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# Normalization of Glomerular Filtration Rate in Children: Body Surface Area, Body Weight or Extracellular Fluid Volume?

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Glomerular filtration rate (GFR) is usually expressed in relation to body surface area (BSA) for standardization and comparison between individuals of different sizes, although relating it to extracellular fluid volume (ECV) is technically much simpler because the ratio GFR/ECV is almost equal to the rate constant of the second exponential of the  $^{51}\text{Cr}$ -EDTA plasma clearance curve. The aim of this study was to investigate the physiological validity of expressing GFR in relation to ECV by comparing it with GFR normalized for BSA and body weight. **Methods:** GFR was measured from a five-sample  $^{51}\text{Cr}$ -EDTA plasma clearance curve. After appropriate scaling, the rate constant of the terminal exponential is equal to GFR/ECV. **Results:** GFR normalized by any of the three variables increased between 0–6 mo, but was less in the case of GFR/weight compared with the other two. From 6 to 24 mo, GFR/BSA continued to increase, whereas GFR/ECV and, in particular, GFR/weight remained relatively constant. It appears that as the child grows to age 6 mo, weight outstrips BSA and ECV but is followed by GFR. From 6 to 24 mo, weight, ECV and GFR increase at a faster rate than BSA. By applying regression analysis to the curves of GFR and its normalization variables versus age, expected (e) and relative (r, i.e., observed/expected) values were obtained for each patient. In the age group 6–24 mo, but not 0–6 mo,  $r[\text{GFR}/\text{ECV}]$  was significantly closer to  $e[\text{GFR}/\text{ECV}]$  than the corresponding comparisons with r and  $e[\text{GFR}/\text{BSA}]$  ( $p < 0.001$ ) and r and  $e[\text{GFR}/\text{weight}]$  ( $p < 0.002$ ), supporting the hypothesis that as ECV deviates from the expected value for the patient's age, it tends to be followed by GFR. **Conclusion:** Our data show that ECV is the optimal normalization variable in children, particularly those over the age of 6 mo.

**Key Words:** glomerular filtration rate; chromium-51-EDTA; extracellular fluid volume

*J Nucl Med* 1994; 35:438–444

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**F**or the comparison of glomerular filtration rate (GFR) between individuals of different sizes, body surface area (BSA) is the usual variable used to scale GFR (1). Alter-

native variables relating to body size for normalizing GFR include body weight and volumes of body fluid compartments: plasma, extracellular fluid and total body water. Weight and BSA are easy to measure, although the latter relies on the accuracy of conversion tables. Body fluid volumes are difficult to measure accurately, are not as convenient as weight and BSA and are little used as normalization variables. Indeed, if GFR is measured by the gold standard technique of urinary inulin clearance, measurement of a body fluid volume would require the use of a separate tracer.

When GFR, however, is measured by the now widely accepted technique based on the plasma clearance of filtration markers following bolus intravenous injection (2), such as  $^{99\text{m}}\text{Tc}$ -DTPA,  $^{51}\text{Cr}$ -EDTA and, of course, inulin, then extracellular fluid volume (ECV), or at least the volume of distribution of the marker, becomes available as a convenient normalization variable for GFR. This is because, for each of these markers, the reciprocal of the mean residence time within its volume of distribution is equal to the plasma clearance divided by the distribution volume, and very nearly equal to the rate constant of the terminal exponential of the plasma clearance curve (3). In other words, insofar as the distribution volume is equal to the ECV and the plasma clearance to the GFR, the ratio GFR/ECV can easily be obtained without separate measurement of either of its components using these markers. This approach to the quantification of GFR is technically very simple and, if  $^{99\text{m}}\text{Tc}$ -DTPA is used, potentially does not even require any blood sampling (4). However, before it can come into routine use as a measurement of GFR, the physiological validity of expressing GFR in terms of ECV in comparison with BSA needs to be established.

One group of subjects in whom it might be possible to compare the physiological validity of normalization variables for GFR is the very young, because, as a result of normal maturation, GFR increases rapidly between birth and age two. They therefore provide an opportunity to see which of the normalization variables is most closely followed by GFR, assuming they increase at measurably different rates from each other. One of us, R.S., was in possession of a very large, well-documented database of

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Received Aug. 17, 1993; revision accepted Nov. 15, 1993.  
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GFR measurements using  $^{51}\text{Cr}$ -EDTA in children between the ages of birth and 2 yr. With the ultimate aim of justifying the physiological validity of expressing GFR in terms of ECV, we set out to compare increases in GFR with those of BSA, body weight and ECV, and to determine how these normalization variables deviated from their expected values, based on age, in those children in whom GFR deviated from the age-based expected value.

## METHODS

The database comprised 1058 GFR measurements using  $^{51}\text{Cr}$ -EDTA in 633 children up to the age of 2 yr that were performed between 1974 and 1991. Indications for the study were varied and in a database of this size a breakdown of the indications is rather difficult and not very helpful.

