

# Methods for Measuring GFR with Technetium-99m-DTPA: An Analysis of Several Common Methods

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Several commonly used scintigraphic methods of GFR measurement were evaluated. Forty-three adult patients with a wide range of ages and renal function were studied. The two-sample plasma method of Russell and the urinary method of Jackson were the most accurate methods overall. The one-sample plasma method of Russell, the volume of distribution method of Fawdry, and a terminal slope method were less reliable, especially at low (0–60 ml/min) GFRs. The renal uptake method of Gates correlated poorly to the standards at all GFR levels even when corrected for body surface area or blood volume. The Russell two point and Jackson urinary GFR's can be used as complementary techniques and are recommended as primary methods of scintigraphic GFR determination.

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Multiple nuclear medicine techniques for measuring renal glomerular filtration (GFR) using technetium-99m-DTPA (diethylenetriaminepentaacetic acid) are in use today. Renal DTPA clearance ( $\cong$ GFR) can be determined from the measurement of activity in single or multiple blood samples (1–15), from the rate of removal of activity from blood or tissue (16,17), from the rate of appearance of tracer in urine (18), and from the rate of renal tracer uptake (19). Several recent studies (3,5,20,21) have evaluated how some of these techniques may be best performed. This paper compares the results obtained in adults from several of the most popular clinical methods (18,19,22,23) with two different reference GFR methods.

## MATERIALS AND METHODS

Forty-three adult renal patients (31 male, 12 female; 18–86 yr; 43–107 kg body weight; 1.39–2.29 m<sup>2</sup> body surface area)

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undergoing routine renal scintigraphy were studied. Seven patients with subcutaneously infiltrated doses, two patients with improperly collected urine samples, and one patient with a computer malfunction during data acquisition were not included in the study group. Patients with upper tract obstruction were also excluded from the study. Patients with edema or ascites were excluded.

Following hydration with 300 ml water, an accurately measured dose (19,24) of 20 mCi (740 MBq) of a commercially available <sup>99m</sup>Tc-DTPA preparation (Techneplex, Squibb Diagnostics (Cintichem)) was administered into an antecubital vein. Images were obtained posteriorly in the supine position using a large field of view scintillation camera such that the kidneys and inferior border of the heart were included in the imaged field. In addition to routine analog images, all data were stored in a nuclear medicine mini-computer system. Dynamic computer data acquisition (128 × 128 byte, 15 sec/frame for 5 min, then 30 sec/frame for 25 min) was started at the moment of injection. At 10 min, 20 min, and 30 min after injection, blood samples were obtained from the arm contralateral to the injection site after which the dynamic acquisition was terminated. Immediately thereafter an anterior static image of the bladder was acquired (128 × 128 word, 60 sec). The patient then voided into a calibrated container and an anterior post-void bladder image was obtained (128 × 128 word, 60 sec). The voided urine volume ( $\pm$ 1 ml) was recorded and a 10-ml aliquot was saved. A second dynamic computer acquisition was acquired immediately following the post-void bladder image acquisition (128 × 128 byte, 30 sec/image for 30 min) anteriorly with the heart centered in the field of view. The injection site was imaged to exclude an infiltrated dose. Blood samples were obtained from the arm contralateral to the injection site at 60, 120, and 180 min following injection. Plasma samples were ultrafiltered at 1,500 g using a fixed-angle centrifuge (22) and filtered and unfiltered plasma values as well as urine and standard (18) activities were counted in duplicate.

## Clearance Methods

The following clearance methods were calculated:

*Six-Point Dual Exponential Plasma Method (Method A)—Filtered Data—Reference Method (25,26).* A dual-compartmental model was assumed to generate and extrapolate to infinity the plasma disappearance curve. The six plasma samples were used to generate the two exponential curves by curve

stripping, the latter three samples (60', 120', 180') to generate the slow compartmental curve, and after subtraction the first three samples (10', 20', 30') to generate the fast compartmental curve. Each curve was generated using least-squares regression analysis. Clearance was calculated using the Sapirstein equation (26):

$$\begin{aligned} \text{GFR} &\cong \frac{Q_0}{\int_0^{\infty} P dt} \\ &= \frac{Q_0}{\frac{C_{10}}{\lambda_1} + \frac{C_{20}}{\lambda_2}} \end{aligned}$$

where:

- $Q_0$  = the injected dose
- $\int_0^{\infty} P dt$  = dual-exponential integration of six-point plasma disappearance curve by curve stripping.
- $C_{10}$  = Value of the monoexponential compartment curves of the above dual-exponential disappearance curve at times 0.
- $C_{20}$  = Value of the monoexponential compartment curves of the above dual-exponential disappearance curve at times 0.
- $\lambda_1, \lambda_2$  = rate constants of the two monoexponential compartment curves.

