therapy. In addition, the findings of this study may also be relevant for the interpretation of ^{111}In-pentetreotide studies in cancer patients investigated for tumor detection since irradiated lung areas may produce false-positive results.

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Measurement of Renal Function with Technetium-99m-MAG3 in Children and Adults

Charles D. Russell, Andrew T. Taylor and Eva V. Dubovsky

Division of Nuclear Medicine, University of Alabama Hospital and Nuclear Medicine Service, Department of Veterans Affairs Medical Center—Birmingham, Birmingham, Alabama; and Department of Nuclear Medicine, Emory University Hospital, Atlanta, Georgia

A single-injection, single-sample procedure for measuring ^{99m}Tc-MAG3 clearance is presented that incorporates scaling for patient size and is valid for both children and adults. **Methods:** The procedure is based on an empirical formula in which all measurements are expressed in dimensionless combinations. The formula was obtained by fitting data collected from 122 adults and 80 children at several centers. **Results:** All results were scaled to standard adult surface area and are presented in units of ml/min/1.73 m^2. For adult subjects, the residual standard deviation (r.s.d.) calculated from a single sample at 45 min was found to be 23, using the plasma clearance calculated from a multi-sample clearance curve as a reference. This did not differ significantly from the value of 22 obtained with our previous formula, which was valid for adults only. For pediatric subjects, an r.s.d. of 24 was calculated by the new formula from a single sample at 35 min; a comparable value of 33 was found using a pediatric formula previously published. **Conclusion:** The new clearance formula is recommended as a replacement for the formula we previously published, since it is based on a larger and more diverse subject population, and since it now holds for children as well, with no loss of accuracy for adult subjects.

Key Words: kidney; technetium-99m-MAG3; radionuclide clearance

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The single-injection, single-sample technique is arguably the most accurate technique for measuring renal function that can be applied routinely in a clinical environment. We present a method for technetium-99m-mercaptoacetyltriglycine (^{99m}Tc-MAG3) clearance that can be used for both adults and children. It depends only on the weight of the patient and, thus, does not require making the sometimes difficult decision of whether a given patient should be classified as a child or an adult. The clearance of ^{99m}Tc-MAG3 is closely correlated with OIH clearance, which in turn is closely correlated with PAH clearance (*1,2*). Technetium-99m-MAG3 clearance thus provides a measure of renal function that can be interpreted clinically in the same way as PAH clearance or ERPF. The ERPF can be estimated by dividing ^{99m}Tc-MAG3 clearance by the factor 0.53 (*3*). At the University of Alabama Hospital, the ERPF (measured originally with OIH and currently with ^{99m}Tc-MAG3) has been used for routine monitoring of renal function for over 20 yr. Currently, it is used in more than 30 ERPF measurements each week. These measurements are performed routinely in all patients undergoing renal scintigraphy and provide supplementary information that contributes to the interpretation of the study, especially when repeated measurements are made in the same patient. The most common clinical uses are to monitor renal transplants for acute change and to monitor patients with spinal cord injury or with obstructive uropathy for progressive loss of function. Although GFR measurements can be used in the same way, they are a greater

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For correspondence or reprints contact: Charles D. Russell, MD, PhD, Division of Nuclear Medicine, University of Alabama Hospital, 619-19th St. South, Birmingham, AL.

burden on the nuclear medicine clinic because they prolong the duration of the study. GFR agents are cleared more slowly so that GFR measurement takes 3 hr or more, while ERPF can be measured in less than 1 hr (*4*). Technetium-99m-MAG3 clearance thus serves as a convenient general-purpose measure of renal function.

We have previously described a single-sample technique for determining ^{99m}Tc-MAG3 clearance in adults (*5–7*). The present method is based on a larger and more varied data pool and incorporates scaling for patient size so that it is valid for both adults and children.

METHODS

Subjects

Adult data (n = 154) were obtained from the University of Alabama Hospital; the Veterans Administration Medical Center in Salt Lake City, Utah; Emory University Hospital; St. Joseph's Health Center, London, Ontario; and by courtesy of Dr. Piepsz, from several sites in Belgium. Pediatric data (n = 109) were provided by members of the Pediatric Task Group of the EANM (*8*). The pediatric subjects ranged in age from 6 mo to 19 yr; four subjects were less than 1 yr old.