Following injection of  $^{51}\text{Cr}$ -EDTA (Amersham, Sweden, AB; dose, 1 or 2  $\mu\text{Ci}/\text{kg}$ , depending on anticipated renal function), blood samples were taken at 5, 15, 60, 90 and 120 min (5) and the plasma counted for  $^{51}\text{Cr}$  in a well-counter. Global GFR was calculated as the ratio of the dose to the area under the plasma clearance curve (5,6). This was treated as bi-exponential, with the second exponential based on a least-squares fit to the data points at 60, 90 and 120 min, and the first on the samples at 5 and 15 min after subtraction of the terminal exponential. The timing of the three samples from which the second exponential was derived is based on the method of Brochner-Mortensen et al. (5) and is somewhat earlier than the timing in adults (6,7).

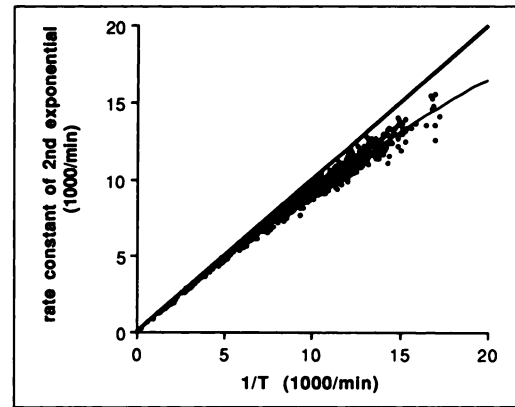
Only studies with a complete set of data were included, which resulted in the elimination of 11 studies. In view of the large size of the database, we felt that we could afford to omit data of suboptimal quality, so further exclusions were 130 studies (of which 49 were of patients 0–6 mo in age) in which the correlation coefficient,  $R$ , of the fit of the terminal exponential to the data points at 60, 90 and 120 min was less than 0.99. This left a total of 917 studies. In view of the fact that the failing kidney will be unlikely to respond to changes in body fluid volumes, 35 patients with a value of GFR/BSA which was more than 2 s.d. below the expected value for a patient of the same age (see below) were also eliminated, because we felt these would make no contribution to the aim of the study. Another 16 with values greater than 2 s.d. above the expected value were also excluded, leaving a total of 866 studies (of which 179 were in patients 0–6 mo in age).

GFR was normalized according to BSA and body weight (normalized GFR). BSA was calculated according to the formula of Haycock et al. (8). GFR normalized for ECV (i.e., the ratio GFR/ECV) was taken as the rate constant,  $\alpha_2$ , of the second exponential with scaling as described by Peters (3). Briefly, the scaling factor takes into account the fact that, with increasing values of  $\alpha_2$ , there is an increasing concentration gradient between extravascular extracellular fluid and plasma (9), and, as a result, an increasing difference between GFR/ECV and  $\alpha_2$ . The scaling factor therefore increases with increasing  $\alpha_2$ .

GFR/ECV was also calculated as the reciprocal of the mean residence time,  $T$ , of  $^{51}\text{Cr}$ -EDTA within the extracellular fluid (3,9):

$$T = \frac{A/\alpha_1^2 + B/\alpha_2^2}{A/\alpha_1 + B/\alpha_2}, \quad \text{Eq. 1}$$

where  $A$  and  $B$  are the zero time intercepts of the two exponentials and  $\alpha_1$  and  $\alpha_2$ , their corresponding rate constants. The rela-



**FIGURE 1.** Correlation between “true” GFR/ECV (measured as the reciprocal of the mean transit time,  $T$ , of  $^{51}\text{Cr}$ -EDTA through the ECV) and the rate constant,  $\alpha_2$ , of the second exponential of the  $^{51}\text{Cr}$ -EDTA plasma clearance curve. The bold line is the line of identity and the faint line the best fit second order polynomial ( $y = -0.036 + 1.022x - 0.0096x^2$ ).

tionship between  $1/T$  and  $\alpha_2$ , without excluding patients with GFR/ECV above or below 2 s.d. of the expected value, is shown in Figure 1. With increasing filtration function,  $\alpha_2$  increasingly underestimates  $1/T$ . This underestimation can be quantified using a second order polynomial fit analogously to that described by Brochner-Mortensen (10) for scaling GFR based on the terminal exponential of the  $^{51}\text{Cr}$ -EDTA plasma clearance. Rather than use a scaling factor for  $\alpha_2$  based on the data in Figure 1, we used the factor derived from adults by Peters (3) as already stated above because we felt that the 5-min plasma sample in the current study might, if equilibrium in the forearm had not occurred by 5 min (11), lead to an underestimation of the area under the first exponential and thereby to a scaling factor which was too small. In any event, GFR/ECV calculated by scaling  $\alpha_2$  with a factor based on adult data correlated very closely with  $1/T$ , so that the two are interchangeable:  $\text{GFR/ECV} = 1.02/T + 0.15 \cdot 10^{-3} \text{ min}^{-1}$  ( $r = 0.99$ ). No independent measurement of ECV was available, and so ECV was calculated as the ratio of scaled  $\alpha_2$  and absolute GFR (i.e., as the product,  $T \times \text{GFR}$ ). ECV was then normalized for BSA and body weight.

