Albumin Synthesis in Premature Infants: Determination of Turnover with [^{15}N]Glycine

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**ABSTRACT. Albumin turnover was studied in seven small
premature infants who received a constant infusion of [^{15}N]
glycine for 60–72 h. Gas chromatography-mass spectrom-
etry was used to measure the rate of appearance of [^{15}N]
glycine in albumin isolated from the blood. By comparing
the linear increment of [^{15}N]glycine in blood albumin with
plateau labelling of urinary [^{15}N]hippurate, which was as-
sumed to reflect intrahepatic isotopic abundance in [^{15}N]
glycine, the fractional synthetic rate for albumin was found
to be 0.09–0.177 day^{-1} (mean ± SD = 0.122 ± 0.041
day^{-1}). The absolute synthesis rate for albumin was 0.3 ±
0.099 g/dl plasma·day^{-1} and the total plasma synthetic
rate was 117.6 ± 37.0 mg/kg·day^{-1}. The glycine flux was
326.0–927.7 μmol/kg·h^{-1} (mean ± SD 516.7 ± 218.4
μmol/kg hr^{-1}). The percentage of the glycine flux incor-
porated into albumin in the total vasculature was 0.425 ±
0.344. The fractional synthetic rate and the absolute syn-
thetic rate for albumin in these small premature infants
are much higher than values obtained in healthy young
adults studied with a similar methodology. The relatively
low serum albumin concentrations typical of premature
infants appear to be referable to more rapid turnover of a
small plasma pool rather than a diminution in the rate of
albumin synthesis. (*Pediatr Res* 21: 49–53, 1987)**

Abbreviations

FSR, fractional synthetic rate
Q$_{Rgly}$, glycine flux

Serum albumin concentrations in infants vary inversely with
the degree of maturity, the blood albumin concentration of the
premature newborn being lower than that of the baby born at
term (1). It is unknown whether this phenomenon reflects re-
duced albumin synthesis or increased albumin turnover in less
mature babies. A diminished synthetic rate appears to explain
the hypoalbuminemia observed in malnourished rats (2–6) and
children (7, 8). However, such nutritional factors probably do
not account for the relatively low albumin of babies whose
growth is appropriate for gestational age. Immaturity of hepatic
mechanisms subserving albumin synthesis might explain the low
albumin. Conversely, the catabolism of albumin might be en-
hanced, especially in light of the observation that total body
protein turnover is inversely related to the degree of maturity of
premature infants (9).

We have measured albumin turnover in a group of premature

babies who received a continuous intravenous infusion of [^{15}N]
glycine. The fractional synthetic rate of albumin was determined
by comparing the rate of [^{15}N]glycine appearance in serum
albumin with the steady state labeling of urinary [^{15}N]hippurate,
the latter value being used as a marker of intrahepatic [^{15}N]
glycine enrichment (10, 11). A modified version of this stable
isotope approach was used by Gersovitz *et al.* (12) to quantitate
rates of albumin synthesis in young adults and elderly subejcts.

The results indicate that the relative hypoalbuminemia of
premature infants is referable to an enhanced rate of albumin
turnover rather than a diminution of albumin synthesis. Indeed,
rates of albumin synthesis in these babies are much greater than
those reported in the adult, with the albumin half-life in prema-
ture babies being less than half the adult value.

MATERIALS AND METHODS

The [^{15}N]glycine (98 atom % excess) was purchased from MSD
Isotopes, Ltd (Montreal, Canada). The isotope was prepared as
a 1 g/dl sterile, pyrogen-free solution in 150 mM sodium chloride
prior to intravenous administration. The isotope was added to
the infants' intravenous solution. Reagents used for derivatiza-
tion were from Regis Chemical Co. (Chicago, IL). Other reagents
were from Fisher Chemical Co. (Silver Springs, MD) and from
Sigma Chemical Co. (St. Louis, MO) and were of the highest
available grade.

