

## Importance of Adequate Vitamin A Status During Iron Supplementation

*Nutritional deficiencies, including iron deficiency, may promote infection by lowering the body's resistance to infectious diseases. However, it has been shown that administration of iron in developing countries can result in increased morbidity, because pathogenic bacteria may compete effectively for iron in the circulation, resulting in an exacerbation of existing infections. Improved vitamin A status may protect against this potentially harmful effect of iron supplementation in environments where infections are highly prevalent.*

Iron deficiency anemia is a serious public health problem affecting millions of people worldwide.<sup>1</sup> The most vulnerable groups are women of reproductive age, pregnant and breast-feeding women, and young children. The consequences of iron deficiency anemia include impaired mental and motor development in children<sup>2</sup> and decreased work capacity in adults. Because the condition is so widespread, interventions to improve iron status usually involve the provision of pharmaceutical supplements. However, a study by Northrop-Clewes et al.<sup>3</sup> showed that the vitamin A status of target groups should be an important consideration when carrying out iron supplementation programs, especially in places where infections are highly prevalent.

In this study, which was conducted in Pakistan, infants less than 2 years old were randomly divided into treatment and control groups. The treatment group received 15 mg iron orally as a sorbitol-based aqueous solution of ferrous sulfate for 12 weeks; the control group received a placebo. The number of children for whom complete blood analyses were available were 95 in the iron-treated group and 96 in the placebo group. After 12 weeks, the iron-treated group showed increases in blood hemoglobin and plasma ferritin. However, iron treatment also resulted in an increase in plasma  $\alpha_1$ -antichymotrypsin, an acute-phase protein. This observation gives support to the notion that iron supplementation may increase the severity of new infections or exacerbate existing infections,<sup>4,5</sup> even though no changes in plasma concentrations of other acute-phase markers such as ceruloplasmin or albumin were observed.

Furthermore, the study by Northrop-Clewes et al.<sup>3</sup> showed that vitamin A may have a protective effect during iron supplementation. During the study, significant increases in plasma retinol occurred owing to a seasonal increase in consumption of fruits and vegetables. How-

ever, among infants who received iron, a negative correlation was observed between changes in plasma retinol and changes in plasma  $\alpha_1$ -antichymotrypsin. Thus, among iron-supplemented infants, those who showed an improvement in vitamin A status also showed reductions in plasma  $\alpha_1$ -antichymotrypsin, as well as reductions in other markers of infection, such as plasma immunoglobulin A, immunoglobulin M, and ferritin (which is both a marker of iron status and a positive acute-phase protein). In contrast, these markers of infection increased the most in iron-treated infants whose plasma retinol values either decreased or showed no improvement. Because vitamin A is an anti-infective agent, this property may account for the protective results observed.

It remains to be documented whether iron supplementation in vulnerable populations can result in oxidative damage. Pathologic circumstances, including infectious diseases, may generate reactions that produce superoxide radicals, which in turn may bring about release of Fe(II) from ferritin. The released Fe(II) forms complexes with compounds that participate in redox reactions, resulting in the generation of hydroxyl radicals that can initiate lipid peroxidation.<sup>4,6</sup>

Complex relationships exist between iron status and infections.<sup>5,7</sup> Chronic infections can lead to anemia, because iron becomes sequestered in hepatocytes. Plasma ferritin concentration can increase dramatically in infections. Similarly, vitamin A deficiency has been associated with increased liver storage of iron.<sup>8</sup> This sequestered iron is not available for incorporation into hemoglobin. Many studies have shown that improvement in the vitamin A status of humans by supplementation or food fortification with vitamin A also improves indicators of iron status.<sup>9-13</sup>

The precise mechanisms explaining the relationships between vitamin A and iron metabolism remain to be elucidated and will be influenced by many factors. One of the most important factors is the presence or absence of infection. Although there is consensus on the importance of eradicating iron deficiency worldwide, with the World Health Organization regarding this as one of its main goals for the year 2000, there is a lack of consensus regarding the best approach to meet nutritional needs of iron. The finding by Northrop-Clewes et al.<sup>3</sup> that interventions to improve vitamin A status should accompany iron supplementation programs in communities where infections are prevalent is an important contribution and should be verified.

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## Retinoic Acid as a Therapy for Emphysema?

*In concert with its action as a morphogen during embryonal development, retinoic acid appears to be able to regenerate lung alveoli in an experimental model of elastase-induced emphysema in rats, thereby inhibiting manifestation of the disease. The application to humans is now an interesting possibility.*

Emphysema is a chronic lung disease that causes 17,000 deaths each year and afflicts some 2 million Americans.<sup>1</sup> Although most of these cases are associated with cigarette smoking, a small fraction (about 5%) are apparently caused by a deficiency of alpha-1-antitrypsin.<sup>2,3</sup> The availability of an animal model makes it possible to test for agents that might reverse this serious condition. Emphysema can be induced in rats by intratracheal instillation of a saline solution of elastase, the enzyme responsible for the destruction of elastin fibers.<sup>4,5</sup> Elastin is a protein necessary for maintaining the structure and breathing function of the alveolar walls in the lung. Collapse of the structure and appearance of the bullae, characteristic of emphy-

sema, are the result of elastase treatment. These emphysematous lungs are further characterized by a lower ratio between the surface area (SA) and the distance between alveolar walls (Lm). For example, it was found that in control rats the SA was  $4952 \pm 259 \text{ cm}^2$  and the Lm was  $71 \pm 1.9 \mu\text{m}$ , whereas in emphysematous rats (elastase-treated rats) these values were  $3992 \pm 118 \text{ cm}^2$  and  $93 \pm 7 \mu\text{m}$ , respectively, with a significant decrease in the ratio from 70 to 43.<sup>6</sup> These measurements also reflect differences in lung volume between control and elastase-treated rats.

Massaro and Massaro recently reported that retinoic acid (RA) can reverse the action of elastase,<sup>6</sup> thereby offering some hope for the eventual treatment of emphysema in humans. These studies were initiated because of their group's previous work<sup>7,8</sup> showing that RA increases the number of alveoli in the lungs of normal newborn rats. Rats treated with instillation of elastase were either maintained as such or given RA by daily injections in the peritoneal cavity for 12 consecutive days. They were eventually sacrificed at day 25. RA apparently permitted the growth of new alveoli,<sup>6</sup> so that the experimental emphysematous condition was not evident in the RA-elastase-treated rats.

The RA-elastase group showed lung volume similar to that of the control group (about  $10 \text{ cm}^3$ ), whereas the elastase-treated group showed a value of 11.8 (an increase of more than 15%). The authors make the important point that because body weight was the same for all groups and lung volume is usually proportional to body mass,<sup>9</sup> the larger lungs of the elastase-treated rats must therefore reflect a diminished elastic recoil, a feature characteristic of emphysema, rather than lung growth. The emphysematous lungs were also characterized by a larger alveolar vol-

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