Hematological effect of supplementing anemic children with vitamin A alone and in combination with iron[1–3]

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ABSTRACT Ninety-nine anemic children aged 1–8 y were divided into four groups. Each group was supplemented for 2 mo with vitamin A, iron, vitamin A plus Fe, or a placebo. Clinical, hematological, and Fe biochemical evaluations were performed at the beginning and end of the study. Vitamin A supplementation produced significant elevations in the serum levels of retinol, blood hemoglobin, hematocrit, erythrocytes, serum Fe, and percent transferrin saturation (%TS) and had no effect on total Fe binding capacity (TIBC) or serum ferritin. Fe supplementation did not affect serum retinol. However, it improved hematological and Fe nutrition indicators, including TIBC and serum ferritin. The simultaneous administration of vitamin A and Fe resulted in a better response of serum Fe and %TS than when the supplement consisted only of vitamin A or Fe alone. Vitamin A benefits hematological condition and Fe metabolism. *Am J Clin Nutr* 1988;48:595–600.

KEY WORDS Vitamin A, iron, anemia, hemoglobin levels, serum iron levels

Introduction

Iron-deficiency anemia and hypovitaminosis A are two of the most prevalent nutritional problems in the Central American region, particularly in children. In some cases the average dietary intake of Fe may be adequate yet Fe-deficiency anemia persists, indicating the importance of other nutritional and environmental factors in its etiology.

Several studies in humans and experimental animals have shown that there is an interaction between vitamin A nutriture and Fe nutrition and metabolism (1–4). These studies indicate that the lack of vitamin A may lead to a mild anemia characterized by low serum Fe and elevated levels of this mineral in storage depots, particularly the liver. Epidemiological studies in both children and adults support this concept (5, 6) and nutritional interventions with vitamin A in humans revealed a positive effect on Fe nutrition (7, 8). This information suggested that vitamin A deficiency impairs the utilization of Fe and that improving vitamin A nutriture may benefit the hematological condition of populations.

Considering that mild vitamin A deficiency is an endemic problem to our region, we felt it important to investigate the effect of supplementing anemic children with vitamin A, with or without additional Fe therapy, on their hematological condition and Fe nutritional status. The result of that investigation is the subject of this report.

Subjects and methods

Subjects

The original participants in the study were 115 anemic children of both sexes, aged 1–8 y. They were attending seven different day-care centers under the patronage of the Guatemalan government (Office for Social Welfare) and a children's nutritional recuperation center sponsored by Guatemala's Lion's Club. Three of the centers (La Florida, La Presidenta, and Bethania) were located in Guatemala City. The others (Escuintla, Zacapa, El Progreso, Cuilapa, and San Juan) were located in smaller cities throughout the country. All the children belonged to urban or rural families of low socioeconomic status.

The children were selected after screening the total population of each center for anemia. Capillary hematocrit levels were obtained on 983 children and those having hematocrits < 1.5 SD below the average normal value for age and place of residence were considered anemic (9). The anemic children did not have any overt clinical signs of severe undernutrition. Their anthropometric characteristics were determined by World Health Organization (WHO) standards (10). Mean percent adequacies of height-for-age and of weight-for-height were 90.0 ± 5.8% (range, 74.5–101.4%) and 95.2 ± 7.2% (range, 70.5–115.4%), respectively.

Parents were immediately informed about the anemic condition of their children and were asked to authorize the children's participation in the study by signing a written consent form. The study protocol was revised and approved by our Institutional Human Rights Committee.

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Experimental design

Anemic children of approximately similar ages were randomly assigned in each center to four different treatment groups to be supplemented orally for 2 mo with vitamin A (G-I), Fe (G-II), vitamin A plus Fe (G-III), or a placebo (G-IV). To ensure an even distribution of ages among groups the anemic children from each center were first divided in two categories, ≤ 3 y and > 3 y. From each age bracket the children's names were randomly drawn as in a raffle and assigned sequentially to groups I, II, III, and IV. Because the number of anemic children in each location was not always a multiple of four, when the data of all centers were pooled, the original numbers of children under study were 30 (G-I), 30 (G-II), 29 (G-III), and 26 (G-IV).

