International Journal for Vitamin and Nutrition Research
Supplement No. 27 (1985)
Reprint

Vitamin A Deficiency as a Factor in Nutritional Anemia

L.A. MEJÍA

Division of Nutrition and Health, Institute of Nutrition of Central America and Panama, Guatemala City, Guatemala

Key Words: Hypovitaminosis A · Anemia · Iron deficiency · Vitamin A · Iron interaction · Hematopoiesis · Vitamin A fortification

Abstract: Epidemiological and experimental studies in both humans and laboratory animals suggest that lack of vitamin A may be a contributing factor in the etiology of nutritional anemia. Human subjects depleted of vitamin A develop anemia which does not respond to iron treatment until their vitamin A status is improved. Chronic vitamin A deficiency in the rat also leads to anemia characterized by low levels of serum iron and elevated amounts of this mineral in the liver and spleen. The incorporation of radioactive iron (^{59}Fe) into erythrocytes is also diminished. Furthermore, preschool children with low serum retinol levels may have low levels of serum iron and a high concentration of serum ferritin. The short-term effect of improving their vitamin A status – for example, through sugar fortification with retinyl palmitate – is a decrease in serum ferritin and a significant elevation in serum iron, percent saturation of transferrin and total iron binding capacity. The available data indicate that there is a biological interaction between vitamin A deficiency and iron nutrition and metabolism.

Effect of Vitamin A on Hematopoiesis and Iron Metabolism

The existing reports on the effect of hypovitaminosis A on hematopoiesis reveal two lines of contrasting evidence. On the one hand the occurrence of anemia and on the other of polycythemia. Early reports of hematopoietic changes associated with vitamin A deficiency in either human, experimental animals or both, have appeared since 1922. Anemia was found to be associated with vitamin A deficiency by a variety of authors [1–9]. In contrast, other researchers observed elevated levels of hemoglobin and hematocrit [10–15]. All these early findings have been reviewed and discussed by HODGES *et al* [16], and there is now data available which may explain this discrepancy.

Recent Studies

In 1978 HODGES *et al* [16] reported an experiment in which vitamin A deficiency was induced by feeding diets deficient or low in vitamin A to eight middle-aged men who voluntarily participated. As expected, the concentration of serum carotene fell rapidly and the concentration of retinol fell slowly during the vitamin A depletion which varied in the different subjects from 359 to 771 days. Despite a daily intake of 18–19 mg of iron in their diet, the men gradually began to manifest a mild degree of anemia accompanied by low serum iron levels. It was observed that during the depletion period there was a simultaneous drop in the levels of both vitamin A and hemoglobin (Fig. 1). When the anemia became manifest, oral medicinal iron (310 mg/day) was given. It turned out that the iron treatment had little or no effect as long as there was a vitamin A deficiency. The subject presented in Figure 1 responded transiently to medicinal iron, but relapsed despite continued therapy. Soon after vitamin A repletion was started with β-carotene, he made a prompt and complete hematological recovery while continuing the same diet.

