estimate of renal clearance in adults with low renal function (low λ values), while it yields an acceptable approximation of this parameter in children with similar absolute clearance values (high λ values). It is however still to be determined whether the single-plasma sample method can be used in children with severe renal failure.

Our choice of the 2-hr distribution volume as parameter was circumstantial. As a retrospective study, only data already available could be used. While it is quite probable that other sampling time could yield even more accurate results, in our opinion the closeness of the relationship between 2-hr distribution volume and slope-intercept clearance observed in this work does not warrant a prospective study, since the population investigated was infants and young children.

For the determination of plasma clearance, the continuous infusion method and single injection with multiple blood sample technique are the two usually accepted reference methods. Unfortunately, these methods are rather unsuitable for routine clinical use in infants and young children. In this study, the reference value for ^{51}Cr-EDTA clearance was calculated from the single exponential derived from the results of blood samples at 2 and 4 hr after injection. Indeed, even if the ^{51}Cr-EDTA in vivo kinetics are much more complex than a single-compartment model, a very close agreement has been repeatedly demonstrated between the two-blood sample technique with the continuous infusion method, multiple blood sampling technique or inulin clearances (*1,2,6,8*).

One may ask whether it is justified, in practice, to use the single-sample technique instead of the well-validated two-sample method. It is obvious that the supplementary data derived from additional blood samples could improve the estimation of renal clearance. However, when dealing with infants and young children, one less blood sample not only saves cost and time but also significantly reduces the physical and psychologic trauma of the patient and parents. Given the accuracy of the single-sample method, the application of this method in children is recommended.

Finally it should be noted that the data presented in this work were based on ^{51}Cr-EDTA. It is still to be demonstrated that the converting equation presented above remains valid when using other glomerular filtration agents (^{99m}Tc-DTPA, ^{125}I-diatrizoate). Given the difference in distribution volume, protein binding, etc. slightly different results could be expected.

REFERENCES

1. Chantler C, Garnett ES, Parsons V, Veall N. Glomerular filtration rate measurement in man by the single injection method using ^{51}Cr-EDTA. *Clin Sci* 1969;37:169–180.
2. Chantler C, Barratt TM. Estimation of glomerular filtration rate from plasma clearance of chromium-51-edetic acid. *Arch Dis Child* 1972;47:613.
3. Winterborn MH, Beetham R, White RHR. Comparison of plasma disappearance and standard clearance techniques for measuring glomerular filtration rate in children with and without vesico-ureteric reflux. *Clin Nephrol* 1977;6:262–270.
4. Tauxe WN, Maher FT, Taylor WF. Effective renal plasma flow: estimation from theoretical volumes of distribution of intravenously injected I-131-orthoiodohippurate. *Mayo Clin Proc* 1971;46:524–531.
5. Tauxe WN. Determination of glomerular filtration rate by single plasma sampling technique following injection of radioiodinated diatrizoate. *J Nucl Med* 1986;27:45–50.
6. Christensen AB, Groth S. Determination of ^{99m}Tc-DTPA clearance by a single plasma sample method. *Clin Physiol* 1986;6:579–588.
7. Fawdry R, Gruenewald S. Three-hour volume of distribution method: an accurate simplified method of glomerular filtration rate measurement. *J Nucl Med* 1987;28:510–513.
8. Russell CD, Bischoff PG, Kontzen FN, et al. Measurement of glomerular filtration rate. Single injection plasma clearance method without urine collection. *J Nucl Med* 1988;26:1243–1247.
9. Tauxe WN, Hagge W, Stickler GB. Estimation of effective renal plasma in children by use of a single plasma sample after injection of orthoiodohippurate. In: *Dynamic studies with radioisotopes in medicine*, volume 1. Vienna: International Atomic Energy Agency; 1974:265–275.
10. Tauxe WN, Bagchi A, Tepe PG, Krishnail PR, Single-sample method for the estimation of glomerular filtration rate in children. *J Nucl Med* 1987;2:366–371.
11. Groth S, Aasted M. Cr-51-EDTA clearance determined by one plasma sample in children. *Clin Physiol* 1984;4,75–83.
12. Brochner-Mortensen J. Routine methods and their reliability for assessment of glomerular filtration rate in adults. *Dan Med Bull* 1978;25:181–202.
13. Chatterton BE. Limitations of the single sample tracer method for determining glomerular filtration rate. *Br J Radiol* 1978;51:981–985.
14. Kamper AL, Nielsen SL. ^{51}Cr-EDTA plasma clearance in severe renal failure determined by one plasma sample. *Scand J Clin Lab Invest* 1989;49:555–559.
15. Waller DG, Keast CM, Fleming JS, Ackery DM. Measurement of glomerular filtration rate with Tc-99m-DTPA: comparison of plasma clearance techniques. *J Nucl Med* 1987;28:372–377.

