Pertechnetate Distribution in Man after Intravenous Infusion: A Compartmental Model

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Using a primed infusion technique, distribution of pertechnetate was monitored in normal volunteer subjects over an 8-hr period. Two groups of subjects were studied, during hours 0–4 (n = 8) and hours 4–8 (n = 7), respectively, of the infusion. At 6.5 hr a large dose of NaI (1000 mg) was administered intravenously to the second group. Plasma, salivary, and urinary radioactivities were assayed, and external counts were made of radioactivities over the neck, thigh, and right upper abdomen. A kinetic model was developed for pertechnetate based upon the distribution data, the iodide perturbation, and known physiology for pertechnetate and iodide. The model has three major subsystems: (1) the thyroid trap; (2) a whole-body distribution, containing plasma and two extravascular compartments; and (3) the gastrointestinal tract, including the salivary, stomach (including upper small intestine), and two lower intestinal compartments. One of the latter, which turns over very slowly, is believed to represent bowel wall. The large NaI dose markedly reduced transport into the compartments of the thyroid trap, the saliva, and the stomach and small intestine. This study shows that, in most respects, pertechnetate is distributed qualitatively but not quantitatively like iodide but that, unlike iodide, large bowel distribution plays an important role, especially in long-term studies.

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Despite the very widespread use of [^{99m}Tc] pertechnetate in clinical nuclear medicine practice, little research has been directed toward its distribution kinetics. Studies by Andros et al. (*1*) showed that the pertechnetate ion is transported in many ways like the iodide ion, including concentration by the thyroid gland. These and other workers also show that all tissues that concentrate iodide also concentrate pertechnetate, though quantitatively to a lesser extent (see review in Ref. *2*). The total volume of distribution of pertechnetate several hours after a single injection was shown by Andros et al. to be considerably greater than the volume of distribution of iodide for the same time interval. Beasley et al. (*3*) studied pertechnetate distribution over much longer time periods, using ^{96}TcO$_4^-$ and ^{95m}TcO$_4^-$, which have half-lives of 4.3 and 60 days, respectively. In their studies, total body profile scanning indicated considerable concentration of the tracer in the gastrointestinal tract.

The present studies used a primed infusion technique to investigate the modalities of ^{99m}TcO$_4^-$ distribution during the first few hours. These studies, supplemented by data from the literature and known physiology, were used for the formulation of a detailed kinetic model. The model was developed and rigorously tested mathematically for uniqueness and consistency using the SAAM26 computer program for the simulation and modeling of kinetic processes (*4–7*).

METHODS

Subjects were paid volunteers: normal college students, at least 21 years old. Before the start of

study, the procedure was explained and informed written consent obtained. A brief history was taken and physical examination performed to establish that the subject was in good general health and was free of apparent thyroid disease. Studies were done in the setting of an active clinical nuclear medicine service.

Population 1. Nine subjects were studied over a 4-hr interval, during which a solution containing $^{99m}TcO_4^-$ was infused constantly. In a preliminary pilot study, one subject received 1 μCi of $^{99m}TcO_4^-$ per minute, without a priming dose. The concentration of radioactivity in his plasma and saliva, and the counting rates over his neck, thigh, and right upper quadrant of the abdomen (RUQ) all increased progressively throughout the experiment, with no evidence of approaching a steady state. Therefore, a "priming" dose was used in the other eight studies to achieve a more constant plasma $^{99m}TcO_4^-$ concentration. These eight subjects constitute "Population 1" of this report. They received 100 μCi of $^{99m}TcO_4^-$ as a priming dose, followed by an infusion of 1 μCi/min. Subjects remained supine on an examination table with their necks extended throughout the experimental period. Radioactivity was monitored by three movable, vertically oriented scintillation detectors, each with a crystal-to-skin distance of 20 cm and a collimator-to-skin distance of 13 cm, kept constant by a plastic spacer. One detector (3-in.-diam $\times$ 1.5-in.-deep crystal) was placed over the thyroid area (neck detector), another (3-in.-diam $\times$ 1.5-in.-deep crystal) was centered over the left thigh at a point 10 cm proximal to the patella (thigh detector), and the third (with a 2-in.-diam $\times$ 1.5-in.-deep crystal) was centered just below the rib margin at the right midclavicular line (RUQ detector). Measurements by these three detectors were made at 5-in intervals throughout the 4-hr experimental period. An indwelling needle was maintained in the arm opposite to that used for the infusion. Through this needle, heparinized blood samples were obtained at 5-min intervals throughout the experimental period. A tube was kept in the patient's mouth throughout the period, and he was instructed to expectorate all saliva through this tube. Saliva was collected in a graduated cylinder, which was changed at 20-min intervals. Urine was collected at the conclusion of the 4-hr experimental period.