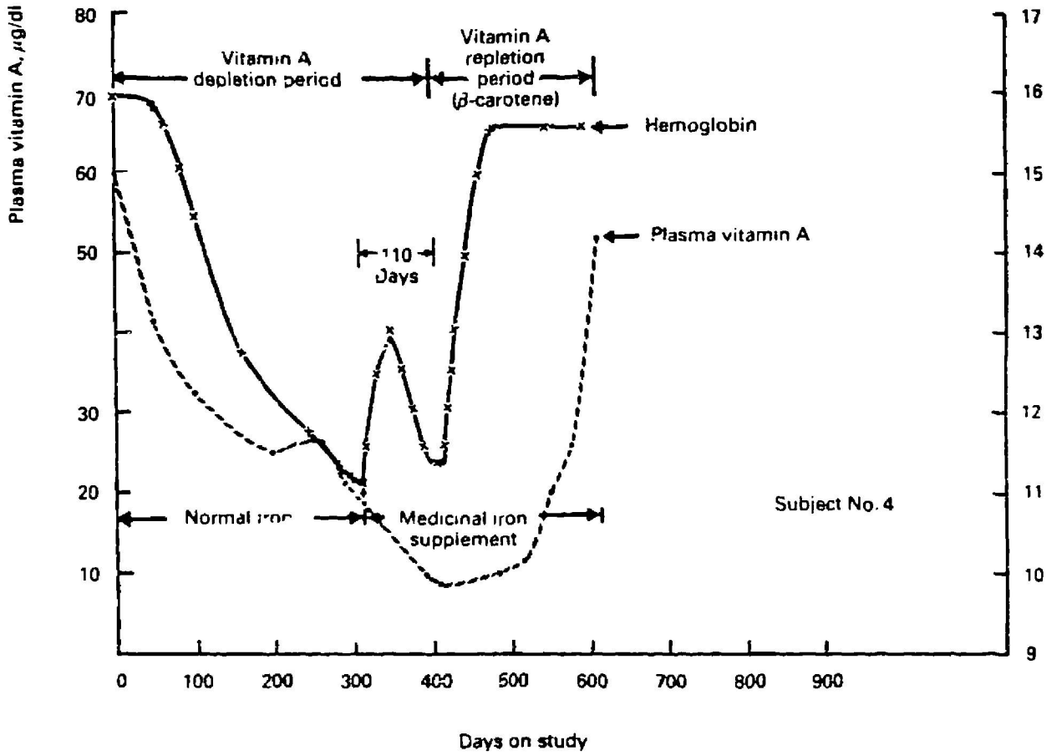

Fig. 1: Effect of vitamin A and iron supplements on plasma vitamin A and hemoglobin levels in a vitamin A depleted human volunteer [16].

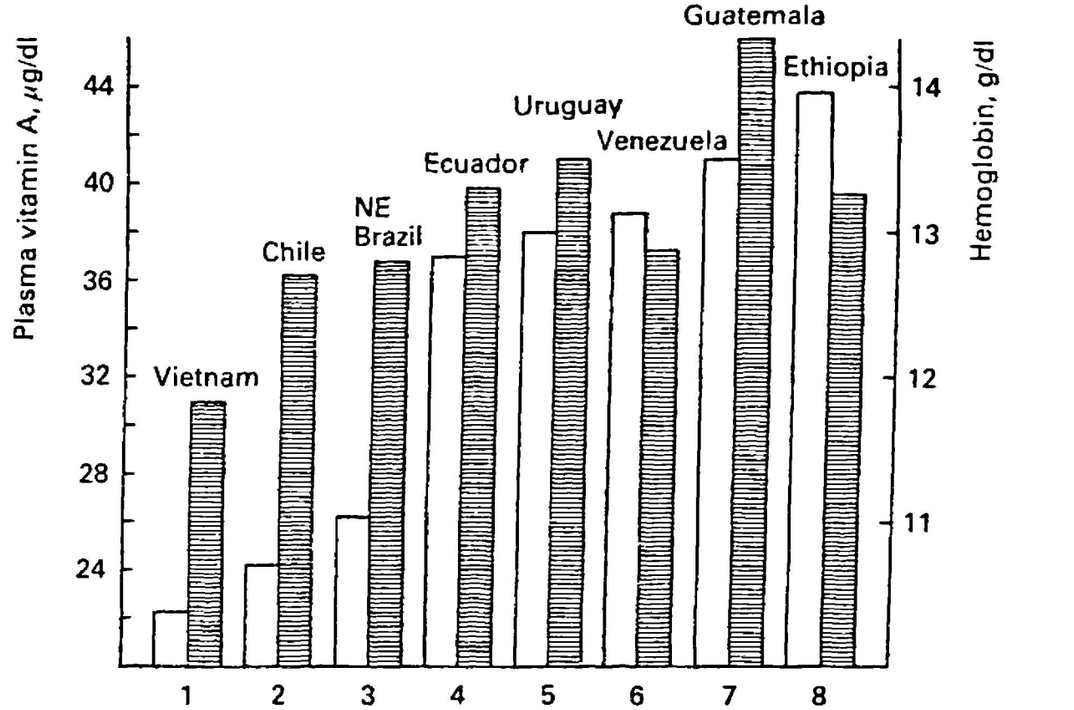

Fig. 2: Relationship of hemoglobin and plasma vitamin A as observed in several ICNND nutrition surveys (non-pregnant, non-lactating females 15–45 years of age) [16].