Study design. Seven premature infants were studied. The
weight of each was appropriate for gestational age. All were
patients in the infant intensive care unit. Both intravenous and
intraarterial catheters had been placed for the purpose of clinical
management. Thus, no additional infusions or venipunctures
were necessary to perform this research, which was approved by
the Children's Hospital Committee for the Protection of Human
Subjects. None of the infants had any clinical signs of hepatic,
renal, or intestinal disease at the time of the study. All of the
infants were recovering from respiratory distress syndrome. None
of the infants had more than trace amounts of urine protein.
Stool losses were nonexistent because the infants received total
parenteral nutrition. Clinical details are given in Table 1.

For at least 4 days prior to study the infants received intrave-
nously 80 kcal/kg·day^{-1}, including approximately 2 g/kg·day^{-1}
of lipid (Intralipid; Kabi Vitrum) and 2 g/kg·day^{-1} of amino
acids (Trophamine, American McGaw, Glendale, CA).

The study was started after obtaining baseline samples of urine
for determination of [^{15}N]hippurate. Baseline samples of blood
also were taken for measurement of the albumin concentration
and isotopic abundance of [^{15}N]glycine. After the baseline sam-
ples were taken, a priming dose of [^{15}N]glycine, either 28 μmol/
kg (three subjects) or 56 μmol/kg (four infants), was administered
intravenously and was followed by a continuous infusion of [^{15}N]
glycine, either 0.4 μmol/kg·min^{-1} (three infants) or 0.67 μmol/
kg·min^{-1} (four infants) for the next 60–72 h. The data from all

seven infants are presented together because the dose of isotope did not affect the results.

Urine was collected as voided in plastic devices. The time of each void was recorded and the urine was analyzed for isotopic enrichment in [^{15}N]hippurate. Blood (1 ml) was sampled every 12 h until 60–72 h. It was placed in heparinized tubes and the plasma separated by centrifugation. All samples were kept at −80° C until analyzed for [^{15}N]glycine.

Determination of [^{15}N]glycine enrichment of albumin. Albumin was isolated from plasma by ethanol extraction of the plasma proteins which had been precipitated with trichloroacetic acid (13). A single band corresponding to albumin was observed with sodium dodecyl sulfate gel electrophoresis. The albumin was hydrolyzed in 6 N HCl (2 ml) at 120° C for 20 hr. The sample was taken to dryness under N$_2$ and the residue was redissolved in 1 ml of water. This was applied to a 4 × 0.5 cm glass column of AG-50 resin (H$^+$; X8; 50-100 mesh). After washing with 3 ml of deionized water, the amino acids were eluted with 3 ml of 4 M NH$_4$OH. The eluate was dried under N$_2$ and the t-butyldimethylsilyl derivative was prepared prior to gas chromatography-mass spectrometry.

Determination of ^{15}N in blood and urine. For determination of isotopic abundance in urinary [^{15}N]hippuric acid, 0.5 ml of urine was acidifed to pH 2–3 with 1 N HCl and applied to a 3 ml C-18 column (Baker Chemical Co., Phillipsburg, NJ). After washing with deionized water (3 ml), hippurate was eluted with 5 ml acetonitrile. The eluate was taken to dryness under nitrogen and the t-butyldimethylsilyl derivative was prepared.

Gas chromatography-mass spectrometry. Isotopic abundance in derivatized samples was determined on a Hewlett-Packard 5990A GC-MS system. Conditions were injector temperature 250° C, detector temperature 280° C, oven temperature program 150° C for 1 min, and then 10° C/min until 300° C. The filament was at 70 eV. The electron multiplier was set at 1800–2330 V, depending on sample size.

^{15}N isotopic abundance was obtained by selected ion monitoring of the m/z 219/218 ratio for glycine and the m/z 207/206 ratio for hippurate.

Isotopic enrichment (atom % excess) was calculated according to Millard (14).

Metabolite determination. Serum albumin was measured with the bromocresol dye method (15).

