Vitamin A deficiency and anemia in Central American children[1, 2]

L. A. Majía, M.A., R. E. Hodges,[3] M.D., G. Arroyave, Ph.D., F. Viteri, M.D., and B. Torún, M.D.

ABSTRACT In order to investigate the role of vitamin A nutriture in the prevalence of anemia in Central America, a retrospective evaluation of the data of the six Institute of Nutrition of Central America and Panama/Office for International Research nutrition surveys of Central America and Panama has been made. Three groups of children: 1 to 4, 5 to 8, and 9 to 12 years old, living between 0 and 2,500 feet above sea level were studied. Several biochemical and dietary parameters related to anemia were correlated with plasma levels of retinol. Children between the ages of 5 and 12 years showed a significant positive correlation between hemoglobin and plasma retinol. Children aged 1 to 4 years did not show a similar correlation. In children of all age groups there were positive correlations between plasma retinol and serum iron. Percent saturation of transferrin was also found to be lower when plasma retinol levels were low. Children with an adequate intake of iron, as classified by both dietary information and socioeconomic level, showed a significant positive correlation between plasma retinol levels and iron in their serum. In contrast, no correlation was found when dietary iron was low. In the light of these findings, a possible relationship between vitamin A deficiency and anemia is suggested. *Am. J. Clin. Nutr.* 30: 1175-1184, 1977.

Deficiency of vitamin A and nutritional anemia have been shown to be two of the major nutritional problems, especially in children, not only in developing countries (1-5) but also in highly developed nations (6).

In most of these countries, an inadequate intake of vitamin A appears to be the underlying cause of low plasma levels of retinol. Nutritional anemia, on the other hand, has been traditionally associated with deficiencies of iron, folate, vitamin B_{12}, and protein. It has also been thought that parasitic infestation plays an important role (7, 8). The roles of vitamin E, vitamin B_6, and some microelements such as zinc and copper have not been fully studied in these populations, thus there is not enough evidence to consider them of primary importance.

Recent studies in humans and in experimental animals by Hodges et al. (9, 10) have demonstrated an apparent association between vitamin A deficiency and anemia. Low values for hemoglobin, hematocrit, red blood cell count, and serum iron, accompanied by elevated levels of iron in the liver have been reported. In vitamin A deficient humans, medicinal iron did not raise hemoglobin levels until after vitamin A was also given.

Since 1922 numerous investigators have shown that anemia may be associated with vitamin A deficiency (9-18). These obser-

[1]From the Departments of Nutrition and Internal Medicine, Nutrition Section, University of California, Davis, California 95616 (L.A.M., R.E.H.) and the Institute of Nutrition of Central America and Panama, Carretera Roosevelt, Zona 11, Guatemala City, Guatemala, Central America (G.A., F.V., B.T.).

[2] Partially supported by research funds from the University of California, Davis, School of Medicine and the Fellowship 45938 of the Organization of American States awarded to L.A.M.

[3]Address reprint requests to: Robert E. Hodges, M.D., Department of Internal Medicine, Section of Nutrition, TB 148, University of California, School of Medicine, Davis, Calif. 95616.

vations have been contradicted by other reports of apparent polycythemia that probably resulted from hemoconcentration that sometimes occurs in hypovitaminosis A (19–22). This disparity may have resulted from alterations in water metabolism as a result of impaired renal function. Polyuria in vitamin A deficient sheep, that would lead to hemoconcentration, has been reported by Webb et al. (23). Alterations in glomerular filtration rate and renal plasma flow have also been found in ewes severely deficient in vitamin A (24). These physiological changes, as in the case of polyuria, would indeed mask any effect of vitamin A deficiency on hematopoiesis and could explain the elevated values of hemoglobin and hematocrit reported by several investigators. The results of Amine et al. (22), however, show that there must be an interaction between vitamin A and iron.

In Central America, from 66 to 88% of the families in the six countries consume less than half the Recommended Dietary Allowance of vitamin A (NRC 1963, adapted to the Central American population; INCAP,[4] 1965), and the average prevalence of "low" and "deficient" serum levels of retinol, according to the ICNND[5] standards, varies in the rural population from 8.5% in Panama to 22.5% in El Salvador (1). Furthermore, based on the normal hematological values for Central America (25), the prevalence in this area of individuals with more than 75% chance of belonging to a population with subnormal hemoglobin is, on the average, 14.7% (26). These nutritional deficiencies affect primarily preschool and school-age children. Interestingly, in these countries, there are some individuals who do not respond to iron supplementation (F. E. Viteri, personal communication). These facts and the recent findings of Hodges et al. led us to perform a careful study of the vitamin A status as it related to anemia in selected groups of Central American children in order to evaluate the possible contribution of vitamin A deficiency to the prevalence of anemia.

Materials and methods

Data from Nutrition surveys performed by INCAP/OIR[6] between 1965 and 1967 for the five Central American countries and Panama were used for this study. From the total Central American population, selected groups of children were chosen according to the criteria used for the determination of normal hematologic values in Central America (25). Thus, hematologic variations due to age, sex, altitude, and physiological state were taken into consideration. The procedure for collecting and analyzing blood samples has been reported elsewhere (25). Three groups of children, 1 to 4, 5 to 8, and 9 to 12 years of age were studied. Their place of residence was between 0 and 750 m (2,500 feet) above sea level. From these categories, groups of rural children were also classified according to dietary information available at the family level as having a high iron intake (≥12 mg/day) or a low iron intake (<10 mg/day). A further grouping was made using socioeconomic indices (27). "High," "medium," and "low" socioeconomic levels were adopted as previously defined by Arroyave et al. (28, 29). Consideration was also given to plasma levels of total proteins and of folate. Seven grams per deciliter and 5 ng/ml, respectively, were arbitrarily considered as adequate levels. No evaluation was made of the vitamin B_{12} status, since this is not generally considered to be a nutritional problem in the Central American area (1). All of the relevant information for this study was entered on IBM cards and a series of correlations was made using computers. Total and segmental analyses of different variables were carried out. Correlation coefficients, regression lines, scatter diagrams and complimentary statistical data were thus obtained. Lack of complete individualized dietary data prevented correlation between biochemical parameters and dietary factors.

