Comments on the Paper by Willumsen et al. (1997)

Dear Dr. Visek:

The objective of this communication is to bring to your attention a likely error in a recently published Journal of Nutrition article. The article in question is: Toxic Damage to the Respiratory Epithelium Induces Acute Phase Changes in Vitamin A Metabolism without Depleting Retinol Stores of South African Children (Willumsen et al. 1997).

One of the problems with this study is that the serum retinol-binding protein (RBP) concentration in the control group is too low for "healthy" children. Pediatric reference values of serum RBP concentration exist for healthy populations. In 6-mo-old infants, the median, lower and upper quartiles of serum RBP concentration are 30.0, 18.0 and 50.0 mg/L (Kanakoudi et al. 1995). In children from 1 to 5 y of age, the 0.025 and 0.975 fractiles of serum RBP concentration are 10 and 76 mg/L (Lockitch et al. 1988). In the study in question, the mean serum RBP concentration of 2- to 3-y-old children, in the control group, was 14.0 mg/L (0.6 μmol/L) with a 95% confidence interval of 11.8±16.6 mg/L (0.56±0.79 μmol/L) (Fig. 2 and in the text). These concentrations are clearly in the lower quartile of the distribution of serum RBP concentration of normal healthy populations.

Additionally, the concentration of serum RBP is much lower than the concentration of serum retinol. Children in the control group had a mean serum retinol concentration of 1.15 μmol/L (95% confidence interval, 1.02–1.3 μmol/L) (Fig. 2 and in the text). The calculated molar ratio of serum retinol to RBP is 1.72 (i.e., the saturation index of RBP). Thus for every mole of serum RBP there are ~2 moles of serum retinol. This is unlikely because the molar ratio of serum retinol to RBP is <0.5 (Mourey et al. 1990, Muto et al. 1972). Moreover, the calculated molar ratio is inconsistent with the reported vitamin A status of these children. Children in the control group were described as having inadequate liver retinol stores at the 3-mo follow-up visit. This is very unlikely to happen in children whose serum retinol concentration was twice that of their serum RBP concentration.

Although low serum RBP concentrations can occur these concentrations are characteristic of children with protein-energy undernutrition or of children with clinical vitamin A deficiency (i.e., xerophthalmia). The children in the control group, however, were described as "healthy" controls (i.e., these children did not have clinical signs of infection or inflammation), and their anthropometric indicators showed that none were wasted nor had suffered from chronic undernutrition (Table 1). Moreover, these children had a mean serum retinol concentration that was higher than 20.0 μg/dL (0.70 μmol/L), which is the cut-off value used to determine subclinical vitamin A deficiency. As far as one can determine from the article, there are no apparent reasons that would explain the low serum RBP concentrations of these children.

The main objective of this article was to assess the effect of inflammation on the metabolism of vitamin A. The serum RBP concentration of children in the control group was critical for the authors in determining this effect because these children were the comparison group. However, their low serum RBP concentration makes them unreliable as a control group. Consequently, use of their serum RBP concentration would bias the results toward the null hypothesis: no differences between the groups (e.g., at admission, the mean serum RBP concentration of cases was not statistically different from that of controls). Thus it is recommended that the authors provide an explanation for the low serum RBP concentration of the control group, and that they, the authors, re-examine the biological plausibility of their findings (e.g., is it possible to develop vitamin A deficiency while the molar ratio of serum retinol to RBP is >1.0?).

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