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# RESEARCH PROJECT STATEMENT

## 1. Project Summary

A. Statistical

Date: February 5, 1976

| | |
|---|---|
| Project Title: | Fortification of Sugar with Iron Field Study Prior to Implementation at a National Level |
| New or Extension: | New |
| Contractor | Pan American Health Organization |
| Principal Investigator: | Fernando Viteri, M.D., D.Sc.<br>Director<br>Biomedical Division<br>Institute of Nutrition of Central America and Panama (INCAP)<br>Guatemala City, Guatemala |
| Co-Principal Investigator: | Miguel Layrisse, M.D.<br>Venezuelan Institute of Scientific Investigation (IVIC)<br>Caracas, Venezuela |
| Duration: | Three years |
| Total Estimated Cost: | FY 1976 $224,282<br>FY 1977 201,426<br>FY 1978 196,091<br>Total $621,799 |
| Project Manager: | S.G. Kahn, TA/N |

B. Narrative

I. Summary

The purpose of this research project is to determine: (a) biological effectiveness of sodium ferric ethylene diamine tetra-acetate (NaFeEDTA) when incorporated into the dietary sugar of a population where iron deficiency is prevalent and (b) feasibility of this system of delivering iron to vulnerable population groups. The population samples to be studied are primary school children and their families taken from four Guatemalan communities representing the two major ecological areas of Central America, highland and lowland.

In the past, fortification of sugar with standard iron salts proved unacceptable because of product discoloration, interaction with other foods, and poor bioavailability of the added iron. NaFeEDTA, a chelated iron compound, previously has been used as an anti-anemia medicament. To date, NaFeEDTA has not been used as an iron fortificant in foods; however, its merits for such use are: (a) no discoloration when added to sugar; (b) consists of bioavailable iron; (c) no undesirable interactions when added to foods and beverages.

The significance of the proposed research rests on the fact that anemia is reported to be the most prevalent nutritional deficiency disease in the world, particularly, anemia due to an inadequacy of iron, per se. Iron deficiency anemia occurs most frequently in infants, growing children, adolescents, and pregnant women. The amounts of iron that may be present in a food is no indication as to the iron nutriture that a person will get from its ingestion. The iron absorbed by the body depends on (1) the total amount in the diet, (2) its absorbability, and (3) regulation of its absorption through the intestinal wall. The availability of food iron is related to chemical properties of the specific iron salt and its association with other substances in a food or diet. Thus, suitable fortification procedures must be developed, particular attention being paid to (a) the form of iron used, (b) the foodstuff consumed by different segments of the population, (d) the adequacy of iron absorption from the fortified diet, and (e) the acceptability of the procedure to the consumers and the indigenous food industry. This project will attempt to do these things. Development of an effective and practical NaFeEDTA-sugar product as means of delivering iron to vulnerable populations will be a major advancement in combating iron deficiency anemia.

II. Research Purpose and Expected Products

(a) The purpose of this project is to evaluate the biological effectiveness and general practicability - including costs

considerations - of iron fortified sugar when fed to populations showing high prevalence of iron deficiency anemia.

(b) The products of this project will be the collection and analysis of data regarding clinical and biochemical hematology, parasitology, work physiology, trace mineral metabolism, diet composition and consumption, morbidity, and cost-effectiveness of iron delivery systems in village populations where high prevalence of iron deficiency anemia exists.

## III. Significance and Rationale for the Research

### A. Significance

Anemia is reported to be one of the more prevalent nutritional deficiency diseases in the world. Nutritional anemias are those deficiency states that are precipitated by either individual or combination of insufficient iron, vitamin B12 and folic acid. However, survey reports indicate that the more prevalent cause of anemia is an inadequacy of iron, per se. Iron deficiency anemia occurs most frequent in infants, growing children, adolescents and pregnant women. In the latter group, a combined deficiency of iron and folic acid is often observed in certain LDCs.

Iron deficiency anemia also is precipitated as a result of combined insufficient available dietary iron aggravated by the additional load of parasites, such as hookworm. Though elimination of parasites is most desirable, the administration of iron itself will benefit the individual by mitigating the anemic condition to an extent dependent on the degree of parasite infestation.

There is evidence that severe anemia impairs work capacity and recent studies suggest that even mild reduction in hemoglobin may result in decreased performance of near maximal efforts. Severe degrees of anemia in pregnant women increase maternal morbidity and mortality and carry an increased risk to the fetus. Milder degrees of anemia during pregnancy can result in reduced birthweight of offspring, in addition to anemia of newborn. The anemic infant does not thrive and death may result because of general aggravation from other diseases. There is increasing evidence that anemia and iron deficiency may play a role in the ability of an individual to resist infection. Studies suggest that iron deficiency results in impaired humoral antibody response as mediated through white cell activity. The amount of iron that may be present in a food is no indication as to the iron nutriture that a person will get from its ingestion. The iron absorbed by the body depends on several factors: (1) the total amount in

the diet, (2) its absorbability, and (3) the regulation of its absorption through the intestinal wall. The availability of food iron is related to chemical properties of an iron salt, such as its chemical association with other substances in a food or diet. Usually these other substances "tie-up" the iron molecule making it not readily available for absorption. Thus, a food with a high iron content may be a relatively poor source of food iron. Overcoming this problem may involve: (a) the addition of iron to a food at a leve that exceeds that of the complexing substance, (b) proper processing of the food and (c) addition of other chemicals that favorably influence the increased absorption of the iron.

B. Rationale

The existing procedures used to evaluate a population for iron anemia are standardized. With careful epidemiological techniques a population can be surveyed for prevalence of iron anemia. The difficulty has been in making absorbable iron available to the population that needs it. Thus the priority problems to be solved include the delivery or absorbable iron to (1) the population groups suffering from severe iron deficiency anemia and (2) the groups that are most vulnerable to iron anemia. The severely anemic should receive immediate treatment with daily therapeutic levels of iron in the form of tablets, capsules, etc. Iron fortification is not intended as a therapeutic treatment but as an addition to the daily diet in order to prevent the development of iron deficiency anemia. Effective procedures of iron supplementation need to be worked out for the severely malnourished, and suitable fortification procedures must be developed, particular attention being paid to (a) the form of iron used, (b) the foodstuff to which it is added, (c) the amount of that foodstuff consumed by different segments of the populations, (d) the adequacy of iron absorption from the fortified diet, and (e) the acceptability of the procedure to the consumers and the indigenous food industry. At the (1970) WHO/IAEA* consultants meeting on the prevention of iron deficiency anemia, it was stated that "the implementation (fortification) of foodstuffs with iron is likely to be the most practical preventative measure for use on a national scale".