Normal values for single-sample ^{99m}Tc-MAG3 clearance in adults were determined from a series of 200 normal renal transplant donors studied preoperatively at the University of Alabama at Birmingham (*3*).

Experimental Measurements

The measurements consisted of plasma activity (expressed as a percentage of the administered dose per liter of plasma) and corresponding sample times (expressed as time after injection) for at least six samples per subject. Typical data consisted of eight points spanning the time interval beginning 5–10 min after injection and ending 90 min after injection for adults, or ending 60 min after injection for children. The height and weight of each subject were available. Further details can be found in the original reports (*5,8*).

Data Screening

Prior to constructing the mathematical model, raw data were screened for quality by operator-independent methods that did not use the clearance itself; in particular, they did not depend upon the agreement between the clearance and its predicted value (in some cases the data had also been screened previously by the contributor).

The screening criteria were as follows. Only smooth curves were used: the exclusion criterion was 10% deviation of any point from the fitted curve. No curve was used that led to an estimated s.d. of more than 20 ml/min for the individual clearance (calculated from the covariance matrix estimated by NL2SOL, a hybrid algorithm) (*9*). This occasionally led to the exclusion of a curve that was smooth to the eye. Note that the statistics used for quality control were at least approximately independent of the quantity of interest (plasma clearance); the intent was to eliminate bad datasets by criteria other than their fit to the model. In the pediatric group, some problems were experienced in collecting early samples. This led to excluding all 5-min samples in the calculations published by Piepsz et al. (Piepsz A, *personal communication*, 1995). We did not exclude these data for fear of overestimating the clearance (*10*) but, rather, relied instead upon mechanical screening to eliminate poor datasets. Of 154 adult and 109 pediatric clearance curves (all data), there remained after screening for curve quality 122 adult and 80 pediatric curves (best data). Unscreened data are also shown below.

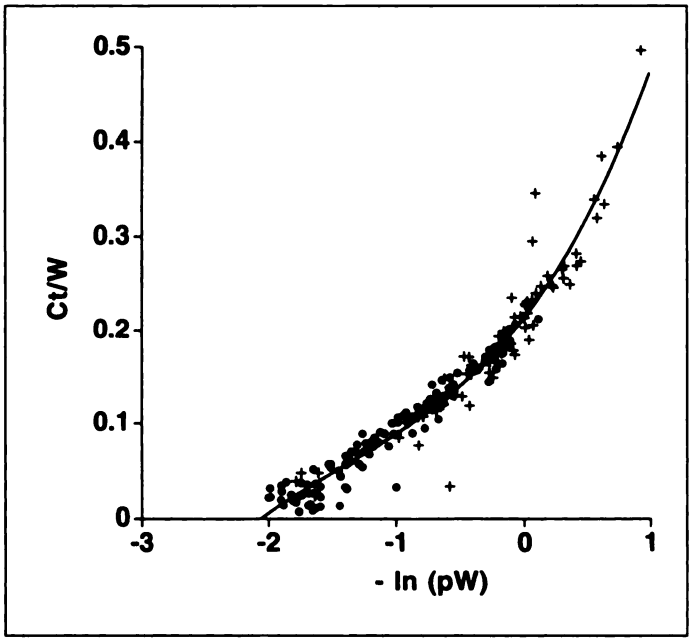

FIGURE 1. Adult and pediatric data expressed in the dimensionless quantities Ct/W and −ln(pW), where C is clearance, t is time, W is body weight and p is plasma concentration. Solid circles = adults (n = 122), plus symbols = children (n = 80).

Data Processing

Multi-sample clearances were calculated from a fitted bi-exponential curve using standard methods (*11*), fitting the plasma time-activity curve by nonlinear weighted regression using the program NL2SOL (*9*) weighted for constant percentage error (This assumes that the dominant errors arise in laboratory manipulations and not in Poisson counting error, so that the s.d. of a measurement is directly proportional to the measured value). The program NL2SOL (as FORTRAN source code) can be obtained by e-mail from netlib@ornl.gov; we used the version from the AT&T Port library, also available from netlib.