The treatments received by the children were as follows:

Group I. Supplemented with 10 000 IU (3.0 mg) of vitamin A/d in the form of a water-soluble preparation (AROVIT®, Hoffman-La Roche, Basel, Switzerland). Each drop of the supplement contained 5000 IU (1.5 mg) of vitamin A; according to WHO guidelines this is the amount of vitamin A suggested as a daily supplement (11). However, in a pilot study we found that when supplementation consisted of only one drop, it often remained on the lips of the children and was not really ingested. Therefore, two drops of the vitamin A preparation were used to ensure that the children received at least 5000 IU (1.5 mg). The drops were put directly into the mouth of the child immediately after the breakfast meal.

Group II. Supplemented with ferrous sulfate in the form of a syrup (Fer-In-Sol®, Mead Johnson, Evansville, IN) at a level of 3 mg of elemental Fe·kg body $wt^{-1} \cdot d^{-1}$. This is the dose of Fe suggested for children by the International Nutritional Anemia Consultative Group (INACG) (12). To avoid gastrointestinal problems the required volume of the iron supplement was divided into two doses which were put directly into the mouth of the child with a dropper at midmorning and midafternoon.

Group III. Supplemented with both vitamin A and Fe as indicated for groups I and II.

Group IV. This was a control group. Children in this group were given a placebo consisting of a solution that simulated the Fe preparation. It was composed of distilled water (800 mL), ethanol (200 mL), thymol blue (10 mL), and 0.5 mol sodium hydroxide/L (3–5 drops). This preparation was also given with a dropper directly into the mouth of each child at a level of 0.4 mL twice a day at midmorning and midafternoon.

All three supplements were provided by the project and the supplementation was performed by the auxiliary nurses of each center with the supervision of the investigators. When possible the appropriate supplements were given to the parents on Friday afternoon for supplementing their children over the weekend.

Evaluation of treatments

At the beginning of the supplementation trial (t_0, base line) and at 1 (t_1) and 2 (t_2) mo of treatment, the children underwent clinical and anthropometric evaluations. The existing clinical characteristics and the weight and length, or height, of each child at the time of the examination were recorded in a standardized fashion on a special form.

To evaluate the effects of the various treatments on hematology and on levels of biochemical indicators of Fe nutrition, a 5-mL sample of venous blood was obtained from each child for laboratory analysis at t_0 and at the end of the 2-mo supplementation (t_2). The following blood analyses were performed: *1*) hemoglobin, hematocrit, red cell count, hematological indices, and leucocyte count by standard methods using an automated cell counter (Royco-Cell Crit®, model 920-A, HIAC/Royco Instruments, Menlo Park, CA); *2*) serum retinol by the ultraviolet inactivation method proposed by the International Vitamin A Consultative Group (IVACG) (13); *3*) serum Fe, total Fe binding capacity (TIBC), and percent transferrin saturation (%TS) by the Ramsay method (14); *4*) serum ferritin by an immunoenzymetric assay with a commercial kit (Tandem-E Fer®, Hybritech Inc, San Diego, CA); and *5*) erythrocyte sedimentation rate (ESR) by the method of Wintrobe (15).

Some children dropped out of the study and were not able to complete the 2-mo period of treatment, mainly because their families moved or the children quit attending the centers. Other children had very irregular attendance and therefore did not fully comply with the treatment; those children were eliminated from the study. Thus, 16 children were lost in the follow-up period: 5 from G-I, 0 from G-II, 5 from G-III, and 6 from G-IV. We ended with a total of 99 children: 25 in G-I, 30 in G-II, 24 in G-III, and 20 in G-IV.