The counts collected by each detector were compared with a 10-μCi $^{99m}TcO_4^-$ standard contained in a plexiglass phantom fashioned to mimic the size and configuration of a normal thyroid. Counts by each of the detectors were then converted to microcuries of technetium-99m, corrected to the beginning of the infusion. Plasma, saliva, and urine counts

were compared with an appropriate dilution of the administered radiopharmaceutical and expressed as μCi/ml. In the case of saliva and urine samples, this result (average of duplicate samples) was multiplied by the total volume collected.

Population 2. The preliminary analysis of the data from Population 1 indicated that the $^{99m}TcO_4^-$ apparent plasma-equivalent volume of distribution was still expanding at 4 hr. For this reason, ten additional subjects were studied during Hours 4–8 of an infusion. These subjects received a "loading" dose of 100 μCi $^{99m}TcO_4^-$, followed by an intravenous infusion of 0.5 μCi/min. No measurements were made on these subjects during the first 4 hr of infusion. During this period they sat quietly and were permitted to eat and drink. After 4 hr, urine was collected, and the subjects then reclined on the examination table as described for Population 1. During the next 4 hours (Hours 4–8 of $^{99m}TcO_4^-$ infusion), measurements similar to those for population 1 were made. In addition, at Hour 6 of the infusion (two subjects) or Hour 6.5 (eight subjects) 1 g of sodium iodide was injected intravenously. This dose was split into a 200-mg test dose followed by 800-mg after a 5-min observation period. In one subject it was not possible to obtain blood samples, and his data are omitted from this report. In averaging data for the development of the mathematical model, the two subjects who received sodium iodide at 6 hr are omitted. The data from the three omitted subjects were similar to those from the other seven subjects.

EXPERIMENTAL RESULTS

Mean values for the eight subjects in Population 1 (first 4 hr) and the seven subjects in Population 2 (Hour 4–8) are presented in Fig. 1. All data are presented as μCi Tc-99m, corrected for radioactive decay. Differences in activity levels for the two populations reflect the differences in infusion rate, efficiency of collection of saliva, and urinary clearance rate, and also the fact that Population 2 subjects swallowed their saliva during the first 4 hr of the study. These factors were taken into account in fitting the model to the data.

Mean urinary Tc-99m excretions, not shown in Fig. 1, were 38.3 μCi and 33.3 μCi during hours 0–4 for Populations 1 and 2, respectively, and 37.0 μCi during Hours 4 to 8 for Population 2.

