IDPAS #148

Fortification of sugar with iron sodium ethylenediaminotetraacetate (FeNaEDTA) improves iron status in semirural Guatemalan populations[1–3]

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ABSTRACT A 32-mo-long, double-blind field study involving one highland control community receiving only vitamin A–fortified sugar and three vitamin A– and FeNaEDTA-sugar-fortified communities, two in the lowlands and one in the highlands of Guatemala, was undertaken to test the effectiveness of this approach in controlling iron deficiency. The communities' population ranged between 1200 and 17000. Sugar fortified with 1 g FeNaEDTA and 15 mg retinol as retinyl palmitate/kg was stable, did not segregate, and was well accepted by the communities. The impact of fortification on iron nutrition was estimated at 8, 20, and 32 mo of intervention. All pregnant women and subjects with severe anemia received supplements or treatment and were excluded from the analysis. Iron stores in the fortified communities increased significantly except for women 18–48 y of age in one lowland community and > 49 y in the highland community. Iron stores in the control community remained unchanged except for a rise among adult males. *Am J Clin Nutr* 1995;61:1153–63.

KEY WORDS Iron, vitamin A, sugar, FeNaEDTA, double fortification, field trial, iron stores, Guatemala

Introduction

Iron deficiency is the most common micronutrient deficiency in the world: nearly 2.5 billion people suffer from it (1). When severe, it produces ferropenic anemia and is associated with poor health, increased risk of maternal perinatal death, and serious functional impairments that diminish human development and productivity (2–4).

In Central America, iron deficiency and ferropenic anemia are widespread and severe especially among the lower-income populations (5, 6). This occurs mostly as a result of insufficient iron intake, diets that impair iron absorption, multiparity, and chronic infections, particularly hookworm in many lowland areas (5–7). Other nutritional deficiencies contribute little to the nutritional anemia problem, and hemoglobinopathies are rare (5, 6) even though vitamin A deficiency in children is widespread (6).

A logical approach to control of iron deficiency and vitamin A deficiency is the fortification with iron and vitamin A of a food that reaches all the population groups at risk and fulfills the accepted criteria for a food vehicle (8). Sugar has been shown to be an adequate vehicle for vitamin A fortification in Guatemala (9), and it does not impair iron absorption (10). Currently, sugar is being fortified with vitamin A in Guatemala.

Consideration of the iron compound to be used in iron fortification of diets rich in inhibitors of nonheme-iron absorption is essential. A nonheme-iron compound becomes part of the nonheme-iron pool and its absorption is dictated by the iron absorption of this pool. We and others (11–13) previously demonstrated that the iron in iron sodium ethylenediaminotetraacetate (FeNaEDTA) mixed at food fortification levels with "typical" meals of the characteristics described above is absorbed better than other nonheminic forms of iron. An added advantage of this compound is that it makes the total nonheme-iron pool, including that contributed by food, as absorbable as that in FeNaEDTA, ≈2.5 times higher than when a similar amount of iron as $FeSO_4$ is added. A small pilot trial in the lowlands of Guatemala proved effective in preventing the recurrence of anemia in a semirural population (14). Fortification of fish sauce and of curry powder with FeNaEDTA has also proven effective in population trials in Thailand (15) and South Africa (16). Studies in vitamin A and iron-deficient rats fed the doubly fortified sugar demonstrated the availability of both nutrients (17).

The research objectives of the study being reported here were to test the feasibility of the field application of sugar doubly fortified with retinyl palmitate and FeNaEDTA, and to measure its effectiveness in controlling iron deficiency in two situations: *1)* in highland populations where the almost exclu-

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[2] Supported by USAID contract AID/TA-C-1341, INCAP, and PAHO/WHO. RAMCO Co (Houston) specially prepared and donated the serum ferritin kits used in this study, and Hampshire Chemical Co (Grace and Co), Nashua, NH, and BASF, AG, Ludwigshafen, Germany, donated the FeNaEDTA used in this trial.

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sive cause of iron deficiency was dietary, and *2)* in lowland populations infected with hookworm, which aggravated the dietary factor. A collateral objective was to evaluate the vitamin A status of these populations receiving the doubly fortified sugar.

Subjects and methods

All procedures were approved by INCAP's (the Institute of Nutrition of Central America and Panama) Committee for the Protection of Human Subjects, according to the Helsinki declaration and the Guatemalan Public Health authorities, who allowed us to take over the management of the health centers that existed in the communities, maintaining their "usual level of care and operational practices."

Feasibility of field application

Production of FeNaEDTA- and retinyl palmitate–fortified sugar. A sugar factory in the lowlands of Guatemala (Ingenio San Diego) agreed to add FeNaEDTA to the vitamin A–fortified sugar already being produced. Addition of FeNaEDTA was achieved by delivering manually, in a sweeping motion, the yellow powder to the last centrifugation of refined sugar, while it still had ≈2% humidity. The amount added was contained in a previously measured cup (adapted to the sugar load each centrifuge delivers). The sugar discharged by each centrifuge fell into a conveying screw that carried and mixed the sugar to its final drying and further mixing stage before packaging. This procedure did not alter the normal flow of sugar production. The goals were to add 1 g FeNaEDTA/kg sugar, providing 130 mg Fe/kg sugar and 15 mg vitamin A/kg sugar. Twelve sugar samples were obtained sequentially at the packaging site, covering the production period of each of five sugar batches produced for the study. Iron and vitamin A determinations were made at INCAP (18, 19).

Stability and segregation of the fortified sugar under tropical conditions. Sugar production and packaging were no different than that for ordinary vitamin A–fortified sugar for internal consumption in Guatemala. The sacks were two-layered paper, sewn at the top. The sugar had a slight brownish hue that helped disguise the slight added yellow color of FeNaEDTA. After production, the sugar (iron-fortified as well as unfortified) was transported to warehouses situated near the communities where the field trials were to take place. One warehouse was in a town located on the tropical Pacific Coast of Guatemala, 110 m above sea level, and another one was located midway between the test communities in the Guatemalan highlands, 1080 m above sea level. These warehouses were chosen to represent the usual storage facilities used by merchants in these communities. Sugar bags were stacked as is usually done, and samples for iron and vitamin A analysis were obtained periodically for up to 1 y, from the upper, middle, and lower portions of 10 randomly chosen bags.

Acceptability of commonly used food recipes prepared with fortified sugar. The added yellowish hue of the sugar containing FeNaEDTA was detectable only if the fortified and unfortified sugars were placed next to each other. Several recipes common in Guatemalan diets were prepared with fortified and unfortified sugar at INCAP's experimental kitchen. These included various kinds of cookies and cakes, various sweet bread preparations, "chuchitos" of various kinds, and fruit-based and corn starch (Duryea)–based deserts. (Chuchitos are solid corn masa buns weighing ≈120 g and wrapped in dry corn husk leaves; they are derived from tamales.) Sugar-added orange, pineapple, and papaya juices, and coffee (with or without milk) and tea (with or without milk or lemon) were also prepared. Each fortified and unfortified food preparation was consumed by a minimum of eight adult volunteers. At least 60% of the volunteers were of rural origin They were to note any difference in taste or in any other characteristic of the foods and beverages they had consumed. They did not know which preparations had the fortified sugar.