On October 28, 1974 in Geneva, AID, in cooperation with WHO and IAEA, sponsored a conference on Nutritional Anemia. The experts gathered represented both LDCs and developed countries. They concluded that nutritional anemias are very prevalent in many countries, and that there is sufficient knowledge concerning the causes, implications, and public health significance of nutritional anemias to justify action for control and eradication of this nutritional disease problem.

*IAEA - International Atomic Energy Agency

Recommendations were: (a) continued research to improve laboratory methodologies that will more accurately define types of anemias, (b) continued studies which will more precisely define the adverse effects of mild anemia, (c) studies that will enable reasonable cost-benefit analysis of action programs, (d) collection of more information regarding bio-availability of iron from different iron compounds and diets, (e) continued and expanded prevalence surveys, (f) initiation of iron and folate supplementation and fortification studies that would lead to national programs for those segments of the population most at risk, (g) education and training programs to combat nutritional anemias in those countries with insufficient specialized personnel to carry out these programs. In principal, AID is interested in participating in all areas recommended for action to the extent that they contribute to the development of iron supplementation and/or fortification programs for those groups in need. This position is supported by Dr. Kissinger's statement before the World Food Conference in Rome of last year, which specified that action be taken to eradicate both iron deficiency anemia and Vitamin A deficiency, and that up to $10,000,000 would be made available for this purpose.

The proposed project is a field demonstration trial that will evaluate both the biological and cost-effectiveness of an iron fortification delivery system. Development of an effective and feasible NaFeEDTA-sugar iron delivery system will be an important step in combatting iron deficiency anemia.

## IV. Plans to Coordinate and to Link Research

The proposed research will link the cooperative efforts of the Institute of Nutrition of Central America and Panama (INCAP) with the Venezuela Institute of Scientific Investigation (IVIC), the Public Health and Social Security departments of Guatemala and the Association of Sugar Producers. It is planned that this research will tie into the World Health Organization's (WHO) activities in combatting iron deficiency anemia around the world. Through an international iron anemia consultative group a network of interested organizations and agencies will join together in an effort to coordinate activities in combatting iron deficiency anemia. The information generated from this project will be fed into this network.

This project is the first in the Agency's efforts to combat iron deficiency anemia. Other activities planned are: prevalence surveys, food fortification development, radio-iron evaluation studies, pilot supplementation trials, field demonstration trials, nutrition education activities, project evaluations, workshops and conferences. Certain activities in the iron program will tie-in with other Agency projects; examples are: (a) prevalence surveys as part of the general nutrition survey program, (b) food fortification development integrated

with food (example cereal) technology activities, (c) education activities coordinated with other nutrition education programs, such as breast feeding, (d) iron-nutrient inter-relationships, such as iron-vitamin A, iron-protein. Every effort will be made to integrate projects where practicable.

## V. Plans to Facilitate Utilization of Research Results

Information and results from this project will be disseminated through: (a) scientific publications and presentations to scientific groups, (b) advisory services of the Pan American Health Organization, (c) international iron anemia consultative group, (d) workshops and conferences, (e) Agency conduits of dissemination to bureaus, missions, international and bilateral agencies and LDCs. Utilization of the project findings by Central American countries will occur after the project's completion. The manner of use will depend on the results obtained. If data show a significant improvement of iron nutriture in the population plus (b) economic and logistical practicability of the delivery system it is extremely likely that certain countries may promulgate laws for iron fortification of surgar. However, if the results do not support use of this method of iron fortification, the information will be used to decide against national sugar fortification with NaFeEDTA.

## VI. Management Considerations

Dr. Fernando Viteri of INCAP is to be the principal investigator of the project, and because of the unique scientific talents in iron anemia research at the Venezuelan Institute of Scientific Investigation (IVIC), Dr. Miguel Layrisse of IVIC has accepted co-principal investigatorship. The project contract will be through PAHO; however, actual field research and data analyses will be the responsibility of INCAP.

## VII. Technical Review

Iron deficiency anemia is a major nutritional problem in large segments of populations throughout the world. In developing countries, the impact of moderate to severe iron deficiency is overshadowed by protein calorie malnutrition; nevertheless, iron deficiency poses a serious health problem in these countries. Iron deficiency occurs when either the amount or biological availability of ingested iron is insufficient to replace the quantities of iron lost daily by the body.

In all countries, pregnant women and infants between 6 and 18 months of age appear to be the principal groups (1) vulnerable to iron deficiency anemia. Severe iron deficiency anemia reduces the ability of pregnant women to tolerate blood loss at the time of delivery and thereby increases risk to both mother and new born (2). The precarious nature of iron balance in the pregnant women is a result of the increased demands made on her during the latter part of pregnancy. Ninety percent (1) of the 1000 milligrams (mg) of iron required for pregnancy is needed during the last four months. Half of this requirement is the cost of pregnancy itself. The average iron reserve in a menstruating woman is about 300 mg (3). This is considerably less than the demands of normal pregnancy; a fact which explains the very common occurrence of iron deficiency during pregnancy if additional iron is not given. Obviously, in those countries where food iron is 6 mg per 1000 calories and the daily iron need is 18 mg and greater, the diet consumed does not permit women (particularly pregnant and lactating women) to maintain an adequate iron balance and to keep their iron stores at the required level. This also can be a concern in areas where whole grain foods are consumed and food iron is biologically unavailable.

The new full-term infant has a reserve of iron to satisfy his needs during the first four months of breast feeding. Breast milk itself will supply an estimated 0.25 mg iron per day (1). Subsequently, especially in thriving, growing infants, the need for iron is greater than breast milk can supply, and an external source of iron is required. At this point in life a child is very vulnerable to becoming iron deficient.

Preliminary data suggest that anemia may limit the work performance of those engaged in hard physical labor and thereby reduce earning potential (4) (5)(6)(7). This is very significant in those countries where physical labor output is important to national product.

Recent studies indicate that iron deficiency may decrease the ability of an individual to resist in ection (8). The concept is that iron plays a role in lymphocyte formation (9). This idea ties together iron deficiency anemia and the extent to which it influences morbidity and mortality from infectious disease.

Finally, although not proven, there is at least suspicion that iron deficiency may impair the growth and development of school aged children. Psychological testing (10) of iron deficient children has indicated reduced attentiveness on the part of the child.

