was equal or above 10 ng/ml during T4 treatment at suppressive doses (*1*). In these patients, infraclinical thyroid abnormalities should be sought by neck ultrasound, as shown in our series (Table 1). These infraclinical nodules may be benign or malignant, but their high incidence argues for performing initially at total thyroidectomy.

Finally, the conclusion that Tg determination cannot replace the WBS is based on the use of a given commercial kit and may be not valid for other methods of Tg measurement (*2–4*). In fact, these two methods of follow-up should be combined (*2–6*).

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Single Plasma GFR in Children

TO THE EDITOR Ham and Piepsz (*1*) showed in their recent article that measurement of glomerular filtration rate (GFR) from a single sample taken 2 hr after ^{51}Cr-EDTA injection correlated very closely with the value calculated from the slope/intercept method using samples at 2 and 4 hr. Since they expressed clearance without scaling for body surface area, it is not clear from their population of children how many had poor renal function, although they made the point that single sample techniques have usually not performed well at low renal function.

This question of function is rather critical because if the value of the rate constant of the slope (i.e., "α") is between about 0.005 min^{-1} and 0.012 min^{-1}, then the 2-hr single-sample clearance *automatically* correlates closely with the double-sample clearance. In other words, it does not really matter where the second point lies in relation to the first point if the y-axis value of the second point is between values that would give an α of between about 0.005 and 0.012 min^{-1}. This is because any error in α is counterbalanced by the resulting zero time plasma concentration. This is illustrated in Figure 1. By fixing the 2-hr plasma concentration at a nominal constant value, a set of clearances can be calculated by varying the second point to give a range of slope rate constants. The subsequent relationship between the calculated clearances and α is shown in Figure 2.

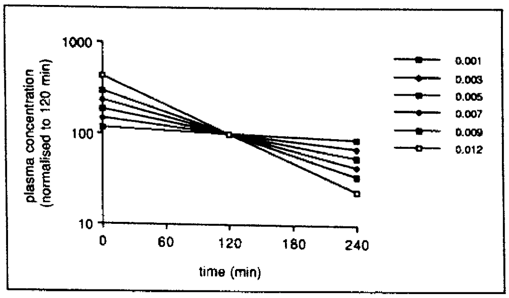

FIGURE 1. Range of values of zero time plasma concentration, which is the denominator in clearance calculation (Equation 1), corresponding to a range of values of α (min^{-1}), which is the numerator. As α increases, the zero time concentration decreases.

It can be seen from Figure 2 that with the two-sample slope/intercept method and the first sample taken at 2 hr, the maximum clearance is obtained when α is 0.0083 min^{-1}; any value of α above or below this figure gives a lower clearance. For values of α lower than about 0.005 min^{-1}, calculated clearance falls appropriately, and the tendency for automatic correlation between single sample and double sample clearances disappears. Hence the critical nature of reduced renal function.

The relationship between clearance and α, as shown in Figure 2, has previously been intimated by Waller et al. (*2*) and by Fawdry and Gruenewald(*3*). Both these groups demonstrated, on theoretical grounds, that the relationship between clearance and the 2-hr apparent, time-dependent, volume of distribution was almost linear at values of t chosen to suit the range of encountered

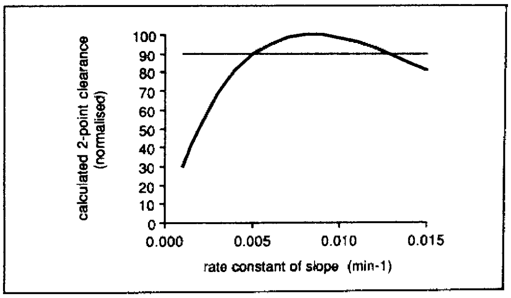

FIGURE 2. Relationship between clearance (C), calculated from the 2-point slope/intercept method, and the rate constant, α, of the slope. The y-axis has been normalized to the maximum value. The horizontal line defines the values of α which give a calculated clearance to within 10% of the maximum. The curve defined by the bold line is given by:

$$C = k \cdot \alpha \cdot e^{-\alpha t} \quad \text{Eq. 1}$$

where

$$k = \text{constant} \times \text{dose} \quad \text{Eq. 2}$$

Therefore

$$dC/d\alpha = k \cdot e^{-\alpha t} - k \cdot \alpha \cdot t \cdot e^{-\alpha t} \quad \text{Eq. 3}$$

when

$$dC/d\alpha = 0, \text{ C is maximal, whereupon } \alpha = 1/t \quad \text{Eq. 4}$$

So, for t = 120 min, maximal calculated two-point clearance is obtained when $\alpha = 0.0083\ min^{-1}$.

clearances. Thus, for poor renal function, t should be greater than 3 hr.