## Analysis

It became evident from the relationships of age with normalized GFR and with normalized ECV (see Figs. 4 and 5), which showed bi-phasic relationships with age, that there was a strong case for analyzing patients aged 0–6 mo separately from those aged 6–24 mo. Accordingly, linear regression analysis was applied to the relationships of these variables with age separately in the two age groups so that, for any variable, an expected value could be calculated as the sum ( $bx + a$ ) where  $b$  is the gradient of the linear relationship,  $x$  is age and  $a$  is the corresponding zero time intercept of the linear regression. Having obtained the expected value for any given variable, it was then divided into the observed value of that variable to derive a relative value (i.e., observed/expected). A relative value of unity means that the patient has a value for that variable which is equal to the expected value for his/her age. Thus, normalized, expected and relative variables, are defined respectively abbreviated as  $n$ ,  $e$  and  $r$  and prefixed to the variables.

The database was used to extract the following information:

1. The relationship between age and the absolute values of GFR, BSA, weight and ECV. As mentioned, linear regression was separately applied to patients 0–6 mo in age and patients 6–24 mo in age, with calculation of expected values of these four variables.
2. The relationship between age and nGFR using the three normalization variables, ECV, BSA and weight. Linear regression was applied to each value of nGFR versus age in the groups 0–6 mo and 6–24 mo. This enables an assessment of the tendencies of GFR to follow each of the three normalization variables, presupposing that the shapes of nGFR versus age are distinguishable from each other.
3. The relationship between age and nECV. This is essentially another way of looking at paragraph 2.
4. The tendencies for rGFR to follow rECV, rweight and rBSA as they deviate from their corresponding expected values. This examines the physiological coupling that may exist between GFR and the three normalization variables. Thus, if a change in ECV was followed by a corresponding change in GFR but not in BSA, then  $r[GFR/ECV]$  would generally be closer to unity, or deviate less from unity, than the corresponding value of  $r[GFR/BSA]$ , and the mean deviation of  $r[GFR/ECV]$  from unity for a group as a whole would be significantly less than the mean deviation of  $r[GFR/BSA]$ .

These analytical approaches are complicated by the potential for artificial correlation between GFR and ECV, which arises from the disadvantage of not having an independent measurement of ECV. Thus, errors in GFR will be passed on as errors in ECV, since ECV is taken as the product,  $GFR \cdot T$ . Nevertheless, useful comparisons are still possible between the two age groups, and body weight can be taken as an approximate index of ECV. This allows us to seek a correlation between relative weight and the difference between  $r[GFR/BSA]$  and  $r[GFR/ECV]$  as a means of testing the hypothesis that, as ECV increases (or decreases), so does GFR, thereby tending to maintain  $r[GFR/ECV]$ , but not necessarily  $r[GFR/BSA]$ , close to unity.

Certain other pitfalls exist which might also bias the results. These include a possible tendency for  $\alpha_2$  to change systematically with age if it were the case that equilibrium (i.e., the time at which mixing throughout the ECV is complete and the clearance curve becomes a single exponential) had not been established by 60 min, and that the time to equilibrium changed with age. The timing of the samples was somewhat earlier than the conventional timing for the terminal exponential, although equilibrium is in fact nearly completed by 60 min, even in adults. Nevertheless, we examined the “straightness” of the terminal exponential (on semi-logarithmic axes) by comparing the natural logarithm of the ratio of the plasma concentrations at 60 and 90 min with the corresponding natural logarithm of the ratio between 90 and 120 min. If the clearance had not reached a single exponential by 60 min, then  $\log_e$  of the ratio of concentrations at 60 and 90 min ( $\ln[C_{60}/C_{90}]$ ) would be greater than the corresponding  $\log_e$  ratio for 90 and 120 min ( $\ln[C_{90}/C_{120}]$ ). In other words, the logarithmic gradient based on 60 and 90 min would be greater than that based on 90 and 120 min.

