AM. Radiochemical purity and stability of commercial ^{99m}Tc stannous DTPA kits using a new chromatography technique. *J Nucl Med Technol* 1975;3:208-9.

364. Ponto J, Patten S. Liver uptake of ^{99m}Tc DMSA. *View Box* 1983;2:1-2.

365. McAfee JG, Grossman ZD, Gagne G, Zens AL, Subramanian G, Thomas FD, et al. Comparison of renal extraction efficiencies for radioactive agents in the normal dog. *J Nucl Med* 1981;22:333-8.

366. Chilton H, Lewis JC, Motsinger SF, Cowan RJ. Reticuloendothelial distribution of a colloid-like material in 6b(^{131}I)-iodomethyl-19-norcholesterol (NP-59) [letter]. *J Nucl Med* 1979;20:803-5.

367. Johnston AS, Colombetti LG, Baker SI, Pinsky SM. Dose calibrator readings due to radionuclidic impurities found in radiopharmaceuticals. *Nuklearmedizin* 1979;19:1-6.

QUESTIONS

1. Which of the following situations LEAST likely results in an increased level of free pertechnetate impurity in most common radiopharmaceuticals?

   A. Al^{+3} concentration of > 10 mg/ml
   B. Monday morning generator eluate
   C. midweek eluate 12 hours post elution
   D. preparation with three times the recommended activity

2. Which of the following effects LEAST likely occurs in association with Al^{+3} contamination?

   A. *in vivo* erythrocyte agglutination
   B. ^{99m}Tc-etidronate (HEDP) localization in liver
   C. ^{99m}Tc-pertechnetate retention in soft tissue
   D. ^{99m}Tc-sulfur colloid localization in lungs

3. The labeling efficiency of which of the following ^{99m}Tc-radiopharmaceuticals is LEAST affected by changes in Sn^{+2} concentration?

   A. exametazime (HMPAO)
   B. oxidronate (HDP)
   C. pyrophosphate (PYP)
   D. red blood cells (RBC)

4. Which of the following radiopharmaceuticals is LEAST affected by an alkaline pH?

   A. ^{99m}Tc-exametazime (HMPAO)
   B. ^{99m}Tc-pyrophosphate (PYP)
   C. ^{99m}Tc-succimer (DMSA)
   D. ^{201}Tl thallous chloride

5. Which of the following ^{99m}Tc-radiopharmaceuticals is LEAST affected by the mixing order during preparation?

   A. albumin colloid
   B. etidronate (HEDP)
   C. *in vitro* red blood cells (RBC)
   D. sulfur colloid

6. Which of the following radiopharmaceuticals is LEAST affected by reagent concentration during preparation?

   A. ^{99m}Tc-macroaggregated albumin (MAA)
   B. ^{99m}Tc-mertiatide (MAG_3)
   C. ^{99m}Tc-red blood cells (RBC)
   D. ^{111}In-leukocytes

7. The presence of radiochemical impurities in which of the following ^{99m}Tc-radiopharmaceuticals is LEAST likely due to inadequate heating during preparation?

   A. damaged red blood cells (RBC)
   B. mertiatide (MAG_3)
   C. sestamibi
   D. sulfur colloid

8. Which of the following radiopharmaceuticals does NOT require incubation for 10-20 minutes in order to achieve maximal radiolabeling?

   A. ^{99m}Tc-lidofenin (HIDA)
   B. ^{99m}Tc-mertiatide (MAG_3)
   C. ^{99m}Tc-red blood cells (RBC)
   D. ^{111}In-leukocytes

9. Which of the following ^{99m}Tc-radiopharmaceuticals LEAST adsorbs to the walls of glass vials over time?

   A. macroaggregated albumin (MAA)
   B. pertechnetate
   C. sestamibi
   D. sulfur colloid

10. Increased amounts of radiochemical impurities is LEAST associated with which of the following manufacturer-related factors?