NL2SOL was used not only for calculating clearance, but also for fitting the clearance measurements to an empirical formula. Only screened data were used in calculating the parameters of the model for best least squares fit. Before fitting the model, clearances were scaled to a standard adult surface area of 1.73 m^2, using the Haycock formula (*12*):

$$A = 0.024265\ h^{0.3964}\ W^{0.5378} \qquad \text{Eq. 1}$$

to calculate surface area A (m^2), from height h (cm) and weight W (kg). Such scaling is mathematically equivalent to a statistical weighting, but no other weighting was used in fitting the empirical model (in contrast to the weighted regression described above for fitting individual plasma clearance curves).

The following reasoning led to a model that consists of a power series in dimensionless quantities. To scale for patient size, dimensional analysis (*13–15*) shows that the empirical formula should be expressed in dimensionless quantities. If a clearance C is expressed as a function of the three variables [sample time t, plasma concentration p (as fraction of administered dose per unit plasma volume) and total-body volume V], then it can be shown by dimensional analysis that the dimensionless quantity Ct/V is a unique function of the dimensionless quantity pV (In practice we use body weight W instead of body volume, assuming proportionality). The simplest example is the one-compartment linear model, which has the exact solution:

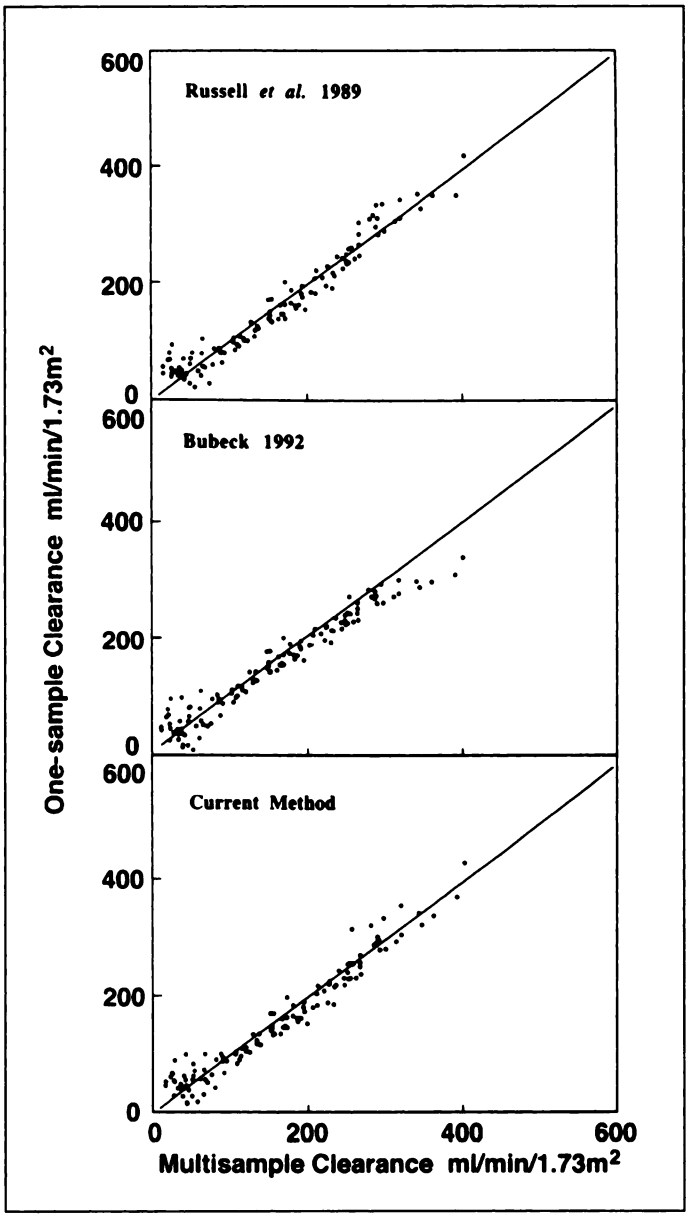

FIGURE 2. Adult subjects: ^{99m}Tc-MAG3 clearance estimated from one sample at 45 min compared to clearance calculated from multiple samples. The line of identity is shown. Top: Earlier method of Russell, et al. (*5*). Middle: Method of Bubeck (*16,17*). Bottom: Current method.