Field acceptability of fortified sugar. Four communities were chosen for this study after screening 38 possible sites: two (T_1 and T_2) with populations of 1144 and 1756, respectively, were involved in sugar cane production in the lowlands (50 m above sea level), and two (T_3 and C) with populations of 1645 and 1095, respectively, were involved in coffee production in the highlands (1100 m above sea level). These semirural low-income community pairs were matched as closely as possible by location, and then, by population, socioeconomic characteristics, and available health profiles from the Department of Public Health. Their cooperation was obtained after several town meetings and discussions with community authorities and leaders to explain in detail what the study involved and what was required from each and all members of the communities. It was clearly understood that the research-team members would accept individual decisions not to participate or discontinue their participation in the study at any time, and that this decision would not carry any detriment. Participants, on the other hand, would benefit by learning whether they had anemia, for which they would receive treatment.

The study was conducted in a double-blind fashion. Community C served as a control, unknown to everybody but to the first three authors of this study. In the original experimental design, a lowland and a highland community were to serve as controls to similar but fortified communities. However, after the basal results showed a large discrepancy in iron nutrition between the two lowland communities (T_1 and T_2) it was decided to fortify both and to use only community C as a control because it was similar to the other highland community (T_3) and differed less from community T_1 than the latter did from community T_2, which showed unexpectedly severe iron deficiency. This situation resulted in the favorable situation of having three fortified communities that differed in iron nutrition from severe to mild, but weakened the design because there was no negative lowland control. The single control community had an intermediate iron nutritional status.

The communities were informed that a new sugar was to be supplied by us to the local stores where they would normally purchase their sugar, that the price would be the same as ordinary sugar, and that it may or may not have added iron. We requested that all sugar purchases be made in these stores.

To make the trial as "real-life" as possible, all sugar distributors and retailers in the communities under study were contacted and were asked to only supply and sell the sugar we produced, which we sold to them at a 15% discount. They all agreed to do so and to keep a record of sugar purchases by each household. Each distributor and store had a very stable clientele. This arrangement allowed us to evaluate each household's sugar purchases every month. Any complaints or other comments received from their clients about the sugar were also noted. Household sugar purchases were compared with expected purchases based on individual sugar-consumption records obtained by periodic household food-consumption surveys. The subjects' exclusive consumption of the sugar we provided could thus be estimated by household.

As an extra check for infiltration of unfortified sugar in the fortified communities, sugar samples were periodically gathered (eight times in 32 mo) from all households, coded, and analyzed for iron content by a Prussian Blue reaction at INCAP's laboratories. Compliance with the consumption of the fortified sugar was also estimated for each household and expressed as percent of positive samples for iron. Households with unfortified sugar in the fortified communities were visited by the head of field operations (EA) and encouraged to consume sugar sold at the community stores. Other households in all the communities were also visited to avoid singling out these households.

Effectiveness in the control of iron deficiency.

All community members aged > 1 y were invited to participate in a fingertip basal hematocrit screening, and all individuals with hematocrit values indicative of anemia beyond a mild-moderate degree (defined as a hematocrit < 30% in the highland communities or < 28% in the lowland communities) were treated with $FeSO_4$ tablets. The proportions of the populations who volunteered for screening were as follows: 62%, 67%, 54%, and 78% for communities T_1, T_2, T_3, and C, respectively. Adult males participated least in the initial screening, particularly in community T_3 where only 20% of all adult males were screened, none having been found anemic. In this community 66% of children and women were screened. The numbers of "treated anemics" in these communities were, respectively, 26, 94, 12, and 22. In this paper all of these "treated subjects", severely undernourished children, and pregnant women were excluded from the estimation of effectiveness. From the remaining nontreated, nonpregnant members in each community, a sample totaling 160 children and adult men and women was chosen randomly among eligible individuals whose hematocrit was below the mean − 1 SD for the hematological norms for Central America (20). The rest of the sample, for a total of 318 individuals in each community, had mean hematocrit values ≥ −1 SD from the same norms. No more than one subject from the same household was selected in the sample. The subjects in the total sample were to undergo sequential detailed dietary, fecal ova and parasite, hematological, and biochemical studies.

The number of subjects by age and sex sought in each community was as follows: 115 children 1–8 y of age, 30 children 9–17 y of age, 80 males ≥ 18 y of age, 63 nonpregnant females 18–44 y of age, and 30 females ≥ 45 y of age. These numbers were chosen in anticipation of obtaining longitudinal information on 163 subjects at the end of the 3 y in each community, assuming a 20% dropout rate per year. The actual initial and final numbers studied and their age and sex distribution are presented in **Table 1.** In the group 9–17 y old the proportion of girls was near 70% in all communities at all evaluation periods. All subjects lost to follow-up had been investigated in terms of their hematological, iron, and other nutritional conditions and with regard to reasons for not continuing in the study. Dropouts did not differ from those continuing in the trial with regard to these conditions (data not shown). When possible, subjects were encouraged to continue in the trials.

The field study lasted 32 mo. The time schedule and the list of procedures implemented in the participating communities are presented in **Table 2.** All conformed to established practices at INCAP and to standardized hematological methods. Quality controls were set up for both field and laboratory procedures. Some results of these procedures not covered in the present paper are the subject of another paper to follow.

Biological effectiveness of FeNaEDTA-fortified sugar is expressed in terms of hematological and biochemical results at the different points of study, as well as by the subjects' estimated iron stores, based on Cook et al's method (33), adapted to the age, sex, and body size of the populations under study. The adaptation consisted of the following:

1) Subjects with hemoglobin concentrations ≤ 20 g/L from the mean norm for age, sex, and altitude were considered anemic (20). For each g/L below that cutoff, a deficit of 0.238 mg body iron stores/kg body wt was assigned. This figure was derived from the iron content of hemoglobin (3.4 mg/g) times 70 mL blood/kg body wt.