### Statistics

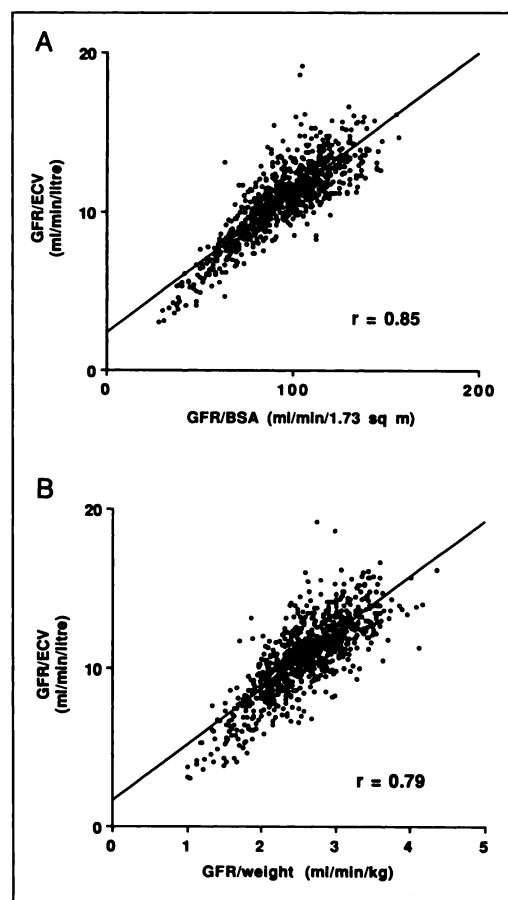
Linear regression analysis was applied to the relationships between age and GFR, nGFR, ECV, nECV, weight and BSA. In each case, the age-related rate of change was expressed as a percentage of the value at 6 mo per year. For comparisons between deviations of relative nGFR from unity, a paired Student's

t-test was used. It is worth noting that with such large patient numbers, even apparently low correlation coefficients may be highly significant.

### RESULTS

There was a moderately good correlation between GFR/ECV and GFR/BSA in both age groups combined (Fig. 2A):  $GFR/ECV = 0.089 \cdot GFR/BSA + 2.3$  ml/min/liter ( $r = 0.85$ ,  $n = 866$ ). The correlation between GFR/ECV and GFR/weight was similarly close (Fig. 2B):  $GFR/ECV = 3.5 \cdot GFR/weight + 1.57$  ml/min/liter ( $r = 0.79$ ,  $n = 866$ ). The corresponding correlations in the two separate age groups were also close but had different regressions. In the 0–6 mo group,  $GFR/ECV = 0.11 \cdot GFR/BSA + 0.54$  ml/min/liter ( $r = 0.9$ ) =  $3.6 \cdot GFR/weight + 0.38$  ml/min/liter ( $r = 0.83$ ), while in the 6–24 mo group,  $GFR/ECV = 0.078 \cdot GFR/BSA + 3.49$  ml/min/liter ( $r = 0.76$ ) =  $2.9 \cdot GFR/weight + 3.34$  ml/min/liter ( $r = 0.74$ ).

The rates of increase of GFR, ECV, BSA and weight with age are illustrated in Figure 3 and summarized in Table 1. Of the normalization variables, weight increased the fastest between 0 and 6 mo (109% of the value at 6 mo per year,  $r = 0.8$ ,  $n = 179$ ); ECV increased the slowest (69%,  $r = 0.62$ ). GFR, on the other hand, increased by



**FIGURE 2.** Relationships between normalized GFR in children aged 0–24 mo. (A) GFR/BSA and GFR/ECV; (B) GFR/weight and GFR/ECV. Regression lines are shown.

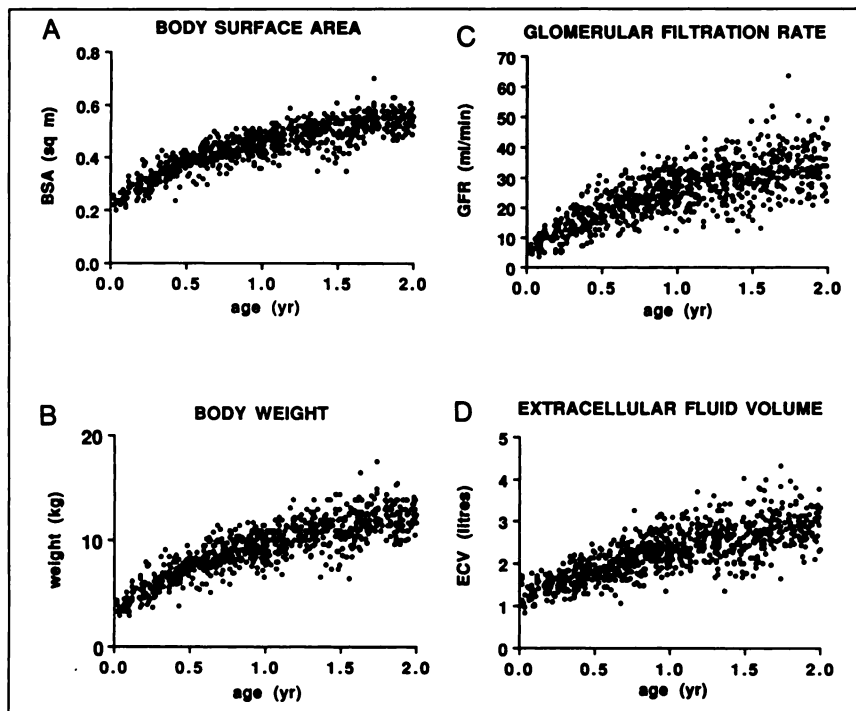


FIGURE 3. Relationships between age and (A) BSA, (B) weight, (C) GFR and (D) ECV in children aged 0–24 mo.