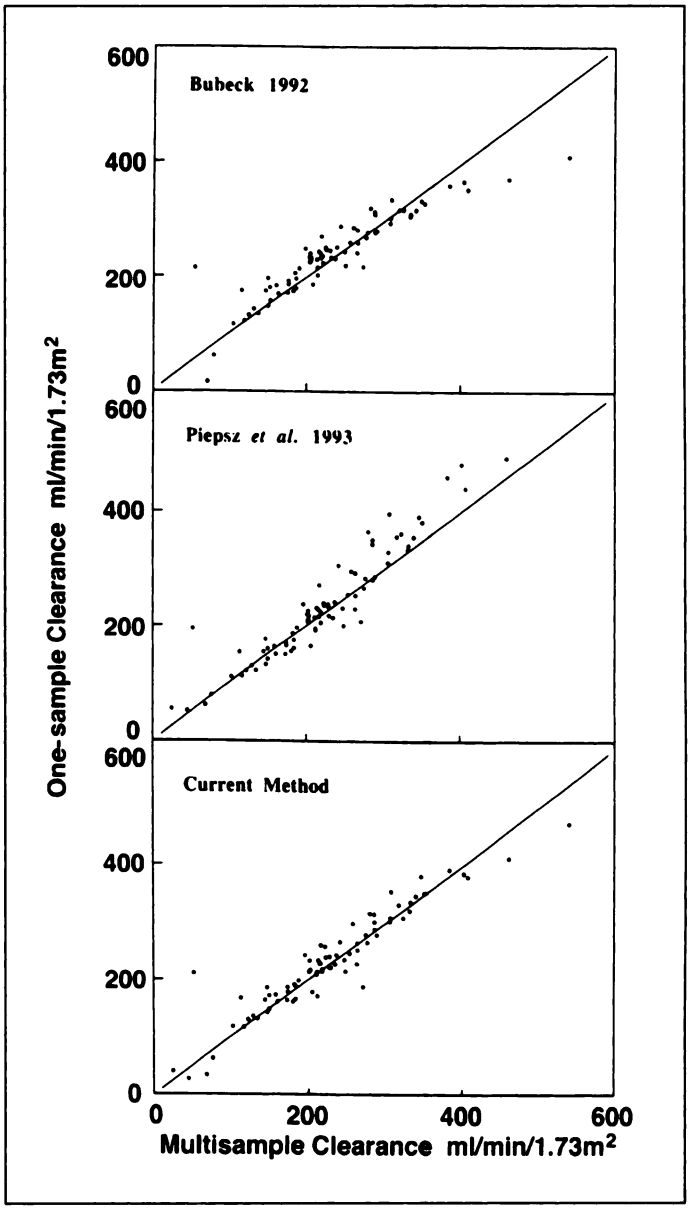

FIGURE 3. Pediatric subjects: ^{99m}Tc-MAG3 clearance estimated from one sample at 35 min compared to clearance calculated from multiple samples. The line of identity is shown. Top: Method of Bubeck (*16,17*). Middle: Method of Piepsz et al. (*8*). Bottom: Current method.

$$Ct/V = \ln (pV), \qquad \text{Eq. 2}$$

but, in general, Ct/V will be a more complicated mathematical function of pV. The nature of this function will be examined next.

RESULTS

The preceding theoretical analysis can be tested by plotting Ct/W versus ln (pW), choosing a logarithmic abscissa since it yields a straight line in the one-compartment case discussed above. Figure 1 shows the results for 202 subjects (122 adults and 80 children), using the sample time of 40 min for each patient. The data can be seen to fall along a smooth curve, which was fitted by least squares to yield the following dimensionless formula:

$$Ct/W = 222.6 - 168.8X + 52.73X^2 - 11.14X^3, \qquad \text{Eq. 3}$$

where X = ln (pW); C = ^{99m}Tc-MAG3 clearance in liters/min, t = time in min, W = weight in kg and p = plasma concentration expressed as the fraction of administered dose per liter of plasma. This formula does not use the height of the patient, but including the dimensionless term $h/W^{1/3}$ to represent the height h failed to improve the fit of the model to the data.