In the preliminary analyses of the data, a "plasma-equivalent volume" for each body region (neck, thigh, and RUQ) was calculated for each subject at each time point; this volume is the ratio of the local Tc-99m level to the concurrent level in the plasma. Salivary and urinary clearances were calculated using
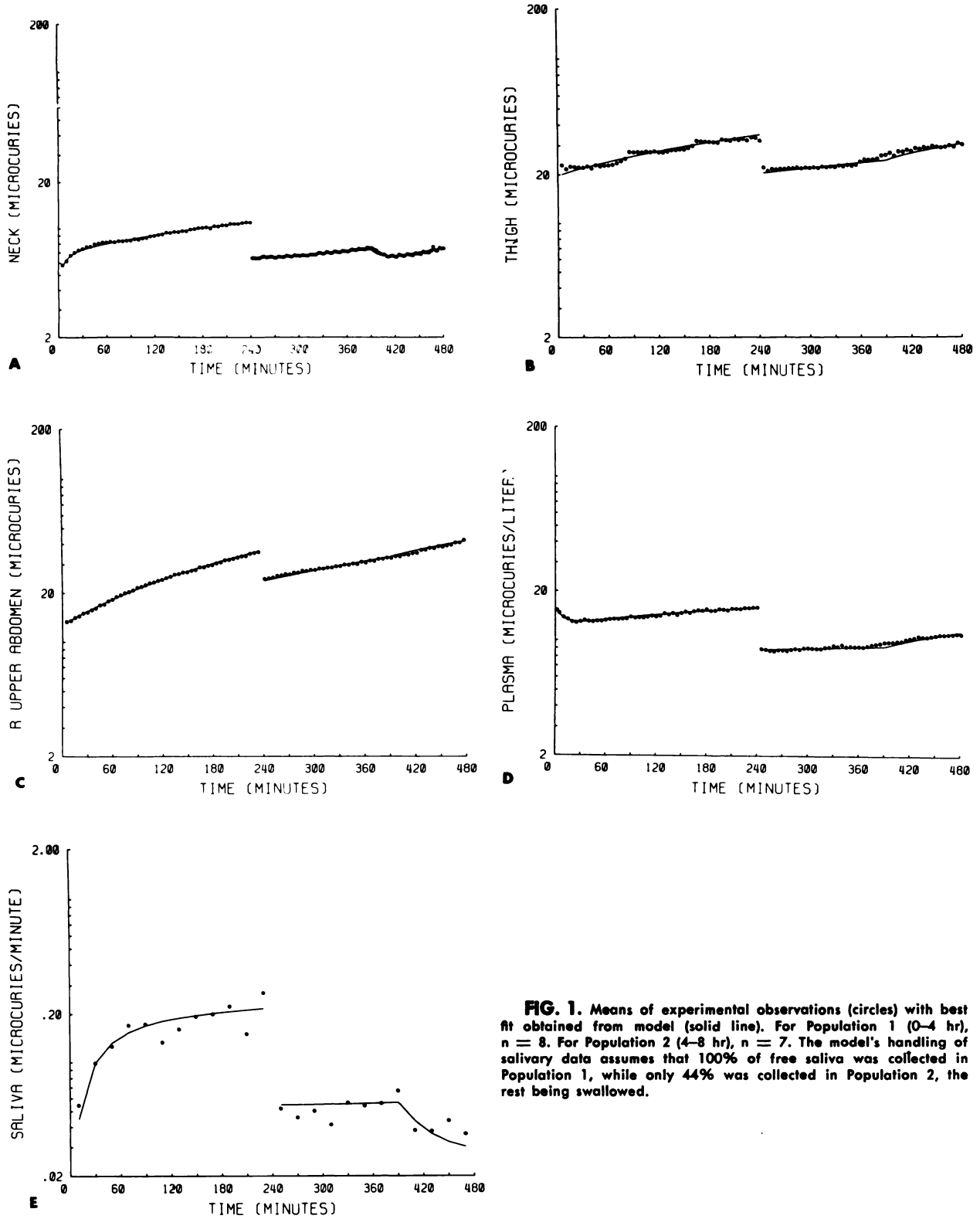
FIG. 1. Means of experimental observations (circles) with best fit obtained from model (solid line). For Population 1 (0–4 hr), n = 8. For Population 2 (4–8 hr), n = 7. The model's handling of salivary data assumes that 100% of free saliva was collected in Population 1, while only 44% was collected in Population 2, the rest being swallowed.

the geometric mean of the plasma Tc-99m levels during the collection period. Temporal patterns for these activity ratios varied little from subject to subject. However, the kinetics were too complex to justify this direct analysis. To deal properly with all the data it was necessary to formalize the kinetics in terms of the model presented below.