The body's functional iron is primarily contained in circulating hemoglobin. There is a variable amount of stored iron which serves as a reserve in case of sudden losses due to blood loss or pregnancy. This reserve varies widely from individual to individual and may not even be present. Daily requirements for iron are dictated by small and constant obligatory losses from the body. To balance these physiologic requirements a constant influx of iron from the diet is required. However, the body has a very limited capacity of absorption, and this fact is apparent when increased iron is required for special body needs (pregnancy, growth, etc.). In human iron nutrition, the most important considerations are the amount of iron, chemical form of iron, and type of diet from which it is consumed. These factors influence the availability of iron ingested. Data collected from animal studies are of limited value because the absorption patterns in man are so different than animals. In recent years, radio-isotopic methods have made it possible to conduct studies in human subjects that accurately determine the biological availability of various iron sources from different diets (11)(12)(13)(14)(15). Out of these and other studies have come the finding that iron from vegetal sources, non-heme iron (legume, cereals, etc.) is of much lower bio-availability than iron from animal tissues, heme iron. Thus, those who consume adequate animal tissues as food will satisfy their iron requirements. Unfortunately, most people in the world survive on diets that are chiefly of vegetal origin. Consumption of even large amounts of their foods will not satisfy their iron needs. A most practicable method of eliminating iron deficiency in these populations would be through the iron fortification of food. This approach was recommended by the group of experts reporting to WHO on nutritional anemias in 1972 (16).

Fortification of foods with iron (17) is not a simple task because many iron compounds interact with other food substances and result in undesirable changes in the quality characteristics of the food fortified. Chemically inert iron substances are used in order to avoid objectionable effects on quality; invariably the inert iron is poorly assimilated. An alternate approach to improving iron nutriture has been to incorporate into food an iron enhancing substance, such as ascorbic acid (Vitamin C). This particularly may be done when adequate iron is in a food but availability is low. However, ascorbic acid has certain limitations one of which is that it can undergo destruction during cooking (18).

To avoid problems encountered in fortifying cereals and legumes, work has been conducted to fortify sugar or table salt with iron. Here again there are limitations as a result of chemical interactions with other food components and reduction in product stability with time (19)(20)(21). Attachment I illustrates the results of Dr. Viteri's preliminary studies to select the most suitable iron compound for fortification of sugar. Iron chelated EDTA (ethylene diamine tetra-acetate) showed to be the most promising compound tested. Other studies indicate that iron EDTA (NaFeEDTA) is stable in sugar and when given to human subjects is equal to or better than ferrous sulfate (iron reference standard) in bioavailability. Absorption characteristics indicate that it may be more similar to heme iron than to non-heme iron pool (22). Recently, NaFeEDTA was incorporated into fish sauce and used in Thailand with evidence of benefit (23). Currently, Dr. Viteri is conducting a small pilot study using sugar fortified NaFeEDTA at 7.5 mg iron per 50 grams sugar. Results indicate that NaFeEDTA fortification is maintaining normal hemoglobin levels. To date, NaFeEDTA has not been considered for use as a food fortificant because of its cost; approximately 8-10 times that of ferrous sulfate (based on iron equivalents). Nevertheless, the estimated annual per capita cost to fortify Central American sugar would be only an increase of 2-3% in sugar price (based on daily consumption of 50 g sugar fortified with 6.5 mg iron). Consideration of NaFeEDTA's chemical and biochemical advantages may make it less expensive in the "long-run". The recent WHO Technical Report on nutritional anemia stated that NaFeEDTA deserves special attention for possible future use in iron fortification (24).

Iron EDTA, in the past, has been employed as a pharmaceutical in iron deficiency anemia, but NaFeEDTA is not a food additive as such. However, closely related, EDTA, NaEDTA and CaEDTA are accepted food additives. The limits set by the FDA (also WHO/FAO standards) for the daily consumption of these substances are higher than the estimated EDTA that would be consumed from fortified sugar. In addition, ongoing long term animal feeding studies at the National Cancer Institute indicate that EDTA is not carcinogenic (25).

Evidence collected to date supports the field testing of sugar fortified with NaFeEDTA. This does not imply that it will be used as an iron fortificant in all foods to be fortified, nor does it suggest that all sugar should be fortified. What is implied is that a new procedure for delivering iron to needy populations will be critically field tested under the most stringent conditions and available for use by those country systems that can best use it not only in sugar but in other commodities.

## VIII. Research Project Design and Methods

The project will be set up in four Guatemalan villages, two highland and two tropical lowland villages. Lowland villagers have the added burden of hookworm, a parasitic disease that causes internal bleeding and loss of blood which results in anemia. The sample population will be primary school children and their families. Approximately 400 children in the public schools will be subjects of the study, and the total sample in each community will be about 1800. One of each pair of communities will be experimental and the other will serve as a control. They will differ in that the experimental village will consume iron-fortified sugar while the control town receives non-iron fortified sugar. All sugar in Guatemala is fortified with vitamin A, and INCAP tests indicate that NaFeEDTA is compatible with the vitamin. As an added incentive to the communities, particularly the communities not receiving iron, a dental program will be initiated and all groups will receive either fluoride tablets or some other appropriate health service that will not influence iron fortification.

The project will run three years. During the initial eight months, project activities will be planned, baseline field data collected and preparations made for fortification. The period of fortification studied will be two years. Total data analyses and preparations of final reports will be carried out during the last four months of the project. A chronological schedule of project activities is illustrated in Figure 1.

The following activities will be conducted during the life of the project. (Note: TA/N proposes that all preliminary stability testing will be completed prior to field work.)

(1) All 1800 subjects in each community (total 7200) will be monitored every eight months by hematocrit.

(2) Diet Surveys: A sub-sample of families will be selected and their diet intakes recorded. A total of 1480 persons (370 per community) will be included in the sub-sample survey. Certain members of those families will be studied for individual diet intakes. Food intake will be estimated by the 24-hour recall method. This will be done before the fortification program begins and at eight-month intervals. Particular attention will be paid to the source of iron and to the consumption of medicinals or other products that could be sources of iron. In addition, total iron will be determined in composite food samples of diets from one of each twenty sub-sample families. This will be carried out twice, before and near the end of the period of fortification. An estimate of twenty families in each community will be sampled. Two collateral surveys will be conducted on smaller stratified samples aimed at determining the sugar intake of the two most iron vulnerable groups, young children and pregnant-lactating women.

(3) Biochemical Determinations: (Iron, folate, trace minerals) Blood and urine samples will be collected from all school children and their families. All subjects will be monitored by hematocrit determinations. Complete hematology, hemoglogin, hematocrit, red cell counts, red cell indices, serum iron, total iron building capacity, serum ferritin, total serum protein and whole blood folates will be determined on the stratified sub-sample of 1480 subjects. Serum ferritin will be measured by radio-immuno assay at the Venezuelan Institute of Scientific Investigation (IVIC). All other laboratory analyses will be carried out at INCAP. Sub-samples will be collected for biochemical analyses every eight months.

Determination will be made for certain traces of minerals in plasma (zinc and copper) and in urine (zinc and magnesium) of all 1480 subjects in the sub-sample. This monitoring will detect any changes in the metabolism of these minerals that may be caused by the feeding of NaFeEDTA. In addition, subjects will be monitored for the possibility of iron overload, though the probability of this occurring is low.