So, when using the slope/intercept method and two plasma samples, the factor which most critically determines the value of clearance is the concentration in the first plasma sample, or, in other words, it is the zero time intercept, and not the slope, that is important. Previous validation of the slope/intercept method against the gold standard multiple sample method has essentially been in adults. In order to demonstrate that the single-sample technique of GFR measurement is acceptable for children, the single- *or* double-sample method must be compared with the multiple-sample technique in a pediatric population.

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REPLY: We wonder whether Drs. Peters and Myers have thoroughly read our article (*1*). In their opinion, it was not clear from the data presented how many children had poor renal function. In fact, this can easily be deduced from Table 1 and Figure 1, where for each age group, the range of clearance values scaled for body surface area and the distribution of clearance values are presented. Furthermore, they underlined the importance of the slope (λ) in the accuracy of single sample method. They seemed to ignore that this point has also been stressed in our manuscript. It was clearly indicated that the relationship between distribution volume at time t and double sample clearance follows a precise function, which is $\lambda \cdot e{-}\lambda t$, and, hence, is dependent on the values of λ in the population studied. We did not develop this point in detail because it has already been done previously by several other authors (*2–3*). We prefer to refer the readers to these original works instead of copying their data and incorporating them in our work.

Concerning the use of the double-sample technique in the pediatric population, we include in the references to this reply some papers that could be useful to Drs. Peters and Myers (*4–6*).

We would like to take this opportunity to thank Dr. Shore for his thoughtful editorial (*7*). We agree with Dr. Shore that theoretically it is preferable to estimate normalized GFR directly (direct estimate) rather than to estimate the true GFR first and then normalize the results for body surface area (indirect estimate). However, in practice, *when using the 120th minute blood sample*, indirect estimate gives significantly better results. Indeed, using the same methodology and population as in our manuscript (*1*), we have compared the correlation between direct and indirect estimates versus BSA normalized slope clearance. The indirect estimate was obtained by estimating the true GFR first and by normalizing the results afterwards whereas the direct estimate was obtained by estimating directly normalized GFR by using the best age specific converting formula. The results presented in Table 1 indicate that direct estimation requires different converting formulae to be used in each age group of children. Furthermore, even when using the best age-specific converting formula, the standard error of estimate obtained in each age group is much larger than that observed when we estimate the true GFR first and then normalize the results (indirect estimate).

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TABLE 1
Correlation Between Estimate and Slope Clearance

		Indirect estimation			Direct estimation		
Age group	n	Converting formula	r	s.e.e.	Converting formula	r	s.e.e.
<1 yr	67	cl = 2.60 (VD120) − 0.27	0.99	3.68	cl = 7.88 (VD120) + 31.9	0.93	8.87
1.00–1.99 yr	41	cl = 2.60 (VD120) − 0.27	0.99	3.07	cl = 7.18 (VD120) + 24.3	0.91	9.91
2.00–3.99 yr	46	cl = 2.60 (VD120) − 0.27	0.99	2.44	cl = 6.32 (VD120) + 19.4	0.95	9.46
4.00–5.99 yr	47	cl = 2.60 (VD120) − 0.27	0.99	3.19	cl = 5.58 (VD120) + 7.7	0.95	10.17
6.00–9.99 yr	58	cl = 2.60 (VD120) − 0.27	0.99	3.76	cl = 3.56 (VD120) + 26.0	0.90	12.72
10.00–14.99 yr	68	cl = 2.60 (VD120) − 0.27	0.99	4.14	cl = 2.58 (VD120) + 27.2	0.87	18.75