2) For nonanemic subjects with serum ferritin concentrations < 12 μg/L, or with serum ferritin concentrations between 12 and 50 μg/L and inadequate iron transport, the same index defined by Cook et al (33) was applied but iron stores were estimated on the basis of body weight (kg) as follows:

$$\text{Iron stores} = (-\,0.952 \times \text{kg}) \times \text{index}$$

TABLE 1
Number of subjects involved in the study by sex and age groups

Sex and age groups	Number sought in each community	Number examined by community							
		T_1		T_2		T_3		C[1]	
		Basal	Final	Basal	Final	Basal	Final	Basal	Final
M and F (1–8 y)	115	91	35	64	27	88	45	103	50
M and F (9–17 y)	30	19	33[2]	23	27[2]	20	39	32	46
F (18–44 y)	63	42	20	30	15	50	29	60	29
F (≥ 45 y)	30	15	12	12	10	19	22[2]	30	29
M (≥ 18 y)	80	55	27	56	27	68	39	68	35
Total	318	222	127	185	106	245	174	293	189
Percent of expected number[3]	—	70	78	58	65	77	107	92	116

[1] Control community.

[2] Final numbers in these age and sex categories are higher than those in the basal examination because all subjects were 32 mo older at the final examination, which moved a proportion of the subjects to a higher age category.

[3] Assuming 20% attrition for each of 3 y.

TABLE 2
Schedule of study, by month

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42
Community involvement	x																					
Census and actualization			x				x			x			x			x			x			
Individual dietary intake (21)			x- - -	-x		x- - -	-x						x - - -	- - -	-x	x- - -	- - -	-x				
Morbidity record (Health Post)			x	x		x	x	x		x	x		x	x		x		x	x			
Morbidity recall of previous 2 wk (22)	x			x			x			x			x			x						
Quantitative fecal ova/parasites (23)	x																	x				
Qualitative test for iron in sugar				x		x		x		x	x			x		x			x			
Fortified sugar production and distribution				|- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- -|		
Hematological evaluation (24, 25)	x							x						x						x		
Evaluation of iron nutrition (26–29)	x							x						x						x		
Blood folate (30)	x							x						x						x		
Plasma vitamin B-12 (31)	x							x						x						x		
Plasma and urine iron, copper, and zinc (32)	x							x						x						x		
Community meeting and debriefing	x			x			x				x			x				x		x		x

Inflammation was recognized by a serum ferritin concentration > 50 μg/L in the presence of anemia or defects in iron transport. This situation occurred only seven times in this study and the iron-store values were discarded.

3) For nonanemic subjects with adequate iron transport and serum ferritin concentrations ≥ 12 μg/L, the following formulas were applied. For children 12–107 mo of age

$$\text{Iron stores} = (4.5 \times \text{kg}) \times (\ln \text{SF} - \ln 12)$$

where ln is the natural logarithm and SF is serum ferritin in μg/L. For females > 9 y old and males between the ages of 9 and 16 y 11 mo

$$\text{Iron stores} = (4.98 \times (\ln \text{SF} - \ln 12)$$

For males ≥ 17 y of age

$$\text{Iron stores} = (6.13 \times \text{kg}) \times (\ln \text{SF} - \ln 12)$$

These algorithms for iron stores, based on age, sex, and body weight, were formulated from literature values of "normal" total body iron for both sexes at different ages (34–36) and adapted for body weights so that when applied to the adult male and female populations reported by Cook et al (33) the values could be superimposed in the three conditions dictated by the blood indicators of iron status. These algorithms also allowed a smooth transition between normal children's values and those for adults of the corresponding sex. Actual body weights of dwellers of the four study communities were used for estimation of their body iron stores.

Statistical analysis

Statistical analysis was performed with SAS software (SAS Institute, Inc, Cary, NC) and included means and SDs. For serum ferritin concentrations, logarithmic transformations were applied because of their positive skewedness. Between-group comparisons were made by various techniques, including chi-square, simple and paired *t* tests (SAS linear models for repeated measurements), analysis of variance with post hoc comparisons using Bonferroni's correction tests for individual conditions, and covariance analysis including post hoc Tukey's tests to control for different basal iron stores in isolating the effect of FeNaEDTA (37).

Results

Feasibility of field application

The produced FeNaEDTA-fortified sugar was very homogeneous, the mean (± SD) iron contents (124.3 ± 18.8 mg/kg) being very close to the amount aimed for (130 mg/kg). This preparation was also very stable except for a very slow progression of brownish discoloration in extreme conditions that was noticeable to the eye after 6 mo of storage in the most severe conditions. In Guatemala, sugar is seldom stored for more than 6–8 mo. No settling of FeNaEDTA or vitamin A to the bottom of the sacks stored under "natural" storage conditions in tropical humid environments was noted (temperature oscillated between 15 and 48 °C, and humidity between 20% and 95%).

Acceptability and organoleptic properties of commonly used food recipes were excellent with the following exceptions: corn starch puddings and gruels acquired a slight pinkish-violet hue that was "strange" to 88% of the testers, but still not objectionable. Light-color baked preparations were slightly darker, but acceptable. Tea was blackened by the addition of FeNaEDTA-fortified sugar, similar to when the same amount of iron was added as $FeSO_4$; however, in contrast with the latter that remained black with the addition of lemon, it reverted to its characteristic color in the case of tea with FeNaEDTA-fortified sugar. Light coffee was slightly darkened also, but not objectionably so. The appearance of tea and coffee did not change with the addition of milk. In no case was taste, texture, or smell altered.

Field acceptability expressed as number of "complaints about the sugar" both from households and storekeepers in the control and experimental communities was excellent. There were eight individual complaints registered in 32 mo from households in community T_1 and none from the other communities. These eight households frequently received sugar as partial payment for work from a neighboring sugar mill. These, as were other households in the same situation, were asked to exchange their sugar for that available in the stores.

Total sugar purchases by each individual household in each community during the 32 mo of intervention could be expressed as percent of expected based on repeated estimates of individual sugar consumption and household composition. The sum of sugar purchases in each community could also be compared with the expected demand for sugar by each community. This estimate provided compliance values of 88%, 98%, 104%, and 92% for communities T_1, T_2, T_3, and C, respectively.

Another estimate of compliance with the fortification was obtained based on the number of positive qualitative sugar-iron tests performed in samples of each household's sugar intake eight times during the intervention. Overall household compliance figures expressed as the percent of positive tests over expected positive tests if all were positive were 72%, 75%, 93%, and 0% in communities T_1, T_2, T_3, and C, respectively. These results indicated that there was no fortified sugar in community C and that infiltration of unfortified sugar was a persistent problem in the lowland communities. It must be indicated that some households failed to provide a sample of sugar one or more times, indicating that at the time they had run out of sugar, even though they bought their sugar from the stores. These cases were considered negative tests. Therefore, these estimates are conservative and lower than community-compliance figures estimated from continuous monitoring of sugar purchases. Despite these difficulties, 79%, 81%, and 97% of households had four or more positive tests in communities T_1, T_2, and T_3, respectively, and only 18%, 14%, and 2% had only two positive tests in the same communities. A total of six households in the fortified communities failed to test positive ever. These coincided with households that made no purchases from the stores and were excluded from the study. They all were from the lowland communities.