The differences observed in attrition rates between groups were probably related to the small sample sizes and/or the relative importance that nurses or mothers gave to the different treatments (ie, Fe alone is a standard well-known treatment for anemia while the other treatments are not). However, the fact that all children came from the same environment, had similar characteristics, and were randomly distributed weakens the potential bias attributed to this phenomenon. On the other hand, only a small proportion of subjects came from rural areas. Because they lived very close to the centers and spent most of their time exposed to the urban environment, no attention was given to this factor when assigning these children to groups.

At the end of the study period, the children in G-IV were supplemented for 2 mo with Fe and vitamin A in a similar fashion as those in G-III. Children from any of the other groups who were still anemic were likewise supplemented with Fe.

Morbidity surveillance

In addition to the clinical information obtained by the pediatrician at the time of examination of the children (t_0, t_1, and t_2), the auxiliary nurses also kept a record in each center of the morbidity of the children throughout the study period. The different illnesses were categorized as upper-respiratory infections, gastrointestinal infections, dermal infections, and others. This information was recorded in a special morbidity form each time there was a morbid event.

Data analysis

The data were entered into a computer (HP-300®, Hewlett-Packard Co, Palo Alto, CA) and analyzed by the *Biomedical Science Program* (program P4V, BMPD Statistical Software, Los Angeles, CA). The analytical model used was analysis of variance (ANOVA) for repeated measurements using a factorial design that takes into consideration unequal replication in the number of subjects among treatment groups (16). The factors were the different treatments and the basal levels of serum retinol (low retinol and high retinol) and of serum ferritin (low ferritin and high ferritin). The cutoff points for defining low and high retinol and ferritin were 30 μg/dL (1.05 μmol/L) and 12 ng/mL (12 μg/L), respectively. Ferritin was analyzed by a log transformation of the ferritin values. The anthropometric data were analyzed according to WHO standards (10). The statistical significance of the differences in base-line values for hematological and biochemical indicators between groups was also tested by one-way ANOVA. In all cases the level of statistical significance was based on two-tailed statistics at a level of $p < 0.05$.

TABLE 1
Effect of treatments on serum retinol levels after 2 mo of supplementation*

Treatment†	*n*	t_0 (basal)	t_2 (2 mo)	$t_2 - t_0$
		μg/dL (μmol/L)	*μg/dL (μmol/L)*	*μg/dL (μmol/L)*
G-I	25	28.9 ± 10.4 (1.01 ± 0.36)	38.8 ± 15.0 (1.35 ± 0.52)	9.9 ± 19.0 (0.35 ± 0.66)
G-II	30	30.8 ± 10.4 (1.08 ± 0.36)	34.4 ± 10.3 (1.20 ± 0.36)	3.6 ± 14.4 (0.13 ± 0.50)
G-III	24	26.7 ± 7.0 (0.93 ± 0.24)	37.0 ± 11.8 (1.30 ± 0.41)	10.4 ± 11.5 (0.36 ± 0.40)
G-IV	20	30.6 ± 9.9 (1.07 ± 0.35)	33.4 ± 9.9 (1.17 ± 0.35)	2.9 ± 13.1 (0.10 ± 0.46)

	Analysis of variance	
Effect of	*p*	*p*
Time	0.0456	—
Vitamin A	0.2565	0.0245
Fe	0.5952	0.8375
Basal retinol	0.0001	—

*$\bar{x} \pm$ SD.
†G-I = vitamin A; G-II = Fe; G-III = vitamin A + Fe; G-IV = placebo.