From the epidemiologic point of view it can be demonstrated not only that vitamin A deficiency and anemia coexist in some populations, but also that there is a significant association between plasma vitamin A and hemoglobin. This is demonstrated in Figure 2, showing a comparison between vitamin A and hemoglobin levels in a selected group of non-pregnant, non lactating females of reproductive age surveyed several years ago in several countries by the Interdepartmental Committe on Nutrition for National Defense (ICNND). In the countries examined, women with low vitamin A levels also had low hemoglobin values. In contrast, countries reporting higher vitamin A levels also showed higher hemoglobin levels.

In the Central American region, MEJÍA *et al* [17] have found significant correlations between plasma retinol and serum iron (Fig. 3). Children with low plasma retinol have low serum iron levels and those with high plasma retinol have high serum levels of iron. These correlations have been confirmed both in Indian children [18, 19] and in a group of elderly persons in Vienna [20].

Experimental animal studies have also shown that anemia may result from a lack of vitamin A [16, 21]. As illustrated in Figure 4, after approximately 40 days of feeding a vitamin A free diet to young adult rats, they exhibited lower hematocrit or hemoglobin levels than the control groups. At around 90 days, however, hematocrit and hemoglobin levels increased even reaching higher levels than those observed in the control groups. Isotopic dilution studies have

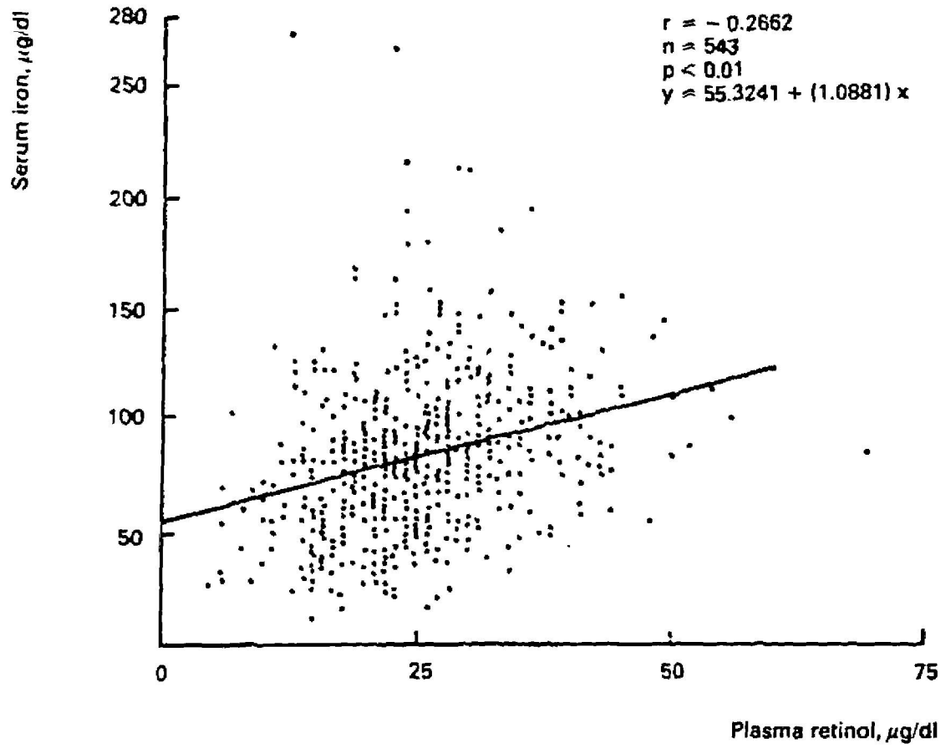

Fig. 3: Plasma levels of retinol versus serum iron in rural Central American children with iron intake ≥ 12 mg/day [17].

shown that this phenomenon is due to a reduction in blood and plasma volume which occurs when the vitamin deficiency becomes severe [22]. At this stage, the anemia is masked by hemoconcentration. This may be the reason why several investigators have failed to observe anemia in hypovitaminosis A. When the anemia developed, these animals also showed a reduction in serum iron and a concomitant elevation of the amount of iron in the liver. As illustrated in Figure 5 the concentration of liver iron began to increase in these animals at approximately the same time when hematocrit levels became lower than normal. Spleen iron also increased when the deficiency became severe.