Methods of calculation. The FSR for albumin was calculated from:

$$\text{FSR (day}^{-1}) = \Delta I_{alb}/I_{hipp} \times 24$$

where ΔI_{alb} is the rate of linear increment (atom % excess/h) of isotopic abundance in [^{15}N]glycine in albumin, as determined by linear regression analysis of the data points from 12 h until the conclusion of the experiment (60–72 h), and I_{hipp} is the steady-state enrichment (atom % excess) in [^{15}N] hippuric acid.

The steady state labeling of [^{15}N]hippuric acid was calculated by computer fitting of the curves of isotopic abundance in urinary [^{15}N]hippurate to the expression: $A + Be^{-kt}$, where the plateau

Table 1. *Clinical summary of infants studied*

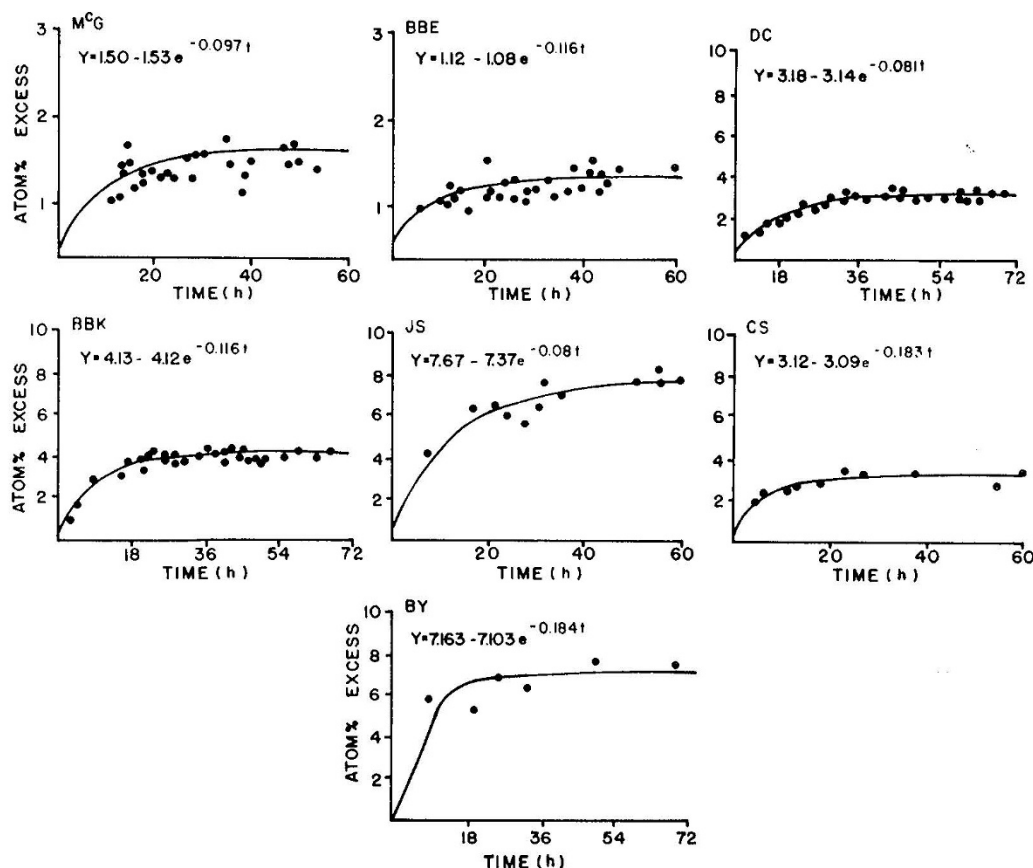| Patient	Gestational age (wk)	Age at study (days)	Wt (kg)	Sex
BK	26	7	0.89	M
BE	32	7	1.20	M
BMcG	30	3	1.04	M
DC	25	7	0.74	M
CS	26	11	0.70	F
JS	26	11	0.78	M
JY	30	5	0.89	M

Fig. 1. The appearance (atom % excess) *versus* time of [^{15}N]hippuric acid in urine in premature infants receiving an intravenous infusion of [^{15}N]glycine.

level of enrichment (atom % excess) is A at t_∞ and the value of B is negative.