Results

Effects of treatments on serum retinol

Table 1 shows the serum-retinol levels of the children at the basal and 2-mo evaluations. Although there was a significant effect of time of retinol values attained after 2 mo of supplementation ($p = 0.0456$), there was not a clear effect of specific treatments. However, the statistical analysis revealed that the time response in serum retinol was highly associated with the basal retinol level ($p < 0.0001$). To account for that relationship and the fact that there was not a statistical difference in retinol levels among the groups in the basal evaluation ($F = 0.9969$, $p > 0.05$), we analyzed the same data as the individual changes in serum retinol between the basal and the 2-mo values ($t_2 - t_0$). This approach showed a highly significant positive effect of vitamin A on serum retinol ($p = 0.0245$). Both vitamin A-treated groups experienced an elevation in serum retinol of ~10 μg/dL (~0.35 μmol/L). By contrast Fe treatment did not have any significant effect on serum retinol levels ($p = 0.8375$). When the cumulative frequency distribution of retinol values before and after the trial for each of the groups was examined it was observed that vitamin A supplementation changed the percent frequency of retinol levels < 30 μg/dL (1.05 μmol/L) from 72 to 20% in G-I and from 70.8 to 33.3% in G-III.

Effect of treatments on hematology

The effect of the different treatments on blood hemoglobin is presented on **Table 2.** Fe treatment had a highly significant effect on hemoglobin ($p = 0.0028$). The children supplemented with only vitamin A (G-I) also had elevated hemoglobin levels. The two-tailed statistical test revealed that the increase was just short of significance ($p = 0.0594$). However, similar analyses of the effect of treatments on hematocrit and red cell count showed that vitamin A supplementation had statistically significant effects on these variables ($p = 0.0425$ and $p = 0.0401$, respectively).

Furthermore, because the hemoglobin response to treatment depended on the basal hemoglobin value ($p < 0.0001$), we analyzed these data again as the change between the basal and the 2-mo values. (The validity of this approach was based on the fact that there were not statistical differences in hemoglobin among groups in the basal evaluation [$F = 0.9500$, $p > 0.05$]). This analysis revealed that vitamin A had a significant effect on hemoglobin ($p = 0.0481$), producing an average increase of 9.3 ± 5.6 g/L ($\bar{x} \pm$ SD) in the group supplemented with only vitamin A (G-I). The cumulative frequency distribution of hemoglobin before and after treatment in each of the groups revealed that hemoglobin values < 110 g/L changed from 80 to 40% in G-I, from 83.3 to 10% in G-II, from 70.8 to 0% in G-III, and from 80 to 50% in G-IV.

The factorial model of analysis also showed that within the range of basal levels of retinol and ferritin in our study the hemoglobin response was not related to the basal retinol level ($p = 0.4813$) or to the basal level of ferritin ($p = 0.2966$). Furthermore, serum ferritin did not correlate with serum retinol ($r = -0.0935$). The median value for serum retinol in the basal evaluation was 27.2 μg/dL (0.95 μmol/L) (range, 12.4–64.0 μg/dL, or 0.43–2.23 μmol/L) and for serum ferritin, 11.0 ng/mL (11.0 μg/L) (range, undetectable–110.4 ng/mL, or undetectable–110.4 μg/L).

No significant effects of treatments were detected on hematological indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and MCH concentration [MCHC]), leucocyte counts, or erythrocyte sedimentation rate (ESR). In the basal evaluation mean ESR values were similar among the groups ($F = 1.0569$, NS). Furthermore, ESR correlated significantly with serum ferritin levels ($r = 0.2430$, $p < 0.02$). At the end of the trial there was an overall decrease in

TABLE 2
Effect of treatments on hemoglobin levels after 2 mo of supplementation (g/L)*

Treatment†	*n*	t_0 (basal)	t_2 (2 mo)	$t_2 - t_0$
G-I	25	103 ± 8	112 ± 8	9.3 ± 5.6
G-II	30	105 ± 6	119 ± 9	13.8 ± 9.6
G-III	24	106 ± 6	120 ± 7	14.2 ± 9.0
G-IV	20	104 ± 7	107 ± 6	3.2 ± 5.7

	Analysis of variance	
Effect of	*p*	*p*
Time	0.0000	—
Vitamin A	0.0594	0.0481
Fe	0.0028	0.0000
Vitamin A × basal retinol	0.4813	—
Vitamin A × basal ferritin	0.2966	—
Vitamin A × basal hemoglobin	0.0001	—

*$\bar{x}$ ± SD.
†G-I = vitamin A; G-II = Fe; G-III = vitamin A + Fe; G-IV = placebo.