When the above formula (Equation 3) was used to calculate clearance, the agreement between observed and predicted values was that shown in Figures 2 and 3. Previous methods are also shown for comparison (*5,8,16,17*). In these comparisons, the screened data were used. To illustrate the effect of screening clearance curves for quality, a corresponding plot of unscreened adult data is shown in Figure 4. Observe that all methods yielded similar results, which were adequate for clinical use in every case. In Figure 2, increased random error is seen at low clearance values for all three methods. It can also be seen in Figure 2 that the Bubeck method gave systematically low results in the high normal range [relative to the reference method used here (single-injection, multiple-sample), which differed from the continuous-infusion reference method used by Bubeck for his measurements in adults].

Figure 3 shows comparable plots of the screened data for

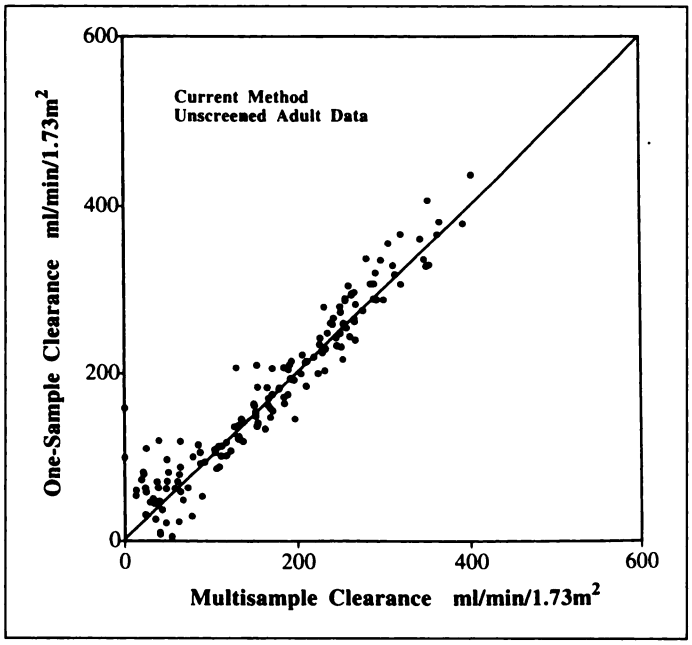

FIGURE 4. Unscreened adult subjects (all data): ^{99m}Tc-MAG3 clearance estimated from one sample at 45 min compared to clearance calculated from multiple samples. The line of identity is shown.

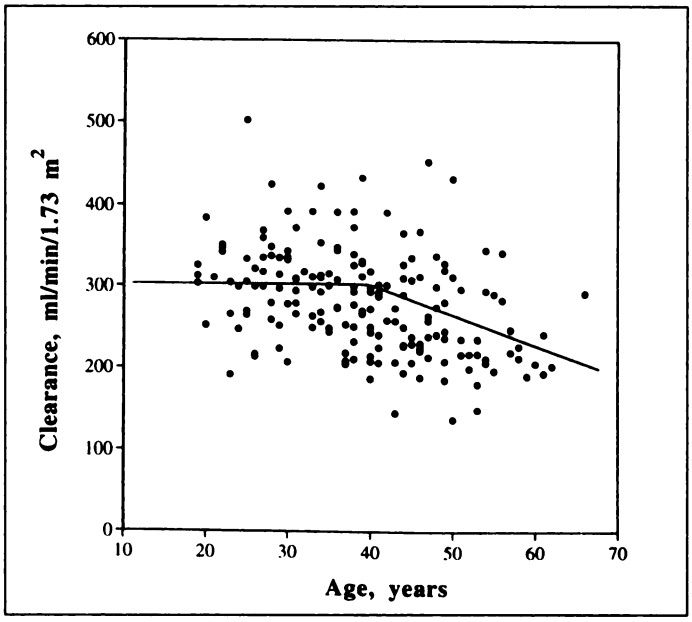

FIGURE 5. Technetium-99m MAG3 clearance versus age for normal subjects.