Results

When segmental analyses of 10µg/dl increments of retinol values were made, in order to investigate the characteristics of the hemoglobin curve with increasing amounts of this vitamin, it was found that in children 1 to 4 years old, there was not a concomitant change in hemoglobin levels. By contrast, there was a positive correlation in older children. Groups of children ages 5 to 8 and 9 to 12, showed rising hemoglobin values when plasma retinol levels increased. In addition, serum iron levels in all three age groups showed a progressive increase when plasma retinol levels increased. When either hemoglobin or serum iron rose, a plateau was eventually reached.

---

[4] Institute of Nutrition of Central America and Panama.

[5] Interdepartmental Committee on Nutrition for National Defense.

[6] Office for International Research. (Formerly, ICNND, and now known as Nutrition Program, Center for Disease Control, United States Department of Health, Education and Welfare).

The overall correlation between plasma retinol and hemoglobin for each one of the age groups (Figs. 1 to 3) showed statistically significant results for children 5 to 8 and 9 to 12 years old; but not for the youngest group, ages 1 to 4 years old. A further step was taken, based on the fact that group hemoglobin levels cannot go above a "normal" limit and also the observation that hemoglobin levels plateau when the plasma level of retinol reaches approximately 30 μg/dl. Accordingly, a correlation was made between levels of hemoglobin and retinol in those cases with plasma retinol levels of 30 μg/dl or below. This yielded a much more significant correlation as shown by the correlation coefficients and the slope of the curves (Figs. 2 and 3), but once again the youngest children failed to show a significant correlation (Fig. 1).

Figures 4 to 6 show the overall correlation between serum iron and plasma retinol. In each age group, there were significant correlations. These three groups were then combined yielding an $r = +0.2181, P < 0.05$.

Total iron binding capacity (TIBC) was

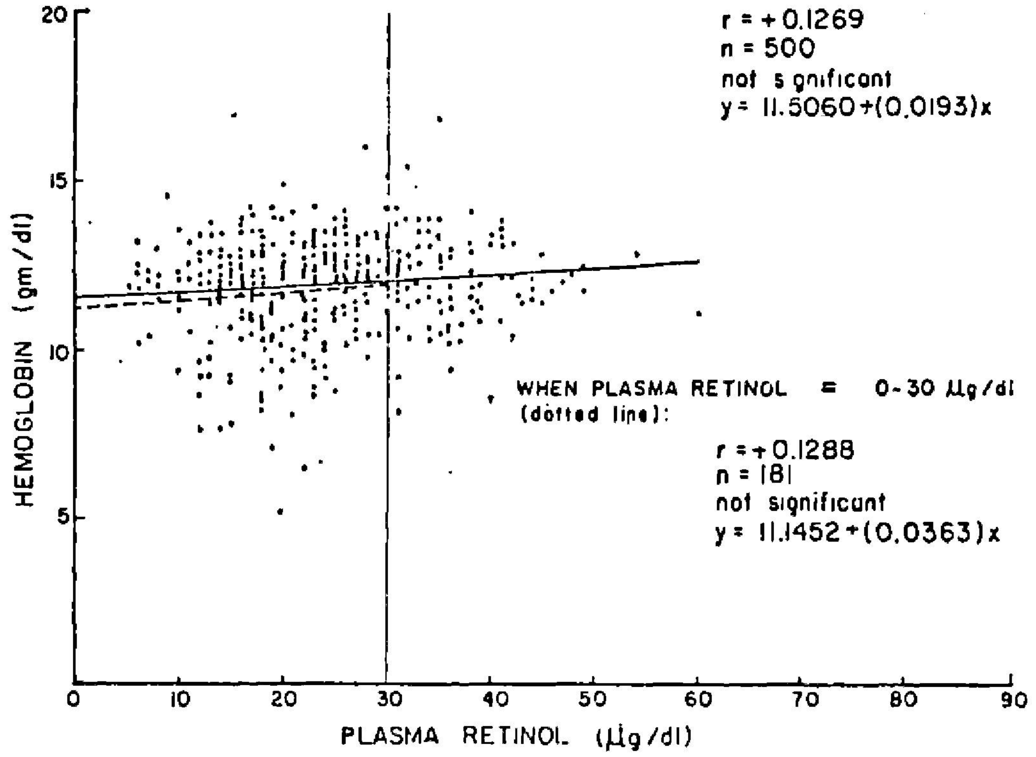

FIG. 1. Total and partial correlation (plasma retinol 0 to 30 μg/dl) of plasma retinol versus hemoglobin in children 1 to 4 years old.