ESR in all groups. However, neither vitamin A (p = 0.7797) nor Fe (p = 0.6730) had any specific effect on the levels of this variable. No significant correlations were found between ESR and serum retinol (r = 0.0269), %TS (r = −0.0652), or hemoglobin (r = 0.0225).

Effect of treatments on biochemical indicators of Fe nutrition

Table 3 summarizes the effect of the various treatments on the levels of serum Fe and %TS. The base-line levels of these two variables did not differ significantly among groups ($p > 0.05$). With treatment, there were significant effects of time on serum Fe and %TS (p = 0.0181 and p = 0.0089, respectively) and the specific effect of vitamin A on serum Fe was also highly significant, both when the data were analyzed as actual values (p = 0.0070) and as the change between the basal and 2-mo evaluations (p = 0.0187). Interestingly, the average change in serum Fe in the group receiving vitamin A and Fe simultaneously was much greater than the group receiving vitamin A or Fe alone. Group III had a change of 21.0 ± 40.6 μg/dL (4 ± 7 μmol/L) whereas G-I and G-II had changes of 10.6 ± 24.1 and 7.9 ± 26.7 μg/dL (2 ± 4 and 1 ± 5 μmol/L), respectively. On the other hand, the effect of Fe treatment on serum Fe levels was not significant (p = 0.0556) and the average increase of the group receiving just Fe was only 7.9 ± 26.7 μg/dL (1 ± 5 μmol/L).

The vitamin A– and Fe-treated groups (G-I and G-II) experienced an increase in the levels of %TS, whereas there was a slight decrease in %TS in the group receiving the placebo (G-III) (Table 3). When the changes in %TS

TABLE 3
Effect of treatments on serum Fe levels and percent transferrin saturation (%TS)*

		Serum Fe (μg/dL)			%TS		
Treatment†	*n*	t_0 (basal)	t_2 (2 mo)	$t_2 - t_0$	t_0 (basal)	t_2 (2 mo)	$t_2 - t_0$
		μg/dL (μmol/L)	*μg/dL (μmol/L)*	*μg/dL (μmol/L)*			
G-I	25	39.3 ± 17.4 (7 ± 3)	49.9 ± 27.5 (9 ± 5)	10.6 ± 24.1 (2 ± 4)	10.2 ± 4.9	13.4 ± 7.9	3.2 ± 6.2
G-II	30	43.5 ± 18.2 (8 ± 3)	51.4 ± 21.8 (9 ± 4)	7.9 ± 26.7 (1 ± 5)	12.0 ± 6.5	15.1 ± 6.7	3.1 ± 9.0
G-III	24	44.6 ± 17.0 (8 ± 3)	65.6 ± 39.0 (12 ± 7)	21.0 ± 40.6 (4 ± 7)	12.6 ± 6.0	17.3 ± 7.9	4.7 ± 8.5
G-IV	20	43.8 ± 16.5 (8 ± 3)	38.6 ± 26.4 (7 ± 5)	−5.3 ± 25.5 (−1 ± 5)	11.9 ± 5.5	10.6 ± 7.8	−1.3 ± 6.3

	Analysis of variance			
Effect of	*p*	*p*	*p*	*p*
Time	0.0181	—	0.0089	—
Vitamin A	0.0070	0.0187	0.0500	0.0616
Fe	0.1461	0.0556	0.3097	0.0620

*$\bar{x}$ ± SD.
†G-I = vitamin A; G-II = Fe; G-III = vitamin A + Fe; G-IV = placebo.