*Six-point Dual-Exponential Urine Method (Method B)—Filtered Data—Reference Method (14,18,26).* This method used the finite portion, from dose injection to the time of the post-void bladder image (T), of the same plasma disappearance curve used in Method A. Total urinary activity (TUA) equals the TUA excreted plus an adjustment (increase) due to unexcreted bladder residual volume (18). The kidneys, renal collecting system, and ureters were not used in the residual volume calculation even though some of the excreted activity resides in these locations. This would result in a systematic undervaluation of TUA and therefore in GFR. Since patients with any evidence of upper tract obstruction were excluded from the study, this was not considered a significant error.

$$\begin{aligned} \text{GFR} &\cong \frac{\text{TUA}}{\int_0^T P dt} \\ &= \frac{\text{TUA}}{\frac{C_{10} - C_{1T}}{\lambda_1} + \frac{C_{20} - C_{2T}}{\lambda_2}} \end{aligned}$$

where:

- TUA = total urinary activity corrected for residual volume (18).
- $\int_0^T P dt$  = that portion of  $\int_0^{\infty} P dt$  curve from 0 to T.
- T = time of post-void bladder image (18).
- $C_{10}, C_{1T}$  = Value of the monoexponential component curves of the above dual-exponential disappearance curve at times 0 and T.
- $C_{20}, C_{2T}$  = Value of the monoexponential component curves of the above dual-exponential disappearance curve at times 0 and T.
- $\lambda_1, \lambda_2$  = rate constants of the two monoexponential compartment curves.

*Terminal Slope Plasma GFR—Filtered and Unfiltered (Method C).* The terminal slope method is an empiric method in which the shape of the initial plasma disappearance curve was determined directly by following the externally detected blood-pool activity (e.g., the curve generated from a region of

interest over the base of the heart) to a finite end point (e.g., the time of the 30-min blood sample) and then extrapolating the curve to infinity based on the slope of the curve at this end point or the slope of a subsequent collection of externally detected blood-pool data rescaled and spliced to the early data (e.g., as in our study a second computer acquisition of cardiac blood-pool images).

$$\begin{aligned} \text{GFR} &\cong \frac{Q_0}{\int_0^t P dt + \int_t^{\infty} P dt} \\ &= \frac{Q_0}{\int_0^t P dt \text{ (directly integrated)} + A/\lambda_A} \end{aligned}$$

where:

- $Q_0$  = the injected dose.
- $\int_0^t P dt$  = direct integration of initial externally detected plasma disappearance curve.
- t = the finite end point of the initial externally detected plasma disappearance curve (30 min in our study).
- $\int_t^{\infty} P dt = A/\lambda_A$  = the integration of the extrapolated (or spliced externally detected) plasma disappearance curve.
- A = plasma value at the start of the extrapolation (30-min plasma value).
- $\lambda_A$  = rate constant of the extrapolated (or spliced externally detected) plasma disappearance curve (i.e., the terminal slope).

*Russell One-Point (180') Plasma GFR—Filtered and Unfiltered (Method D).*

$$\text{GFR} \cong 82.42 \ln \left( \frac{Q_0}{P_{180}} \right) - 800.5,$$

where:

- $Q_0$  = the injected dose.
- $P_{\text{time}}$  (e.g.,  $P_{180}$ ) = activity of plasma samples drawn.

*Russell Two-Point (30' and 180') Plasma GFR—Filtered and Unfiltered (Method E).*

$$\text{GFR} = \left[ \frac{Q_0 \ln(P_{30}/P_{180})}{150 \times \exp \frac{30 \ln P_{180} - 180 \ln P_{30}}{150}} \right]^{0.979}$$

where:

- $Q_0$  = the injected dose.
- $P_{\text{time}}$  (e.g.,  $P_{180}$ ) = activity of plasma samples drawn.

*Russell Two-Point (60' and 180') Plasma GFR—Filtered and Unfiltered (Method F).*

$$\text{GFR} \cong \left[ \frac{Q_0 \ln(P_{60}/P_{180})}{120 \times \exp \frac{60 \ln P_{180} - 180 \ln P_{60}}{120}} \right]^{0.979}$$

where:

- $Q_0$  = the injected dose.
- $P_{\text{time}}$  (e.g.,  $P_{180}$ ) = activity of plasma samples drawn.

Russell (22) obtained two-point and two-point GFR estimates by fitting their data to the open linear two-compartment

model of Sapirstein. From their formulas, the above GFR methods were evaluated.

**Fawdry Effective Volume of Distribution Plasma GFR (23)—Filtered and Unfiltered (Method G).** This method is based on the relationship between the dose administered and the 180' plasma value ( $Q_0/P_{180}$  = "effective volume of distribution") and is thus similar to the Russell one-point (180') method.

$$\text{GFR} \cong 31.94 \times \left( \frac{Q_0}{P_{180} \times 1000} + 16.92 \right)^{0.5} - 161.7,$$

where:

$Q_0$  = the injected dose.