children. A data point on the left side of the graph is an outlier by all methods; inspection of the raw data suggests that the initial 5-min data point may have been erroneously high for this subject. It can also be seen from Figure 3 that the Piepsz method gave systematically high results for children with high clearance. This can be explained by the tendency of the multisample method to overestimate clearance (by underestimating the first exponential component) when sampling is begun too late (*10*), and resulted from exclusion of the 5-min data points from the reference measurements used in deriving the Piepsz formula. Both scaled formulas (Bubeck's and ours) that are intended for combined use with adults and children appear to give system-

TABLE 1
Errors in Replacing Multisample by Single-Sample Measurement for Screened Data*

	Adult	Low function adult†	Pediatric	Low weight pediatric†
Sample size	122	41	79	28
Current method	22.6	26.4	24.3	28.2
Russell 1989	22.2	26.0	—	—
Bubeck 1992	26.2	27.0	31.6	38.2
Piepsz 1993	—	—	32.6	41.1

*Residual s.d. in ml/min/1.73 m². Sampling at 35 min for children and 45 min for adults.
†Low weight <20 kg; low function <100 ml/min/1.73 m².

TABLE 2
Errors in Replacing Multisample by Single-Sample Measurement for Unscreened Data*

	Adult	Low function adult†	Pediatric	Low weight pediatric†
Sample size	154	45	109	37
Current method	20.7	25.4	33.6	35.5
Russell 1989	20.7	24.5	—	—
Bubeck 1992	25.8	25.5	39.0	41.7
Piepsz 1993	—	—	41.5	51.3

*Mean error in ml/min/1.73 m². Sampling at 35 min for children and 45 min for adults.
†Low weight <20 kg; low function <100 ml/min/1.73 m².

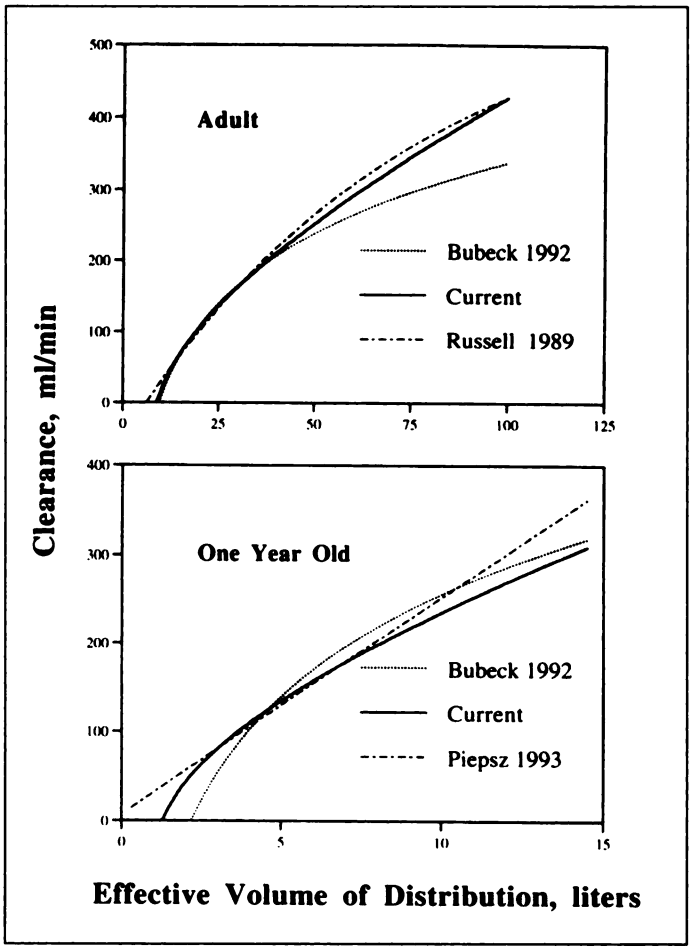

FIGURE 6. Comparison of one-sample methods in adult (top) and 1-yr-old child (bottom) of average height and weight.

atically low results in children with very high clearance, but the number of data in this range is few; the calculated clearances at the deviant points, after scaling for body surface, were higher than for any adult studied and might conceivably be spurious.

