Bone Marrow Dosimetry for Radioimmunotherapy: Theoretical Considerations

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In most implementations of radioimmunotherapy, the red marrow is the dose-limiting organ. Estimates of the radioactivity concentration in this organ are usually based on blood sampling or bone marrow biopsy. This work presents a simple equation which may be used to calculate the red marrow-to-blood activity concentration ratio given the hematocrit and the red marrow extracellular fluid fraction of a patient. Also presented are a series of equations which may be used to correct the activity concentration in bone marrow biopsies for bone, yellow marrow and blood contamination. Assuming a hematocrit of 0.47 and a red marrow extracellular fluid fraction of 0.19, the predicted red marrow-to-blood activity concentration ratio is 0.36. This value is consistent with experimental studies. Depending upon the characteristics of the bone marrow biopsy sample, the red marrow activity concentration may be underestimated by a factor of 1.5–5. The correction factor for an "average" biopsy is 2.73. If the cortical bone cap is removed before the sample is weighed and counted, the correction factor is 1.92.

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Due to its intrinsic radiosensitivity (*1*) and the rapid equilibration of intravenously administered radiolabeled antibodies within its extracellular fluid volume (*2,3*), the red marrow is the dose-limiting organ in most implementations of radioimmunotherapy (*4*). Estimates of the absorbed dose in this organ require an assessment of the radioactivity concentration as a function of time. A variety of techniques have been suggested for making such a determination (*5*). The simplest of these relate the blood time-activity curve to the red marrow by a factor that accounts for the activity concentration ratio between red marrow and blood. In this approach, blood kinetics multiplied by some factor are assumed to represent red marrow kinetics. Based upon both human (*6*) and animal (*7,8*) experimental evidence, the appropriate factor appears to lie between 0.2–0.4 (*5*). These studies also show, however, a very wide variability with values well outside the 0.2–0.4 range.

This paper derives a simple mathematical relationship between the activity concentration in blood and that in the red marrow by assuming that intravenously administered antibody rapidly distributes within the plasma and the extracellular space of the red marrow and that the antibody does not bind to any blood, marrow or bone component. The errors associated with using bone marrow biopsies as the "gold standard" for determination of the activity concentration in the red marrow are also determined. A series of equations are derived that provide factors which may be used to correct for cortical and trabecular bone, fatty tissue (i.e., yellow marrow) and blood contamination of the biopsy sample. The equations that are presented may provide an explanation for some of the variability that has been observed in experimental studies.

METHODS

Red Marrow-to-Blood Concentration Ratio

Intravenously administered radiolabeled antibody is assumed to distribute uniformly within the plasma and the extracellular fluid space of the red marrow. The activity concentration in plasma is, therefore, equal to the concentration within the extracellular fluid space of the red marrow. Given the concentration in blood, the plasma activity concentration ($[A]_P$) is given by:

$$[A]_P = \frac{[A]_{BL}}{1 - HCT}, \qquad \text{Eq. 1}$$

where $[A]_{BL}$ is activity concentration in blood and HCT is hematocrit (volume fraction of red blood cells in blood). Since the concentration of antibody in plasma and the extracellular fluid space of marrow is assumed to be the same, then the total activity in marrow is simply the product of the marrow extracellular fluid volume with the plasma concentration. Dividing this by the total volume of the red marrow yields the activity concentration in the red marrow ($[A]_{RM}$):

$$[A]_{RM} = \frac{[A]_P \times V_{RMECF}}{V_{RM}}, \qquad \text{Eq. 2}$$

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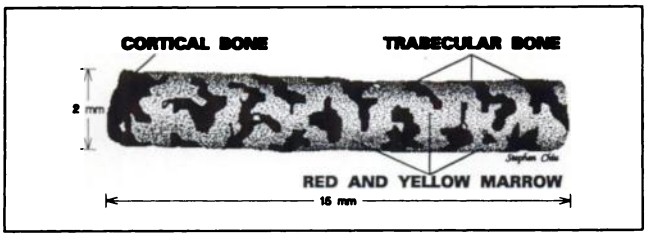