$P_{\text{time}}$  (e.g.,  $P_{180}$ ) = activity of plasma samples drawn.

**Jackson Urinary GFR (18)—Filtered and Unfiltered Data (Method H).** This method is similar to Method B. The excreted activity was collected as in Method B with the same adjustment for residual volume. For the plasma disappearance curve, however, the same externally detected data were used as in the terminal slope in Method C but extrapolated only to the time of the post-void bladder image (time T).

$$\text{GFR} \cong \frac{\text{TUA}}{\int_0^T P dt} = \frac{\text{TUA}}{(\bar{p})(T)},$$

where:

TUA = total urinary activity corrected for residual volume (18).

$\int_0^T P dt$  = that portion of  $\int_0^T P dt$  curve from 0 to T.

T = time of post-void bladder image (18).

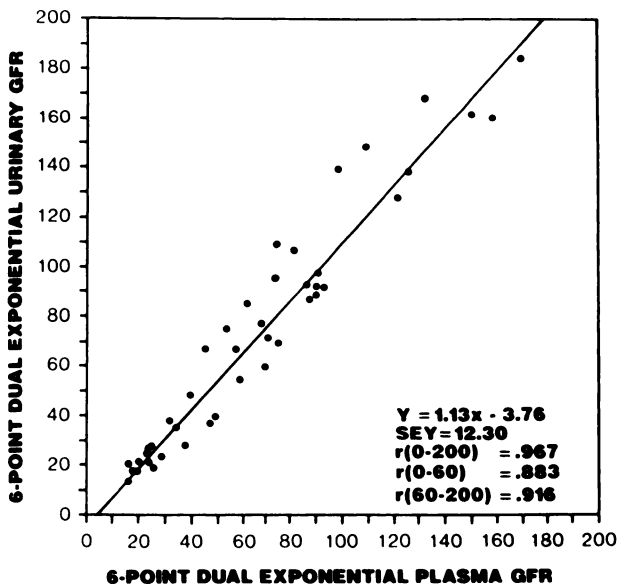
$\bar{p}$  = mean plasma activity.

**Gates Renal Cortical Uptake GFR (19) (Method I).** A 1-mCi (37 MBq) dose of  $^{99m}\text{Tc}$  activity was counted (~3.5K cps) using the scintillation camera and the counting efficiency was determined (cpm/mCi). The dose administered in milluries (~20 mCi) as measured by the dose calibrator (preinjection minus postinjection) was multiplied by the counting efficiency to determine the actual dose administered in "camera counts." The three scintillation cameras used in this study performed linearly (without dead-time count rate losses) up to 15K cps (140 keV, 15% window). The data acquired from 2 to 3 min after the first arrival of renal tracer were used to calculate GFR. The count rate during the 2-3-min post-arrival acquisition never exceeded 10K cps. The above modification of dose measurement allowed for accurate calculation of Gates GFR with an ~20-mCi dose.

$$\text{GFR} \cong \frac{\frac{\text{RIGHT RENAL CTS} - \text{BKG}}{e^{-0.153(13.3(W/H)+0.7)}} + \frac{\text{LEFT RENAL CTS} - \text{BKG}}{e^{-0.153(13.2(W/H)+0.7)}}}{\text{dose in "camera counts"}} \times 975.621 - 6.19843,$$

where: W = Wgt (kg) and H = Height (cm).

Because the actual activity of  $^{99m}\text{Tc}$ -DTPA in the kidneys prior to the leading edge transit is a product of clearance and



**FIGURE 1**  
The relationship between GFR values obtained by the two reference methods.

mean plasma tracer concentration (cortical content (Bq) =  $\bar{p}$  (Bq/ml)  $\times C_{\text{DTPA}}$  (ml/min)  $\times$  time (3 min)) (27), and tracer concentration = dose/volume of distribution, and at 3 min the volume of distribution approximates the intravascular space, the Gates method was also evaluated as Gates  $\times$  blood volume/5.0 liters (28) and as Gates  $\times$  body surface area/1.73 m<sup>2</sup>.

### Data Analysis

All of the clinical methods studied were compared to the two selected standards (vide supra) using linear least-squares regression analysis with standard error of the Y coordinate

**TABLE 1**  
Correction Factors to Improve GFR Accuracy\*

Method	A	B	A'
Russell two-point GRF			
60'/180' Filtered	1.26	-8.7	1.15
Unfiltered	1.60	-14.6	1.38
30'/180' Filtered	1.36	-17.1	1.16
Unfiltered	1.72	-23.7	1.38
Jackson urinary GFR			
Filtered	1.05	-3.5	1.02
Unfiltered	1.21	-4.5	1.16

