Infection-induced depression of serum retinol—a component of the acute phase response or a consequence? 1, 2

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This issue of the Journal contains closely linked articles by Mitra et al (1, 2) about acute (but transient) depression of serum retinol and retinol losses in the urine of children suffering from dysenteries caused chiefly by Shigella species. Whereas these articles provide new information about pathophysiologic mechanisms that contribute to these infection-induced changes in retinol metabolism, they also raise important questions about how these new data are to be interpreted.

The 1968 monograph by Scrimshaw et al (3) reviewed instances in which severe infections were followed by an abrupt development of xerophthalmia or other optical manifestations of vitamin A deficiency. It thus seemed evident that infectious diseases could deplete vitamin A stores by accelerating metabolic losses, impairing intestinal absorption, or both (3, 4). The concept that infections could deplete hepatic stores of retinol was strengthened further by Stephensen et al (5), who showed that vitamin A was lost via the urine in patients with pneumonia or sepsis. New estimates (2) suggest that urinary losses in children with severe infection could deplete marginal stores of hepatic retinol within 1 or 2 wk. But these new data (1, 2) also indicate that infectious illnesses influence retinol metabolism in ways far more complex than the simple depletion of vitamin A stores.

Infection-related declines in serum vitamin A have been noted since the 1950s, with numerous reports this decade (1–4, 6). The experimental design of Mitra et al’s study (1) was strengthened by important variables included in their patient population. The 90 children with dysentery ranged in age from 5 mo to 5 y and had different degrees of preexisting malnutrition and severities of illness. Dysentery varied with etiology, ie, 66 children (73%) had Shigella infections, and of these, 49 (54%) were infected with highly virulent S. dysenteriae type 1 strains.

Type 1 strain Shigella infections were manifested by high fevers, higher white cell counts, more prominent acute phase serum protein responses, more bloody diarrhea, and longer illnesses than those caused by other strains and species of bacteria (1). In addition, severity of type 1 S. dysenteriae infections correlated with larger depressions in serum retinol, urinary losses of retinol, and more preexisting malnutrition (as estimated by several anthropometric indexes) (1).

In contrast with the de novo cytokine-induced hepatic production of acute phase reactant serum proteins during these infections, there was a reduction in the production and serum concentrations of retinol binding protein and transthyretin. Normally, 85% of retinol binding protein forms a complex with serum transthyretin (2). Reduced serum concentrations of these 2 proteins contribute to the reduced serum concentrations of retinol during infection, but other mechanisms appear to be involved.

Of considerable importance is the observation by Mitra et al (1) that at the time of hospital discharge and before any postillness administration of vitamin A, serum retinol concentrations had rebounded to or above serum retinol concentrations at the time of admission. In most patients, this previously unrecognized rebound occurred in a matter of only several days. Marked improvements in serum retinol values were also observed in each of the sickest patients, who had yet to recover from their acute phase responses to infection. Serum retinol binding and transthyretin values also showed a similar rebound in early convalescence.

Because of their abrupt rebound in early convalescence, the observed transient decreases in serum concentrations of retinol, retinol binding protein, and transthyretin during infectious illnesses do not seem to be linked directly to the quantity of stored hepatic retinol. Although retinol stores are presumably being depleted during acute infection, the decreases in serum retinol seem to be related to the timing and magnitude of acute phase responses induced by proinflammatory cytokines.

Proinflammatory cytokines, eg, tumor necrosis factor and interleukins 1, 6, and 8, are known to induce fever and the hepatic synthesis of acute phase reactant proteins, inhibit production of serum albumin and transthyretin, and cause dramatic shifts in plasma concentrations of certain essential micronutrients (7). During acute phase responses, iron becomes bound to newly synthesized ferritin and is sequestered within body cells; about half of plasma zinc becomes bound to newly synthesized hepatic metallothionein; and copper leaves the liver as a component of ceruloplasmin, one of many newly synthesized acute phase proteins (7). Could transient reductions in serum retinol during infections merely be a secondary consequence of cytokine-induced inhibition of retinol binding protein and transthyretin production? Or should these transient declines in serum retinol be classified together with altered serum concentrations of iron, zinc, and copper as apparently purposeful, cytokine-induced components of acute phase reactions?

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The acute alterations in serum concentrations of iron, zinc, and copper induced by proinflammatory cytokines have each been linked to specific host-defense mechanisms (7). Could it be that transient declines in serum retinol during infectious illnesses also have specific defensive purposes? If so, what could they be? Iron, zinc, copper, and vitamin A all support immune system functions (7, 8). Furthermore, immunologic support provided by vitamin A is clearly related to the adequacy of its body stores (8). If transient infection-induced decreases in serum retinol are not related to falling retinol stores, do such transient decreases in serum retinol benefit or harm immune system functions?

The fraction of serum retinol binding protein that is not complexed with serum transthyretin is normally filtered in the renal glomerulus and is then reabsorbed by proximal tubular cells, thereby preventing the escape of vitamin A into the urine. To explain the apparent paradox of high urinary retinol losses at a time when serum retinol values were low, Mitra et al (2) theorized that these losses might be due to impaired reabsorption of retinol by proximal renal tubule cells. To investigate this possibility, they measured urinary losses of another low-molecular-weight protein, β₂-microglobulin as a surrogate marker for retinol binding protein. Normally, β₂-microglobulin is filtered through the glomerulus and then reabsorbed by proximal tubule cells. In the 59% of patients with urinary retinol losses, parallel losses of β₂-microglobulin provided strong evidence that proximal tubular cell dysfunctions cause urinary losses of retinol. Although many patients had depressed glomerular filtration rates (a common finding in generalized protein energy malnutrition), proximal tubular dysfunction was the only other detectable defect in renal function. Sudden development of this tubular dysfunction probably accounts for the apparent threshold effect in urinary retinol loss (2), but pathogenic mechanisms accounting for this apparently isolated transient defect remain an enigma.

The many unanswered questions raised by these reports (1, 2) should provide fertile ground for new investigations in laboratory animals and, when appropriate, in human subjects.

REFERENCES