FIGURE 1. Schematic representation of a typical bone marrow core biopsy obtained using a Jamshidi needle.

where V_{RMECF} is red marrow extracellular fluid volume and V_{RM} is total red marrow volume. By replacing Equation 1 for $[A]_P$, expressing the red marrow extracellular fluid volume as a fraction of the total red marrow volume and canceling terms, we get the following expression for the red marrow-to-blood activity concentration ratio:

$$\frac{[A]_{RM}}{[A]_{BL}} = \frac{RMECFF}{1 - HCT} = RMBLR, \qquad \text{Eq. 3}$$

where RMECFF is red marrow extracellular fluid fraction and RMBLR is red marrow-to-blood (activity concentration) ratio.

Bone Marrow Biopsy

Correction for Cortical Bone. The top 1 or 2 mm of a needle biopsy contain cortical bone. If the biopsy sample is weighed and counted for radioactivity without removing the top layer of cortical bone (Fig. 1), the weight of the bone will lead to an underestimate of the activity concentration in the red marrow. In this case, the activity concentration of the biopsy may be expressed as follows:

$$[A]_{BIOPSY} = \frac{A_{RM}}{(1 - CBF) \times V_{BIOPSY} \times \rho_{RM} + CBF \times V_{BIOPSY} \times \rho_{CB}}, \qquad \text{Eq. 4}$$

where $[A]_{BIOPSY}$ is activity concentration of the biopsy; A_{RM} is activity in the red marrow portion of the biopsy; CBF is cortical bone fraction (by volume) of the biopsy; V_{BIOPSY} is volume of the biopsy sample; ρ_{RM} is density of red marrow; and ρ_{CB} is density of cortical bone.

Since the marrow biopsy is generally cylindrical, CBF is simply the length of the cortical bone portion divided by the total length of the biopsy (Fig. 1). Recognizing that A_{RM} divided by the first term in the denominator is the true red marrow activity concentration and rearranging the equation's terms, the following may be derived for the cortical bone correction (CBC) factor:

$$\frac{[A]_{RM}}{[A]_{BIOPSY}} = \left[1 + \left(\frac{CBF}{1 - CBF}\right) \times \frac{\rho_{CB}}{\rho_{RM}}\right] = CBC. \qquad \text{Eq. 5}$$

Correction for Trabecular Bone. As shown in Figure 1, the red marrow is intertwined with trabecular bone in a honeycomb-like structure. Even after the cortical bone portion of the biopsy is removed, the remainder will contain a significant portion of trabecular bone which will lead to an underestimate of the activity concentration in the red marrow. Following the derivation outlined above for cortical bone, the following equation may be derived for the trabecular bone correction (TBC) factor:

$$\frac{[A]_{RM}}{[A]_{BIOPSY}} = \left[1 + \left(\frac{TBF}{1 - TBF}\right) \times \frac{\rho_{TB}}{\rho_{RM}}\right] = TBC, \qquad \text{Eq. 6}$$

where TBF is trabecular bone fraction (by volume) of a cortical bone-free biopsy sample and ρ_{TB} is density of trabecular bone. It is important to note that this equation applies to a biopsy sample that is free of cortical bone.

Correction for Fatty Tissue. Given a completely bone-free biopsy sample, a certain fraction of the volume will contain fatty tissue, i.e., yellow marrow. Assuming that the radiolabeled antibody is excluded from the volume occupied by this fatty tissue, the derivation outlined above for cortical bone applies. The following equation may be obtained for the fatty tissue correction (FTC) factor:

$$\frac{[A]_{RM}}{[A]_{BIOPSY}} = \left[1 + \left(\frac{FTF}{1 - FTF}\right) \times \frac{\rho_{FT}}{\rho_{RM}}\right] = FTC, \qquad \text{Eq. 7}$$

where FTF is fatty tissue fraction (by volume) of a bone-free biopsy sample and ρ_{FT} is density of fatty tissue.