The average per capita amounts of sugar consumed in each community by age and sex groups are presented in **Table 3.** Each individual value is itself the average of 11 sugar consumption surveys. Sugar consumption tended to be lower among children < 4 y of age and higher among adult males. Individual sugar consumption varied in the different surveys. When sugar intake in each survey for each age-sex group was divided into highest, intermediate, and lowest intake categories, < 5% of all subjects always remained in the same category whereas 50–54% of subjects fluctuated between the three categories. The rest fluctuated between two adjacent categories. No special attributes were detected among the households with the higher or lower sugar consumption.

Effectiveness in the control of iron deficiency

Table 4 presents the basal (or preintervention) and final values (32 mo later) of various hematological and iron-nutrition indicators by community, and within it, by age and sex cohorts of subjects having complete information on both occasions. Final age determined the age and sex group to which each subject was assigned. Because clearly anemic subjects were excluded, extremely low hemoglobin values were not included in the means. This makes the differences in this study between pre- and posthemoglobin concentrations insensitive. Despite this, all but one age and sex group in community T_2 presented lower hemoglobin concentrations than community T_1 in the basal evaluation and all but two in the final evaluation. This finding is compatible with the higher basal prevalence of severe anemia in community T_2. Also as expected, hemoglobin values were higher in the highland communities.

Mean hemoglobin concentrations increased in the majority of instances, but mean changes > 10 g/L (statistically significant) occurred only in the two groups with lower relative mean basal values in the lowland communities. In both instances the final mean values approached normality. Mean hemoglobin decreased significantly in females > 45 y of age and males > 18 y of age, which were high on initial examination. Final values in these groups, however, remained within the normal range.

Percent saturation of total-iron-binding capacity between the basal and final evaluation increased in all instances, including community C. Again, the lowland communities, and particularly community T_2, presented lower basal values than did the highland communities. In all instances, even in the most iron-deficient lowland community, this biological indicator of iron transport approached normality at the end of the study, the fortified communities exhibiting a greater response.

In the lowland communities (T_1 and T_2) basal free erythrocyte protoporphyrin (FEP) values were elevated, indicative of iron-deficient erythropoiesis. Again, community T_2 presented a greater deficiency. Significant improvements in this indicator were observed in the fortified communities, although in five instances in the lowland communities the mean values remained abnormally elevated (> 700 μg/L red blood cells) after 32 mo of fortification.

TABLE 3

Amount of sugar consumed per person in the study communities based on 11 individual measurements in 36 mo[1]

	Community			
	T_1	T_2	T_3	C[2]
			g/d	
Total population	37.8 ± 23.5 [246–271][3]	37.3 ± 20.6 [360–412]	34.6 ± 15.7 [338–400]	36.1 ± 16.3 [204–239]
Mean by age and sex groups				
M and F (1–17 y)	35.5	32.8	31.2	36.2
F (18–44 y)	39.5	37.7	35.7	39.1
F (≥ 45 y)	36.8	43.0	35.0	36.4
M (≥ 18 y)	42.5	43.8	40.6	39.5

[1] Two of the 11 surveys were performed before the 32 mo of intervention.

[2] Control community.

[3] $\bar{x}$ ± SD; number of observations per survey in brackets.

TABLE 4

Basal and final values of indicators of iron nutrition by community, based on final age and sex groups[1]