The results are compared statistically in Table 1 (screened data) and Table 2 (unscreened data). For screened data, the r.s.d. is given (omitting the single pediatric outlier mentioned above); for unscreened data, the mean absolute deviation (mean error) is given, which is a more robust measure of dispersion (i.e., insensitive to outliers). At the suggestion of an anonymous reviewer, separate comparisons were also made for pediatric patients of low weight and for adult patients with low renal function. The number of pediatric patients with low renal function was too small for separate statistics, but the corresponding data are shown in Figure 2.

The differences in Tables 1 and 2 are small and are, at most, of borderline significance. (For 100 data points, the F-test requires a difference of nearly 20% for significance at the 95% confidence level; for 30 data points a difference of 44% is required.) Thus, there are no convincing statistical differences among the alternative methods.

To establish the adult normal range for the new formula, it was applied to a group of 200 subjects studied and verified as normal by evaluation as prospective renal transplant donors (*3*). The pretransplant evaluation included not only renal function tests, but also excretory urography and renal arteriography. The normal range (mean ± s.d.) was found to be 302 ± 73 ml/min/1.73 m^2 for patients under 40 yr of age, and 302 − 3.77 (age-40) ± 73 ml/min/1.73 m^2 for patients over 40. The data are plotted in Figure 5. As seen from the plot, the data are widely scattered and do not clearly disclose the form of the underlying relationship. The piecewise-linear model that we employed was chosen for consistency with the published literature on geriatric nephrology (*18–23*).

DISCUSSION

Comparison of Methods

The methods compared in Table 1 are not identical, though they are essentially equivalent in terms of their statistical agreement with the measured data. The differences can be seen in Figure 6, which compares the clearance by different methods as a function of plasma concentration for a 70 kg, 170 cm adult with sampling at 45 min, and for a 10 kg, 76 cm child with sampling at 35 min. For the adult, observe that the new general-purpose formula agrees closely with our previous adult formula. In the range of clearances that are of greatest clinical interest, there are only small differences among the different formulas, though the Bubeck formula gives distinctly lower results in patients with high normal clearance.

Differences can also be seen at low clearance. Observe that in the limiting case of zero clearance, corresponding to a functionally anephric patient, the Piepsz formula predicts a negative volume of distribution (Fig. 6). The other formulas predict an effective volume of 1–2 liters at 35 min for a 10 kg child, and 5–10 liters at 45 min for a 70 kg adult, when clearance is zero.

Choice of Sampling Time

The accuracy of a single-sample method depends on the time of sampling, as many studies have shown. The optimum sample time varies with renal function. The best results were obtained with early sampling for patients with high clearance and later sampling for patients with low clearance (*24–29*). Tauxe et al. (*28*) even suggested varying the sample time according to the expected clearance. This improves the results, and could be used to partially overcome the increased error at low clearance noted in Figure 2, but it is cumbersome in practice. More commonly and more conveniently, however, a fixed sampling time is used that reflects a compromise between high- and low-clearance patients. For convenience to patient and clinic staff, the sample should be obtained as early as possible, but accuracy is impaired if sampling is too early. The compromise we recommend is to draw the sample at fixed times of 35 min in children and 45 min in adults. Transit times are shorter in children than in adults, thereby permitting earlier sampling times (*15*). This is advantageous because it shortens the study, but when the patient is of adult size and the clearance is low, later sampling gives better results. The 45-min sampling time should be used if one is in doubt about when to sample. With later sampling for children, 45 min rather than 35 min, the r.s.d. increased from 24.3 ml/min/1.73 m^2 to 26.8. With earlier sampling for adults, 35 min rather than 45 min, the r.s.d. increased from 22.6 to 25.9 and the scatter seen at low clearance in Figure 2 was increased. In practice, samples cannot always be obtained precisely when desired, and the formula can be used with satisfactory results for either children or adults over the entire range from 35–50 min.