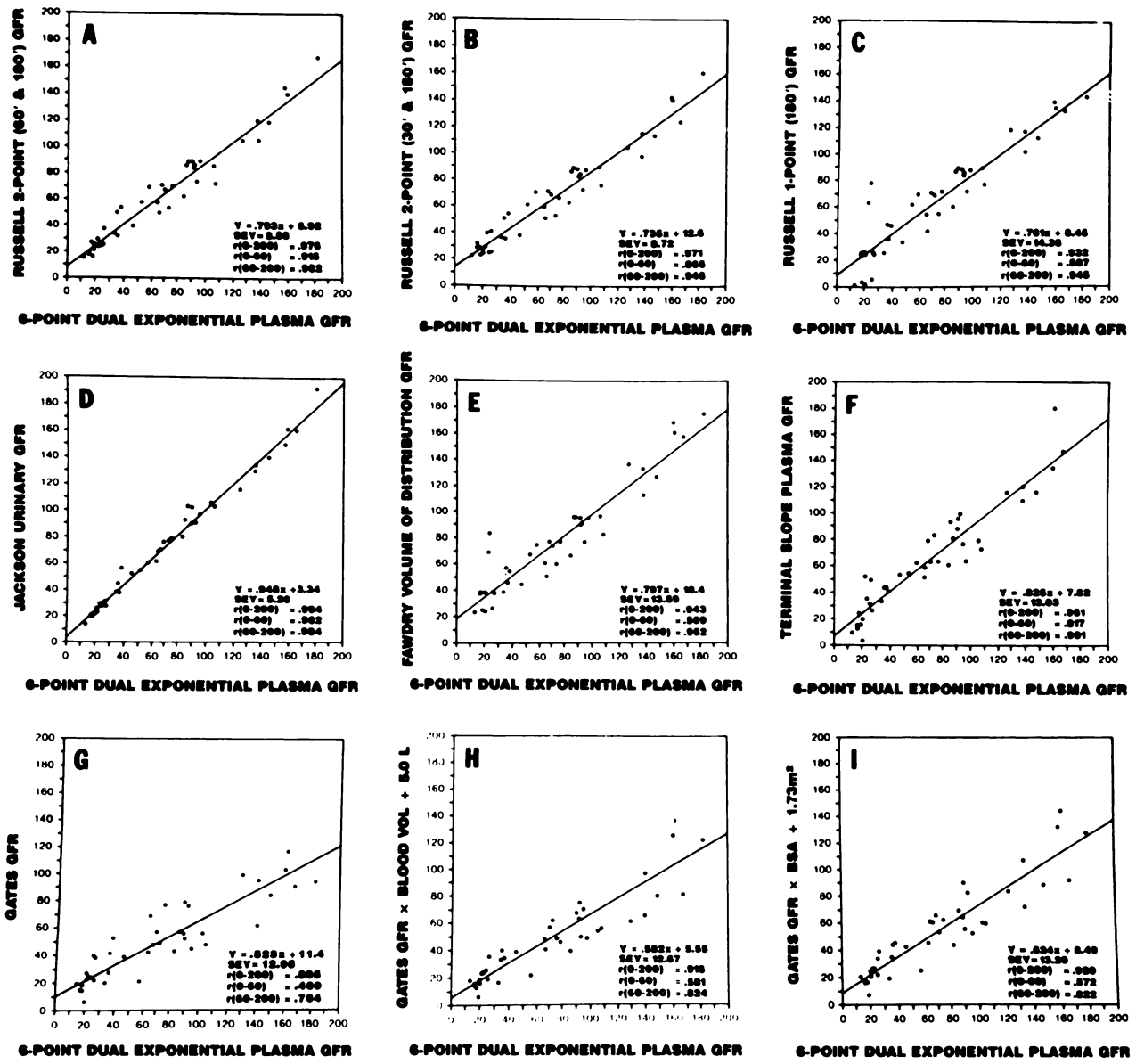
\*Correction factors derived from least-squares regression equations (Figs. 4-5) comparing each method to the urinary reference GFR:

$$\text{GFR}_{\text{CORRECTED}} = A \times \text{GFR}_{\text{UNCORRECTED}} + B.$$

A simplified correction factor is derived by least-squares regression through the origin:

$$\text{GFR}_{\text{CORRECTED}} = A' \times \text{GFR}_{\text{UNCORRECTED}}.$$

Example: The Russell 60'/180' filtered two-point GFR = 100 ml/min. Corrected GFR = (1.26  $\times$  100) - 8.7 = 117 ml/min or 1.15  $\times$  100 = 115 ml/min.



**FIGURE 2**  
 Comparison of several currently used GFR methods and variations (18,19,22,23) with the six-point dual-exponential PLASMA reference model. A = Russell two-point (60' and 180') GFR; B = Russell two-point (30' + 180') GFR; C = Russell one-point (180') GFR; D = Jackson urinary GFR; E = Fawdry volume of distribution GFR; F = Terminal slope plasma GFR; G = Gates GFR; H = Gates GFR x blood volume - 5.0 liters; and I = Gates GFR x body surface area - 1.73 M<sup>2</sup>. Definition of terms applies to all figures.

