Percentile Estimates of Reference Values for Total Protein and Albumin in Sera of Premature Infants (<37 Weeks of Gestation)
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We measured the concentrations of total protein and albumin in sera of 281 well-fed premature infants, gestational ages 22–36 weeks, and calculated reference values from the 10th to 90th percentiles. The mean serum albumin concentration (27.6 ± 4.4 g/L, X ± SD) and total protein concentration (49.2 ± 6.7 g/L) at a postnatal age of 14.5 days were lower than reference values for full-term infants. We detected a significant positive correlation between albumin concentration and gestational age (r = 0.34, p < 0.01) and total protein concentration and gestational age (r = 0.43, p < 0.01). Even though albumin values were low, generalized edema was not present. We conclude that values for total protein and albumin in the preterm infant are lower than in the full-term infant but are an expected physiological response to premature birth.

Reference values of many analytes—including IgG, prealbumin, thyroxin, and hemoglobin—differ between premature and full-term infants (1–4). Clinical reference values for total protein and albumin have been determined in several studies for adults (5, 6) and for several ranges of ages within childhood (7, 8); however, reference values for the infant born prematurely are largely unavailable. In the one earlier study that addressed this issue, few preterm infants were studied, and preterm infants were defined as those born after less than 39 weeks of gestation (9). Because it is now widely accepted that preterm infants are by definition born in less than 37 weeks of gestation, values from this study are not necessarily applicable for current use.

We and others (10, 11) have observed that when the reference values for full-term newborns are applied to the premature infant, values for serum albumin and total protein consistently fall below those for the full-term infant. Yet, other than mild subcutaneous edema of the hands and feet in the first few postnatal days, premature infants who maintain consistently "low" values for serum total protein and albumin are notably free of generalized edema (12).

Our objective here was to evaluate the effect of gestational age and nutrient intake on plasma total protein and albumin concentrations in preterm infants.

Subjects and Methods
Selection of Subjects
A retrospective review was completed on 286 infants, all of whom received total parenteral nutrition (TPN) in our neonatal intensive-care unit during an 18-month period from January 1984 to June 1985. We selected infants receiving TPN because they received a standard nutrient intake and blood tests were performed on these infants on a regular basis. Infants were included in this retrospective analysis if their admitting diagnoses gave no indication of liver disease. During analysis of the data, infants were excluded from the study if there was any biochemical or clinical evidence of liver dysfunction. Infants were excluded if their serum bilirubin concentrations exceeded 260 µmol/
Although with variations in the estimation, liver function tests (e.g., aspartate aminotransferase (EC 2.6.1.1) values exceeded 67 U/L (13).

Procedures

Feeding procedures and sample collection. All infants received nutrients parenterally, including amino acids (Vamin-N; Pharmacia (Canada), Dorval), lipid (Nutralipid; Pharmacia), dextrose, minerals, vitamins, and trace metals according to standard protocol (14). These infants also received various amounts of enteral nutrients (by bottle or gavage tube). Nutrient intakes were monitored daily by the TPN monitoring team according to hospital routine. Venous blood was sampled from all infants once weekly during routine TPN monitoring.

Albumin and total protein assay. Samples were assayed for total protein and albumin in an "Ektachem" analyzer (Kodak Canada Inc., Toronto, Canada) (15). The precision of the analyses was determined by using commercial controls for total protein and albumin (Monitrol I and II; Dade, Miami, FL). Control values consistently had a CV of <2.5%.

Statistical methods. All data were stored in an IBM PC with use of the "Ashton Tate dBase III" data-base management system. For statistical analyses we used the same IBM PC and the NH Analytical Software "Statistix" statistical program.

The correlation coefficient (r) was determined to evaluate the relationship between albumin and total protein concentrations, and gestational age, protein intake, and energy intake (16). The lines drawn for males and females according to the regression formulas were compared by Student’s t-test to determine if their slopes were significantly different. Although the mean postnatal age at the time of blood sampling was 14.5 ± 9.7 days (X ± SD), many infants included in the study had blood sampled during several weeks and thus had more than one value determined for albumin. In an attempt to determine if there was a significant postnatal age effect upon the serum albumin concentration among the infants who had more than one value, we did a regression analysis for postnatal age and serum albumin and total-protein concentrations.