TABLE 4
Effect of treatments on median serum ferritin levels at the basal and 2-mo evaluations (μg/L)*

Treatment†	*n*	t_0 (basal)	t_2 (2 mo)
G-I	25	8 (u–46)	8.1 (u–60)
G-II	30	12 (u–56)	17.5 (u–63)‡
G-III	24	11 (u–110)	16.4 (u–52)‡
G-IV	20	13 (u–92)	8.1 (u–68)

* Median (range). u = undetectable.
† G-I = vitamin A; G-II = Fe; G-III = vitamin A + Fe; G-IV = placebo.
‡ Effect of Fe: $p = 0.0324$.

between the basal and the 2-mo evaluations were analyzed, the vitamin A and Fe treatments showed a strong tendency to have a significant effect on %TS ($p = 0.06$). Again, the group receiving vitamin A plus Fe (G-III) showed the highest elevation. However, despite the significant elevation in serum Fe in the vitamin A group (G-I) after 2 mo, its mean level of %TS remained lower than the Fe-treated groups.

The vitamin A treatment did not have the expected lowering effect on the levels of TIBC ($p = 0.8445$) as did iron alone. TIBC levels in G-I were 395.4 ± 70.7 μg/dL (71 ± 13 μmol/L) in the basal evaluation and 388.1 ± 52.6 μg/dL (70 ± 9 μmol/L) after the trial, whereas G-II changed from 380.9 ± 54.4 to 345.2 ± 54.0 μg/dL (68 ± 10 to 62 ± 10 μmol/L).

The median serum ferritin values at the basal and 2-mo evaluations are presented in **Table 4.** Before the trial the mean basal values of this variable were not significantly different among groups ($F = 0.6952$, NS). With treatment, only Fe supplementation had a significant positive effect ($p = 0.0324$) on the serum levels of this Fe-storage protein. There was no effect of vitamin A treatment on serum ferritin and the median ferritin value of the group receiving only vitamin A (G-I) remained unchanged. The cumulative frequency distribution of serum ferritin before and after the trial showed that the percent of children with < 12 μg/L ferritin dropped substantially in both groups supplemented with Fe: from 53 to 27% in G-II and from 54 to 29% in G-III. By contrast no important change was observed in the distribution of serum ferritin in the vitamin A group (G-I).

Anthropometric evaluation

There were no significant effects of any of the treatments on anthropometric indices (weight-for-height, weight-for-age, or height-for-age).

Morbidity observations

The most commonly observed infections during the study were respiratory diseases, diarrhea, dermal infections, and conjunctivitis. Respiratory infections had the highest incidence in the four groups. Diarrhea was most commonly found in the groups supplemented with vitamin A and/or Fe (G-I, G-II, G-III), especially in children who received Fe (G-II and G-III). No distinction was made between diarrhea resulting from Fe therapy and that caused by gastrointestinal infections. The Fe-treated groups also showed a higher incidence of dermal infections than the groups treated with only vitamin A or placebo. During the study the adjusted percent rates of dermal infections (new cases divided by number of observations, times 100) were 13.3 and 15.6% in G-II and G-III, respectively, and only 8.7% in G-I and 6.1% in the control group (G-IV).

Discussion

Our data indicate that in populations with low socioeconomic status vitamin A supplementation can improve the hematological condition of anemic children. This confirms previous observations in experimental animals (1–4) and humans (1, 7) showing an association between vitamin A nutritional status and anemia. Our study demonstrates that vitamin A supplementation of anemic children for 2 mo at ~10 000 IU/d (3.0 mg/d), leads to an average increase in hemoglobin of about 9 g/L.

Hodges et al (1) reported several years ago that human adult subjects depleted of vitamin A developed mild anemia that responded to Fe treatment only after vitamin A status was improved. Mohanram et al (7) showed that oral supplementation of vitamin A–deficient children with 8000 mg of retinyl palmitate/d results in a modest although significant increase in hemoglobin level. Our study confirms such observations and our use of an experimental design with a randomized-control trial strengthens the observations.