Correction for Blood. Given a bone- and fat-free biopsy sample, the concentration of activity in the sample may be expressed in terms of red marrow and blood activity as follows:

$$[A]_{BIOPSY} = \frac{A_{RM} + A_{BL}}{(1 - BLF) \times V_{BIOPSY} \times \rho_{RM} + BLF \times V_{BIOPSY} \times \rho_{BL}}, \qquad \text{Eq. 8}$$

where A_{BL} is activity in the blood portion of the biopsy sample; BLF is blood fraction (by volume) of a bone- and fat-free biopsy sample; and ρ_{BL} is density of blood.

By rearranging terms and recognizing that A_{RM} divided by the first term in the denominator is the red marrow activity concentration, the following equation may be derived:

$$[A]_{RM} = [A]_{BIOPSY} \times \left[1 + \left(\frac{BLF}{1 - BLF}\right) \times \frac{\rho_{BL}}{\rho_{RM}}\right] - \frac{A_{BL}}{(1 - BLF) \times V_{BIOPSY} \times \rho_{RM}}. \qquad \text{Eq. 9}$$

Replacing A_{BL} using:

$$A_{BL} = [A]_{BL} \times V_{BL} \times \rho_{BL} \qquad \text{Eq. 10}$$

and recognizing that V_{BL}/V_{BIOPSY} = BLF, Equation 9 may be rewritten as:

$$[A]_{RM} = [A]_{BIOPSY} \times \left[1 + \left(\frac{BLF}{1 - BLF}\right) \times \frac{\rho_{BL}}{\rho_{RM}}\right] - [A]_{BL} \times \left[\frac{BLF}{1 - BLF} \times \frac{\rho_{BL}}{\rho_{RM}}\right]. \qquad \text{Eq. 11}$$

Since the blood concentration is easily obtained, Equation 11 may be used directly to correct for blood contamination of a biopsy sample. By solving Equation 3 for $[A]_{BL}$ and substituting into Equation 11, an equation that expresses the effect of blood contamination as a blood correction (BLC) factor may be obtained:

$$\frac{[A]_{RM}}{[A]_{BIOPSY}} = \left[\frac{1 + \frac{BLF}{1 - BLF} \times \frac{\rho_{BL}}{\rho_{RM}}}{1 + \frac{1 - HCT}{RMECFF} \times \frac{BLF}{1 - BLF} \times \frac{\rho_{BL}}{\rho_{RM}}}\right] = BLC. \quad \text{Eq. 12}$$

Conditions Under Which Equations Are Valid

All of the equations derived above apply only to radiolabeled antibody that does not cross-react with cellular components of the blood, marrow or bone. The absence of any such cross-reactivity must be conclusively demonstrated since, depending upon the degree of cross-reactivity, the equations herein derived may dramatically underestimate the marrow activity concentration and resulting absorbed dose. Catabolism of the antibody and/or dissociation of the radionuclide from the antibody also are not considered in the derivation of these equations; the distribution of antibody is assumed to reflect the distribution of radioactivity.

Parameter Values

Table 1 lists the baseline values for parameters that were varied over a range of values in the correction factor calculations. Table 2 lists the parameters that were kept fixed in all of the calculations. Mean values for TBF and FTF were obtained from a study of anterior iliac crest biopsies obtained from 158 healthy individuals (*9*). Schulz and Delling (*10*) report a value of approximately 20% in adults for the fraction of spongy bone space occupied by trabeculae. The higher value of 26% reported by Bartl et al. (*9*) was used as the baseline value for TBF since it yields a correction factor that leads to the more conservative estimate of bone marrow dose. The baseline estimate of CBF was obtained from a typical anterior iliac crest biopsy taken using a Jamshidi needle (*9*). In general, Jamshidi needle core biopsies of the anterior iliac crest yield samples that are 2 mm in diameter by 15 mm in length. The red marrow extracellular fluid fraction, RMECFF, was obtained from a study of the albumin space in the red marrow of rabbit femur (*11*).