137% of the 6-mo value per year ( $r = 0.7$ ) and BSA by 83% ( $r = 0.83$ ). Between 6 and 24 mo, GFR continued to increase at a faster rate (51% of the 6-mo value,  $r = 0.6$ ,  $n = 687$ ) than any of its normalization variables: weight 40% ( $r = 0.73$ ), ECV 36% ( $r = 0.62$ ) and BSA 28% ( $r = 0.78$ ).

Normalized GFR increased at a faster rate between 0–6 mo than between 6–24 mo (Table 1, Fig. 4). From 0–6 mo, GFR/ECV showed the greatest rate of increase (95% of the value at 6 mo per year,  $r = 0.58$ ,  $n = 179$ ), and GFR/weight showed the slowest rate of increase (52%,  $r = 0.33$ ,  $p < 0.001$ ). GFR/BSA increased by 85% of the 6-mo value per year ( $r = 0.52$ ). From 6 to 24 mo, GFR/BSA increased at a rate of 16% of the 6-mo value per year ( $r = 0.32$ ,  $n = 687$ ,  $p < 0.001$ ), which is significantly faster than either GFR/ECV (9.1%,  $r = 0.21$ ,  $p < 0.001$ ) or GFR/weight (6.5%,  $r = 0.15$ ,  $n = 687$ ,  $p < 0.001$ ).

These age-related increases are reflected in the age-related increases in normalized ECV (Table 1, Fig. 5). Thus, ECV/weight decreased rather sharply between 0–6 mo (–87% of the value at 6 mo,  $r = -0.62$ ,  $n = 179$ ) and then only slightly between 6 and 24 mo (–2.4%,  $r = -0.084$ ,  $n = 687$ ,  $p < 0.02$ ). ECV/BSA looked almost flat between 0–24 mo, although, between 0–6 mo, there was a significant decrease of 23% ( $r = -0.26$ ,  $n = 179$ ,  $p < 0.001$ ) followed by a significant increase of 5.9% ( $r = 0.2$ ,  $n = 687$ ,  $p < 0.001$ ) between 6–24 mo.

$r[\text{GFR}/\text{ECV}]$  was significantly closer to  $e[\text{GFR}/\text{ECV}]$  (i.e., unity) than  $r[\text{GFR}/\text{BSA}]$  to  $e[\text{GFR}/\text{BSA}]$  in the 6–24-mo group but not in the 0–6-mo group (Table 2). Thus, in the 6–24 mo group, the mean deviation from unity of  $r[\text{GFR}/\text{ECV}]$  was 0.13 (0.11), which is significantly less ( $p < 0.001$ ) than the deviation of  $r[\text{GFR}/\text{BSA}]$ , which was 0.15 (0.11). In the 0–6-mo group, corresponding respective

mean deviations were 0.2 (0.13) and 0.19 (0.14). The same was true when BSA was replaced by weight.

In view of the finding that ECV/weight was relatively constant, while ECV/BSA increased with age in the 6–24-mo group, relative weight can be used as an approximate index of ECV. The difference,  $r[\text{GFR}/\text{BSA}] - r[\text{GFR}/\text{ECV}]$ , correlated significantly and positively with relative weight ( $r = 0.16$ ,  $n = 687$ ,  $p < 0.001$ ) in spite of the fact that weight is a component of the denominator of the first term in the difference, whereas no corresponding correlation was seen in age group 0–6 mo ( $r = 0$ ). By means of a comparison with relative weight as an index of ECV, no correlation was seen when the difference  $r[\text{GFR}/\text{BSA}] - r[\text{GFR}/\text{ECV}]$  was compared with patient age ( $r = 0$ ).