	Lowlands				Highlands			
	T_1		T_2		T_3		C^2	
Sex and age groups	Basal	Final	Basal	Final	Basal	Final	Basal	Final
Hemoglobin (g/L)								
M and F (1–8 y)	120 ± 16^{a} [35]	$130 \pm 13^{e,3}$ [35]^{3}	122 ± 15^{a} [27]	122 ± 21^{e} [27]	134 ± 10^{b} [45]	136 ± 9^{f} [45]	132 ± 9^{b} [50]	$139 \pm 7^{f,3}$ [50]
M and F (9–17 y)	134 ± 13^{a} [33]	137 ± 12^{e} [33]	123 ± 20^{a} [27]	131 ± 21^{e} [27]	144 ± 10^{b} [39]	145 ± 14^{f} [39]	141 ± 10^{b} [46]	148 ± 10^{f} [46]
F (18–44 y)	131 ± 12^{ab} [20]	132 ± 19^{e} [20]	127 ± 27^{b} [15]	132 ± 15^{e} [15]	140 ± 14^{c} [29]	144 ± 12^{f} [29]	138 ± 12^{ac} [29]	141 ± 12^{f} [29]
F (≥ 45 y)	133 ± 12^{a} [12]	136 ± 7^{e} [12]	123 ± 16^{b} [10]	119 ± 19^{f} [10]	146 ± 11^{c} [22]	$138 \pm 11^{e,3}$ [22]	141 ± 10^{ac} [28]	141 ± 9^{e} [28]
M (≥ 18 y)	149 ± 13^{a} [27]	144 ± 14^{e} [27]	132 ± 26^{b} [27]	$144 \pm 21^{e,3}$ [27]	163 ± 9^{c} [39]	$155 \pm 13^{f,3}$ [39]	154 ± 18^{a} [35]	155 ± 13^{f} [35]
Saturation of total-iron-binding capacity (%)								
M and F (1–8 y)	20.3 ± 11.9^{ab}	$26.0 \pm 11.1^{ef,3}$	17.0 ± 8.0^{a}	$22.5 \pm 10.8^{e,3}$	22.2 ± 7.9^{bc}	$30.1 \pm 12.3^{f,3}$	24.5 ± 7.7^{c}	$30.4 \pm 6.8^{f,3}$
M and F (9–17 y)	23.4 ± 10.3^{a}	$28.4 \pm 10.6^{e,3}$	15.1 ± 8.1^{b}	$21.8 \pm 9.1^{f,3}$	21.6 ± 8.3^{a}	32.1 ± 9.5^{e}	27.1 ± 9.1^{c}	29.4 ± 7.9^{e}
F (18–44 y)	19.1 ± 10.9^{a}	22.9 ± 9.6^{e}	18.9 ± 10.6^{a}	24.1 ± 9.3^{ef}	22.4 ± 12.6^{a}	$31.4 \pm 11.7^{g,3}$	29.8 ± 11.7^{b}	30.3 ± 10.5^{fg}
F (≥ 45 y)	23.7 ± 9.8^{ab}	$31.0 \pm 10.1^{e,3}$	17.9 ± 11.1^{a}	$25.4 \pm 7.0^{e,3}$	27.1 ± 9.2^{b}	30.2 ± 8.0^{e}	29.0 ± 11.5^{b}	30.3 ± 10.0^{e}
M (≥ 18 y)	27.1 ± 14.9^{a}	28.7 ± 8.6^{e}	20.1 ± 13.7^{b}	$29.6 \pm 10.9^{e,3}$	30.6 ± 8.9^{a}	$36.6 \pm 9.0^{f,3}$	27.3 ± 10.4^{a}	$33.6 \pm 12.9^{ef,3}$
Free erythrocyte protoporphyrin (μg/L red blood cells)								
M and F (1–8 y)	1520 ± 1360^{a}	$800 \pm 480^{e,3}$	1190 ± 590^{a}	$1090 \pm 440^{e,3}$	770 ± 380^{b}	$470 \pm 190^{f,3}$	560 ± 410^{b}	460 ± 200^{f}
M and F (9–17 y)	860 ± 570^{a}	$620 \pm 340^{e,3}$	1340 ± 1120^{b}	910 ± 740^{f}	570 ± 260^{a}	$430 \pm 220^{e,3}$	500 ± 310^{a}	460 ± 300^{e}
F (18–44 y)	1190 ± 840^{a}	820 ± 600^{e}	1190 ± 970^{ab}	890 ± 850^{e}	860 ± 620^{bc}	$490 \pm 310^{f,3}$	580 ± 580^{c}	530 ± 210^{f}
F (≥ 45 y)	1160 ± 620^{ab}	$650 \pm 180^{e,3}$	1460 ± 1280^{b}	$620 \pm 240^{e,3}$	850 ± 640^{a}	$550 \pm 280^{e,3}$	800 ± 660^{a}	890 ± 1400^{e}
M (≥ 18 y)	780 ± 540^{a}	560 ± 360^{ef}	1110 ± 860^{b}	$610 \pm 490^{g,3}$	460 ± 180^{c}	420 ± 210^{f}	660 ± 620^{ab}	$490 \pm 490^{ef,3}$
Serum ferritin (ln μg/L)								
M and F (1–8 y)	8.27 ± 3.93^{a}	$20.30 \pm 1.84^{e,3}$	5.97 ± 2.57^{a}	$15.97 \pm 2.18^{f,3}$	16.48 ± 2.02^{b}	$26.04 \pm 1.77^{g,3}$	15.35 ± 1.81^{b}	15.83 ± 1.62^{f}
M and F (9–17 y)	13.99 ± 2.00^{a}	$22.08 \pm 2.03^{e,3}$	6.06 ± 4.12^{b}	$18.66 \pm 1.94^{f,3}$	19.02 ± 1.78^{c}	$25.37 \pm 1.91^{g,3}$	20.27 ± 2.00^{a}	$15.00 \pm 2.26^{h,3}$
F (> 18–44)	11.93 ± 3.12^{a}	$21.07 \pm 1.84^{e,3}$	7.38 ± 2.47^{b}	$17.04 \pm 2.05^{f,3}$	15.28 ± 2.56^{c}	$25.25 \pm 2.43^{g,3}$	19.88 ± 2.44^{a}	19.08 ± 2.34^{h}
F (≥ 45 y)	19.38 ± 3.16^{a}	$44.68 \pm 2.30^{e,3}$	8.50 ± 3.91^{b}	$31.49 \pm 2.22^{f,3}$	39.25 ± 1.92^{c}	$46.88 \pm 2.18^{g,3}$	29.27 ± 2.08^{d}	$30.57 \pm 2.30^{h,3}$
M (≥ 18 y)	22.41 ± 2.15^{a}	$31.38 \pm 2.31^{e,3}$	7.48 ± 3.75^{b}	$21.30 \pm 2.17^{f,3}$	29.95 ± 1.91^{c}	$46.93 \pm 2.17^{g,3}$	21.76 ± 2.69^{d}	$24.38 \pm 2.37^{f,3}$
Iron stores (mg)[4]								
M and F (1–8 y)	-26 ± 62^{a}	$41 \pm 75^{e,3}$	-35 ± 33^{a}	$9 \pm 104^{e,3}$	21 ± 49^{b}	$79 \pm 54^{f,3}$	24 ± 33^{b}	31 ± 35^{e}
M and F (9–17 y)	30 ± 114^{a}	$150 \pm 149^{e,3}$	-85 ± 122^{b}	$42 \pm 212^{f,3}$	71 ± 109^{ac}	$171 \pm 120^{e,3}$	80 ± 79^{c}	81 ± 94^{f}
F (18–44 y)	8 ± 228^{ab}	68 ± 274^{e}	-156 ± 321^{b}	$67 \pm 238^{e,3}$	37 ± 233^{a}	$182 \pm 226^{e,3}$	128 ± 203^{a}	122 ± 210^{e}
F (≥ 45 y)	27 ± 264^{a}	$206 \pm 271^{ef,3}$	-91 ± 229^{a}	$124 \pm 240^{e,3}$	262 ± 134^{b}	307 ± 210^{f}	215 ± 172^{b}	199 ± 262^{ef}
M (≥ 18 y)	168 ± 283^{a}	$333 \pm 342^{e,3}$	-157 ± 426^{b}	$169 \pm 354^{e,3}$	347 ± 198^{c}	$490 \pm 248^{f,3}$	184 ± 360^{a}	$277 \pm 285^{e,3}$

[1] $\bar{x} \pm$ SD; *n* in brackets (the number of subjects is the same as listed for hemoglobin values for all biochemical determinations and iron store estimates for each age and sex group in each community. Values with different superscript letters are significantly different from one another (between-community comparisons for a particular age and sex group), $P < 0.05$. ^{a,b,c,d} = Basal means with the same superscripts do not differ from each other.

[2] Control community.

[3] Significantly different from basal value within same community group, $P < 0.05$ (paired *t* test).

[4] Negative iron stores indicate iron deficiency.

Serum ferritin values demonstrated that a large proportion of the lowland populations, including adult men in community T_2, had depleted iron reserves. As with the other indicators, the fortified communities responded very positively to iron fortification. The changes in ferritin concentration in community C (one downward and two upward) were small compared with those in the fortified communities.

In summary, with few exceptions, hemoglobin values rose when they were lower to begin with even though overall they were good at basal evaluation after removal of the values of the clearly anemic subjects. Overall, the fortified communities demonstrated remarkable improvements of individual indicators of iron status within the 32 mo of study. In contrast, community C showed very little change. It is important to note that in all the communities there was a trend for an improvement in hemoglobin concentration among the groups with lower values at the beginning of the study. Few changes, however, were significant. There was also an overall indication of regression to the mean, particularly in community T_3. When comparisons were made only between the control and the fortified highland communities (C and T_3) that started the study with similar iron status, differences in final values favored the latter, particularly for serum ferritin concentrations.