The plasma albumin synthesis rate (g/dl·day^{-1}) was calculated from the product of the serum albumin and the FSR. The rate of total intravascular albumin synthesis was calculated by assuming the plasma volume to be 4% of body weight (16) and multiplying total plasma albumin by the plasma albumin synthesis rate.

The (Q_{gly} was calculated from

$$Q_{gly}\ (\mu mol/kg \cdot h^{-1}) = 100\left(\frac{d}{I_{gly}}\right) - d$$

where d is the isotope infusion rate ($\mu mol/kg \cdot h^{-1}$) and I_{gly} is the steady state isotopic abundance in blood [^{15}N]glycine.

RESULTS

In Figure 1 are shown data for the appearance of [^{15}N]hippuric acid in the urine of the seven infants studied. In each instance a steady-state with respect to isotopic abundance was attained no later than 20 h after the start of the [^{15}N]glycine infusion. A plateau level of labeling in [^{15}N]hippurate probably was attained in the liver much sooner, but could not be appreciated from the urinary data because of the relatively low glomerular filtration rate in these immature babies. For this reason, the data points representing the appearance of [^{15}N]glycine in albumin from 12 h until the end of the experiment were used to estimate by linear regression the initial rate of incorporation of labeled glycine in albumin.

The appearance of [^{15}N]glycine in albumin is illustrated by the data in Figure 2. In each study the initial rate of incorporation was linear during the period of observation. As shown in Table 2, the serum albumin concentrations were lower than those

anticipated in term infants (2.32 ± 0.48 versus 3.6 ± 0.5 g/dl) (17). Comparable values for the serum albumin concentration in premature infants of this weight have been reported by others (1). The fractional synthetic rates (day^{-1}) ranged between 0.059–0.177, corresponding to albumin half-lives of 3.9–11.7 days. The total plasma synthetic rates, referring to albumin present in the intravascular space, were 62.4–161.0 mg/kg·day^{-1}.

No correlation could be identified between the albumin fractional synthetic rate and gestational age or weight.

Values for Q_{gly} and the fraction of Q_{gly} incorporated into albumin in the intravascular space are given in Table 3. Q_{gly} of these infants (516.7 ± 218.4 $\mu mol/kg \cdot h^{-1}$) was higher than comparable values in the healthy postabsorptive adult (18, 19), a finding similar to that reported previously by others (20). Less than 0.5% of the glycine flux represents glycine incorporated into intravascular albumin. Total body albumin synthesis could not be estimated because the precise albumin distribution volume in these premature babies is unknown. However, even if the albumin distribution space were much greater than the intravascular space, as it is in the adult (21), it is evident that only a very small fraction of Q_{gly} would have been incorporated into albumin in these infants.