Although relative to marrow aspirates, blood contamination of core biopsy samples is generally not considered significant. No published estimate of the blood fraction in a biopsy was found; a value of 10% by volume of a bone-free biopsy sample was used as the baseline value. The density of trabecular bone chosen for the calculations was determined from iliac and vertebral bone samples (*12*). Density measurements of the bone alone were performed without any of the intertwined red or yellow marrow. This is an important distinction because some reports of trabecular bone density are based on measurements that include marrow and fatty tissue (*13*). The densities of cortical and trabecular bone are considered fixed parameters; the effect of age-related changes is not specifically considered in the calculations. Most of the parameters values chosen were measured in the iliac crest; parameter values for other biopsy sites may be expected to differ (*14,15*).

TABLE 1
Baseline Values for Adjustable Parameters

Parameter	Description	Value	Reference
CBF	Cortical bone fraction	0.18	9
TBF	Trabecular bone fraction	0.26	9
FTF	Fatty tissue fraction	0.28	9
RMECFF	Red marrow extracellular fluid fraction	0.19	11
BLF	Blood fraction	0.10	
HCT	Hematocrit	0.47	18

TABLE 2
Fixed Parameter Values

Parameter	Value (g/cm³)	Reference
ρ_{CB}	1.99	19
ρ_{TB}	1.92	12
ρ_{FT}	0.98	19
ρ_{BL}	1.06	19
ρ_{RM}	1.03	19

RESULTS

Red Marrow-to-Blood Concentration Ratio

The red marrow-to-blood concentration ratio (RMBLR) is depicted as a function of the red marrow extracellular fluid fraction (RMECFF) and the hematocrit (HCT) in Figure 2. RMBLR ranges from 0.19 (RMECFF = 0.15; HCT = 0.2) to 0.63 (RMECFF = 0.25; HCT = 0.6). The baseline value of RMBLR is 0.36 (RMECFF = 0.19; HCT = 0.47).

Bone Marrow Biopsy Correction Factors

Figures 3 through 6 depict the cortical bone, trabecular bone, fatty tissue and blood correction factors, respectively, over a range of volume fractions for each contaminant. Each curve was generated by keeping all other parameters fixed at the baseline values.

The correction factor for cortical bone ranges from 1.1 to 1.9 for a cortical bone volume fraction of 0.06–0.32, respectively. The corresponding values for trabecular bone are 1.3–2.1 for a trabecular bone volume fraction of 0.12–0.38. The correction for fatty tissue ranges from 1.1 to 1.7 for a fatty tissue volume fraction of 0.08–0.44.

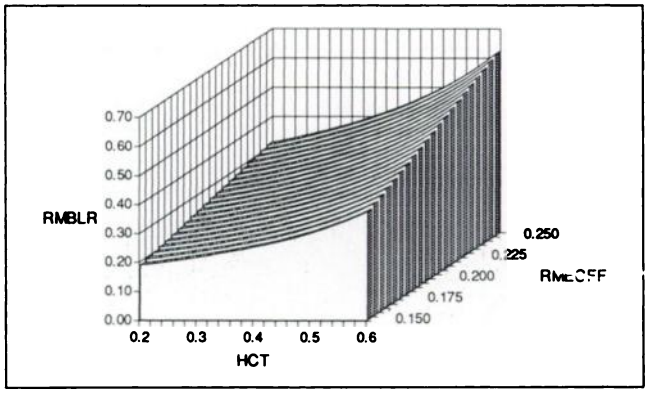

FIGURE 2. The red marrow-to-blood radioactivity concentration ratio (RMBLR) plotted as a function of hematocrit (HCT) and the red marrow extracellular fluid fraction (by volume) (RMECFF).