These findings are supported by the radioisotope data presented in Table I which shows a greater incorporation of ^{59}Fe in the liver and spleen of the vitamin A deficient rats as compared with the control group [22]. All these data indicate that in hypovitaminosis A there is a shifting of body iron resulting in an elevation of iron stores and a decrease in plasma iron. Thus iron becomes less available to the erythropoietic tissue for red cell formation. In addition, it has been also demonstrated that in vitamin A deficient rats, there is a lower incorporation of ^{59}Fe into erythrocytes, suggesting that in vitamin A deficiency iron utilization for red cell formation is also impaired [22].

Tab. I: Absorption of ^{59}Fe and specific activities of liver and spleen in experimental rats [22]

	Absorption, %	Specific activity, C g tissue	
		liver	spleen
Control	43.9 ± 14.6[a] [1]	242 ± 22.4[a]	533 ± 97.2[a]
Pair-fed	12.0 ± 12.8[b]	180 ± 18.1[a]	280 ± 77.3[b]
Deficient	38.3 ± 6.7[a]	552 ± 85.4[b]	1217 ± 185.0[b]

[1] Means ± SEM. Means with differing superscripts are significant at $p < 0.005$.

Effect of Vitamin A Fortification

In Central America, nutrition surveys have revealed a high prevalence of hypovitaminosis A. Children in this region of the world have a low vitamin A intake, and the prevalence of serum retinol levels less than 20 µg/dl in rural children varied in the six countries from approximately 20% in Nicaragua to 50% in El Salvador. In an attempt to overcome this nutritional problem of the area, the Institute of Nutrition of Central America and Panama (INCAP) began a national vitamin A fortification program in Guatemala at the end of