Effect of Body Weight

For adults, it may be useful to have a method that does not depend on patient weight, since this may be unknown, inaccurate or inconvenient to obtain. We therefore tested the use of a standard weight of 70 kg for all adult subjects. With sampling at 45 min, the r.s.d. was found to be 22.0 ml/min (n = 122) using the correct height and weight, and 22.4 ml/min using a fixed value of 70 kg for all patients (Note that these results have not been normalized to 1.73 m^2, unlike the other data in this report, since the height and weight are regarded as unknown in this context). Using an assumed weight thus gave excellent overall results for the adult subjects. It seems plausible that individual adults who depart markedly from average size should benefit from scaling, but attempts to demonstrate this statistically were unsuccessful. Thus, for adult subjects, if it is not intended to scale the final results to 1.73 m^2, the height and weight can be dispensed with, and a fixed standard weight of 70 kg used for all adult patients. For children, on the other hand, the correct height and weight are essential when using the method presented here.

One Formula Versus Two

One may ask whether it is better to use a single-scaled formula or to use separate formulas for adults and children. Having used separate formulas for OIH clearance for many years (*29,30*), we are convinced that a single formula is best as long as there is no loss in accuracy. Technologists ask which formula to use in the case of adolescents, unusually large children and unusually small adults. When a child becomes an adult, switching formulas introduces a small discontinuity into serial measurements of renal function. Beyond these practical considerations, a single formula is preferred on theoretical grounds. A good formula should remain correct in limiting cases. For children, adulthood represents a limiting case, and vice versa.

CONCLUSION

The new clearance formula is recommended as a replacement for the formula we previously published, since it is based on a larger and more diverse subject population, and since it now holds for children as well, with no loss of accuracy for adult subjects. The formula can be used in the range of sample times from 35–50 min. To keep the duration of the study as short as possible without undue loss of accuracy at low clearance values, we recommend sampling at 35 min for children and at 45 min

for adults. Whenever there is doubt regarding whether the subject should be regarded as a child or an adult, the 45 min sampling time should be used.

The differences among the methods evaluated here are small and probably inconsequential in clinical use. The agreement among them should be reassuring to users, whichever method they choose, and suggests that significant further improvement is unlikely.

APPENDIX: SAMPLE CALCULATIONS

It is expected that the calculations will normally be performed by a computer or programmable calculator using Equation 3. The detailed hand calculations shown here can be used to check the program.

Obtain a single ^{99m}Tc-MAG3 plasma sample at some time between 35–50 min after injection. For illustration, we shall use the same numerical example as in our previous report (*5*): an adult patient for which the plasma sample was drawn at 44 min, so that

$$t = 44 \text{ min.}$$

The administered dose (standard × dilution factor) was 33994×10^4 counts/min, and the plasma activity expressed per liter of plasma was 11558×10^3 cpm/liter. Dividing the plasma activity by the dose gives

$$p = 0.0340 \text{ liter}^{-1}.$$

For adults, we found no demonstrable loss of precision by assuming a standard weight of 70 kg, regardless of the true weight of the patient. Thus, it may be assumed that

$$W = 70 \text{ kg.}$$

From p and W one calculates the dimensionless quantity X,

$$X = \ln (pW) = \ln (0.0340*70) = 0.86710$$

The value of X is substituted into Equation 3 to give:

$$Ct/W = 222.6 + (- 168.8)(0.867) + (52.73)(0.867)^2$$

$$+ (- 11.14)(0.867)^3$$

$$= 108.6$$

Solving for C then yields

$$C = (108.6)(70)/44 = 173 \text{ ml/min.}$$

The final value of 173 ml/min differs little from the value of 172 obtained by our previous formula (*5*), but the new formula is supported by a larger database and holds for children as well.

Note that this value is not scaled for surface area. Scaling for surface area, if desired, must be done in the usual manner, with an appropriate surface area formula or nomogram. Suppose that the patient weighed 75 kg and measured 182 cm. Then the Haycock formula (*12*) (Eq. 1) predicts a surface area of 1.95 m^2, and the clearance scaled to a standard adult surface area of 1.73 m^2 would be

$$173 \times (1.73/1.95) = 154 \text{ ml/min/1.73 m}^2.$$

Several surface area formulas are in use, as reviewed in the Geigy Scientific Tables, (*31*) and nomograms based on various of these formulas can be found in many textbooks. The differences among the different surface area formulas are small and are of little consequence in clinical applications.

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