EDITORIAL

Glomerular Filtration Rate in Children: Where We Have Been; Where We Are Going

In this issue of the *Journal*, Drs. Ham and Piepsz present some very encouraging data on the estimation of the glomerular filtration rate (GFR) in children by the use of a single blood sample 2 hr after the administration of ^{51}Cr-EDTA (*1*). Fourteen years ago, these same authors published an appealing method for estimating GFR from the ^{99m}Tc-DTPA renogram (*2, 3*). In these few pages, I would like to review the progress that has been made over the years in the evaluation of renal function with radionuclides, with attention to those considerations which are unique to children.

A major strength of radionuclide examinations of the urinary tract is the evaluation of function. Not only

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are the tracers handled by the kidney in physiologically specific ways, but they can also be quantified. Early work emphasized several parameters that were derived directly from the time-activity (renogram) curve, such as time to peak, although the intrinsic meaning of these values was limited. Subsequently, the emphasis shifted to using radionuclides to determine those aspects of renal function such as GFR and effective renal plasma flow (ERPF) that were already defined by the renal physiologist and understood by clinicians. These techniques fall into two major categories: those that evaluate renal function from the quantitative data in imaging studies and a variety of nonimaging studies that can either be used alone or combined with imaging.

During imaging studies, differential renal function can be estimated either by techniques which measure tracer uptake early in the examination or by relative counts on static images obtained much later with cortical radiopharmaceuticals. However, it would be more useful if the function of each kidney could be expressed not only as a percentage of the total, but in terms of individual kidney GFR. In 1977 and 1987, Drs. Piepsz, Ham, and their co-workers (*2,3*) described a thoughtful method for estimating GFR from the renogram. Based on the premise that the rate of tracer uptake into the kidney is the product of clearance and the plasma concentration, they measured single kidney GFR as the rate of tracer uptake in the kidney (slope of the renogram during the accumulation phase) divided by the plasma concentration. They determined the plasma concentration by the combined use of a blood-pool time-activity curve calibrated by a single blood sample at 20 min, which enabled them not only to account for plasma concentration, but also changes in it during the time of data collection. Although theoretically sound, problems with their technique included the inconvenience of a 20-min blood sample and the need for multiple corrections to account for factors such as photon attenuation within the patient and the relative sensitivities of the scintillation camera and well counter. and well counter.

Rather than calculate GFR from direct measurements of tracer uptake and plasma concentration, Gates (*4*) derived an empiric regression between tracer uptake and creatinine clearance that could then be used prospectively to estimate GFR. This use of an empiric regression circumvented the need for the multiple corrections used in Piepsz's technique. Because the Gates' formulation divides kidney counts by the radiopharmaceutical dosage (syringe counts) rather than plasma concentration, it implicitly assumes that all subjects must be approximately the same size. While this may be an acceptable assumption in adults, it clearly cannot be assumed in children, and this has limited its usefulness in that group. Based on these two techniques, we have developed a method designed for use in children which combined Piepsz's recognition of the importance of the plasma concentration with the simplicity of an empiric method as described by Gates (*5*). Instead of measuring the plasma concentration directly, we assumed that it should be directly proportional to dosage and inversely proportional to body size. More recent advances in the renographic estimation of GFR include a method described by Russell (*6*), which corrects for changing blood levels and intrarenal vascular "background" activity. Intrarenal vascular background can represent a significant contribution to total renal activity, yet it is not activity that has been filtered and, therefore, does not represent function. Further verification of this technique would be valuable.