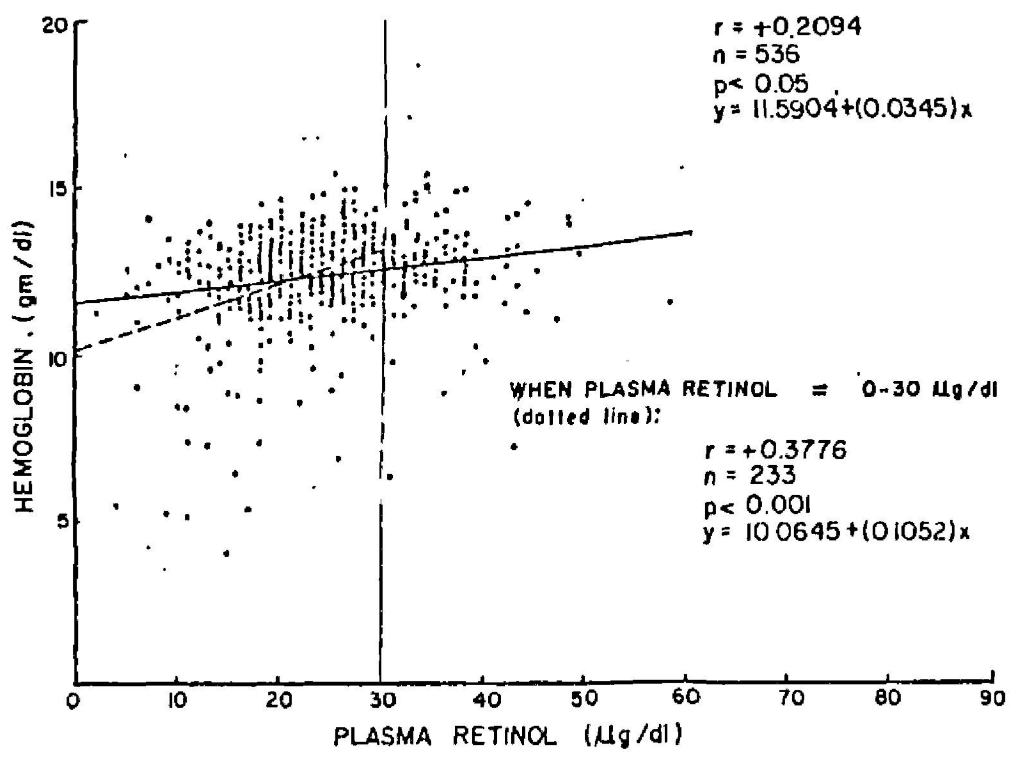

FIG. 2. Total and partial correlation (plasma retinol 0 to 30 μg/dl) of plasma retinol versus hemoglobin in children 5 to 8 years old.

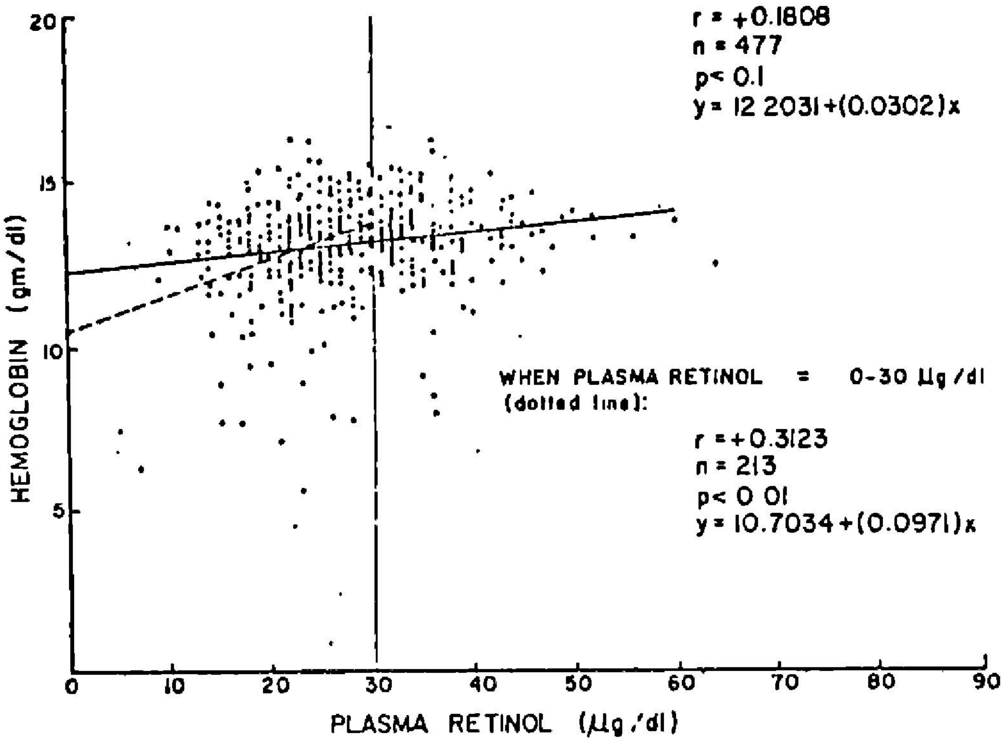

FIG. 3. Total and partial correlation (plasma retinol 0 to 30 µg/dl) of plasma retinol versus hemoglobin in children 9 to 12 years old.