When it was based on plasma  $^{51}\text{Cr}$ -EDTA concentrations at 60 and 90 min only, the gradient of the terminal exponential,  $\alpha_2$ , was 15% (s.d. 34) greater than when it was

TABLE 1  
Increases in GFR, Normalization Variables and Normalized GFR and ECV with age (Expressed as %6 Month Value/Year)

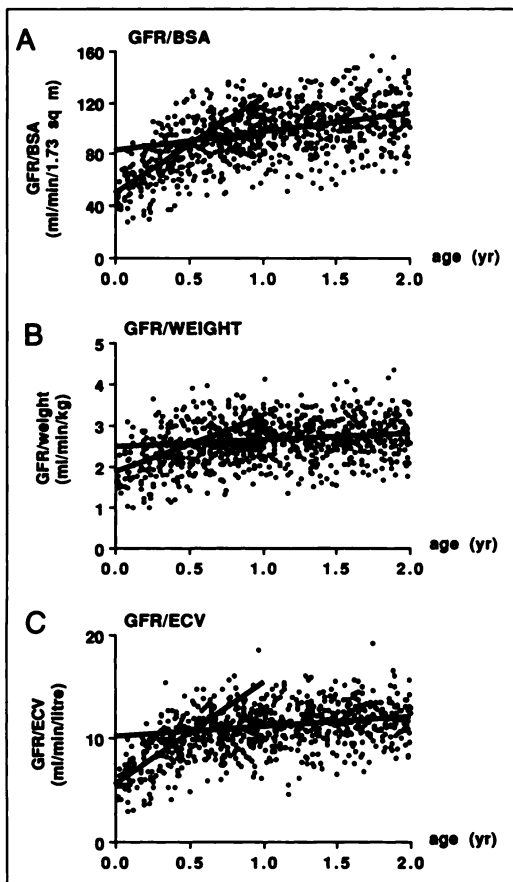
	0–6 mo	6–24 mo
GFR	137	51
BSA	83	28
Weight	109	40
ECV	69	36
GFR/BSA	85	16
GFR/Weight	52	6.5
GFR/ECV	95	9.1
ECV/BSA	–23	5.9
ECV/Weight	–87	–2.4

based on the concentrations at 90 and 120 min ( $p < 0.001$ ). This overestimation showed a trend towards correlating with age, but it was not significant. Nor did it correlate with renal function (expressed as  $\alpha_2$ ), or with the correlation coefficient ("goodness") of the fit of the terminal exponential to the three data points, even when those patients with a correlation coefficient of less than 0.99 for the fit (otherwise excluded) were included.

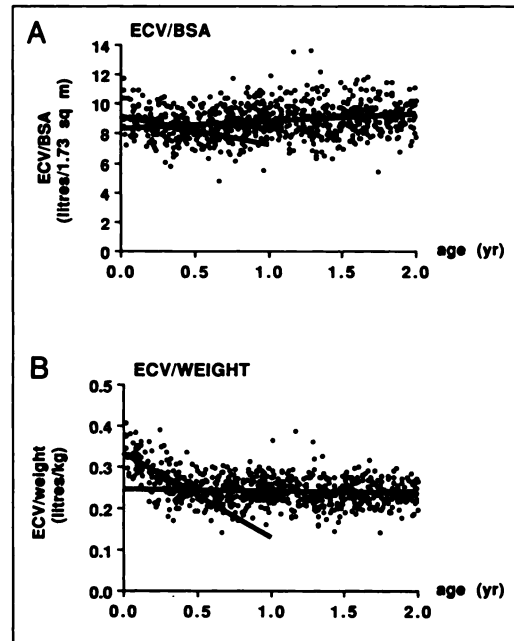
## DISCUSSION

BSA became established as an index of body size for comparison with GFR because, along with basal metabolic rate, it correlates closely with kidney size (12,13). Nevertheless, good physiological arguments have been advanced to support the use of body fluid volumes for normalizing GFR, particularly total body water, and also ECV (3,13,14) and, related to these, lean body mass (15). Firm physiological validation, particularly for ECV, has, however, been lacking. Because of their rapidly increasing size and renal maturation, infants may give some insight into the relative merits of some normalization variables. We have therefore compared weight, BSA and ECV in such a population.

Before discussing further the potential merit of ECV as



**FIGURE 4.** Relationship between age and normalized GFR in children aged 0–24 mo. (A) GFR/BSA; (B) GFR/weight; and (C) GFR/ECV. Separate regression slopes are shown for 0–6 mo and 6–24 mo, respectively.



**FIGURE 5.** Relationships between age and (A) ECV/BSA and (B) ECV/weight in children aged 0–24 mo. Separate regression slopes are shown for 0–6 mo and 6–24 mo, respectively.

a normalization variable for GFR, it should be appreciated that it is not an easily definable discrete volume, but a function of the tracer used to measure it (16). For instance, inulin, on account of its size (MW 6000), has a smaller distribution volume than  $^{51}\text{Cr-EDTA}$  (MW 342) or  $^{99\text{m}}\text{Tc-DTPA}$  (MW 492), which in turn have smaller distribution volumes than bromine. It is therefore more correct to say that the normalization variable used in this study is the  $^{51}\text{Cr-EDTA}$  distribution volume rather than ECV. Nevertheless, considering the range of distribution volumes given by different markers, ECV based on either  $^{51}\text{Cr-EDTA}$  or  $^{99\text{m}}\text{Tc-DTPA}$  distribution volume is a reasonably good marker for ECV, especially as the small solutes, bromine, sulphate and thiocyanate, show some degree of intracellular penetration, while the larger solutes, such as inulin, require a significantly longer period of equilibration (17). The attraction of expressing GFR in relation to the distribution volume of the marker used to measure it is that renal function is measured as the average time an individual molecule of the marker has to wait, after equilibration within its distribution volume, before it is filtered at the glomerulus.