Because of its simplicity, the Gates' method has achieved the most widespread use. There has been a wide range of reports regarding how well it works, and these reports are often difficult to compare because of differences in the way that results are reported. Some investigators have described very poor results with the method (*7*). Chachati et al. (*8*) claimed a good correlation between the Gates' technique and inulin clearance and concluded that they had validated the method, but in their work the error of GFR estimation was twice as great as initially reported (*4*). Recent reports which compare scintigraphic methods to nonimaging techniques based on blood samples reach similar conclusions that the latter are more accurate (*9,10*).

There are a variety of nonimaging techniques for estimating renal function. Conceptually, the most easily understood approach is the use of a constant infusion to establish a stable plasma concentration. This concentration combined with a timed urine collection permits clearance to be calculated by its classic definition. This is the same technique that is often used for standard inulin clearances, and the use of radiotracers simply offers the ease of counting samples compared to the chemical determination of inulin.

More widely used are those techniques based on tracer kinetics with plasma disappearance monitored by samples following tracer administration. After intravenous injection, the tracer leaves plasma by two routes: excretion by the kidney and equilibration with non-plasma extracellular fluid. Initially, there is a rapid loss of tracer from plasma into the extracellular fluid compartment until equilibrium is reached. Then, as the plasma concentration steadily falls with renal excretion, the tracer is brought back into the plasma compartment and tracer concentrations in these two compartments fall together. This is the model that the single-injection, dual-exponential technique is based upon. It calculates clearance from blood sample data with the use of early samples to measure equilibration with extracellular fluid and later samples for renal clearance (*11*). Although this method is quite accurate, the need for a large number of samples has limited this technique primarily to research use.

If the admittedly oversimplified as-

sumption is made that there is instantaneous equilibration between plasma and extracellular fluid, then clearance can be estimated from two or three blood samples used to calculate the exponential plasma disappearance constant and the theoretical volume of distribution, generally referred to as the single-exponential technique. Because this method neglects part of the denominator included in double-exponential analysis, it will tend to systematically overestimate GFR. This can then be corrected with a constant applied in either a linear (*12*) or exponential (*13*) manner. Some reports indicate more reliable results using ultrafiltered samples to eliminate the effects of protein binding (*10*), but most investigators have not found this necessary. These methods have become widely used, and although their accuracy is not as great as double-exponential analysis, reports in which several methods have been compared simultaneously conclude that single-exponential analysis or its modified "two-sample" approach is acceptably close to the reference techniques and is significantly better than methods based on renogram analysis (*9*).

More recently, the plasma disappearance techniques have been simplified even further, down to the use of a single sample. Rather than actually calculate clearance by tracer kinetics, the single sample techniques are based on an empiric correlation between the degree to which the tracer is effectively diluted and an independent measure of clearance. The plasma concentration at the time of sampling relative to the radiopharmaceutical dose defines a hypothetical "volume of distribution," which is not meant to correspond to any real volume, but rather describes how well the kidneys have eliminated the tracer from plasma. Initially, this technique was used for ERPF with ^{131}I-hippuran (*14*), and more recently it has been used for GFR with a variety of tracers including ^{99m}Tc-DTPA (*15*), ^{131}I-diatrizoate (*16,17*), and ^{51}Cr-EDTA (*1, 18*). There is considerable variability in the sampling times used for GFR agents, with 2 hr used by Ham and Piepsz in their study reported in this issue (*1*), 3 hr used by Fawdry and Gruenewald (*15*), and Waller et al. (*19*) found the best results at 4 hr, although even their best results with a single sample were not as good as those with two samples at 2 and 4 hr. There also appears to be a difference in optimal sample times between children and adults (*20*).

There has been relatively little reported usage of the single-sample techniques in children. Tauxe et al. examined ^{131}I-hippuran (*20*) and ^{131}I-diatrizoate (*17*) clearance, and in this issue of the *Journal* Ham and Piepsz (*1*) describe their experience with ^{51}Cr-EDTA, comparing a 2-hr sample to simultaneous single-exponential analysis with two samples. The results of these studies are encouraging and actually appear better than expected based on the adult studies mentioned above.