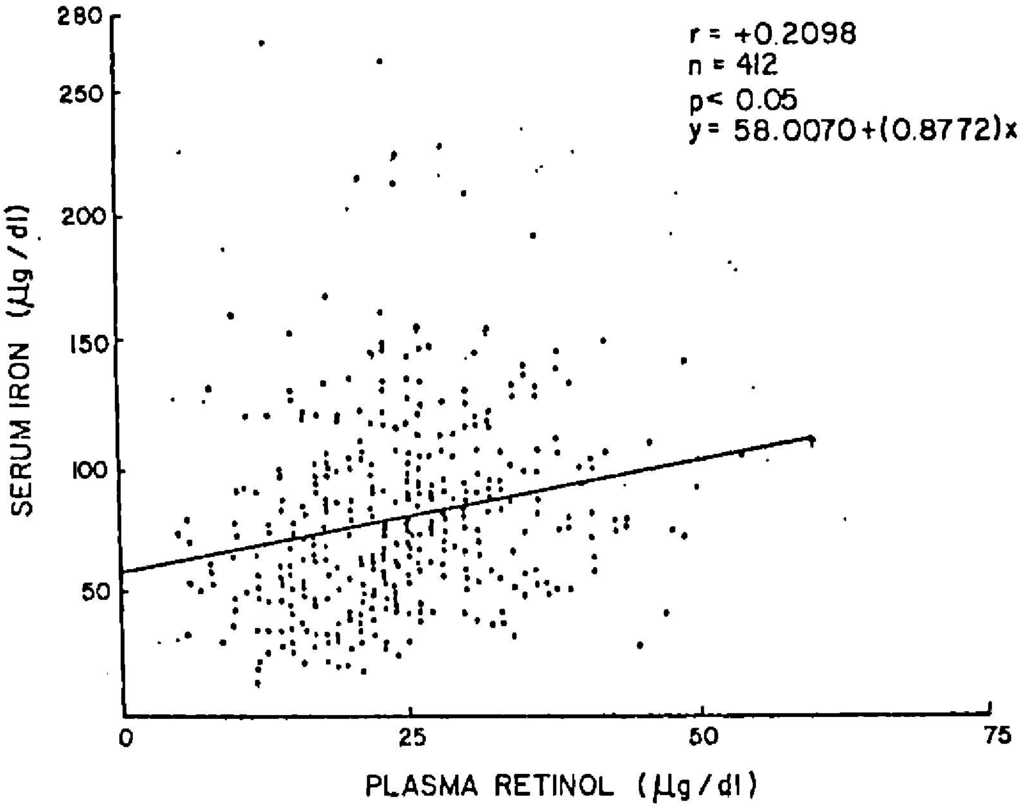

FIG. 4. Correlation between plasma retinol levels and serum iron in children 1 to 4 years of age.

not found to be statistically different at low levels of plasma retinol (<20 µg/dl) than at high levels (>20 µg/dl), in any of the three age groups. Percent saturation of transferrin on the other hand, was found to be low at low levels of retinol and elevated at high levels of this vitamin, except for the 5- to 8-year-old group in which this difference was not significant (Table 1).

Analysis using dietary information

Children 1 to 12 years of age, with a high iron intake showed a significant positive correlation between plasma retinol levels and serum iron levels. However, when the iron intake was low, there was no significant correlation (Figs. 7 and 8).

A similar pattern of correlation between serum iron and plasma retinol was observed when each age group was analyzed independently. Positive correlation coefficients as high as +0.2386 (n = 154, $P < 0.02$), +0.2737 (n = 192, $P < 0.01$), +0.3432 (n = 167, $P < 0.001$) were reached when segmental correlations of vitamin A (from 0 to 40 µg/dl) were made for children 1 to 4, 5 to 8, and 9 to 12 years old, respectively, having a high iron intake in the diet. By contrast, when the same statistical procedure was followed for children whose dietary iron was low, there was not a significant correlation for any of the three age groups.

Analysis by socioeconomic level

A significant positive correlation was found between plasma retinol and serum iron in children belonging to the highest socioeconomic level (Fig. 9). This group revealed 71.2% prevalence of cases above 70 μg/dl of serum iron, compared with prevalence in only 48.1% children of the lowest socioeconomic level, who showed no correlation between serum iron and plasma retinol (Fig. 10).

Consideration of other hematinic factors

Correlation coefficients were calculated for hemoglobin versus plasma retinol and