Before fitting the kinetic model, the data from

the individual subjects were pooled. Coefficients of variation (s.d./mean) were calculated for every time point. Consistent with observed similarity in temporal trends among subjects, these coefficients of variation were relatively constant throughout the experiment. Mean coefficient of variation for the plasma time points (n = 98) was 27%; for neck (n = 144), 31%; for thigh (n = 96), 37%; for RUQ (n = 96), 27%; for saliva (n = 24), 33%; and for urine (n = 3), 33%.
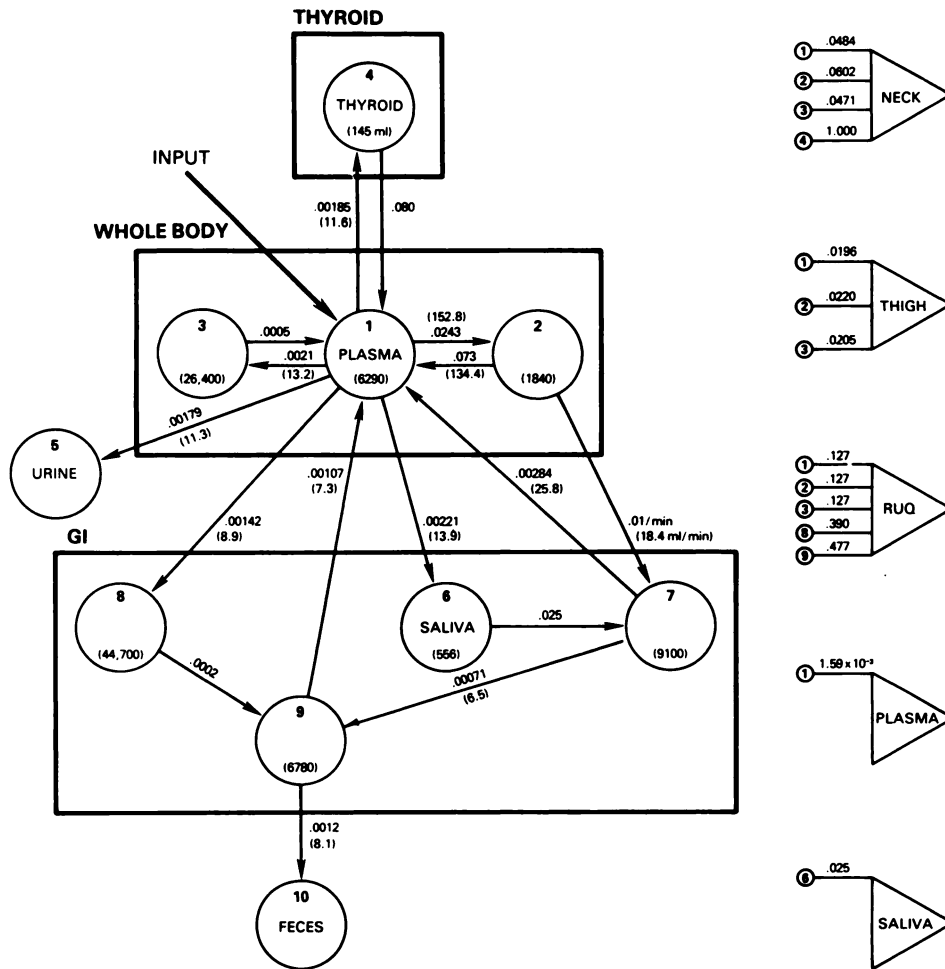
KINETIC MODEL

In developing the kinetic model for pertechnetate distribution we have tried to keep it simple. In checking it against our experimental data and data from the literature, however, additional features had to

be introduced. Long-term data from Beasley et al. (3) were used in testing the slowest components of the model. The derived model is shown in Fig. 2. Certain of its features were introduced as assumptions and others were made necessary by the data. Because a wide diversity of data were fitted simultaneously by the model, no attempt is made here to reconstruct in detail the entire rationale leading to its final form.

The following assumptions were introduced in formulating the model.

1. The administration of a large dose of iodide completely blocks the uptake of pertechnetate by the thyroid.
2. A massive dose of iodide affects pertechnetate transport at a minimal number of sites believed to involve active transport.

FIG. 2. Model of pertechnetate kinetics in man. The rate-constant values next to the arrows are per min and values in parentheses next to them are steady-state plasma equivalent clearances in units of ml/min. Values in parentheses inside circles are plasma equivalent volumes of distribution. All steady-state calculations are based on a constant input into plasma. Triangles indicate measured or sampled quantities. Values next to lines connecting triangles to numbered circles indicate fraction of a particular compartment 'seen' or sampled by data. While precise identification of compartments cannot be made with certainty in all cases, the following labels refer to probable anatomic equivalents of the compartments: 1. Plasma containing compartment. 2. Rapidly equilibrating whole-body compartment. 3. Slowly equilibrating whole-body compartment. 4. Thyroid. 5. Urine. 6. Salivary glands. 7. Stomach and upper small intestine. 8. Large bowel (probably bowel wall). 9. Large bowel (probably contents). 10. Feces.

3. The effects of the massive dose of iodide on the rate constants of the model are instantaneous.

4. Compartment 6, the salivary glands, accounts only for the TcO_4- that appears in the saliva. The salivary gland TcO_4^- that exchanges with plasma is lumped with compartment 2.