My only desire with regards to these reports is that I would prefer to see the results expressed in terms of ERPF or GFR normalized for body surface area (normalized GFR), since these are the units that are of use clinically. Although they may initially seem equivalent, there are two different ways that normalized GFR can be estimated (*5*). One way would be to estimate GFR and then normalize that result. The other would be to estimate normalized GFR directly, which could be accomplished by a regression between the volume of distribution normalized for surface area and an independent measure of GFR also normalized for surface area. There are several reasons why this approach might be preferable. The first relates to the y-intercept of the regression formula. This has an increasingly large contribution in small children, and we have found it to limit our ability to use the Tauxe (*20*) formula in very small children with significantly impaired renal function. In that formula,

$$\text{ERPF} = 19.33 + (3.78 \times \text{V}),$$

where V is the hypothetical "volume of distribution." The y-intercept of this regression, 19.33 ml/min, may seem small, but in small children it represents a relatively greater contribution to ERPF, and in some of our smallest children with poor renal function, the intercept alone formed the largest contribution to their ERPF. If the regression were in terms of normalized ERPF, then the contribution of the intercept would be the same for everyone, and it would not be unduly magnified in small children for whom there is a large multiplication factor used to convert standard to normalized GFR or ERPF.

This problem with the intercept is only one aspect of a generalized problem which is that the goal and mathematical function of any regression formula is to minimize the error for the quantity of interest. Since we are actually interested in the estimation of normalized GFR, we may as well try to minimize that error. For example, in our work with estimating GFR from the renogram, we found that even though there was a higher correlation for estimating GFR than normalized GFR, the latter served to estimate normalized GFR more accurately. This was particularly apparent in those children below 10 kg for whom the error of prediction was twice as great if GFR were first estimated and that result was then normalized for body surface area, as compared to using a direct regression for normalized GFR. Additionally, expressing results directly as normalized GFR would allow us to more easily assess the ability of these methods to estimate renal function without the compounding effects of variation in subject size. Suppose, for example, that a method of "estimating GFR" did nothing other than predict that everyone had the mean normalized GFR for that population. If we plotted out the results in terms of normalized GFR, it would be clear that we predicted only the mean, and that our flat line "regression" explained none of the population variance about the mean. But now suppose that for the

same method we were to plot out the results in terms of simple GFR, not normalized for surface area. We would now get a plot that had the smallest children near the origin and the larger children in the upper right hand part of the graph. There would be some variation around the line due to unaccounted for variation in actual renal function (normalized GFR), but that component of variance due to variation in patient size would still leave us with a clear correlation between actual and "predicted" GFR. How high this correlation would be depends on the relative variance of subject size and renal function. In the case of the current report by Ham and Piepsz (*1*), it is highly unlikely that their excellent results are an artifact of variation in subject size, since the regressions were not drawn across the entire pediatric age group, but rather were broken into six age groups, and within each of these, the correlations were still excellent.

So where have we been and where are we going? There are a large number of techniques for estimating GFR and ERPF, the multiplicity of which is a striking tribute to the probability that none have been ideal. Piepsz, Ham et al. (*2,3*) provided us with one of the theoretically best approaches to estimating GFR from the scintigraphic data, although some of its complexities have prevented widespread utilization. More recent methods, which include correction for intrarenal vascular activity (*6*), are of great interest and further validation would be desirable. In general, however, scintigraphic methods have not been found to be as accurate as the blood sample methods, and there is growing consensus that the blood sample methods are the preferred way of measuring renal function. Although not quite as accurate as double-exponential analysis, the "two-sample" or modified single-exponential techniques are quite dependable and coupled with their relative ease of performance can be routinely utilized in most clinical settings. To simplify this even further to a single sample would also be desirable, and the current study by Ham and Piepsz (*1*) suggests its plausibility. If these findings can be substantiated not only with ^{51}Cr-EDTA but also with ^{99m}Tc-DTPA, then we may finally have an easy and accurate method of evaluating single kidney GFR, with differential function derived from the renogram, and total GFR from a single sample. This sounds good enough to suspect that it would also be a system to which everyone could agree and that finally there would be uniformity on the way that studies are performed. If this were a few years ago, it may have been true, but now we will have another choice to make: whether to use ^{99m}Tc-DTPA for its GFR data or switch to ^{99m}Tc-MAG$_3$. It appears that our ability to finally derive a simple and accurate method for estimating GFR may be outstripped by our ability to create new radiopharmaceuticals and thereby change the rules.