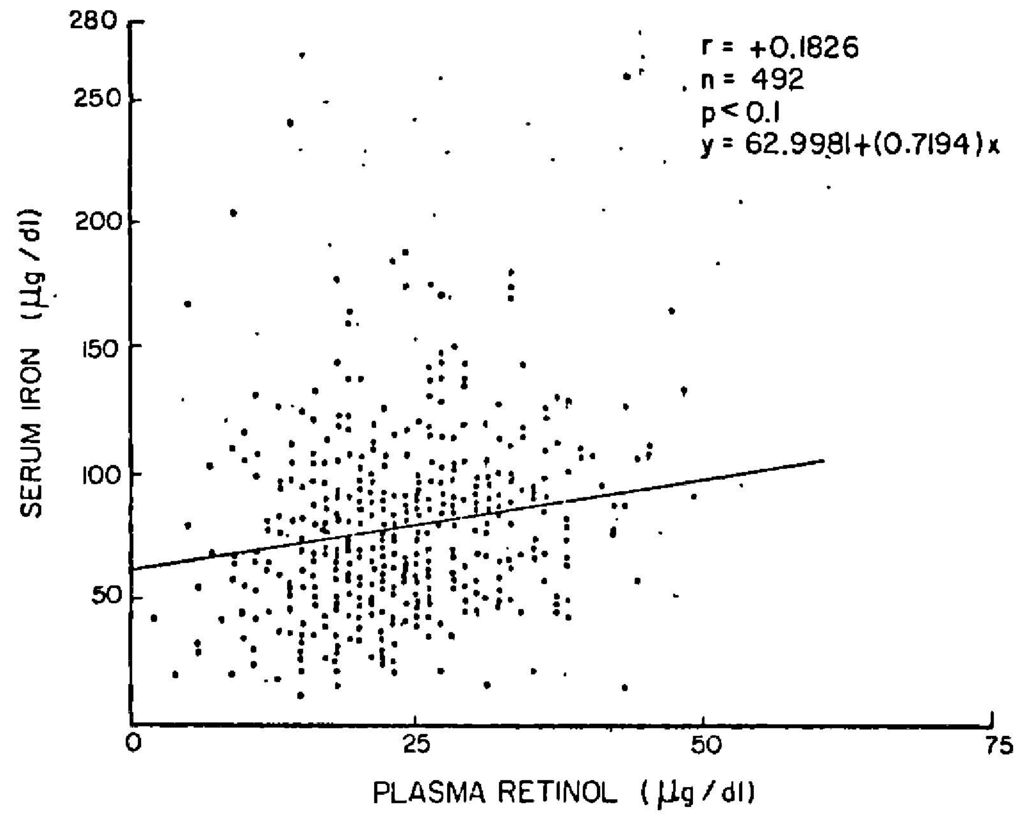

FIG. 5. Correlation between plasma retinol levels and serum iron in children 5 to 8 years of age.

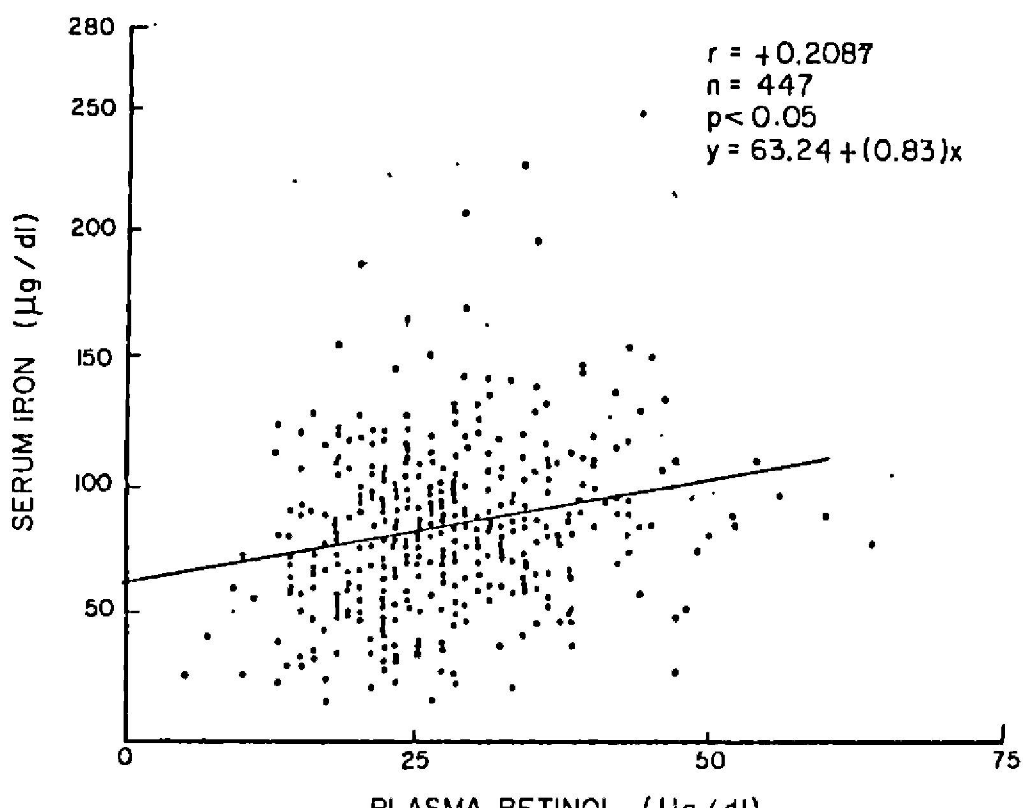

FIG. 6. Correlation between plasma retinol levels and serum iron in children 9 to 12 years of age.

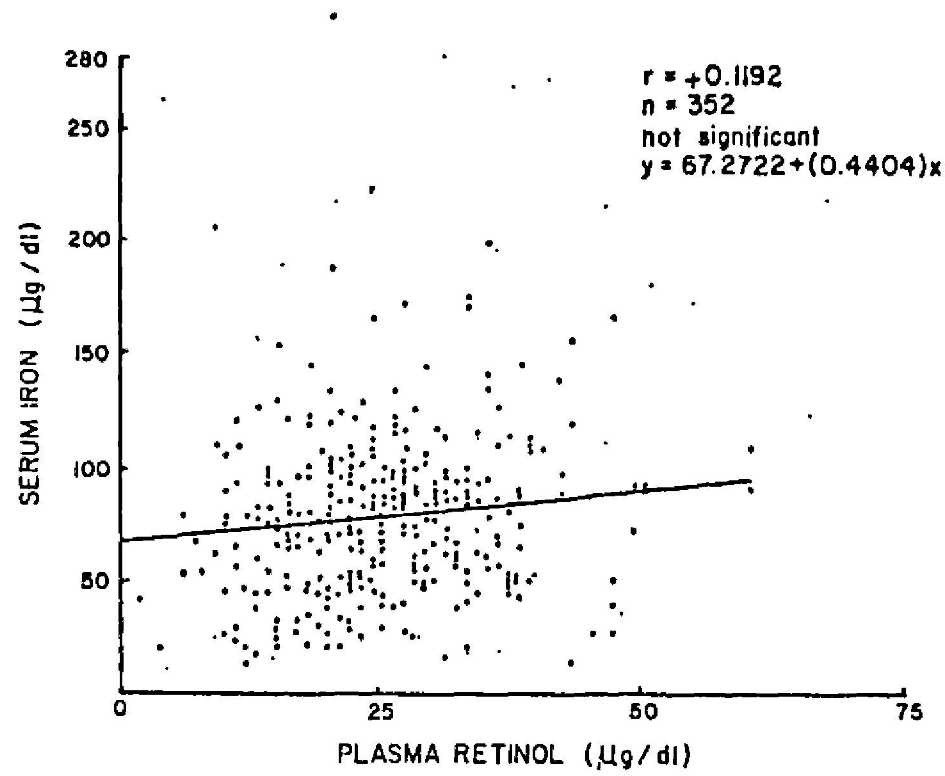

FIG. 8. Plasma levels of retinol versus serum iron in rural children 1 to 12 years of age with "low" dietary iron (<10 mg/day).