(4) Physiology: Determination of physical work capacity will be conducted in each community four times using 12 male and 12 female adults (18-44 years of age). Lean body mass estimates and urinary creatinine output will be determined in conjunction with work output studies. Subjects will be selected so that the total sample will represent a range of hemoglobin values.

(5) Morbidity: Study villages will have out-patient clinics where health records of all subjects will be kept. Record keeping will begin 3 months prior to iron intervention and maintained throughout the study. All subjects will be monitored for anemia, parasites (particularly hookworm), and other infectious conditions.

(6) Economics: Expense records will be maintained in all villages and at all stages of fortification so that cost evaluation of the delivery system can be made. Estimates of cost of treatment for iron deficiency anemia in the control and other similar communities will be made and compared with the iron treated villages. Both cost and effectiveness of programs will be evaluated.

The study is designed to determine the effectiveness of iron fortification under conditions of inadequate iron utilization alone (highlands) and when added chronic blood loss is superimposed in the form of hookworm (lowlands). It is expected that within two years a progressive decrease will be seen in the incidence of anemia in populations of treated subjects plus essentially no new cases of iron deficiency anemia occurring, in contrast to the control untreated populations. Moreover, serum ferritin data will indicate build-up in iron stores among those previously anemic and treated subjects.

NaFeEDTA has not been used as a food additive and sugar is not a common carrier for iron salts. If the study proves to be: (1) effective in alleviating iron deficiency anemia and (2) economically feasible, the tested delivery system would have application in many areas of the world.

## IX. Overall Cost Estimates

Tables 1-3 present budget information for the three years life-of-the project. Table 1 outlines first year dollar allocation by activity. Total cost for the first year is estimated at $224,282. Table 2 lists the budget for three calendar years and breaks out expenses according to 10 categories. The total 3 year budget is projected at $621,799. Table 3 outlines the percent time assigned for each person according to project activity.

## X. General Appraisal

This project was first submitted in the summer of 1975. It has been reviewed and reshaped by the Office of Nutrition with advisory assistance from Dr. Howarde Sauberlich, Chief, Nutrition Division, Department of the Army, Presidio, California. Dr. Sauberlich is a member of the Food and Nutrition Board of the National Academy of Sciences and is recognized as an expert in laboratory procedures and nutrition field research operations. Dr. Sauberlich has lived in LDCs and is familiar with problems existing under such conditions.

The project has been reviewed by Dr. Clement Finch, an international authority in hematology with special recognition in iron deficiency anemia. Dr. Finch is professor and chairman of hematology at Washington University Medical School, Seattle; a member of the National Academy of sciences, he is considered dean in the field of iron deficiency anemia in the U. S.

Drafts of the project proposal also have been reviewed by Dr. James Cook, Chairman, Division of Hematology, Kansas University Medical School and Dr. Ernest Beutler, Chairman, Division of Medicine, City of Hope Hospital, Duarte, California.

All reviewers support the project and find the experimental design satisfactory. The original budget was considered generally high. It has been significantly reduced (25%) by modifying staff assignments and changing emphases in certain project activities. The principal issue concerns the biological value of NaFeEDTA as compared to ferrous sulfate ($FeSO_4$). Dr. Viteri's data suggests improved absorption of NaFeEDTA, particularly in anemic children and at least equal availability in non-anemic individuals. Drs. Finch and Cook have raised the question that relatively large amounts of EDTA may inhibit the absorption of iron (26) In the proposed study, the EDTA-iron molar ratio will be low. In conversation with Dr. Cook, he agreed that under the conditions in which the product is to be used, NaFeEDTA may be the most practical way of getting iron to the population.

This project is of great interest to the World Health Organization. Attachment II is a letter from Dr. DeMaeyer, WHO, to Dr. Viteri indicating this interest and awarding Dr. Viteri a grant for support of studies in iron fortification.

The U.S. - Japan Malnutrition Panel has endorsed the concept that NaFeEDTA should be studied as an iron fortificant.

On December 17, 1975 this project was reviewed and approved to be forwarded to the RAC by the Agency's Research and Development Committee.

## XI Ethical Concerns

The project has been reviewed by the INCAP committee concerned with human experimentation. This group is composed of INCAP staff and representatives from the Guatemalan Government.

The rights and privileges of all subjects will be protected as required in part 45, Protection of Human Subjects, Title 45 of the Code of Federal Regulations of the United States, and as prescribed by the Government of Guatemala. All subjects, regardless of which test village they reside (control or treated), will be treated for diagnosed anemia.

## XII. Environmental Impact

It is not expected that this study will have any adverse affect on the environment.

## Proposing Office Evaluation

The Office of Nutrition supports this research proposal and recommends that it be funded. The fortification of selected foods with iron is a significant activity in the Agency's nutrition program. While this specific project is to be conducted in Guatemala, its findings will be equally important to all countries where iron deficiency anemia is a major problem.