5. The thyroid and thigh probes do not "see" any of the gastrointestinal compartments.

6. The two populations of subjects used in the infusion studies differ only in their urinary and gastric clearance rates. Differences in infusion technique and efficiency of saliva collection are embedded in the model. Analysis of the data from individual subjects has confirmed that the two populations are similar.

The first three assumptions are based upon other experience in this laboratory indicating that this dose of iodide blocks thyroidal $^{99m}TcO_4{}^-$ uptake by competitive inhibition, and that this blockade is prompt and complete. While iodide equilibration with tissues is far from instantaneous, the dose used is so great that sufficient iodide to effect competitive inhibition reaches the active transport sites very quickly.

Certain structure was forced on the model as a result of qualitative features in the data or known physiology:

1. There are diffusely distributed fast and slow compartments for TcO_4^- throughout the whole body.

2. A compartment that turns over very slowly —probably in the wall of the large bowel— is required, for example, by the long-range technetium retentions observed by Beasley et el. (3).

3. The neck probe sees all of the thyroid contents (Compartment 4), and nearly the same fractions each of Compartments 1, 2, and 3—namely, the plasma-containing compartment and the fast and slow whole-body compartments. The slightly greater fraction of Compartment 2 observed in the data fit is probably due to a portion of the exchangeable salivary component seen by this probe.

4. The thigh probe sees nearly the same fraction each of Compartments 1, 2, and 3.

5. The RUQ probe sees the same fraction each of Compartments 1, 2, and 3, and a major fraction of Compartments 8 and 9.

The least-squares fitting of all the data simultaneously served as the major constraint in deriving estimates of parameter values.

Description of the model. The model (Fig. 2) contains three basic blocks: (A) diffusely distributed whole-body spaces, (B) the gastrointestinal subsystem, and (C) the thyroid.

The diffusely distributed whole-body spaces are described by three compartments. The initial distribution compartment for pertechnetate (Compartment 1) is larger in volume than plasma and is referred to as the *plasma-containing compartment*. This compartment was sampled directly as plasma. Two additional compartments, exchanging with Compartment 1, were also necessary to fit the data. Compartment 2 exchanges rapidly (turnover about 12 min), while Compartment 3 exchanges very slowly (turnover about 1.4 days). For the different anatomic regions sampled (neck, thigh, and RUQ), nearly the same fraction from each of these compartments was required to satisfy the measured quantities, and the value of the fraction depended on the size of the region. The parallel arrangement of the compartments is arbitrary since we cannot differentiate among various three-compartment configurations. The path of urinary excretion is from Compartment 1.

The gastrointestinal subsystem was modeled after the iodide system (8). It was modified, as necessary, to conform to direct measurements of salivary secretion and to known differences between iodide and pertechnetate regarding clearance by salivary glands and gastric juice (9–11), and to intestinal absorption (10). Published data about fecal pertechnetate excretion (3) were also incorporated. The gastrointestinal subsystem consists of four compartments. Compartment 6 simulates the salivary glands and Compartment 7 is considered to be stomach and part of the small intestine, with their contents. Compartment 6 secretes into Compartment 7, and is also the excretion route when saliva is sampled. Ideally, there should also be a direct path from Compartment 6 back to Compartment 1 or Compartment 2, but this could not be resolved from our data. Compartment 7 passes Tc-99m on to Compartment 9, considered to be the lower small bowel and the large bowel, and also to plasma (Compartment 1). From Compartment 9 some of the Tc-99m is recycled to plasma, and the balance is lost to the feces. Compartment 8 is a compartment that turns over very slowly, possibly the bowel wall. It is supplied by Compartment 1 (*not* Compartment 7) and secretes its contents into Compartment 9. Compartments 8 and 3 are responsible for the very long retention of technetium, shown in the data by Beasley et al. (3).

The thyroid is represented by Compartment 4, exchanging directly with Compartment 1.

Results of kinetic analysis. The final parameter

TABLE 1. PARAMETER VALUES FOR THE MODEL

Rate Constant	Population 1 (min⁻¹)	Population 2* Before I⁻ (min⁻¹)	Population 2* After I⁻ (min⁻¹)
$L_{2,1}$	0.0243		
$L_{3,1}$	0.0021		
$L_{4,1}$	0.00185		0.000
$L_{5,1}$	0.00179	0.00242	0.00295
$L_{6,1}$	0.00221		0.00088
$L_{8,1}$	0.00142		
$L_{1,2}$	0.073		
$L_{7,2}$	0.010	0.012	0.000
$L_{1,3}$	0.0005		
$L_{1,4}$	0.080		
$L_{7,6}$	0.025		
$L_{1,7}$	0.00284		
$L_{6,7}$	0.00071		
$L_{9,8}$	0.0002		
$L_{1,9}$	0.00107		
$L_{10,9}$	0.0012		

$\tau = 4940$ min $= 3.43$ days†

* Rate constants shown for Population 2 (before or after iodine administration) are given only when they differ from those for Population 1.