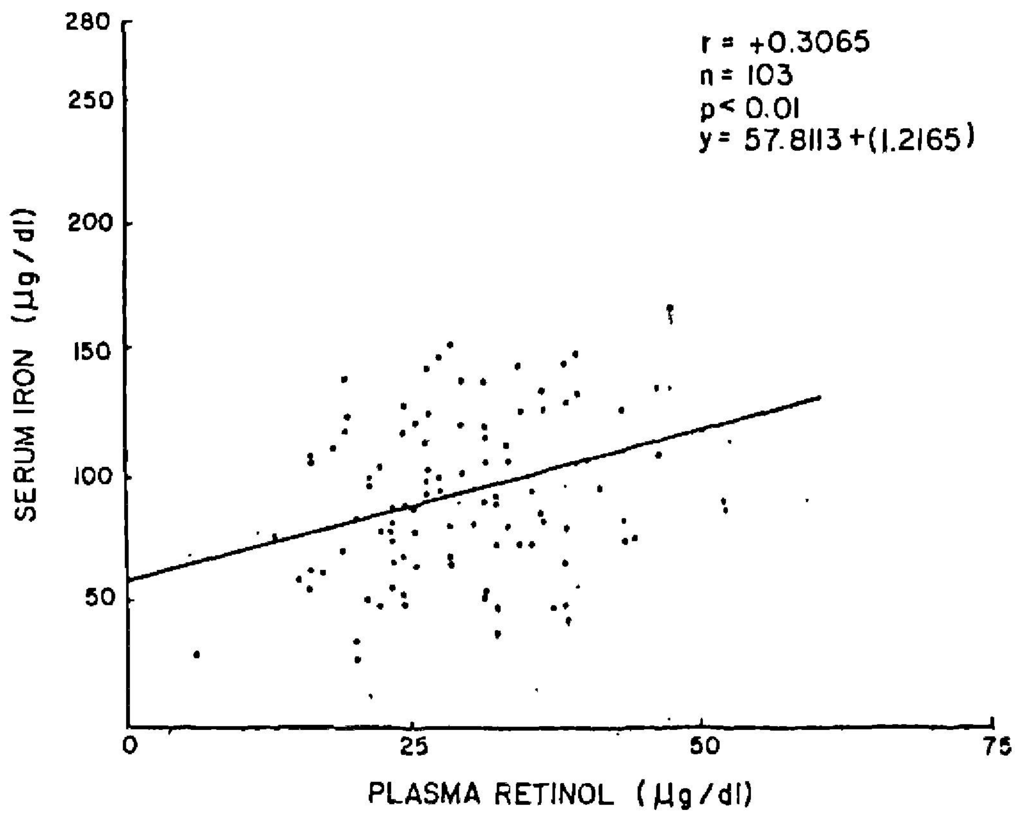

FIG. 9. Plasma levels of retinol versus serum iron in children 1 to 12 years old, belonging to a "high" socioeconomic level.

is not efficiently released into the circulation for tissue use. In other words, iron mobilization may be impaired. This would explain the iron deficiency anemia found in humans and in experimental animals lacking adequate amounts of vitamin A. It can also be inferred from this study, that there is a delay between the onset of vitamin A deficiency, low serum iron levels and the development of anemia. This is illustrated by the relatively high hemoglobin levels observed in the youngest group of children who also had low plasma values of retinol and low serum iron levels (Fig. 1). This also suggests that serum iron could be a better index than hemoglobin, of the action of vitamin A on hematopoiesis.

The absence of significant differences in total iron binding capacity at low or high plasma retinol levels, suggests that vitamin A deficiency may not affect the iron transport protein, transferrin. On the other hand, a high percentage of saturation of transferrin at high plasma retinol levels as