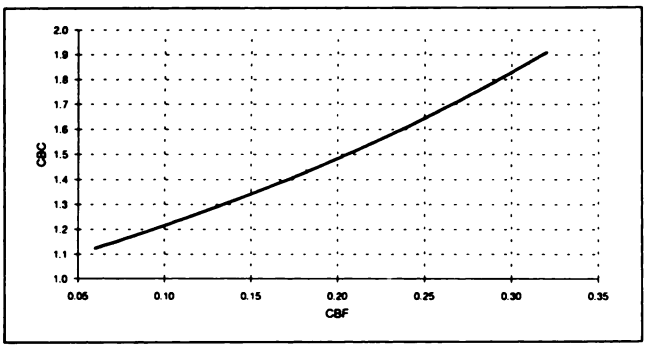

FIGURE 3. The cortical bone correction (CBC) factor as a function of the volume fraction of cortical bone in a bone marrow biopsy sample. The range of the x- and y-axes has been adjusted to best depict the curve over a range of physiologically achievable values.

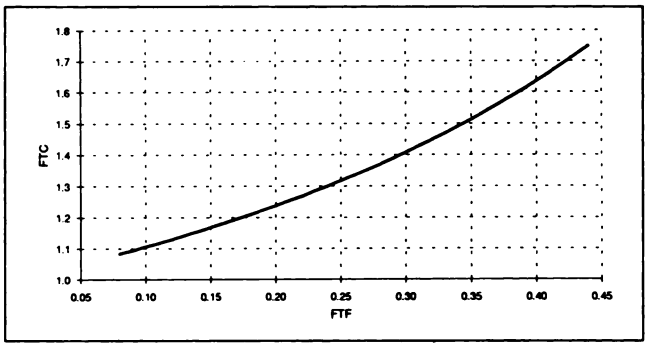

FIGURE 5. The fatty tissue correction (FTC) factor as a function of the volume fraction of fatty tissue in a bone-free biopsy sample. The range of the x- and y-axes has been adjusted as in Figure 3.

Since blood contamination leads to an overestimate of the red marrow activity concentration, the correction factor is less than one. The values range from 0.96–0.69 for a blood volume fraction of 0.02–0.24.

An average estimate of the sensitivity of each correction to changes in each contaminants' volume fraction may be obtained by using the minimum and maximum correction values listed above to calculate an average slope for each curve. Table 3 depicts the correction sensitivities along with the correction factors that arise when the baseline values of Table 1 are used.

DISCUSSION

A series of equations have been derived which relate the radioactivity concentration in blood (Equation 3) and in bone marrow biopsies (Equations 5–7 and 12) to that in the red marrow.

Using the single basic assumption that the radiolabeled antibody uniformly distributes within the plasma and the extracellular fluid volume of the red marrow, a relationship between blood and red marrow activity concentration has been derived which provides a theoretical confirmation of experimental measurements. The range of RMBLR values depicted in Figure 2 include the 0.2–0.4 recommendation of the American Association of Physicists in Medicine (AAPM) Task Group on Bone Marrow Dosimetry (*5*). By relating the red marrow-to-blood activity concentration ratio to hematocrit and to the extracellular fluid fraction of red marrow, Equation 3 also provides a means for adjusting the conversion ratio to account for differences in patient characteristics. The simplest implementation of Equation 3 in patients whose marrow has not been compromised by therapy or disease would be to use the baseline value of RMECFF (Table 1) and the actual patient hematocrit to obtain the appropriate RMBLR. A noninvasive approach to estimating bone marrow cellularity using nuclear magnetic resonance spectroscopy has been described (*16*). Such an approach might also provide a measure of RMECFF in patients with compromised bone marrow (RMECFF does not necessarily equal 1-cellularity since fatty tissue is also present in the red marrow).