Samuel G. Kahn
Project Manager

Martin J. Forman
Director, TA/N

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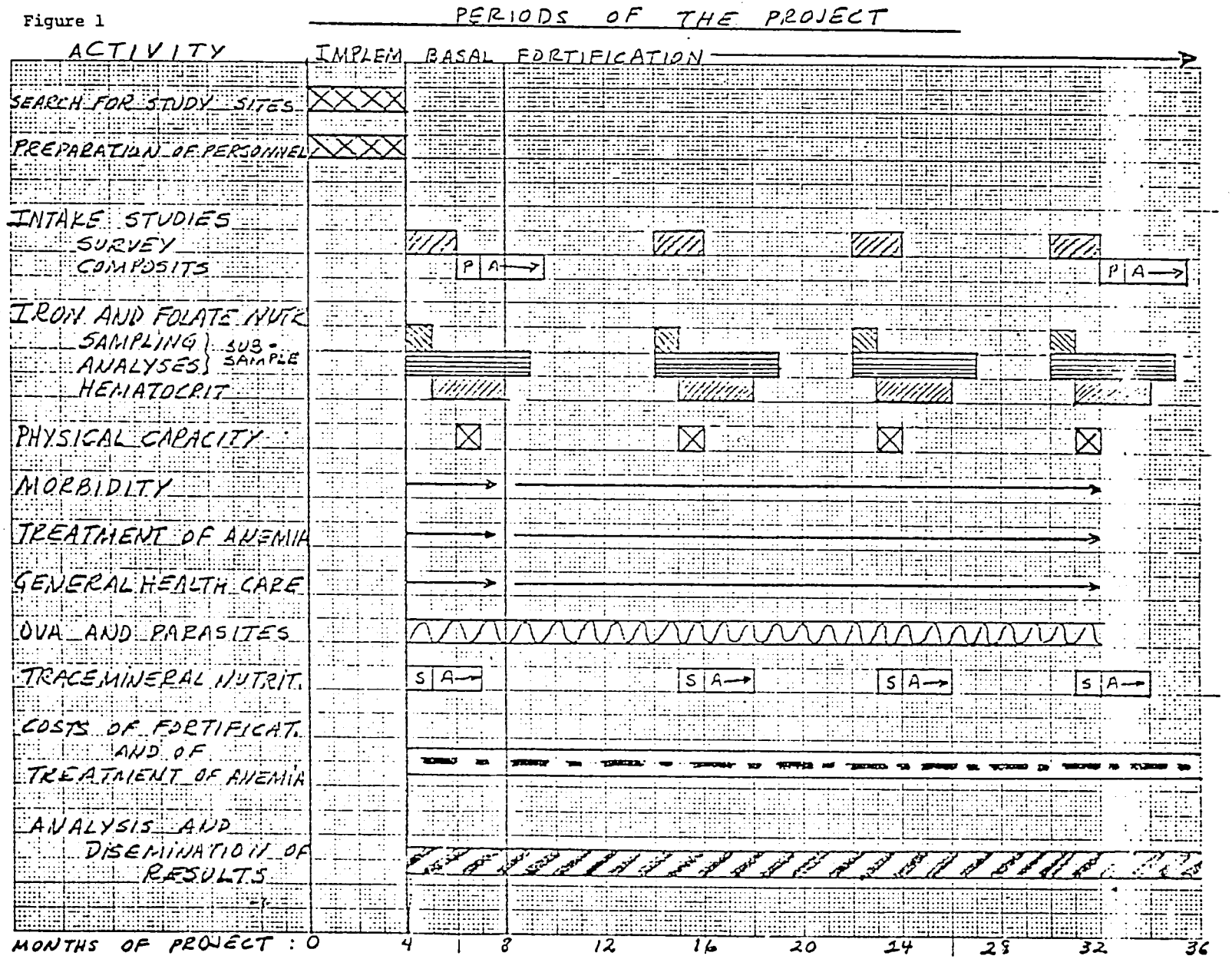
Figure 1


PERIODS OF THE PROJECT
ACTIVITY
IMPLEM
BASAL FORTIFICATION
SEARCH FOR STUDY SITES
PREPARATION OF PERSONNEL
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SAMPLING
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SUB-SAMPLE
HEMATOCRIT
PHYSICAL CAPACITY
MORBIDITY
TREATMENT OF ANEMIA
GENERAL HEALTH CARE
OVA AND PARASITES
TRACE MINERAL NUTRIT.
S
COSTS OF FORTIFICAT. AND OF TREATMENT OF ANEMIA
ANALYSIS AND DISEMINATION OF RESULTS
MONTHS OF PROJECT : 0
4
8
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32
36

TABLE 1

| ACTIVITIES | PERSONNEL | OTHER DIRECT COSTS | TOTAL DIRECT COSTS | APPORTIONED RESEARCH EXPENSES | TOTAL |
|---|---|---|---|---|---|
| 1. Direction, organization, etc. | 33,445 | 7,375 | 40,820 | 7,348 | 48,16[illegible] |
| 2. Dietary | 16,607 | 4,425 | 21,032 | 3,786 | 24,818 |
| 3. Measured intakes | 4,671 | 9,500 | 14,171 | 2,551 | 16,722 |
| 4. Iron and folate status | 24,683 | 27,750 | 52,433 | 9,438 | 61,871 |
| 5. Physical working capacity | 5,400 | 3,425 | 8,825 | 1,587 | 10,412 |
| 6. Morbidity | 18,593 | 11,570 | 30,163 | 5,429 | 35,592 |
| 7. Trace mineral nutrition | 9,866 | 5,155 | 15,021 | 2,704 | 17,725 |
| 8. Cost of fortification | 4,605 | 3,000 | 7,605 | 1,369 | 8,9[illegible] |
| TOTAL | 117,870 | 72,200 | 190,070 | 34,212 | 224,282 |

TABLE 2

BUDGET

1. Personnel

| a) Professionals | 1st year | 2nd year | 3rd year |
|---|---|---|---|
| 1 Physician, chief of field project | 38,060 | 33,500 | 36,700 |
| 1 Physician, assistant | 15,900 | 15,900 | 11,925 |
| 1 Nutritionist | 15,900 | 15,900 | 11,925 |
| b) Non professionals | | | |
| 1 Assistant administrator | 3,620 | 3,785 | 2,962 |
| 4 surveyors | 11,140 | 11,740 | 9,270 |
| 4 Auxiliary nurses | 8,920 | 9,230 | 7,290 |
| 2 Laboratory assistants | 7,240 | 7,570 | 7,900 |
| 1 Lab. assist. (IVIC, Venezuela) | 4,000 | 4,400 | 4,840 |
| 1 Parasitology technician | 3,620 | 3,785 | 1,975 |
| 2 Data clerks | 7,240 | 7,570 | 7,900 |
| 2 Drivers | 2,230 | 2,330 | 1,822 |
| | US117,870 | 115,800 | 104,509 |

2. Travel and Transportation

| | | | |
|---|---|---|---|
| a) 3 round trip/year Caracas-Guatemala + per diem | 2,400 | 2,400 | 2,400 |
| b) Mileage charge $0.20 per km, 36,000 Km/year (gasoline and maintenance) | 7,200 | 7,200 | 5,400 |
| c) Per diem professional personnel $10 x 84 days x 3 | 2,520 | 2,520 | 1,890 |
| d) Per diem for non-professionals $5 x 84 days x 9 | 3,780 | 3,780 | 2,835 |
| | 15,900 | 15,900 | 12,525 |