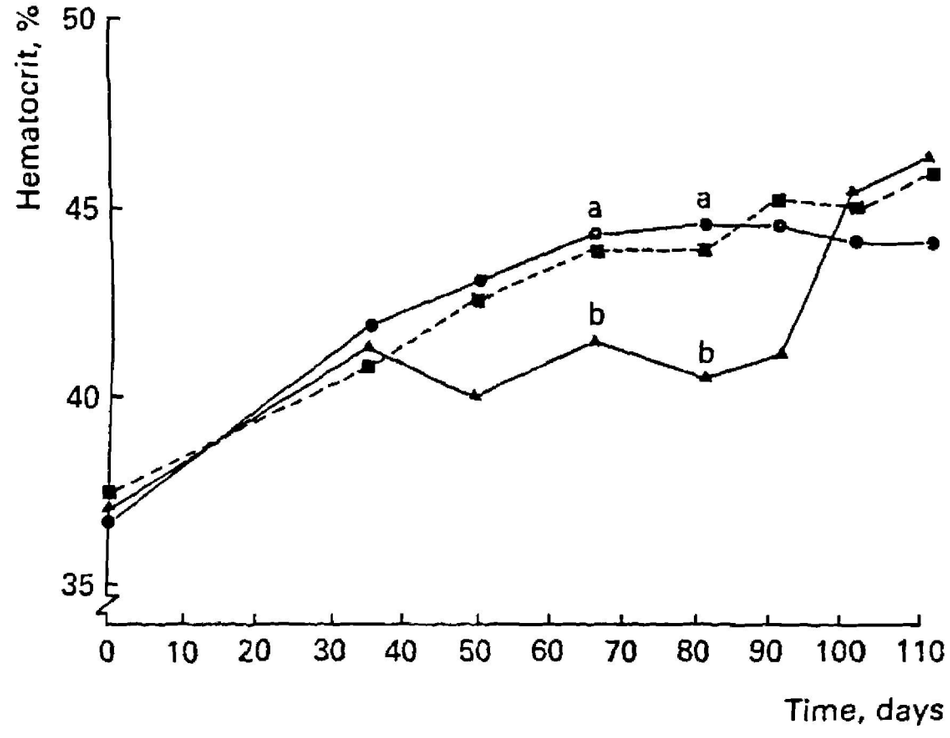

Fig. 4: Changes in the levels of hematocrit during depletion of vitamin A in the young adult rat [21]. Points bearing different superscript letters are significantly different at $p < 0.05$. ● = Control; ■ = pair-fed; ▲ = deficient.

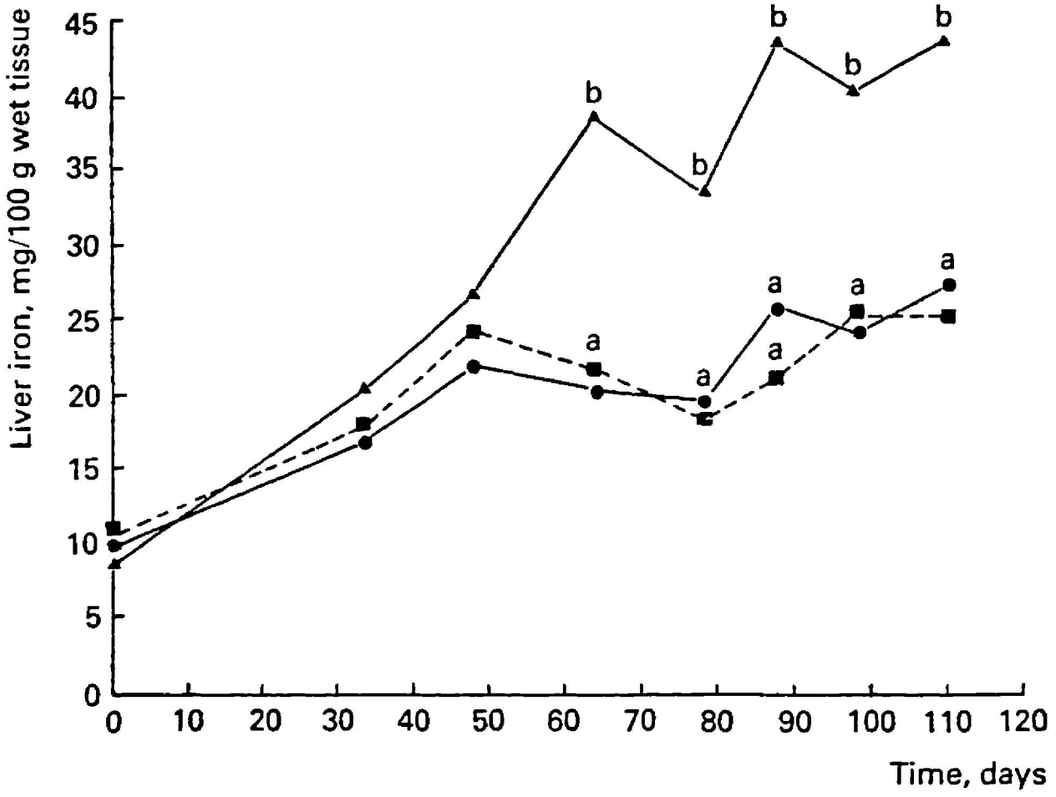

Fig. 5: Levels of iron in liver tissue of the young adult rat during depletion of vitamin A [21]. Points bearing different superscript letters are significantly different at $p < 0.05$.
● = Control; ■ = pair-fed; ▲ = deficient.