It is important to note that the use of blood kinetics to characterize red marrow kinetics represents a reasonable and justifiable approximation to the true time course of

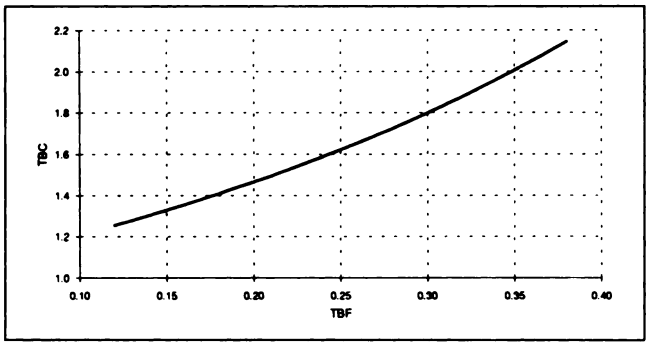

FIGURE 4. The trabecular bone correction (TBC) factor as a function of the volume fraction of trabecular bone in a cortical bone-free biopsy sample. The range of the x- and y-axes has been adjusted as in Figure 3.

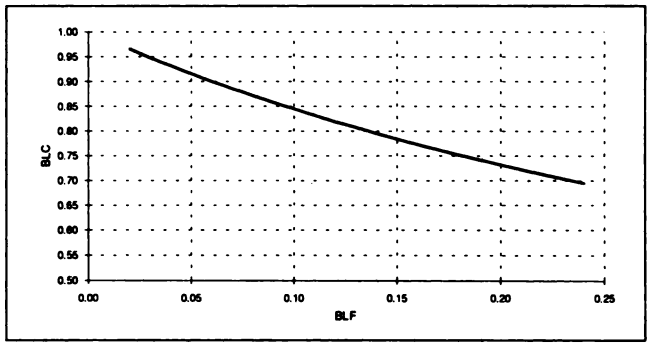

FIGURE 6. The blood correction (BLC) factor as a function of the blood volume fraction in a bone and fatty tissue-free biopsy sample. The range of the x- and y-axes has been adjusted as in Figure 3.

TABLE 3
Correction Factor Sensitivities and Baseline Values

Correction factor	Description	Sensitivity	Baseline value
CBC	Cortical bone correction	3.08	1.42
TBC	Trabecular bone correction	3.08	1.66
FTC	Fatty tissue correction	1.67	1.37
BLC	Blood correction	−1.23	0.85

red marrow activity. As experimental measurements have shown (*6*), the two are not strictly equivalent. Equation 3, therefore, may not apply to postinjection times of radiolabeled antibody.

Using a range of values that represent the extremes of bone, fatty tissue and blood contamination that one might expect in bone marrow biopsies of patients, the overall correction factor for converting the biopsy sample activity concentration to that in red marrow ranges from 1.47 to 4.97. If the cortical bone cap is removed, the overall correction factor ranges from 1.17 to 2.60. As shown in Table 3, the correction factor is most sensitive to changes in the bone fraction of the sample. The results indicate that by removing the cortical bone cap before weighing and counting the sample, a significant reduction in the correction factor is achieved.

By multiplying each of the correction factors listed in Table 3 together, a correction factor of 2.73 is obtained which converts the activity concentration in an average, untreated bone marrow biopsy core to the activity concentration in the red marrow. If the cortical bone cap is removed before the biopsy sample is weighed and counted for radioactivity, the correction factor becomes 1.92. It is noteworthy that the correction factor may be improved for a given bone and fatty tissue contamination if the blood contamination is increased.

Bone marrow biopsies have been used as the "gold standard" for assessing RMBLR (*6–8*) and relating quantitative imaging information to the activity concentration in red marrow (*17*). The large variability that has been observed in these data may be explained by differences in the sample preparation or in the bone, fatty tissue and blood characteristics of the sample. A first-order improvement in sample preparation would be to remove the cortical bone cap from the marrow biopsy. The baseline volume fractions for trabecular, fatty tissue and blood contamination that are listed in Table 1 then could be used to correct the activity concentration in the sample for these contaminants. Further refinements can be made by accounting for known changes in bone density or in the fatty tissue fraction that may be associated with age.