Results

Of the 286 infants selected to be included in the study, six were excluded from the final analysis of data because their laboratory values indicated possible liver dysfunction. Gestational ages ranged from 22 to 36 weeks (mean = 30 ± 3.7 weeks) as determined by the date of the last menstrual period and substantiated by clinical examination (12). For more precise statistical analysis, we grouped infants in seven ranges of gestational ages: <25; 25.0–26.9; 27.0–28.9; 29.0–30.9; 31.0–32.9; 33.0–34.9; and 35.0–36.9 weeks (Figure 1). Within the study population, there was no significant sex-related difference; thus, data for males and females have been combined (Figure 1). Mean birthweights fell within the normal range for gestational age (17). The most common clinical diagnoses were, in order of frequency, prematurity, respiratory distress syndrome, and sepsis.

The mean (± SD) serum albumin concentration was 27.6 ± 4.4 g/L, that of total protein was 49.2 ± 6.7 g/L at a postnatal age of 14.5 days. There were significant positive correlations between albumin concentration and gestational age (r = 0.34, p < 0.01) and total protein and gestational age (r = 0.43, p < 0.01). There was no statistical relationship between albumin and total protein and postnatal age.

All of the infants received either total parenteral nutrition or a combination of oral and parenteral nutrition. The average interval during which infants received parenteral nutrition was 26.4 days. Mean protein intake was 2.6 ± 0.6 g/kg per day and energy intake was 74.7 ± 15.7 kcal/kg per day for the seven days before blood was sampled for analysis. There was a significant but weak correlation between protein intake and albumin concentration (r = 0.20, p < 0.01; however, there was no correlation between albumin concentration and energy intake.

To give some indication of the dispersion of albumin and total protein concentrations in the study population, we also show the median (50th percentile) for each gestational age group in graphical form, along with the 10th, 25th, 75th, and 90th percentiles (Figures 2, 3).
Discussion

Our results demonstrate that total protein and albumin concentrations in serum increase with increasing gestational age and are lower than published normal values for the full-term infant (10, 11). We have established reference percentile values for premature infants between 23 and 37 weeks of gestation that can be used in clinical practice. Values included in the current study were from infants who were two weeks of age (postnatal age) at the time of the study, whose nutrient intakes were approximating estimated nutrient requirements for their age and size.

Others (7) have reported that the distribution of total protein and albumin for subjects 12 to 20 years old follow a gaussian (normal) distribution. Before puberty, however, values are directly related to age (8). Ward and Hirst (18) noted an initial decrease in total protein and albumin during the first three postnatal months, with an increase thereafter to adult values by age 10 years. Few data have been published regarding values in preterm infants. Nadeau et al. (2), while studying various biochemical markers for the assessment of protein–calorie malnutrition in premature infants, noted values for total protein and albumin that were lower than reference values for full-term infants and documented that concentrations of albumin and total protein did not differ in relation to nutritional intakes (2). Similar to our findings, values for total protein and albumin did not change during the first 12 postnatal weeks.

Infants in the current study were moderately well fed, and a weak correlation was documented between protein intake and total protein and albumin values. Because albumin has a biological half-life of 21 days and the infants were studied at age 14 days, we did not expect a strong dietary correlation. Nevertheless, the weak correlation between protein intake and serum albumin concentrations is probably the result of albumin synthesis, because synthesis depends on availability of amino acids.

Serum albumin and total protein values are monitored routinely to assess nutritional status in hospitalized patients of all ages (19). Low albumin values are often associated with signs of protein deficiency, such as edema (20). In the current study, despite low albumin values in the infants, generalized edema was not detected. Nevertheless, even in the absence of edema, because low albumin concentrations are usually associated with protein deficiency, albumin transfusions may be given in an attempt to improve intravascular albumin status and prevent edema. The results of the current study lead us to conclude that total protein and albumin values in the preterm infant are normally lower than in the older infant and child, and are not indicative of protein deficiency. Making use of these values as reference standards for the preterm infant may obviate the need for potentially dangerous and unnecessary albumin transfusions.

References