DISCUSSION

Albumin turnover in premature infants was studied by administering a constant [^{15}N]glycine infusion and utilizing gas chromatography-mass spectrometry to measure appearance of this isotope in blood albumin. By comparing the linear rate of increment of [^{15}N]glycine in albumin with the steady-state enrichment of urinary [^{15}N]hippurate, which was assumed to represent the intrahepatic enrichment of [^{15}N]glycine, the FSR for albumin was calculated.
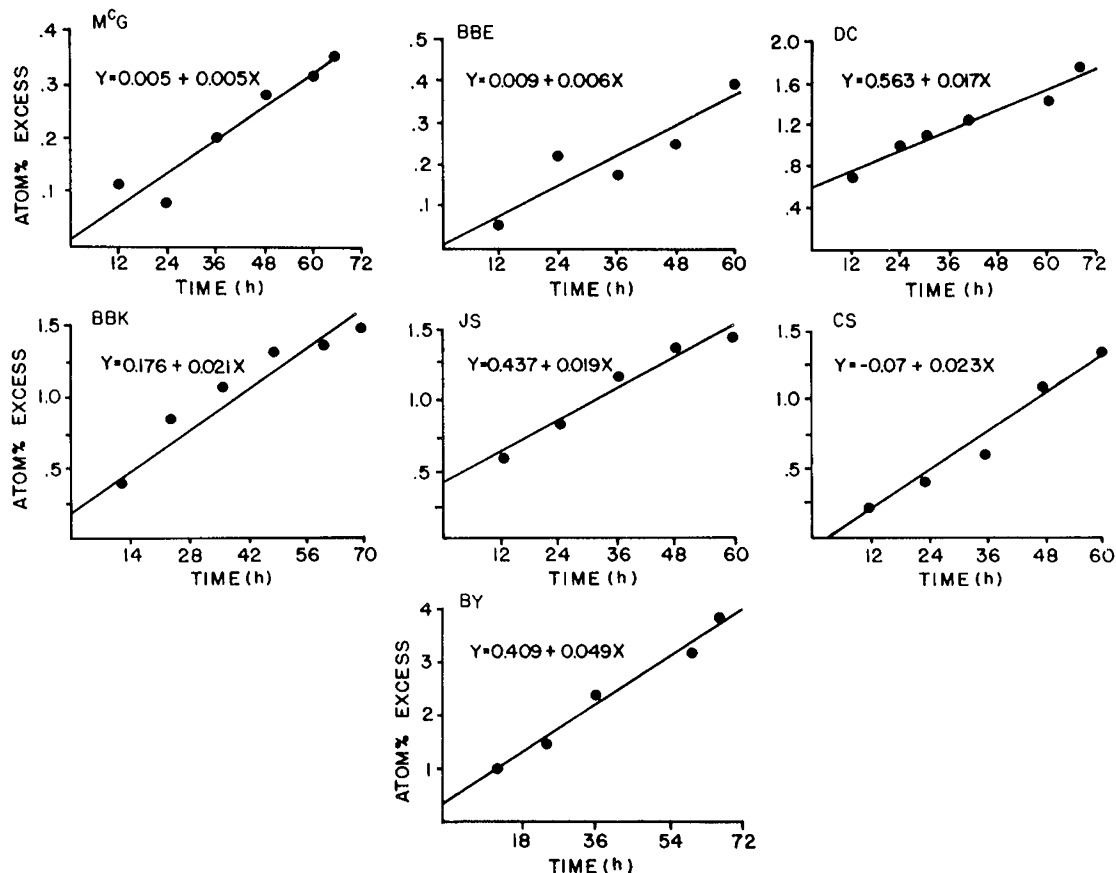

Fig. 2. The appearance (atom % excess) versus time of [^{15}N]glycine in blood albumin of premature infants receiving an intravenous infusion of [^{15}N]glycine.

Table 2. Albumin synthetic parameters

Patient	Serum albumin (g/dl)	FSR (day^{-1})	Synthesis rate (g/dl·day^{-1})	Total plasma synthesis rate (mg/kg·day^{-1})
BK	2.40	0.122	0.292	117.0
BE	3.12	0.130	0.406	162.0
BMcG	2.54	0.080	0.203	81.2
DC	2.10	0.128	0.268	107.2
CS	1.60	0.177	0.381	152.4
JS	2.00	0.059	0.156	62.4
BY	2.50	0.159	0.397	141.3
Mean ± SD	2.32 ± 0.48	0.122 ± 0.041	0.300 ± 0.099	117.6 ± 37.0

Table 3. Q_{gly} and fraction (%) of Q_{gly} utilized for total plasma albumin synthesis