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REFERENCES

1. Ham HR, Piepsz A. Estimation of glomerular filtration rate in infants and in children using a single-plasma sample method. *J Nucl Med* 1991;32;1294–1297.
2. Piepsz A, Dobbeleir A, Erbsmann F. Measurement of separate kidney clearance by means of ^{99m}Tc-DTPA complex and a scintillation camera. *Eur J Nucl Med* 1977;2:173–177.
3. Piepsz A, Denis R, Ham HR, et al. A simple method for measuring separate glomerular filtration rate using a single injection of ^{99m}Tc-DTPA and the scintillation camera. *J Pediatr* 1987;93:769–774.
4. Gates GF. Glomerular filtration rate: estimation from fractional renal accumulation of ^{99m}Tc-DTPA (stannous). *AJR* 1982;138:565–570.
5. Shore RM, Koff SA, Mentser M. Glomerular filtration rate in children: determination from the Tc-99m-DTPA renogram. *Radiology* 1984;151:627–633.
6. Russell CD. A comparison of methods for GFR measurement using Tc-99m-DTPA and the gamma camera. Dubovsky EV, Gates GF, Russell CD. Three approaches to computer-assisted function studies of the kidney and evaluation of scintigraphic methods. In: Tauxe WN, Dubovsky EV, eds. *Nuclear medicine in clinical urology and nephrology.* Norwalk, CT: Appleton-Century-Crofts; 1985:173–189.
7. Ginjaume M, Casey M, Barker F, Duffy G. Measurement of glomerular filtration rate using technetium-99m DTPA [Letter]. *J Nucl Med* 1985;26:1347–1348.
8. Chachati A, Meyers A, Godon JP, Rigo P. Rapid method for the measurement of differential renal function: validation. *J Nucl Med* 1987;28:829–836.
9. Mulligan JS, Blue PW, Hasbargen JA. Methods for measuring GFR with technetium-99m-DTPA: an analysis of several common methods. *J Nucl Med* 1990;31:1211–1219.
10. Goates JJ, Morton KA, Whooten WW, et al. Comparison of methods for calculating glomerular filtration rate: technetium-99m-DTPA scintigraphic analysis, protein-free, and whole-plasma clearance of technetium-99m-DTPA and iodine-125-iothalamate clearance. *J Nucl Med* 1990;31:424–429.
11. Sapirstein LA, Vidt DC, Mandel MT, et al. Volume of distribution and clearance of intravenously injected creatinine in the dog. *Am J Physiol* 1955;181:330–336.
12. Chantler C, Garnett ES, Parsons V, Veall N. Glomerular filtration rate measurement in man by the single injection method using ^{51}Cr-EDTA. *Clin Sci* 1969;37:169–180.
13. Russell C, Bischoff P, Kontzen F, et al. Measurement of glomerular filtration rate: single injection plasma clearance method without urine collection. *J Nucl Med* 1985;26:1243–1247.
14. Tauxe WN, Maher FT, Taylor WF. Effective renal plasma flow: estimation from theoretical volumes of distribution of intravenously injected I-131-orthoiodohippurate. *Mayo Clin Proc* 1971;46:524–531.
15. Fawdry RM, Gruenewald SM. Three-hour volume of distribution method: an accurate simplified method of glomerular filtration rate measurement. *J Nucl Med* 1978;28:510–513.
16. Tauxe WN. Determination of glomerular filtration rate by single plasma sampling technique following injection of radioiodinated diatrizoate. *J Nucl Med* 1986;27:45–50.
17. Tauxe WN, Ansuman B, Tepe PG, Krishnaiah PR. Single-sample method for the estimation of glomerular filtration rate in children. *J. Nucl Med* 1987;28:366–371.
18. Groth S, Aasted M. Cr-51-EDTA clearance determined by one plasma sample in children. *Clin Physiol* 1984;4:75–83.
19. Waller DG, Keast CM, Fleming JS, Ackery DM. Measurement of glomerular filtration rate with technetium-99m-DTPA: comparison of plasma clearance techniques. *J Nucl Med* 1987;28:372–377.
20. Tauxe WN, Hagge W, Stickler GB. Estimation of effective renal plasma flow in children by use of a single plasma sample after injection of orthoiodohippurate. In: *Dynamic studies with radioisotopes in medicine, volume 1.* Vienna: International Atomic Energy Agency; 1974:265–275.