    A. chemical contaminants leached from rubber or plastic components
    B. intra- and inter-lot variability of reagent kits
    C. source of ^{99m}Tc-pertechnetate
    D. vial size

11. Which of the following is MOST effective at maintaining stannous ion in the desired oxidation state?

    A. nitrogen or argon atmosphere
    B. preparation with high specific concentration ^{99m}Tc-pertechnetate
    C. reconstitution with LDO (low dissolved oxygen) saline
    D. refrigeration

12. Which of the following is LEAST effective at inhibiting radiolytic decomposition of ^{99m}Tc-radiopharmaceuticals?

    A. addition of ascorbic acid
    B. limiting introduction of air into the vial
    C. maintenance of highest possible specific activity
    D. refrigeration

13. Which of the following radiopharmaceuticals exhibits the LEAST alteration in biodistribution as a function of specific activity?

    A. ^{57}Co-cyanocobalamin
    B. ^{67}Ga-citrate
    C. ^{99m}Tc-macroaggregated albumin (MAA)
    D. ^{131}I sodium iodide

14. Which of the following ^{99m}Tc-radiopharmaceuticals requires a reconstitution volume of > 3 ml in order to effect and maintain dissolution?

    A. disofenin (DISIDA)
    B. medronate (MDP)
    C. pentetate (DTPA)
    D. teboroxime

15. Which of the following pairs is LEAST likely to exhibit altered biodistribution?

A. ^{99m}Tc-mebrofenin -- methyl and propyl parabens
B. ^{99m}Tc-oxidronate (HDP) -- isopropyl alcohol
C. ^{99m}Tc-pertechnetate -- benzyl alcohol
D. ^{99m}Tc-succimer (DMSA) -- cetrimide/chlorhexidine

16. In the preparation of which of the following radiopharmaceuticals is heparin preferred over ACD?

A. ^{99m}Tc-red blood cells (RBC), *in vitro* technique
B. ^{99m}Tc-red blood cells (RBC), *in vivo - in vitro* technique
C. ^{111}In-leukocytes
D. ^{111}In-platelets

17. For which of the following is stereoisomeric form NOT applicable as a factor in its biodistribution?

A. ^{18}F fludeoxyglucose (FDG)
B. ^{99m}Tc-exametazime (HMPAO)
C. ^{99m}Tc-medronate (MDP)
D. ^{99m}Tc-succimer (DMSA)

18. Which of the following is NOT a problem associated with encapsulation of ^{131}I sodium iodide?

A. enhanced volatility
B. formation of iodinated gelatin
C. formation of radiochemical impurities
D. poor dissolution

19. Recommendations to separate the administration of the two Dicopac™ dosages by two hours are based on the problem of:

A. competitive dissolution in the presence of achlorhydria.
B. inadequate intrinsic factor in stomach to complex the combined B_{12} mass.
C. radiocyanocobalamin exchange with intrinsic factor complex.
D. saturation of ileal absorption sites.

20. Tap water should not be used for dilution of ^{131}I sodium iodide solution because oxidation to volatile forms of iodine is catalyzed by each of the following, EXCEPT:

A. chlorine.
B. dissolved carbon dioxide.
C. heavy metal ions.
D. sodium bisulfite.

21. Which of the following problems is LEAST likely a result of radionuclidic impurities?

A. enhanced radiolytic decomposition
B. errors in radioactivity measurements
C. image degradation
D. increased radiation dose to patient

22. Which of the following factors is MOST influenced by the nuclear pharmacist when preparing and dispensing ^{99m}Tc-exametazime (HMPAO)?

A. formation of "secondary complex"
B. radiolytic decomposition
C. stannous-to-ligand ratio
D. stereoisomeric form

23. Visualization of thyroid and stomach during bone imaging with ^{99m}Tc-medronate (MDP) is MOST likely due to which of the following?

A. excess Al^{+3}
B. excess ascorbic acid
C. inadequate incubation time
D. preparation with bacteriostatic saline

24. A radiochemical impurity with which of the following characteristics is MOST likely to be excreted in the urine by glomerular filtration?

A. hydrophilic, non-protein bound
B. hydrophilic, protein bound
C. lipophilic, non-protein bound
D. lipophilic, protein bound

25. Formulation problems best managed by nuclear pharmacists are those that:

A. are detected by routine quality control.
B. involve polymeric complexes.
C. occur after dispensing.
D. occur *in vivo*.