1975 using table sugar as the dietary vehicle. The concentration used was 15µg retinol equivalent (RE)/g sugar. The experimental design and methodology of this program and its evaluation have been published previously [23]. In summary, preschool children and lactating mothers from 12 small rural communities were studied for two years in five consecutive surveys; one prior to vitamin A fortification (Survey I), and four additional ones (Surveys II–V), at six month intervals after the intervention began. The dietary data revealed that in comparison with the pre-fortification survey, the implementation of sugar fortification resulted in a significant three-fold increase in the average daily intake of RE. As a result, there has been a highly significant reduction in the prevalence of low and deficient serum retinol levels in children. Similar results have been obtained in breast milk of lactating mothers. The average intake of iron, however, did not change throughout the two-year period of evaluation. This vitamin A program provided a unique opportunity to evaluate the effect of this single intervention on iron nutrition and metabolism at the population level. The results showed that vitamin A fortification alone had a positive effect on the iron nutriture of this population [24]. Figure 6

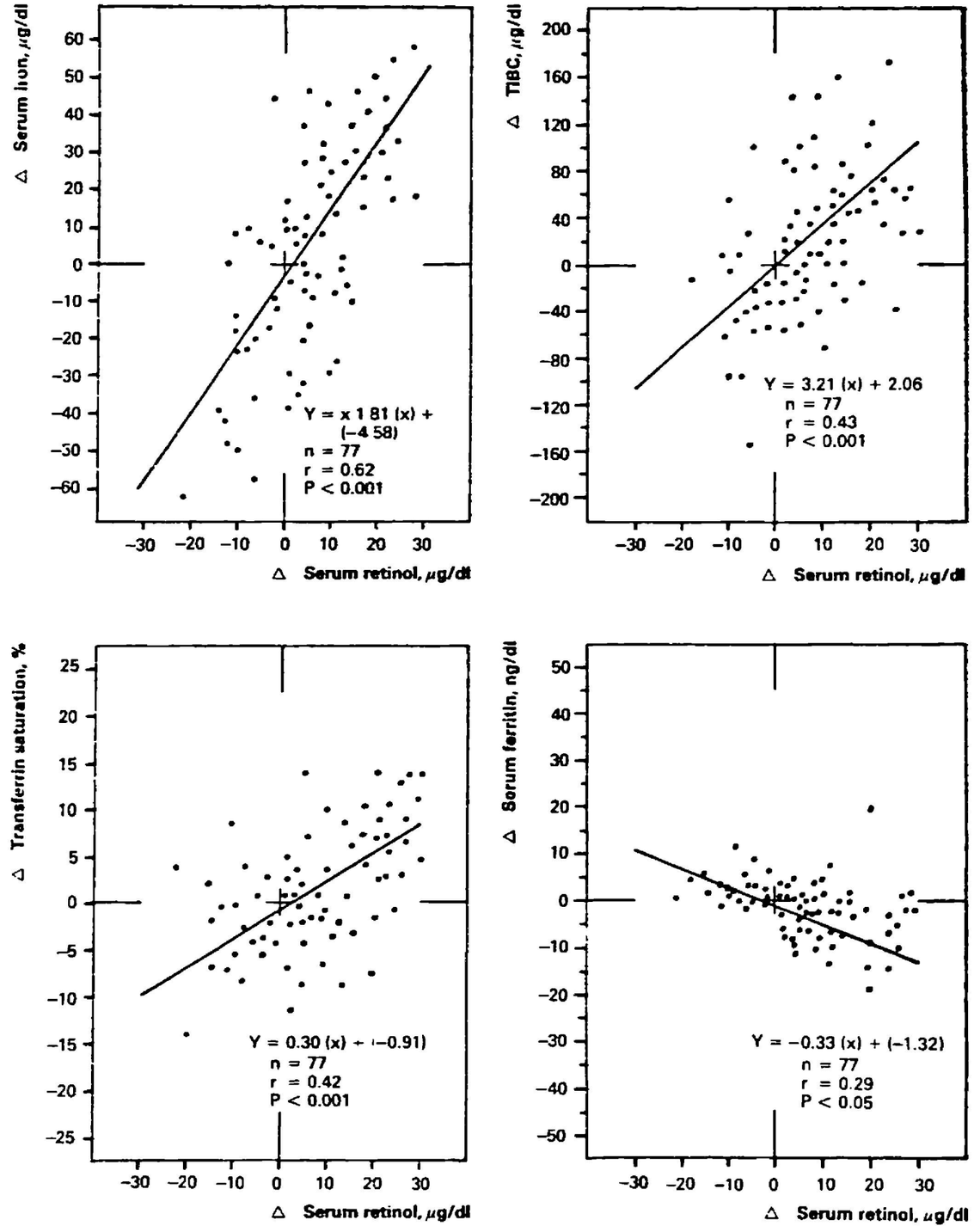

Fig. 6: Correlations between changes in serum retinol and changes in serum levels of iron parameters after six months of vitamin A fortification of Guatemalan children.
Δ = Change [24].