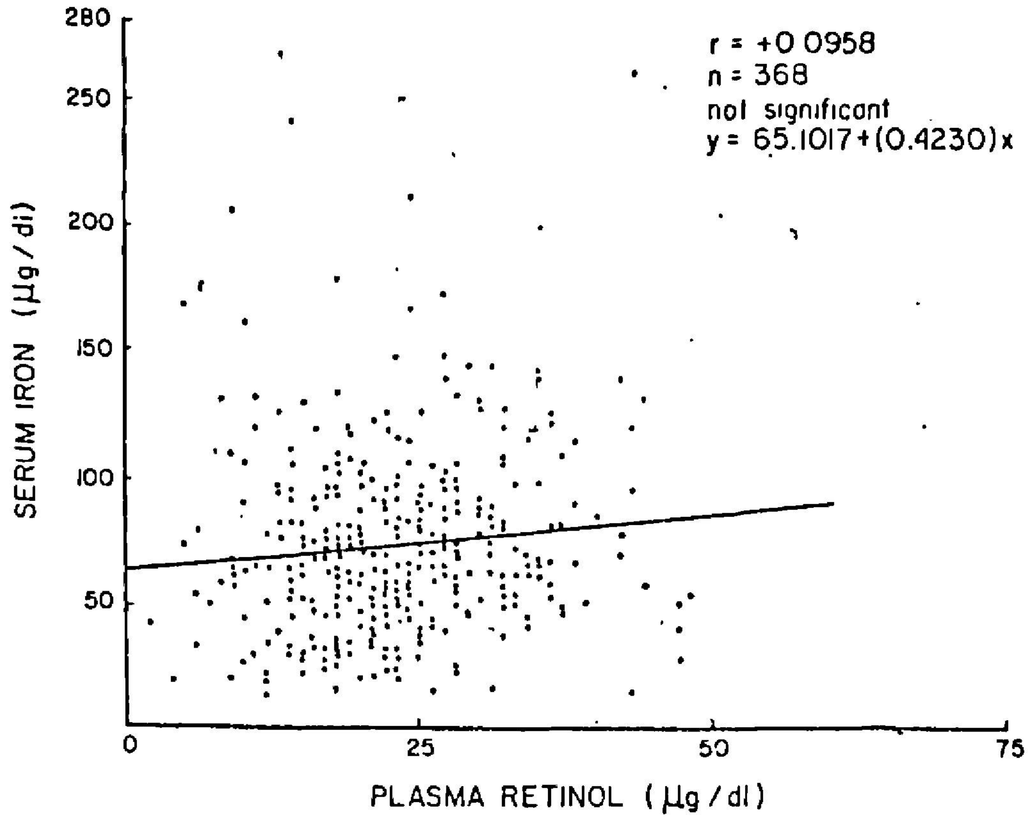

FIG. 10. Plasma levels of retinol versus serum iron in children 1 to 12 years of age, belonging to a "low" socioeconomic level.

compared with low retinol levels, indicates that vitamin A may indeed affect serum iron levels.

These results, however, should be interpreted cautiously, because the correlations observed might be merely a reflection of dietary patterns or availability of iron in a given type of diet rather than an alteration of iron metabolism. Nevertheless, this possibility can be excluded in part by the finding of a positive correlation between serum iron and plasma retinol when dietary iron is high but not when dietary iron is low. This is illustrated by a greater slope of the curve when dietary iron was "adequate." This phenomenon of a positive correlation with high intakes of iron and no correlation with low intakes of iron was further supported by a similar finding when Central American children were classified by socioeconomic levels. It has been previously reported that in Central America there is an association between the socioeconomic level and the nutritional status (28, 29). It can logically be assumed that at the low socioeconomic level, the iron intake is probably low because the diet contains more plant foods but that at high socioeconomic levels the iron intake is likely to be high because of more animal foods in the diet. At the same time, if the dietary iron status is adequate and there is a considerable storage of iron, then iron can be released into the circulation when retinol levels increase; thus a positive correlation is found. On the other hand if there is a lack of iron, the effect of vitamin A on this element cannot be seen and therefore, since there is nothing that can be released from storage into the circulation, there is no correlation between plasma retinol and blood hemoglobin.

Folate deficiency has been shown to exist in Central America, but in our study, low folate levels did not appear to influence correlations between plasma retinol and hemoglobin. Cook et al. (31) previously reported that in Lain American countries, there is no correlation between hemoglobin levels and folate or vitamin B_{12}, except during pregnancy. Iron deficiency has been considered the major cause of anemia in these populations.

The importance of different levels of plasma protein in our study is less clear. The INCAP/OIR surveys reported only a few cases showing clinical signs of severe protein deficiency.

The fact that our sample constitutes a somewhat heterogenous population strengthens our confidence that the significant correlations may have a true biological meaning. In any event, it is certain that in Central America, hypovitaminosis A and iron deficiency can and do occur simultaneously. Shank et al. (32), in an evaluation of the cause of mild anemia in adolescent girls in the State of New York, also found that plasma retinol levels were significantly different between groups of girls with low and those with high serum iron levels. Our findings confirm that observation.

The deleterious effects of even mild anemia on physical work capacity has been shown by Viteri and Torun (33), and more recently by Gardner et al. (34). Periods of rapid growth as in childhood and during pregnancy, also create greater oxygen demands. Thus, if deficiency of vitamin A or any of its metabolities is involved in the etiology of anemia, this would be another important reason to strengthen our efforts to improve the supplies of vitamin A in those countries where dietary intakes of this vitamin are limited.