Means and SDs of individual iron stores estimated on the basis of the above indicators and by age and sex groups, are also presented in Table 4. These reflect even better the basal iron status of the age and sex groups in the four communities and the changes observed in iron status during the study. To begin with, iron stores behaved as expected in terms of age and sex groups and community characteristics. They were lowest in small children and consistently increased with age. Women of reproductive age had lower iron stores than older children except in community C. Iron stores were higher in older women and in adult men, who, in general, exhibited the highest values. As seen before, the lowland communities had lower basal iron stores for the same age and sex groups than those of the highland communities, and all the groups were, on average, iron deficient in community T_2. Increments in iron stores were significant in the fortified communities in all but two age and sex groups, and remained static in community C, except for the adult males, who increased their iron stores with time. This increment did not differ ($P > 0.07$) from that registered for the same group in community T_3.

Figure 1 depicts the sequential changes observed in mean iron stores in the four instances when blood sampling was programmed: basal (before intervention) and at 8, 20, and 32 mo of intervention. The data include only the "cohort" subjects for whom complete information was available in each sampling period: 89, 74, 154, and 132 subjects for communities T_1, T_2, T_3, and C, respectively. In other words, they constitute 70%, 70%, 88%, and 70% of the cohort with complete basal and final values in the respective communities. For this reason, the two groups of children were combined into a single group. In this subset of subjects, none of the groups in community C showed a significant change in iron stores whereas all the fortified groups, except for women of reproductive age in community T_1 and older women in community T_3, showed significant increments in iron stores.

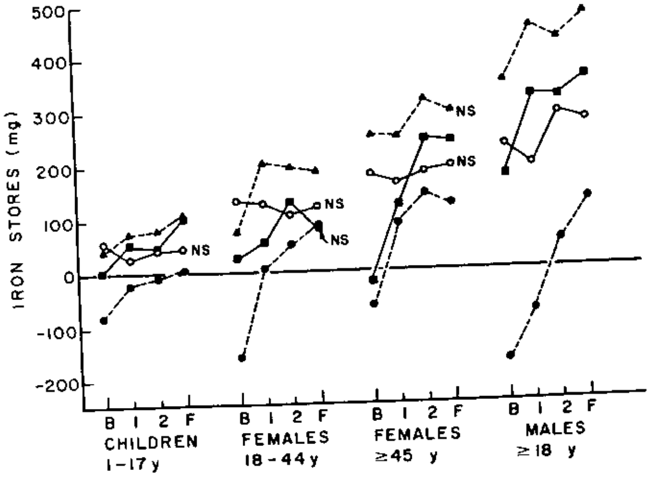

FIGURE 1. Evolution of individual iron stores grouped by age and sex at four evaluation periods during 32 mo of iron fortification in communities T_1 (■), T_2 (●), and T_3 (▲). Community C (○) is the unfortified control community. B, basal evaluation before intervention; 1, evaluation after 8 mo of intervention; 2, evaluation after 20 mo of intervention; and F, final evaluation after 32 mo of intervention. All changes from basal to final evaluations are significant except those indicated by NS.

The shape and magnitude of the response to iron fortification is particularly revealing. The fastest and highest increments occur among the more deficient groups at the start of fortification and in general, with time, mean rates of change become slower as iron deficiency disappears and stores become larger. It must be realized that positive iron stores (> 0) represent iron reserves, whereas negative values reflect an iron deficit, including that due to reduced hemoglobin values.

Given that iron reserves are greatly determined by body size (a normal child would be expected to have less iron reserves than a fully grown adult), they can be expressed as a percent of the norm for individuals of the same sex and similar size. The norm for iron reserves was estimated by subtracting the total normal circulating iron from normal total body iron derived from the published data, which also served to generate the algorithms used to estimate iron stores (explained under Methods). By expressing reserves as a percent of the norm, the effect of age and sex on iron reserves was controlled for. As for iron stores, negative values represent iron deficiency (< 0 reserves) and are expressed also as percentile units of the norm. Therefore, − 100% represents an iron deficit of the same magnitude as the normally expected reserves for that individual. This allows the expression of results as weighted averages in the total sample by community, and even by fortified compared with control populations as a whole. **Figure 2** presents the basal and final results of this mode of expression, where 100% reflects the norm, 0% indicates no iron reserves, and negative values reflect iron deficiencies as percents of expected normal iron reserves. The effect of sugar fortification with FeNaEDTA as well as the stability of community C are evident.

Covariance analysis (data not shown) in which basal values were controlled for demonstrated that significant positive changes in iron stores occurred in each fortified community in relation to community C. The fortified communities as a group were also different from the control community in both absolute as well as in normalized iron store values.

Other results of this study, including detailed data on anemia prevalences among treated and nontreated groups, morbidity, dietary intake, plasma and urinary trace mineral concentrations,

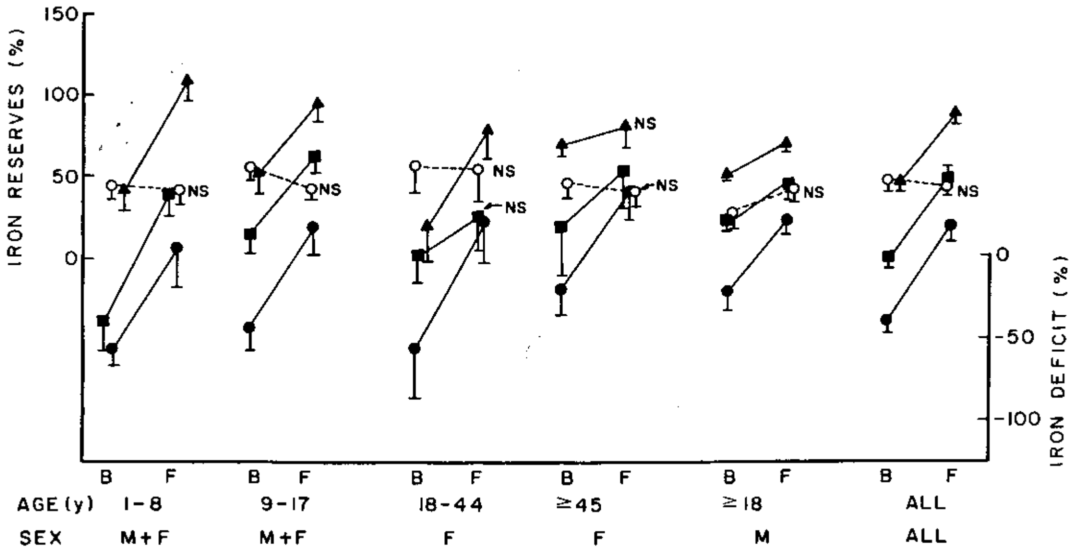

FIGURE 2. Iron reserves and deficit expressed as percent of individual norm grouped by age and sex and for the total population (all) in the control community (○, n = 189) and in the fortified communities T_1 (■, n = 127), T_2 (●, n = 106), and T_3 (▲, n = 179). All changes from basal to final evaluations are significant except those indicated by NS. B, basal evaluation before intervention; F, final evaluation after 32 mo of intervention; M, male; F, female; ALL, weighted mean and SD for the community as a whole. $\bar{x} \pm$ SD.

vitamin A nutrition, and parasite loads among the subjects studied are the object of another publication (in preparation). Suffice it to state that both lowland communities, and particularly community T_2, exhibited greater morbidity and fecal blood loss due to hookworm infection than did the highland communities, and that the rest of these variables were similar in all the communities. No undesirable effects of sugar fortification with FeNaEDTA, under the conditions of this trial, could be detected.