shows the change observed in serum retinol in relation to changes in iron indicators in a group of pre-school children sampled in the basal survey and at six months after fortification began. In these children, there were significant positive correlations between the experienced change in serum retinol and changes in serum iron, total iron binding capacity (TIBC) and saturation of transferrin. In contrast, stored iron, as defined by serum ferritin levels, correlated negatively. These results suggest that vitamin A mobilized the stored iron into the circulation and also support previous observations in experimental animals. It is interesting to note that in these children, despite an increase in serum iron levels, there is also an elevation in TIBC suggesting that vitamin A could have affected the levels of the glycoprotein iron carrier, transferrin. However, a recent separate study has shown that this is not a direct effect of vitamin A, but rather an improvement on protein nutritional status probably mediated through this vitamin [25].

After a more prolonged intervention, the effect of vitamin A on iron nutriture changed particularly in relation to iron stores (Table II). When comparing, in a group of children, the distribution of cases by categories of levels of adequacy of iron indicators between the basal and the last survey, an overall improvement in the levels of iron indicators can be observed. This

Tab. II: Percent distribution of cases in surveys I and V by categories of iron parameters

	Survey I[1], %	Survey V[2], %
Serum iron, µg/dl		
< 50	43.1	25.5[3]
50–75	27.5	39.2
> 75	29.4	35.3
Serum TIBC, µg/dl		
< 250	5.9	2.0
250–350	37.3	49.0
> 350	56.9	49.9
ST, %		
< 15	39.2	27.5
15–20	33.3	33.3
> 20	27.5	39.2
Serum ferritin, ng/ml		
< 10	64.7	21.6[3]
10–20	23.5	58.8
> 20	11.8	19.6

[1] Basal survey.
[2] Two years after initiation of vitamin A fortification.
[3] The distributions are significantly different ($p < 0.05$ or better).

favorable effect was more marked in regard to the amount of stored iron. There was a lower prevalence of children with low serum ferritin levels in survey V than in survey I, prior to vitamin A fortification. SIIMES *et al* [26] have shown that in healthy children the levels of serum ferritin remain constant from 6 months to 16 years of age; therefore, the observed favorable change in iron reserves cannot be attributed to the fact that the children were two years older at the end of the study. Most probably this elevation in iron stores observed after two years is due to an enhancement of dietary iron absorption triggered as a response to the initial depletion of iron reserves experienced after 6 months of vitamin A fortification, and in addition to a possible increment on hematopoietic utilization of this mineral. Since this was a retrospective study performed in stored blood serum samples, no hematological data were available.

Conclusion

Although further information about the impact of vitamin A nutriture on the hematological condition of given populations must be obtained, the existing data indicate that there is a metabolical interaction between vitamin A and iron nutrition. Through this relationship vitamin A deficiency may contribute to the occurrence of nutritional anemia, especially in areas where hypovitaminosis A is highly prevalent and endemic. When planning nutritional interventions, proper consideration should be given to this interaction.