Patient	Q_{gly} (μmol/kg·h^{-1})	Fx. (%) Q_{gly} in albumin*
BK	330.5	0.409
BE	544.9	0.343
BMcG	447.2	1.154
DC	662.8	0.187
CS	927.7	0.190
JS	377.5	0.190
BY	326.0	0.500
Mean ± SD	516.7 ± 218.4	0.425 ± 0.344

* Calculated from: $\dfrac{\text{Total plasma synthesis rate} \times 0.0205}{Q_{gly} \times 75/1000 \times 24} \times 100$ where 0.0205 represents glycine residues in albumin, 75 is the weight of glycine, 1000 converts from micromoles and 24 converts to day^{-1}.

This technique entails several assumptions. The most important of these is that urinary [^{15}N]hippurate enrichment accurately reflects steady-state isotopic abundance of liver [^{15}N]glycine. Rigorous validation of this assumption would require the direct determination of [^{15}N]glycine bound to hepatic t-RNA. Although such demonstration clearly is impossible in the human neonate, available evidence suggests that steady-state labeling of urinary [^{15}N]hippurate can be used in this way. Weissman *et al.* (22) administered both [^{15}N]glycine and [^{14}C]glycine to adults and compared values for albumin synthesis based on urinary [^{15}N] hippurate data as well as the decay curves of plasma [^{14}C] albumin. The concordance of results obtained by these two disparate methods suggested that enrichment of hippurate nitrogen is a good marker for enrichment of hepatic glycine nitrogen. Studies of [^{15}N]urate synthesis following the intravenous administration of [^{15}N]glycine also indicate close agreement between decay curves of urinary hippurate and plasma glycine (23–25). Cryer *et al.* (26) recently found that the steady-state labeling of [^{15}N]glycine in apolipoprotein B, which is synthesized only in the liver, is very similar to that of urinary [^{15}N]hippurate in healthy adults receiving a constant infusion of [^{15}N]glycine.

The current method also assumes that hepatic [^{15}N]hippurate enrichment is constant when measurements are made of the increase of [^{15}N]glycine in albumin. We utilized the time points from 12 h until the end of the study to calculate enrichment of serum albumin with [^{15}N]glycine. In the adult mixing of the [^{15}N]hippurate pool should be complete by 12 h (27). In the premature infant, whose glomerular filtration rate is relatively low, a steady-state with respect to labeling of hepatic [^{15}N] hippurate probably existed by 12 h but may not have become manifest in measurements made in urine. The fact that enrichment of [^{15}N]glycine in albumin increased linearly after 12 h (Fig. 2) suggests that steady-state conditions obtained in the liver before a plateau of urinary [^{15}N]hippurate was noted. The final result for FSR would not have been altered substantially by waiting longer than 12 h to make the initial measurement.

The method also assumes negligible reentry of [^{15}N]glycine from the catabolism of albumin. As indicated by the data of Table 2, a trivial portion of Q_{gly} is directed into the synthesis of albumin. This would be the case even if the total body albumin pool were four or five times the size of the intravascular pool. Significant reentry of [^{15}N]glycine from albumin into the amino acid pool utilized for protein synthesis must therefore be minimal.

The FSR, as determined from the [^{15}N]glycine data, is much greater in premature infants than in adults studied with a similar methodology (12). Thus, the mean value for FSR was 0.122 day^{-1} in the infants and 0.03–0.04 day^{-1} in healthy young adults (see Table 2) (12). The absolute plasma synthetic rate also is substantially higher in premature infants than in adults: 0.3 *versus* 0.12–0.16 g/dl·day^{-1}, assuming a mean serum albumin in the adults of 4 g/dl (12). A relatively high rate of albumin synthesis in the newborn corresponds with the finding that the rates of total body protein synthesis and degradation vary inversely with age throughout the human life span, being especially high in premature infants (9, 28, 29). The relatively low concentration of blood albumin in prematures (Table 2), therefore, does not appear to be referable to a diminished rate of synthesis, but to the more active turnover of the relatively small plasma pool.