References

1. Nutritional evaluation of the population of Central America and Panama. Regional Summary (1965–1967). Institute of Nutrition of Central America and Panama, and Nutrition Program. Center for Disease Control. U.S. Department of Health, Education and Welfare, Publication No. (HSM) 72-8120.
2. Hypovitaminosis A in the Americas. Report of a PAHO Technical Group Meeting. Washington, D.C.: Pan American Health Organization Scientific Publication No. 198, 1970.
3. Oomen, H. A. P. C., D. S. McLaren and H. Escapini. Epidemiology and public health aspects of hypovitaminosis A. A global survey on xerophthalmia. Trop. Geograph. Med. 16: 271, 1964.
4. Simmons, W. K., and A. Vieira de Mello. Blindness in the nine states of Northeast Brazil. Am. J. Clin. Nutr. 28: 202, 1975.
5. Gandra, Y. R. Iron deficiency anemia in Latin America and Caribbean populations. In: Iron Metabolism and Anemia. Washington, D.C.: Pan American Health Organization Scientific Publication No. 184, 1969, p. 56.
6. Ten State Nutrition Survey of the United States. Reports I-V. Atlanta, Georgia: Center for Disease Control, 1972.
7. Roche, M. The relationship between hookworm infection and anemia. In: Iron Metabolism and Anemia. Washington, D.C.: Pan American Health Organization Scientific Publication No. 184, 1969. p. 72.
8. Viteri, F. E., M. A. Guzman and L. J. Mata. Anemias nutricionales en Centro America, influencia de infeccion por uncinaria. Arch. Latinoamer. Nutr. 23: 33, 1973.
9. Hodges, R. E., H. E. Sauberlich, J. E. Canham, L. A. Mejia, C. Lykke and D. L. Wallace. Iron deficiency anemia and hypovitaminosis A. Kyoto, Japan: Xth International Congress of Nutrition, 1975 (abstr. 3307).
10. Hodges, R. E., H. E. Sauberlich, J. E. Canham, D. L. Wallace, R. B. Rucker, L. A. Mejia and M. Mohanram. Hematopoietic studies in vitamin A deficiency. Am. J. Clin. Nutr. 30: 1977.
11. Findlay, G. M., and R. D. MacKenzie. The bone marrow in deficiency diseases. J. Pathol. 25: 402, 1922.
12. Wolbach, S. B., and P. R. Howe. Tissue changes following deprivation of fat-soluble A vitamin. J. Exptl. Med. 42: 753, 1925.
13. Koessler, K. K., S. Maurer and R. Loughlin. The relation of anemia, primary and secondary, to vitamin A deficiency. J. Am. Med. Assoc. 87: 476, 1926.
14. Sure, B., M. C. Kik and D. J. Walker. The effect of avitaminosis on hematopoietic function: I. Vitamin A deficiency. J. Biol. Chem. 83: 375, 1929.
15. Blackfan, K. D., and S. B. Wolbach. Vitamin A deficiency in infants, a clinical and pathological study. J. Pediat. 3: 679, 1933.
16. Frank, M. Beitrag zur Hämatologie der A-avitaminose. Monatrisschrift fur Kinderheilkunde. Leipzig 60: 350, 1934.
17. Wagner, K-H. Die experimentelle Avitaminosé-A beim Menschen. Hoppe-Seyler Zeitschrift fur Physiologische Chemie 264: 153, 1940.
18. O'Toole, B. A., R. Fradkin, J. Warkany, J. G. Wilson and G. V. Mann. Vitamin A deficiency and reproduction in Rhesus monkeys. J. Nutr. 104: 1513, 1974.
19. McLaren, D. S., E. Shirajian, M. Tchalian and G. Khoury. Xerophthalmia in Jordan. Am. J. Clin. Nutr. 17: 117, 1965.
20. McLaren, D. S., M. Tchalian and Z. A. Ajans. Biochemical and hematologic changes in the vitamin A-deficient rat. Am. J. Clin. Nutr. 17: 131, 1965.
21. Corey, J. E., and K. C. Hayes. Cerebrospinal fluid pressure, growth and hematology in relation to retinol status of the rat in acute vitamin A deficiency. J. Nutr. 102: 1585, 1972.
22. Amine, E. K., J. Corey, D. M. Hegsted and K. C. Hayes. Comparative hematology during deficiencies of iron and vitamin A in the rat. J. Nutr. 100: 1033, 1970.
23. Webb, K. E., Jr., G. E. Mitchell, Jr., C. O. Little and G. H. Schmitt. Polyuria in vitamin A-deficient sheep. J. Animal Sci 27: 1657, 1968.
24. Webb, K. E., Jr., G. E. Mitchell, Jr. and C. O. Little. Renal clearances in vitamin A-deficient ewes. J. Animal Sci. 30: 941, 1970.
25. Viteri, F. E., V. de Tuna and M. A. Guzman. Normal haematological values in the Central American population. Brit. J. Haematol. 23: 189, 1972.
26. Viteri, F. E., and M. A. Guzman. Haematological status of the Central American population: Prevalence of individuals with haemoglobin levels below "normal." Brit. J. Haematol. 23: 725, 1972.

27. MENDEZ, A. Metodo para medir la situacion socio-cultural de las familias rurales centro americanas y su applicación a los programas de salud. Arch. Latinoamer. Nutr. 20: 281, 1970.
28. ARROYAVE, G., A. MENDEZ AND W. ASCOLI. Relacion entre algunos indices bioquimicos del estado nutricional y nivel sociocultural de las familias en el area rural de Centro America. Arch. Latinoamer. Nutr. 20: 195, 1970.
29. ARROYAVE, G., M. A. GUZMAN AND M. FLORES. El nivel socioeconomico de la familia y la nutrición en el area rural de Centro America y Panama. Arch. Latinoamer. Nutr. 26: 47, 1976.
30. SIFRI, M., AND J. L. SELL. Effect of vitamin A on zinc mobilization from chick liver. Valley City, North Dakota: Proceedings of the North Dakota Academy of Sciences 29: 27, 1975.
31. COOK, J. D., J. ALVARADO, A. GUTRISKY, M. JAMRA, J. LABARDINI, M. LAYRISSE, J LINARES, A. LORIA, V. MASPES, A. RESTREPO, C. REYNAFARJE, L. SANCHEZ-MEDAL, H. VELEZ AND F. VITERI. Nutritional deficiency and anemia in Latin America: a collaborative study. Blood 38: 591, 1971.
32. SHANK, R. E., H. B. BURCH, O. H. LOWRY AND O. A. BESSEY. Evaluation of iron deficiency as a cause of mild anemia in adolescent girls. Enzyme 18: 240, 1974.
33. VITERI, F. E., AND B. TORUN. Anaemia and physical work capacity. Clin. Haematol. 3: 609, 1974.
34. GARDNER, G. W., V. R. EDGERTON, R. J. BARNARD AND E. M. BERNAUER. Cardiorespiratory, hematological and physical performance responses of anemic subjects to iron treatment. Am. J. Clin. Nutr. 28: 982, 1975.