Discussion

This iron-fortification study included testing a series of preliminary steps to the implementation of a field trial conducted among low-income, semirural communities in Guatemala, where iron deficiency and its consequent anemia are prevalent and the 32-mo field trial itself. Both highland and lowland populations were included in the field trial to test the effectiveness of sugar fortification with vitamin A and FeNaEDTA under conditions leading to different degrees of iron deficiency and ferropenic anemia. All aspects of this study were successful in proving the feasibility, organoleptic advantages, simplicity of execution, and biological effectiveness of FeNaEDTA- and vitamin A–fortified sugar in controlling iron deficiency in semirural Guatemala.

The field trial was not without problems, some of which could weaken or invalidate the results obtained. Four main issues are addressed in this regard.

1) The reduction in number of subjects with time could be responsible for explaining some of the results if there was a "natural selection process" that excluded from follow-up preferentially iron-deficient subjects in the fortified communities. The confounding situation can be rejected with confidence based on extensive analysis of the hematological and socioeconomical characteristics of the dropouts in comparison with those remaining in the trial, which showed that the populations did not differ. Also, there were no instances in which the discontinuation in the trial was due to the fortified sugar. The great majority of subject and household desertions were due to economically triggered migration. The reduced number of subjects in the cohort with basal and final evaluation, and also in the cohort with complete data in the four periodic evaluations, reduces the probability of significant differences between groups and within groups at the different evaluation periods. Despite this, results are clear in favor of the fortified population except for hemoglobin concentration.

2) Because iron fortification is primarily a preventive rather than a therapeutic measure for iron deficiency, and for ethical reasons, any individual with moderate or severe anemia (hematocrit < 30% in the highlands and < 28% in the lowlands) was given a course of iron therapy and other medical attention usually provided in the study communities by Health Service personnel. These subjects, as well as any women pregnant during the 32-mo trial, were not included in the present report. As a consequence of excluding individuals with low hemoglobin values, the sensitivity of hemoglobin response to fortification was markedly reduced. In effect, only 20 of a total cohort of 596 subjects had hemoglobin values < 100 g/L in the basal sample (3.3% prevalence). Of these, 19 resided in the lowlands, 6 were children between 1 and 8 y of age, and 5 were adult males in community T_2. At the final evaluation, 13 subjects had hemoglobin concentrations < 100 g/L (2.2% prevalence). Twelve of these resided in the lowlands and five of them were children between 1 and 8 y of age. Two adult males in community T_2 belonged to this group.

3) As indicated before, the original experimental design called for two control communities, one in the highlands and one in the lowlands. Because of the great disparity in iron nutritional status in the lowland communities, one could not serve as a control for the other. The time and overall resource effort already invested when the disparity became clear made it impractical to seek a third lowland community. The fact that the control community showed a remarkable stability in iron nutrition and biology during the 32 mo of study, while the three fortified communities, including a similar highland community (T_3), showed a significant improvement in the same indicators makes us confident of the results obtained even with this imperfect design.

4) Infiltration of unfortified sugar into the fortified communities was detected almost exclusively in the lowland communities (T_1 and T_2), located near sugar-cane plantations and mills that employed most of the men in these communities. During sugar-production periods (≈4 mo of the year) employees could receive some sugar at the mills as pay in kind. This practice was reduced when the mills were approached early in the intervention period, but did not fully disappear. Based on household sugar-purchase monitoring, those purchasing less than expected and receiving sugar directly from the mills were encouraged to exchange this sugar for that being sold. A qualitative test to detect iron in sugar was also introduced to reinforce the exchange policy. The end result was that on the basis of continued sugar purchases and exchange $\geq 77\%$ of households consumed fortified sugar $> 50\%$ of the time, and $\geq 67\%$ of households consumed fortified sugar $> 90\%$ of the time.

Despite these shortcomings, the results of this study demonstrate the effectiveness of sugar fortification with FeNaEDTA. If anemia is estimated by using criteria of the World Health Organization (WHO) corrected for altitude (highland cutoff hemoglobin values are increased by 5 g/L), there was a decline in the prevalence of mild-moderate anemia in both lowland communities: -13.9% from a basal prevalence of 27.3% in community T_1, and -16.9% from a basal prevalence of 41.7% in community T_2. This fall in prevalence occurred primarily among young children, women > 45 y of age and adult men in community T_1, and among all age and sex groups in community T_2. There was also a 2.6% decline in anemia prevalence in the highland community (T_3), from a basal prevalence of 10.2% to a final prevalence of 7.6%. Community C also showed a decline in prevalence from 13.9% to 5.2%, a reduction of 8.7%. These reductions are significant except for those in community T_3. The reduction in anemia prevalence in the lowland communities was also significantly greater than that in community C ($P < 0.05$). Given the sample structure of the trial, these results are encouraging and support the efficacy of sugar fortification with FeNaEDTA in improving iron nutrition even among populations with overall mild-moderate anemia prevalence as high as 41.7%.

At final evaluation 66 subjects had hemoglobin values below the WHO cutoff. Of these, 20 individuals had lower hemoglobin concentrations at the final than at the basal evaluation. Twelve of these were lowland residents and of them eight were adults: two women of reproductive age, one woman > 45 y of age, and five adult men. In the highland communities, six resided in community T_3: two subjects between 9 and 17 y of age, one adult woman in each age and sex category, and two male adults, whereas two adult women in each age and sex category resided in community C.

We have no explanation for the improvement in hemoglobin concentrations in community C. We could claim regression to the mean and greater efficiency in health care (under our control), including the treatment of anemia in all the communities, including the control. However, these are only possible explanations. The possibility of an effect of vitamin A fortification of the sugar in this and all other communities is highly improbable because sugar fortified with vitamin A was being consumed in Guatemala for several years before this trial and we did not detect vitamin A deficiency in plasma samples at any time during the trial (data not shown).