**TABLE 2**  
Deviation from Unity of Relative Normalized GFR (s.d.)

	r[GFR/BSA]	r[GFR/weight]	r[GFR/ECV]
0–6 mo	0.19 (0.14)	0.19 (0.14)	0.2 (0.13)
6–24 mo	0.15 (0.11) <sup>†</sup>	0.15 (0.11) <sup>*</sup>	0.13 (0.11)

<sup>\*</sup> $p < 0.002$  versus r[GFR/ECV].

<sup>†</sup> $p < 0.001$  versus r[GFR/ECV].

GFR, expressed in terms of any of these three normalization variables, correlated well with GFR expressed in terms of either of the other two, and any one of these variables is generally likely to be adequate for routine clinical use. It is interesting to look further at the regression equations relating GFR/ECV to GFR/BSA. Thus, if we regard 125 ml/min and 12.5 liters (17) as the normal values of GFR and ECV respectively for an adult of 1.73 m<sup>2</sup>, then, whereas GFR/ECV would be 10 ml/min/liter in the adult, it would be considerably higher at 14.3 and 13.3 using the regression equations relating GFR/ECV and GFR/BSA based on the 0–6-mo and 6–24-mo age groups. These comparisons imply that GFR/ECV in young children tends to be similar to GFR/ECV in adults in contrast to GFR/BSA which is smaller in children. This is analogous to comparative values between adult males and females; thus while males have a higher GFR/BSA, GFR/ECV values are identical (18). On the other hand, the regression equations relating GFR/ECV to GFR/weight, using normal adult data (1.79 ml/kg), would give values of GFR/ECV less than expected in the adult: 6.75 and 8.7 ml/min/liter using equations from 0 to 6-mo and 6–24-mo age groups, respectively.

Within a routine referral population, it will be difficult to find advantages for any one of the normalization variables over the other two. Nevertheless, the size of the database did allow some interesting differences to emerge between the three normalization variables. Before further discussion, however, it is essential to appreciate that there is a risk of spurious correlations between variables that respectively include ECV and GFR without an independent measurement of ECV.

On the basis of the relationships observed between age and both normalized GFR and normalized ECV, it seemed justifiable to analyze children aged 0–6 mo separately from those aged 6–24 mo. ECV/weight was particularly striking in this respect in that it decreased quite sharply from 0 to 6 mo and then remained relatively constant thereafter. It is already known that infants have a higher ECV per unit body weight than adults (19). Indeed, it is reassuring that the technique described here for measuring ECV shows this well and gave ECV values in the newborn (of about 350 ml/kg) very similar to the values of Coulthard (20) using inulin, Shaffer et al. (21,22) using bromide and Bauer et al. (23) using sucrose. Compared with adults, very young children contain a high fraction of water, which gradually decreases as the kidneys mature. Early rapid renal maturation is also reflected by the relatively sharp increases in GFR/ECV and GFR/BSA and to a lesser extent, in GFR/weight. From birth to 24 mo, weight increases relatively more rapidly than either BSA or ECV, but all three variables are outstripped by GFR, particularly from 0 to 6 mo. This suggests weight is generally the optimal variable for normalizing GFR, particularly up to 6 mo, as previously suggested by Coulthard and Hey (24). BSA appeared to be the least suitable in that GFR/BSA showed the greatest rate of increase between 6–24 mo. GFR/ECV also increased with age at a greater rate than GFR/weight, imply-

ing that in this age group weight is the closest determinant of GFR.

Although the above comparisons of the maturation rates of normalized GFR give a strong clue as to which of the normalization variables most closely follows GFR, and is therefore the most appropriate, a closer scrutiny of how GFR responds to extremes in the normalization variables in individual patients should give a clearer view of their relative merits. We attempted to do this by expressing normalized GFR and the normalization variables themselves as quotients of the corresponding expected values based on patient age. We then compared corresponding deviations from unity of relative nGFR for all three normalization variables in each patient, arguing that the variable to which GFR was functionally most closely coupled would give values of normalized GFR with the smallest average deviation from unity, or, in other words, be least scattered about unity. Thus, if GFR changed in response to a change in ECV but not to a change in BSA, then GFR/ECV would tend to remain more closely clustered around the mean value for any particular patient age than GFR/BSA. This was observed in children 6–24 mo of age for GFR/ECV in comparison to GFR/BSA and, to a slightly lesser extent, in comparison to GFR/weight, but not in the 0–6-mo group. However, a bias towards this result is possible since, in contrast to GFR/ECV which is based on  $\alpha_2$  only, the calculation of absolute GFR requires several measurements and random errors tend to scatter GFR/BSA and GFR/weight from their respective age-expected values. Proof for the physiological validity of GFR/ECV therefore remains unestablished by this approach, even though much of the random scatter in GFR/BSA (and to a similar extent GFR/weight) would be removed by eliminating patients from the database with GFR/BSA values greater than 2 s.d. from the age-expected mean value.