References

1 FINDLAY, G M, MCKENZIE R D: The bone marrow in deficiency diseases. J Pathol *25*, 402–403, 1922.
2 WOLBACH, S B, HOWE, P R: Tissue changes following deprivation of fat soluble A vitamin. J Exp Med *42*, 753–781, 1925.
3 KOESSLER, K K *et al:* The relation of anemia primary and secondary to vitamin A deficiency. J Am Med Ass *87*, 476–482, 1926.
4 SURE, B *et al:* The effect of avitaminosis on hematopoietic function. I. Vitamin A deficiency. J Biol Chem *83*, 375–385, 1929.
5 BLACKFAN, K D, WOLBACH, S B: Vitamin A deficiency in infants. A clinical and pathological study. J Pediatr *3*, 679–706, 1933.
6 FRANK, M: Beitrag zur Hämatologie der A-Avitaminose. Monatsschr Kinderheilk *60*, 350–355, 1934.
7 WAGNER, K H: Die experimentelle Avitaminose A beim Menschen. Hoppe-Seylers Z physiol Chem *264*, 153–159, 1940.
8 US Department of Health Education and Welfare. Nutrition Survey of Paraguay, May–August 1965, pp 1–241. US Government Printing Office, Washington, 1967.

9 O'TOOLE, B A *et al:* Vitamin A deficiency and reproduction in Rhesus monkeys. J Nutr *104,* 1513–1524, 1974.
10 MCLAREN, D S *et al:* Xerophthalmia in Jordan. Am J Clin Nutr *17,* 117–130, 1965.
11 MCLAREN, D S *et al:* Biochemical and hematological changes in the vitamin A deficient rat. Am J Clin Nutr *17,* 131–138, 1965.
12 NOCKLES, C F, KEINHOLZ, E W: Influence of vitamin A deficiency on testes, bursa Fabricius, adrenal and hematocrit in cockerels. J Nutr *92,* 384–388, 1967.
13 AMINE, E K *et al:* Comparative hematology during deficiencies of iron and vitamin A in the rat. J Nutr *100,* 1033–1040., 1970.
14 COREY, J E, HAYES, K C: Cerebro-spinal fluid pressure, growth and hematology in relation to retinol status of the rat in acute vitamin A deficiency. J Nutr *102,* 1585–1593, 1972.
15 MEE, J M L, STANLEY, R W: Association between blood vitamin A and packed cell volume in dairy animals. Nutr Rep Int *9,* 401–406, 1974.
16 HODGES, R E *et al:* Hematopoietic studies in vitamin A deficiency. Am J Clin Nutr *31,* 876–885, 1978.
17 MEJÍA, L A *et al:* Vitamin A deficiency and anemia in Central American children. Am J Clin Nutr *30,* 1175–1184, 1977.
18 MOHANRAM, M *et al:* Hematological studies in vitamin A deficient children. Int J Vit Nutr Res *47,* 389–393, 1977.
19 JAGADEESAN, V, REDDY, V: Interrelationship between vitamins E and A: a clinical study. Clin Chim Acta *90,* 71–74, 1978.
20 WENGER, R *et al:* Beziehungen zwischen dem Vitaminstatus (Vitamine A, B_1, B_2 und C), klinischen Befunden und den Ernährungsgewohnheiten in einer Gruppe von alten Leuten in Wien. Wien Klin Wochenschr *91,* 557–562, 1979.
21 MEJÍA, L A *et al:* Clinical signs of anemia in vitamin A deficient rats. Am J Clin Nutr *32,* 1439–1444, 1979.
22 MEJÍA, L A *et al:* Role of vitamin A in the absorption, retention and distribution of iron in the rat. J Nutr *109,* 129–137, 1979.
23 ARROYAVE, G *et al:* Evaluation of sugar fortification with vitamin A at the national level. Sci Publ No. 384. Pan American Health Organization, Washington, 1979.
24 MEJÍA, L A, ARROYAVE, G: The effect of vitamin A fortification of sugar on iron metabolism in preschool children in Guatemala. Am J Clin Nutr *36,* 87–93, 1982.
25 MEJÍA, L A, ARROYAVE, G: Lack of direct association between serum transferrin and serum biochemical indicators of vitamin A nutriture. Acta Vitaminol Enzymol *5,* 179–184, 1983.
26 SIIMES, M A *et al:* Ferritin in serum: Diagnosis of iron deficiency and iron overload in infants and children. Blood *43,* 581–589, 1974.

L. A. Mejía, PhD, Division of Nutrition and Health, Institute of Nutrition of Central America and Panama (INCAP), PO Box 1188, Guatemala City, Guatemala