These results do not include subjects who had hematocrit values $< 30\%$ in the highlands or $< 28\%$ in the lowlands, corresponding to hemoglobin concentrations close to 95 and 90 g/L, respectively, at any of the evaluations before the final evaluations or at visits to the clinics. The details of these groups of more severely anemic subjects are to be considered in a following article (in preparation). Suffice it to say that new cases of more severe anemia declined significantly with time in all the communities to the point that only nine new cases were detected in the last 12 mo of intervention, eight of which occurred in community T_2, and that recurrences among treated subjects in the fortified communities were significantly lower in communities T_1 and T_3 (7.5% and 4.0%, respectively) than in community C (28.9%). Recurrences in community T_2 were similar to those in community C (27.2%) despite their having a much greater hookworm infestation and a precarious iron nutritional status before fortification.

The more important results, given the preventive approach of the trial, are those that reflect the biological aspects of iron nutrition in these populations. As was evident in Table 4, community T_2 was consistently the most iron-deficient community by all indicators, followed by the other lowland community. The two highland communities had very similar iron statuses and were less deficient at the start of the trial. The concordance of results in iron biology with those expected by altitude and by age and sex groups give strong support to the findings in these indicators and in the estimations of iron stores and relative iron reserves despite small numbers in some of the age and sex categories. Moreover, the sequence of change observed with time of fortification depicted in Figure 1 and the characteristics of relative iron reserves shown in Figure 2 agree with biological expectations.

Results from this field trial show the clear tendency of iron stores to stabilize as they reach certain levels that appear characteristic of each age and sex group and community, suggesting that in some situations a new equilibrium in iron status is approached in 32 mo. This appears to be the case among the adult populations of communities T_1 and T_3. This new equilibrium is greatly determined by the degree of iron needs (requirements plus pathological losses). Iron stores will most probably continue to increase until this equilibrium is reached. This is evident in most groups of community T_2. The implications of this phenomenon are that in response to fortification programs, iron stores and reserves in communities with poor diets and large losses will take longer to stabilize at lower values than desirable until losses are reduced (deparasitization, environmental health, and birth spacing). The ideal of bringing iron reserves among women of reproductive age to an amount that will prevent iron deficiency during pregnancy will most probably not occur under most present conditions in the developing world. This could probably be achieved only by preventive supplementation of this vulnerable group (8, 39). At the same time, under these circumstances the risks of producing iron overload as a consequence of iron-fortification programs are minuscule. Five cases at basal and six cases at end evaluations had estimated iron reserves > 130% of normal, all of which occurred in children and women of reproductive age with elevated serum ferritin concentrations without other laboratory indicators of iron deficiency. The distribution of cases by age and sex groups and the lack of persistence of elevated serum ferritin concentrations from basal to final evaluations in these cases suggest an artifact of inflammation.

The magnitudes of response in iron stores during the trial agree with expectations in that community T_2 had the greatest response whereas community T_3 had the smallest one, in direct proportion to initial degree of iron deficiency. Results from covariance analysis of the response to fortification, with differences in basal iron stores controlled for, indicate that when iron stores were not deficient at the start of the trial, iron fortification had an insignificant effect on iron reserves. However, these increased similarly and only in the fortified communities, especially when they were negative before fortification. Also, in the groups of children increments in iron reserves in the fortified communities were in keeping with their physical growth. In other words, sugar fortified with FeNaEDTA was accomplishing exactly what it was hoped to accomplish in the populations studied: it was bringing normality to iron nutritional status and maintaining it when iron needs were elevated. At the same time it posed essentially no danger of iron overload.

The results obtained in community T_3 are particularly illustrative in that this community as a whole was reaching normality in the final evaluation because mean iron reserves were 86% of the norm. The distribution of final iron reserves in adult males in this community can be superimposed on that estimated from Cook et al's data for adult men (33), adjusted for the smaller body size of the Guatemalan adult male population of that community. This suggests that the data for this age and sex group conform to that for iron nutritional status of adult males in the US National Health and Nutrition Examination Survey, and that, taking that as the norm, complete normality in iron nutrition can be achieved with FeNaEDTA-fortified sugar among men even when the quality of their diet is poor (6). The low overall prevalence of anemia in that community at the end of the trial supports the near normality of this population. In contrast, even though community C had the same low prevalence of anemia, iron reserves were only 42% of the norm and were stable.

Estimates of percent iron absorption from the diet plus that provided by the FeNaEDTA-fortified sugar adjusted for compliance can be obtained by a factorial method in these communities where iron requirements, including a growth component in children during the 32 mo of fortification, median fecal iron losses from hookworm, and changes in iron stores have been estimated. The figures for mean iron absorption estimates for different communities and age and sex groups range from 0.95 to 3.06 mg Fe/d, or 3.5–14.1% of total iron intake, and are within the range of absorption values obtained in specific, double-isotope radioiron studies previously conducted with Guatemalan diets similar to those consumed by these communities, with and without FeNaEDTA-fortified sugar (11). Thus, the changes in iron stores and reserves are in line with possible absorption estimates.

Recently a Joint FAO/WHO Expert Committee on Food Additives (JECFA) (40) concluded that FeNaEDTA is "provisionally considered to be safe in food fortification programmes" and that "The Committee provisionally concluded that sodium iron EDTA (ethylenediaminotetraacetate) meeting the tentative specifications prepared at the meeting does not present a safety problem when used in supervised food fortification programmes in iron deficient populations." These conclusions are based on exhaustive tests in experimental animals and humans, which essentially show that EDTA is a safe food additive over a wide range of doses. Acute and chronic toxicity occurs with doses that are completely out of proportion to those used in iron-fortification programs. Currently the acceptable daily intake (ADI) for EDTA is 2.5 mg/kg. This makes sugar fortification with FeNaEDTA at the amounts used in this trial even safe for 9.3-kg infants consuming 30 g fortified sugar/d. The trials reported here were conducted with batches of agricultural-grade FeNaEDTA that were bacteriologically and chemically analyzed for heavy metals and other contaminants. Results of these analyses and the very low consumption of EDTA as a food additive in semi-rural Guatemalan diets as compared with industrially advanced countries indicate the complete safety in the use of FeNaEDTA-fortified sugar by humans.

Given these developments and because of the organoleptic and stability advantages of FeNaEDTA, its ease in handling in fortification programs, its proven efficacy as an iron source in doubly fortified sugar (vitamin A and iron) to improve iron nutritional status of populations even under very unfavorable conditions, and the extremely low risk of inducing iron overload in iron-deficient populations, FeNaEDTA should be considered an excellent choice in iron-fortification programs (41). As with all fortification and other nutrition-intervention programs, a systematic monitoring of compliance and of changes in nutritional status should be established. This monitoring should include serum ferritin determinations in well-defined samples of adult males to prevent any long-term risk of iron overload (42), though at present this effect appears very remote.

Cost-benefit analysis of sugar fortification with FeNaEDTA proves extremely favorable and cost projections for the control of iron deficiency even suggest that after a few years of its establishment as a national program, present costs of supplementation and therapeutic programs for the control of iron deficiency in some regions of the developing world may actually be reduced (2, 43).

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