An approach which will eliminate any remaining bias imposed by random error is to correlate the differences between  $r[\text{GFR/ECV}]$  and  $r[\text{GFR/BSA}]$  with an independent variable which reflects ECV, or, ideally, an independent measurement of ECV itself. For example, in acromegaly, GFR/BSA is elevated, whereas in hypopituitarism, it is decreased, although GFR/ECV is relatively normal in both (25). Thus, the tendency for GFR/ECV to remain more clustered around the normal value than GFR/BSA is not due to random error scattering GFR/BSA because the difference between  $r[\text{GFR/BSA}]$  and  $r[\text{GFR/ECV}]$  clearly correlates with pituitary status, or, more precisely, with ECV. Although we have no independent measurement of ECV in our patients, it can be seen from the mutual tendencies for GFR/weight and GFR/ECV to remain essentially constant between 6–24 mo that weight is a reasonable approximate index of ECV in much the same way as pituitary status is an index of ECV. The difference between  $r[\text{GFR/BSA}]$  and  $r[\text{GFR/ECV}]$  in individual patients was therefore correlated with relative weight. In spite of the fact that weight is part of the denominator of GFR/BSA, thereby tending to generate a spurious inverse correlation,

there was a positive significant correlation, confirming the tendency for GFR to follow ECV when the latter deviates from the age-expected value. In contrast, when  $r[\text{GFR}/\text{BSA}] - r[\text{GFR}/\text{ECV}]$  was correlated with age, the correlation coefficient was zero, excluding any age-related bias. It was not possible to adopt the same approach to the difference between  $r[\text{GFR}/\text{weight}]$  and  $r[\text{GFR}/\text{ECV}]$  because we have no alternative independent estimate of ECV. Nevertheless, the finding that the difference between relative and expected GFR/ECV was smaller than the difference between relative and expected GFR/weight to about the same extent compared with the difference between relative and expected GFR/BSA (see above) suggests that GFR follows ECV more closely than weight when they deviate from the age-expected values. It is also worth noting that the alternative possibility that ECV follows GFR, i.e. that ECV expands as a result of impaired renal function, is not compatible with the positive correlation between relative weight and  $r[\text{GFR}/\text{BSA}] - r[\text{GFR}/\text{ECV}]$  nor with the greater tendency for  $r[\text{GFR}/\text{ECV}]$  to be clustered around unity compared with  $r[\text{GFR}/\text{BSA}]$ .

The differences observed between the two age groups with respect to this significant tendency for GFR to be linked most closely to ECV is consistent with the hypothesis that the immature kidney (i.e., in patients less than 6 mo of age) is less able to adjust its GFR in response to changes in ECV. Nevertheless, other confounding factors need to be considered. One possibility is that there is incomplete mixing of  $^{51}\text{Cr}$ -EDTA within its distribution volume prior to the terminal exponential. Indeed, complete mixing is unlikely in view of the finding that the gradient of the terminal exponential,  $\alpha_2$ , was significantly greater when based on 60–90 min than 90–120 min (i.e.,  $\ln[C_{60}/C_{90}]$  was significantly greater than  $\ln[C_{90}/C_{120}]$ ). There was a tendency for this difference in gradients to increase with age, but it was weak and did not reach statistical significance. Thus, incomplete mixing, particularly in the 6–24-mo group, is an unlikely explanation for the differences in the two age groups. Another possibility is that, a significantly lower value of R in the 0–6-mo group when compared with the 6–24-mo group may have resulted in greater scatter in  $r[\text{GFR}/\text{ECV}]$  and consequently no difference in its deviation from unity compared with either  $r[\text{GFR}/\text{BSA}]$  or  $r[\text{GFR}/\text{weight}]$ . However, the difference between  $r[\text{GFR}/\text{BSA}]$  and  $r[\text{GFR}/\text{ECV}]$  showed no correlation whatsoever with either R or the ratio,  $\ln(C_{60}/C_{90})/\ln(C_{90}/C_{120})$ .

In conclusion, ECV is a physiologically valid variable against which to express GFR, and is probably preferable to BSA. We suggest that, although ECV and body weight are closely related, GFR tends to be linked to ECV more closely than weight, to which ECV may therefore also be preferable. Nevertheless, we have shown that ECV is valid as a normalization variable for GFR and that its obvious

technical advantages can therefore be exploited using  $^{51}\text{Cr}$ -EDTA or  $^{99\text{m}}\text{Tc}$ -DTPA.

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