SLF 2 (continued)

| | 1st year | 2nd year | 3rd yea |
|---|---|---|---|
| 3. Supplies and equipment | | | |
| Coulter counter, 2 microhematocrit centrifuges and 2 freezers | 8,000 | ---- | |
| $O_2$ cells (4) | 600 | 600 | |
| Spare parts for equipment | 1,500 | 1,500 | |
| Equipment for blood collection | 1,200 | 1,300 | 1,300 |
| Equipment for urine collection | 200 | 200 | 200 |
| Stationery and miscellaneous | 1,000 | 1,000 | 1,000 |
| Two vehicles for exclusive use of Project (Field and other activities) | 12,000 | ------ | ------ |
| | 24,500 | 4,600 | 2,500 |
| OTHER DIRECT COSTS | | | |
| 4. Blood and urine analyses | 7,600 | 15,400 | 7,600 |
| 5. Composite analyses of food | 4,800 | | 4,800 |
| 6 Medicines for out-patient care | 6,000 | 6,000 | 4,500 |
| 7 Contractual services | 2,000 | 2,000 | 1,500 |
| 8. Advisory services (STC) | | | |
| a) Short term consultants 2 months at $3,000 | 6,000 | 6,000 | 6,000 |
| b) Review meeting | | | 5,000 |
| 9. Data processing and writing report | 5,400 | 5,000 | 15,000 |
| 10. Publication costs | | | |
| 3 articles x 15 pages x $50/page | | | 2,250 |
| 11. Apportioned Research Expenses | 34,212 | 30,726 | 29,912 |
| | 66,012 | 65,126 | 76,562 |
| Total Budget for each year | 224,282 | 201,426 | 196,091 |
| Total Budget for 3 year period | | | [illegible] |

TABLE 3

Time assigned for each activity (%)

| Activities | Princ. Invest. | Co-Princ. Invest. | Assist. Administrator | Field Director | Assist. Field Director | Nutritionist | Surveyors | Aux. nurses (4) | Lab. Assistants (2) | Lab. Assistants IVIC | Parasitol Tech. | Contracts |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Direction, organization, etc. | 20* | 10* | 80 | 50 | 35 | 30 | | | | | | |
| 2. Dietary | | | | 5 | | 50 | 50 | | | | | |
| 3. Measured intakes | | | | 2 | | 10 | 5 | | 8 | | | |
| 4. Iron and folate status | | | | 20 | 25 | | | 40 | 60 | 100 | | Profesional |
| 5. Physical working capacity | | | | 5 | 10 | | | | 10 | | | Subject costs |
| 6. Morbidity | | | | 8 | 15 | | 35 | 50 | | | 100 | |
| 7. Trace mineral nutrition | | | | 5 | 10 | 10 | 10 | 10 | 22 | | | Profesional |
| 8. Cost of fortification | | | 20 | 5 | 5 | | | | | | | Other profesional activities at INCAP |

The drivers are needed for all field activities. The data clerks will be involved in processing data from all sources.

* No cost.

Attachment I

## OBSERVATIONS ON DIFFERENT IRON COMPOUNDS

1. Ferric sodium pyrophosphate -- essentially unabsorbable

2. Ferric orthophosphate -- essentially unabsorbable

3. Ferrum reductum -- settles when sugar is used in drinks, which is its most common use in Central America

4. Ferrous saccharate -- marked black color, adds metallic taste

5. Ascorbic acid -- could be used as enhancer but the price is 2½ times that of NaFeEDTA for the amount required to enhance Fe absorption. A slight acid flavor is detected at 50 mg ascorbic acid/10 g of sugar. Undergoes destruction (oxidation) during cooking.

6. Ferrous sulphate -- Has definite metallic taste and produces very rapid discoloration to unrefined sugar. Highly reactive.

7. NaFeEDTA -- No metallic taste under most uses. Stability is high Absorbability is at least as good as $FeSO_4$.

Attachment II

WORLD HEALTH ORGANIZATION

1211 GENEVA 27 - SWITZERLAND
Telegr.: UNISANTE-Geneva

ORGANISATION MONDIALE DE LA SANTÉ

1211 GENÈVE 27 - SUISSE
Télégr.: UNISANTÉ-Genève

Tél: 34 60 61 Télex. 27821

In reply please refer to: N3/181/4(E)
Prière de rappeler la référence:

22 January 1976

Dear Dr Viteri,

I sent you on 6 January copy of the agreement for a research grant of $10 000. This grant is awarded for studies on iron fortification but it is also intended to facilitate the obtention of a larger grant from USAID by indicating the great interest that this organization has in the problem of combating iron deficiency. It is our hope that you will be able to obtain some additional funds for research in this field in addition to our continued support.

With kind regards,

Yours sincerely,

E. M. DeMaeyer, M.D.
Medical Officer
Nutrition Research

Dr F. E. Viteri
Chief, Biomedical Division
Institute of Nutrition of Central
America and Panama (INCAP)
Carretera Roosevelt Zona 11
Guatemala City, C.A.
Guatemala

RESEARCH & DEVELOPMENT COMMITTEE MEETING

Minutes of January 14, 1976

Project: Fortification of Sugar with Iron - Field Study Prior to Implementation at a National Level (new), 3 years, $811,694

Contractor: Pan American Health Organization

Project Manager: S.G. Kahn, TA/N

Discussion Highlights:

Discussion regarding the choice of sugar as a vehicle (Woodrow Leake, ASIA/DA) and the objective of fortification (Erven Long, AA/TA) clarified that a fortificant should not modify the product in any way or change its consumption pattern (Sameul Kahn, TA/N). Sugar was chosen as the vehicle because it is naturally consumed as a calorie source in Guatemala and fortification can readily be accomplished through the central processing operation.

Long asked if anemia in these populations is caused primarily by a deficiency of dietary iron or nonabsorption due to some other factor? John Welty, PPC/DPRE, inquired if the presence of parasites would inhibit absorption of the iron, and Von Yoder, ASIA/TD/HD, suggested the inclusion of vitamin B complex with the fortificant. Kahn indicated the principal investigator has determined the primary cause of anemia in populations chosen for this study, and for Guatemala in general, is lack of dietary iron. He also indicated that anemia caused by other factors, such as hookworm and vitamin B12 deficiency, will be accounted for in the design of the study. Clinical anemia is to be treated therapeutically in both the control and treatment villages. Kahn emphasized the objective of this fortification is to provide a preventive as opposed to a therapeutic treatment against iron deficiency.

Long noted that the facts regarding alleviation of deficiency anemia appear to be in place and asked what other factors are missing. Kahn replied the primary objective of the study is to determine if NaFe-EDTA can be effectively used as a fortificant on a field scale. Long then asked if, given the knowledge available on this subject, the purpose of the study could be accomplished for less than $800,000 and suggested this be evaluated before RAC presentation.

The analysis of data on individuals as a source of critical information for evaluating and interpreting differential results within and between the villages was discussed and Long urged that statistical considerations in the design be carefully reviewed to insure meaningful results. Irwin Hornstein, TA/N, expressed confidence that the degree of success of the study could be determined by comparison with baseline data on the village level. Kahn pointed out there is only one treatment in the study and sophisticated statistical analysis is not expected to be a

problem, however a competent statistician is to be assigned on the project. He said the results of this study with accompanying analytical information should be sufficient to transfer the methodology to other countries, particularly in Central America.

Long suggested the following be considered in preparation for RAC review: (1) budget review for reduction in costs, (2) further evaluation of the analytical design and (3) adequacy of project to provide expected results.