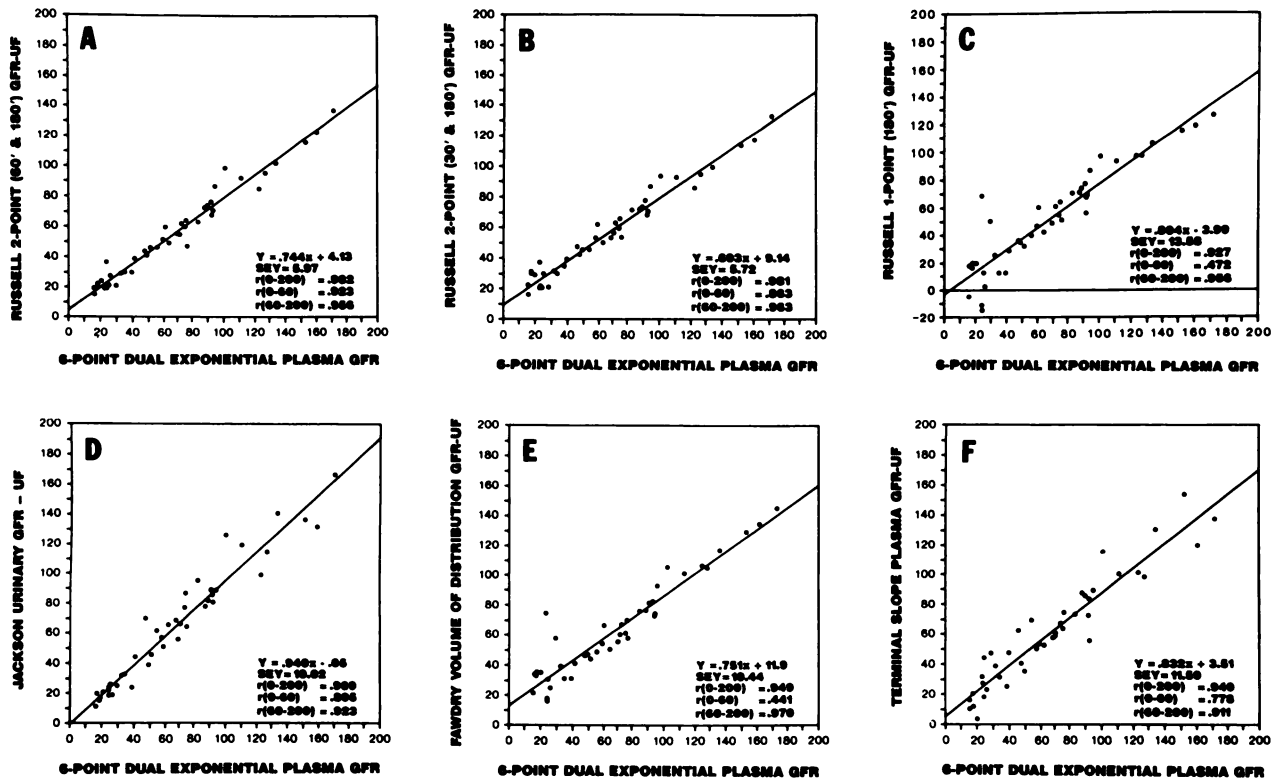
(SEY) and coefficient of correlation (r) values. Separate correlations were generated over the ranges of GFR of 0-60, 60-200, and 0-200 ml/min.

**RESULTS**

The six-point urinary GFR reference method produced the highest GFR of all methods evaluated. As the major sources of error in this method (e.g. plasma-protein binding of DTPA, incomplete urinary tracer collection, etc. (see Discussion)) can only result in an underestimation of the true GFR, and conversely the true GFR must equal or exceed the urinary standard

method, accuracy as a true measure of GFR can be improved by applying appropriate correction factors to those methods (all of them) that are consistently less than the urinary standard (Table 1).

Figures 2-5 show a comparison of several currently used GFR methods and variations (18-19,22-23) with the six-point dual-exponential PLASMA reference (Figs. 2-3) and URINARY reference (Figs. 4-5). Russell's two-point method calculated with 30' and 180' samples and with 60' and 180' samples were nearly equivalent. Russell's two-point method and the Jackson urinary method compared best with the two standards.



**FIGURE 3**

Comparison of the various methods with the six-point dual-exponential PLASMA reference model using UNFILTERED plasma samples.

The other techniques were less reliable especially in the low GFR (0–60 ml/min) range, and the Gates GFR correlated poorly at all levels of GFR.

Reliability (correlation) did not suffer significantly when unfiltered plasma samples were used (Figs. 3 and 5). If appropriate correction figures are used (Table 1), the routine use of ultrafiltration of plasma samples to offset any inaccuracies due to protein binding is unnecessary.