Our results also indicate that the clearest effect of vitamin A supplementation is on the levels of serum Fe. As a consequence the levels of %TS, which represents the amount of Fe delivered to body tissues, become elevated. The magnitude of change in these Fe parameters is greater in children receiving both vitamin A and Fe than in those receiving Fe alone. Animal studies indicated that the deficiency in vitamin A reduced the levels of serum Fe (2, 4). Furthermore, epidemiological data in children (5) and elderly subjects (6) showed a clear association between serum Fe and retinol levels. That type of association is not as clear between serum retinol and hemoglobin (5). All these data indicate that the main effect of vitamin A is to maintain adequate levels of Fe in plasma to supply the different body tissues, including the bone marrow, with proper amounts of this essential mineral. This may be the mechanism by which the hematopoietic tissue becomes favored with more available iron.

Vitamin A supplementation did not affect TIBC levels. Despite the increase in serum Fe in the vitamin A group, TIBC levels remained unchanged and did not experience the expected decrease. A previous study showed that improving vitamin A nutrition of children results in both an increase in serum Fe and TIBC (8). These observations suggest that in children from populations with low socioeconomic status, vitamin A supplementation may also increase the levels of transferrin. This in turn may favor the elevation of serum Fe.

Other vitamin A studies suggested that a probable function of the vitamin is to mobilize Fe from storage into the circulation (8, 17, 18). However, such an effect is not evident from the levels of serum ferritin in our study. In the vitamin A–supplemented group there was no change in the levels of serum ferritin between the basal and 2-mo evaluations, indicating that in this group the Fe stores did not become lower after supplementation. Furthermore, there was no correlation between serum levels of retinol and ferritin. Additionally, our factorial analysis revealed that hemoglobin response was not related to the basal ferritin levels. These observations indicate that the high ferritin levels in this study had no relationship to vitamin A deficiency. As shown by the significant correlation between ESR and ferritin, such high ferritin values were caused primarily by inflammation.

The possibility of improved utilization of dietary Fe as an explanation for the results obtained in this study cannot be eliminated, however. Although vitamin A deficiency does not alter the absorption of Fe in rats (17), the improvement of vitamin A nutriture in children through vitamin A fortification of sugar resulted in a significant increase in Fe stores (8). It may be that as a result of improving the metabolic utilization of Fe with vitamin A supplementation, the body's physiological response is better Fe absorption.

Another important aspect of our findings is their possible relation to infection. There was clinical evidence of mild infections throughout the supplementation period. This was further demonstrated by the large variation in ferritin levels even in the basal evaluation. Vitamin A deficiency even of a mild degree has been associated with a higher incidence of morbidity (19). On the other hand, infections can lower the serum levels of Fe (20) and hemoglobin (21). Over the short term of our study, however, we did not find any clinical evidence that the vitamin A–treated groups (G-I and G-III) had fewer infections than the control group (G-IV). This observation was supported by the fact that we did not observe any significant effect of the treatments on leukocyte count or ESR. It is interesting, however, that the group of children who received Fe and vitamin A simultaneously (G-III) had higher levels of serum Fe than the group that received Fe alone (G-II), and that both groups had very similar, high incidence of morbidity. Whether vitamin A had a protective effect on the serum Fe levels of G-III, perhaps through conditioning less severe infections, cannot be ascertained from our data and remains as an important and fascinating question. The higher incidence of morbidity, particularly of dermal infections, in the Fe-treated groups is an important observation that also needs investigation. In our study, because of the lack of microbial examinations and the small number of children observed during a short period only, no conclusions can be drawn regarding any adverse effect of the supplements on morbidity.

In conclusion, the primary effect of vitamin A supplementation of anemic children is a significant elevation in serum Fe levels. Such a change may favor hematopoiesis, resulting in an increase in hemoglobin and hematocrit. Furthermore, the elevation in serum Fe is greater when both vitamin A and Fe are supplemented together than when either is given alone.

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