Motion: That the proposal be approved.

Moved by Woodrow Leake; seconded by William Feldman

Vote: approved; 3 aye, 1 nay (ASIA)

PD-AAL-695 9310227 (5)

2p

Informal Minutes of the Research and Development Committee
Meeting of December 16, 1975

Projects: 1. Development of Vitamin A Delivery Systems, GTS, KPA #9

2. Combatting Iron Deficiency Anemia, GTS, KPA #9

Project Manager: Dr. Samuel Kahn, TA/N

1. Vitamin A Delivery Systems, GTS, KPA #9
Dr. Irwin Hornstein, TA/N, gave a summary of the PROP revision pointing out that the project focuses on five major areas: (1) determining the prevalence of vitamin A deficiency; (2) developing intervention programs; (3) developing cost-effectiveness of the programs; (4) evaluating ongoing programs; and (5) developing indicators for predicting when vitamin A may become a public health problem. He stated that the request for the expansion of the project reflects the recommendations made by the Secretary of State at the World Food Conference in May 1975.

2. Combatting Iron Deficiency Anemia, GTS, KPA #9
Anemia is reported to be one of the more prevalent nutritional deficiency diseases in the world. Survey reports indicate that the more prevalent cause of anemia is an inadequacy of iron. Iron deficiency anemia occurs most frequently in infants, growing children, adolescents and pregnant women. In the latter group, a combined deficiency of iron and folic acid is often observed in certain LDCs.

In October 1974 in Geneva, AID, in cooperation with WHO and IAEA, sponsored a conference on Nutritional Anemia. The experts gathered represented both LDCs and developed countries. They concluded that nutritional anemias are very prevalent in many countries, and that there is sufficient knowledge concerning the causes, implications, and public health significance of nutritional anemias to justify action for control and eradication of this nutritional disease problem. Recommendations were: (a) continued research to improve laboratory methodologies that will more accurately define types of anemias, (b) continued studies which will more precisely define the adverse effects of mild anemia, (c) studies that will enable reasonable cost-benefit analysis of action programs, (d) collection of more information regarding bio-availability of iron from different diets, (e) continued and expanded prevalence surveys, (f) initiation of iron and folate supplementation and fortification studies that would lead to national programs for those segments of the population most at risk, (g) education and training programs to combat nutritional anemias in those countries with insufficient specialized personnel to carry out these programs.

Dr. Hornstein stated that the PROP for this activity outlines those areas of activity for which AID/W will mount an effort. In principal, A.I.D. is interested

in participating in all areas recommended for action to the extent that they contribute to the development of iron supplementation and/or fortification programs for those groups in need. This position is supported by Dr. Kissinger's statement before the World Food Conference.

Discussion Highlights for Iron Deficiency & Vitamin A Projects

AID has been cooperating with other donor agencies in Vitamin A programs. Both WHO and AID funded a conference in Djakarta to examine the widespread effect of vitamin A, the ways for detecting vitamin A deficiency, areas of research and to determine what should be done. The result of this conference was the creation of the International Vitamin A Consultative Group (IVACG).

The Vitamin A program is not a unilateral activity. Other donor agencies are involved in some aspect of Vitamin A delivery system. Mr. William Feldman, LA/DP, stated that a major concern should be the contribution of LDCs to the activities and the institutions available to continue the activities once AID support has phased out. He suggested that this be addressed in the PROP.

Ms. Sue Gibson, NE/DP, added that the PROP revision needs to define how the LDCs will be involved, the criteria for selecting them and their commitment.

Mr. Feldman moved that NE/DP's comments be addressed in the PROP revision, and that there be some type of a formal commitment defining joint support of AID and the LDC. The formal commitment could concelvably be a Project Agreement.

Mr. John Welty, PPC/DPRE, raised some concern about the education component and suggested inclusion of this in both project papers.

Ms. Gibson suggested the development of more research activities and specificity on alternatives for what is to be tested.

Mr. Von Yoder, ASIA/TD, stated that the justification for increased funding at a specific level was insufficient. Mr. John Gunning, TA/PPU commented that the Secretary of State had made some quantitative commitments at the World Food Conference. When pledging U.S. support for major programs in this area, Mr. Fritz informed the group that significant reductions in the TA Bureaus FY 77 funding level undoubtedly would result in significant cuts for those projects.

Action Required

The R&DC recommended that the following comments be addressed in the PROPs

PD-ABL-695 9310227 (6)

RESEARCH & DEVELOPMENT COMMITTEE MEETING

9-227

Minutes of January 14, 1976

Project: Fortification of Sugar with Iron - Field Study Prior to Implementation at a National Level (new), 3 years, $811,694

Contractor: Pan American Health Organization

Project Manager: S.G. Kahn, TA/N

Discussion Highlights:

Discussion regarding the choice of sugar as a vehicle (Woodrow Leake, ASIA/DA) and the objective of fortification (Erven Long, AA/TA) clarified that a fortificant should not modify the product in any way or change its consumption pattern (Sameul Kahn, TA/N). Sugar was chosen as the vehicle because it is naturally consumed as a calorie source in Guatemala and fortification can readily be accomplished through the central processing operation.

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problem, however a competent statistician is to be assigned on the project. He said the results of this study with accompanying analytical information should be sufficient to transfer the methodology t other countries, particularly in Central America.

Long suggested the following be considered in preparation for RAC review: (1) budget review for reduction in costs, (2) further evalu tion of the analytical design and (3) adequacy of project to provide expected results.

Motion: That the proposal be approved.

Moved by Woodrow Leake; seconded by William Feldman

Vote: approved; 3 aye, 1 nay (ASIA)

PD-AAL-695 9310227(1)

Minutes of the March 22-23, 19 RAC meetin



Fortification of Sugar with Iron: Field Study Prior to Implementation at a National Level (New), Institute of Nutrition Central America and Panama (INCAP)

(Iron Deficiency Anemia) 9-227

Dr. Schweigert, Chairman of the Subcommittee composed of Drs. Carter and Linder, and Mr. Ludington, summarized this project to study the fortification of dietary sugar with iron, in the form of EDTA-iron, as an intervention mechanism for prevention and control of iron deficiency anemia. He noted that observed anemia in control groups will be treated which should satisfy any question of medical ethics in the procedures. In critique of the proposal he noted several concerns.

1) The type of fortification appears inconsistent with the National Academy of Sciences, Food and Nutrition Board guidelines in the sense that sugar is not expected to be a dietary source of iron, and this approach may not be applicable in many countries because sugar consumption patterns vary widely among nations.

2) Adequate provision for following the effects of the iron supplement on food during the distribution, processing, and cooking uses would increase the value of information on use of the EDTA form of iron. Better information on sugar and food intake would increase confidence on amount of iron actually delivered by this system.