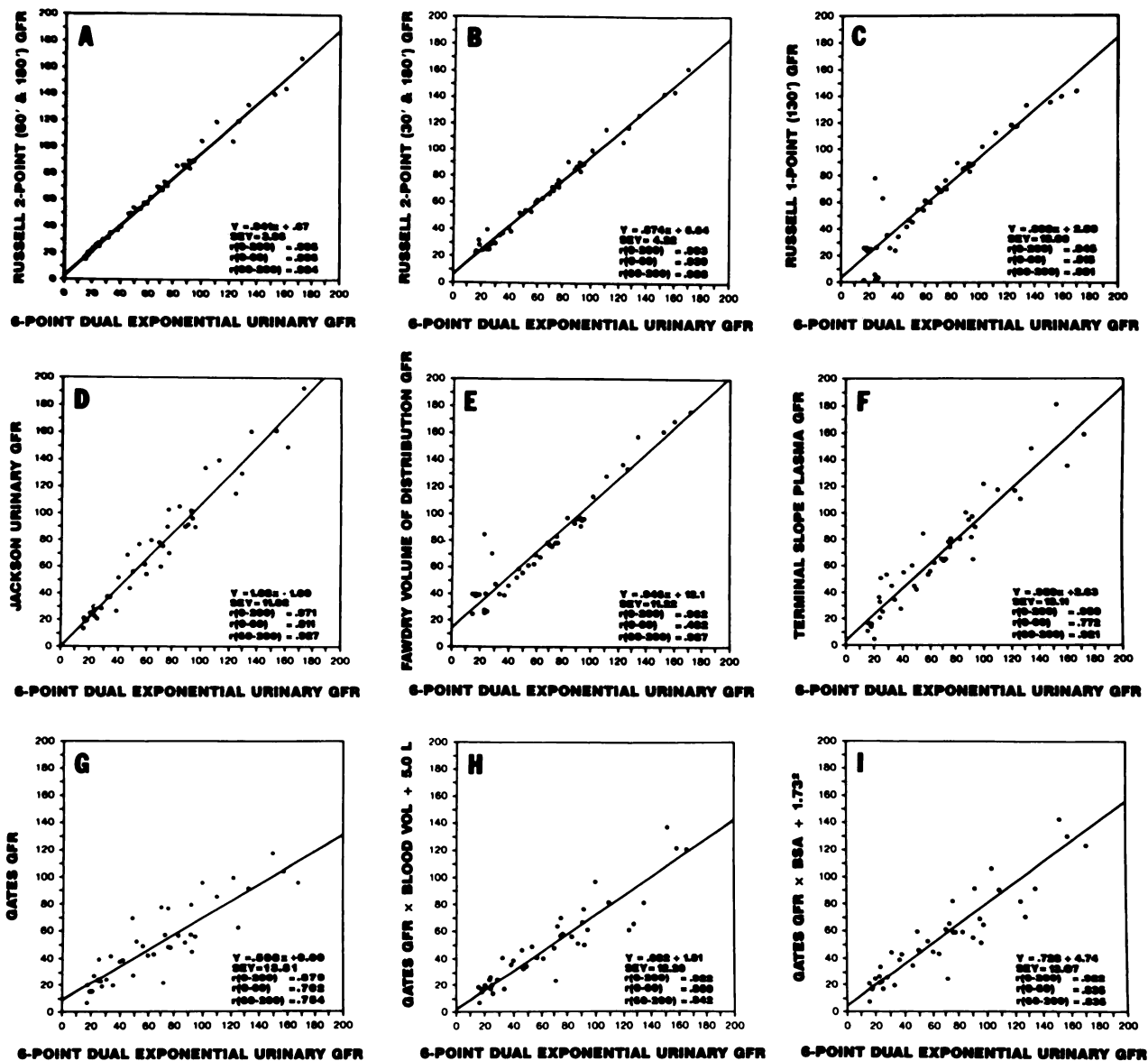
Based on these findings, we conclude that the Russell two-point plasma GFR and the Jackson urinary GFR are the best techniques overall. The Russell (30'/180') and the Jackson GFRs can be conveniently performed together as a complementary study.

## DISCUSSION

Multiple-sample plasma techniques for radionuclide GFR determination using  $^{99m}\text{Tc}$ -DTPA have been shown to correlate well with continuous-infusion inulin GFR calculation (9) and single injection inulin GFR determination (15). This forms the basis for the six-point dual-exponential plasma method as one of our two reference methods. Since the plasma disappearance curve is extrapolated beyond 180 min and a dual-compartmental model may erroneously represent this

extrapolated portion of the curve, we also chose to use a urinary/plasma standard in which a finite (unextrapolated) portion of the six-point curve is used as well as the actual amount of urine excreted.