The precise determination of the albumin distribution volume would require the parenteral administration of radiolabeled albumin in order to develop a decay curve from which the albumin pool size could be described. In infants this approach clearly is impossible, and the distribution volume and total body albumin synthesis rate cannot be determined unequivocally. We estimated the total plasma synthesis rate (Table 2) by utilizing the data of Friis-Hansen (16) to calculate the plasma volume. In adults only 31–42% of the exchangeable albumin pool is located in the plasma compartment (30). An additional pool, localized to skin and muscle, is characterized by a much slower turnover rate (31, 32). The exchangeable albumin pool of the newborn, in whom the extracellular fluid constitutes a relatively large fraction of body weight (16), undoubtedly extends beyond the intravascular albumin pool. Evidence for this is the observation that more than two-thirds of albumin administered to infants as treatment of hyperbilirubinemia diffuses into the extravascular space within 2–3 h (33, 34).

If we assume, for the purpose of approximation, that in our study population 25% of body albumin is present in the vasculature, then the mean value for total body albumin synthesis would be about 500 mg/kg·day^{-1}. Since the rate of whole body protein synthesis in infants of this size is between 5-13 g/kg·day^{-1} (9, 28), it follows that albumin production accounts for 4-10% of overall protein synthesis. This fraction is comparable to that of the adult, in whom albumin synthesis is 120-200 mg/kg·day^{-1} (30) and the rate of body protein synthesis is estimated to be 2-3 g/kg·day^{-1} (35).

The reason for increased albumin synthesis in these infants cannot be determined with certainty from the present data. Synthesis conceivably could be enhanced in response to unusual losses from the body, but only trace amounts of protein were

present in the urine and stool losses were nil in these babies receiving total parenteral nutrition.

Nor are nutritional factors a likely explanation for the enhanced albumin turnover. The intake of amino acids and energy was 2 g/kg·day^{-1} and 80 kcal/kg·day^{-1}. Each value is lower than the estimated nutritional requirement for premature infants (36), although each is typical of the short-term nutritional support offered to infants recovering from hyaline membrane disease and receiving nourishment via a peripheral vein. Substantial evidence from both *in vivo* and *in vitro* studies suggests that malnutrition or undernutrition is associated with diminished albumin turnover, not the augmented FSR observed in this investigation (2-8). The available data suggest that the FSR could have been even greater if the infants had received more amino acids and total calories.

Rather than being the result of nutritional factors, the relatively high albumin synthesis rate probably is referable to the more generalized intensification of whole body protein turnover which is characteristic of such small infants (9, 28, 29). Indeed, Nissim *et al.* (9) found that protein turnover may be inversely related to gestational age. The concept of whole body protein turnover is necessarily artificial because it represents the integral of many different protein pools, each of which has a unique rate of metabolism (35). Nor is it certain that maturational changes in the kinetics of individual protein pools must be similar, as is evidenced by the differing patterns of excretion of 3-methylhistidine and dimethylarginine in human prematures (9, 27). The current data show that turnover of the blood albumin pool is, indeed, very high in premature babies.

A great deal of additional investigation regarding albumin turnover in infants is needed. The relationship between this kinetic parameter and such variables as dietary intake, the degree of maturity, and anthropometric data are of interest. Raiha *et al.* (38) found that the blood albumin concentration in babies receiving a formula containing 3.0 g protein/dl exceeded that of a group receiving either breast milk or a preparation containing 1.5 g/dl. Although such studies improve our understanding of the nutritional requirements of infants, the determination of a serum protein concentration alone provides no information with respect to the mechanism underlying an increase or decrease of the blood level. Such kinetic data can only be obtained with an isotopic technique similar to the one described in this investigation. The current method is safe, involving the use of stable isotopes only, and does not invoke the use of a complex experimental design. The amounts of blood necessary to perform the study are small enough that measurements can be made of albumin turnover in even the smallest premature babies.

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