† τ is the mean residence time in the body, as predicted by the model, for pertechnetate particles introduced into the plasma.

values for the model are presented in Table 1. The curves generated using these values are presented as solid lines in Fig. 1.

DISCUSSION

This study of pertechnetate distribution during intravenous infusion was originally designed to provide a "steady" state in which fluxes and clearances could be measured directly. It soon became apparent that the slow equilibration of pertechnetate was critical for such calculations and that to understand more fully the distribution data, a more extensive analysis would be needed. The mathematical model presented here was designed to meet this requirement. The model was further expanded by inclusion of previously published data (3).

Initially, we were puzzled by the steadily rising radioactivity seen by the right upper quadrant detector, which was intended to monitor liver radioactivity. In the present model the steadily rising radioactivity is accounted for mostly by a slow-turnover compartment considered to be associated with the large bowel. A series of rectilinear scans performed over the same field of view as that of the RUQ detector—performed 4–6 hr after a single intravenous dose of pertechnetate in patients undergoing diagnostic studies—confirmed that most radioactivity was in the large bowel.

This report does not provide direct evidence about the anatomic nature of the gastrointestinal Compartments 7, 8, and 9. Compartment 7 probably incorporates the stomach and upper small intestine. Compartments 8 and 9 are probably large intestinal wall and contents. The fact that Compartment 8 turns over and is fed directly from the circulating pools suggests that it represents, in large part, the cells of the bowel wall, which are slowly sloughed into the lumen (Compartment 9). The model requires plasma reabsorption of pertechnetate from the large bowel ($L_{1,9}$) as well as the small bowel ($L_{1,7}$). No direct evidence for absorption of pertechnetate from the large bowel has come too ur attention, but this is known to occur with iodide (12).

Compartment 1 (plasma) reflects not only free pertechnetate in plasma but also pertechnetate in the red cells and much of that in the interstitial space. In pilot studies we found that after the addition of pertechnetate (in vivo or in vitro) to whole blood, the erythrocyte-to-plasma concentration ratio was approximately 0.4. Assuming a hematocrit of 45%, we would expect the erythrocytes to increase the apparent plasma pertechnetate volume by [0.4 × 0.45/0.55] = 0.33, or 33%. Because pertechnetate binds to albumin (about 80% in plasma) (13) and because of the low concentration of albumin in the interstitial space, the contribution to Compartment 1 of the interstitial space is diminished. Correcting for this effect, one would predict Compartment 1 to contain approximately 9 l, compared with the 6.25 l actually observed. This suggests that parts of Compartment 2 (1.5 l), and perhaps also of Compartment 3, are contained in the interstitial space.

The anatomical identification of Compartment 3 is uncertain. It represents widely distributed tissue with a very large capacity for the injected label, and has a slow turnover. The latter suggests either binding or chemical alteration of the pertechnetate molecule such as might occur in the matrix of bone. Further studies are needed to identify this important compartment.

Both the neck detector and the thigh detector measured, in equal proportions, the three "uniformly distributed" whole-body compartments. The fact that the fraction of each compartment seen by the neck detector was greater than the fraction seen by the thigh detector is compatible with the clinical observation that thigh counts undercorrect for neck background in thyroid counting.

Compartment 4, the thyroid trap, can be distinguished by the model from Compartment 2, the rapidly exchanging tissue compartment, only if one accepts the hypothesis that after an iodide load $L_{4,1}$ becomes zero and the pertechnetate in the trap is discharged. Since the "neck" measurement could

include in its field of view other iodide-concentrating pools of Tc-99m (e.g., salivary) which may be blocked by iodide, the calculated "trap" would also include these. More specific analysis of this portion of the model by means of quantitative imaging techniques is currently under way. Parenthetically, the values for thyroidal pertechnetate clearance derived in the current model are compatible with the published results of others (14).