There are several reasons for using two reference standards. The multiple plasma sample serum and urinary methods should theoretically give the same values for the GFR: one calculates clearance based on the rate of disappearance of tracer from plasma and the other on the rate of appearance of tracer in the urine, which should be identical. Sources of error in the serum method include that resulting from extrapolation to infinity of a curve based on a finite number of blood samples, as well as uncertainty regarding the effect of protein binding on the slope of the terminal portion of the curve. Protein binding has been said to increase with time (24) and has been demonstrated to cause error in GFR calculations (24). Errors in the urinary method stem from inaccuracies in determining the true amount of activity excreted. Error could result from miscalculation of residual volume, persistence of tracer in the intrarenal collecting system, or conceivably other phenomena such as tracer adherence to tubular cells. The six-point urinary method should not overestimate GFR, as all sources of error (intrarenal collecting system retention, tubular cell adherence, etc. and the exclusion of these same from the residual volume calculation (see Materials and Methods)) lead to underestimation of



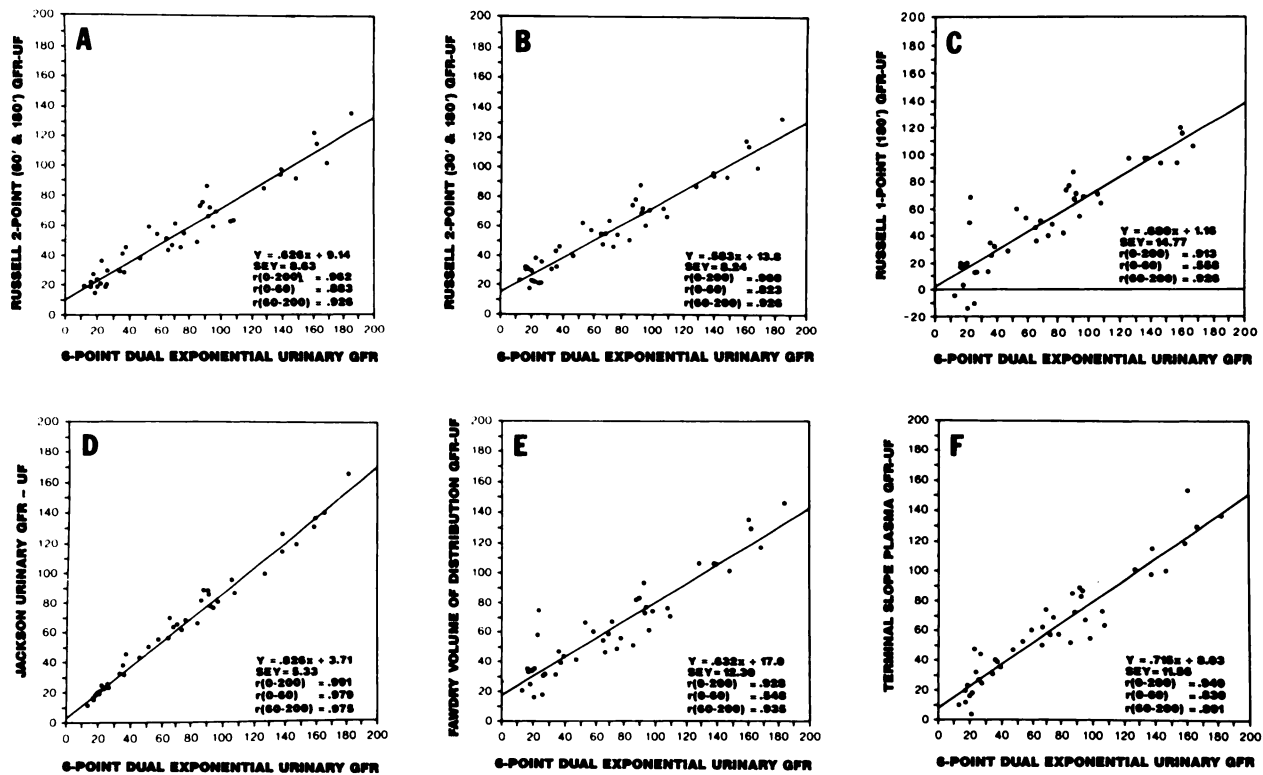
**FIGURE 4**  
 Comparison of the various methods with the six-point dual-exponential URINARY reference model.

TUA and therefore the GFR. Since the filtered plasma values represent the concentrations of tracer actually available for glomerular filtration by the urinary method and no extrapolation of these data is used, no error in the denominator (the plasma disappearance curve) should occur.