3) A number of nice-to-know features in the study should be scrutinized for both validity of purpose and economy of design. AID staff should determine final inclusion through careful study.

4) Amount of additional equipment requested by INCAP to do this study should be examined closely.

5) Political stability of the test villages should be reassured; also will the recent earthquake damage to INCAP interfere with the study?

6) The role of Panama which is referenced in the project should be clarified.

As a minor point he noted the Asia Bureau did not support the study and the reason was not clear from the Research and Development Committee minutes. He complimented the AID staff and principal investigator for their efforts in improving this proposal during its evolution over the past few years. He also noted the competency of the principal investigator and associates and the external peer evaluation.

Dr. Linder referenced the total sample of 7200 persons which is to be studied over a 2½ year period and expressed concern that the proposal does not adequately provide for recording, systematizing, and analyzing the large volume of data to be generated. He urged that peripheral aspects of the study, such as work capacity and morbidity, be reassessed to assure adequate evaluation of the more important variables. Overindulgence, he said, should not be a feature of studies in malnutrition.

Dr. Carter indicated that a lot of good work had been done and favored the project, but that it should be re-designed and re-written. He focused his comments on three areas.

1) Although the study will probably be approved by the Government of Guatemala and the INCAP Committee on Human Experimentation, he agreed with Mr. Ludington that for ethical reasons it would be preferable to eliminate the control villages and do a before and after study on the treated villages.

2) He suggested that several aspects of the design should be improved. Evaluation of the effectiveness of EDTA-iron as a fortificant should be supported by better information on its interaction with sugar and other foods, absorption from the intestinal tract, and its utilization. For example, it would seem necessary to know the amount of hookworm infectic and blood loss in the lowland population, and it would seem desirable to have Dr. Layrisse, who is an authority in this area, more involved with this phase.

3) The feasibility of implementing the fortification process at a national level should be included as part of the research design. He believes this is a researchable problem which INCAP is capable of doing with a few consultants. He referenced previous INCAP experience with Vitamin A fortification of sugar on a national level as justification for this concern.

In addition to the question of control groups, Mr. Ludington expressed concern about biochemical interaction of EDTA-iron when the sugar is used in the preparation of foods and if absorption would be changed. He indicated there are sufficient uncontrolled variables in the study to completely confound the treatment effect and asked how the amount of iron to be delivered to each person would be assured and monitored. Although additional effort and material may be necessary to ensure delivery of adequate iron, he said the assurance of valid results would justify the cost. He commented that this project is a mixture of a clinical study and a mass feeding trial, and expressed reservation that it will not resolve the issue of calories versus protein but only provide more data for discussion.

Dr. Whitney noted that EDTA has been used for many years as a chelating agent in plant nutrition. He said the nutrition should be alerted that it can interfere with plant absorption of zinc, copper, manganese, and other trace elements, and asked if this could occur in humans. Dr. Schweigert indicated there is a potential for iron to interfere with absorption of trace elements, and for this reason they should be monitored as planned. Dr. Carter agreed that too much EDTA could be harmful.

Dr. Whitney indicated the design appeared satisfactory and asked if treatment of anemic individuals in the control groups would affect their validity as a control. He was favorable to the suggestion that iron-sulfate fortified sugar treatment be used for comparison instead of a zero control. Dr. Schweigert said iron-sulfate is a strong oxidant which discolors food and should be avoided.

Dr. Wishik stated that the control group design does not appear to be unethical if one is not sure the treatment will be beneficial. The control group should benefit in some way, however, and if the treatment does prove successful he suggested it be given to the control village after the study is concluded.

Dr. Wishik agreed there should be potential for implementation built into the project. He noted, however, that for utilization the data must be presented to the proper audiences. INCAP's experience with Incaparina was referenced as an example. Dr. Carter said fortification becomes an economic problem for the producer where price is controlled and where export is involved.

Dr. Hornstein, TA/N, reported the capability of INCAP to conduct the study was not impaired by the recent earthquakes. The area where the villages will be selected was not affected. Panama had been considered for inclusion early in the planning but was omitted for economy. He noted that non-support for the project from the Asia Bureau was not due to lack of technical merit. The sample of 24 persons for study of work input was considered adequate by the statisticians, but this will be checked. He indicated that committee comments will be examined carefully.

Data from previous studies support 13 mg iron per 100 gm of sugar as an adequate fortification level. It cannot be assured that 100% of the population will get this amount each day. Effectiveness of the fortification must be interpreted in terms of the level provided. Dr. Kahn, TA/N, said one-half the level proposed has been effective in previous small studies by the principal investigator. Dr. Hornstein indicated this is an intervention which can be implemented, and the Nutrition Office wants to learn abou the problems. He said the information should be useful also for developing other fortification programs.

Dr. Kahn said the design of this study for protection against iron anemia has been developed over the past two years. EDTA-iron is not new and the principal investigator has considerable experience with it. He said, Dr. Layisse became involved as a consultant but will be an active participant in the ongoing project.

Dr. D. Peterson inquired if the fortificant could be used in soft drink beverages. Dr. Kahn indicated it could. However, sugar was chosen as the carrier because it was considered to be the best way to deliver iron to the population.

Dr. Carter said there is a ~~general~~ consensus among the subcommittee to do the study but not in its present form, and suggested approval in principal with provision for review. Dr. Schweigert indicated this is a procedural question and asked if there were restrictions on time, personnel, etc. to be considered. Dr. Long indicated the Agency would probably loose the money for the project unless it can be moved along this year. He said there are various techniques to assure documentation before contracting and suggested referral to the subcommittee for this purpose.

Dr. Schweigert moved, with a second by Dr. Linder, that the project be approved in principle with provision that the contractor consider and incorporate suggestions from RAC and peer evaluation and submit a revised project for information with the May RAC as a target date. Dr. Montgomery offered, as a friendly amendment, that the sub-committee be provided documentation by May 1 for study, so their review capacity would be retained. Dr. Carter said he would like to see the revised project before funding. Dr. Long favored the amendment as an additional tool. Approval by the sub-committee then would clear the project for contracting, but if there was a negative response then no action would occur. Drs. Schweigert and Linder accepted and the amended motion was:

<u>Motion</u>: That the project be approved as requested subject to incorporation by AID staff into a revised project proposal, the suggestions made by RAC and the peer reviewers. This revised proposal is to be reviewed by members of the RAC sub-committee. If the revised proposal is acceptable to the RAC sub-committee it may be

immediately implemented; if major objections are made by the RAC sub-committee, the project will not be implemented until further review by the RAC, preferably at the May, 1976 meeting.

Moved by Dr. Schweigert and seconded by Dr. Linder

Vote: Approved with one nay response