Renal Tc-99m clearance is about one-third of the published I^- clearances, presumably due to the binding of $^{99m}TcO_4^-$ to albumin. This is compatible with values obtained by Dayton et al. (15). Renal clearance differed somewhat between Population 1 (11.3 ml/min) and Population 2 (15.2 ml/min). Renal clearance was further increased (22%) after iodide administration, probably because of partial saturation of tubular reabsorption of Tc-99m.

There are other quantitative differences between I^- and Tc-99m kinetics. Salivary and gastric clearances of pertechnetate are about 50% of those for I^- (9,10), again probably because of pertechnetate's binding to albumin. Thyroid trapping of TcO^- is probably more nearly equal to that of I^- because thyroidal active transport sites may compete successfully with albumin for free pertechnetate.

One important difference between the kinetics of TcO_4^- and I^- occurs in the large bowel. Both ions may well exchange between plasma and the small and large bowels (2,16) but only TcO_4^- is excreted in the feces or bound to the bowel wall. Pertechnetate, unlike iodide, is incompletely absorbed in the small intestine, apparently due to binding by bowel contents. Hence, the role of the bowel in TcO_4^- kinetics becomes increasingly important with time, whereas I^- tends to stabilize after a few hours (8).

The model suggests that the administration of a single massive dose of iodide reduced salivary clearance by 60% and obliterated gastric clearance of pertechnetate. Other observations in our laboratory have demonstrated that such a dose of iodide completely inhibits the thyroid trap. These changes are compatible with an abrupt competitive inhibition of the active transport known to occur in these tissues.

It should be pointed out that this study was performed on subjects who were supine throughout the period of observation. Analyses currently under way

suggest that a number of the rate constants are faster in ambulatory subjects. Factors such as blood flow and gastric emptying time are undoubtedly important.

REFERENCES

1. ANDROS G, HARPER PV, LATHROP KA, et al: Pertechnetate-99m localization in man with applications to thyroid scanning and the study of thyroid physiology. J Clin Endocrinal 25: 1067–1076, 1965

2. LATHROP KA, HARPER PV: Biologic behavior of ^{99m}Tc from ^{99m}Tc-pertechnetate ion. Prog Nucl Med 1: 145–162, 1972

3. BEASLEY TM, PALMER HE, NELP WB: Distribution and excretion of technetium in humans. Health Phys 12: 1425–1435, 1966

4. BERMAN M, SHAHN E, WEISS MF: The routine fitting of kinetic data to models: A mathematical formalism for digital computers. Biophys J 2: 275–287, 1962

5. BERMAN M: A postulate to aid in model building. J Theor Biol 4: 229–236, 1963

6. BERMAN M, WEISS MF: SAAM Manual. Washington, DC, US Public Health Service Publ No 1703, 1967, p 200

7. BERMAN M, WEISS MF: SAAM Manual. Bethesda, Md, NIH, 1976, p 240

8. HAYS MT, WEGNER LH: A mathematical and physiological model for early distribution of radioiodide in man. J Appl Physiol 20: 1319–1328, 1965

9. HARDEN RM, ALEXANDER WD: The relation between the clearance of iodide and pertechnetate in human parotid saliva and salivary flow rate. Clin Sci Mol Med 33: 425–431, 1967

10. HAYS M: ^{99m}Tc-pertechnetate transport in man: absorption after subcutaneous and oral administration; secretion into saliva and gastric juice. J Nucl Med 14: 331–335, 1973

11. BICKEL JG, WITTEN TA, KILLIAN MK: Use of pertechnetate clearance in the study of gastric physiology. Gastroenterology 63: 60–66, 1972

12. REVIS VA, MURAVEI IP: Absorption of radioiodine by various portions of the gastrointestinal tract. Klin Med (Mosk) 37: 51, 1959

13. HAYS MT, GREEN FA: In vitro studies of ^{99m}Tc-pertechnetate binding by human serum and tissues. J Nucl Med 14: 149–158, 1973

14. SHIMMINS JG, HARDEN RM, ALEXANDER WD: Loss of pertechnetate from the human thyroid. J Nucl Med 10: 637–640, 1969

15. DAYTON DA, MAHER FT, ELVEBACK LR: Renal clearance of technetium (^{99m}Tc) as pertechnetate. Mayo Clin Proc 44: 549–551, 1969

16. PASTIN I: Absorption and secretion of iodide by the intestine of the rat. Endocrinology 61: 93–97, 1957