In our study, the six-point urinary standard produced consistently higher values for GFR than did the six-point serum standard (Fig. 1). Since the true GFR must always be equal to or greater than the urinary standard (vide supra), it follows that the multiple sample serum reference method systematically underestimates GFR. Since the urinary and plasma standards use the same plasma activity data, this difference cannot be attributed to protein binding. Although the reason(s) are not clear,

the two-compartment model in fact underestimates the GFR when extrapolated to infinity as required by the plasma method. It is not possible to say from this study which of the two reference methods constitutes a more accurate test; to do this would require direct comparison of both methods to a third standard known to be accurate, e.g., continuous-infusion inulin. The test with a better correlation with respect to this third standard would be a more reliable index of renal function; if the test underestimates GFR accuracy as does the six-point plasma standard, it could be improved by an appropriate correction factor (Table 1).

Comparing our data to the six-point plasma standard GFR (Fig. 2), the Russell two-point (60-min and 180-min filtered samples) GFR was the best test followed



**FIGURE 5**  
Comparison of the various methods with the six-point dual-exponential URINARY reference model using UNFILTERED plasma samples.

by the Russell two-point (30' and 180'-filtered) GFR and the Jackson urinary (filtered) GFR. The Fawdry volume of distribution (filtered) GFR, the terminal slope (filtered) GFR, and the Russell one-point (180'-filtered) GFR correlated well overall but these three correlated poorly in the abnormal (0–60 ml/min) range. The Gates GFR was the method that correlated most poorly with the plasma standard. Adjusting the Gates method for the effects of volume of distribution definitely improved its correlation with the plasma standard but not enough to improve its value as a test compared to the other methods. Figure 3 illustrates the comparison of the same tests but with the GFRs calculated using unfiltered plasma samples. The two Russell two-point GFR methods and the Jackson urinary GFR were almost as reliable compared to the plasma standard using either filtered or unfiltered data for calculation of the respective GFRs.

Comparing our data to the six-point urinary standard GFR (Fig. 4), the Jackson urinary (filtered) GFR was the best test followed by the Russell two-point (60' and 180'-filtered and 30' and 180'-filtered) GFRs, respectively. The terminal slope (filtered) GFR, the Fawdry volume of distribution (filtered) GFR, and the Russell one-point (180'-filtered) GFR correlated well overall but poorly in the abnormal (0–60 ml/min) range. The

Gates GFR similarly correlated poorly with this standard. Adjusting the Gates method for the effects of volume distribution similarly improved its correlation with the urinary standard but not enough to improve its value as a test compared to the other methods. Comparison of the same tests with GFR values derived from unfiltered plasma samples is depicted in Figure 5. The Jackson urinary GFR and the two Russell two-point GFR methods were almost as reliable compared to the urinary standard using either filtered or unfiltered data for calculation of the respective GFRs.

In clinical practice, it is most important to generate an accurate reproducible GFR in those patients with changing renal function and in those patients who will require multiple GFR determinations. This occurs most critically in patients with abnormal renal function. Whereas many of the methods produced adequate GFRs over the normal range, the Jackson urinary and Russell two-point GFRs performed exceptionally well in both the normal (GFR = 60 to 200 ml/min) and low (GFR = 0 to 60 ml/min) ranges.

Although the Jackson urinary and Russell two-point GFRs are good tests (high degree of correlation with standards), both tests underestimate GFR as does the plasma standard (vide supra). Since the true GFR is greater than the urinary standard GFR, we have pro-

vided correction factors for the Jackson urinary and the Russell two-point tests to improve their accuracy (Table 1).

We conclude from our data that the Jackson urinary GFR and the Russell two-point GFR are equally valid estimates of the true glomerular filtration rate. Since the Russell two-point (30' and 180') GFR is almost as good a test as the (60' and 180') test, for patient convenience we recommend the use of this (30' and 180') test in conjunction with the Jackson urinary GFR for evaluation of most patients. In those patients who have had an unfiltered dose or who cannot return for a three-hour blood sample, the urinary GFR will suffice. In those patients who cannot produce a urine sample or who have major upper urinary tract obstruction, the Russell two-point GFR will suffice. In all cases, the GFR calculations using the appropriate correction factors should be employed (Table 1). Since we found the tests not to be significantly different with filtered or unfiltered plasma samples, for practical purposes we recommend the use of unfiltered GFR determinations, at least for the  $^{99m}\text{Tc}$ -DTPA preparation we used. Since protein binding has been well shown to vary among various commercial DTPA preparations (24,29), the use of unfiltered plasma data using other commercial products should be tested and specific correction factors be generated as in Table 1. In the absence of this testing, filtered data should be used if possible.

Finally, it must be stated that this study was performed in adult patients with normal volumes of tracer distribution. It is well reported that indirect GFR methods correlating activity of plasma samples (6,13) or renal uptake (19,30-32) with clearance may be significantly inaccurate if the subject's volume of tracer distribution is not in the adult normal range. Before any of these methods can be applied with certainty to such patients [children and very small adults, very large adults, and patients with expanded blood and extracellular spaces (edema, congestive heart failure, nephrosis, etc.)], these groups need to be studied and compared.

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