Although the equations and results presented in this work are directly relevant to radioimmunotherapy, their applicability is not restricted to radiolabeled antibodies. Equations 3, 5, 6, 7 and 12 are suitable for any labeled agent that does not localize to bone or marrow components and that rapidly equilibrates within the extracellular fluid volume of the red marrow.

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(continued from page 688)

SELF-STUDY TEST
Gastrointestinal Nuclear Medicine

QUESTIONS *(continued)*

True statements concerning this patient include which of the following?

8. There is excessive free ^{99m}Tc pertechnetate as a result of poor red blood cell labeling efficiency.
9. A small bowel enteroclysis study would not be helpful in this patient.
10. A bleeding site would have been better localized by scintigraphy with ^{99m}Tc sulfur colloid.
11. An intravenous injection of glucagon prior to imaging would have reduced free ^{99m}Tc pertechnetate activity in the small bowel.

True statements concerning red blood cell labeling techniques with ^{99m}Tc include which of the following?

12. When the modified in vivo ("in vivtro") method is used, heparin rather than acid citrate dextrose (ACD) is preferred as the anticoagulant.
13. Stanous pyrophosphate and ^{99m}Tc should be injected through the same indwelling catheter when either the in vivo or the modified in vivo technique is used.
14 The bladder is the organ receiving the highest radiation exposure when the in vivo method of red blood cell labeling is used.
15. Technetium-99m binds predominantly to the red blood cell membrane.

SELF-STUDY TEST
Gastrointestinal Nuclear Medicine

ANSWERS

Items 1-4: Scintigraphy for Meckel's Diverticula

Answers: 1, F; 2, T; 3, F; 4, F

The histamine-2 receptor antagonist, cimetidine, enhances imaging of Meckel's diverticulum by causing continued accumulation of ^{99m}Tc pertechnetate in ectopic gastric mucosa and by reducing secretion of ^{99m}Tc activity into the bowel. By decreasing the amount of pertechnetate entering the small bowel, cimetidine helps to reduce the frequency of false-positive studies.

Up to 73% of menstruating women have been shown to demonstrate a uterine "blush" following ^{99m}Tc pertechnetate administration during the menstrual or secretory phase of their menstrual cycle. This may lead to a false-positive interpretation. In general, premenarchal, postmenopausal, and menstruating patients in the proliferative phase do not show this uterine "blush."

Small bowel duplications occasionally contain ectopic gastric mucosa and may simulate Meckel's diverticulum on scintigraphy with ^{99m}Tc pertechnetate. Because the position within the abdomen of a small bowel duplication can mimic that of Meckel's diverticulum and because both anomalies contain ectopic gastric mucosa, it usually is not possible to distinguish Meckel's diverticulum from a small-bowel duplication by ^{99m}Tc pertechnetate imaging.

Autoradiographic studies have shown that, after intravenous administration, ^{99m}Tc pertechnetate is selectively concentrated by the mucous-producing cells of gastric mucosa, rather than by parietal cells or chief cells. Experimental animal studies have demonstrated that at least 2 cm of functioning ectopic gastric mucosa is necessary for visualization.

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Items 5-7: Meckel's Diverticula in Adults

Answers: 5, F; 6, F; 7 F

Although Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract, with a prevalence of approximately 1%, most are not symptomatic. Additionally, those that cause symptoms usually do so in the first 2 years of life. Ectopic gastric mucosa is more frequently encountered in symptomatic Meckel's diverticula, but may also be present in asymptomatic Meckel's diverticula. Lower gastrointestinal bleeding is the most frequent presentation of symptomatic Meckel's diverticulum in the pediatric population. In adults, the most common presentation is acute inflammation (Meckel's diverticulitis). Obstruction is seen less often and gastrointestinal bleeding occurs rarely. Several studies have clearly shown that the sensitivity of ^{99m}Tc pertechnetate scintigraphy for Meckel's diverticulum is greater than 80% in the pediatric population. In adults, however, the sensitivity of Meckel's scintigraphy is approximately 60%. The precise reasons for this are unclear.

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